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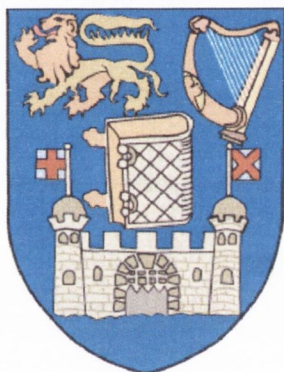
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Towards Novel Constrained Resorcarene-Based Platforms

Deborah Moore

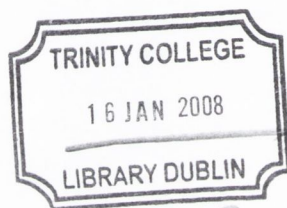


**School of Chemistry
Trinity College**

A thesis submitted to the University of Dublin for the degree of
Doctor of Philosophy

May 2007

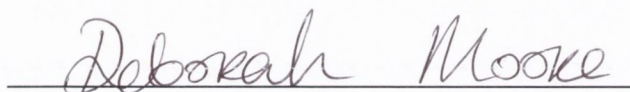
Based on research carried out under the direction of Dr. Susan Matthews and Prof.
Thorfinnur Gunnlaugsson



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8309

Declaration

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A handwritten signature in cursive script, reading "Deborah Moore", is written over a horizontal line.

Deborah Moore

Abstract

This thesis entitled “Towards Novel Constrained Resorcarene-Based Platforms” is divided into seven chapters.

In Chapter 1, an introduction to resorcarene chemistry is given and a discussion of the various possible isomers is included. A review of further reactions that can be carried out on the resorcarene macrocycle is then given. This chapter also describes the aims of this project.

In Chapter 2, work towards synthesising a novel resorcarene tail-to-tail dimer is described. Various synthetic methods were attempted, and the use of different catalysts and resorcinol derivatives in the initial resorcarene condensation reaction were investigated. Some success was had with a step-wise approach and this led to the isolation of novel resorcinol dimers.

In Chapter 3, work on octamethylresorcarenes is presented. A study of the conditions that favour different conformers is presented and discussed which led to the development of a synthetic method selective for the chair conformer. Preliminary computational results to study the relative energies of the chair and boat conformers indicate that the chair isomer is the more thermodynamically favourable conformation. The post-condensation alkylation of novel OMRA macrocycles is also reported.

In Chapter 4, a range of synthetic routes to upper and lower rim calix[4]arene aldehydes are reported. The subsequent reaction of these aldehyde derivatives with resorcinol is then discussed.

In Chapter 5, the synthesis of a number of cavitand platforms, suitable for ligand attachment, is discussed. The synthesis of four novel cavitands and a preliminary study of their interaction with metal salts are also described.

Finally, Chapter 6 details the proposed future work and Chapter 7 outlines the experimental procedures used in chapters 2, 3, 4 and 5, and presents the characterisation of the novel compounds prepared.

Acknowledgements

I would like to thank Dr Susan Matthews for her supervision throughout this project and for being a constant source of motivation and enthusiasm. I would also like to thank Prof. Thorfinnur Gunnlaugsson, who welcomed me into his group at the end of my second year, and has given me the benefit of his advice and experience ever since.

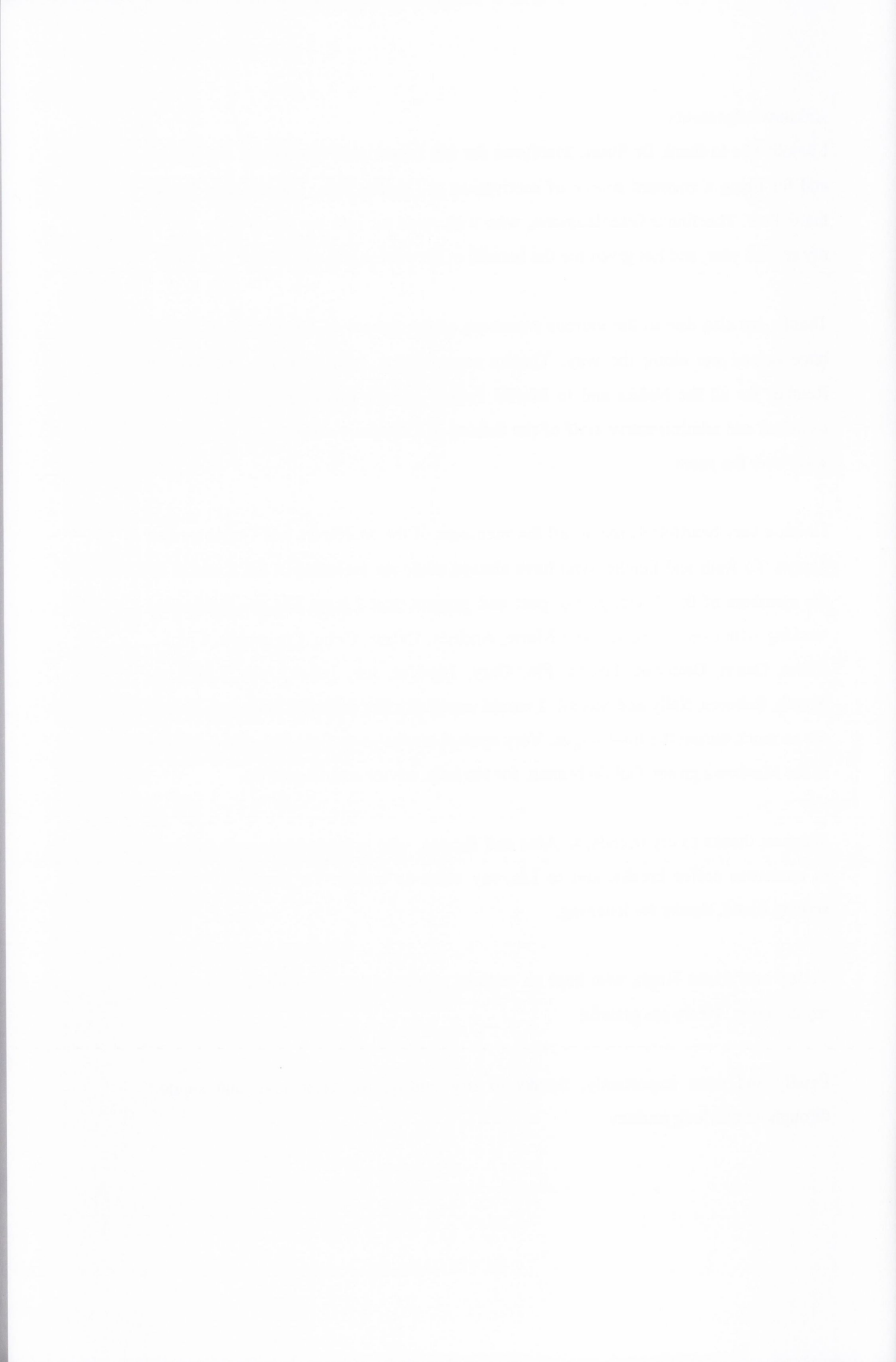
Thanks are also due to the various members of the School of Chemistry, TCD that have helped me along the way. Thanks especially to John O'Brien and Manuel Reuther for all the NMRs and to Martin Feeney for the mass specs and to all the technical and administrative staff of the School of Chemistry who helped in so many ways over the years.

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Finally and most importantly, thanks to my family, for their love and support throughout this long journey.



Abbreviations

Ar	Aromatic ring
Bu	Butyl
<i>t</i>Bu	<i>tert</i> -Butyl
CHCl₃	Chloroform
CH₂Cl₂	Dichloromethane
CH₃CN	Acetonitrile
CHN	Elemental analysis
CDCl₃	Deuterated chloroform
(CD₃)₂SO	Deuterated dimethylsulfoxide
[]	Concentration
δ	Chemical shift (in ppm)
d	Doublet
DMF	<i>N,N</i> -Dimethylformamide
DMSO	Dimethylsulfoxide
ESMS	Electrospray mass spectrometry
equiv.	Equivalents
Et	Ethyl
EtOH	Ethanol
G	Guest
h	Hour
HCl	Hydrochloric acid
H₂SO₄	Sulfuric acid
IR	Infrared
<i>J</i>	Coupling constant (in Hz)
λ	Wavelength (in nm)
lit.	Literature
LUMO	Lowest unoccupied molecular orbital
m	Multiplet
MeOH	Methanol
m.p.	Melting point (in °C)
m/z	Mass to charge ratio
NMR	Nuclear magnetic resonance

OMRA	Octamethylresorcarene
Ph	Phenyl
ppm	Parts per million
q	Quartet
RT	Room temperature (in °C)
s	Singlet
t	Triplet
THF	Tetrahydrofuran
TLC	Thin layer chromatography
UV-vis	Ultraviolet-visible
v/v	Volume per volume
λ	Wavelength (in nm)

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Chapter 1

Introduction

1.1 The Discovery of Resorcarenes

The first recorded synthesis of a resorcarene dates back to 1872. It was reported by Baeyer that on the addition of sulfuric acid to benzaldehyde and resorcinol a red-coloured, solid product was formed.¹ Almost ten years later an extensive study of this reaction, the necessary conditions and an analysis of the products formed was published.³ It was found that the acid was necessary only in catalytic amounts, that any prolonged exposure to air led to a “reddish tinge” appearing in the product (due to its oxidation) and most importantly, through the study of both the original product and its acylated derivative, their correct elemental compositions were reported as $(C_{13}H_{10}O_2)_n$ and $(C_{13}H_8O_2(OCCH_3)_2)_n$ respectively. Although the study correctly concluded that this product was formed by the combination of an equal number of moles of resorcinol and benzaldehyde, and the loss of an equal number of moles of water, Bayer was unable to determine the molecular weight of the product and so, incorrectly, proposed that the structure of the product was actually a carbon-carbon double bond, with a resorcinol and a phenyl group attached to each carbon.

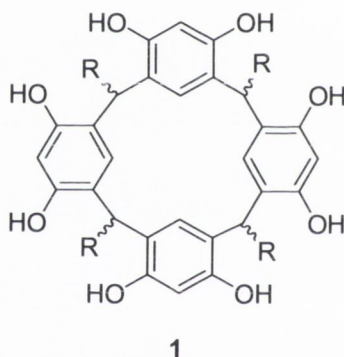


Figure 1.1: Generalised structure of resorcarene

The correct structure of resorc[4]arene was not reported until much later, in 1940 by Niederl and Vogel.⁴ They studied the condensation products of resorcinol with acetaldehyde, propionaldehyde and isovaleraldehyde as well as the acetates, propionates and methyl ethers of these resorcinol compounds. Molecular weight determinations indicated that the ratio of aldehyde:resorcinol in the product was 4:4, while the formation of the octa-substituted compounds, listed above, indicated the presence of eight free phenolic groups. The reaction of this product with reagents such as alcoholic sulfuric acid and hydroiodic acid, ruled out the presence of acetal and ether linkages respectively. Furthermore, they also deduced that the

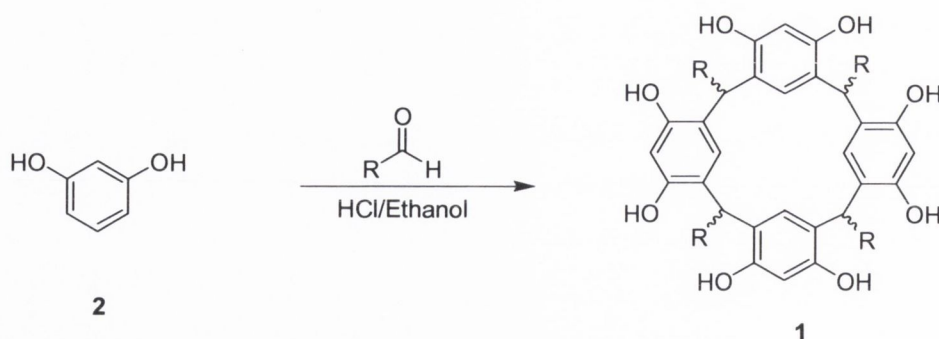
products were most likely cyclic, due to their high melting points and the consistent formation of a tetrameric product. Drawing on the established parent structure of porphyrin, they proposed, correctly, that the product had a cyclic tetrameric structure (**1**), shown in **Figure 1.1**. It was however, not until much later that conclusive proof for this cyclic tetramer was obtained when the first single crystal X-ray structure of a resorcarene, that of the acylated product from the condensation of resorcinol and 4-bromobenzaldehyde, was solved in 1968.^{5,6}

Although these compounds have been known since 1872 and fully characterised since 1968 there is still no universally used and accepted naming system for this family. The IUPAC naming of these compounds is quite complicated, for example, for the parent structure **1** in **Figure 1.1** (if we take R = alkyl), the official IUPAC name would be 2,8,14,20-tetraalkylpentacyclo-[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacos-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecane-4,6,20,12,16,18,22,24-octol.⁷ Unfortunately agreement has never been reached on a suitable trivial name for these compounds and they can be found throughout the literature under many different aliases, such as resorcinarenes,⁸ resorcarenes,⁹ calix[4]resorcinarenes,¹⁰ resorcinol derived calix[4]arenes,¹⁰ Högberg compounds¹¹ and octols.¹² Throughout this thesis they will be referred to as resorcarenes.

This chapter will describe the most common methods of preparation of resorcarenes and the further modification of the basic structure of resorcarenes to form functional derivatives.

1.2 The Synthesis of Resorcarenes

Resorcarenes today are synthesised in a one-pot, acid catalysed condensation reaction between resorcinol (**2**) and an aldehyde, **Scheme 1.1**. Generally, HCl is used as the catalyst and ethanol as the solvent in these reactions and the product is obtained after heating for several hours.¹² However, the optimum conditions vary depending on the exact reactants used.



Scheme 1.1: Synthesis of a resorcarene

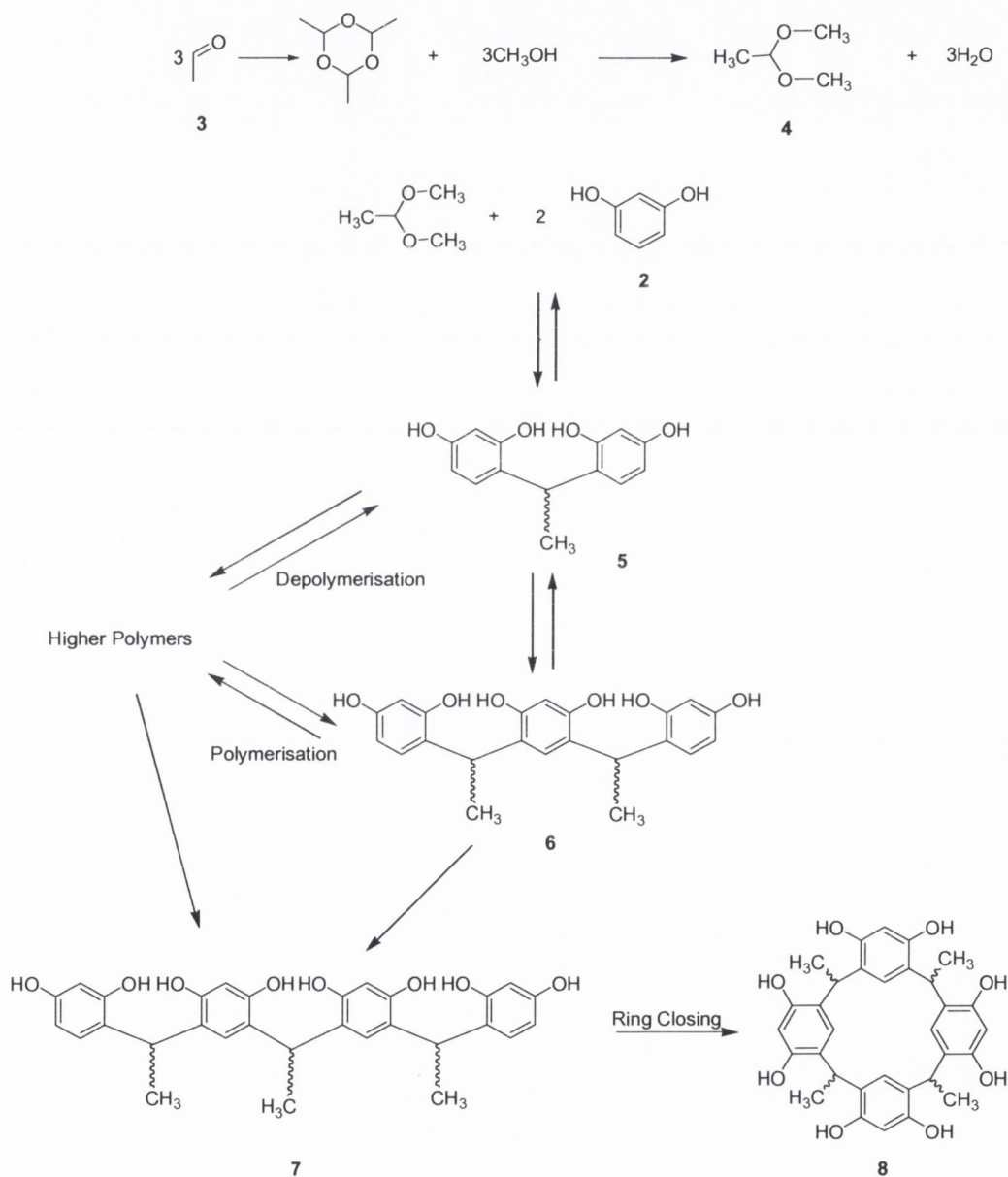
Although unsubstituted resorcinol is most commonly used, there are many examples of the use of pyrogallol,¹³ 2-methylresorcinol¹² and 1,3-dimethoxybenzene¹⁴ in its place. There is almost unlimited variation allowed in the choice of aldehydes, both aliphatic and aromatic can be used in this reaction, with the exceptions being aldehydes that are too sterically bulky to allow formation of the tetramer, such as 2,4,6-trimethylbenzaldehyde¹⁵ and those that have functionality too close to the reaction centre, such as glucose.¹² Another notable exception is that of the simplest of all aldehydes, formaldehyde, which will be discussed in **Section 1.2.1**.

The mechanism for the formation of resorcarenes was studied by Weinelt and Schneider.¹⁵ They examined the condensation of resorcinol (2) and acetaldehyde (3) in methanol, a homogeneous reaction, which allowed a full study of the kinetics and thermodynamics to be conducted. They found that, under these conditions, the electrophilic species reacting with the resorcinol nucleophile is not the aldehyde itself but the rapidly formed dimethyl acetal (4). The formation and degradation of oligomers and ring products was followed by ¹H NMR spectroscopy, which showed that dimeric, trimeric and higher oligomeric (>4) acyclic species were all observed during the reaction. The higher oligomers accounted for up to 45% of material present in the early stages of the reaction but these had largely disappeared by the completion of the reaction due to their back reaction to tetramers. Acyclic tetramers were however, not observed and this is believed to be a consequence of fast cyclisation preventing them from accumulating in observable quantities. According to molecular mechanics calculations reported by Weinelt and Schneider this is most likely due to the low-energy, folded structure of the tetramer which allows the formation of hydrogen bonds between the adjacent phenolic groups. In all cases, the intermediates had resorcinol and not hydroxyethyl

units in their terminal positions, which is due to the fast reaction of benzhydrols under acidic conditions. The authors drew a number of conclusions from their work, these are summarised below.

- (i) Ring closure is as fast as chain propagation.
- (ii) The macrocyclic products form the thermodynamic sink of the reactions.
- (iii) The degradation of higher oligomers (>4) is faster than ring opening.

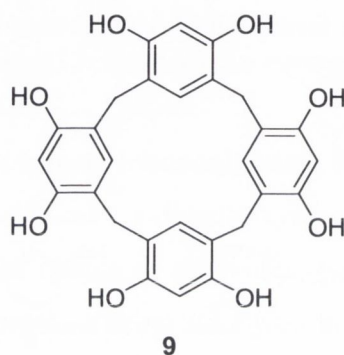
An overview of the pathway for the formation of resorcarenes is outlined in **Scheme 1.2**.



Scheme 1.2: Proposed pathway for the formation of a resorcarenene

1.2.1 Synthesis of the Parent Resorcarene

The parent resorcarene (**9**) is a derivative which has no substituents on its methylene bridges, 2-position or at the hydroxyl groups. Logically, it should be available from the condensation of resorcinol and formaldehyde under standard conditions. However, the extreme reactivity of the formaldehyde leads to the formation of polymers under these conditions.



Nevertheless, resorcarenes unsubstituted at their methylene bridges were obtained under standard condensation conditions when resorcinol was replaced with either 2-methylresorcinol¹⁶ or pyrogallol.¹⁷ Attempts have been made to isolate the unsubstituted parent resorcarene from the self-condensation of 2,4-dimethoxybenzylalcohol and subsequent reaction with BBr₃ to convert the ethers to alcohols. While a material was isolated from this method it was nevertheless proved to be too insoluble to be fully characterised.¹⁸ An analogous method, using 2,4-bis(allyloxy)benzyl alcohol, also yielded the parent resorcarene. While this product was still slightly impure, a full characterisation was reported.¹⁹ The cyclooligomerisation of 2,4-diisopropoxybenzyl alcohol catalysed by chlorotrimethyl silane allowed the isolation of the parent resorcarene (after subsequent deprotection and columning steps) in high yield and purity.²⁰ The parent resorcarene was finally synthesised without the use of protecting groups, on either the hydroxyl groups or the 2 position of the resorcinol, by the reaction of resorcinol and formaldehyde catalysed by sodium hydroxide. Subsequent acidification of the reaction mixture and slow precipitation from MeOH at -18 °C led to the synthesis of the desired product in high purity.²¹

1.3 The Stereochemistry of Resorcarenes

Although so far, for the purposes of clear illustration, resorcarenes have been drawn as flat molecules, they are in fact non-planar. This means that, in theory, resorcarenes could exist in numerous different isomeric forms. Their stereochemistry depends on the combination of three stereochemical elements, which are detailed below.

(i) *The conformation of the macrocyclic ring.*

The ring itself can adopt five extreme macrocyclic arrangements: the *crown* (C_{4v}), the *boat* (C_{2v}), the *chair* (C_{2h}), the *diamond* (C_s) and the *saddle* (D_{2d}). These are illustrated in **Figure 1.2**.

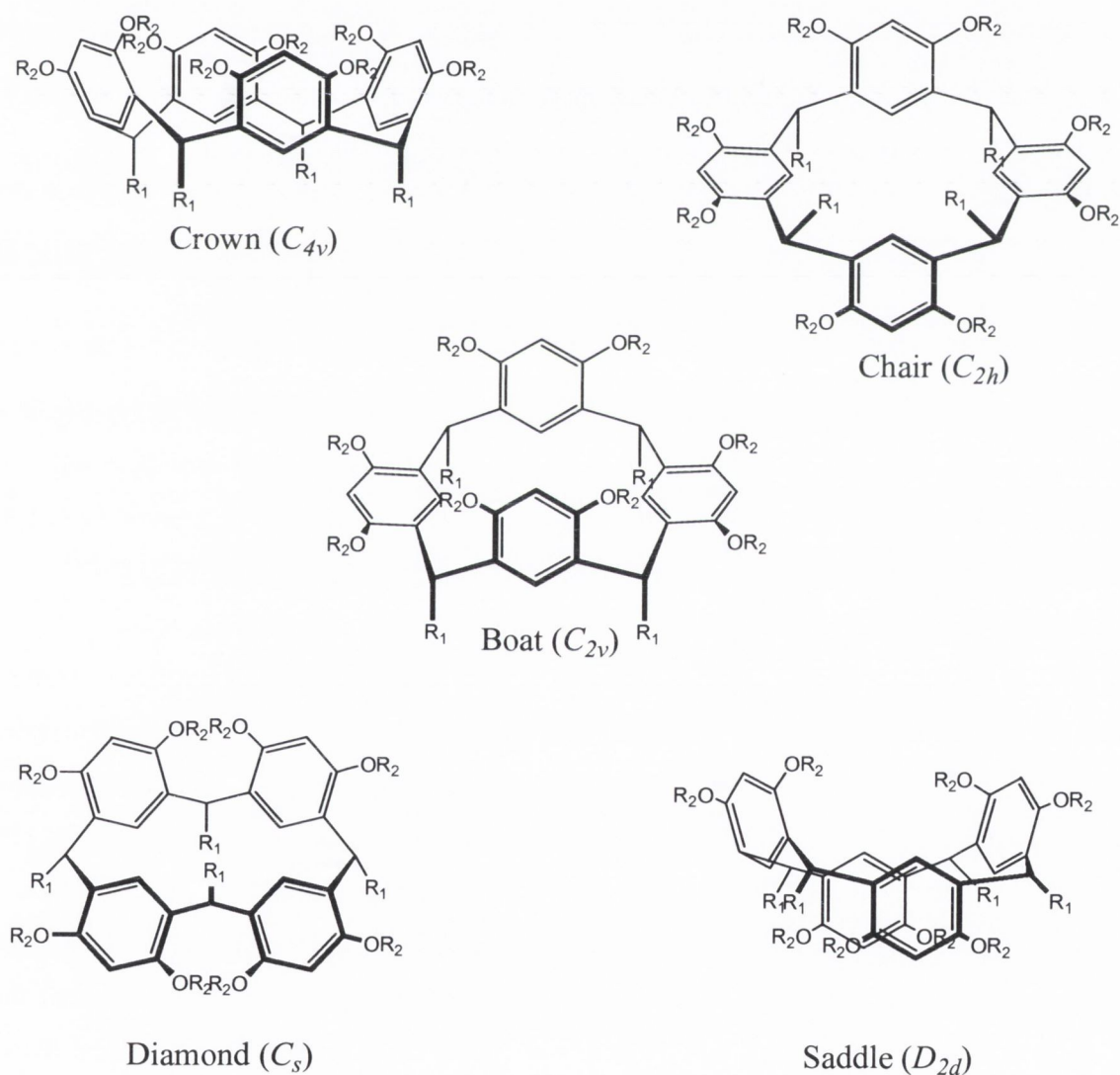


Figure 1.2: The five possible conformations for resorc[4]arenes

(ii) *The relative configuration of the substituents at the methylene bridges.*

The relative configurations of the substituents, with respect to the substituent R^* , can lead to four different possibilities: all-*cis* (*rccc*), *cis-cis-trans* (*rcct*), *cis-trans-trans* (*rctt*) and *trans-cis-trans* (*rtct*), **Figure 1.3**.

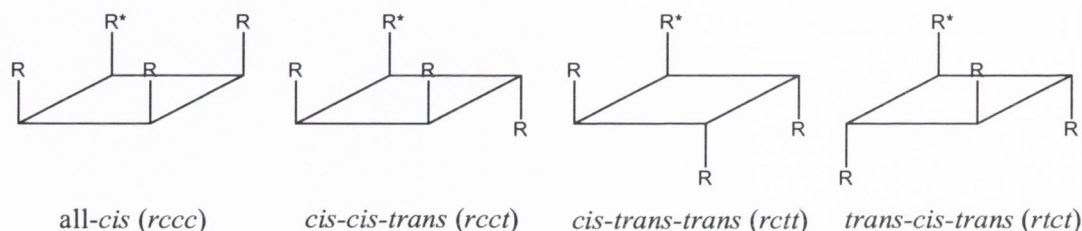


Figure 1.3: Possible configurations of substituents at the methylene bridges

(iii) *The individual configurations of substituents at the methylene bridges.*

In each of the macrocycles with C-symmetry the substituents may have either axial or equatorial geometry.

The combination of these three stereochemical elements obviously leads to many possible stereoisomers. However, to date only three diastereomers have been found experimentally for resorcarenes, with an additional diastereomer reported for those resorcarenes derived from 1,3-dimethoxybenzene, octamethylresorcarenes (OMRAs) (**Figure 3.1**).²²

In 1976 Palmer *et al.* reported the synthesis, separation and characterisation of two isomers from the reaction of resorcinol and benzaldehyde.²³ The crystal structures of the octabutyrate of these molecules show them to be the boat form, with the R groups in the all axial position, all *cis* conformation and that of the chair form, with the R groups in the all axial position, *cis-trans-trans* conformation. Initially, most of the work on the assignment of conformations and the substituent configurations relied on crystal structure analysis. However, in 1988 Dalcanele *et al.* reported the use of ^1H and n.O.e. NMR studies to fully elucidate the structure of the diamond conformation.²⁴ The reaction of resorcinol with either heptanal or dodecanal led to the isolation of three separate isomers, all showing the same major peaks in their mass spectra

but differing in their ^1H NMR spectra, melting points and R_f values.²⁴ In addition to the previously observed chair and boat conformers, the diamond conformer, with an all axial, *cis-trans-cis* configuration in the R groups, was also seen. All the isomers in this case were characterised as their corresponding octaacetates.

There are a few reports of the saddle isomer in resorcarene literature.^{22,25} The saddle conformer is only observed when the upper rim is under steric constraint due to the functionalisation of the hydroxyl groups. In this conformation, the -OR groups on adjacent rings are placed at the furthest distance apart. On the phosphorylation of the upper rim with bulky substituents, Maslennikova *et al.* have reported the formation and the crystal structure of the intermediate between the flattened boat and the saddle.²⁵ Botta *et al.* reported two saddle resorcarene based molecules from the self condensation of (*E*)-2,4-dimethoxycinnamic acid ethyl and isopropyl esters.²² In this case, the conformations were assigned by extensive NMR studies and to date, no crystal structure of the saddle conformer has been reported. Of these four isomers, only two are routinely observed, the boat conformation with all axial, all *cis* arrangement of the R groups and the chair, with an all axial, *cis-trans-trans* arrangement of the R groups. The next section deals with the possible interconversions between these resorcarene isomers and the conditions under which they can take place.

1.3.1 The Relationship and Interconversion of the Resorcarene Isomers

The crown, diamond, chair and saddle isomers shown previously in **Figure 1.2** are not, as would first appear, conformational isomers, as these structures cannot be interconverted by rotation through the annulus of one, or more, aromatic rings. Although such rotation would give the correct conformation of the macrocyclic ring, it would result in some of the substituents changing from axial to equatorial, or *vice versa*, giving rise to conformations with altered configurations of substituents at the methylene bridges. For the interconversion between these isomers to take place the breaking of at least two covalent bonds is required. That is not to say, however, that the interconversion, by the rotation of aromatic rings, does not take place. A ^1H NMR study was undertaken, by Dalcanale *et al.*, of the solvent dependent behaviour of the free resorcarenes obtained in the condensation reaction between resorcinol and hexanal.²⁶ The crown, chair and diamond isomers were all isolated from the reaction

mixture. Here, the ^1H NMR of the crown conformer (**10a**), in either $\text{DMSO}-d_6$ or acetone- d_6 , remained unchanged even at low temperatures and no interconversion to other ring conformations was observed. In the case of the chair (**10b**) and the diamond (**10d**) conformers, the ^1H NMR spectra in $\text{DMSO}-d_6$ show only that conformer in solution. However, in acetone- d_6 they become more complicated.

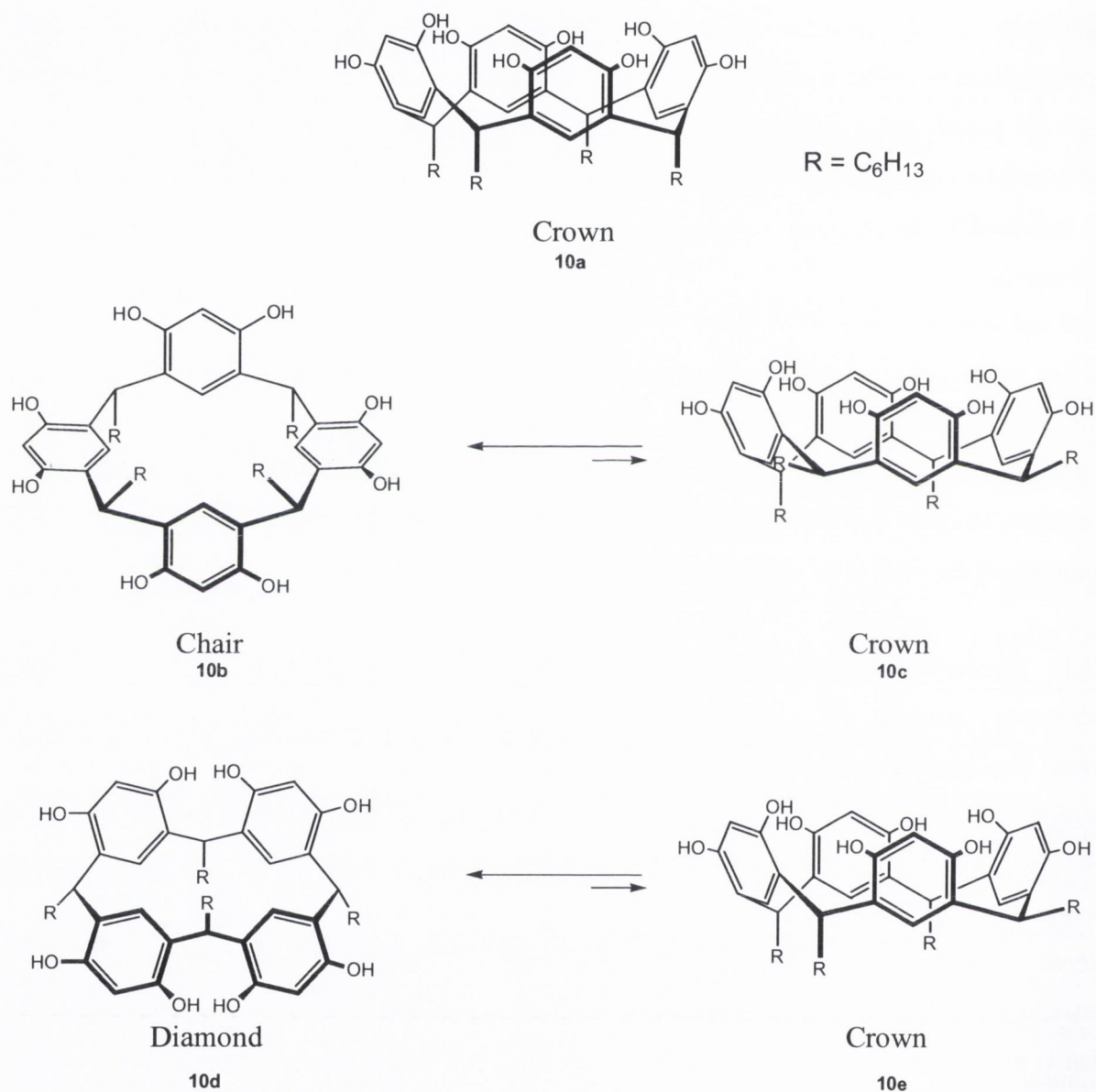


Figure 1.4: Interconversion of resorcarenes

In acetone the chair isomer (**10b**) exists in equilibrium with the crown isomer (**10c**), an isomer produced from the rotation of aromatic rings, that has two R groups in equatorial positions. A similar result was observed for the diamond isomer (**10d**), which exists in equilibrium with the crown conformer (**10e**) that has one R substituent in the equatorial position. In both cases, the crown conformer is present as the minor isomer. These findings have led to the conclusion that two main factors govern which resorcarene conformation is formed:

- (i) The maximum number of hydrogen bonding interactions is favoured, and*
- (ii) Axial substituents are more favourable than equatorial ones.*

Hence, in the crown conformer (**10a**), the ideal situation is observed for both of these requirements and no conversion is observed regardless of the solvent used. However, in acetone-*d*₆, the chair (**10b**) and the diamond (**10d**) forms try to counterbalance these two requirements. This rotation of the rings, to give the crown isomers, leads to a greater degree of hydrogen bonding at the expense of having all the substituents in the axial position. In the above case, the resorcarene conformers are interconverting through the rotation of the aromatic rings without the need for bonds to be broken. Usually, conformer interconversion occurs during the condensation reaction in which resorcarenes are formed. This interconversion process will be discussed in the next section.

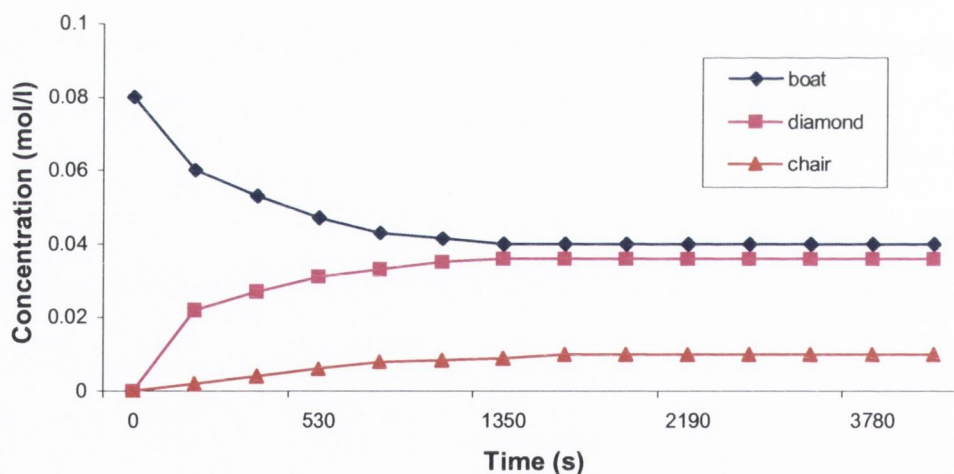
1.3.2 The Conditions that Favour the Formation of Different Diastereomers

The formation of the different diastereomers during the condensation reaction is a reversible process, which allows for their isomerisation through the breaking and reforming of covalent bonds. The ratio of the different diastereomers present at the end of the reaction strongly depends on the conditions used during the reaction. To gain a better understanding of this, studies have been undertaken of the formation of the relative ratios of the isomers throughout the reaction.^{15,27,28} The studies are separated into two broad categories based on whether the reaction under investigation is homogeneous or heterogeneous, as these different types of reactions are controlled by different factors.

1.3.2.1 Homogeneous Conditions

As previously stated, the condensation reaction of resorcinol with aldehydes is reversible under acid catalysis conditions. In homogeneous conditions, where all the products remain in solution, the ratio of the products formed when the reaction has reached equilibrium is simply a reflection of the thermodynamic stability of the different isomers in solution.

A study carried out by Weinelt and Schneider¹⁵ investigated the isomerisation of the boat isomer (*rccc*) from the condensation reaction between resorcinol and acetaldehyde when heated in a 5% conc. HCl in MeOH solution at 50 °C for 4320 s. Under these conditions the mixture reached its equilibrium point at *ca.* 1200 s. At this time the concentration of the boat isomer was almost half of its initial value. The remainder had been converted to a 4:1 mixture of the diamond and the chair isomers. For this particular resorcarenene and under these particular conditions studied, the boat is the most thermodynamically favourable isomer, although its stability is only slightly greater than that of the diamond. Both the diamond and the boat isomers are, however, significantly more stable than the chair which is the least favoured of the three. Their findings are summarised in **Graph 1.1**.



Graph 1.1: The interconversion of the boat resorcarenene under homogeneous conditions over time. The study was carried out using methanol-*d*₄ as a solvent with HCl as a catalyst, reaction was monitored by ¹H NMR over a period of 72 min. The reaction mixture reaches equilibrium at *ca.* 1200 s, the relative amounts of isomers present at this time reflect their relative stabilities which are: boat>diamond>>chair.¹⁵

1.3.2.2 Heterogeneous Conditions

When the condensation reaction is carried out under heterogeneous conditions, the most influential factor in determining the product ratio at equilibrium is the different solubilities of the various isomers in the reaction solvent.²⁷ A study of the heterogeneous reaction of resorcinol and benzaldehyde was reported by Högborg.²⁸ Here, both the boat and chair isomers were precipitated during the course of the reaction; while formation of the diamond isomer was not detected at all. The yield of the boat isomer, and the overall yield of the reaction, both increased over the course of the reaction. However, the amount of chair isomer reached a maximum after one hour and then declined until, after a period of 10 hrs, only the boat isomer remained. To further confirm these results, a sample of the chair isomer was heated in acidic solution. After 5 hrs, half of the reaction mixture was observed to have successfully isomerised to the boat form, while after ten hours, the isomerisation was complete and no chair isomer remained in the reaction mixture. The same study carried out on the boat isomer showed no change over time, indicating that the boat isomer is favoured under these reaction conditions. These results lead to the conclusion that, under heterogeneous conditions, the least soluble isomer acts as a thermodynamic sink for the reaction, driving it towards the formation of a single macrocyclic product.

Although generally it is true that under homogeneous conditions thermodynamic stability is the deciding factor, while under heterogeneous conditions the relative solubilities of the conformers is of the most importance, there are some other factors that may also play a role. In the case of 4-cyanobenzaldehyde, for example, the electronic and steric effects of this R group mean that the chair is the only product isolated.¹² In the work discussed so far the synthesis of resorcarenes has been protic acid catalysed and carried out in an alcohol solvent. The next section will introduce alternative conditions for the formation of resorcarenes.

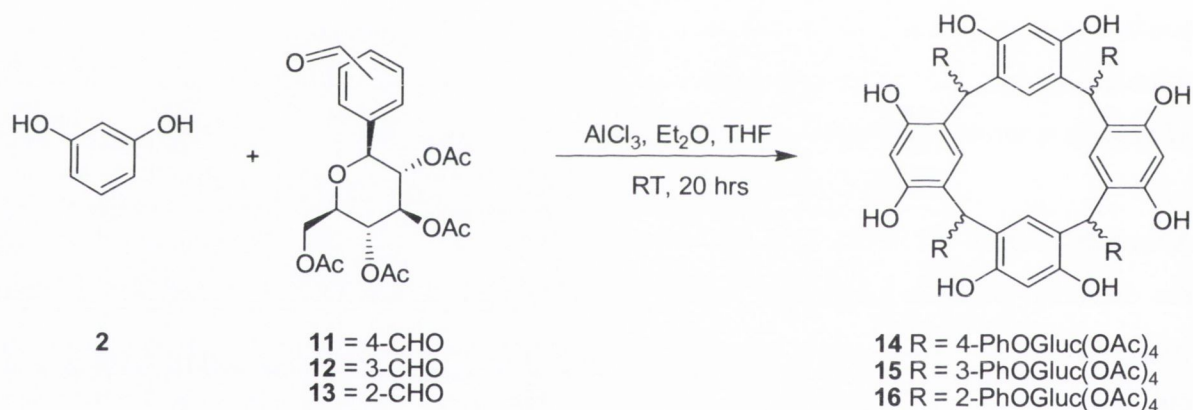
1.4 Alternative Methods of Resorcarene Synthesis

Although traditional methods, such as those discussed above, are still the most common way of synthesising resorcarenes alternative routes have also been investigated to: (i) improve the relative ratios of different conformers isolated,¹⁴ (ii) allow the incorporation of R groups

whose incorporation is not easy under standard conditions²⁹ and (iii) improve the environmental effects of the reaction.³⁰ All these will be considered in the next sections.

1.4.1 Lewis Acid Mediated Synthesis of Resorcarenes

There are many examples in the literature^{14,31} where condensations between alkylated resorcinol and aldehydes are catalysed by Lewis acids rather than protic acids. These will be described in detail in **Chapter 3** which details work carried out on octamethylresorcarenes (OMRAs). The use of Lewis acids in the condensation of unsubstituted resorcinol is also known although it has not been as widely employed.^{29,32} One of the advantages of Lewis acids, over protic acids, is that they are milder and so have a greater tolerance to functionality in the starting materials and products. This was put to use in the synthesis of resorcarenes (**16a-c**) from resorcinol and glycosidic aldehydes (**11**, **12** and **13**), **Scheme 1.3**,²⁹ where the reaction was successfully catalysed by using AlCl_3 .



Scheme 1.3: Synthesis of resorcarenes using AlCl_3 as the Lewis acid catalyst

Perioni *et al.* reported the successful synthesis of a resorcarene derived from resorcinol and benzaldehyde catalysed by a range of Lewis acids, including SnCl_4 and $\text{BF}_3(\text{Et}_2\text{O})$.³² In both these papers,^{29,32} two diastereomers, the boat and the chair were formed. In contrast to what has been observed with protic acids, where longer reaction times result in the conversion of the chair conformer to the boat/crown under homogenous conditions,²⁸ the ratio of these two isomers was fixed regardless of the length of reaction time.³² The use of $\text{Yb(III)(F}_3\text{CSO}_3)_3(\text{H}_2\text{O})_9$ as a catalyst has also been reported.³³ This catalyst can be used in

much lower equivalents than had previously been reported for Lewis acids. In the Yb(III)(F₃CSO₃)₃(H₂O)₉ catalysed reaction of resorcinol and benzaldehyde, the ratio of isomers is time dependent; with the amount of the isolated chair conformer decreasing with increasing reaction time. It is believed to be the result of some of the triflate counter ion being converted into triflic acid during the reaction. The use of the less toxic bismuth triflate (Bi(F₃CSO₃)₃) gave similar results to Yb(III) and required shorter reaction times.³⁴

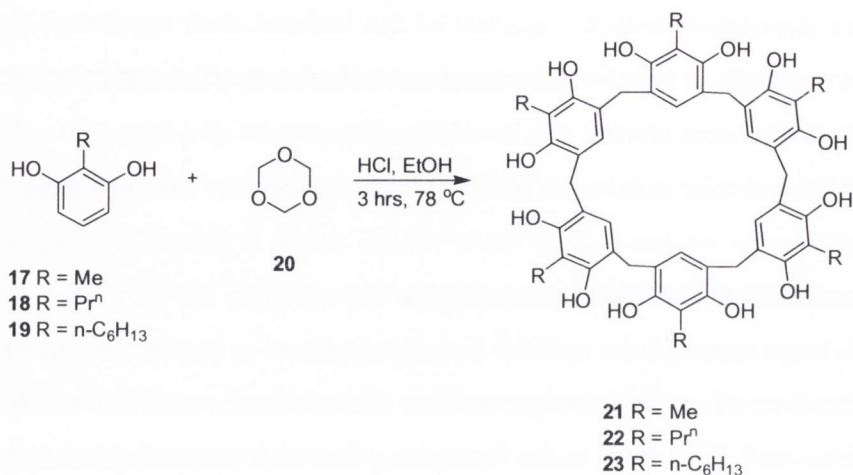
1.4.2 Alternative Synthesis Methods – Green Chemistry

Roberts *et al.* have reported the solvent free synthesis of a number of resorcarenes.³⁰ The resorcarenes are formed on the grinding together of resorcinol, an aldehyde and the solid acid, *p*-toluenesulfonic acid. This leads to the formation of viscous pastes that, when left to stand for a short period of time, yield the desired resorcarene. The reaction times are generally shorter than in traditional synthesis and the yields are comparable or improved using this method for aromatic aldehydes. In general, the relative ratios of different conformers formed reflect that reported in the literature.⁷ However, this approach is not suitable for aliphatic aldehydes as the yield obtained decreases with increasing chain length. Another approach to resorcarene synthesis is microwave assisted synthesis. This method maintains high yields but requires less solvent, less acid and far shorter reaction times.³⁵

1.5 Resorc[n]arenes where n>4

The synthesis of members of the resorcarene family with greater than four aromatic rings has also been attempted. For instance, resorc[6]arenes were first isolated in 1995.³⁶ The reaction between either 2-methylresorcinol (**17**), 2-propylresorcinol (**18**) or 2-hexylresorcinol (**19**) with 1,3,5-trioxane (**20**) led to the isolation of both tetrameric and hexameric (**21**, **22** and **23**) resorcarenes from the reaction mixture (**Scheme 1.4**).³⁶ Moreover, resorc[5]arenes were isolated a year later from the condensation reaction of 2-propylresorcinol and formaldehyde diethyl acetal.³⁷ The amount of these higher resorcarenes isolated largely depended on the reactions conditions used, especially the length of the reaction time. Higher oligomers are favoured by shorter reaction times, as over time, they will eventually break back down into tetramers. Morikawa and co-workers have reported that,³⁸ in the reaction of resorcinol dialkyl ethers under high dilution conditions, the use of the catalyst Sc(III)(F₃CSO₃)₃ was seen to

stabilise the higher resorc[n]arenes, where $n = 4 - 9$,³⁸ which were successfully isolated from these reactions.



Scheme 1.4: Synthesis of resorc[6]arenes

1.6 Further Functionalisation of Resorcarenes

The resorcarene macrocycle is very open to further functionalisation and indeed this has been exploited intensively over the last few years.⁷ There are currently three main areas targeted in these types of reactions, these being:

- (i) *hydroxyl groups on the upper rim,*
- (ii) *unsubstituted aromatic carbon on the upper rim,*
- (iii) *functional groups on the lower rim that can be introduced during the condensation, by the choice of aldehyde.*

Each of these functionalities will now be discussed in detail.

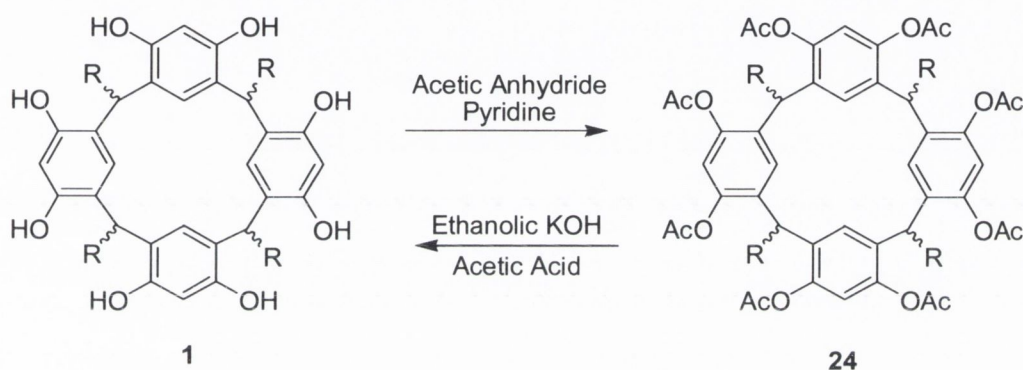
1.6.1 Further Reaction of the Hydroxyl Groups at the Upper Rim

The hydroxyl groups on the upper rim of resorcarenes provide eight active sites that can be further reacted to give rise to the formation of a large number of new products. There are two main types of reactions that are carried out at these positions, these being acylation, using acyl chlorides, anhydrides, *etc.* and alkylation using various types of alkylating agents.

1.6.1.1 Acylation of the Hydroxyl Groups at the Upper Rim

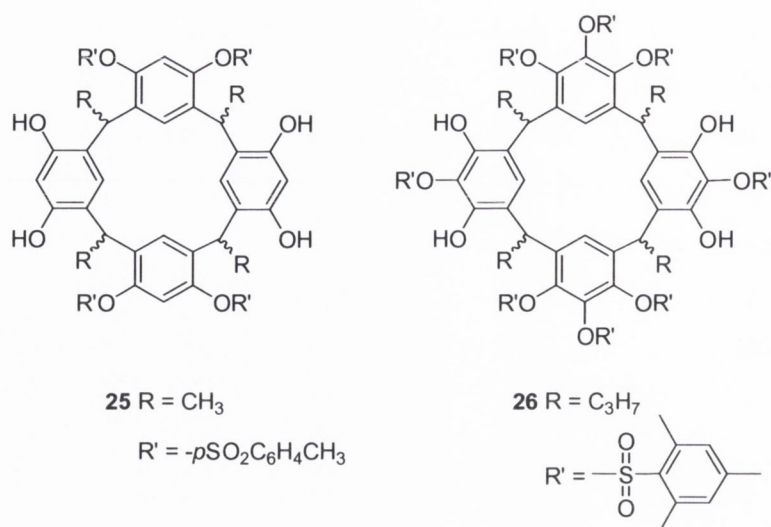
Acylation is a widely used method to increase the solubility of resorcarenes to enable their purification and has also been useful for obtaining single crystals for X-ray crystallographic studies.⁴ A typical acylation reaction is carried out using acetic anhydride as a solvent and pyridine as a catalyst and the product is often isolated in quantitative yields by precipitation with methanol.⁷ Importantly, the product can easily be converted back to an unprotected resorcarene by refluxing in ethanolic KOH solution and subsequent treatment with acetic acid,

Scheme 1.5.



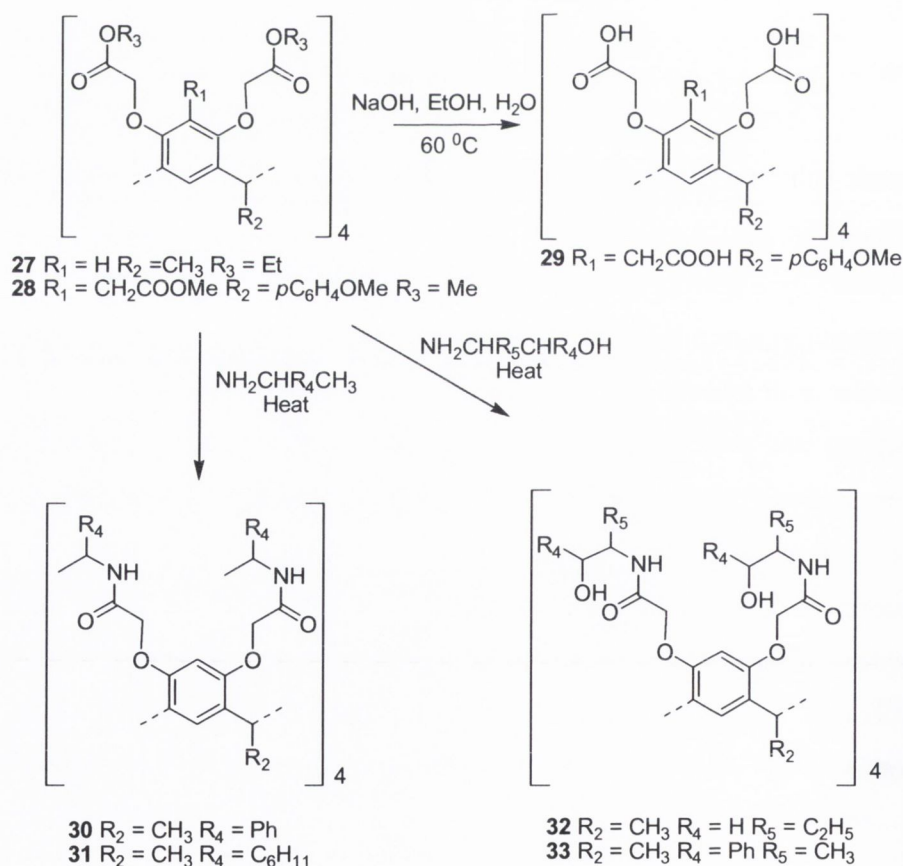
Scheme 1.5: Acylation and Deacylation of Resorcarene

Although acetic anhydride is by far the most common agent used to incorporate the acyl group at this position, the functionalisation of resorcarenes with numerous other acid anhydrides such as butyric,²⁸ propionic,⁴ isobutyric,²⁹ and acid halides such as benzoyl chloride,³⁹ 6-dodecyloxy-nicotinyl chloride,⁴⁰ chlorocarbonyl ferrocene,³⁹ and 2-bromo-2-methyl-propionyl bromide⁴¹ is also well known. Selective acylation of resorcarenes is also possible when bulky acylating agents are used. The reaction of resorcarene with *p*-toluenesulfonyl chloride, chlorobenzenesulfonyl chloride or 2,4,6-trimethylbenzenesulfonylchloride in CH₃CN at room temperature leads to the selective acylation of only four of the eight hydroxyl groups,⁴² on alternate resorcinol subunits (**25**). Partial acylation of pyrogallarenes has also been achieved using mesitylenesulfonyl chloride.⁴³ Eight of the twelve hydroxyl groups are acylated in this reaction, where the unacylated hydroxyl groups are in the 1 and 3 positions on opposite rings (**26**). This effect is not seen for less bulky acylating agents such as acetic anhydride and tosyl chloride.



1.6.1.2 Alkylation of the Hydroxyl Groups on the Upper Rim

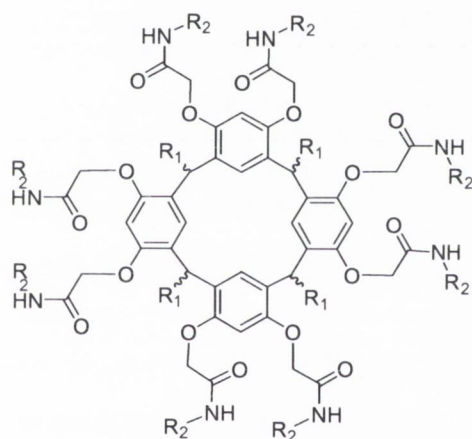
Alkylations can also be used to incorporate new functional groups into the macrocycle as is the case with the upper rim ethyl ester derivative (**27**) which is synthesised by reaction with ethylbromoacetate and K_2CO_3 in acetone.⁴⁴



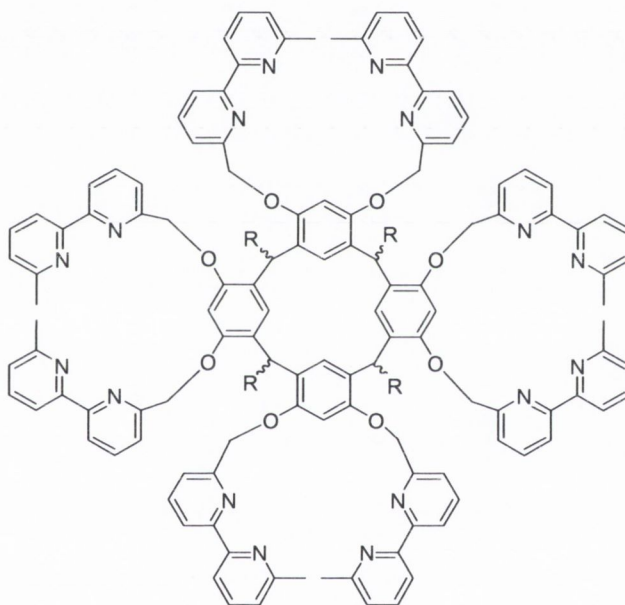
Scheme 1.6: Synthesis of ester and amide derivatives of resorcarenes

The methyl ester derivative (**28**) have also been successfully synthesised in an analogous manner.⁴⁵ These ester groups easily undergo further reaction, heating in ethanol/water with sodium hydroxide gave the acid (**29**)⁴⁵ while chiral octaamide derivatives (**30**, **31**, **32** and **33**) are easily obtained by subsequent heating with amines or amino alcohols⁴⁴ and refluxing in base with 3-bromopropene yields an upper rim alkene.⁴⁶

Octaurea resorcarenes (**34** and **35**) are also readily available, synthesised in a multi-step synthesis *via* the ester, the acid, an amine and finally reaction with isocyanates.⁴⁷ The hydroxyl groups on the upper rim are very nucleophilic and will react with even large groups containing a bromomethyl derivative such as 6-bromomethyl-6-methyl-2,2'-bipyridine (**36**)⁴⁸ and bulky diamide groups.⁴⁹



- 34** $R_1 = C_{11}H_{23}$
 $R_2 = (CH_2)_6NHC(O)NHCH(CH_3)C_6H_4$
35 $R_1 = C_{11}H_{23}$
 $R_2 = (CH_2)_{12}NHC(O)NHCH(CH_3)C_6H_4$

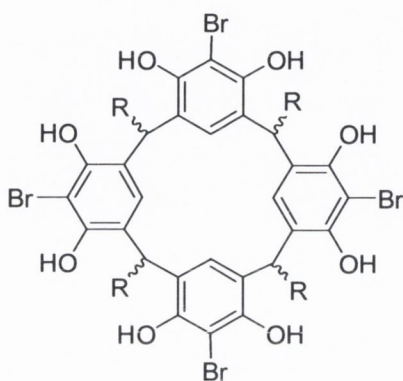
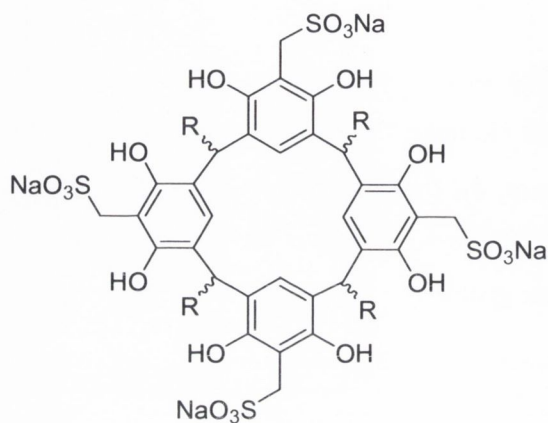


36 $R = CH_3$

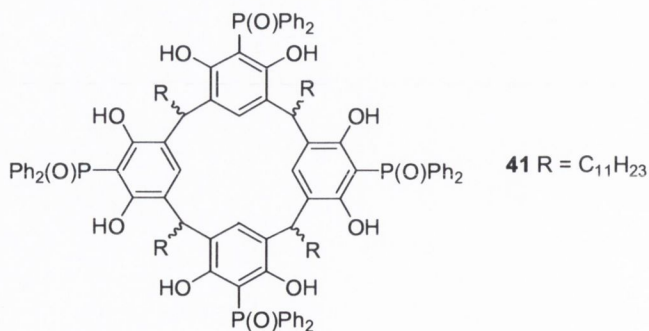
Resorcarenes where four of the eight hydroxyl groups have been substituted symmetrically with hydrophosphinoyl groups are also known. The resorcarene is first reacted with *N,N,N',N'*-tetraethyl-*P*-ethylphosphonous diamide to give a cavitand containing four dioxaphosphocine groups and this is subsequently hydrolysed to give the desired product. The authors have also been able to modify this procedure to give the mono-substituted derivative.⁵⁰

1.6.2 Substitution at the Aromatic Carbon on the Upper Rim

The unsubstituted carbon on the upper rim resides between two activating hydroxyl groups on adjacent carbons. For this reason it is very readily reacted by electrophilic substitution. This position is easily and selectively brominated by stirring with an excess of *N*-bromosuccinimide (NBS) giving the tetrabromo derivative (**37**) in high yield.⁵¹

37 R = CH₃38 R = CH₃39 R = C₉H₁₉40 R = C₆H₄OC₁₂H₂₅

Further functionalisation can greatly change the properties of the resorcarenes, as is the case in the work reported by Habicher *et al.*⁵² Resorcarenes with alkyl chains on their lower rim, of varying lengths, were made water soluble by the incorporation of four sulfonatomethyl (SO₃Na) groups on their upper rim (**38-40**). This was carried out by reaction of the resorcarene with sodium sulfite and a formaldehyde solution.⁵² The upper rim can also be functionalised with phosphorus containing moieties.⁵³ Reaction of resorcarenes with potassium diphenylphosphide leads to the incorporation of phosphinoyl groups on the upper rim (**41**).^{53,54} Water soluble tetradiazonium salts of resorcarenes have also been obtained by the reaction of resorcarene *p*-sulfonatobenzenediazonium.⁵⁵

41 R = C₁₁H₂₃

1.6.2.1 Mannich Reactions and Resorcarenes

Derivatisation of the upper rim of resorcarenes based on Mannich type reactions is an area that has attracted great interest over the last few years and has been much investigated leading to the generation of a large number of new resorcarene derivatives. A number of pertinent examples are given below. Condensation of *rccc* resorcarenes with an excess of formaldehyde (minimum of ten equivalents) and primary amines leads to the formation of benzoxazine rings at the upper rim.⁵⁶ The formation of these derivatives is completely regioselective, as all rings are either formed clockwise (**42a**) or anti-clockwise (**42b**),⁵⁷ shown in **Figure 1.5**.

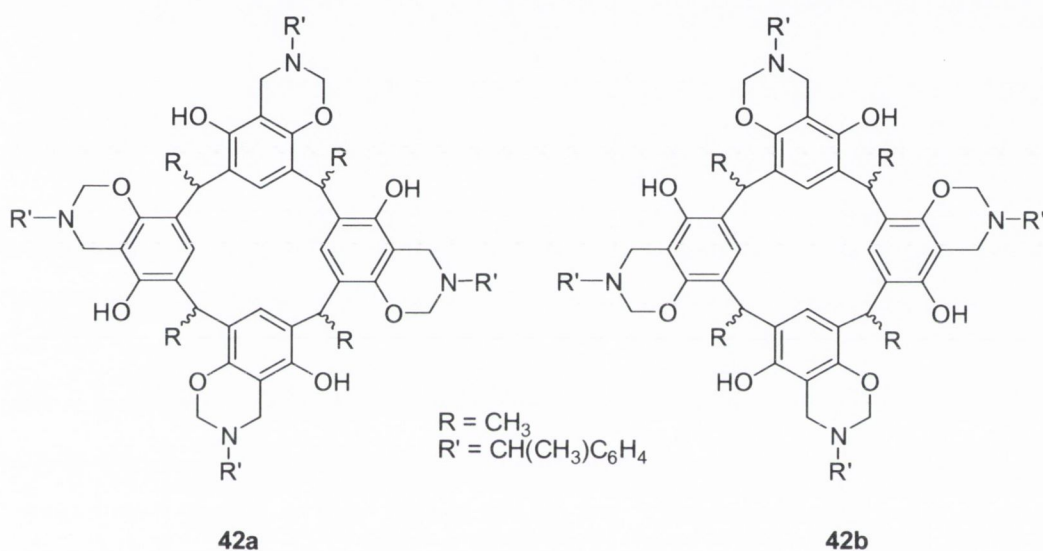
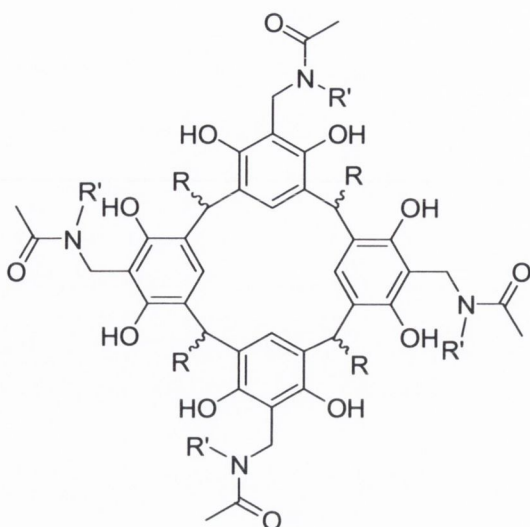
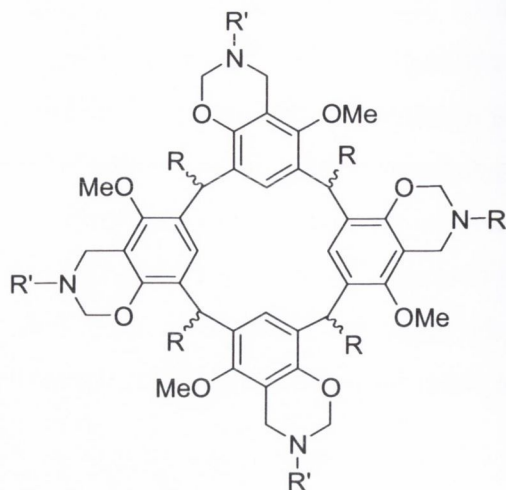


Figure 1.5: Clockwise and anti-clockwise orientation of benzoxazine rings on a resorcarene

The separation of these two enantiomers though has been problematic, as the benzoxazine rings undergo epimerisation in the presence of even trace amounts of acid.⁵⁸ One strategy investigated to overcome this, was to functionalise the four remaining unsubstituted hydroxyl groups, using acetic anhydride. However, the only products isolated were the corresponding tetra amides.⁵⁹ The acyl groups had reacted at the more nucleophilic nitrogen rather than the hydroxyl group. Alkylation of the four hydroxyl groups was more successful. It was achieved by deprotonation with *n*BuLi and methylation with methyl triflate to give the resorcarene **44**.⁶⁰



43 $R = C_6H_{13}$ $R' = C_4H_9$



44 $R = \text{undecyl}$ $R' = (R)\text{-}\alpha\text{-methylbenzyl}$

The reaction of resorcarenes with various amino alcohols was published almost simultaneously by several research groups.^{57,61,58} Böhmer *et al.* elaborated on this work in a study to better understand the factors which control the formation of five- or six-membered *O/N* acetals.⁹ Unsubstituted amino alcohols of the form of $NH_2(CH_2)_nOH$ where $n = 2, 4$ or 6 all gave resorcarenes with upper rim benzoxazine groups (**45**, **46** and **47**), six membered rings which include the aromatic hydroxyl group.⁹ When $n = 3$, there are two possibilities for the formation of the six-membered ring systems; as either the aromatic or the aliphatic hydroxyl group can be used. The 1H NMR spectrum of this mixture shows the formation of oxazine rings, a six-membered ring containing the aliphatic oxygen, on the upper rim of the resorcarene (**48**). Aminoethanol with substituents at the 2 position tend towards formation of five-membered oxazolidines rings (**49**, **50** and **51**).⁹ Recently the methylaminoacetaldehyde dimethyl acetal has also been used in the Mannich reaction to yield resorcarenes with acetals in their upper rim.⁶² The synthesis of tetraalkoxymethyl derivatives using a Mannich type reaction has also been reported.⁶³ The resorcarene was reacted with formaldehyde and a catalytic amount of iminodiacetic acid in a mixture of water and the appropriate alcohol.

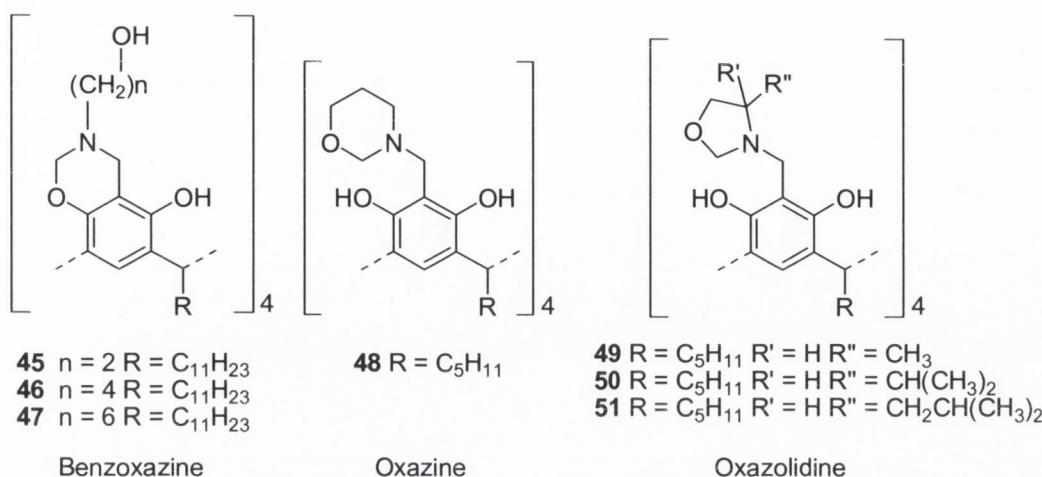
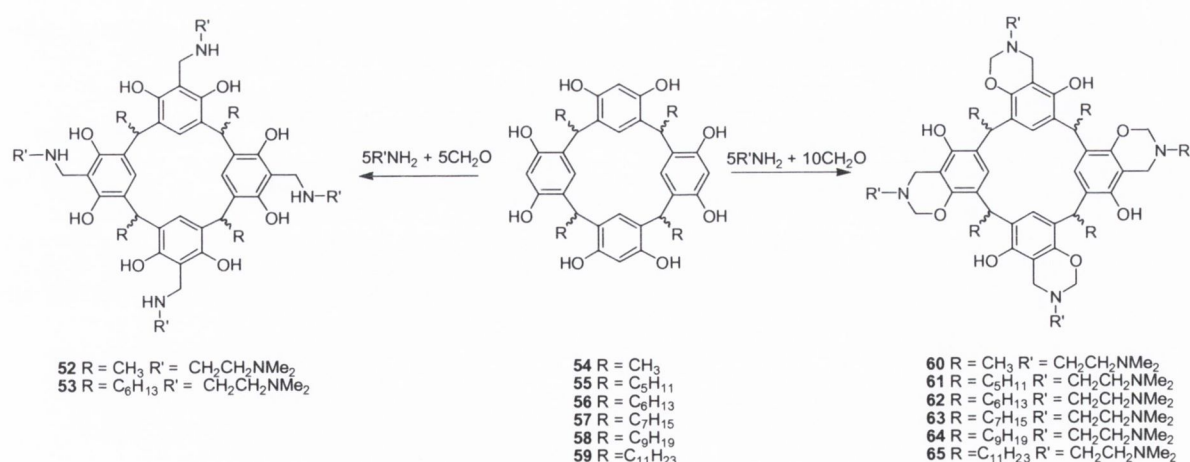


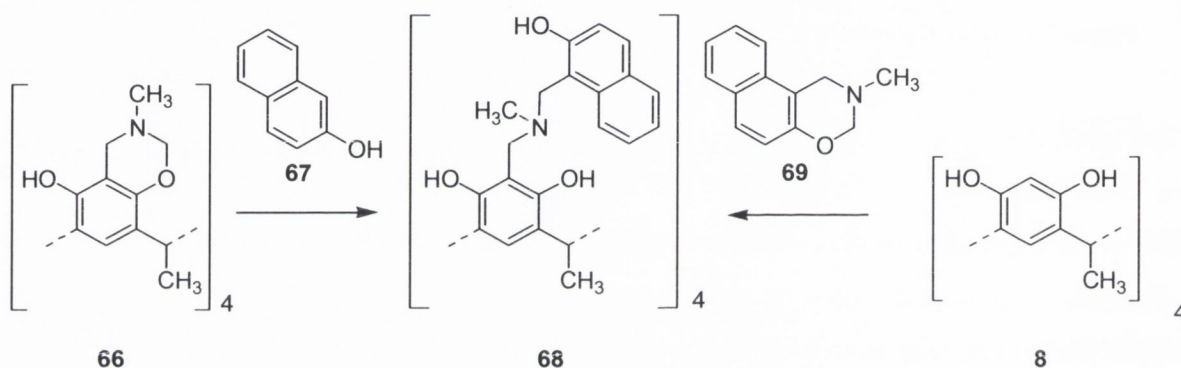
Figure 1.6: Isolated products in the reaction of resorcarenes with amino alcohols and formaldehyde

The synthesis of aminomethylated resorcarenes using the Mannich reaction was first reported in 1993.⁶⁴ However, the reaction was not selective, affording a complex mixture of products that were impossible to separate. Konovalov *et al.* reported, for the first time, the selective synthesis of aminomethylated resorcarenes where the aminomethyl groups are localised on the upper rim. This was achieved by the introduction of *N,N*-dimethylethyldiamine into the reaction mixture. The ratio of formaldehyde to resorcarene was important in these reactions, although the use of five equivalents of formaldehyde led to the formation of the aminomethylated derivatives (**52** and **53**), the use of ten equivalents led to the formation of the oxazinyl groups at the upper rim (**60** - **65**).⁶⁵



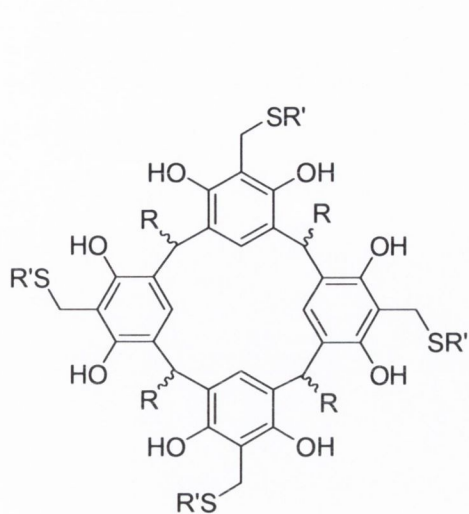
Scheme 1.7: The effect of the number of equivalents of formaldehyde on the outcome of the Mannich reaction

Selective formation of partially aminomethylated resorcarenes has also been possible. While the reaction of a resorcarene with the bulky substrate, diisopropylamine, results in the formation of the trisubstituted derivative, an analogous reaction between the aforementioned amine and the tetratosylate resorcarene leads to the monosubstituted derivative⁶⁶. Maynard *et al.* have shown that the reaction of tetrabenzoxazines with naphthol (**67**) leads to aminoalkylation and in an analogous reaction unsubstituted resorcarenes can be reacted with naphthoxazine (**69**) to yield the same product, this is shown in **Scheme 1.8**.⁶⁷

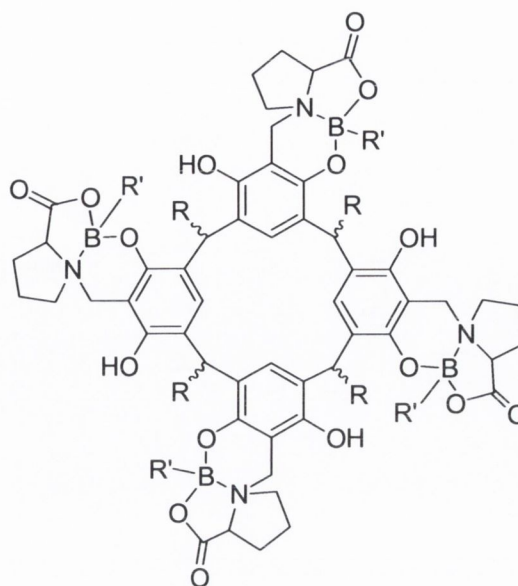


Scheme 1.8: Aminomethylation of resorcarenes *via* two different routes. The products were isolated as precipitates, formed when the two reactants were stirred together in EtOH:benzene 1:1

The Mannich reaction has been used to incorporate both sulfur and boron groups into the upper rim of resorcarene.^{68,69} Thiomethylation of the upper rim has also been achieved using formalin, triethylamine and arenethiols.⁶⁸ In an analogous reaction using ethanethiol a resorcarene capable of binding metal cations was synthesised (**70**).⁷⁰ The synthesis of oxazaborolo-benzoxazaborininone derivatives of resorcarene (**71-74**)⁶⁹, was achieved by further reaction of an *L*-proline derivative of resorcarene synthesised by the Mannich reaction.⁸ The boron atom, it was hoped, would retain some of its Lewis acid properties and allow the use of the resorcarene as a supramolecular asymmetric catalyst.

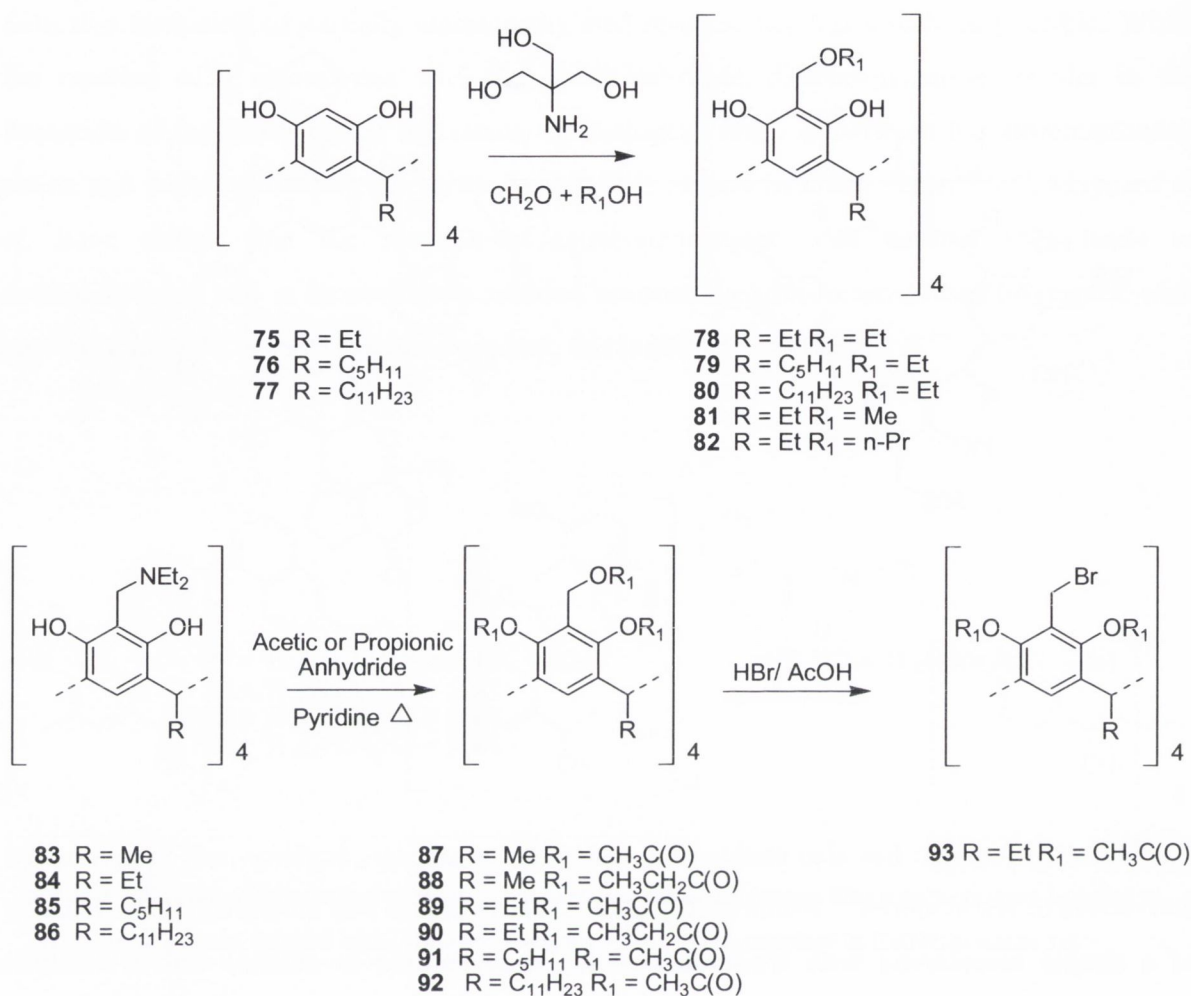


70 $R = CH_3$ $R' = CH_2CH_3$



71 $R = CH_2(CH_3)_2$ $R' = Ph$
72 $R = CH_2(CH_3)_2$ $R' = Et$
73 $R = CH_2(CH_3)_2$ $R' = OMe$
74 $R = CH_2(CH_3)_2$ $R' = OH$

The Mannich reaction has also enabled the formation of alkoxy-, acyloxy- and bromomethyl derivatives of resorcarenes.⁷¹ Aminomethylation of resorcarenes was attempted by the reaction of a simple resorcarene with tris(hydroxymethyl)methylamine in ethanol with a catalytic amount of acetic acid. The authors, however, isolated the tetraethoxymethyl resorcarene from the reaction mixture (**78**), shown in **Scheme 1.9**.⁷¹ This was repeated using different alcoholic solvents and a number of alkoxymethyl derivatives were isolated (**79-82**). In a similar manner, aminomethyl derivatives of resorcarenes underwent acylation. The acylation reaction resulted in complete acylation of all of the eight hydroxyl groups and the substitution of the four amino groups for acyloxy groups (**87-92**). These could then be further reacted with HBr to give the tetrabromomethyl derivative (**93**).

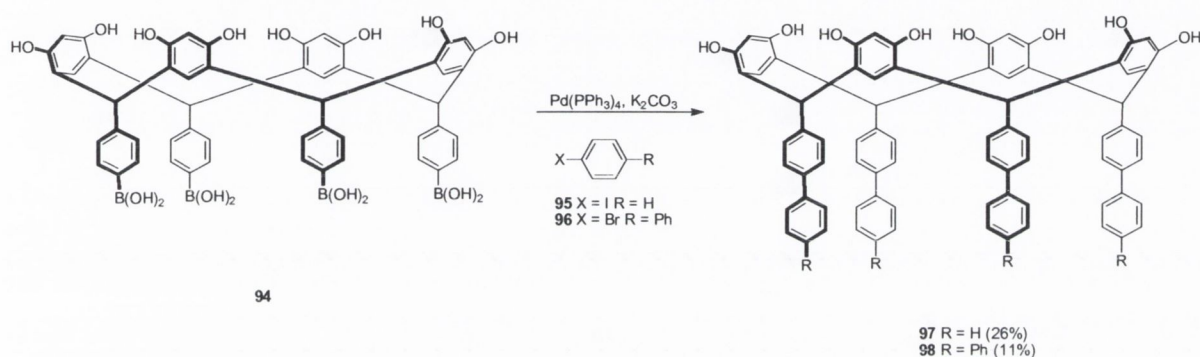


Scheme 1.9: Synthesis of alkoxy, acyloxy and bromomethyl derivatives of resorcarenes

1.6.3 Further Reaction of Functional Groups on the Lower Rim

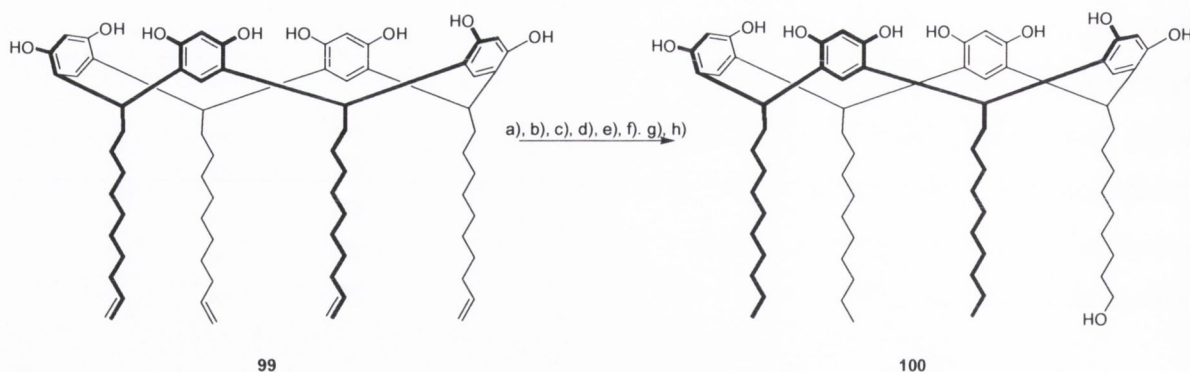
Most of the resorcarenene literature published to date focuses on modifications of the upper rim, leaving the lower rim somewhat ignored and usually only put to use to impart solubility.⁷² The lower rim still has a lot of unexploited potential; through the use of aldehydes bearing additional functionality and the subsequent reactions of these groups post-condensation there are almost endless possibilities for novel resorcarenenes. Post-condensation functionalisation of the lower rim becomes important for the incorporation of larger pendant groups as direct condensation with the respective aldehyde often leads to mixtures of conformations which can be hard to separate.⁷³ The majority of the research so far carried out in this area is detailed in the following section.

Strongin and Lewis reported the further functionalisation of both a cavitand with a phenyl bromide appendage on the lower rim and a resorcarene with a lower-rim boronic acid group using post-condensation Suzuki coupling reactions.⁷³ In each case, the macrocycle conformation was preserved. In a subsequent paper, the first resorcarenes incorporating chiral groups on the lower rim were synthesised from the boronic acid resorcarene and its reaction with pinacol and pinanediol.⁷⁴



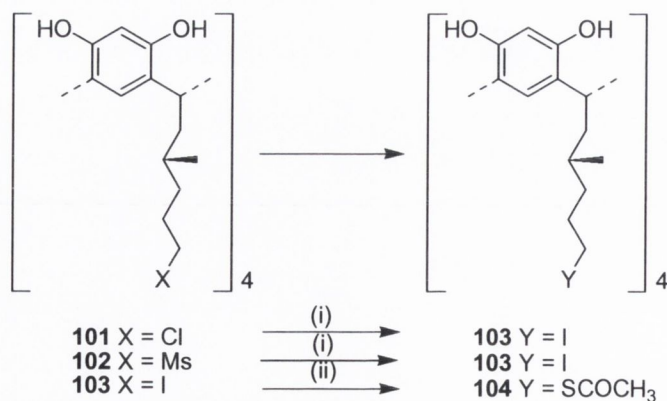
Scheme 1.10: Post-condensation reaction of the lower rim using a Suzuki coupling reaction

Functionalisation of the lower rim of resorcarenes has also been investigated for possible applications as solid supports.⁷⁵ An alkene terminated resorcarene (**99**) was successfully synthesised from 10-undecenal. The upper rim hydroxyl groups were protected and through the use of mild oxidising condition a lower rim monoepoxide was isolated. The remaining alkene groups were reduced and through a series of steps the epoxide was converted to a lower rim hydroxyl group (**100**), which could later be used as an attachment site to a solid support, **Scheme 1.9**. This is the first example of the lower rim of the resorcarene being partially functionalised.⁷⁵ An alkene terminated resorcarene has also been used in the synthesis of resorcarene tetrasulfides to be used in the generation of self-assembled monolayers.⁷⁶ This was achieved by the reaction of the alkene terminal groups on the lower rim with $\text{CH}_3(\text{CH}_2)_9\text{SH}$ and 9-BBN in THF.



Scheme 1.11: Multi-step synthesis of a resorcarene mono-functionalised at the lower rim, a) $t\text{-BuCOCl}$, $(i\text{-Pr})_2\text{NEt}$, DMAP, CH_2Cl_2 (56%), b) $m\text{-CPBA}$ (1.2 eq.), CHCl_3 (34%), c) H_2 , Pd-C, AcOEt , d) $\text{CF}_3\text{SO}_3\text{H}$, $\text{THF-H}_2\text{O}$ (10:1) (65% - two steps), g) TBDMSOTf , $(i\text{-Pr})_2\text{NEt}$, CH_2Cl_2 (86%), h) LiAlH_4 , Et_2O (100%).

Mattay *et al.* have published work which deals exclusively with the functionalisation of the lower rim of resorcarenes for the introduction of both chirality and functionality into the macrocycle.⁷⁷ In these reactions, dimethyl acetals were used in place of aldehydes. In a series of condensation reactions with resorcinol and dimethyl acetals derived from either citronellal or carvone a number of chiral resorcarenes were synthesised. Dimethyl acetals have previously been shown to be the attacking species in solution when the reaction is carried out in methanol.¹⁵ The terminal groups on the lower rim of these resorcarenes included methyl halides, hydroxyls and mesylates, all of which are open to further functionalisations. Preliminary results on the post-condensation alteration of the lower rim was also reported, where the mesylate and chloro groups were exchanged for iodo groups simply by stirring in NaI /acetone (**103**) while the iodo group can then be converted to a thioester by stirring in KSac /MeOH (**104**).



Scheme 1.12: Conversion of functional groups on the lower rim (i) NaI , acetone, (ii) KSac , MeOH

Where the desired conformation can be obtained from the direct condensation of the resorcinol with a moiety already containing the desired functionality, this one-pot, one-step route is obviously preferred. Konovalov *et al.* have reported the first synthesis of a resorcarenene bearing phosphinoylalkyl fragments on the lower rim of the molecule by the condensation of resorcinol with a phosphorus containing acetal.⁷⁸

This previous section has given a broad overview on the further functionalisation of resorcarenenes, at the upper and lower rims. It has also dealt with the alkylation and acylation of the hydroxyl groups on the upper rim. The next section deals with a particular type of alkylation reaction carried out on the upper rim hydroxyl groups. This type of alkylation reaction results in the synthesis of a new class of compounds, cavitands, where the hydroxyl groups on adjacent resorcinol subunits are linked by a bridging group.

1.7 The Synthesis of Cavitands

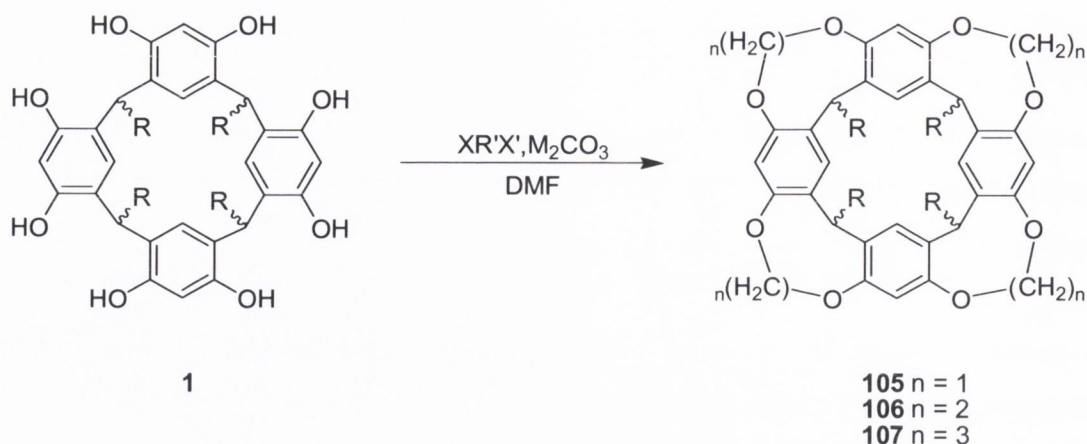
Cavitands are a type of host molecule, derived from resorcarenenes, which contain an enforced, concave cavity that is large enough to accommodate other molecules or ions.⁷ There are many types of cavitands,⁷ formed through a base promoted alkylation reaction that joins the hydroxyl groups on neighbouring resorcinol units together using a dihalide alkylating agent. These cavitands can be broadly classified based on the bridging group used in their synthesis. The main classes are:

- (i) *Alkylenedioxy*,
- (ii) *Heterophenylene*,
- (iii) *Phosphorous*,
- (iv) *Dialkylsilicon*.

The following sections will deal with examples of cavitands from each of these classes.

1.7.1 Synthesis of Alkylenedioxy-bridged Cavitand

These are by far the most exploited type of cavitand as well as the first reported.⁷⁹ In 1982 the boat isomer from the reaction of acetaldehyde and resorcinol was treated with an excess of BrCH_2Cl to give the cavitand shown below in low yield, 23%.⁷⁹



Scheme 1.13: General synthesis for a cavitand, where X and X' are either Cl, Br or F, R is the chosen bridging group e.g. CH₂, M is either K or Cs and the solvent used is either DMF or DMSO

These were synthesised by the use of the Williamson ether synthesis. Usually under such conditions the hydroxyl groups are deprotonated, using K₂CO₃ or Cs₂CO₃, and are then reacted with alkyl dihalides of various lengths. The use of resorcarenes with bromine or methyl groups in the four free positions on the upper rim led to a 100-200% increase in yield, possibly due to an increase in stability of the phenoxy ion intermediate.⁸⁰ Another advantage of having four methyl or bromine groups on the upper rim of the cavitand is that this allows for the further functionalisation of the cavitand. This methodology will be discussed in detail in **Chapter 5**.

Cavitands are much more rigid molecules than the resorcarenes, from which they are derived. In the solid state, methylene bridged cavitands have a crown-like conformation with a C_{4v} symmetry which is only slightly distorted in solution.⁵¹ Cavitands with ethylene and propylene bridges can also be prepared using the appropriate dihalide, but the use of such longer bridges leads to an increase in the flexibility of the molecule and these cavitands adopt a boat like conformation in the solid state.⁵¹

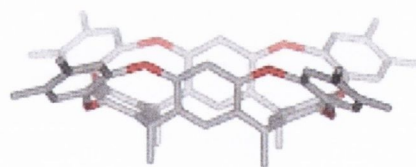
Cavitands where n>4 have been successfully isolated by Sherman *et al.*⁸¹ through the condensation reaction of 2-methylresorcinol with formaldehyde. This led to the formation of a mixture of resorc[n]arenes and subsequent reaction and purification led to the successful isolation of cavitands where n = 4,5,6 and 7.

1.7.2 Synthesis of Heterophenylene-bridged Cavitands

Bridging of the upper rim of resorcarenes using aromatic groups as spacers allows the cavity already present to be greatly enlarged.⁷⁹ The reaction of resorcarene with 2,3-dichloroquinoxaline led to the isolation of two new types of cavitands denoted as either vase (108a) or kite (108b), dependant on the orientation of the aromatic bridging groups.^{82,83} In the vase conformation, the quinoxaline groups were all in axial positions and lead to the formation of a vase-like cavity, whereas in the kite conformer, the quinoxaline groups were all in the equatorial position. Hence, the spacers are all in the same plane, while the cavitand itself takes on a boat like conformation. The relative ratios of these two conformations (formed under different reaction conditions) using different aromatic spacers and with different resorcarene starting materials have been investigated by Cram and co-workers.⁸³ It has been found that the presence of a methyl or an ethyl substituent in the 2 position of the resorcinol subunit leads to the exclusive formation of the kite conformer, while the vase conformation is favoured at higher temperatures.



Vase (108a)

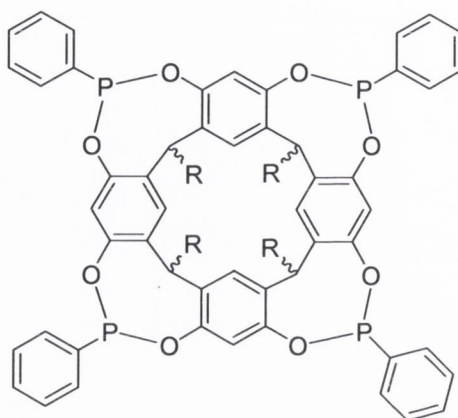


Kite (108b)

1.7.3 Synthesis of Phosphorus-bridged Cavitands

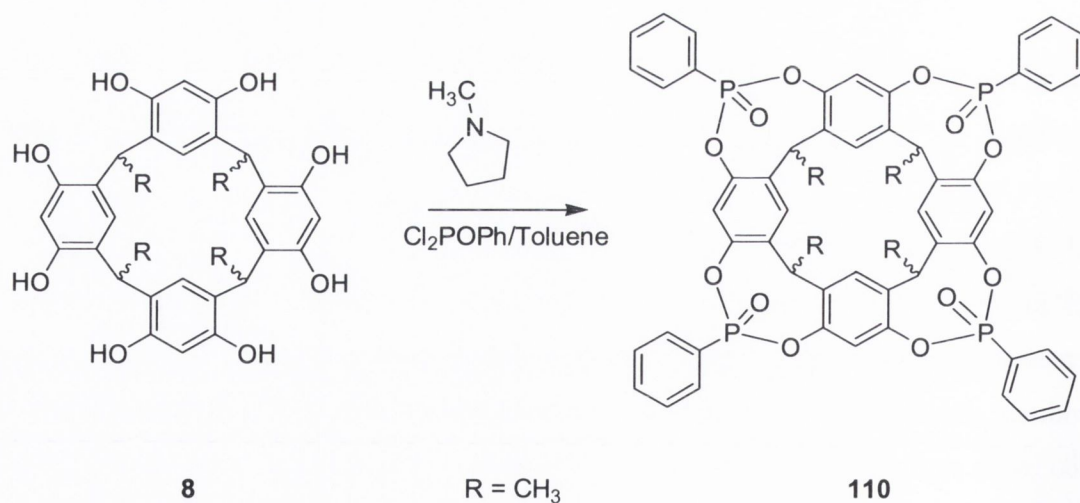
Initial attempts to form phosphorus-bridged cavitands involved the alkylation of resorcarene, with methyl pendant groups, with dichlorophenylphosphonate.⁸⁴ This led to a complex mixture of products, due to the four stereogenic P(V) centres. Unfortunately, the different diastereomers formed were not successfully isolated and no further research has been reported on these products. However, the reaction of phenylethyl substituted resorcarene with dichlorophenylphosphane led to the formation of one isomer of a P(III) phosphonito cavitand 109.⁸⁵ In each of the PPh groups, the lone pair was found to be orientated inward with respect

to the cavitand; this isomer is denoted as T_{iii} . Further study of the complexing abilities of this compound has been hindered by its susceptibility to oxidation in the gas or solution phase.



109 $R = \text{CH}_2\text{CH}_2\text{Ph}$

A further study of the reaction of resorcarenes, with methyl pendant groups, with various aryldichlorophosphates was carried out by Dalcanele *et al.*⁸⁶. In all cases, regardless of the phosphate used, five of the possible six isomers were obtained. Unfortunately, the missing isomer was the desired T_{iii} isomer, which is the most interesting isomer from a guest binding point of view. However Dutasta *et al.* selectively synthesised the desired isomer through template synthesis by using an ammonium guest formed *in situ*, **Scheme 1.14**.⁸⁷

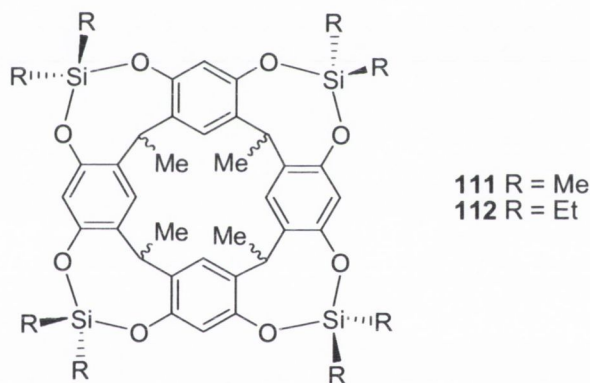


Scheme 1.14: Synthesis of T_{iii} isomer of phosphonate bridged cavitand (**110**)

In an analogous manner to the synthesis described above, cavitands with one or two phosphorus bridges have also been successfully prepared from the partially bridged compounds often isolated in the synthesis of methylene bridged cavitands by their reaction with dichlorophosphorus compounds.

1.7.4 Synthesis of Dialkylsilicon-bridged Cavitands

The reaction of dichlorsilanes and resorcarenes in THF/ NEt_3 leads to the isolation of highly base sensitive and acid sensitive dialkylsilicon-bridged cavitands (**111** and **112**).⁸⁸ The orientation of the substituents on the silicon in the bridges results in the narrowing of the cavitand cavity, allowing these molecules to bind only very “slim” guests. Hence these cavitands form complexes with linear molecules such as CS_2 , $\text{CH}_3\text{C}=\text{CH}$ and O_2 . The complexation of oxygen is perhaps the most remarkable result here due to its biological importance.

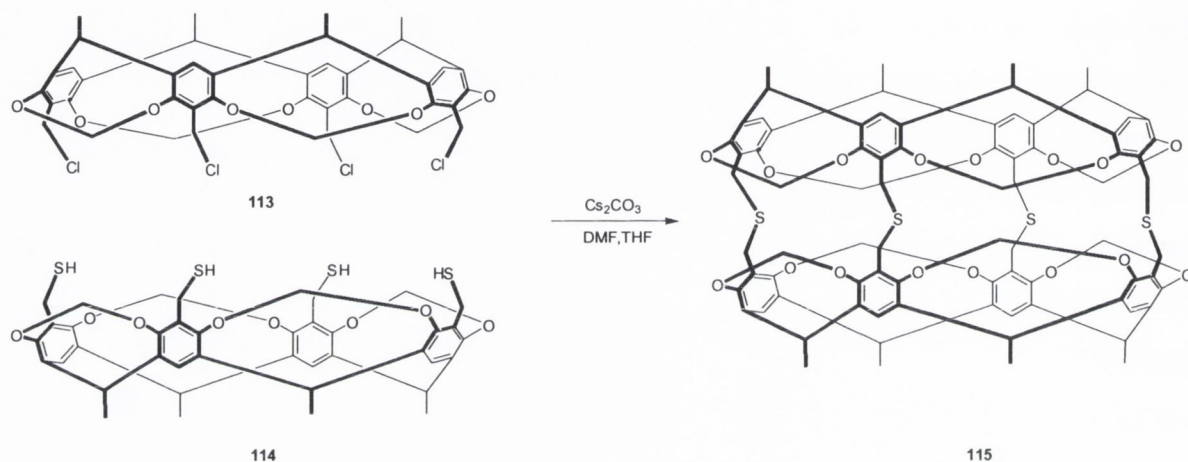


The previous section has detailed the synthesis of various types of cavitands and the diverse bridging groups already known. In the next section the work on the covalent assembly of cavitands to form large supramolecular host-guest structures, known as carceplexes and hemicarceplexes, will be discussed.

1.7.5 Synthesis of Carceplexes and Hemicarceplexes

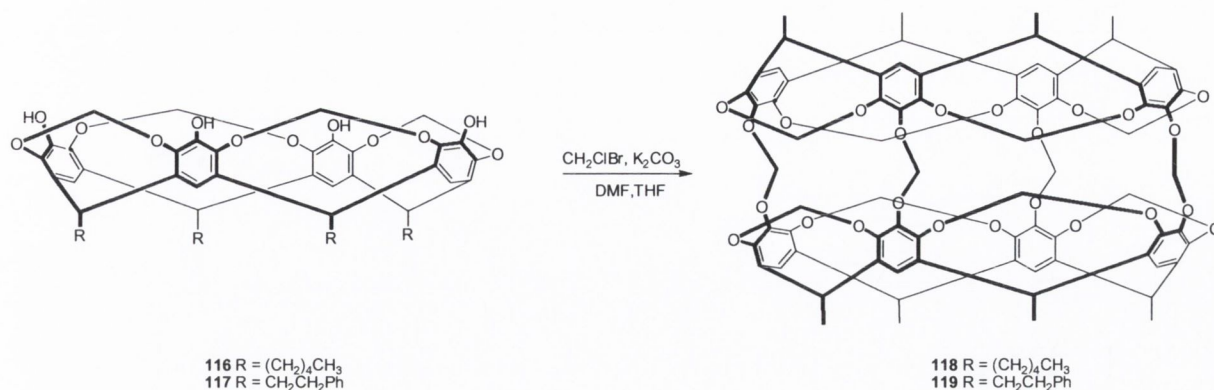
Carceplexes are defined as closed surface compounds where the guest molecules within are permanently trapped,⁸⁹ and can only escape by the breakage of covalent bonds in the carceplexes. In contrast, the guests contained within hemicarceplexes can escape through their larger portals with sufficient heating.⁸⁹ Carceplexes were first reported by Cram in 1985⁹⁰ and

were synthesised by the head-to-head bridging of two cavitands at four positions at the upper rim, **Scheme 1.15**. The two cavitands, one with chloromethyl groups on its upper rim (**113**), the other with thiol groups (**114**), were reacted with base in DMF and THF under high dilution conditions. The carceplexe's existence was confirmed by HRMS mass spectrometry but no other analysis could be carried out due to its insolubility.



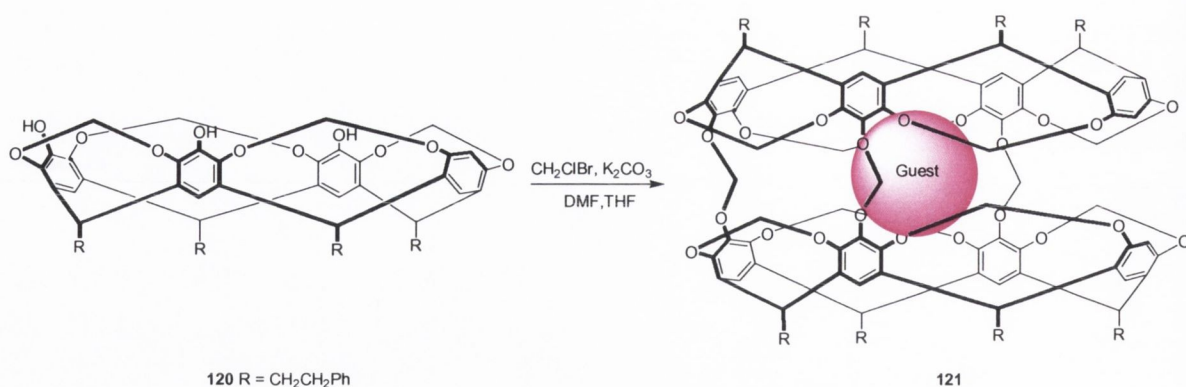
Scheme 1.15: Synthesis of the first reported carceplex

The next examples of carceplexes reported were those based on the bridging of two identical cavitands. These tetrol cavitands were subjected to the same reaction conditions as used to form the methylene bridged cavitands and a new carceplex was made.⁷² In these, the methyl “feet” of the earlier carceplex had been replaced with more solubilising groups which facilitated the characterisation of these compounds. The use of resorcarenes with pendant $-\text{CH}_2\text{CH}_2\text{Ph}$ groups led to an increase in the solubility that allowed for a full analysis to be carried out on the product and a crystal structure to be obtained⁹¹ which confirmed the formation of the carceplex. The use of alkyl chains showed similar results.⁹¹ On all occasions, the carceplexes were isolated with a guest within their cavity. When the reaction was carried out in solvent too large to be encapsulated as a guest within the carceplex cavity, no carceplex formation was observed. This implies that this reaction is most likely due to a templation effect. The same pendant groups were also utilised to make sulfur bridged carceplexes that were more soluble.^{92,93} Furthermore, the number of cavitands linked covalently together to form carceplexes is not only limited to two,⁹⁴ as carceplexes consisting of three,⁹⁵ four⁹⁶ and six⁹⁷ covalently linked cavitands have all been reported.



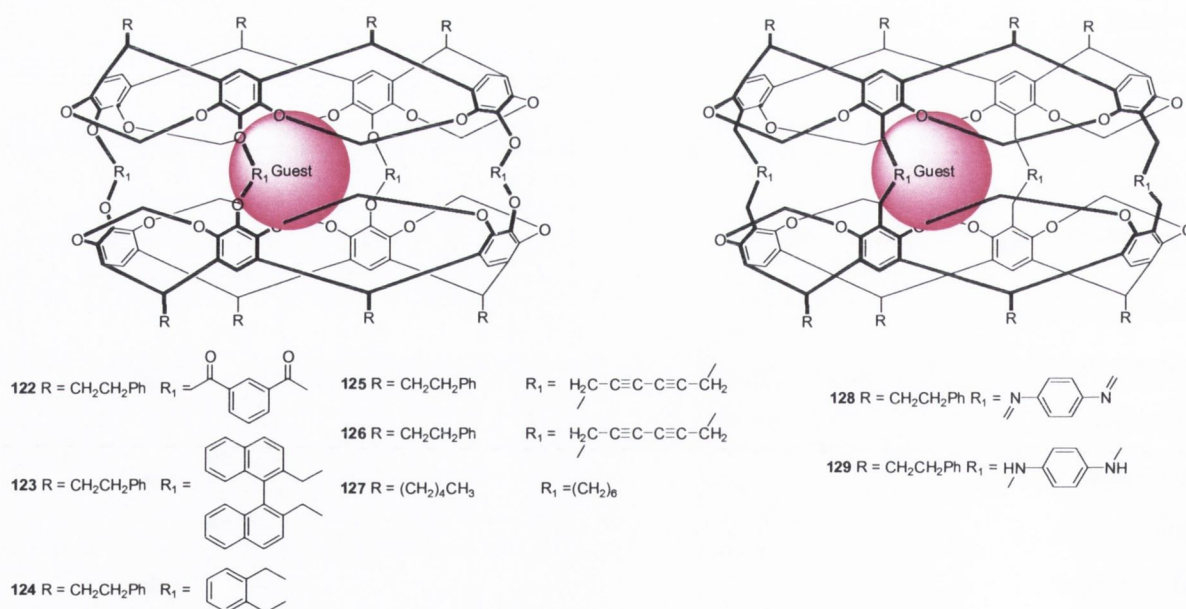
Scheme 1.16: Synthesis of soluble carceplexes from tetrol cavitands

The first hemicarceplex **121**⁹⁸ reported, was derived from the triol cavitant **120**, a side product isolated in the synthesis of the previously mentioned tetrols.⁹¹ Hemicarceplexes were synthesised from these molecules in the same way as carceplexes from the tetrols, giving a head-to-head covalently linked cavitant dimer bridged in three places instead of four, **Scheme 1.17**. Hemicarceplexes were initially formed with an encapsulated solvent molecule, which varied depending on the solvent used in the hemicarceplex synthesis. Unlike the previously described carceplexes, this guest could be removed by heating for a number of hours in a solvent too large for encapsulation, such as 1,3,5-dichlorobenzene.⁹⁹ New hemicarceplexes, *e.g.* **121**, could then be formed by mixing the empty hemicarcerand with a suitable guest. Host-guest complexes of **121** containing the following guests were formed in this way benzene, THF, pyridine, diethylamine, *n*-butylamine, MeCN, CS₂, DCM, dibromomethane, α -pyrone, xenon, H₂O, CO₂, O₂ and N₂.⁹⁹



Scheme 1.17: Synthesis of the first hemicarceplex

After these initial reports, subsequent hemicarceplexes were not just based on tribridged cavitands but also on cavitands with four bridges using larger bridging units. This gave rise to the formation of four “portals” in the walls of the cavitand.^{100,101} A variety of bridging units were also used in these new complexes. Hence, the imine bridged hemicarceplexes (**128**) were synthesised by the reaction of cavitands with four aldehyde groups on their upper rim using 1,3-diaminobenzene.¹⁰² Reduction of these imine bridged complexes to amine bridged complexes (**129**) has also been reported.¹⁰³ Lactone bridged hemicarceplexes have also been obtained by the reaction of tetrols with isophthaloyl chloride (**122**).¹⁰⁴ Moreover, lactam hemicarcerands have been synthesised by the reaction of tetra acid chloride cavitands with 1,3-aminobenzene.¹⁰⁵



Larger bridging groups have also been successfully incorporated. Binaphthyl bridged carceplexes (**123**) were successfully synthesised by the reaction of 2-(bromomethyl)-1-(2-bromomethyl)naphthalene-1-yl)naphthalene with tetrol cavitand.¹⁰⁶ *o*-Xylyl bridges were also incorporated by the reaction of 1,3-dibromomethylbenzene with the tetrol cavitand (**81**).¹⁰⁷ A number of hemicarceplexes based on alkyne (**125 - 127**),¹⁰⁸ alkene and alkyl (**121**)¹⁰⁹ bridging groups are also known. The use of a dicarboxylic acid group as a bridging unit has led to the synthesis of the first water soluble hemicarceplexes.¹¹⁰

So far, the synthesis of resorcarenes, their derivitisation and their use in the formation of supramolecular hosts has been reviewed. The remaining part of this introduction will deal with the aspects of supramolecular and resorcarene chemistry that are particularly relative to the aims of this project, such as the benefits of the preorganisation of ligands on a rigid molecular scaffold, the formation of resorcarene oligomers through covalent and non-covalent bonding and the strapping of resorcarenes *via* their lower rim.

1.8 The Preorganisation of Ligands and its Benefits

The benefits of designing ligands so that the size and shape of the binding site are complimentary to the proposed guest and of having the binding site already arranged so the ligand does not have to undergo structural change upon binding were first conclusively shown by Cram and co-workers.^{111,112} The comparison of the binding ability of rigid, directional and flexible crown ether analogues showed that, in general, the more preorganised the host is, the greater the binding. The same paper also showed that CPK models are a good predictor of host-guest compatibility and that generally, ligands that are designed to have a binding cavity of suitable size and shape for a particular guest, will generally bind that guest preferentially.¹¹¹ The preorganisation of ligands can therefore lead to more selective binding, as there is greater control over cavity size. Some examples of this from the field of calixarene chemistry are discussed below.

Böhmer and co-workers have reported the synthesis of calixarenes with carbamoylmethylphosphine oxide (CMPO) groups attached at either their upper (wide)¹¹³ or lower (narrow)¹¹⁴ rim. CMPO (**130**) is a ligand currently in use the remediation of nuclear

waste. The ions are coordinated by three nitrate ions and three CMPO ligands to form an overall neutral complex as shown in **Figure 1.7**.

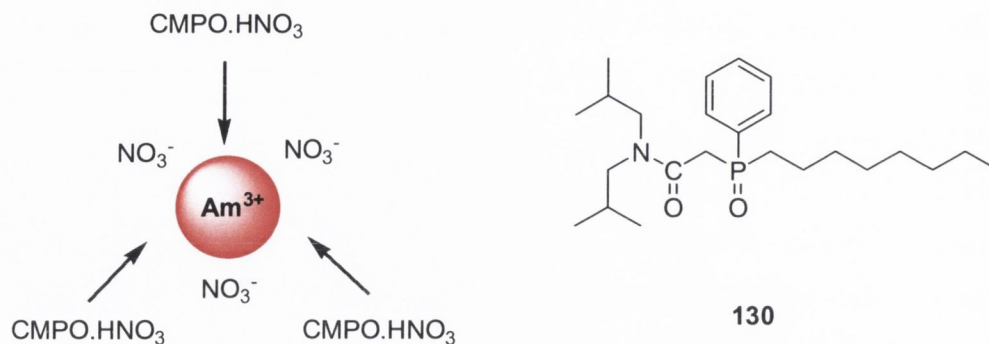
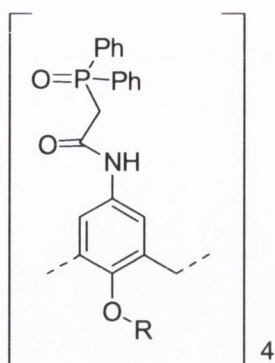
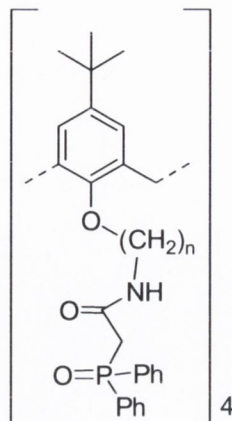


Figure 1.7: Illustration of the binding between CMPO and actinides and (*N,N*-diisobutylcarbamoylmethyl) octylphenylphosphine oxide (**130**), a CMPO derivative

Given the binding mode of CMPO, the attachment of three or more of these ligands to a molecular platform, such as a calixarene, which provides a pre-organised binding site should lead to increased binding efficiency. The upper rim derivatised calixarenes (**131-137**)¹¹³ were the first of their kind to be reported and they showed higher extraction efficiency than CMPO, even when CMPO was used at a ten-fold greater concentration. Calixarenes with CMPO moieties at their lower rim (**138-140**)¹¹⁴ have also shown increased extraction ability over CMPO. In particular, an increased affinity for Th^{3+} compared to upper rim calixarene analogues showing that the selectivity of the calixarenes can be tuned to suit different guests.



- 131** $R = C_5H_{11}$
132 $R = CH_2CH(C_4H_9)C_2H_5$
133 $R = C_{10}H_{21}$
134 $R = C_{12}H_{25}$
135 $R = C_{14}H_{29}$
136 $R = C_{16}H_{33}$
137 $R = C_{18}H_{37}$



- 138** $n = 2$
139 $n = 3$
140 $n = 4$

1.9 The Covalent and Non-Covalent Assembly of Resorcarenes

The self-assembly of unfunctionalised resorcarenes, in general due to hydrogen bonding of the hydroxyl groups on the upper rim, is a well known and studied phenomenon. The formation of hexamers and their encapsulation of guests both in the solid state and in solution has been reported.^{115,116} A recent example from this field is shown in **Figure 1.8**. This hexamer was formed on the crystallisation of a pyrogall[4]arene where the lower rim was substituted with four bromide terminated eight carbon chains.¹¹⁷

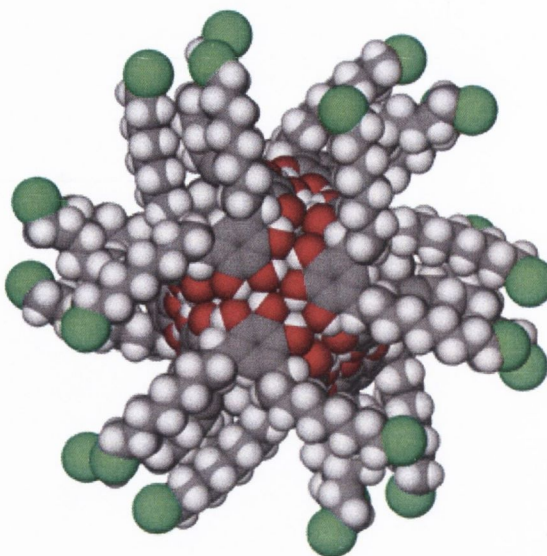


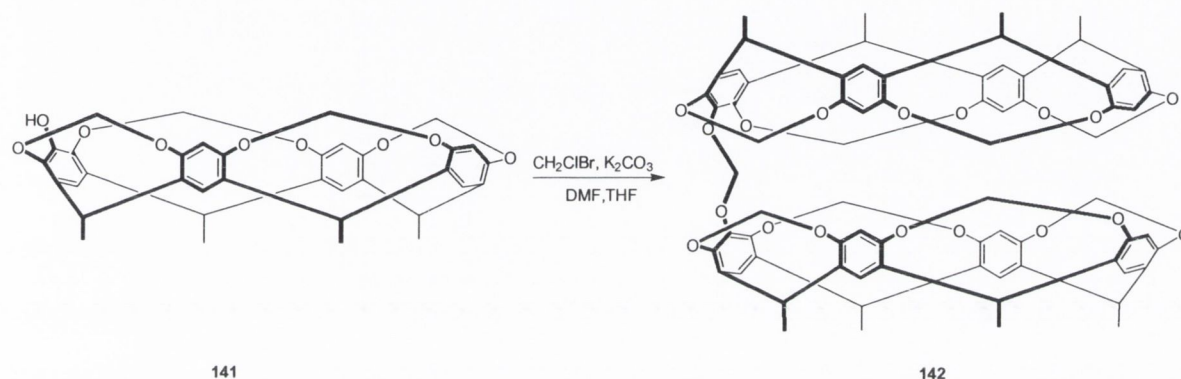
Figure 1.8: Space filling representation of a hexameric resorcarene nanocapsule¹¹⁷

Non-covalently bonded dimeric resorcarene capsules have also been reported. A head-to-head dimer of resorcarenes bonded indirectly through eight propan-2-ol molecules has been the subject of a crystallographic study and was found to have a larger cavity than is typically found in head-to-head dimers of resorcarene.¹¹⁸ Self-assembly of resorcarene hetero^{119,120} and homo¹²¹ dimers through the use of complimentary binding groups on the upper rim has also been reported, as has the use of metal complexation to form dimers.

Covalently linked resorcarene dimers are also known. In 1998 Murayama *et al.* reported a head-to-head dimer encapsulating a tetraethyl ammonium ion.¹²² A head-to-head dimer linked by four diamine bridges has also been reported and was obtained by the reaction of a resorcarene with ethylene damine and formaldehyde in a Mannich reaction and the subsequent reduction of the benzoxazine derivatives isolated.¹²³ Resorc[4]arene dimers with a head-to-tail configuration have been synthesised by Kazakova *et al.* through the incorporation of an aromatic aldehyde on the upper rim of a resorcarene and the further reaction of this compound with resorcinol.¹²⁴

Cavitands have also been successfully dimerised *via* one bridge at the upper rim. Previously in **Section 1.7.5** cavitands were used to form carceplexes and hemicarceplexes by the dimerisation of cavitands with three or four hydroxyl groups on their upper rim. Through the

same methodology, using milder conditions, a mono hydroxyl cavitand was successfully synthesised and dimerised **142**.¹²⁵ Cavitands, where only three of the bridges are in place, have been dimerised by the introduction of an alternative bridging unit for the fourth bridge, examples of which include 2,3,5,6-tetrafluorocyclohexa-2,5-diene-1,4-dione and tetrachloro-tetraazaanthracene.¹²⁶ These bridging units bridge not only the two remaining hydroxyl groups on the cavitand but the two cavitands to each other.



Scheme 1.18: Dimerisation of cavitands *via* one ether linkage

The dimerisation of resorcarenes in the tail-to-tail configuration is far less common. In 1994, through the use of statistical mixtures approach, the condensation of resorcinol or 2-methylresorcinol with octanal and 4,4-diformylbiphenyl led to the formation of a resorcarene dimer linked together by one biphenyl bridge in low yield (16.4%). Subsequent reaction of the dimer derived from resorcinol led to the isolation of the 2-bromo derivative.¹²⁷ These structures have been cavitanded, by reaction with bromochloromethane, and a single crystal X-ray structure obtained for the bromo derivative.¹²⁸ The crystal structure showed that the diphenyl linker in each of the joined resorcarenes is in an axial position and that the two macrocycles lie on opposite sides of this linker, rather than providing a cavity as shown in Figure 1.9.

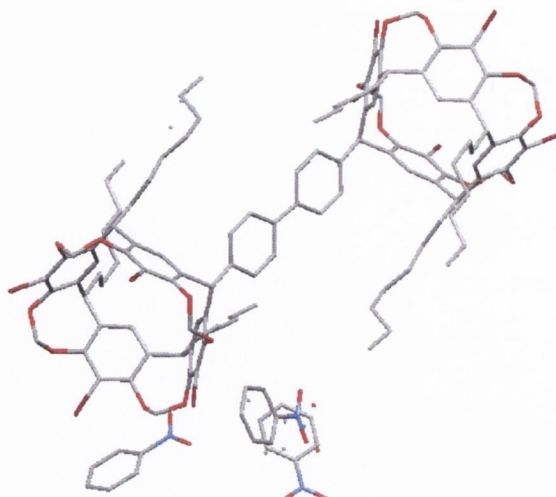
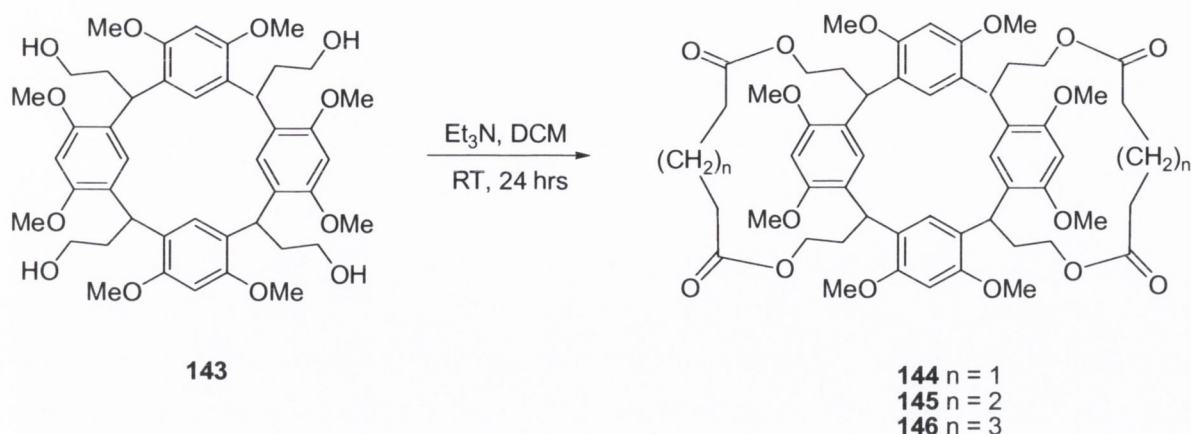


Figure 1.9: Crystal structure of resorcarene dimer¹²⁸

1.10 Strapped Resorcarenes

Resorcarenes strapped at both the upper rim and lower rim are also known. Resorcarenes strapped at the upper rim were obtained by the reaction of a simple resorcarene with two equivalents of a flexible diamine and eight equivalents of formaldehyde in a Mannich type reaction¹²⁹ as discussed earlier (**Section 1.6.2.1**). This leads to the isolation of tetrabenzoxazine derivatives in which adjacent pairs of oxazine rings are connected by an aliphatic chain. Hydrolysis of these compounds gives the secondary amine derivatives. Chirally strapped resorcarenes, also derived from a Mannich reaction, have been reported by Hunter and co-workers.¹³⁰ These molecules were subsequently used as templates in asymmetric catalysis reactions.^{131,132} Tetramethyl resorcarenes have also been strapped at the upper rim by reaction with tetra(ethyleneglycol) ditosylate.¹³³ The resulting crown ether moieties in the upper rim of these molecules have been shown to complex alkali metal ions.

Octamethylresorcarenes (OMRAs), where the hydroxyl groups on the upper rim of the resorcarenes are replaced with methoxy groups, have been strapped *via* two bridges on the lower rim when the pendant hydroxyl terminated alkyl chains on the molecule were reacted with adipoyl chloride (**Scheme 1.19**).¹³⁴ Strangely, in this reaction, standard conditions favoured the formation of the strapped structure while high dilution conditions resulted in a “jelly fish” like products that featured one to four tentacles.



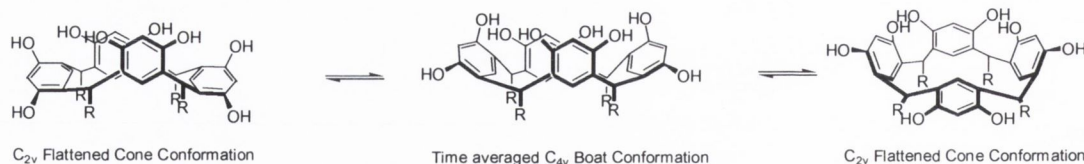
Scheme 1.19: Synthesis of OMRA molecules strapped at the lower room

The strapping of a tetrol cavitand through all four positions by one central aromatic unit, which in effect caps the molecule, has been reported by Watanabe *et al.*¹³⁵ The cavity formed by doing this was utilised for the synthesis and trapping of simple enols, notoriously unstable compounds.¹³⁶

In this introduction the historical literature in the field of resorcarenes has been documented and a brief overview has been given of the many divergent areas into which resorcarene chemistry has since evolved. There is still much scope for the further development of these versatile molecules as host molecules and we believe that the rigidification of these molecules to provide a preorganised guest binding site is an area that is, so far, unexploited.

1.11 Aims of this Project

The aim of this PhD project was to design and synthesise new families of rigid resorcarene-based supramolecular scaffolds, which after the attachment of ligands, would be expected to have many interesting properties due to the prearranged binding site. The attachment of ligands to resorcarenes in the boat conformation leads to a prearranged, convergent binding site. This is not the case for other resorcarene conformations discussed previously. It is desirable that the scaffold be as rigid as possible to have the greatest degree of ligand preorganisation. However, the resorcarene in the boat conformation is quite flexible and the ^1H NMR spectra observed is actually the time averaged structure of two interconverting boat structures.



Scheme 1.20: Interconversion of flattened cone resorcarenes

We propose to rigidify the resorcarene structure, and by doing so, fix it in the boat conformation through the modification of the lower rim. For the interconversion of one flattened cone conformation to another, there has to be some freedom of rotation around the methine bridging carbon to allow the resorcinol subunits to “move”. It follows from this, that if the substituents on the lower rim were rigidified, either by strapping of the resorcarene or its dimerisation *via* the lower rim with another resorcarene macrocycle, they would then be restricted in their movement. This lack of freedom should then prevent the interconversion of the two flattened boat structures.

1.12 Work Described in this Thesis

This thesis will be divided into four chapters, three of these chapters look at different approaches to the rigidification of resorcarenes *via* the lower rim while the fourth details the synthesis of cavitands, well known rigidified resorcarene-based ligand platforms, and their functionalisation with ligands. A brief summary of each of these chapters is given below.

In **Chapter 2** work towards the synthesis of rigidified resorcarenes derived from resorcinol and derivatives of resorcinol with electron withdrawing substituents is described. A number of routes are investigated, including one-pot synthesis, Lewis acid catalysed synthesis, synthesis using deactivated resorcinol derivatives, a multi-step synthesis using protecting groups and a post condensation oxidation of the lower rim.

In **Chapter 3** the work on the condensation reactions of 1,3-dimethoxybenzene and various aldehydes will be described. A study of the conditions that favour different conformers is reported.

In **Chapter 4** routes to lower rim and upper rim calixarene aldehydes and their subsequent condensation reactions with resorcinol are detailed.

In **Chapter 5** the synthesis of some previously reported alkylenedioxy-bridged cavitands is carried out and an investigation of the conditions required for the attachment of pyridine and organic acid ligands is undertaken. Preliminary binding studies for the novel cavitands synthesised are presented.

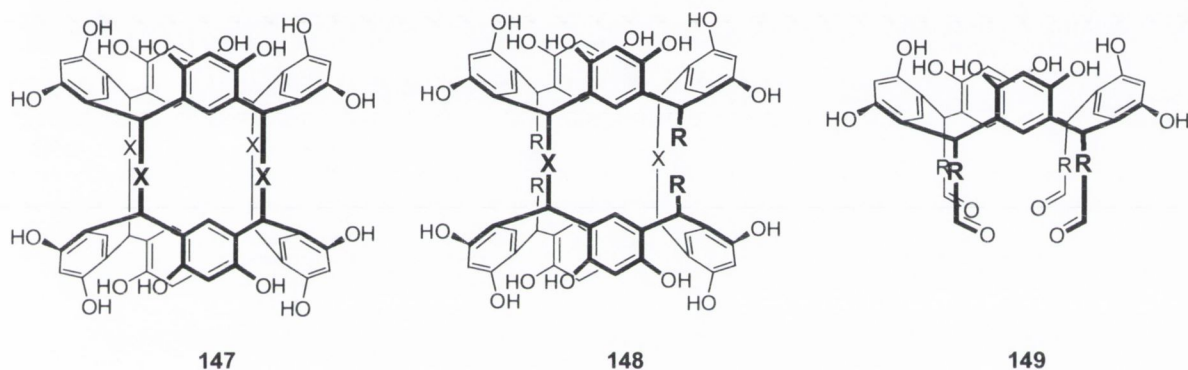
In **Chapter 6** the possible future work arising from this thesis is discussed.

Chapter 2

Synthesis of Novel Resorcinol Derived Molecules

2.1 Introduction

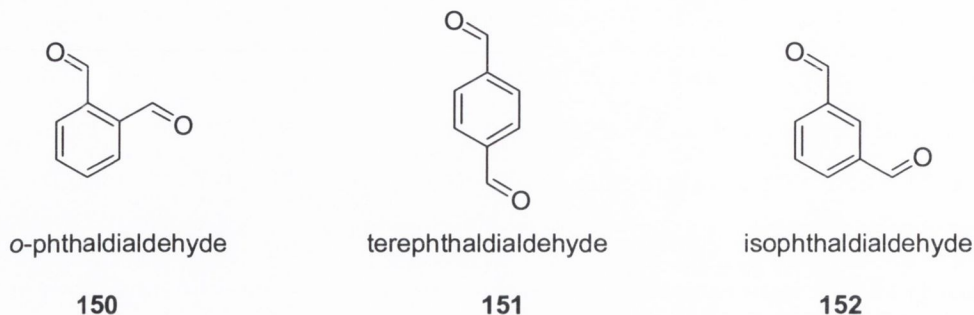
In this chapter the work carried out towards the rigidification of the resorcarene framework will be presented and discussed. Encompassed in this, will be the study of the condensation reaction between resorcinol and dialdehydes, both under standard¹² and high dilution conditions in an attempt to isolate a dimeric resorcarene joined through four positions on the lower rim (**147**). The effect of varying the acid type used to catalyse this reaction will also be discussed. Following this, the stepwise syntheses towards the dimeric resorcarene bridged in two positions (**148**) will be examined, with the effects of altering both the resorcinol and the aldehyde starting materials being investigated. Finally, the results of the attempts to alter the resorcarene post condensation to introduce a lower rim aldehyde (**149**) will be reported.



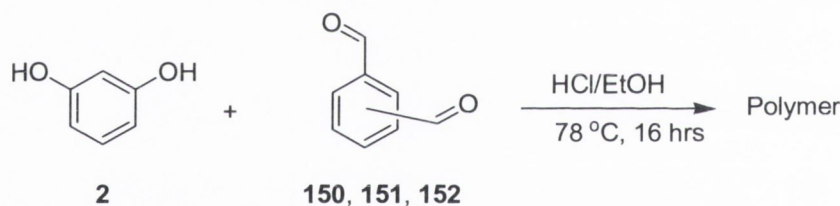
2.2 The Condensation of Resorcinol and Simple Dialdehydes

As previously discussed in **Chapter 1, Section 1.11**, our aim was to rigidify the resorcarene framework through the dimerisation of resorcarenes at the lower rim, *via* two or four bridges. The simplest method of accomplishing this, involves the use of dialdehydes under standard condensation techniques (resorcinol and aldehyde stirred together at reflux in ethanol with HCl overnight) and was the first to be investigated.¹² Three aldehydes were chosen for this initial synthesis. These were *o*-phthaldialdehyde (**150**), terephthaldialdehyde (**151**) and isophthaldialdehyde (**152**). These aldehydes were chosen for a number of reasons; such as being commercially available, the aromatic core had the desired rigidity and because changing the position of the aldehyde functional groups relative to each other was likely to give rise to the formation of new interesting products where the size of cavity produced would be different. All of these compounds would however be isomers of the general formula

[C₄₀H₂₈O₈] where n = 1 or 2, depending on whether the resorcarene structures are strapped or dimerised.



Aldehyde **151** was considered the most likely to form a resorcarene dimer whereas it was hoped that the ortho and the meta aldehydes might form strapped resorcarenes. Initially the condensation reaction was investigated using standard reaction conditions developed for the preparation of resorc[4]arenes.⁷ The resorcinol was reacted with each of the aldehydes shown above in a 2:1 ratio, **Scheme 2.1**. The starting materials were heated at reflux together with HCl in ethanol. The products precipitated during the reaction and were isolated by filtration.



Scheme 2.1: Reaction of resorcinol and dialdehydes under standard conditions

In every reaction attempted the product was a brown solid that could not be analysed successfully by ¹H or ¹³C NMR due to its insolubility in all available deuterated solvents. It was presumed that in each of these cases the reaction had produced an insoluble polymeric material. This is known to occur in the reaction of resorcinol and formaldehyde, where the high reactivity of the formaldehyde leads to the isolation of a polymer.¹⁰ Other alternative reaction conditions were investigated such as the use of high dilution conditions and the addition of the reagent over a long period of time.

Longer chain oligomers are known to form during the synthesis of cyclic, tetrameric resorcarenes.⁷ However, their rate of degradation is much faster than their rate of formation and they are rarely present at the end of a synthesis,¹⁵ as discussed in **Chapter 1**. The materials isolated above, were however, too insoluble for proper analysis to be carried out. Hence the possibility that they were actually forming longer chain oligomers, which were precipitating out of solution due to their insolubility, had to be investigated further. It is well known in macrocyclic chemistry that the use of high dilution/slow addition conditions often favour the formation of the desired macrocycle over polymers.¹³⁷ Aldehyde **151** was considered the most likely candidate for the formation of the target resorcarenes, so a study of its reaction with resorcinol was undertaken where the reaction time and temperature was kept constant but the concentration of the resorcinol and the rate of addition of **151** were varied. The reactions carried out and the results obtained are summarised in **Table 2.1**.

Table 2.1: Summary of High Dilution/Slow Addition Reactions. All reactions were carried out at 78 °C and each reaction ran for 16 hrs.

Concentration of Resorcinol	Aldehyde Addition	Result
0.373M	4 hr	Polymer
0.091M	4 hr	Polymer
0.045M	8 hr	No Reaction
0.001M	8 hr	No Reaction

As can be seen from **Table 2.1**, conditions for the formation of the desired resorcarene dimer were not achieved. The polymers isolated in the first two reactions were comparable with those isolated under standard conditions described previously. They were again brown in colour and insoluble powders. In the second two reactions no product was isolated. This could be distinguished by examination of ¹H NMR spectra, although there were numerous signals in the aromatic region, the absence of a resonance centred at *ca.* 5-6 ppm and characteristic of the bridging methine proton, showed that the desired product, or indeed any condensation product between resorcinol and the aldehyde, had not been formed. To summarise, up to a certain point of dilution the results are comparable with those found under standard condensation

conditions and after this point the reaction rate has become so slow that a reaction does not take place. Due to this drawback we decided to investigate alternative synthetic routes.

2.3 The Condensation of Resorcinol and Dialdehydes Catalysed By Lewis Acids

In all the previous reactions, hydrochloric acid was used as a catalyst. To investigate whether changing the catalyst would affect the outcome of the reaction; it was decided to investigate the condensation reaction using a Lewis acid catalyst, as they have previously been shown to give different results to protic acids.³² The ratio of conformers formed in Lewis acid catalysed reactions is fixed³² and shows no dependence on time or temperature unlike protic acids.¹⁵ Also the choice of Lewis acids in the condensation reaction between 1,3-dimethoxybenzene and various aldehydes was shown to be a deciding factor in the conformations present in the products formed.¹⁴

The reaction of resorcinol and terephthalaldehyde using $\text{BF}_3(\text{Et}_2\text{O})$ as a catalyst¹³⁸ led to the formation of a yellow powder which ^1H NMR spectroscopy ($\text{DMSO}-d_6$, 400 MHz) showed to be a mixture of unreacted aldehyde and a polymer whose presence was deduced from the broad signals observed. An IR spectrum of this material showed signals corresponding to an OH group at 3284 cm^{-1} and to aromatic groups at 1573, 1505 and 1602 cm^{-1} .

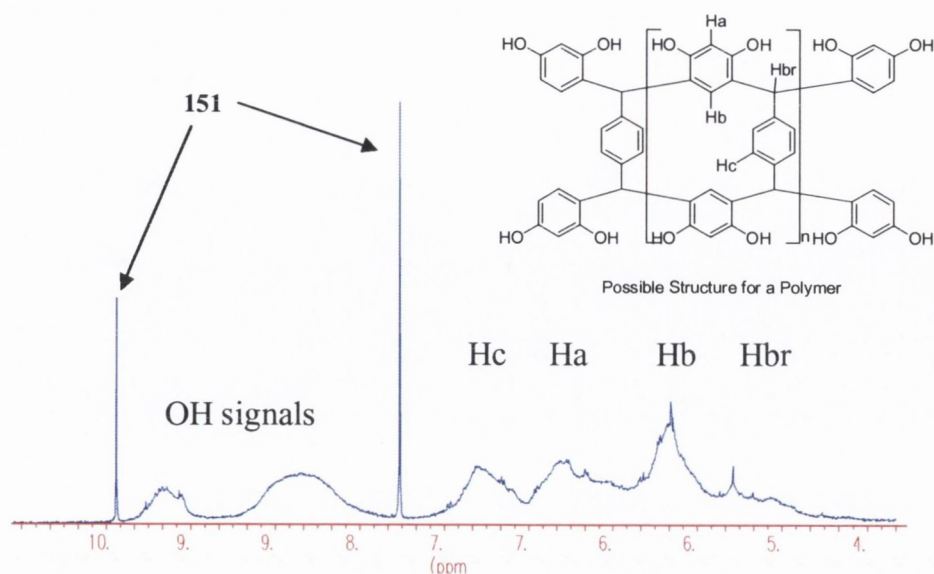


Figure 2.1: ^1H NMR (400 MHz, $\text{DMSO}-d_6$) of polymer produced in $\text{BF}_3(\text{Et}_2\text{O})$ catalysed reaction of 2 and 97 and possible spectral assignment

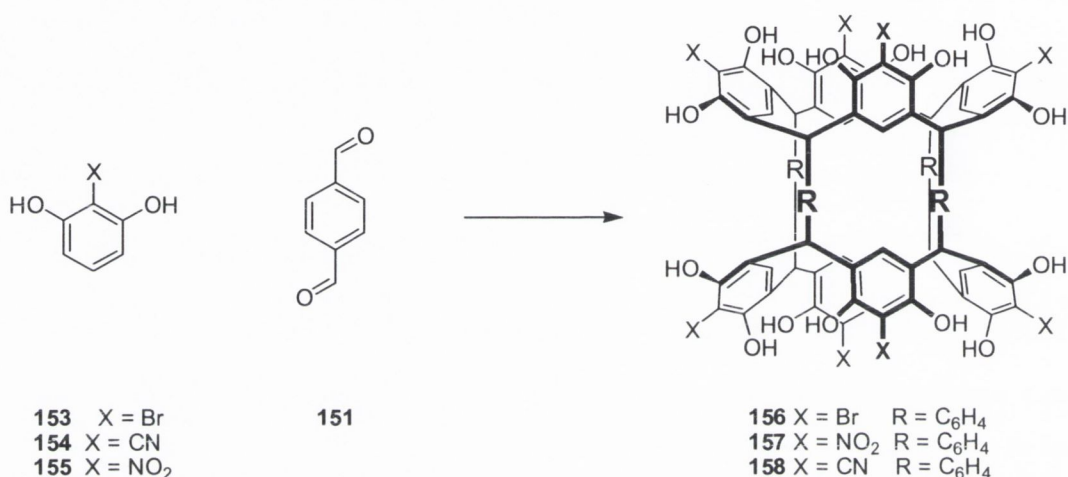
Although a polymer was again isolated the change in the catalyst was still believed to have resulted in the formation of a different product to that observed when HCl was used. This was concluded not only from the appearance of the product but also because of its increased solubility. A possible structure for the polymer is shown in **Figure 2.1** based on the sequence of events that occurs during the resorcarene reaction. This product is the most probable one as it is known that chain propagation occurs during the condensation reaction. It is believed to be a shorter chain oligomer than that formed in the HCl catalysed reaction due to its increased solubility.

2.4 The Use of Deactivating Substituents on Resorcinol

High dilution or slow addition conditions did not prove efficient in slowing down the polymer propagation. Nevertheless, as it was still hoped that slowing down the propagation of the polymers would allow the formation of the stable resorcarene tetramer we decided to pursue the impedance of the reaction *via* a different route.

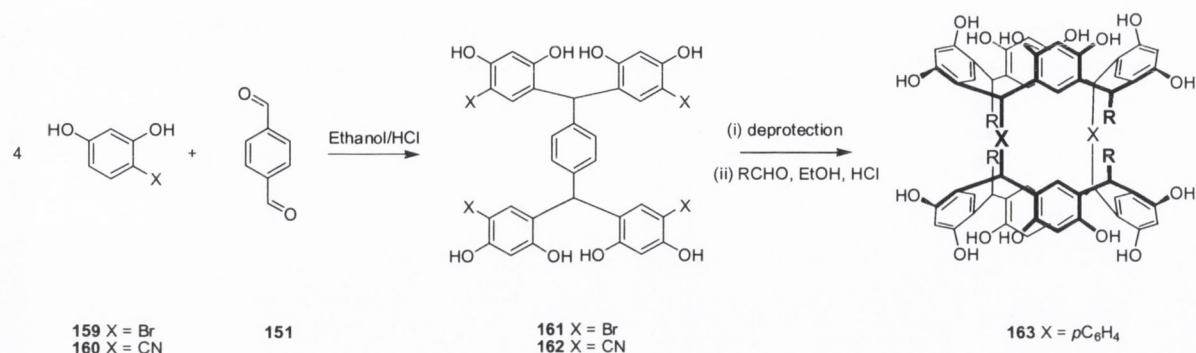
It is well known in electrophilic aromatic substitution chemistry that the substituents already present on an aromatic ring can greatly affect its reaction and the substitution pattern with

further substituents. Commonly, those substituents that are electron withdrawing deactivate the ring while those that are electron donating cause the ring to be more activated. Resorcinol already has two substituents present on its aromatic ring, both hydroxyl groups, which are ortho, para-directing and activate the ring towards electrophilic substitution. This means that the carbons at positions 4 and 6 on the ring, those involved in resorcarenene formation, are strongly activated.



Scheme 2.2: Proposed pathway for synthesis of resorcarenene dimers 156-158

To reduce the activity of the resorcinol starting material, there are a number of ways the ring could be further functionalised. Firstly, the positions on the ring which could be substituted were examined. The presence of substituents in the 2 position of the ring (**153**), which could later undergo further reactions to allow functionalisation of the resorcarenenes formed, seemed the most useful. It was decided to also investigate substitution at the 4 position (**154**). These resorcinol analogues could be used to form dimers that, upon deprotection, could undergo a further condensation reaction to yield the cyclic tetramer.



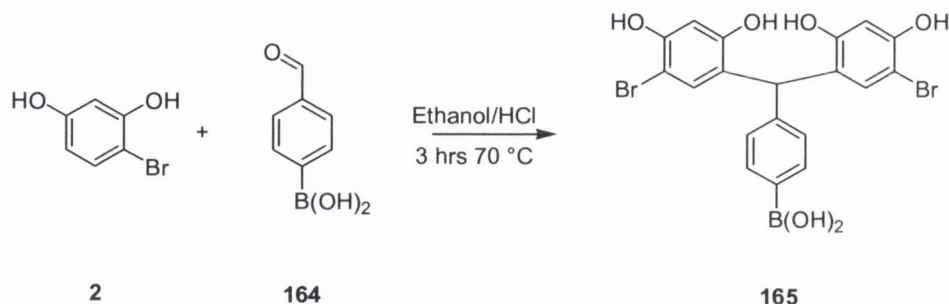
Scheme 2.3: Proposed pathway for synthesis of resorcarene dimer 163

Secondly, the deactivating substituents had to be chosen carefully for this idea to be successful. Bromine was chosen from the deactivating halogens. Although it deactivates the ring by the inductive effect, the deactivating effect would be somewhat lessened by its ability to also donate electrons. In addition to this, the bromine group should be facile to remove, using a sodium sulfite mediated reduction, or convert, using a BuLi reaction, at a later stage. The nitro and cyano groups were also chosen as alternative deactivating groups. These substituents are both strongly deactivating and *meta* directing, which would be ideal for the resorcarene reaction as the reaction takes place at the carbon *meta* to the 2 and 4 positions of resorcinol. Again their presence might be easily dealt with post condensation which also would allow for the further modification of the product. Hence, the nitro and cyano group could be converted to an amine and methyl amine groups respectively, which are highly desirable from a synthetic point of view.

2.4.1 Bromoresorcinol Derivatives

An attempted HCl catalysed condensation reaction between 2-bromoresorcinol (**153**) and acetaldehyde has previously been reported by Tunstad *et al.*¹² The exact products isolated were not reported but the authors found that only acyclic oligomers were formed. However, it has been shown that the deactivating effect of the bromo group can be overcome when the much stronger protic acid, triflic acid, is used. Morikawa *et al.* reported successful resorcarene formation in the presence of triflic acid in the reaction between 2-bromoresorcinol (**153**) and a variety of aliphatic and aromatic aldehydes.¹³⁹ Resorcinol dimers, synthesised through the

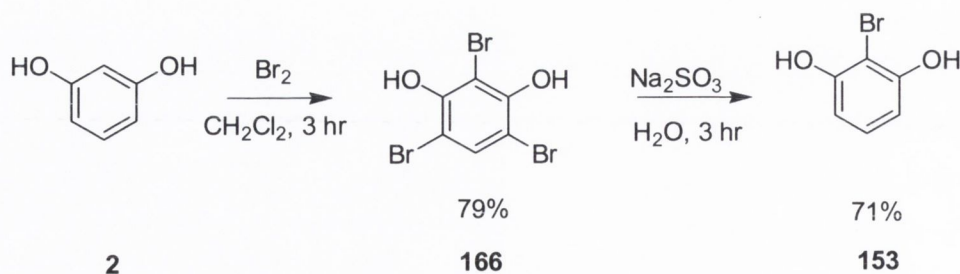
condensation of 4-bromoresorcinol (**159**) and 4-formylboronic acid, have also been reported as simple colourimetric sugar sensors (**Scheme 2.4**).^{140,141}



Scheme 2.4: Synthesis of simple sugar sensors^{140,141}

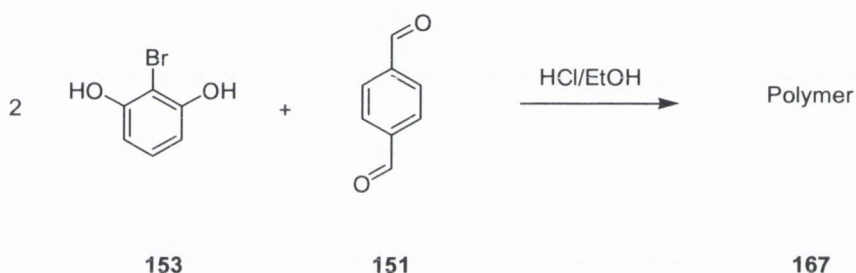
They have also been used in the synthesis of calix[4]arenes with resorcinol units incorporated in the 2,6-positions.¹⁴² The same methodology, this time using phenylpropionaldehyde, was used to synthesise resorcinol dimers for the preparation of resorcarenes with alternating pendant groups.¹⁴³

2-Bromoresorcinol (**153**) was synthesised from resorcinol in a two step synthesis; **Scheme 2.5**. In the first step resorcinol (**2**) was exhaustively brominated with excess Br₂ leading to the isolation of 2,4,6-tribromobenzene-1,3-diol (tribromoresorcinol) (**166**) in 79% yield.¹⁴⁴ Reduction of this compound was then carried out by stirring with sodium sulfite in water for three hours, followed by acidifying the reaction mixture and warming to 40 °C to expel sulphur dioxide.¹⁴⁵ Initial attempts to convert this product to 2-bromoresorcinol (**153**) led to the synthesis of 2,4-dibromoresorcinol. However, an increase in the amount of sodium sulfite used and longer reaction times led to the isolation of the desired product in 71% yield.



Scheme 2.5: Synthesis of 2-bromoresorcinol (**153**)

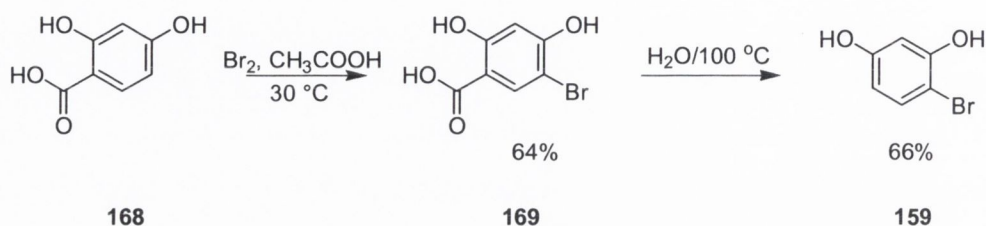
The condensation of 2-bromoresorcinol (**153**) was carried out with an half an equivalent of terephthalaldialdehyde (**151**) in a 4:1 v/v solution of ethanol and conc. HCl, **Scheme 2.6**. The product was isolated as an orange powder that precipitated out of solution as the reaction proceeded. Solubility is known to be an issue for tetrabromoresorc[4]arenes, synthesised in triflic acid catalysed reactions, where the ^1H NMR spectra had to be recorded in DMSO at temperatures, as high as 130 °C. In this case however, although many solvents and temperatures were tried, the product would not redissolve and no further analysis could be carried out. It was concluded that the deactivating effect of the bromo group in the 2 position was not strong enough to prevent the aforementioned polymerisation.



Scheme 2.6: Reaction of 2-bromoresorcinol (153**) and terephthalaldialdehyde (**151**)**

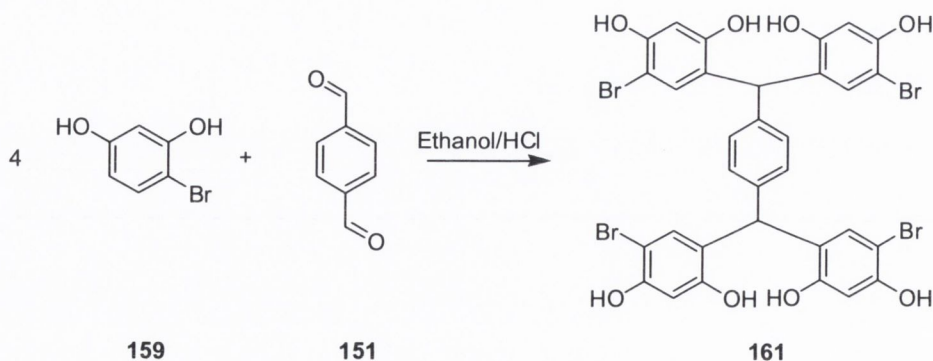
Despite the failure of **153** to prevent the undesirable polymer formation, it was hoped that the use of 4-bromoresorcinol (**159**) would be more successful. 4-Bromoresorcinol (**159**) should not only deactivate the resorcinol but will also effectively block the polymerisation by only allowing the resorcinol to react at one carbon. A number of different methods were investigated for the synthesis of 4-bromoresorcinol (**159**). The first method attempted used *N*-bromosuccinimide (NBS) as a source of bromine.¹⁴⁶ However, at the end of this reaction there was still unreacted starting material present and the desired product was only isolated in low yield after column chromatography. The use of bromine instead of NBS gave comparable results,¹⁴⁷ again leading to a low yield of 4-bromoresorcinol (**159**) and the necessity for purification by column chromatography. A more lengthy but ultimately more productive synthesis proved to be the bromination of 2,4-dihydroxybenzoic acid (**168**) with bromine in acetic acid,^{148,149} **Scheme 2.7**. This led to the isolation of the crude product 2,4-dihydroxy-5-bromobenzoic acid (**169**) with some 2,4-dihydroxy-3,5-dibromobenzoic acid impurity present. This impurity was converted to the very soluble 2,4-dibromoresorcinol on heating at reflux in

H₂O for 1 hr and separated from the solid product by hot filtration. Refluxing this product in H₂O for a further twenty four hours removed the acid group, leading to the isolation of the desired product, 4-bromoresorcinol (**159**), without the need for further purification in 42% overall yield.



Scheme 2.7: Synthesis of 4-Bromoresorcinol

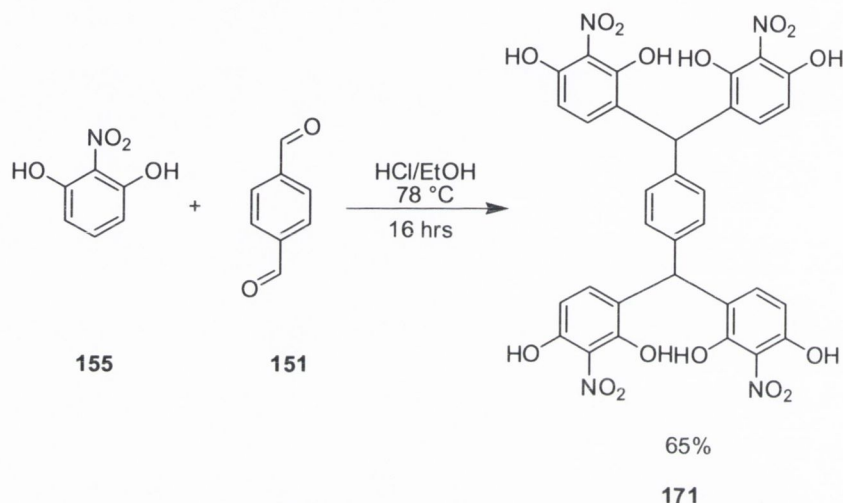
An attempt was then made to synthesise a resorcinol dimer from 4-bromoresorcinol (**159**) and terephthalaldehyde (**151**). The method used has been previously described by both Strongin *et al.*¹⁴⁰ and Rumboldt *et al.*¹⁴³ The two reagents were reacted together in a 2:1 ratio at 70 °C in 2:1 v/v solution of conc. HCl in ethanol, **Scheme 2.6**. The resultant ES mass spectra from these reactions seem to show the presence of the desired product, as a peak corresponding to M was observed (853.1332). However, ¹H NMR (DMSO-*d*₆, 400 MHz) showed the formation of a mixture of products and the reactions themselves are low yielding. The use of triflic acid in place of HCl and longer reaction times did not lead to any significant improvements. Because of these draw backs, this method was not pursued any further.



Scheme 2.8: Synthesis of 4-bromoresorcinol dimers

2.4.3 Synthesis of 2-Nitroresorcinol Dimers

2-Nitroresorcinol (**155**) is a cheap, commercially available starting material. Its reaction with aldehydes has previously been reported to yield only the acyclic resorcinol dimer in low yields of *ca.* 30%.¹² Because of this **155** was reacted with terephthaldialdehyde (**151**) in a 4:1 v/v ethanol/conc. HCl solution at 78 °C. Varying the reaction time from 9 hrs to 72 hrs did not however, have any significant effect either on the yield or the product formed, **Scheme 2.10**.



Scheme 2.10: Synthesis of 2-Nitroresorcinol Dimers

In all cases the yield was around 65% and the only product isolated was the acyclic dimer (**171**). For the purpose of purification, it was acylated and subjected to flash column chromatography (hexane:ethyl acetate 1:1). The ¹H NMR (DMSO-*d*₆, 400 MHz) was indeed found to be that of the dimeric product (**171**), shown in **Figure 2.2**.

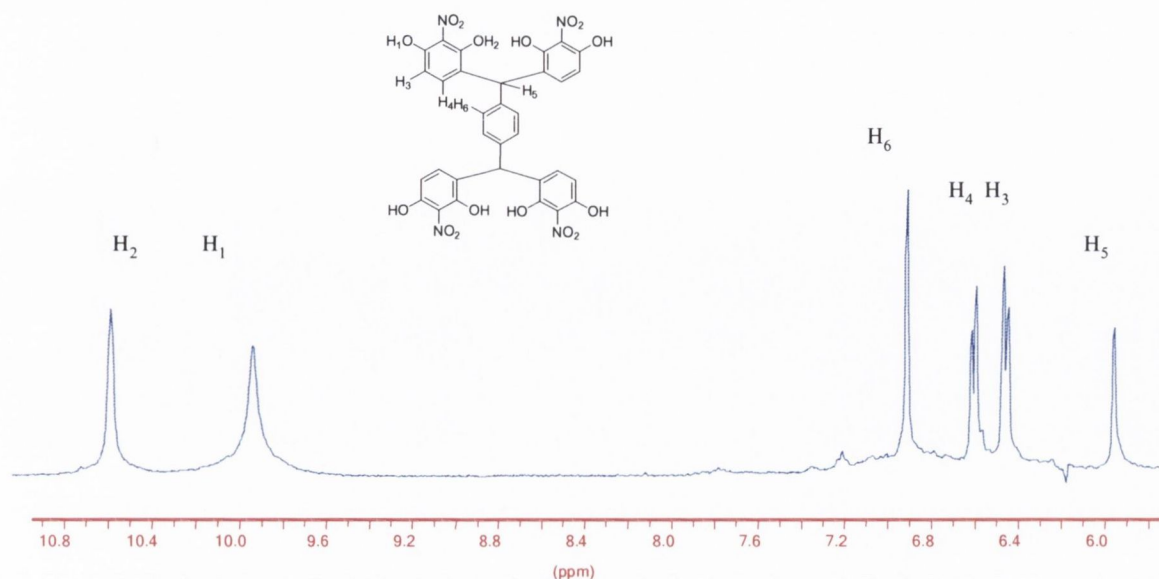
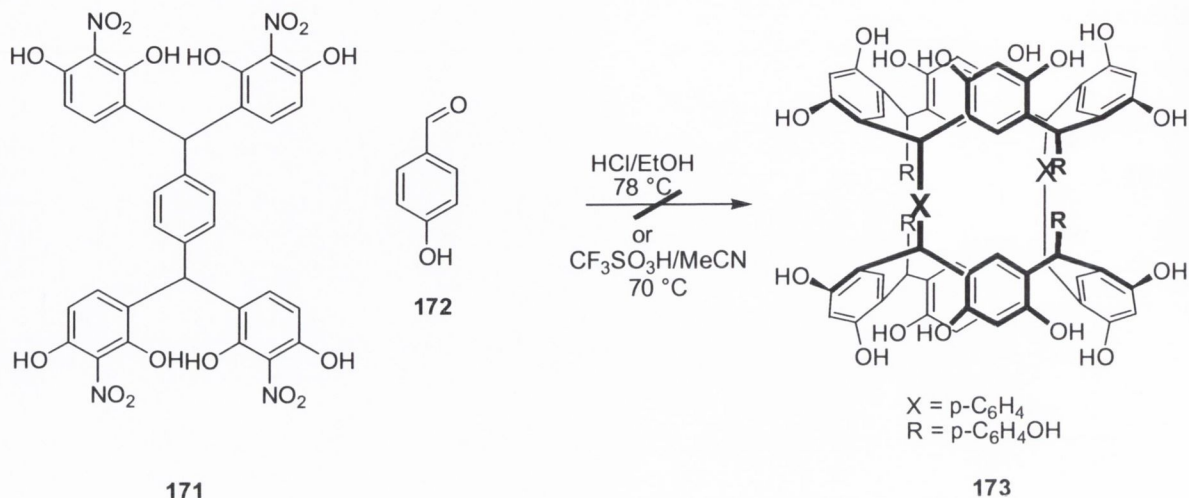


Figure 2.2: ^1H NMR (400 MHz, $\text{DMSO}-d_6$) of nitroresorcinol dimer **171**

In the ^1H NMR spectrum, only six signals were observed due to the high symmetry of the molecule. The bridging methine proton appeared as a singlet at 5.96 ppm, which is characteristic for these molecules. The protons on the nitroresorcinol subunit appeared as a pair of doublets at 6.4 and 6.6 ppm, and due to the molecule's four-fold symmetry the protons on the central aromatic group appear as a singlet at 6.9 ppm. A one-step route to a nitroresorcinol dimer from terephthalaldehyde had now been established using a synthesis that was readily reproducible and easy to scale up. Having successfully made the dimer the next step was to form the desired nitroresorcicarene.

The nitroresorcinol dimer (**171**) could now be used to form part of a resorcicarene tetramer, joined together at two points instead of four *via* the xylene bridge. To make this cyclic, dimeric resorcicarene it would be necessary to react **171** with a second equivalent of another aldehyde. The first aldehyde chosen was 4-hydroxybenzaldehyde (**172**). Initially **172** was heated at reflux with **171** in HCl/EtOH for 16 hrs. However, this led to the reisolation of the unreacted starting materials. The reaction was next carried out using $\text{BF}_3(\text{Et}_2\text{O})_2$ as a Lewis acid catalyst, but the same results were obtained. A final reaction between **171** and 4-hydroxybenzaldehyde (**172**) was carried out using $\text{CF}_3\text{SO}_3\text{H}$ as a catalyst. As previously

stated, this acid has been an effective catalyst in overcoming the deactivating effect of bromine substitution on resorcinol.¹³⁹ However, in this case, it failed to yield the desired product.

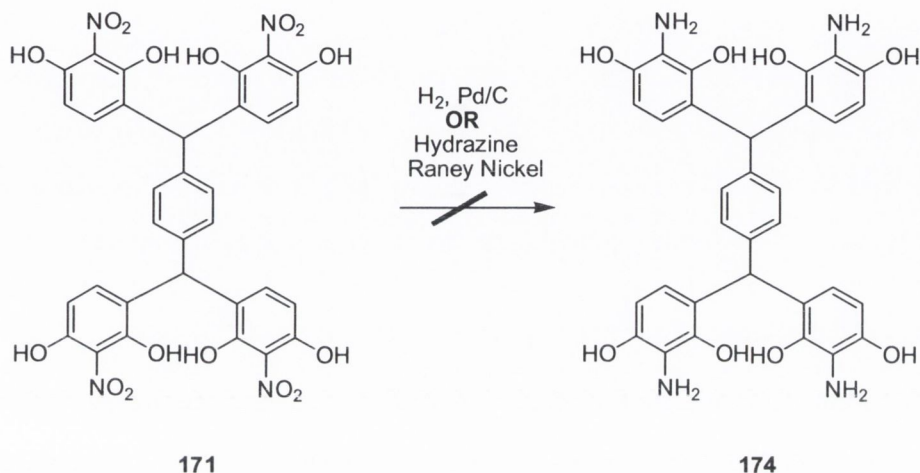


Scheme 2.11: Desired product from the reaction of nitroresorcinol dimer (171) and 4-hydroxybenzaldehyde (172)

To ensure that the lack of reaction was not due to the choice of aldehyde for this synthesis, a number of reactions were carried out with 171 and acetaldehyde, a less bulky and more reactive aldehyde. However, the reactions catalysed by HCl, $\text{BF}_3(\text{Et}_2\text{O})$ and $\text{CF}_3\text{SO}_3\text{H}$ each yielded again the unreacted acyclic dimer.

At this point 2-nitroresorcinol (155) was reacted with a number of aldehydes such as acetaldehyde, 4-hydroxybenzaldehyde (172) and terephthalaldehyde (151), in the presence of $\text{CF}_3\text{SO}_3\text{H}$ to ascertain if the acid was strong enough to overcome the deactivating effect of the nitro substituent. Surprisingly, given that no reaction was observed in any of the reactions described above, the triflic acid catalysed these reactions but only yielded undesirable polymers. To ensure that the broadening of the ^1H NMR ($\text{DMSO-}d_6$, 400 MHz) spectrum was due to the formation of these polymers and not the mixture of a large number of resorcarenes in different conformations, or due to a slow interconversion of different conformers on the NMR timescale, a number of ^1H NMR spectra were recorded at various temperatures. No significant changes were however, observed in the spectra between -20°C and 60°C indicating that, most likely, only the polymers were formed. The fact that the dimer failed to react even in the presence of triflic acid and that no scrambling in the pendant group was ever observed led to the conclusion that 171 is a very stable and unreactive molecule and that in

order to successfully use this molecule in further reactions it needed to be activated. The most obvious choice was the reduction of the 3-nitro groups to the corresponding 3-amino groups, which would change the substituents from deactivating to activating.



Scheme 2.12: Attempted Reduction of nitroresorcinol dimer 171

In an initial attempt the reduction was carried out using a Parr hydrogen shaker apparatus with a 10% Pd/C catalyst and under 3 atm. H₂ for 20 hrs. While the reaction did not go to completion; a number of partially reduced compounds were however formed. Reduction of the compound was also attempted using hydrazine and Raney nickel. Despite the use of over fifty equivalents of hydrazine and the reaction being left to react for up to one week, the desired product was not obtained. Again numerous partially reduced derivatives were observed by TLC but could not be successfully separated or analysed further. Because of this we did not continue with this synthesis.

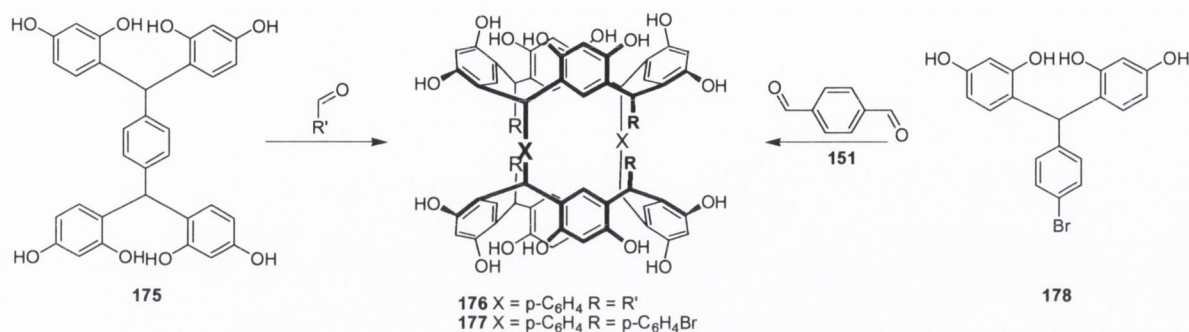
2.5 Resorcinol Dimers

Resorcarenes derived from more than one type of aldehyde or resorcinol starting material are known.¹⁴³ They are available by two different approaches, statistical mixtures synthesis or stepwise synthesis.

The statistical mixtures method refers to the use of various ratios of aldehyde or resorcinol starting materials in the hope that this ratio will be observed in the resultant product. Ichimura

and co-workers carried out a study on the one-pot reaction of resorcinol with varying amounts of butanal and 3-(pyren-1-yl)propanal. In the first attempt, the ratio of butanal to 3-(pyren-1-yl)propanal was 3:1, in the second attempt the ratio of the aldehydes was 1:1. Each run led to a mixture of products. Using HPLC, the amount of each separate product could be calculated as well as the number of pyrene residues ($n = 0-4$) present in each of these products. The results tied in well with predicted values. In the first run, products where $n = 0$ or 1 accounted for over 76% of the reaction mixture. In the second run, the amount of products where $n = 2$ or more greatly increased.¹⁵³ Using similar methodology Rebek *et al.* synthesised a resorcarene monofunctionalised on the lower rim with one hydroxyl group by the reaction of resorcinol with a 3:1 ratio of hexanal:2,3-dihydrofuran.¹⁵⁴ The ratio of different types of resorcarene can also be varied, Tunstad *et al.* reported the synthesis of mono-, di- and trisubstituted resorcarenes through the reaction of hexanal with a 1:1 mixture of resorcinol and 2-methylresorcinol.¹⁵⁵ Aoyama and co-workers reported the synthesis of a resorcarene trimer, where each resorcarene subunit was linked to another by one bridge on the upper rim.¹⁵⁶ This was accomplished through a statistical mixtures approach where resorcinol and a diresorcinol unit bridged in the 2 position, in a 6:1 ratio, were reacted with eight equivalents of dodecanal.

However, these reactions are generally very low yielding, resulting in a complex mixture of products which can be difficult and time consuming to separate. To date, there are only two examples of the synthesis of a resorcarene derived from two different aldehydes *via* a stepwise route.^{143,157} This is achieved by synthesising a resorcarene dimer from one aldehyde and a second condensation reaction then takes place to give a resorcarene with two different R groups in alternating positions. In the previous section, where a resorcinol dimer was formed, the initial deactivating substituent becomes a problem after the first condensation reaction, requiring its removal or conversion before a second condensation reaction could take place. Therefore, it was desirable to be able to synthesise these dimers directly from unsubstituted resorcinol by controlling the reaction conditions. Although resorc[4]arenes are the favoured products of the acid catalysed condensation reaction of resorcinol with an aldehyde,⁷ it has been reported that combining shorter reaction times, an excess of resorcinol and lower reaction temperatures can lead to resorcinol dimer formation.¹⁴³

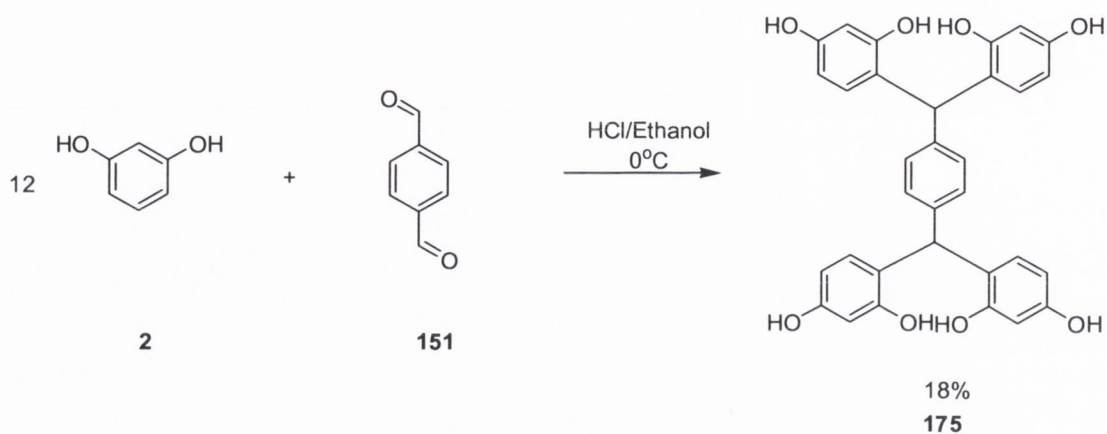
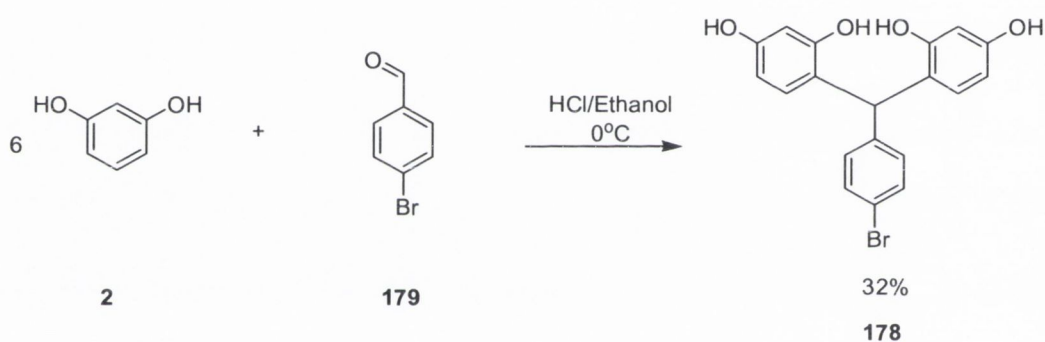


Scheme 2.13: Two possible approaches to the synthesis of resorc[4]arene dimers (**176**, **177**) bridged in two positions

This synthesis of resorcarene dimers **176** and **177** involves two steps, the synthesis of an acyclic resorcinol dimer (**175** or **178**) and the subsequent reaction of this dimer with a second aldehyde to give a cyclic resorc[4]arene. This means there are two possible approaches available towards the synthesis of resorcarene dimers, **Scheme 2.13**. Firstly, the strapping group can be contained within the dimer and a monoaldehyde can be used in the second condensation. However, the dimer can also be synthesised from a monoaldehyde where the strapping group can be introduced by using the dialdehyde **151** in the the second step. It was decided to investigate both routes and dimers, derived from terephthalaldehyde and 4-bromobenzaldehyde, were chosen as targets for the first step.

2.5.1 Synthesis of Resorcinol Dimers

Initially, a procedure reported by Harden and Reid in 1932 was investigated.¹⁵⁸ This proposed a ratio of 3:1 of resorcinol to aldehyde, but without detailed further reaction conditions. This was attempted by heating the aldehyde (**151**) and resorcinol (**2**) in HCl/ EtOH at 30 °C for 3½ hrs. Whilst some success was had with this reaction, the outcome was unreliable, often yielding the cyclic tetramer instead of the dimer. A more reliable method has since been developed which involved using a resorcinol: aldehyde ratio of 6:1 at 0 °C,¹⁴³ this method yields a small amount of dimer with a large excess of unreacted resorcinol, but the dimer can be purified successfully by column chromatography, **Scheme 2.14**, **2.15**. Both dimers **175** and **178** were successfully isolated, their low yields, 18% and 32% respectively, being a result of the mild reaction conditions used.

Scheme 2.14: Synthesis of resorcinol dimer **175**Scheme 2.15: Synthesis of resorcinol dimer **178**

The ^1H NMR spectrum (DMSO- d_6 , 400 MHz) of compound **175** is shown in **Figure 2.3**. As for the nitroresorcinol dimer, it is simplified by the high symmetry of the molecule and the protons on the central aromatic group appear as a singlet. As with resorc[4]arenes, the methine proton is seen as the most upfield shifted resonances. The formation of a dimer is confirmed by the separate signals observed for two non-equivalent hydroxyl groups and by the doublets obtained for H_4 and H_5 .

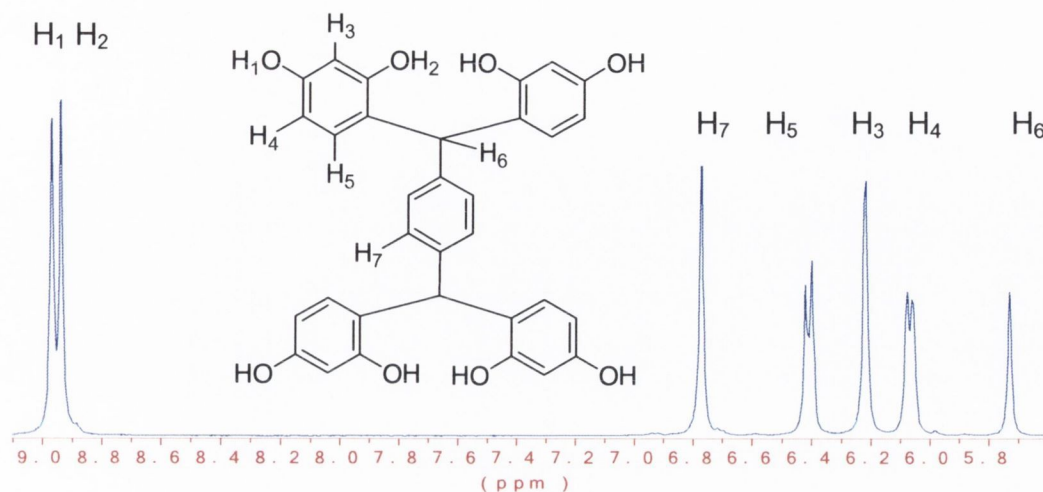
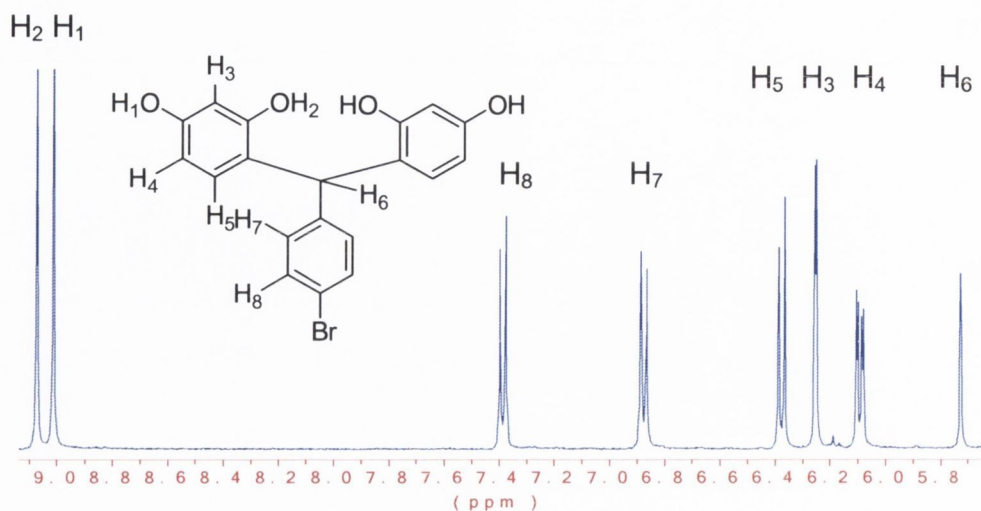


Figure 2.3: ¹H NMR (400 MHz, DMSO-*d*₆) of 175

The ¹H NMR spectrum (400 MHz, DMSO-*d*₆) of **178** is shown in **Figure 2.4**. It shows more clearly the characteristic AMX splitting pattern associated with the positions of the substituents on the resorcinol subunit due to the long range coupling of the protons on the aromatic ring. The expected doublet for H₄ undergoes further splitting due to long range coupling to H₃ and a similar effect was seen for the singlet expected for H₃. This has allowed the accurate assignment of all signals observed for the protons on an aromatic ring not only in this spectrum, but also due to their similarities, for the spectrum of **175** in **Figure 2.3** where the long range coupling is not so obvious.

Figure 2.4: ^1H NMR (400 MHz, $\text{DMSO}-d_6$) of 178

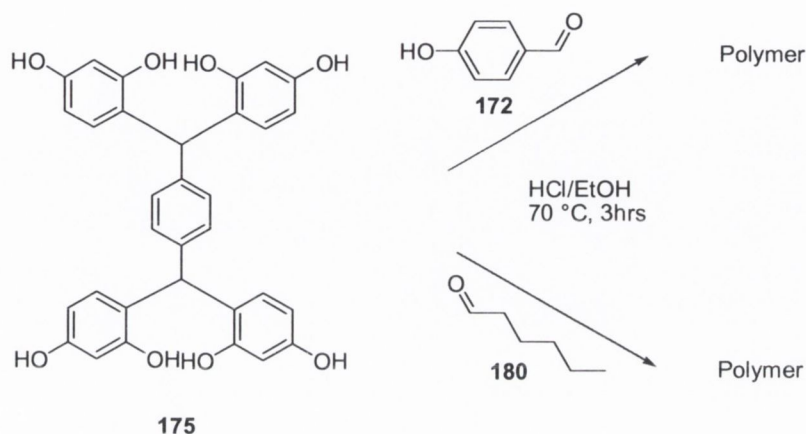
Now that two novel unsubstituted resorcinol dimers had been successfully isolated the next objective was their condensation with an aldehyde to give the cyclic tetramer.

2.5.2 Reaction of Resorcinol Dimers with a Second Aldehyde

The resorcarene condensation reaction is a reversible one so the introduction of a second aldehyde under these reversible conditions has to be controlled carefully. If the conditions are too strong then the resorcinol dimer starting material may break up. This would lead to a variety of products as there are numerous possibilities for arranging each of the two aldehydes on the four sites of the lower rim. This effect is known as scrambling.¹⁴³ To help prevent scrambling the reaction of the dimers with a second aldehyde was carried out under mild conditions. Resorcarene formation is usually carried out at 78 °C and the reaction time is usually at least 16 hrs, for this reaction the reaction temperature was lowered to 70 °C and the reaction length shortened to 3 hrs.

The first aldehyde studied was 4-hydroxybenzaldehyde (**172**), this had previously been used successfully in an analogous reaction.¹⁴³ The isolated product from this reaction was observed to be a polymer by ^1H NMR. A second aldehyde, hexanal, was then investigated to see if its

increased flexibility and reactivity would have a positive effect on the outcome of the reaction. Again after three hours only the polymer was isolated.



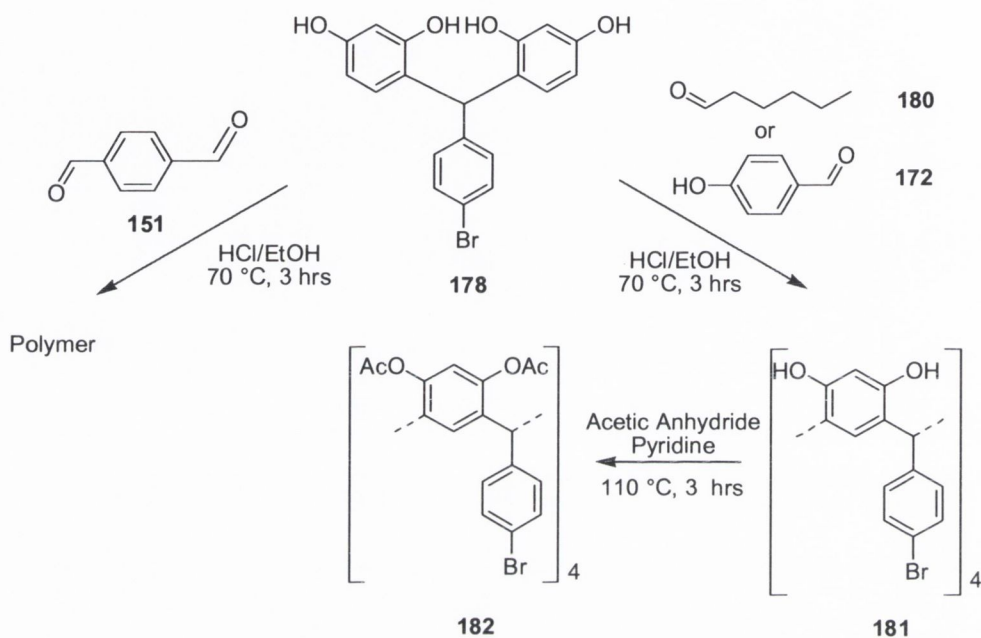
Scheme 2.16: Further reaction of resorcinol dimer 175 with 4-hydroxybenzaldehyde (172) and hexanal (180)

As the resorcarene reaction is reversible there is a possibility of scrambling even under these mild conditions. To overcome the formation of the oligomeric/polymeric material a variety of reaction conditions were investigated. Shorter reaction times were investigated, but even at thirty minutes the only product isolated was a polymer. Lowering the reaction temperature to 0 or 25 °C did not yield the desired product either. Unreacted starting materials were isolated at the end of these reactions.

Table 2.2: Further Reaction of Dimer 175

Temperature (°C)	Time (min)	Aldehyde	Result
70	180	172	Polymer
70	60	172	Polymer
70	180	180	Polymer
70	30	180	Polymer
25	60	180	No Reaction
0	30	180	No Reaction

Because of the problems with the synthesis in the previous section and the formation of an insoluble polymer under all conditions screened, it was difficult to tell if scrambling was occurring even under mild reaction conditions.



Scheme 2.17: Further reaction of resorcinol dimer **178** with terephthalaldehyde (**151**), 4-hydroxybenzaldehyde (**172**) and hexanal (**180**)

To test the reliability of the reported reaction,¹⁴³ dimer **178** was reacted with hexanal (**180**). The resorcarenene made with just two bromine functionalities on the lower rim would still be of interest, as the bromines could be utilised, for example, in a Suzuki coupling reaction with a bisboronic acid.⁷³ It has been shown previously that resorcarenenes can be dimerised *via* one lower rim linkage using this reaction.⁷³ Although this molecule is still flexible and lacks an enforced cavity,¹⁵⁹ we believe that a second linkage would provide the desired rigidity. As the resultant resorcarenene is anticipated to be quite insoluble it was decided to use a second aldehyde with an alkyl chain to increase solubility.

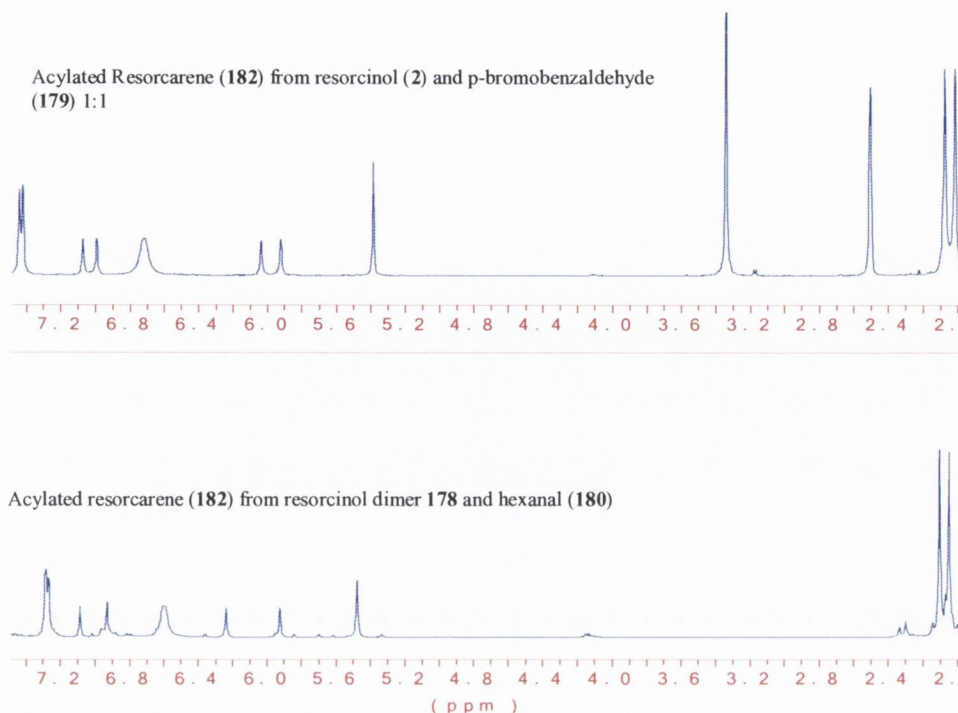


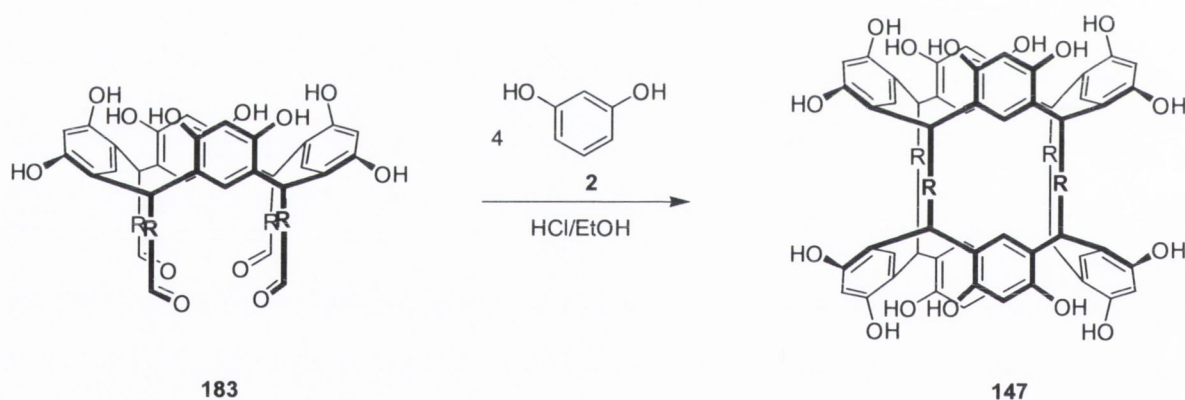
Figure 2.5: ^1H NMR (400 MHz, $\text{DMSO}-d_6$) spectra of a) resorcarene derived from bromobenzaldehyde and b) product from the reaction of dimer 178 and hexanal

Unexpectedly this led to scrambling in the reaction and the only product isolated was similar to a resorcarene obtained through the reaction of resorcinol with bromobenzaldehyde in a 1:1 ratio. Interesting, the ^1H NMR spectra above are slightly different. The complete absence of any alkyl groups in the ^1H NMR (400 MHz, $\text{DMSO}-d_6$) from the reaction of dimer **178** with hexanal (**180**) is further proof that the desired product has not been obtained. A second reaction was carried out with 4-hydroxybenzaldehyde (**172**) chosen as an alternative aldehyde but again scrambling during the reaction was observed and the same product as before was isolated. This scrambling is in contrast to results previously reported by Böhmer *et al.* for similar aldehydes.¹⁴³ In the first instance, where hexanal (**180**) is used, it may be that the resorcarene isolated (**181**) acts as a thermodynamic sink for the reaction. Any resorcarene containing one or more hexyl chain pendant groups would be more soluble than the isolated product. The less soluble the resorcarene is the more likely it is to be precipitated from the reaction mixture, removing it from the equilibrium and allowing its formation to be favoured. This has been observed where there are differences in the solubility of various conformers of the same resorcarene and the most insoluble conformer can be isolated as the sole product

under optimum conditions²⁸. In the reaction of the dimer with 4-hydroxybenzaldehyde (**172**) the difference in the solubilities of the various possible products should be less pronounced so it is less clear why the same product is favoured. Perhaps in this case, this is due to the effect the bromo and hydroxyl groups already present on the aromatic ring have on the reactivity of the aldehyde. The hydroxyl group is better able to donate electrons into the ring, making the carbon of the aldehyde less electropositive and therefore less reactive.

2.6 Attempts at Synthesising a Resorcarene with Lower Rim Aldehyde Functionality

A resorc[4]arene molecule that had four lower rim aldehyde groups was also a desirable target. In the *rccc* boat conformation the aldehyde moieties of such a resorcarene would be suitably arranged to form a dimeric resorcarene molecule when reacted with a further four equivalents of resorcinol under mild conditions. These aldehyde groups cannot be present in the initial condensation. Hence, they must either be protected for this step or introduced post-condensation. Both approaches have been investigated herein.

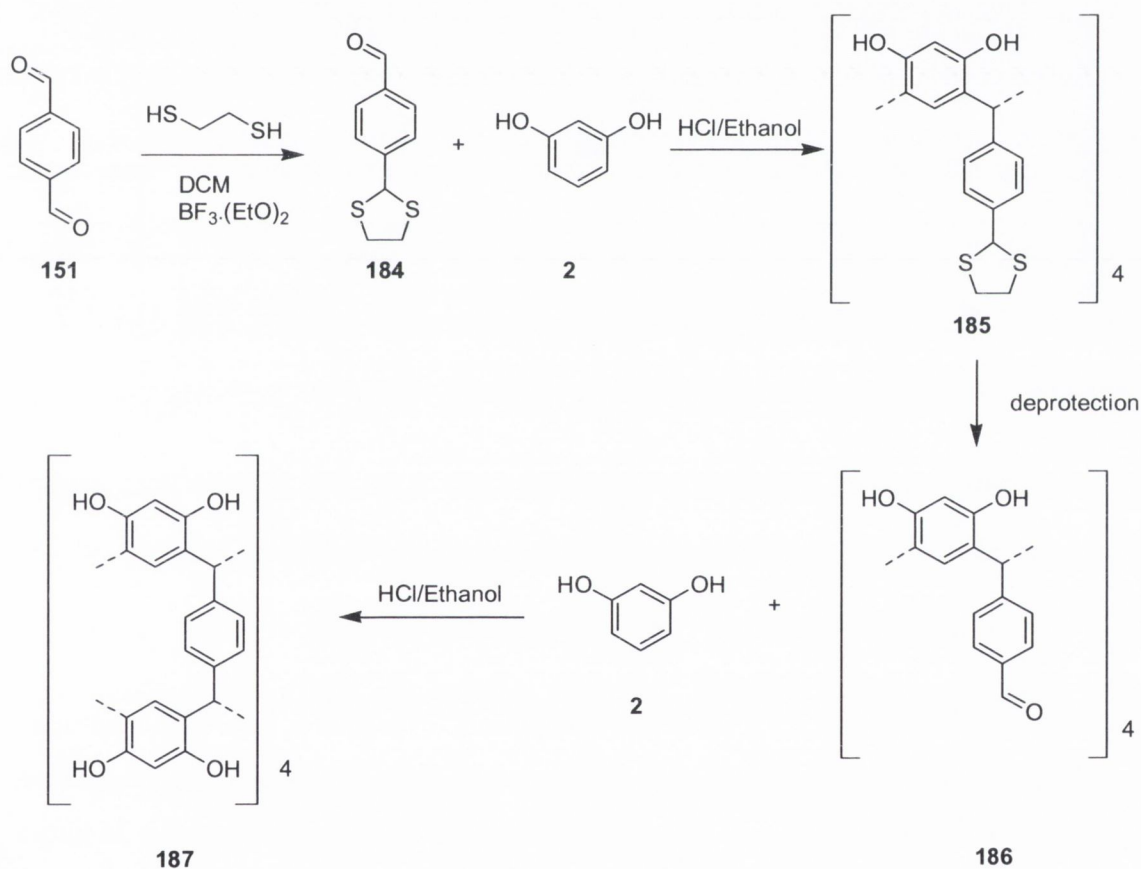


Scheme 2.18: Target compound (**183**) for this section and its possible subsequent reaction to give a resorcarene dimer

2.6.1 Synthesis of a Lower-Rim Aldehyde Resorcarene through the use of Protecting Groups

The resorcarene condensation reaction takes place under harsh acidic conditions so the protecting group chosen needs to be acid stable. The most widely used protecting groups in aldehyde chemistry are the acyclic and cyclic acetals and thioacetals.¹⁶⁰ Acetals are cleaved in

the presence of acid and in resorcarene chemistry, aldehydes that were used in the protected dimethyl acetal form still underwent resorcarene formation¹⁶¹ so they are not suitable in this case. It was decided instead to use a cyclic dithio acetal as these groups are not acid cleaved. The protection of aldehydes with ethanedithiol forms an acid stable dithiolane ring.¹⁶² It can be cleaved in high yields using mercury perchlorate ($\text{Hg}(\text{ClO}_4)_2$) in THF under mild conditions (30 min, RT).¹⁶³ Terephthalaldehyde (**151**) was reacted with one equivalent of ethanedithiol and $\text{BF}_3(\text{Et}_2\text{O})$ to give both the mono- and diprotected aldehyde (**184**). The mono aldehyde was successfully separated from the **184** by column chromatography (silica, hexane: ethyl acetate, 4:1 v/v) in 20% yield. The aldehyde was reacted with resorcinol (**2**) under standard conditions and a resorcarene (**185**) was isolated from the reaction mixture by filtration.



Scheme 2.19: Synthesis of resorcarene **185** with a protected aldehyde group on the lower rim

It can be concluded from the ^1H NMR (400 MHz, $\text{DMSO}-d_6$) of this resorcarene (**Figure 2.6**), which showed two signals for each of the protons on the resorcinol subunit, that a chair conformer was the sole product. This may be due to steric crowding on the lower rim due to

the large R groups on the aldehyde. In some cases flattened boats exhibit similar ^1H NMR spectra when large groups are present on the lower or upper rim and they are sterically constrained.¹³⁴ It was decided to proceed with the deprotection step; the removal of the ditholane ring would remove some of the steric repulsion on the lower rim and if the product was a boat should allow us to see a more time averaged structure.

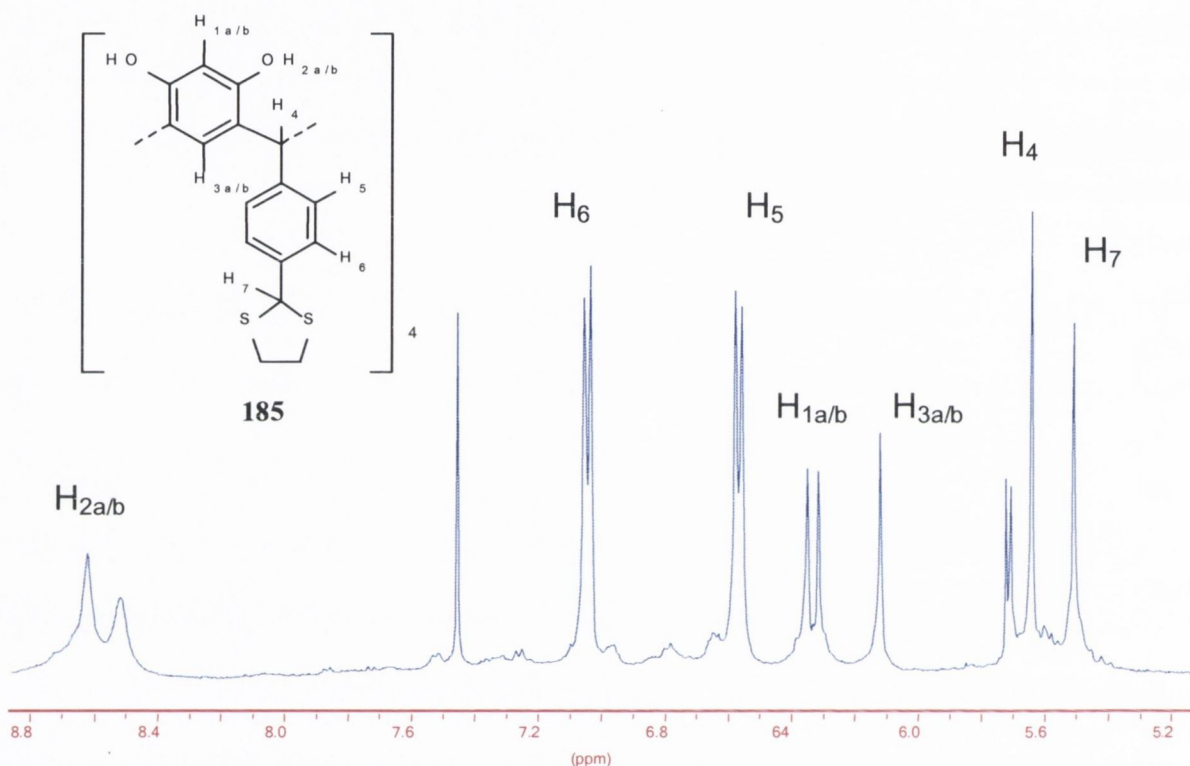


Figure 2.6: ^1H NMR (400 MHz, $\text{DMSO}-d_6$) partial spectra of resorcarene 185

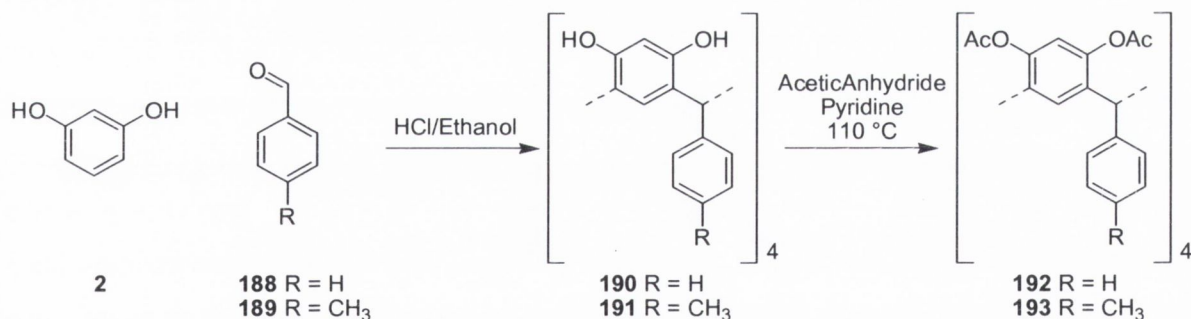
Deprotection using $\text{Hg}(\text{ClO}_4)_2$ in THF was attempted. Usually it requires very mild conditions. As previously stated this reaction is usually complete after thirty minutes at room temperature. However, no reaction occurred even after being left to stir at room temperature for 24 hours. The use of higher temperatures likewise had no effect. The lack of reaction is believed to be due to the insolubility of the resorcarene. Attempts at acylation, commonly used to increase the solubility of resorcarenes, failed despite the forcing conditions used in this reaction (neat acetic anhydride, cat. pyridine, $110\text{ }^\circ\text{C}$). The insolubility of this compound has thus unfortunately prevented any successful further reaction.

2.6.2 Synthesis of a Lower-Rim Aldehyde Resorcarene through Oxidation

As stated in the introduction, the post-condensation derivitisation of the lower rim has not been widely investigated. There are currently no published reports of oxidation of the lower rim. The choice of aldehyde used in the resorcarene formation must take into account a number of considerations:

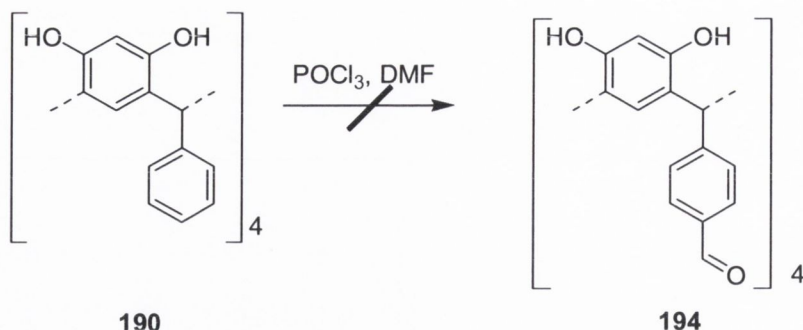
- Any functionality in the aldehyde must be tolerant of the harsh acidic conditions used.*
- The group must be chosen so that its method of oxidation will not affect the upper rim hydroxyl groups.*
- The aldehyde chosen should, if possible, lead to the sole formation of the boat/crown isomer.*

With these facts in mind benzaldehyde (**188**) and *p*-tolualdehyde (**189**) were chosen. The condensation of resorcinol with these aldehydes has previously been reported.¹² Both are known to form resorcarenes solely in the boat conformation in high yields.



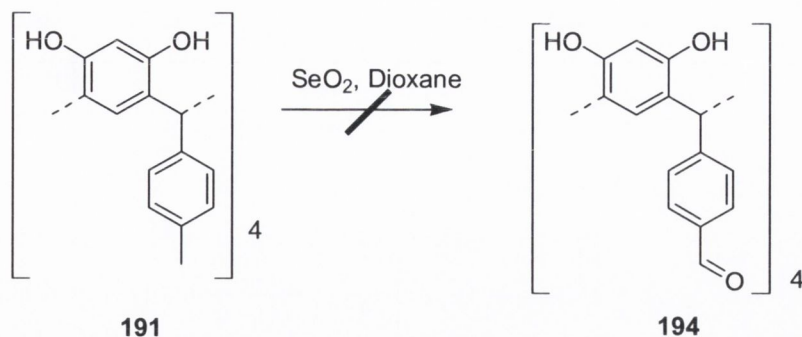
Scheme 2.20: Synthesis of resorcarenes (**190**, **191**) from resorcinol and either benzaldehyde (**188**) or *p*-tolualdehyde (**189**) and their subsequent acylation to form **192** and **193**

The resorcarenes shown above (**190** and **191**) were prepared in 86 % and 98 % yield respectively and confirmed by ¹H NMR (400 MHz, DMSO-*d*₆) spectra to be in the boat conformation.



Scheme 2.21: Attempted oxidation of resorcarene 190 to resorcarene 194

The use of the Vilsmeier reaction for the formylation of aromatic compounds is well known,¹⁶⁴ although not in resorcarene chemistry. Aromatic compounds can be oxidised to give aldehydes when dimethylformamide (DMF) and phosphoryl chloride (POCl_3) are used together in the Vilsmeier reaction. In this reaction, the first step involves the reaction of DMF with POCl_3 to give a carbon electrophile in the form of an iminium cation. This cation will then react with the aromatic ring to form a more stable iminium salt, which is hydrolysed during the basic work up to give the desired aldehyde. For the above compound there are a number of places that this reaction could take place. The unsubstituted aromatic carbon on the upper rim is a likely position for this reaction to occur due to the activating effects of the two hydroxyl groups on adjacent carbons. The carbon *para* to the substituted position of the benzene pendant group on the lower rim is also activated by substitution and is less sterically hindered than the position on the upper rim. Nevertheless, this reaction was unsuccessful, and only the unreacted starting material was reisolated, most likely due to the high insolubility of this resorcarene. Compound **190** was then acylated by heating in acetic anhydride/pyridine for 3 hrs at 110 °C to increase its solubility. The desired compound was obtained in quantitative yield but further reaction again failed to yield the aldehyde derivative.



Scheme 2.22: Attempted oxidation of resorcarene 191 to resorcarene 194

The oxidation of the resorcarene **191** derived from *p*-tolualdehyde (**189**) was attempted using selenium dioxide in dioxane. Selenium dioxide is known to react with alkenes in a [4+2] cycloaddition reaction. Initially a selenic acid complex is formed containing a very weak C-Se bond. This reaction intermediate undergoes allylic rearrangement to give a very unstable complex, which rapidly decomposes to give an allylic alcohol. When the group being oxidised is a methyl group (as is the case here) this primary alcohol undergoes further reaction to give an aldehyde. Again for this reaction solubility was a major issue and the desired product was not isolated. The resorcarene **191** was successfully acylated, using the same method as for the acylation of **190**, to improve its solubility but this did not have any positive effect on the outcome of the reaction.

2.7 Conclusions

A number of pathways towards the targets shown in **Section 2.1** have been investigated. These strategies and their outcomes are summarised below.

- The synthesis of resorcarene dimers through a one-step condensation reaction of resorcinol with a dialdehyde was not successful, resulting in the formation of polymeric material.
- The use of deactivating groups on the resorcinol unit was, in some cases, successful in stopping the polymerisation reaction but unfortunately did not lead to the desired tetramer. This work did however lead to the isolation of a novel nitroresorcinol based compound, **171**, which consisted of four nitroresorcinol units joined by a central

aromatic core. Further possible cyclisation reactions of this compound with a second equivalent of aldehyde were hindered by its insolubility and limited reactivity.

- Two novel resorcinol dimers derived from unsubstituted resorcinol were successfully synthesised and isolated containing either four (**175**) or two (**178**) resorcinol subunits. The further cyclisation of these products, through a second condensation reaction with an equivalent of another aldehyde, to give resorcarene dimers bridged *via* two positions on the lower rim was attempted but again the formation of undesirable polymers was observed. A further investigation into this reaction showed scrambling was occurring during the second condensation reaction.
- A novel resorcarene, **185**, was synthesised with four protected aldehyde groups on its lower rim. The insolubility of this product prevented its deprotection and further reaction.
- A study into the possibility of oxidising the lower rim functional groups of two known resorcarenes was undertaken but neither resorcarene was successfully converted to the desired product.

The investigation of a number of possible routes to a dimerised resorcarenes whilst ultimately not successful did yield some interesting novel acyclic products. A completely new strategy was devised based on the use of 1,3-dimethoxybenzene in place of resorcinol in the initial macrocycle synthesis. The results obtained from this work will be detailed in the next chapter.

Chapter 3

Synthesis of Novel

Octamethylresorcarenes and their

Derivatives

3.1 Introduction

Often referred to as *C*-alkylcalix[4]arenes, octamethylresorcarenes (OMRAs) are a variation on the standard resorcarene skeleton where the hydroxyl groups of the upper rim have been replaced by methoxy groups, **Figure 3.1**.

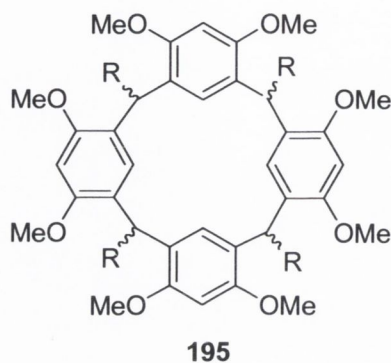
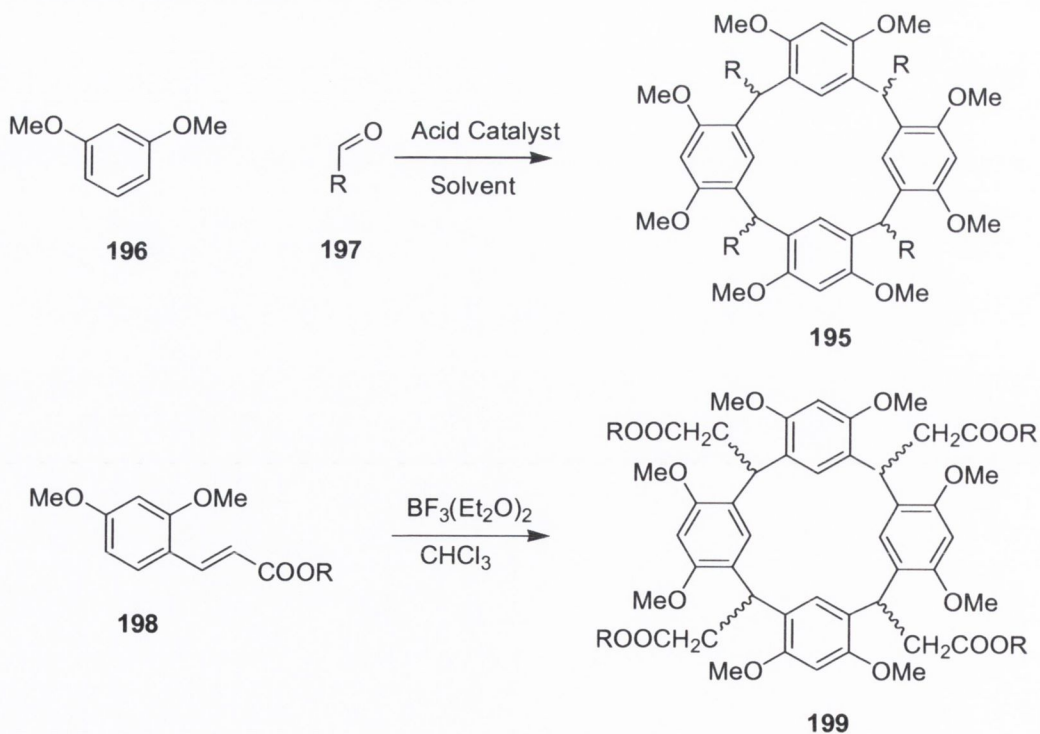


Figure 3.1: General structure of octamethylresorcarenes (OMRAs)

They are obtained predominantly by either of two routes: (i) the substitution of 1,3-dimethoxybenzene for resorcinol in the initial condensation reaction,¹⁴ or (ii) alkylation with methyl iodide subsequent to the formation of a resorcarene.¹⁶⁵ OMRAs with ester pendant groups have also been synthesised by the Lewis acid catalysed reaction of 2,4-dimethoxycinnamates (**198**), **Scheme 3.1**.¹⁶⁶



Scheme 3.1: Synthesis of OMRAs from 1,3-dimethoxybenzene or 2,4-dimethoxycinnamates

The chemistry of octamethylresorcarenes is still relatively unexplored in comparison to that of calixarenes and resorcarenes, yet what is known is quite diverse. Through the use of appropriately functionalised monomers, Botta *et al.* have successfully synthesised OMRA with ester (**200-202**)²² or cyano (**203**)¹⁶⁷ lower rim functionality, **Figure 3.2**.

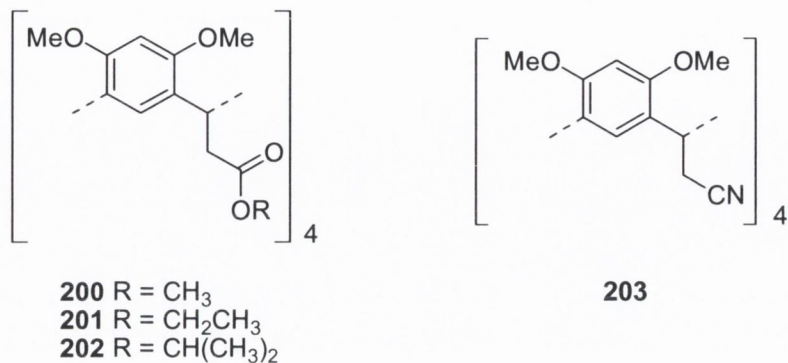
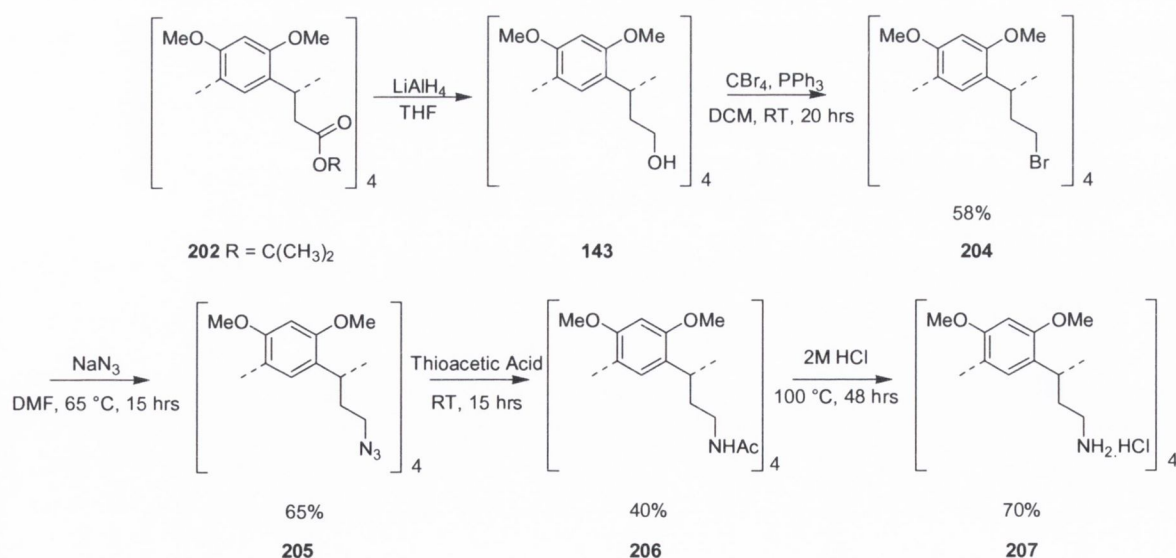


Figure 3.2: Ester and cyano derivatives of OMRA

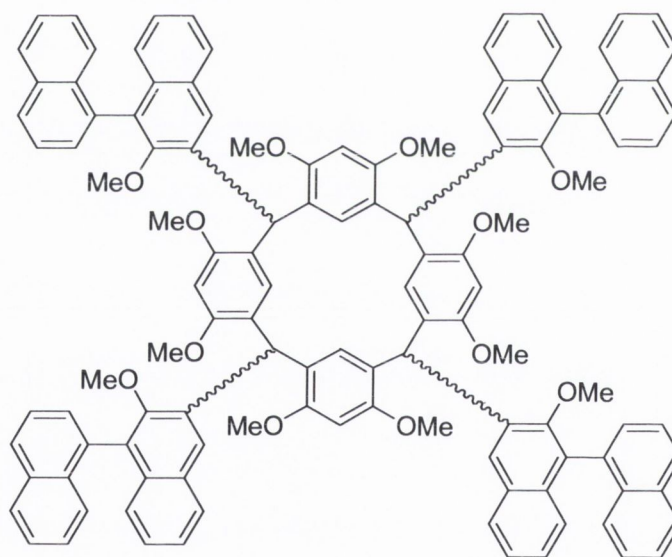
The ester derivatives can, by functional group interconversion, open the lower rim up to many further possibilities. Reduction of the ester derivative using LiAlH₄ in THF leads to the hydroxyl terminated OMRA (**143**), **Scheme 3.2**.²² This compound can be further reacted with CBr₄ and PPh₃ to give the lower-rim bromomethyl derivative (**204**).¹⁶⁸ Treatment of this tetrabromide with an excess of NaN₃ in DMF yields the corresponding tetraazide derivative (**205**) which can then, by stirring with a large excess of thioacetic acid, lead to an aminoacetyl derivative (**206**).¹⁶⁷ The HCl salt of the amine derivative (**207**) was isolated after heating compound **206** in 2M HCl at 100 °C for 48 hrs.¹⁶⁷



Scheme 3.2: Synthesis of OMRA derivatives with various functional groups on the lower rim of OMRA

A study of the binding affinity for Fe(III) and Ga(III) of the tetraester (**202**) and the tetrabromo (**204**) derivatives showed that when there were carbonyl groups present at the lower rim of these systems, there were two active binding sites, one at the upper rim and one at the lower rim.¹⁶⁸ When no carbonyl groups were present at the lower rim, only binding at the upper rim was observed. The cone cyano (**203**) and amino terminated OMRA's both displayed binding ability towards Cu(II). However, a full understanding of this interaction was hampered by the insolubility of the host molecules in a range of solvents.¹⁶⁷

Chiral OMRA's have also been successfully synthesised in a one-step process by the cyclisation of chiral 2,4-dimethoxycinnamamides¹³⁴ and the interaction of these compounds with chiral amino acids has been investigated.^{167,169} Pietraszkiewicz *et al.* have carried out preliminary investigations on the use of simple OMRA's as chromatographic bed modifiers¹⁷⁰ and non-linear optic materials.¹⁷¹ The use of a 1,1'-binaphthyl substituted OMRA (**208**) in sugar sensing has also been reported.¹⁷²



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Like standard resorcarenes, octamethylresorcarenes can form various conformational isomers. The most common conformers are the cone, boat (flattened cone) and diamond, although chair and saddle conformers have also been observed (see **Figure 1.2**).^{166,173,167} As mentioned in **Chapter 1** the saddle conformer has never been isolated when resorcinol was used in the initial condensation reaction and to date no crystal structure for this conformation has been reported for the saddle obtained when 1,3-dimethoxybenzene is

used. It has previously been reported that the reaction conditions can be employed to control the formation of the conformer or relative ratios. Iwanek *et al.* screened a range of Lewis acids as catalysts for such reactions and found that using SnCl_4 , in either CHCl_3 or Et_2O , to catalyse the reaction between 1,3-dimethoxybenzene and isovaleraldehyde led solely to the formation of the cone conformer, when the reaction was carried out in CHCl_3 .¹⁴ This held true for a number of straight chain aldehydes. However, for branched chain aldehydes to yield similar results, a change of solvent to ether was necessary.¹⁴ A detailed study on the effects of Lewis acid equivalents, reaction time and temperature was carried out by Botta *et al.* on the cyclisation of 2,4-dimethoxycinnamates.²² A study of the relative ratios of the different isomers formed under varying conditions showed that increasing equivalents of Lewis acid, longer reaction lengths and higher reaction temperatures, all favoured the formation of the flattened-cone conformer at the expense of the diamond. This led to the conclusion that, in the case of these OMRAs, the diamond was the kinetically favoured product while the flattened cone was the thermodynamically favoured product.²² To understand the experimental data further, molecular modelling studies were then carried out. Firstly, due to the complexity of the molecules, OMRAs unsubstituted at the bridging position were examined. These initial studies indicated that the flattened cone, as expected, was the lowest energy structure, while surprisingly, the diamond conformer had the highest steric energy. However, when adjustments were made for the ester side chains, the diamond was shown to have lower energy and was in fact, quite similar in energy to the flattened cone.²² In addition to type of acid, the equivalents used, temperature, reaction time and solvent, it has also been reported that the length and steric hindrance of the side chains play an important role in the stereoselectivity of the reaction.¹³⁴

3.2 Aims for this Chapter

One of the advantages of OMRAs, is that they are in principle, resorcarenes where the hydroxyl groups on the upper rim are “protected” by alkyl groups. This makes the upper rim relatively inert to further reaction and opens up the opportunity to functionalise the lower rim using a variety of reactions. In this project we hope to take advantage of this, by synthesising an octamethylresorcarene with hydroxyl groups on the lower rim. Hence our target would be **209**, shown in **Figure 3.1**. Resorcarenes with lower-rim hydroxyl groups are known and were obtained by the reaction of resorcinol with 2,3-dihydrofuran¹⁵⁴ or

hydroxybenzaldehyde.¹⁵ It should be possible to form others, through the use of aldehydes that have hydroxyl groups as part of their structure in the initial condensation reaction. To-date, the synthesis of these hydroxyl footed compounds has been mainly been focused towards increasing the water solubility. This is because, in standard resorcarenes, the presence of hydroxyl groups means selective functionalisation of hydroxyl groups on the lower rim would be difficult. The use of 1,3-dimethoxybenzene, in place of resorcinol, in the condensation reaction effectively leads to the selective protection of the upper rim hydroxyl groups and opens up the lower rim to further reaction. These upper rim protecting groups can later be removed using BBr_3 .¹⁷⁴

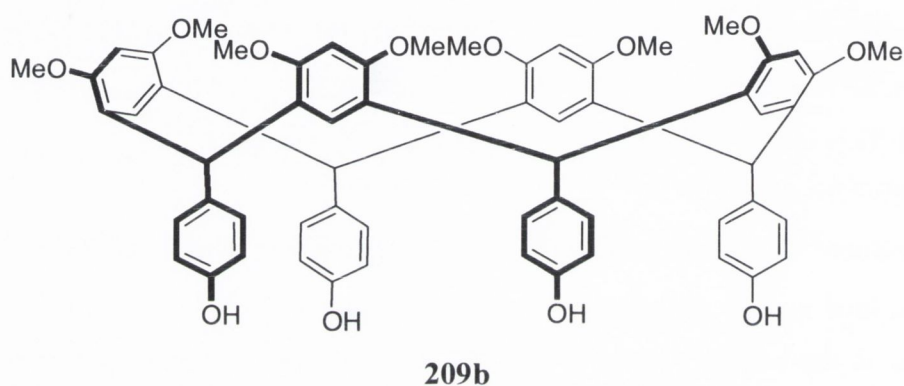


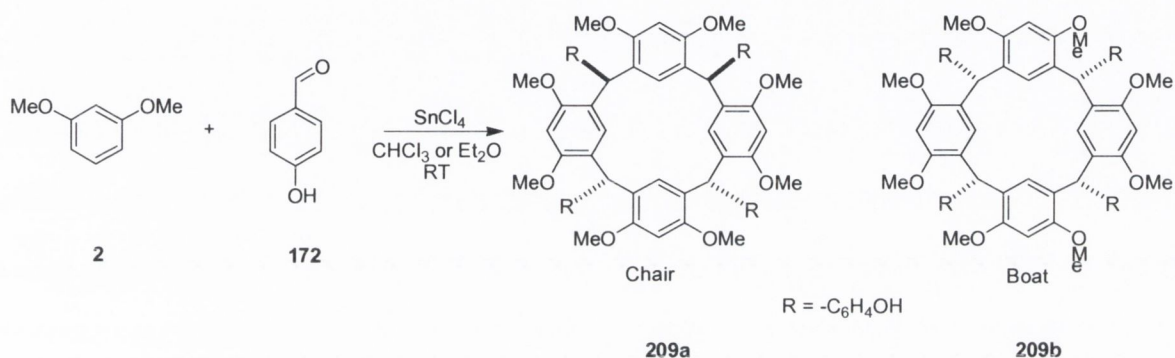
Figure 3.1: Target molecule, the boat isomer of 209

This chapter continues the work described in **Chapter 2** in the search for a synthetic route to constrained resorcarene based hosts that are rigidified *via* dimerisation, at the lower rim. The initial focus was on the synthesis of a phenol terminated OMRA, which, as previously stated, would allow for the selective functionalisation of the lower rim. With the boat conformer **209b** in hand from this reaction, preliminary results from the further alkylation of these systems is reported.

Unexpected results from this investigation led to the scope of this work being extended to include an extensive study of the condensation reactions of alkylated resorcinols with various aldehydes.

3.3 Condensation of 1,3-Dimethoxybenzene and 4-Hydroxybenzaldehyde using Lewis Acids

As mentioned in **Section 3.1**, Iwanek found that the use of SnCl_4 as a catalyst in the condensation reactions between 1,3-dimethoxybenzene (**196**) with various aldehydes, led to the formation of the boat isomer on all occasions. For this reason, this was the first method employed in the reaction between 1,3-dimethoxybenzene (**196**) and 4-hydroxybenzaldehyde (**172**), **Scheme 3.3**.



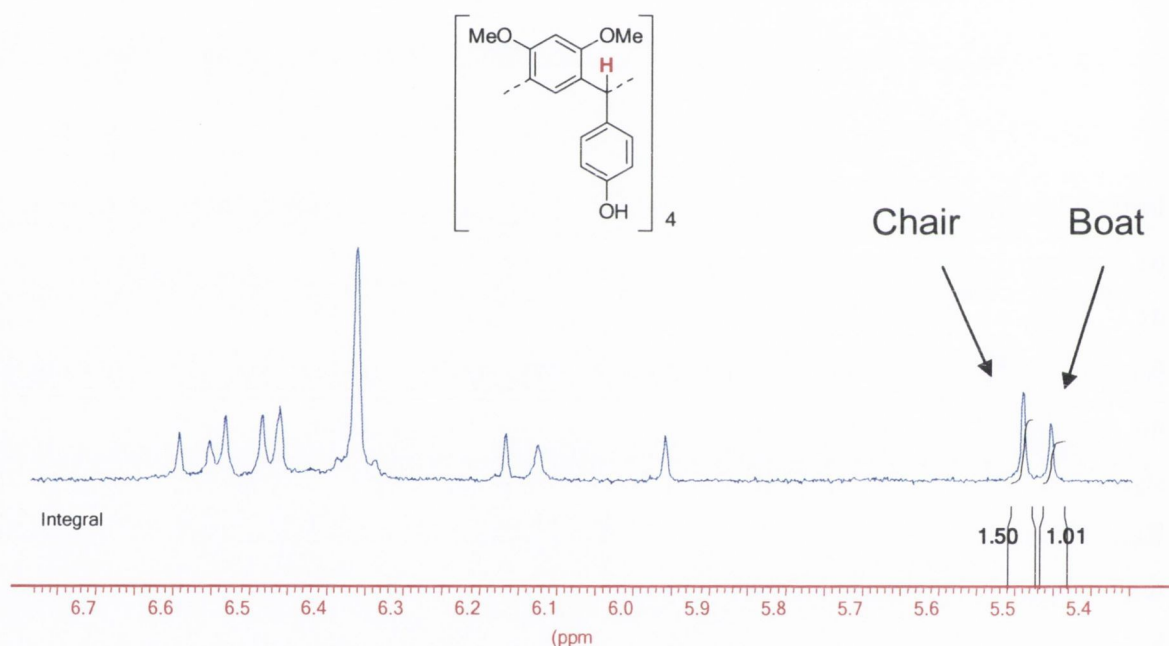
Scheme 3.3: Synthesis of the octamethylresorcarenes **209a** and **209b**

Initially the reactions were carried out in CHCl_3 . It was found to give **209** but as a mixture of the chair (**209a**) and the boat (**209b**) conformers (**Scheme 3.3**). Following the methods of Iwanek, who found that the use of Et_2O gave rise to the cone conformer of OMRAs (derived from more complicated aldehydes)¹⁴ the solvent was switched to Et_2O . Although no real change was observed in the overall yield of the reaction, this change did have a significant effect on the product distribution; favouring the isolation of the boat product. Reaction times were also shown to have some effect on the relative ratios of these isomers, with longer reaction times yielding the boat isomer in higher yield. This was accompanied by an increase in the overall yield of the reaction. However, the boat isomer was on no occasion isolated as the sole conformer. These findings are summarised in **Table 3.1**.

Table 3.1: The effect of changing the reaction time and solvent in the formation of 209, SnCl₄ was used as a catalyst at RT.

Run	Solvent	Reaction Length (hrs)	209a	209b	Total % Yield
1	CHCl ₃	16	72%	28%	61%
2	CHCl ₃	72	63%	37%	69%
3	Et ₂ O	16	60%	40%	70%
4	Et ₂ O	72	25%	75%	76%
5	Et ₂ O	334	25%	75%	75%

A partial ¹H NMR (400 MHz, DMSO-*d*₆) obtained from Run 3, is shown below (**Figure 3.2**). The % ratio of conformers present was determined using the signal for the bridging proton (highlighted in red).

**Figure 3.2:** Partial ¹H NMR (400 MHz, DMSO-*d*₆) of the mixture of the chair and the boat conformers of 209.

3.4 Condensation Reaction of 1,3-Dimethoxybenzene and 4-Hydroxybenzaldehyde with Protic Acids

In the past, the use of protic acids has been shown to give different relative ratios of conformers, in comparison to the use of Lewis acids in reactions with resorcinol.³² It has

recently been reported that, even at room temperature, in the synthesis of the parent OMRA, the use of acetic acid as a solvent, combined with a protic acid catalyst, yield exclusively the boat isomer.¹⁷⁵ Because of this, an extensive study was undertaken on the use of protic acids to catalyse the reaction of 1,3-dimethoxybenzene and 4-hydroxybenzaldehyde. The effect of changing the reaction temperature from room temperature to 80 °C was also investigated. The reaction was also run without the acid catalyst to see if the acetic acid used as solvent, which is itself a protic acid, played a synthetic role in the reaction. Additionally, the reactions were also studied using a protic acid in EtOH, to see if the change of the solvent had any effect. The results from these reactions are summarised in **Tables 3.2** and **3.3**.

Table 3.2: Results from the reaction of 1,3-dimethoxybenzene with 4-hydroxybenzaldehyde in acetic acid to give 209a and 209b. In each reaction acetic acid was used as a solvent.

Run	Acid	Temperature	209a	209b	% Yield
1	None	RT	0%	0%	0%
2	HCl	80 °C	100%	0%	54%
3	H ₂ SO ₄	80 °C	100%	0%	50%
4	HNO ₃	80 °C	0%	0%	0%
5	TFA	80 °C	0%	0%	0%
6	HCl	RT	66.6%	33.3%	55%
7	H ₂ SO ₄	RT	33%	67%	50%
8	HNO ₃	RT	0%	0%	0%
9	TFA	RT	0%	0%	0%

Interestingly, only two of the protic acids, HCl and H₂SO₄, successfully catalysed the reaction in acetic acid. However, when the condensation reaction was catalysed by either nitric acid or TFA, or acetic acid was used alone, only the starting materials were isolated. Whilst room temperature reactions again yielded a mixture of conformers, interestingly, on increasing the reaction temperature to 80 °C, the reaction was successfully driven to yield only one isomer. On changing the solvent used to ethanol, again the reaction proceeded to yield a mixture of conformers at both room temperature and 80 °C, biased in favour of the chair. It is interesting that in this more amenable solvent, changes to the reaction length did not significantly alter the conformer ratio observed and on reducing the temperature to

slow the reaction, and thus potentially allow isolation of the kinetic product, condensation was halted.

Table 3.3: Summary of results from the reaction of 1,3-dimethoxybenzene and 4-hydroxybenzaldehyde in EtOH with HCl as an acid catalyst.

Temperature	Reaction Length	209a	209b	Overall Yield
-20 °C	16 hrs	-	-	0%
0 °C	16 hrs	-	-	0%
75 °C	5 hrs	75%	25%	70%
75 °C	16 hrs	79%	21%	68%
75 °C	72 hrs	79%	21%	73%

In almost all cases, the chair conformer (**209a**), which can be seen from the ^1H NMR (400 MHz, $\text{DMSO}-d_6$), was isolated as the major product (**Figure 3.3**). The chair conformer would be expected to be less symmetrical than the cone conformer and four resonances for the protons on the aromatic ring, two for the OMe groups and only a single set for the bridging proton and the pendant groups would be expected.¹⁶⁷

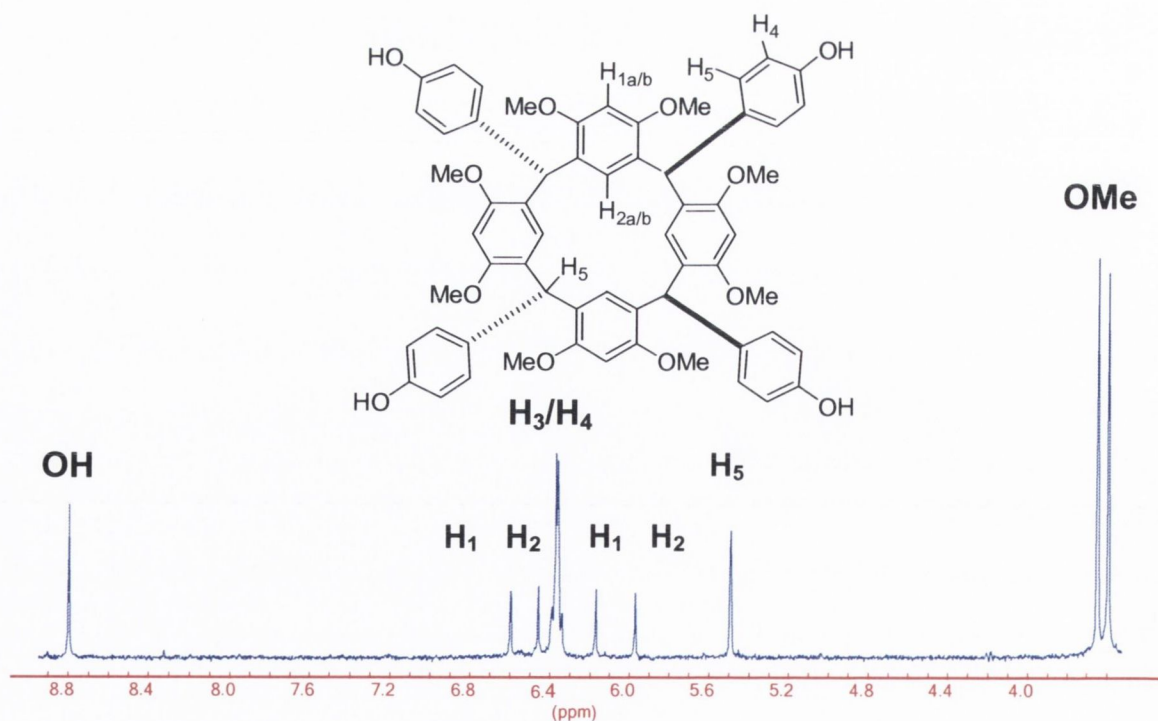


Figure 3.3: ^1H NMR (400 MHz, $\text{DMSO}-d_6$) spectrum of 209a

Indeed, these are the resonances observed in **Figure 3.3**. To rule out the possibility that this spectrum might indicate the flattened cone conformation, which would show the same number of resonances as a chair conformer, the ^1H NMR spectrum was recorded at various temperatures. At higher temperatures, the barrier for the interconversion of the flattened boat conformers (see **Figure 1.20**) is overcome and the symmetry is increased, usually this is evidenced by a convergence of the signals for the protons of the resorcinol subunit, from four peaks to two peaks. However, at all temperatures only the four distinct signals were observed, ruling out the possibility of this being the flattened boat conformer. A number of n.O.e experiments were carried out on the acylated derivative of this compound (*vide infra* **223a**) which enabled the assignment of the upper and lower rim protons H_1 and H_2 .

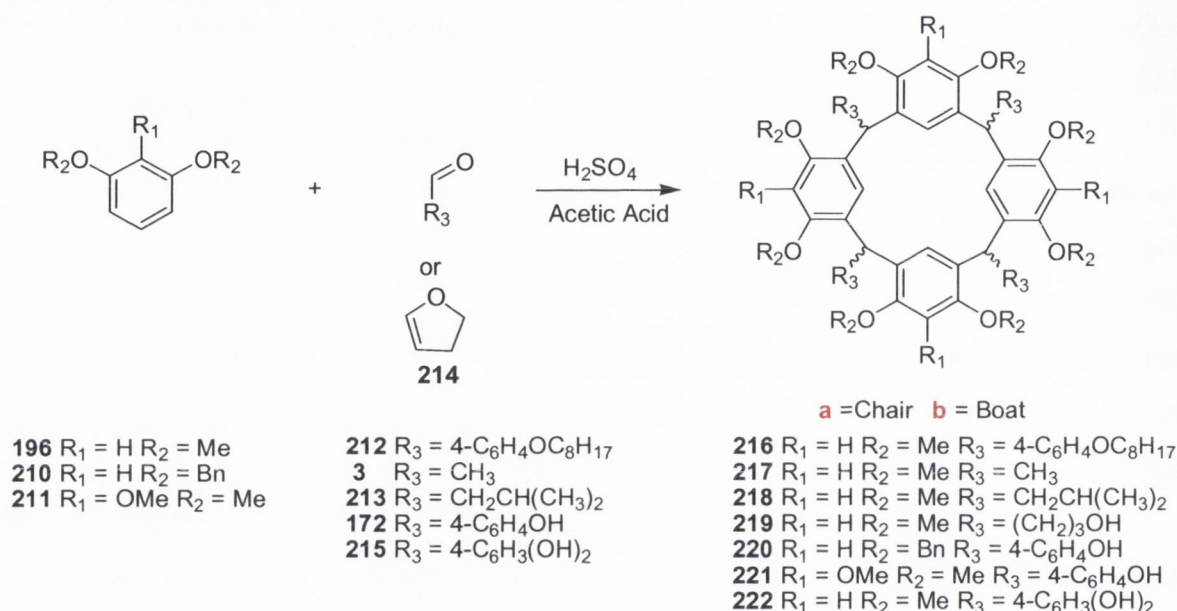
As discussed in **Chapter 1**, in homogeneous resorcarenene formation reactions, the use of higher reaction temperatures generally leads solely to the formation of the boat isomer,¹⁵ however, where the reaction is heterogeneous, longer reaction time and higher reaction temperatures usually drive the reaction towards the formation of the least soluble isomer.²⁸ A quick comparison of the solubility of the boat (**209b**) and the chair (**209a**) conformers in CH_3CN or MeOH showed the chair to be the less soluble of the two.

The ability to drive the condensation reaction to the formation of the *rcct* chair isomer is nonetheless somewhat unique, and therefore worthy of further investigation. This reaction will be discussed in the next section.

To summarise, the condensation reaction of 1,3-dimethoxybenzene and 4-hydroxybenzaldehyde was investigated using either the Lewis acid SnCl_4 or a range of protic acids. Additionally, reactions were carried out in EtOH with a HCl catalyst. The effect of changing the reaction times and the reaction temperatures was studied, with the aim of screening for their effect on the distribution of the conformers. The protic acids proved more efficient than the Lewis acid at driving the reaction to yield a single conformer. Although this is the chair rather than the boat conformer it is, nevertheless, a very interesting and important result which will now be elaborated on.

3.5 A Study of the Effect of Varying the Starting Materials on the Relative Ratios of Conformers Formed

To investigate if the above surprising findings could also be applied to other alkylated resorcinols and aldehydes, a number of further reactions were carried out. The condensation of various alkylated resorcinol derivatives and a variety of aldehydes were carried out in acetic acid using H_2SO_4 as a catalyst (**Scheme 3.4**). The reactions were carried out at room temperature and at 80 °C. The outcomes of these reactions are summarised in **Table 3.4**.



Scheme 3.4: The condensation reaction of alkylated resorcinols with various aldehydes

Initially, it was investigated whether the results obtained from the reaction of 1,3-dimethoxybenzene with 4-hydroxybenzaldehyde was the consequence of intramolecular hydrogen bonding on the lower rim. Both the boat and the chair conformations of **216** were isolated from the reaction of 1,3-dimethoxybenzene and **212**, at room temperature, while at 80 °C, the chair conformer (**216a**) was the only conformer observed. These results still showed a preference for the chair isomer, indicating that intramolecular hydrogen bonding was not the reason the chair isomer had previously been selectively obtained.

Table 3.4: Results from the effect of varying the starting materials on the relative ratios of the chair and boat isomer formed. *HCl catalysis

	R ₁	R ₂	R ₃	Temperature	Chair (a)	Boat (b)	Total % Yield
216	H	Me	<i>p</i> C ₆ H ₄ OC ₈ H ₁₇	80 °C	100%	0%	54%
	H	Me	<i>p</i> C ₆ H ₄ OC ₈ H ₁₇	RT	83%	17%	21%
217	H	Me	CH ₃	80 °C	100%	0%	70%
	H	Me	CH ₃	RT	60%	40%	91%
218	H	Me	CH ₂ CH(CH ₃) ₂	80 °C	100%	0%	31%
	H	Me	CH ₂ CH(CH ₃) ₂	RT	48%	52%	88%
219	H	Me	(CH ₂) ₃ OH*	60 °C	100%	-	61%
	H	Me	(CH ₂) ₃ OH*	RT	100%	-	17%
220	H	Bn	<i>p</i> -C ₆ H ₄ OH	80 °C	17%	83%	76%
	H	Bn	<i>p</i> -C ₆ H ₄ OH	RT	-	-	0%
221	OMe	Me	<i>p</i> -C ₆ H ₄ OH	80 °C	-	-	0%
	OMe	Me	<i>p</i> -C ₆ H ₄ OH	RT	-	-	0%
222	H	Me	C ₆ H ₃ (OH) ₂	80 °C	-	-	0%
	H	Me	C ₆ H ₃ (OH) ₂	RT	-	-	0%

The next step was to investigate if the preference for the chair isomer was the result of the use of larger substituent groups. This may lead to the formation of a conformation which places these substituents further apart. For this purpose, the use of the less bulky aldehyde, acetaldehyde (**3**) was also investigated. In the condensation of **196** and acetaldehyde (**3**) the same pattern was however upheld. A preference for the chair (**217a**) was observed, under both sets of reaction conditions. When the reaction was carried out at 80 °C, the chair was the only conformer present. This result has previously been explained, using **209**, as the logical effect of the chair conformer being the least soluble isomer. However, the reaction with acetaldehyde (**3**) at high temperatures was homogeneous and the product (**217a**) must be precipitated from the reaction mixture. This implies that the insolubility of the chair isomer **209a** is not the only reason for its formation.

To compare our protic acid catalysis method for the synthesis of OMRA, with that of the previously reported Lewis acid catalysis method, this reaction was carried out on 1,3-dimethoxybenzene and isovaleraldehyde (**213**). Iwanek had previously found that when the reaction of **196** with isovaleraldehyde was carried out in CHCl_3 with AlCl_3 as a catalyst, the diamond conformer was preferentially formed, with the chair conformer also isolated in low yield (<10%).¹⁴ In contrast to this, our method resulted in the sole formation of the chair isomer (**218a**) when the reaction was carried out at 80 °C.

The reaction of 1,3-dimethoxybenzene and 2,3-dihydrofuran was also explored with the aim of testing if this reaction would work using masked aldehydes. Again at high temperature, only the chair conformation of **219** was observed. Previously, this type of hydroxyl functionalised OMRA has been synthesised *via* a multi-step strategy, starting from the corresponding $\text{CH}_2\text{CO}_2\text{R}$ OMRA.²² In this case only the cone and diamond conformations were accessible. Yet again, our method, the H_2SO_4 / acetic acid combination, gives rise to a previously unobtainable conformer.

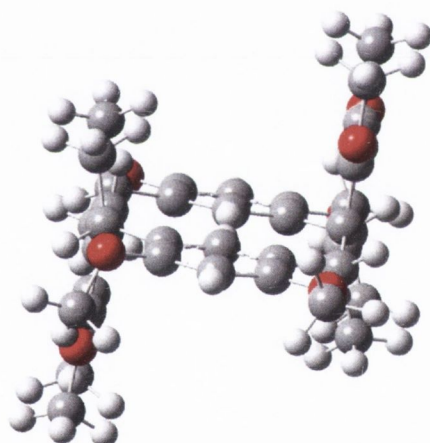
To investigate if this reaction was universally applicable to all alkylated resorcinols, a reaction was carried out between benzylated resorcinol (**210**) and 4-hydroxybenzaldehyde under these conditions. OMRA **220** was successfully synthesised in 76% yield, but only at higher temperature. In this reaction the chair was again the dominant product. One possible explanation for the failure of these materials to react at lower temperatures, or to induce full selectivity at higher temperatures, could be due to the fact that the benzylated resorcinol is more sterically demanding than 1,3-dimethoxybenzene previously used and this may influence both the rate of the reaction and the distribution of conformers obtained. Interestingly, the reaction of 1,2,3-trimethoxybenzene (**211**) and 4-hydroxybenzaldehyde (**172**) failed to yield a cyclised product. Neither was any resorcarene isolated from the reaction of the bulky aldehyde, 3,5-dihydroxybenzaldehyde (**215**) with 1,3-dimethoxybenzene (**196**). On both occasions, this is most likely due to steric factors inhibiting the reaction.

In resorcarenes, it is the hydrogen bonding between adjacent hydroxyl groups that makes the boat the thermodynamically favoured isomer,²⁶ whereas in the SnCl_4 catalysed formation of OMRA, it is the templating effect of the metal ion that favours the boat.¹⁴ In

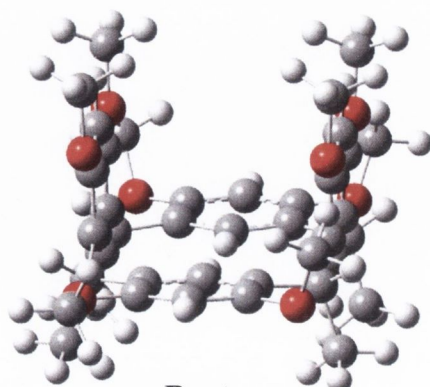
our syntheses, where both of these considerations had been removed, we believe that the chair isomer may in fact be the more thermodynamically favoured isomer, possibly due to a lesser degree of steric repulsion between the upper rim methoxy groups and the lower-rim substituents. To the best of our knowledge this is the first example of the chair conformer being the lowest energy conformation in resorcarene chemistry.

3.6 Computational Studies of Chair and Boat OMRA

To confirm the above experimental findings some computational studies were also carried out, in collaboration with Professor Graeme Watson, at the School of Chemistry, TCD, on the chair and boat conformations of **217**. Hybrid density functional theory calculations were conducted at B3LYP level with a 6-31G(d) basis set in the Gaussian 03 package.¹⁷⁶ Calculations were performed on a range of starting conformations of the two fixed configurations (*rccc* and *rectt*) of **217** which feature methyl residues at the methylene bridges. The energy minimised structures obtained from these preliminary calculations are shown in **Figure 3.5** and the results are summarised in **Table 3.5**.



Chair



Boat

Figure 3.5: Energy minimised structure of a) the chair and b) the boat conformations of 217 obtained from computational studies

Table 3.5: Summary of the results obtained from computational studies of 217a and b

Level of Theory	Chair – Boat (kJ/mol)
AM1	-7.5
B3LYP / 6-31G(d)	-10.9

The calculations predict an energy difference of 10.9 kJmol^{-1} , in favour of the chair conformation, which is in line with the experimental results obtained. Inspection of the optimised conformer for **217b** showed that the OMRA exists in a flattened boat arrangement, with the methyl groups orientated above the plane, such that the methyl hydrogen atoms interact with the methoxy oxygen on the adjacent ring. For **217a** a normal chair conformation is obtained, once again, with the methyl groups on the co-planar rings orientated to maximize their interaction with adjacent methoxy groups.

To ensure validation of the results obtained for **217a** and **217b** calculations were also performed on the known analogous resorcarenes **8a** and **8b**. These resorcarenes are identical to **217a** and **b** aside from the replacement of the methoxy groups with hydroxyl groups. This resorcarene has been shown experimentally to preferentially exist in the *rccc* boat stereoisomer (**8b**). The results of this study are shown in **Table 3.4** and the optimised structures are shown in **Figure 3.5**.

Table 3.5: Results obtained from computational studies of 8a and b

Level of Theory	Chair – Boat (kJ/mol)
B3LYP / 6-31G(d)	+ 22.4

As expected the lower energy configuration is the *rccc* boat conformation **8b**. This conformation achieves maximum hydrogen bonding ($1.92 \text{ \AA}$ between hydroxyl groups on adjacent resorcinol subunits) with the angle between opposite aromatic units of 77° . In contrast to this, the higher energy *rcct* chair conformation **8a** has minimal hydrogen bonding ($3.25 \text{ \AA}$).

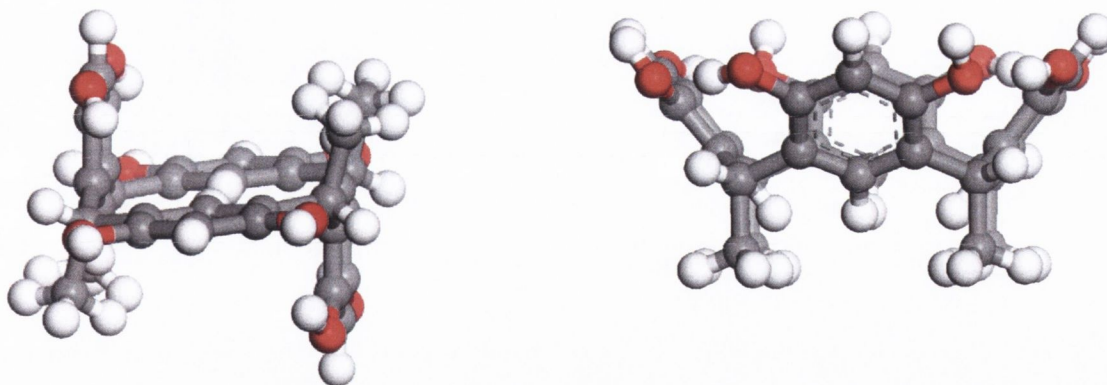


Figure 3.5: Energy minimised structure of the a) the chair and b) the boat conformations of resorcarene 8 obtained from computational studies

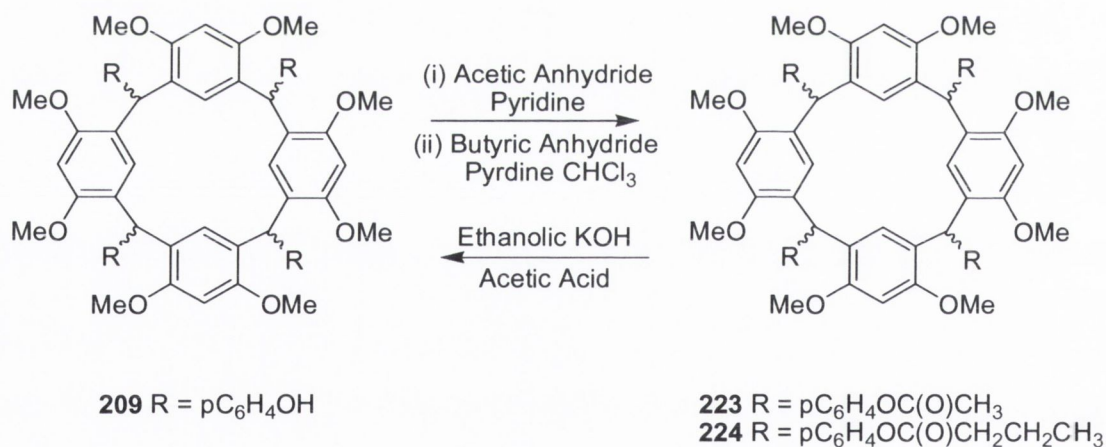
These findings provide confirmation for what we have observed experimentally, that is that the chair is the most favourable conformer for the OMRA macrocycles.

Hence, the experimental and computational results both provide strong support that the chair conformer is the most thermodynamically favourable of the two conformations studied. Furthermore, the method developed *i.e.* acetic acid and H_2SO_4 at 80 °C, provides, in many cases, access to a previously unobtainable conformer.

3.7 Purification of OMRA 209

Despite the interesting results obtained in the previous section, for synthetic reasons, the boat isomer is still a very important product. It is therefore, essential to be able to separate this conformer from the mixture obtained when the reaction is conducted at room temperature. This separation was far more problematic than was initially anticipated. Some success was achieved by capitalizing on the differing solubilities of the two isomers in MeOH. As previously stated, the chair (**209a**) conformer is the more insoluble isomer of the two and was isolated in its pure form by hot filtration after the mixture of the two isomers had been heated at reflux in MeOH. The filtrate was concentrated at reduced pressure and the residue was triturated with Et_2O to give a purple powder, which was isolated by filtration to yield the desired boat isomer (**209b**). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) however, showed that there was still almost 10% of residual chair isomer present in this isolated product.

Often in the separation of resorcarene isomers, acylation of the products using acetic anhydride leads to an increase in their solubility, allowing purification by column chromatography. Although, in **209** the upper rim hydroxyl groups have been replaced with methoxy moieties, there are still four lower rim hydroxyl groups that could be protected in this way. Because of this, the modification was carried out, and **223** was successfully isolated after heating at 110 °C for 16 hrs in acetic anhydride with a catalytic amount of pyridine. A small amount of the boat isomer (**209b**) was eventually separated from the above mixture by column chromatography (silica, hexane: ethyl acetate, 4:6 v/v) and subsequent deacylation by heating at reflux for 3 hrs in ethanolic KOH solution (Scheme 3.5). Although some pure boat isomer was obtained by this method, purification in this manner was ultimately not very successful. The insolubility of the mixture, even when acylated, led to the crude product being loaded onto the column in a very wide band, which in turn led to poor separation and very low yields. As **209b** was the sole target isomer of this synthesis, it was necessary to devise a simpler purification procedure that would lead to its isolation in the amounts needed for further reaction. Consequently, other strategies were explored.

Scheme 3.5: Acylation of **209** and deacylation of **223** and **224**

A reliable method was finally developed by acylation of the mixture with butyric anhydride. The longer alkyl chain in the compound had the desired effect on the solubility and the two isomers were successfully separated by column chromatography (DCM: ethyl acetate, 93:7 v/v). Moreover, the boat isomer compound (**224b**) successfully underwent deacylation as described previously (Scheme 3.5).

The ^1H NMR (400 MHz, $\text{DMSO-}d_6$) spectrum of the boat conformer (**209b**) is shown in **Figure 3.6**, and clearly demonstrates the presence of the four-fold axis of symmetry in the molecule, where a single peak was observed for each of the protons of the resorcinol subunit (H_1 and H_2) and that there is only a single resonance for the methoxy protons. This is characteristic of the boat conformer.

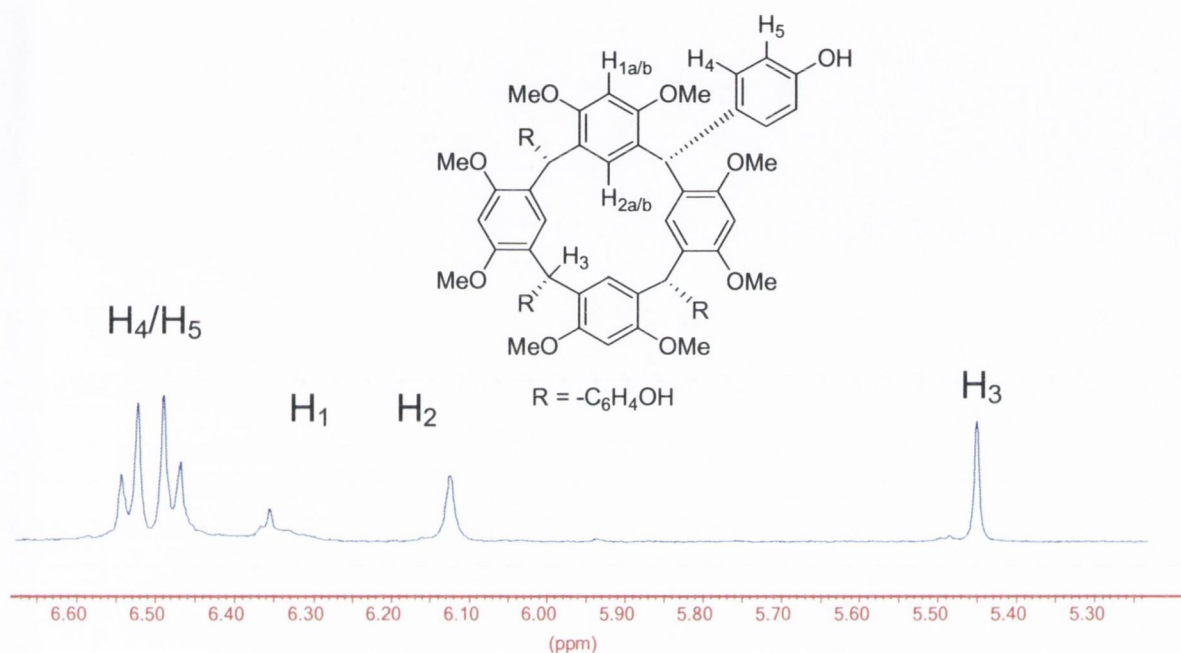


Figure 3.6: Partial ^1H NMR (400 MHz, $\text{DMSO-}d_6$) spectrum of **209b**

The ^1H NMR spectra (400 MHz, CDCl_3) of both the boat and chair conformers of **224** are illustrated below in **Figures 3.7** and **3.8** respectively. In fact, the two conformers could not initially be told apart until the butyric groups were again removed, as both displayed C_2 symmetry. Deprotection of **224b** gave **209b**, indicating that the decrease in symmetry in **224b** was most likely due to the cone conformer adopting a more flattened boat conformation. This is believed to be an effect of the increased steric strain on the molecule. This can be seen in the ^1H NMR (400 MHz, CDCl_3) spectrum, **Figure 3.7**. This modification resulted in a decrease in the symmetry of the molecule, which gave rise to a doubling in the signals observed for the H_1 and H_2 protons, as well as for the methoxy groups.

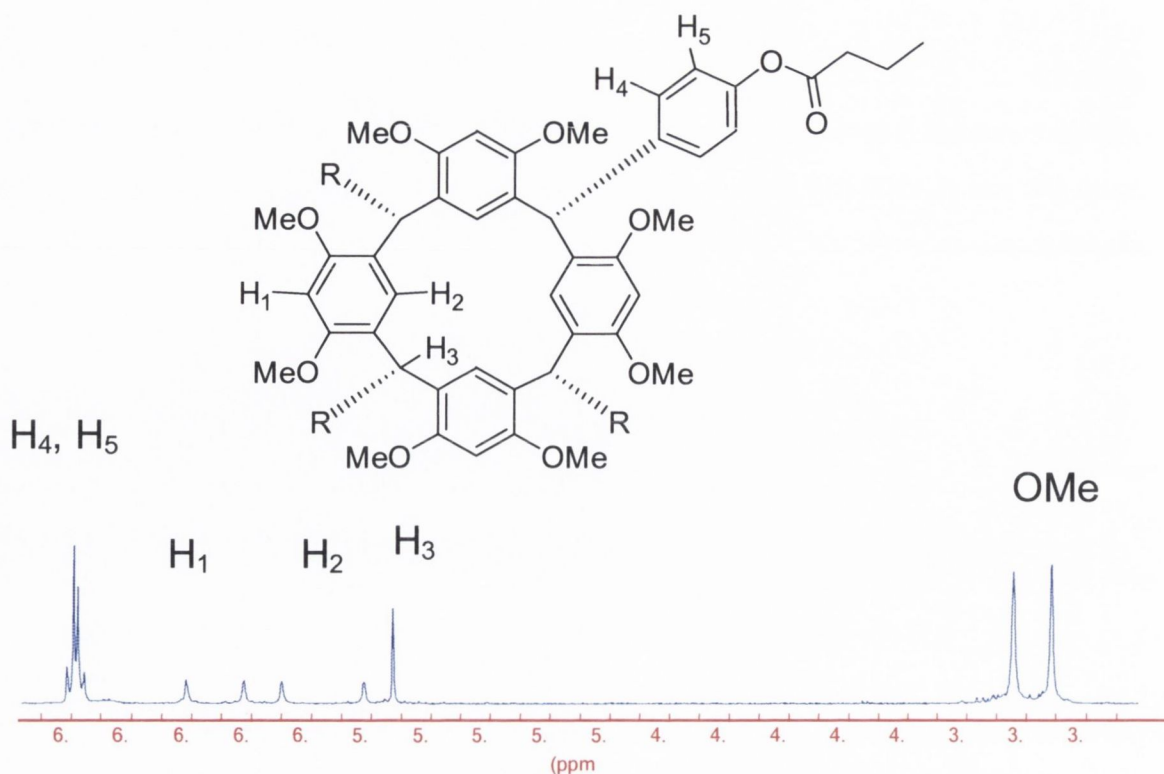


Figure 3.7: Partial ¹H NMR (400 MHz, CDCl₃) of 224b (Boat conformer)

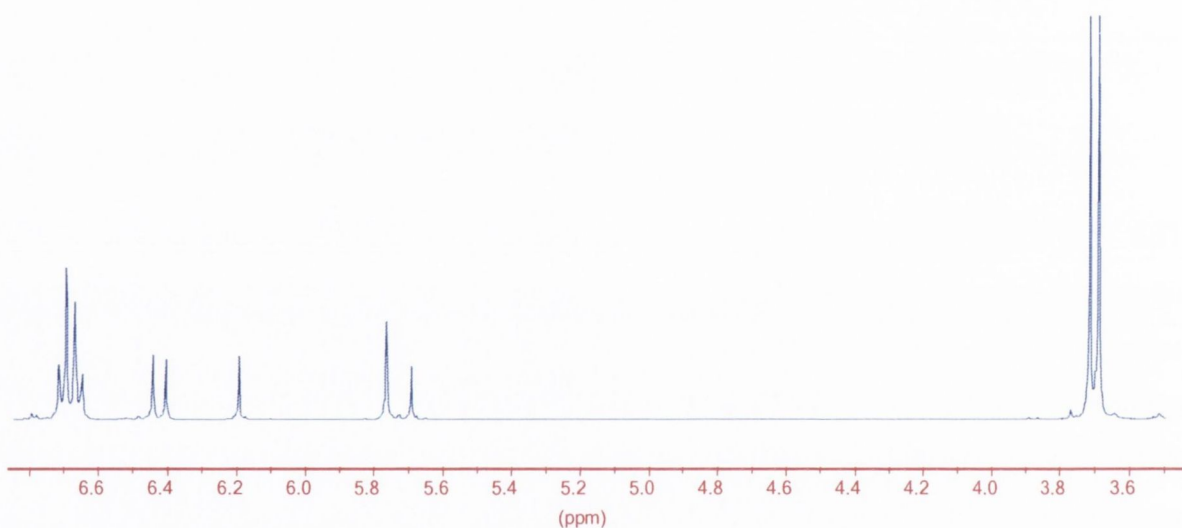
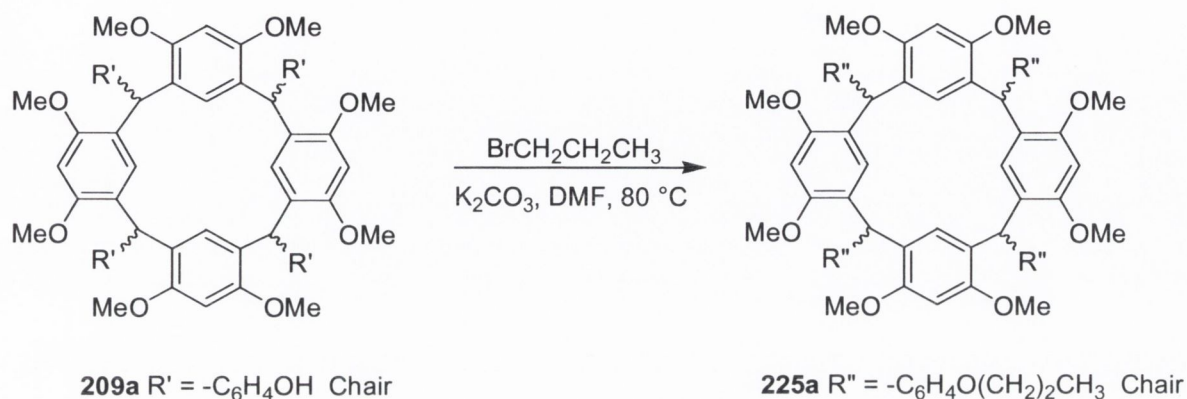


Figure 3.8: Partial ¹H NMR (400 MHz, CDCl₃) of 224a (Chair conformer)

Having developed a successful means of synthesising and isolating both the chair and the boat conformers of **209**, the next step was to find a reliable synthetic method for their post condensation functionalisation.

3.8 Reaction of OMRA 209a with Bromomethyl Compounds

The isolation of these conformers should allow for further modification. The synthesis of novel OMRA's through alkylation of the lower rim hydroxyl groups was the first reaction explored. Preliminary work towards this goal is reported in this section.



Scheme 3.6: Alkylation of 209a with bromopropane

The first attempted post-condensation alkylation reactions on OMRA **209a** were carried out to investigate the feasibility of the reaction. Initially the chair conformer was used, as it was readily available in high purity and in large quantities. The first alkylating agent, bromopropane, was chosen for its simplicity and also because of its low boiling point (71 °C) as these would aid analysis of the NMR data and facilitate the purification of the desired product. Two similar methods were explored, both involving the reaction of **209a** with a large excess (16 equiv.) of bromopropane and base, in DMF at 65 °C for 16 hrs (Scheme 3.6). Both K_2CO_3 and Cs_2CO_3 were used as bases and both reactions led to the isolation of yellow powders that were proven by ^1H NMR (400 MHz, CDCl_3) to be the desired product (**225a**), Figure 3.9. The crude yield from the K_2CO_3 reaction (71%) was significantly higher than that achieved using Cs_2CO_3 (51%), however, the crude product from the K_2CO_3 reaction still had some unreacted **209a** present.

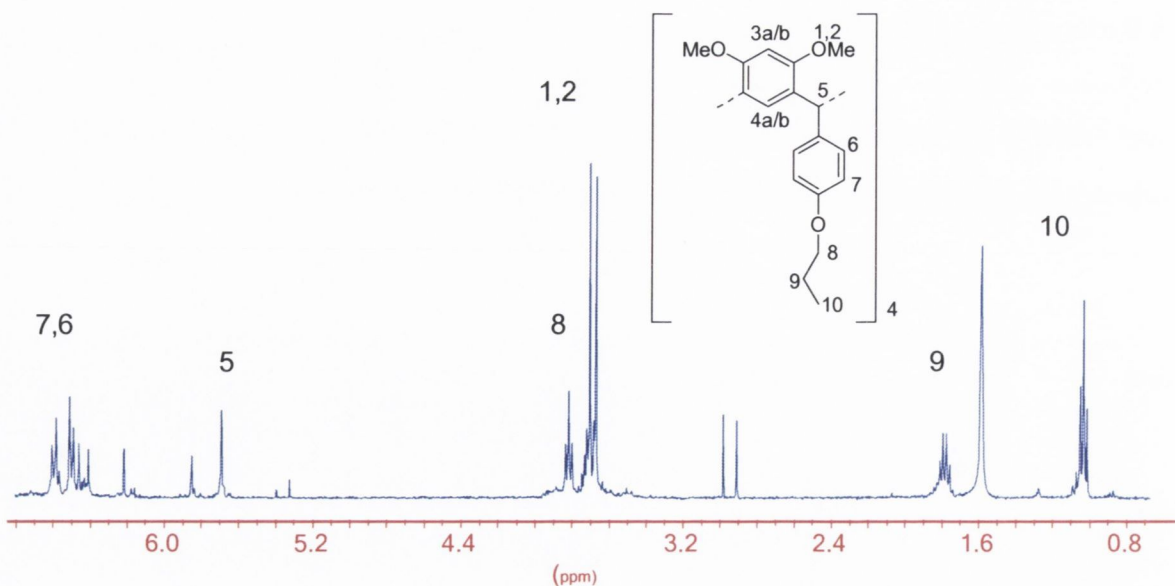
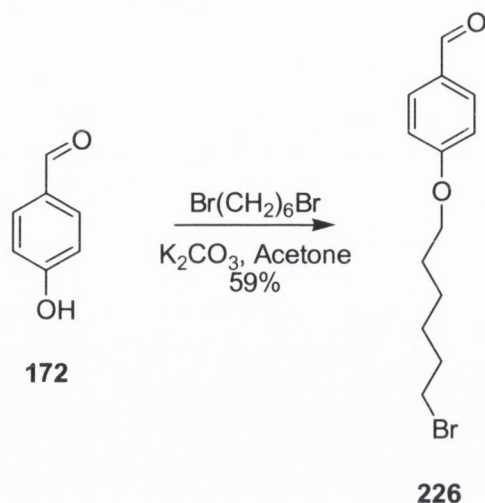


Figure 3.9: ^1H NMR (400 MHz, CDCl_3) of compound **225a** from Cs_2CO_3 reaction (chair conformer)

The conclusions from these results are that compound **209** can be successfully alkylated. However, it should be noted that, in the chair conformation, the substituent groups are in a less sterically demanding arrangement than in the boat conformation and therefore should be more amenable to functionalisation.

3.9 Synthesis of an OMRA with Four Lower Rim Aldehyde Groups

The incorporation of an aldehyde moiety on the lower rim of an OMRA through alkylation, would, in effect, lead to one of the target products mentioned in **Chapter Two**, that of a resorcarene with four lower-rim aldehyde groups (**183**). To this end, 4-(6-bromohexyloxy)-benzaldehyde (**226**) was synthesised by the alkylation of 4-hydroxybenzaldehyde with a large excess of 1,6-dibromohexane. The inclusion of a hexyl chain in this molecule would hopefully aid the solubility of the end product. The reaction was carried out by heating the reagents at reflux in acetone for 16 hrs using K_2CO_3 as a base. The product was isolated by column chromatography (silica, hexane: ethyl acetate, 8:2 v/v) as a crystalline solid in 59% yield.



Scheme 3.7: Synthesis of 2-(6-Bromo-hexyloxy)-benzaldehyde (226)

An excess of **226** was then reacted with a mixture of chair and boat conformers of **209** following standard alkylation conditions (K_2CO_3 , DMF, 16 hrs, 80°C). In this instance, the purification procedure was not deemed necessary as the alkylation would make the isomers more soluble and so allow column chromatography without the necessity for protection and deprotection steps. The crude ^1H NMR showed the alkylation had been successful with multiple peaks being observed in the aldehyde region. The presence of new peaks in the bridging proton region also indicated the presence of new product. Unfortunately, to date, the desired product has not yet been successfully isolated from this mixture and this work is still in progress.

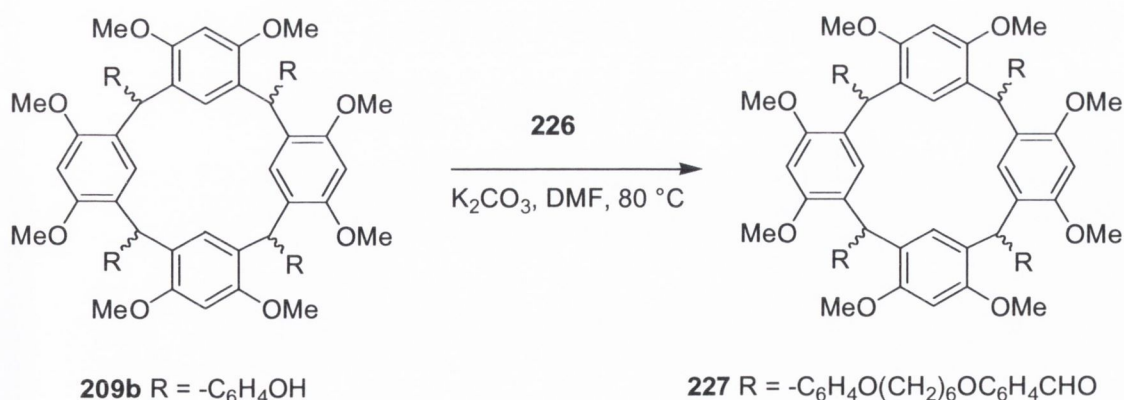


Figure 3.8: Synthesis of 227, an OMRA with four aldehyde groups on the lower rim

3.10 Conclusions

In this chapter a number of novel OMRA molecules that have been synthesised through either condensation or through post-condensation reactions are reported. The findings from these reactions are summarised below.

- A study of the conditions required to optimise the yield of the desired boat conformation of **209** was undertaken. The chair is the sole isomer formed when the reaction is carried out in acetic acid with H_2SO_4 or HCl at high temperatures.
- A study was undertaken to establish if these findings extend to other alkylated resorcinols and aldehydes. The results show that the previous findings have widespread application and a method for the selective synthesis of the chair isomer in OMRA chemistry is established.
- A computational study on the relative energies of the chair and boat conformers of octamethylresorcarenes showed the chair to be the more thermodynamically favourable conformation of the two.
- The alkylation of **209a** with bromopropane was successfully carried out and preliminary results from the alkylation of **209** with **226** look promising.

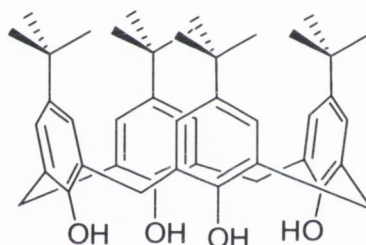
Chapter 4

Towards Calixarene-Resorcarene

Heterodimers

4.1 Introduction

Today the name calixarenes is often applied to any type of macrocycle which has aromatic or heterocyclic subunits joined *via* their 1 or 3 position, but originally it was coined to describe the products obtained from the condensation of *para*-substituted phenols with formaldehyde and the subsequent derivatives of these products. The name itself, originally introduced by Gutsche, derives from the Greek word for *chalice*, denoting the “bowl-like cavity” they are capable of forming and arene, denoting their aromatic nature.¹⁷⁷ Calix[4]arenes are of a similar structure and size to resorcarenes. They too are large macrocycles made up of four aromatic ring subunits joined together by methylene bridges. With these similarities in mind they seem a likely choice for the formation of a heterodimer. ^tBu-calix[4]arene (**228**) is synthesised on a large scale from the base catalysed condensation of ^tBu-phenol and formaldehyde, followed by refluxing in diphenyl ether, and is usually obtained in *ca.* 65% yield.¹⁷⁸ The alkyl groups can subsequently be removed, using AlCl₃ catalysed alkyl group transfer,¹⁷⁹ to provide a site for functionalisation on the upper rim.



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Calixarene chemistry is a very active area of research; in 2006 it resulted in over six hundred papers and a number of reviews and books have been written on the subject.¹⁸⁰⁻¹⁸⁴

It is far too wide a field to be summarised within this work. The areas most relevant to the synthesis described in this chapter are the use of calixarenes to form calix tubes, in heterodimers and in combination with resorcarenes and only these are discussed herein.

4.1.1 Calixarene Dimers

This work can be separated into two main areas, *head-to-head dimers*, where the dimerisation is carried out *via* reaction at the upper rim of the calixarene and *tail-to-tail dimers*, where the calixarenes are dimerised *via* groups on the lower rim.

4.1.1.1 Head-to-Head Calixarene Dimers

The synthesis of calix[4]arene dimers, also known as calix tubes, has been very successful. The first calixarene dimers were derived from calixarenes in the 1,3-alternate conformation (referred to as a saddle in resorcarene chemistry – **Figure 1.3**). Shinkai and Ikeda reported the dimerisation and trimerisation of calix[4]arenes which had first been immobilised in the 1,3-alternate conformation through the alkylation of their phenol groups with propyl chains.¹⁸⁵ The desired conformation is ensured by using Cs_2CO_3 as the base in the alkylation step.¹⁸⁶ Functional groups such as phenol and chloromethyl were introduced on the *para* positions of the calixarenes to allow the generation of multi-calixarenes using aromatic linkers. Gutsche and co-workers reported the synthesis of 1,3-alternate calix[4]arene dimers linked by two diyne bridges.¹⁸⁷ The first crystal structure of a 1,3-alternate calixarene dimer was reported in 1996² and showed the dimer had a tubular like structure with an inner diameter ranging from 3.3 to 4.5 Å, the crystal structure of this molecule (**229**) is shown in **Figure 4.1**. An “end on” view of this molecule has also been included in this figure to show the cavity within the dimer.

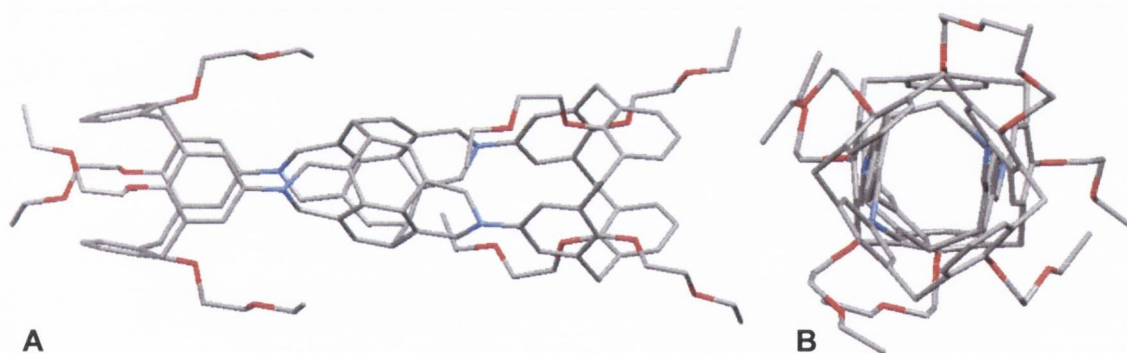


Figure 4.1: Crystal Structure of 1,3-Alternate Calixarene Dimer **229**², a) side view, b) end view

4.1.1.2 Tail-to-Tail Calixarene Dimers

There are many examples of calixarenes dimerised through the lower rim *via* either two or four bridges in the literature. Those dimerised *via* four bridges are generally referred to as calix[4]tubes while those dimerised by only two bridges are denoted as partial calix[4]tubes. The first calix tube was reported in 1997 and was synthesised by the base catalysed reaction of *t*-Bu-calix[4]arene with *t*-Bu-calix[4]arene tetratosylate.¹⁸⁸ Although numerous bases were tested, such as Na_2CO_3 , K_2CO_3 and Cs_2CO_3 , the reaction was only successful when K_2CO_3 was used, implying that the potassium ion may be acting as a

template in the synthesis of the tube. Through the use of functionalised calix[4]arenes with various groups on the upper rim, many more examples of calix[4]tubes (**230-238**) have since been synthesised, these include both symmetrical and asymmetrical derivatives, where the symmetry is with respect to the two calixarene subunits and these are illustrated in **Figure 4.2**.¹⁸⁹

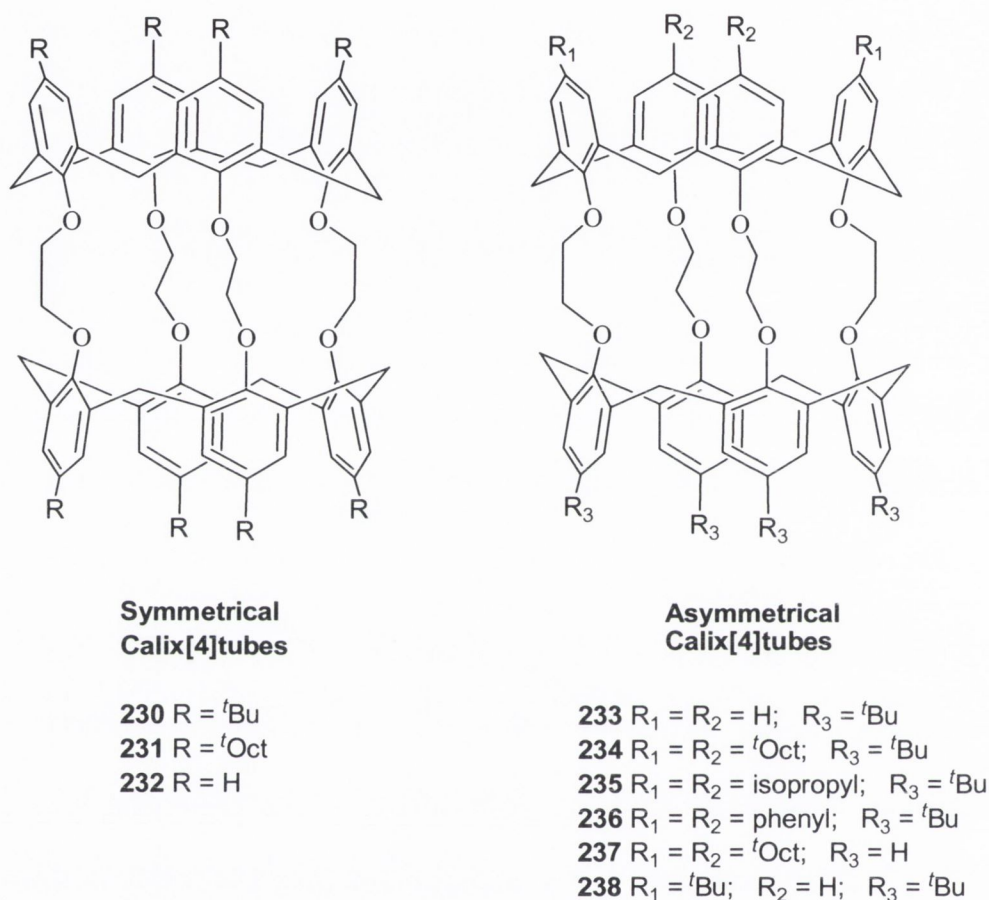


Figure 4.2: Symmetric and asymmetric calix tubes by Beer and co-workers

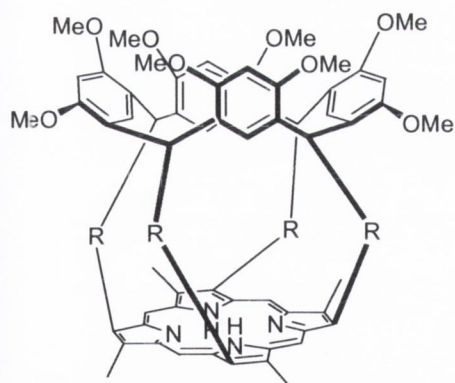
Calix[4]tubes containing at least one calix[4]arene subunit that is unfunctionalised at the upper rim have been successfully iodinated using AgTFA and I₂.¹⁹⁰ Calix[4]tubes have been shown to be selective and strong binders of K⁺ and can successfully transport K⁺ ions through a membrane. Due to the differing rates of cation complexation, dependent on the bulkiness of substituents on the upper rim of the calixarenes, the K⁺ ions are believed to enter the calix tubes through the portals within the calixarenes.¹⁹¹

Calix[4]partial-tubes are synthesised in an analogous manner using ditosylate calixarene derivative in place of the tetratosylate derivative previously used.^{192,193} After the reaction

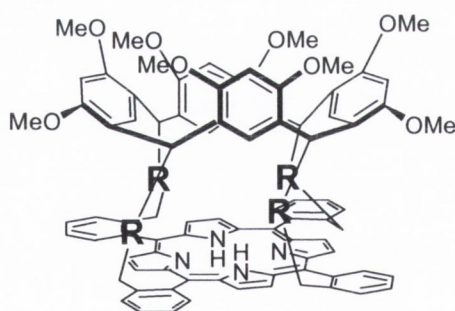
of the ^tBu-calixarene with the functionalised ditosylate calixarene, there remain two unfunctionalised hydroxyl groups on the lower rim of each of the calixarenes. These groups activate the *para* positions on the aromatic ring, making them amenable to further functionalisation. This has led to the synthesis of quinone¹⁹⁴ and urea¹⁹⁵ functionalised partial-tubes. Partial-tubes also show good binding affinity for Group I metal ions and have faster binding kinetics.

4.1.2 Heterodimers with Resorcarenes

Botta and co-workers have reported the successful synthesis of heterodimers derived from the reaction of appropriately functionalised octamethylresorcarenes (OMRA) and porphyrins (**Figure 4.3**).¹⁹⁶ Three different strategies were used to produce three novel heterodimers that differed in the porphyrin skeleton, the bridging groups and the size of the cavities formed. The strategies involved: a) the reaction of a hydroxyl terminated OMRA with an acid chloride functionalised porphyrin (**239**), b) the reaction of a phenol functionalised porphyrin with an OMRA with lower rim bromoalkyl chains (**240**) and c) the reaction of the hydroxyl terminated OMRA previously mentioned with a porphyrin functionalised with an aromatic isocyanate group (**241**). The porphyrin with ether linkages **240** was subsequently shown to inhibit the oxidation of Co(II) to Co(III).¹⁹⁶



239 R = CH₂CH₂CO₂CH₂CH₂



240 R = OCH₂CH₂
241 R = NHCCO₂CH₂CH₂

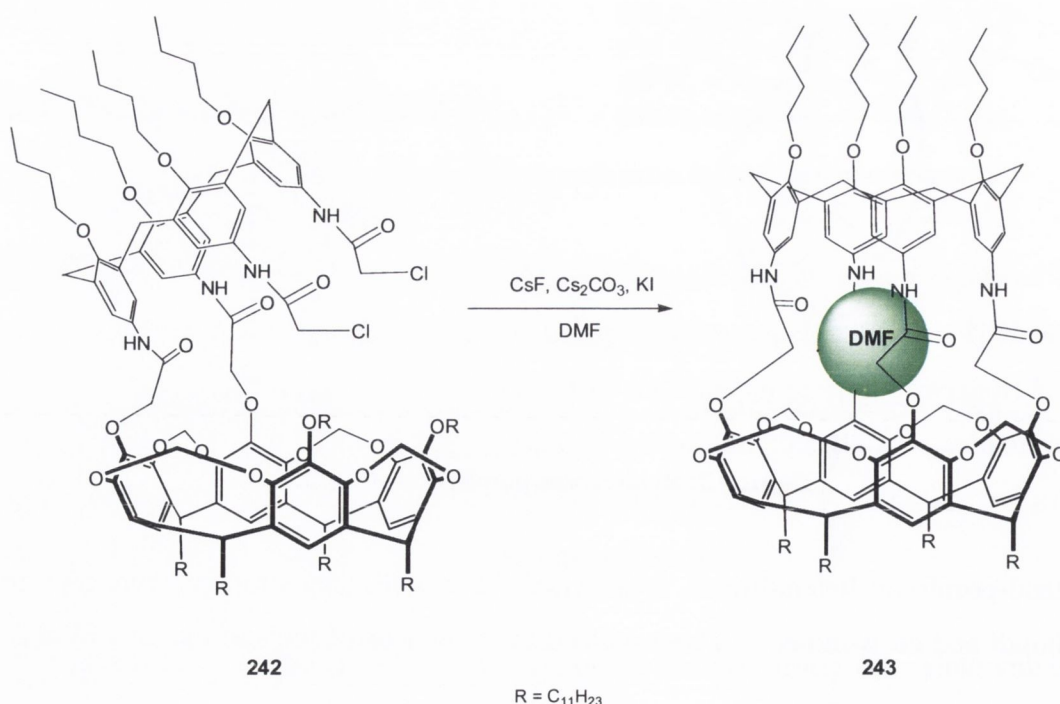
Figure 4.3: Resorcarene-porphyrin heterodimers

Cavitand-porphyrin heterodimers, synthesised *via* a multi-step strategy, were reported by Reinkoudt and co-workers.¹⁹⁷ These molecules, when treated with an excess of Zn(OAc)₂,

formed stable cavitand Zn(II) porphyrins which showed a 10 - 200 fold increase in their ability to bind *N*-heterocycles over the porphyrin itself.

4.1.3 Calixarene-Cavitand Heterodimers

The combination of calixarenes and resorcarene type molecules to form heterodimers has also previously been explored. Reinhoudt and co-workers reported the synthesis of a carceplex where one of the cavitands had been replaced with a calixarene molecule.^{198,199} Unlike standard carceplexes, these macrocycles required a multi-step synthesis, where initially a cavitand with four hydroxyl groups on the upper rim, was reacted with a calixarene with two chloroamide groups and two nitro groups on its upper rim. The reaction of the chloroamide groups of the calixarene with two of the hydroxyl groups on the upper rim of the cavitand gave rise a calixarene-cavitand dimer joined *via* two bridges. The two remaining hydroxyl groups of the cavitand were then silylated and the NO₂ groups on the upper rim of the calixarene were reduced to their corresponding amines using Raney Ni metal and hydrazine hydride. The amine groups were then converted to the α -chloroamides by reaction with α -chloroacetyl chloride to give **242**. The synthesis of a calixarene-cavitand carceplex was then completed by desilylation of the hydroxyl groups by heating **242** in DMF in the presence of CsF, Cs₂CO₃ and KI for 48 hrs, giving compound **243** in 27% yield (Scheme 4.1). The corresponding calixarene-cavitand tetramer, referred to as a holand was also observed in 26% yield.



Scheme 4.1: Synthesis of calixarene-cavitand dimer

Using the same methodology, a calixarene-cavitand dimer was synthesised from a cavitand with terminal alkene groups on its lower rim.¹⁹⁹ Reaction of the molecule with a thiol and 9-BBN led to the inclusion of sulfide groups on the lower rim of the molecule. These molecules have since been shown to form ordered self-assembled monolayers on a gold surface.¹⁹⁹

4.2 Aims for this chapter

The aim of this chapter is to synthesise calix[4]arenes with four aldehyde groups, either on the lower (244) or the upper rim (245), which can then undergo a condensation reaction with resorcinol to generate a resorcarene-calixarene heterodimer. In the upper rim the aldehyde groups are spaced out due to the structural nature of the macrocycle and the cavity size is larger than would normally be observed for a resorcarene. However, the upper rim shows more flexibility as the aromatic groups can rotate to give a more suitable arrangement. The lower rim, also called the narrow rim, offers a cavity more suited in size to the formation of a resorcarene, while also providing the possibility of more flexible arrangement through the incorporation of alkyl chains in the R position.

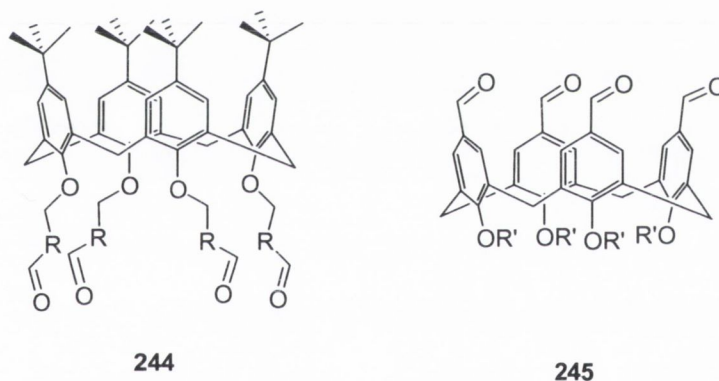


Figure 4.4: Aldehyde functionalised calixarene targets

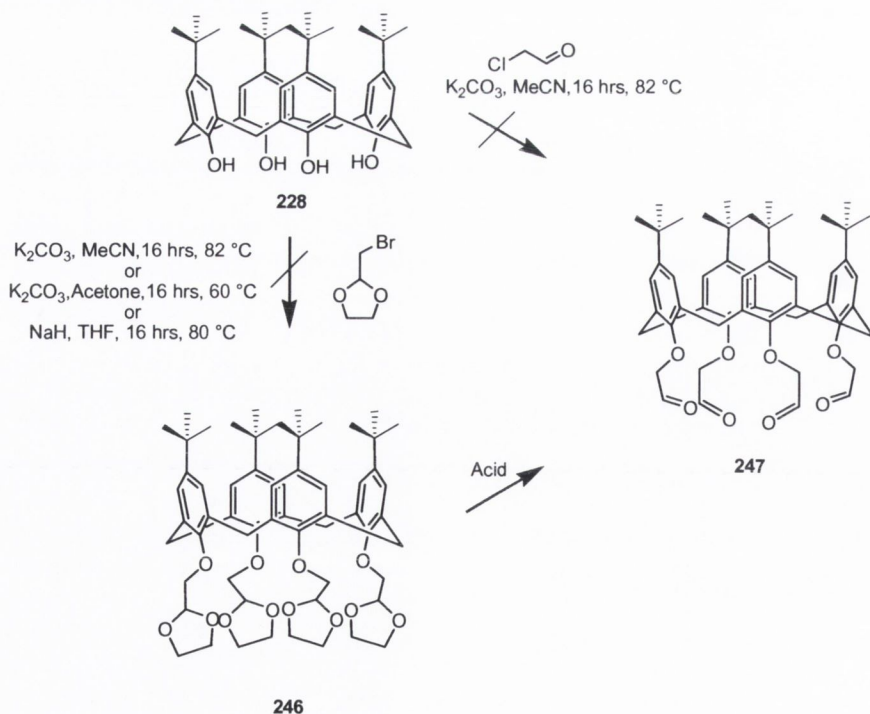
The use of calix[4]arene, with suitable functionality, to form heterodimers in one step, has been demonstrated by Gale *et al.* in the production of calixarene-calixpyrrole heterodimers. The synthesis of calix[4]arenes and calix[5]arenes containing lower rim ketone groups allowed for the synthesis of the calix[4]arene-calix[4]pyrrole²⁰⁰ and the calix[5]arene-calix[5]pyrrole²⁰¹ heterodimers under standard calixpyrrole synthesis conditions ($\text{BF}_3(\text{OEt})$ catalysed reaction of equal equivalents of pyrrole and a ketone).²⁰²

4.3 Calixarenes with Lower Rim Aldehyde Groups

Initially, work focused on the ^tBu-calix[4]arene as a rigid template onto which to build the resorcarene heterodimer. To this end, we hoped to synthesise **244**, a calixarene bearing four aldehyde groups on the lower rim, which we could then react with resorcinol to give the desired product. Various routes towards the synthesis of a lower-rim calixarene aldehyde **244** were investigated and these will be detailed in the following sections (Sections 4.2.1 – 4.2.3).

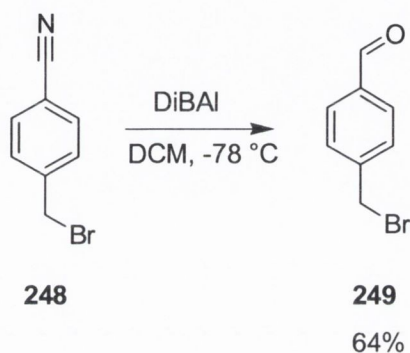
4.3.1 Synthesis of Lower Rim Aldehyde Calixarenes through Alkylation and their Further Reaction with Resorcinol

Initially, ^tBu-calix[4]arene was reacted with the commercially available 2-bromomethyl-1,3-dioxalane. This pendant group could later be deprotected by heating with pyridinium tosylate in acetone/water to yield the desired target, compound **247**. The synthesis was attempted using a number of different base/solvent systems such as K₂CO₃/MeCN, K₂CO₃/acetone and NaH/THF (Scheme 4.2). However, these reactions were unsuccessful, leading to the isolation of starting materials after each attempt. The next synthetic approach was the reaction of the calixarene with chloroacetaldehyde, which it was hoped, would yield compound **247** in one step. Again only unreacted starting materials were isolated at the end of this reaction (Scheme 4.2).



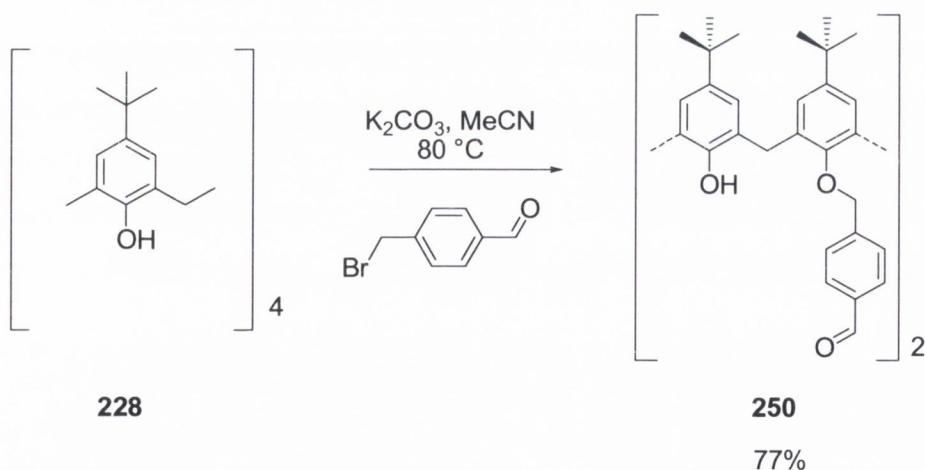
Scheme 4.2: Attempted synthesis of the lower rim aldehyde calixarene (**247**) by alkylation using chloroacetaldehyde or bromomethyl-1,3-dioxalane.

As no success was had using aliphatic aldehydes or protected aldehydes, alkylation with aromatic aldehydes was investigated next. The reaction of ^tBu-calix[4]arene (**228**) with bromomethylphenyl functionalised aldehydes proved more successful. The first aldehyde chosen, 4-bromomethyl-benzaldehyde (**249**), was synthesised in 69% yield, from the oxidation of 4-bromomethyl-benzonitrile (**248**) with DiBAL (**Scheme 4.3**).²⁰³ It was hoped, that this product would provide the desired rigidity for the core of the calix[4]arene-resorcarene heterodimer.



Scheme 4.3: Synthesis of 4-bromomethyl-benzaldehyde (**249**)

An excess of 4-bromomethyl-benzaldehyde was reacted with ^tBu-calix[4]arene to give a mixture of products, which upon purification by column chromatography (flash silica, DCM:EtOAc 9:1) gave the 1,3-disubstituted calixarene **250** as the major product. Using only two equivalents of **249** was also found to lead to the sole formation of **250** in similar yields of *ca.* 77% (**Scheme 4.4**).



Scheme 4.4: Reaction of ^tBu-calix[4]arene (**228**) with 4-bromomethylbenzaldehyde (**249**)

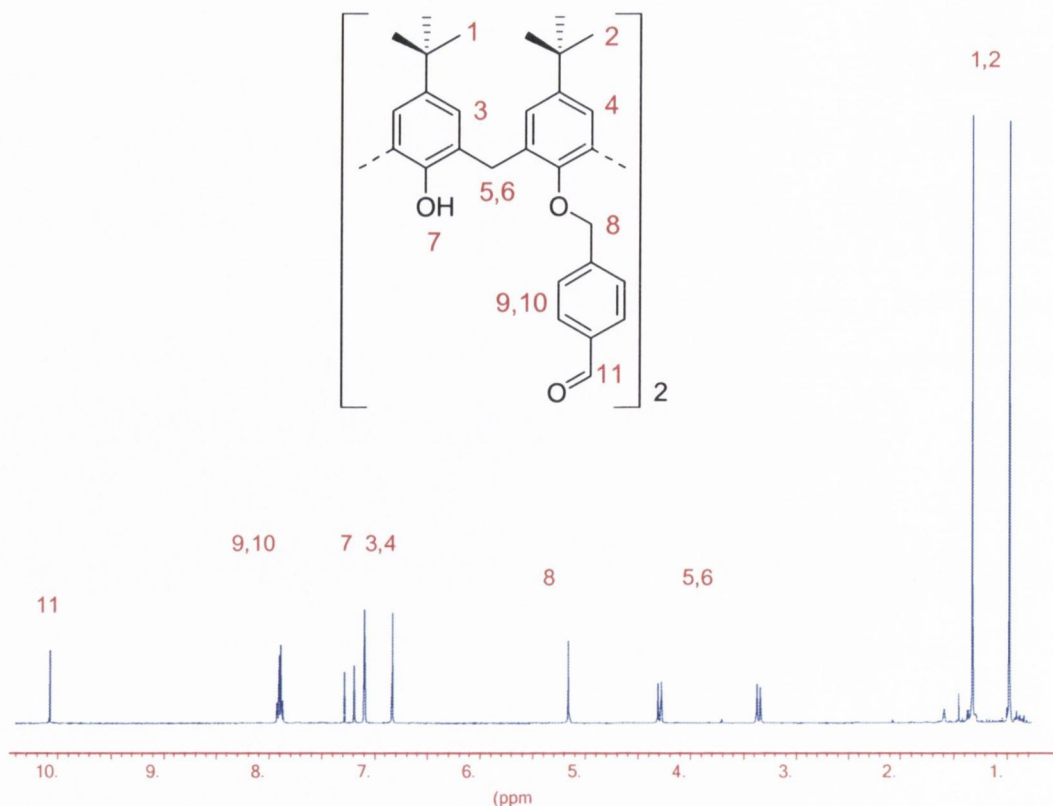


Figure 4.5: ¹H NMR (400 MHz, CDCl₃) of 1,3-disubstituted 'Bu-calix[4]arene (**250**)

The disubstitution of calixarene **250** is clearly evident from the ¹H NMR (400 MHz, CDCl₃) spectrum (**Figure 4.5**). It has higher complexity than would be expected for a tetrasubstituted derivative, with two resonances being observed for the protons on the phenol subunit of the calixarene as well as two separate signals observed for the 'Bu groups on the upper rim at 1.32 and 1.10 ppm. Additionally, the integration of the aldehyde peak at 10 ppm to two protons confirms such a substitution pattern. The substitution pattern is confirmed as 1,3 rather than 1,2 as there are only two doublets present for the *exo* and the *endo* protons of the bridging CH₂ group, showing that the molecule has at least two-fold symmetry.

Since this synthesis was carried out, Stibor and co-workers have published a two-step and three-step synthesis of **250** in an overall yield of 47% and 55%, respectively.²⁰⁴ In the two-step method, 4-bromomethyl-benzonitrile was reacted with 'Bu-calix[4]arene and the nitrile groups were subsequently converted to the aldehyde groups using DiBAL while the three step route involved the reaction of 'Bu-calix[4]arene with methyl-4-(bromomethyl)benzoate and the subsequent reduction of the ester group to the corresponding alcohol using LiAlH₄, before oxidising these to the desired aldehyde using pyridinium chlorochromate (PCC).

The observed preference for the distally disubstituted derivative, even in the presence of a large excess of aldehyde, suggests that the reaction may not go to completion, possibly due to steric reasons. To overcome this, a more flexible aldehyde, 4-(6-Bromo-hexyloxy)-benzaldehyde, was employed. The synthesis of 4-(6-Bromo-hexyloxy)-benzaldehyde (**226**) is reported in **Chapter 3, Scheme 3.7**. The long alkyl chain on this molecule may provide the necessary flexibility to allow the desired tetra-alkylation to occur.

Initially ^tBu-calix[4]arene was reacted with an excess of **226** under the same conditions described in **Scheme 4.4**. The reaction led to a mixture of products, which were purified by column chromatography (Silica, DCM 100%). The main product was once again the dialkylated derivative. In addition to this product, a small amount of the monoalkylated derivative was also obtained (2%). To maximise the yield of **251** the reaction was repeated using two equivalents of **226**. In addition to the unreacted **226** and the monoalkylated calixarene **252** (9.5%), the desired product (**251**) was isolated in high yield (70%).

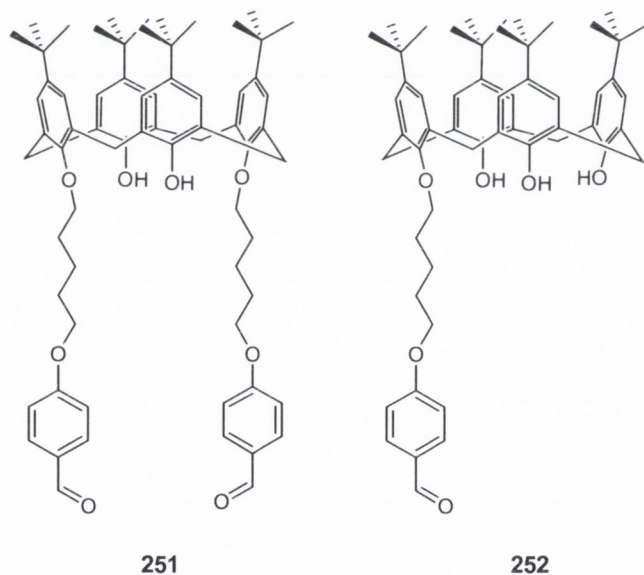


Figure 4.6: Calixarene derivatives isolated from the reaction of ^tBu-calix[4]arene and aldehyde **226**

The ¹H NMR (400 MHz, CDCl₃) spectrum of the monoalkylated compound **252** is shown in **Figure 4.7** and clearly shows that alkylation in only one position reduces the symmetry of the molecule. In the downfield region of the spectrum, two peaks are observed for the hydroxyl proton in a 2:1 ratio. A third singlet, corresponding to the aldehyde proton, is also observed in this region. The ^tBu protons on the upper rim of the calixarene give rise to three signals in a 1:2:1 ratio, at 1.25, 1.24 and 1.22 ppm, respectively. The aromatic region

provides further evidence that the mono derivative has been obtained; being more complex than would be expected for tetra- or dialkylated derivatives, displaying overlapping resonances due to the protons on the upper rim of the calixarene and the substituent group. Finally, instead of the two doublets observed for the bridging CH₂ groups in the tetra- and dialkylated calixarenes, a doubling of these signals is observed at 4.2-4.4 and 3.4-3.5 ppm. The integration of the signals arising from the alkyl chain also helps to confirm the mono-substitution of the calixarene.

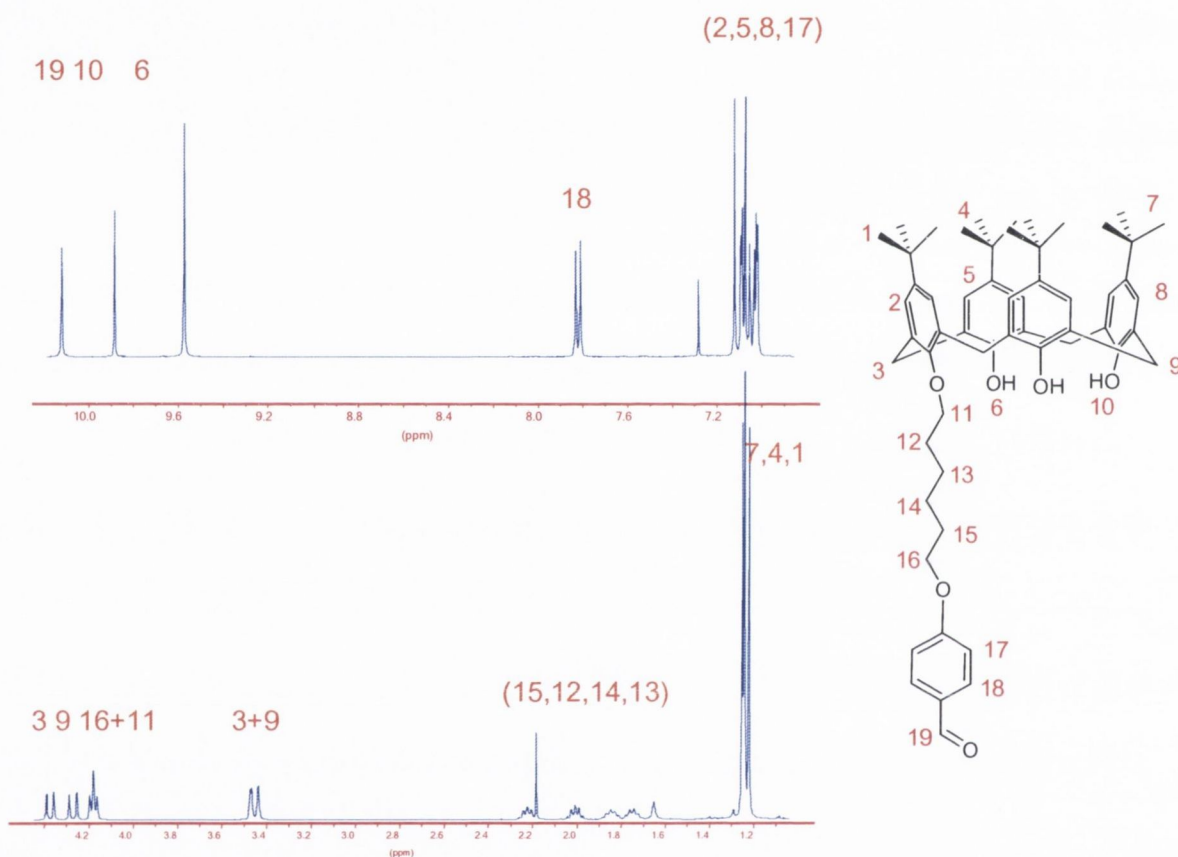
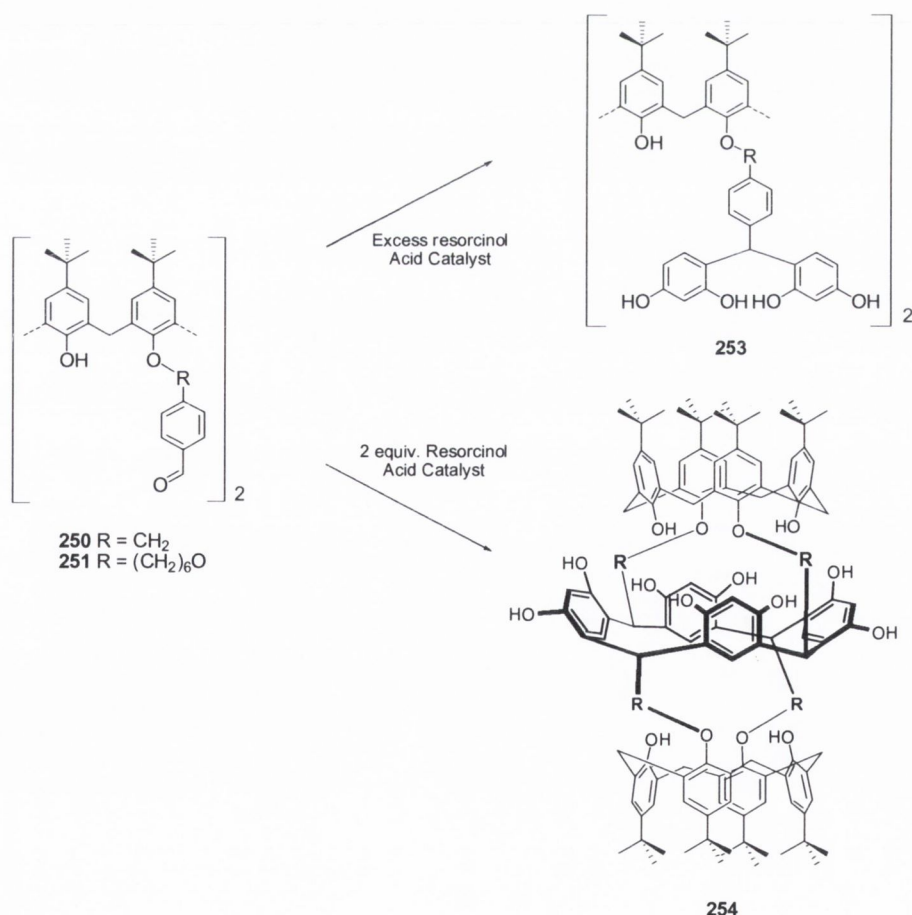


Figure 4.7: ¹H NMR (400 MHz, CDCl₃) of mono-substituted calixarene 252

The use of the more flexible aldehyde still resulted in only partial alkylation. So far, the combination of bromoalkoxybenzaldehydes and K₂CO₃ has only lead to the partial alkylation of the calixarene macrocycle. The next variation, aimed to ensure the complete alkylation of the lower rim, was to change the base from K₂CO₃, to much stronger bases such as NaH. This would hopefully ensure the complete deprotonation of the calixarene hydroxyl groups, enabling exhaustive alkylation. Consequently, the calixarene was reacted with both aldehydes, this time with a large excess of NaH, in dry DMF. Analysis of the crude product showed that the desired tetra-functionalised calixarenes were not observed,

either in the ^1H NMR spectra or by mass spectrometry, which also showed that the dialkylated derivatives **250** and **251**, were the dominant products.

The alkylation reactions described so far did not lead to the successful isolation of the desired target possessing the four aldehyde groups on the lower rim (**244**). Instead, two different calixarenes, each with two aldehyde groups on their lower rim were successfully synthesised. Two possible products could result from reaction of these dialdehydes with resorcinol and these are illustrated in **Scheme 4.5**. If the resorcinol is used in a large excess, then there is a possibility of generating resorcinol dimers (**253**) similar to those discussed in **Chapter 2, Section 2.5**. If however, the resorcinol:calixarene ratio used in the reaction is 2:1, there is the possibility of forming a calixarene-resorcarene tube, where the resorcarene is located in the middle of the tube and a calixarene at either end (**254**), this is depicted in **Scheme 4.5**. In the case of compound **253**, an additional condensation reaction, with a second aldehyde, could also possibly lead to the formation of a calixarene-resorcarene dimer. The reactions, carried out with the aim of developing some novel supramolecular systems, are summarised in **Table 4.1**.



Scheme 4.5: Possible outcomes of the reaction of **4.22** or **4.23** with resorcinol derivatives

Table 4.1: Summary of the reactions of calixarene aldehydes (250 and 251) with resorcinol derivatives.
SM = Starting material reisolated, **NP** = New product, **NO** = Desired product not observed, according to ^1H NMR.

Aldehyde	Resorcinol Derivative	Acid/Solvent	Reaction Conditions	Outcome
250	5 eq. 2	HCl/EtOH	48 hrs, 78 °C	NO
250	12 eq. 2	HCl/EtOH/DMF	1 hr, 0 °C	NO
251	2 eq. 196	$\text{SnCl}_4/\text{CHCl}_3$	16 hrs, RT	SM
251	12 eq. 196	$\text{SnCl}_4/\text{CHCl}_3$	1 hr, RT	NP

The reactions of the dialdehydes with 12 equivalents of either resorcinol (**2**) or 1,3-dimethoxybenzene (**196**) are analogous to the reactions carried out in **Chapter 2** to synthesise the acyclic resorcinol dimers **175** and **178**.

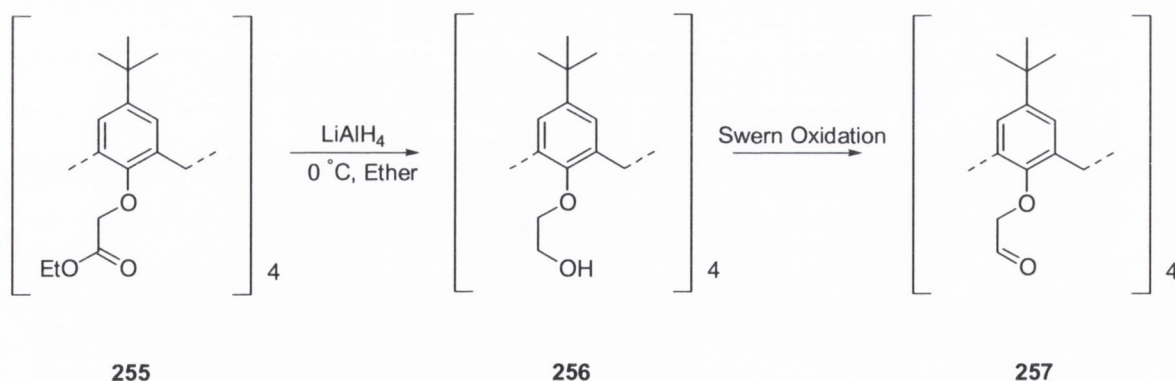
In the first two reactions the desired product was not observed. While some reaction had taken place, the attempted purification by column chromatography failed to yield any product with sufficient complexity in the aromatic region of the ^1H NMR spectrum to be the target compound. Mass spectrometry also failed to show any evidence of the desired compounds. In these reactions, **250** was not very soluble in the HCl/EtOH solvent system. To investigate if the failure of these reactions was down to solubility issues alone, reactions were carried out using **251**, which was the more soluble of the two calix[4]arene aldehydes. Moreover, the reaction conditions were changed to those previously used for the OMRA synthesis (SnCl_4 and CHCl_3 at RT) as **251** is readily soluble in CHCl_3 . Both two and twelve equivalents were used in the hope of isolating **254** and **253** respectively. When two equivalents were used, a white powder was isolated. The ^1H NMR spectrum (CDCl_3 , 400 MHz) of this product showed it to be a calixarene and the presence of the aldehyde signal led to the conclusion that no reaction had, in fact, taken place. This was confirmed by mass spectrometry which showed a $\text{M}+\text{Na}^+$ peak for **251**. When twelve equivalents of 1,3-dimethoxybenzene were used, the formation of a new calixarene product was evident from the ^1H NMR. Mass spectrometry, does not however, give any assignable peaks and as of yet a suitable solvent system for the purification of this complex mixture of products has not yet been found.

It was decided at this stage to pursue the synthesis of **244** through functional group interconversion rather than alkylation and the work done in this area is described in the next section.

4.3.2 Synthesis of Lower Rim Aldehyde Calixarenes through Oxidation/Reduction

As attempts at direct attachment of aliphatic aldehyde functionality did not yield the desired tetra aldehyde product, a multi-step synthesis was decided on. Two pathways were proposed, both starting at a lower rim ester (**255**). The desired ester (**255**) could be easily synthesised *via* alkylation with ethyl bromoacetate.²⁰⁵ This ester could then be either reduced to an alcohol (**256**) and followed by oxidation to an aldehyde (**257**), or directly reduced to the aldehyde. Both routes were investigated and are illustrated in **Schemes 4.6** and **4.7**.

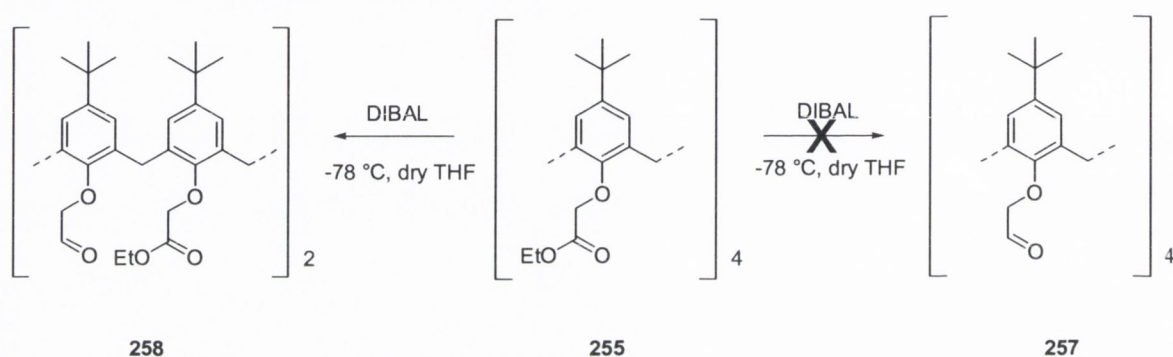
Synthesis of the ester (**255**) was carried out according to literature procedures,²⁰⁵ by stirring *t*Bu-calixarene with K_2CO_3 and ethyl bromoacetate in acetone at 56 °C for 16 hrs. The desired product was isolated in 70% yield. The ester was then successfully reduced to the tetra alcohol (**256**) in 69% yield using $LiAlH_4$ in Et_2O , initially the reaction flask was at 0 °C and this was allowed to slowly rise to room temperature over 16 hrs.²⁰⁶ The next step, the oxidation of a primary alcohol to an aldehyde, can often prove difficult. Aqueous methods of oxidation would initially give the aldehyde, but this would form a hydrate in solution, which would react further to give the unwanted acid derivative. For this reason it is essential to carry out these reactions under anhydrous conditions.



Scheme 4.6: Attempted Synthesis of Calix Aldehyde (257) through Reduction and then Oxidation

The method chosen was the Swern oxidation.²⁰⁷ In this reaction DMSO and oxalyl chloride react in dry DCM to form an electrophilic sulphur compound. This compound then reacts with the alcohol to form a sulfonium salt, which undergoes a redox reaction on addition of base resulting in the oxidation of the alcohol to an aldehyde and the reduction of the sulphoxide to a sulphide. Although this reaction is well known for achieving this functional group conversion no aldehyde peaks were observed in the ^1H NMR spectra obtained and mass spectrometry also failed to show the presence of the desired compound.

In the second method, the direct reduction of the ester to the aldehyde was attempted. The problem here is that the aldehyde is more easily reduced than the ester, so terminating the oxidation at the aldehyde stage rather than the alcohol, can prove problematic.



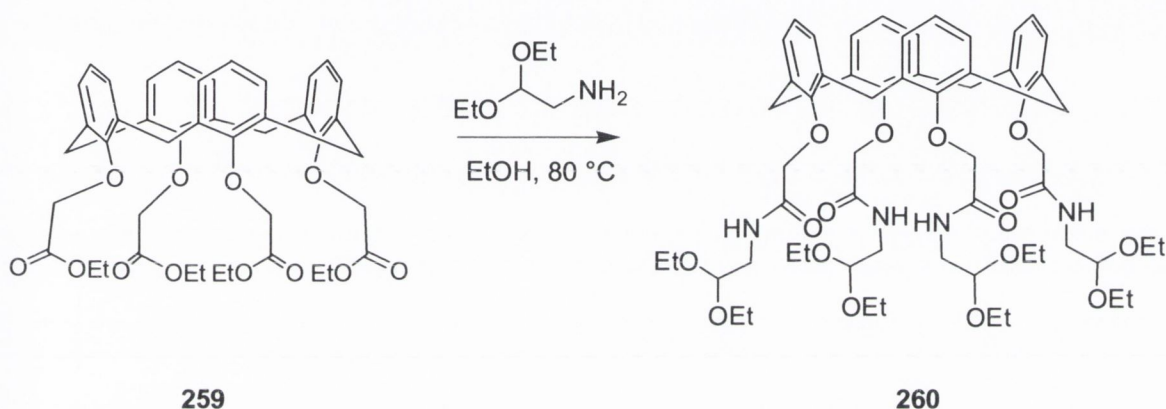
Scheme 4.7: Attempted reduction of calix ester (255) to calix aldehyde (257) using DiBAL

Diisobutylaluminium hydride (DiBAL) has proven itself useful in such transformations.¹⁶⁴ It forms a tetrahedral intermediate, bonded through the oxygen, which protects the compound from further reduction. This intermediate is stable until the addition of acid quenches all the excess DiBAL. Early experiments with DiBAL gave some indication of success, where ^1H NMR analysis showed the presence of a new calixarene product; although complete conversion was not observed. Mass spectrometry also indicated the presence of a new product, the dialdehyde (**258**). With this limited success, the next logical step was to make the conditions of the reaction more forcing. However, increasing the number of equivalents of DiBAL, and the lengthening the reaction time had no noticeable effect on the outcome of this reaction. If the formation of the partially substituted calixarenes **250** and **251** discussed earlier, is indeed due to steric factors, these factors may also play a part in the outcome of this reaction. It is possible that the tetrahedral intermediate formed by DiBAL at each reduction site, could possibly be too bulky to allow for the full reaction at the lower rim. If this intermediate is present when the reaction is

quenched with acid, it may block the reduction of the two unreacted ester groups. Because of this possible setback this method was not explored any further.

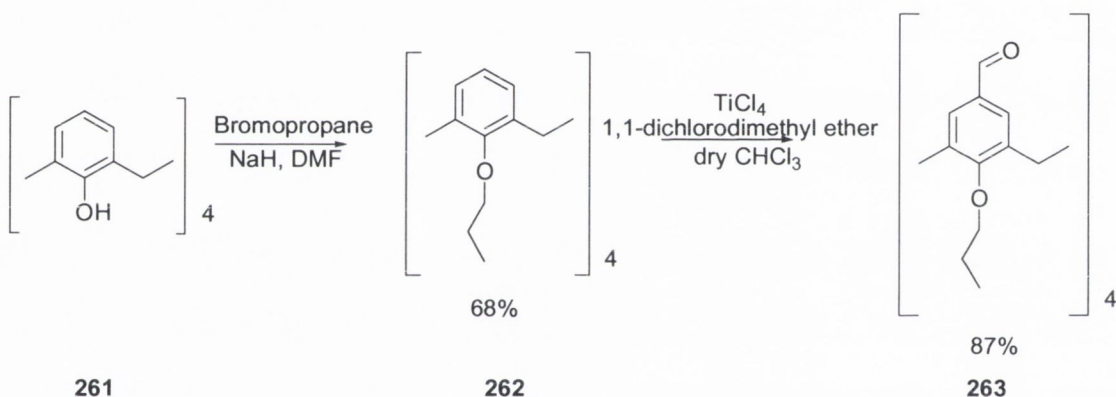
4.3.3 The Use of Protecting Groups in the Synthesis of a Calixarene with Lower Rim Aldehyde Groups

With the aim of overcoming the aforementioned problems, an alternative synthesis was attempted. This involved the use of compound **260**, which was obtained by stirring **259** with a large excess of aminoacetaldehyde diethyl acetal in EtOH at reflux for 16 hrs. This compound contains four lower-rim aldehyde groups, in their protected diethyl acetal form, **Scheme 4.8**.



4.4 Calixarenes with Aldehyde Groups on the Upper Rim

The second synthetic target, the calixarene with four upper rim aldehyde groups **245**, is known in the literature.²⁰⁹ In this work, the lower rim was also functionalised with a propyl chain. Compound **263** was synthesised according to literature procedures, **Scheme 4.9**, in two steps. In the first step, the phenol groups of the calixarene **261** are alkylated using bromopropane in the presence of NaH, giving compound **262** (68%).²¹⁰ This step protects the hydroxyl group from involvement in the subsequent reactions, while also fixing the calixarene in the cone conformation. In the second step, the aldehyde group was introduced to the upper rim by the simultaneous addition of TiCl₄ and **262**, both in dry CHCl₃, to 1,1-dichlorodimethyl ether, in dry CHCl₃.²⁰⁹ The literature method includes a lengthy purification procedure but slow precipitation from ethanol was found to be equally effective in isolating **263** in 87% yield.



Scheme 4.9: Synthesis of calixarene with upper rim aldehyde group

The reaction of **263** with resorcinol was investigated under six different reaction conditions. The exact reaction conditions and the results of each attempt are summarised in **Table 4.2**.

Table 4.2: Reaction of calixarene (263) with resorcinol under standard and high dilution conditions

Run	Solvent	Catalyst	Relative Total Solvent (ml)	Aldehyde	Resorcinol	Result
1	EtOH	HCl	70	Present at start	Present at start	Polymer
2	EtOH	HCl	100	Added over 200 min	Present at start	Polymer
3	EtOH	HCl	100	Added over 200 min	Added over 200 min	Polymer
4	CHCl ₃	SnCl ₄	7	Present at start	Present at start	Insoluble polymer
5	CHCl ₃	SnCl ₄	100	Added over 200 min	Present at start	Insoluble polymer
6	CHCl ₃	SnCl ₄	100	Added over 200 min	Added over 200 min	Polymer

Initially the reactions were carried out using standard reaction conditions using either EtOH/HCl¹² or CHCl₃/SnCl₄¹⁴ as the solvent/catalyst systems. Different products were obtained from both of these reactions. In the HCl catalysed reaction, the product was an off-white powder, while in the SnCl₄ catalysed reaction, a dark red solid was obtained. The ¹H NMR spectrum of the product from **Run 1** was obtained and the characteristic broadening of the resonances confirmed that the product was a polymer. The product from **Run 4** was too insoluble to be characterised by NMR spectroscopy. The use of high dilution and slow addition techniques was investigated next. Again the reactions were investigated in both solvent/catalyst systems. In **Run 2** and **Run 5** the reaction was conducted at a higher dilution than previously used, and a solution of the **263** was added slowly to a stirred solution of resorcinol in either CHCl₃/SnCl₄ or EtOH/HCl at room temperature and 78 °C respectively. In **Run 3** and **Run 6** the reactions were conducted as for **Run 2** and **Run 5**, except both the resorcinol and the aldehyde were added over a 200

min period. In **Run 3**, a yellow powder was isolated by filtration after the addition of H₂O (to aid precipitation). The ¹H NMR (400 MHz, DMSO-*d*₆) spectrum of this product showed it to be a polymer. In **Run 5**, a red powder precipitated during the reaction, that product was isolated by filtration and again shown to be a polymer by ¹H NMR. The change in reaction conditions does result in a change in the outcome of the reaction as is evidenced from the differing colours of the products isolated, as well as their varying solubility. However, where the ¹H NMR spectra are successfully obtained, only polymeric materials are observed. It can be concluded that, despite attempts to stifle this polymerisation using high dilution and slow addition techniques, the correct set of conditions that would overcome the tendency of these materials to polymerise has not yet been found and this synthesis will not be investigated further.

4.5 Conclusions

This chapter, although failing in its aim to synthesise a resorcarene-calixarene heterodimer, nevertheless, led to the synthesis of several novel calixarenes and a number of interesting findings. The results described in this chapter are summarised below.

- Although the synthesis of a calixarene with four lower rim aldehyde groups was ultimately not successful a number of novel mono- and dialkylated calixarene compounds were isolated during the various synthetic attempts.
- The reaction of **250** and resorcinol did not produce any of the desired products.
- The reaction of **251** with 1,3-dimethoxybenzene did lead to some novel products however these were not successfully isolated.
- A novel calixarene with protected aldehyde groups on the lower rim **261** was successfully synthesised. Deprotection of **261** to yield the tetra aldehyde was not successful. Interestingly, the direct reaction of resorcinol with the **261** did not yield the desired resorcarene-calixarene heterodimer.
- The synthesis of the calixarene target **245** with four aldehyde groups on the upper rim was achieved following literature procedures. The subsequent reaction of this calixarene with resorcinol was investigated under a number of different conditions. Although, changes in reaction conditions were found to yield different materials the desired resorcarene-calixarene heterodimer was not isolated.

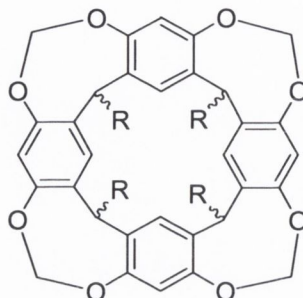
Although the ultimate target of a resorcarene-calixarene heterodimer was not obtained this work has produced promising results which will be further investigated.

Chapter 5

Cavitands as Molecular Platforms for Ligand Attachment

5.1 Introduction

As discussed in Chapter One (Section 1.7), cavitands are resorcarene derivatives with a deeper pocket and a more rigid structure with a general formula as shown below (Figure 5.1).



105

Figure 5.1: General Structure of a Cavitand

Although initially most cavitand research focused on the synthesis of hemicarceplexes and carceplexes, the use of cavitands as rigid molecular platforms for the attachment of ligands for both cation and anion binding has become an area of great interest.^{211,212,80,213} Cavitands that have methylene bridges (**105**) are very rigid structures and consequently, are a good starting point for the formation of a pre-organised binding site or sites. The benefits of such pre-organisation were discussed in Section 1.8.

5.1.1 Cation Recognition

In the first paper to exploit cavitands as a platform for ligand attachment Reinhoudt *et al.* reported the synthesis of six new cavitands, each with four (carbamoylmethyl)phosphine oxide (CMP(O)) or (carbamoylmethyl)phosphonate (CMP) based ligands attached to their upper rim.⁸⁰ These ligands were investigated for use in nuclear waste processing for the removal of lanthanides and actinides (Figure 5.2). The cavitand extractants (**264-269**) showed an increased affinity and selectivity for Eu(III) over UO₂ and Fe(III) compared to simple CMP(O) extractants.

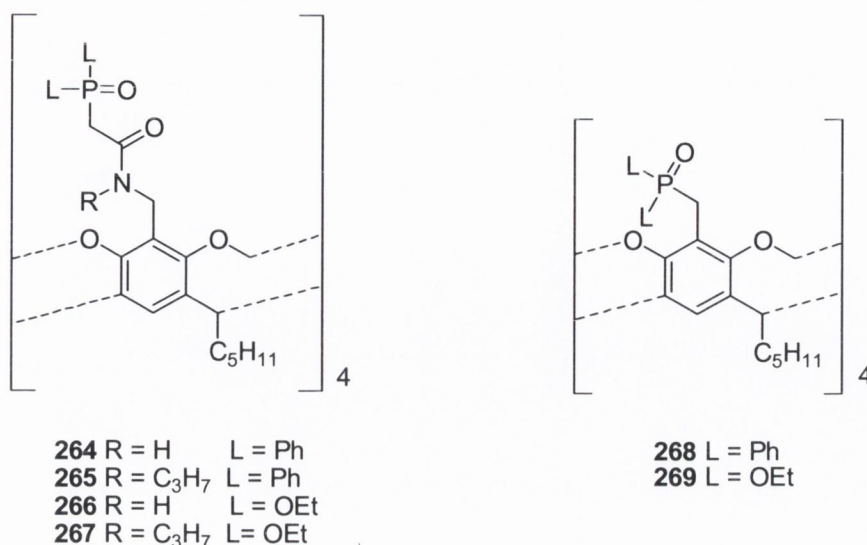


Figure 5.2: CMP(O) and CMP based cavitands

In a continuation of this work the group synthesised an additional two cavitands with -NH-C(S)-NHC(O)Ph and -NH-C(O)-NHC(O)Ph groups on the upper rim.²¹⁴ The selectivity of these new cavitands towards metal ions was compared with those of the CMP and CMP(O) cavitands prepared previously (**Figure 5.2**) to see if changing of the donor atoms from the “hard” to “soft” had any effect. This was found to be the case as, the CMP(O)/CMP derivatives showed a preference towards hard ions, such as Eu^{3+} and UO^{2+} , while the amide and thioamide carbonyls show a preference for softer cations such as Ag^+ . The selective extraction of lanthanides with cavitands functionalised with four phosphinic acid groups has also been achieved and here a selectivity for Eu(III) over the actinide Am(II) was observed.²¹²

Cavitands capable of binding group I and II metals as well as ammonium ions were synthesised by Paek *et al.* by the inclusion of four aromatic sp^2 nitrogens in the upper rim through the incorporation of imidazole (**270** and **271**), pyrazole (**272**), benzimidazole (**273**) or indazole (**274**) groups (**Figure 5.3**).²¹⁵ The pyrazole derivative also shows particular affinity for silver picrate salts.

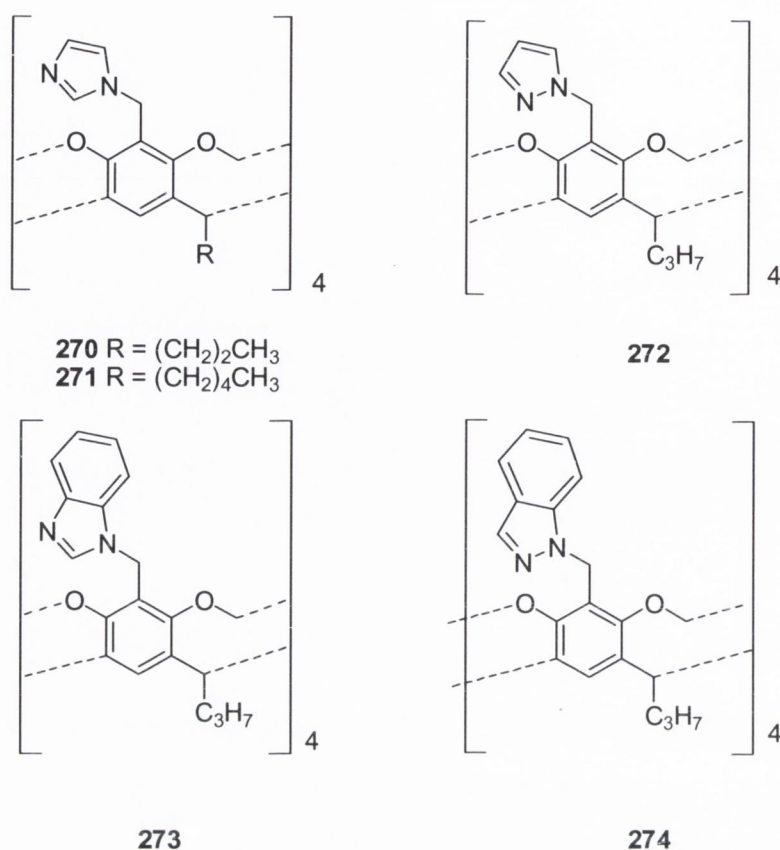
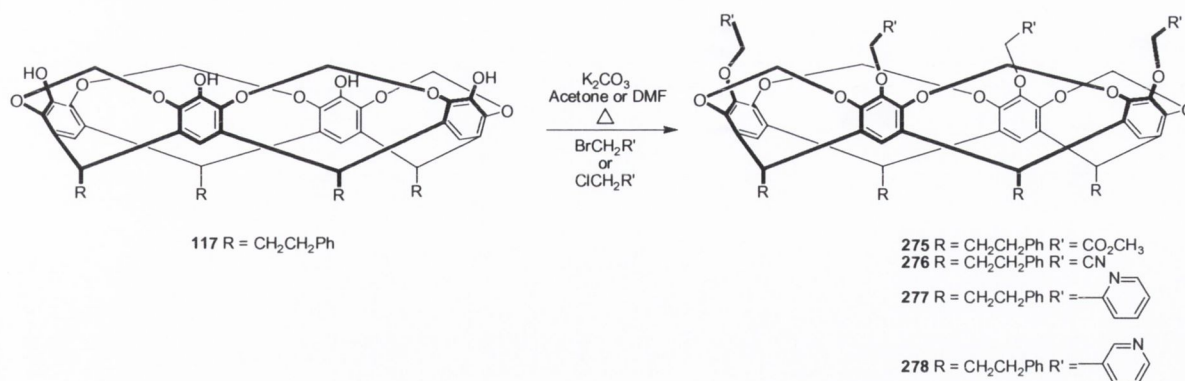


Figure 5.3: Imidazole, pyrazole, benzimidazole and indazole functionalised cavitands

Fluorescent cavitands selective for Cu(II) ions have also been developed by the inclusion of coumarin residues on the upper rim of cavitands.²¹⁶ Cavitands with four hydroxyl groups on their upper rim have been used to synthesise tetra ester, nitrile and 2 or 3-pyridyl cavitands for cation binding (Scheme 5.1).²¹⁷ For the alkali metals, each cavitand tested showed a marked preference for Rb(I) over other alkali metals while the pyridyl cavitands additionally showed selectivity for Ag(II) and Zn(II).²¹⁷ The 3-pyridyl cavitands were able to form complexes with Pd(II), which gave water soluble receptors for carboxylates.²¹⁸ The 4-pyridyl cavitands underwent complexation reactions with both Pt(II) and Pd(II).^{219,220} In this case the formation of molecular capsules *vs.* bowls could be modulated through the choice of reaction conditions.



Scheme 5.1: Synthesis of ester, nitrile and pyridyl functionalised cavitands

In a different approach isonicotinoyl groups on the lower rim of cavitands have been used to form complexes with silver, palladium and nickel.²²¹ The authors found that the conformational mobility of ligands on the lower rim, as opposed to the inherent rigidity of the upper rim, made it more difficult to control the outcome of the complexation reaction and the molecules show a preference for the formation of intramolecular complexes.

5.1.2 Anion Recognition

A series of tri- and tetra-functionalised thiourea and urea cavitands (**279** - **285**) were reported by Reinhoudt and co-workers.²²² The tetra(thio)urea derivatives were synthesised from the known tetraaminomethylcavitand⁸⁰ by reaction with the appropriate iso(thio)cyanates, or in some cases, by the reaction of the aminomethylcavitand with phosgene or thiophosgene to first give the isocyanate or isothiocyanate, respectively, which then underwent further reaction with an appropriate amine. Tri(thio)urea derivatives were made in an analogous manner, starting from the previously reported triaminomethylcavitand.²¹³

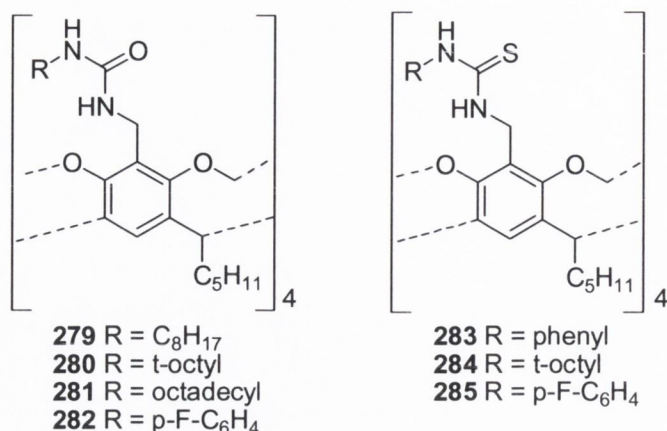


Figure 5.4: Urea and thiourea cavitands

These urea compounds were then screened for their binding affinity for Cl⁻, Br⁻ and I⁻ ions. In all cases 1:1 binding was observed in binding studies and the molecules showed a slight preference for chloride. The tetra functionalised cavitands bind anions 9-15 times more strongly than the trisubstituted cavitands. Moreover, the thioureas proved to be slightly stronger binders than the urea cavitands, and showed approximately a hundred fold increase in the association constants of the corresponding tetrathioureacalixarenes.

The incorporation of positively charged phenylamidinium groups on the upper rim of a cavitand for the purpose of anion binding was reported by Diederich *et al.*²²² This enables the cavitand to bind negatively charged isophthalates and nucleotides. The reaction of aminomethyl cavitands with ruthenium bipyridyl and ferrocenyl acid chlorides has also led to the isolation of compounds that could act as anion sensors.²²³

5.1.3 Recognition of Neutral Species and Complex Guests

The recognition of species other than anions and cations is also an area under investigation in cavitand chemistry.²²⁴ A series of amino acid and peptide cavitands were reported by Berghaus *et al.*, where the C-termini of amino acids or short peptide chains were attached to the cavitand.²²⁴ These molecules were designed as potential hosts for the recognition of proteins. Some examples of this work are shown in **Figure 5.5**.

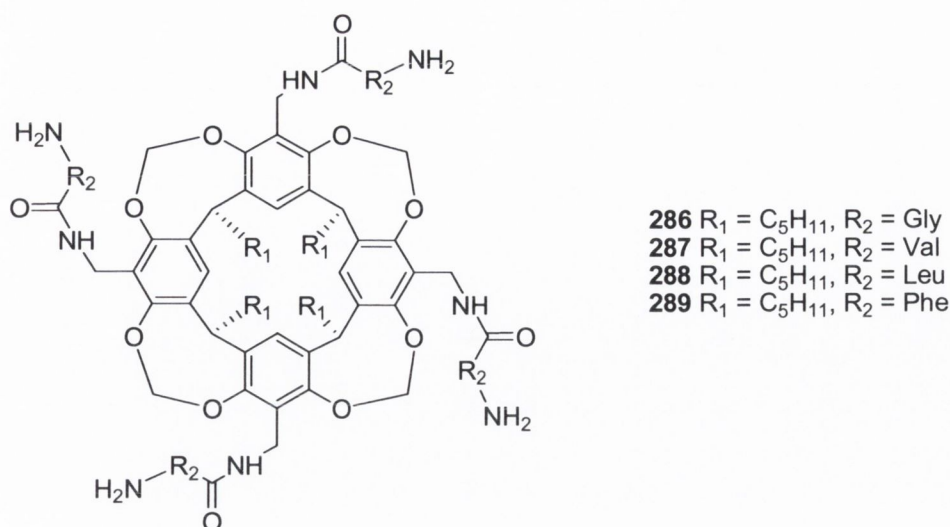


Figure 5.5: Amino acid functionalised cavitands

5.2 Synthesis of Cavitands for Ligand Attachment

The purpose of this part of the project was to investigate new approaches to designing novel ligands for the binding of lanthanide ions. Previous work within the Gunnlaugsson group has led to the development of amidopyridine ligands which have shown ability to bind lanthanides.²²⁵ The potential attachment of these ligands to a cavitand platform was considered a desirable target, not only for their own unique binding properties, but also as a useful comparison to similarly derivatised rigidified resorcarene hosts.

To enable the attachment of ligands to the upper rim of cavitands it is necessary to first functionalise the upper rim with groups amenable to further reaction. Two known cavitand molecules, available from a multi-step synthesis, were chosen as initial targets for this purpose (**Figure 5.6**). These tetraamino (**290** and **291**) cavitands should be suitable for alkylation reactions with suitably functionalised ligand molecules, for instance those with terminal methylhalide groups. The use of methylene bridging groups in these molecules ensures that they will be a rigid platform on which to attach the ligands.

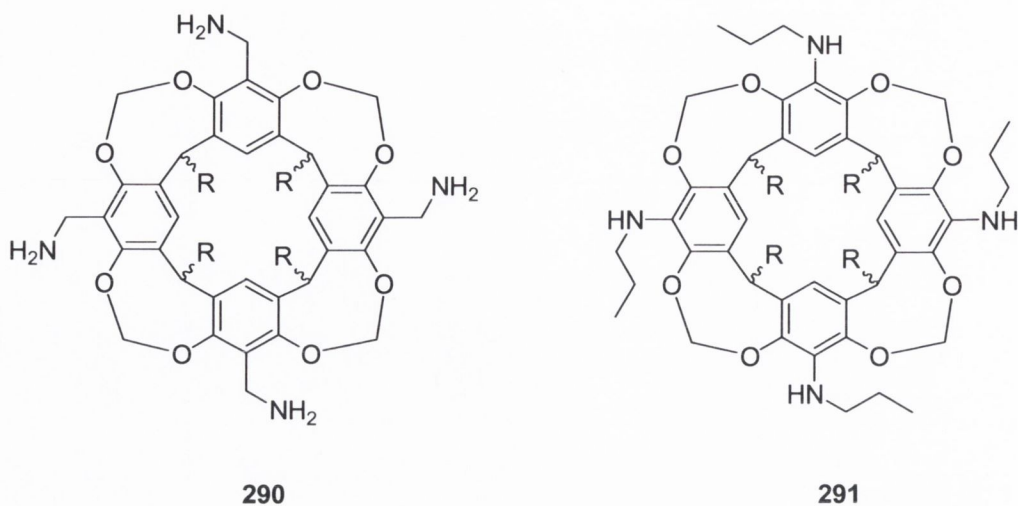
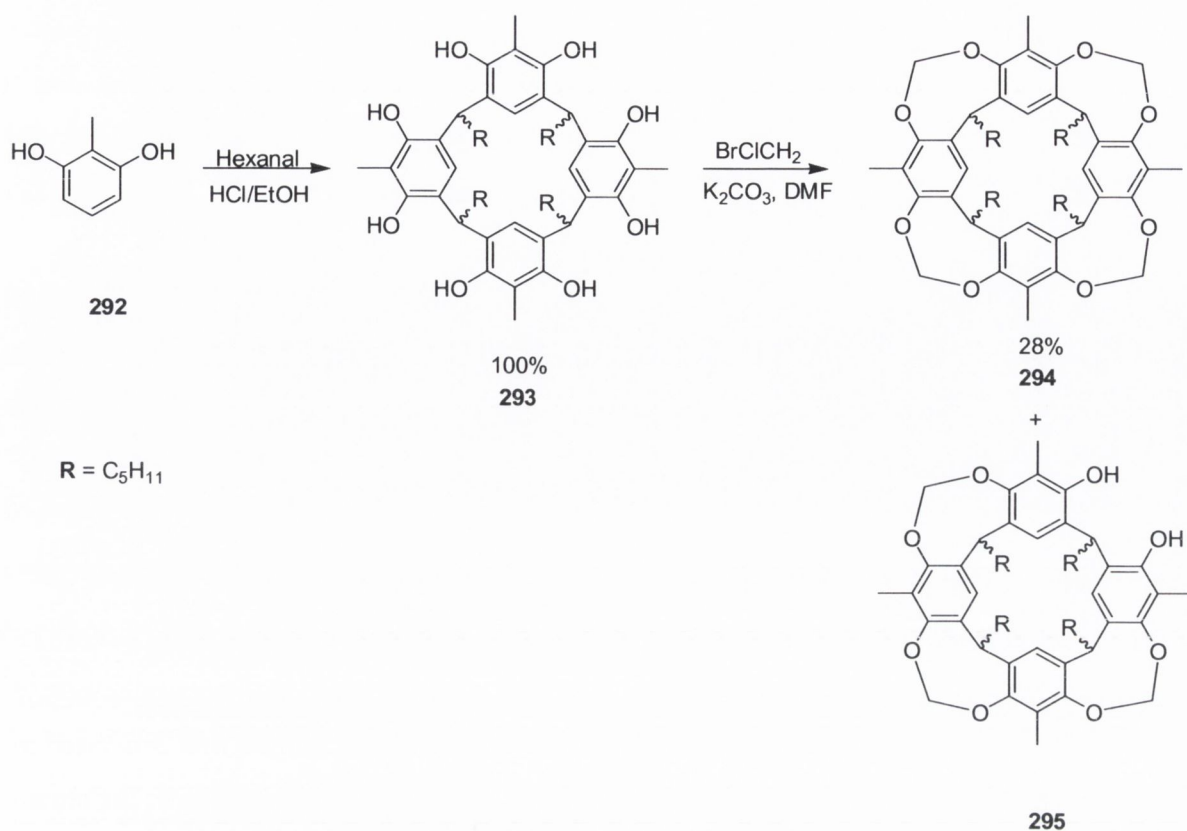


Figure 5.6: Cavitand targets for ligand attachment

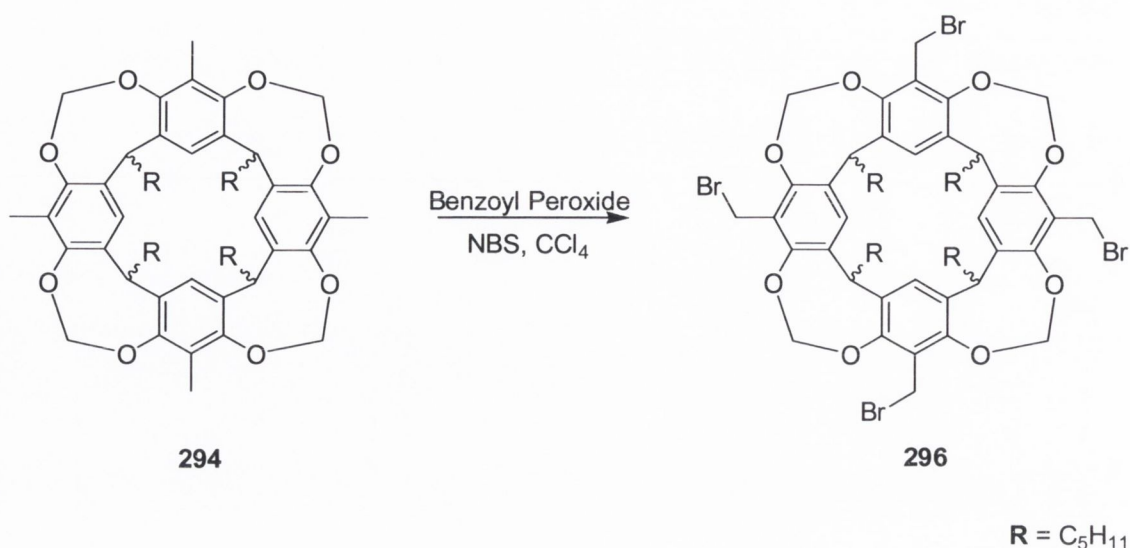
5.2.1 Synthesis of Aminomethyl Cavitand

The tetramethyl cavitand **294** was obtained in two steps, following literature procedures.^{12,80} Hexanal and 2-methylresorcinol (**292**) were refluxed together using standard conditions to give the desired resorcarene, solely in the boat conformation, and in quantitative yield.¹² Alkylation of **293** using a large excess of bromochloromethane gave cavitand **294**.⁸⁰ The low boiling point of this alkylating agent prevented the reaction being heated at high temperatures. The crude product was purified by column chromatography (silica, 100% DCM). The yield from this reaction was quite low (28%), and a large amount of tribridged product was formed as a side product. The final bridging step is known to be the slowest and hardest in this reaction due to the steric constraints it places on the molecule.⁵¹ Unfortunately, an increase in the amount of bromochloromethane used, longer reaction time, or the use of higher temperatures, combined with the use of a pressure tube failed to show any marked improvement in the yield of the desired tetrabridged material.



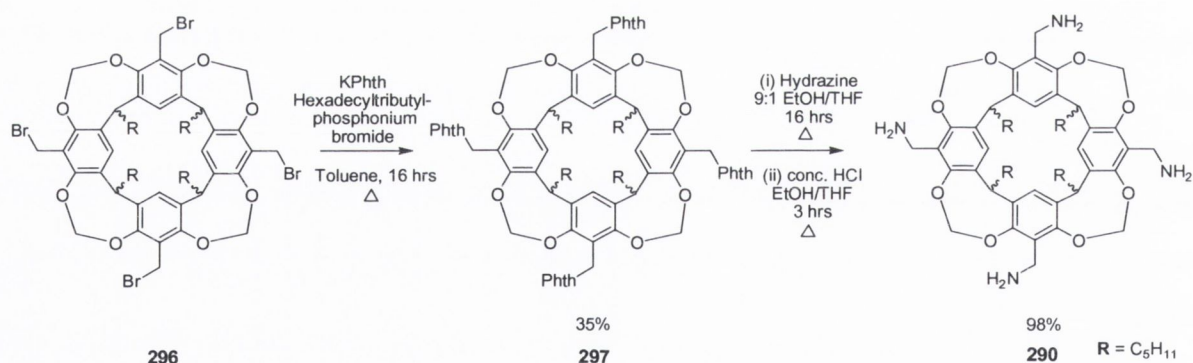
Scheme 5.2: Synthesis of tetramethyl cavitand

The radical bromination of the upper rim methyl group in tetramethyl cavitands was carried out using NBS in CCl₄ in the presence of a radical initiator, using either benzoyl peroxide²²⁶ or AIBN.²²⁷ Of these, the benzoyl peroxide proved to be more reliable, consistently yielding the desired product in over 83% yield, after purification by precipitation. No unwanted side reaction at the methine lower rim bridging groups was observed, most likely due to steric hindrance.



Scheme 5.3: Synthesis of tetrabromomethyl cavitand

The bromomethyl cavitand was then converted to the first target, the tetraaminomethyl cavitand (**290**). In the literature, the bromomethyl groups in cavitand **296** are first converted to the phthalimido groups (**297**), which are then further reacted, with hydrazine, to give the amino groups shown in cavitand **290**, in an overall yield for the two steps of 68% (Scheme 5.4).

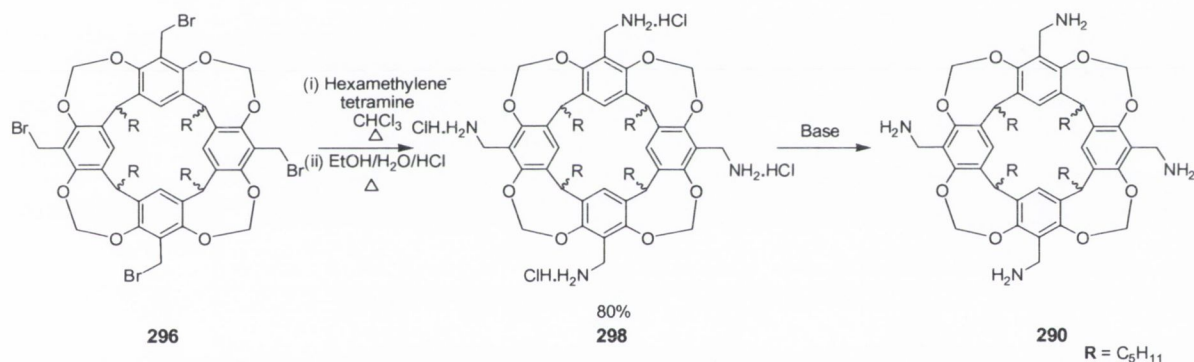


Scheme 5.4: Literature synthesis of tetraaminomethyl cavitand

The first step in this synthesis was the reaction of tetrabromomethyl cavitand (**17**) with potassium phthalimide and tributylhexadecylphosphonium bromide used as a phase transfer catalyst in toluene. The crude product had to be further purified, after the initial work up, by column chromatography. Despite repeated attempts at this synthesis, following the reported procedures exactly, only low yields of *ca.* 35% of the desired product were obtained. The

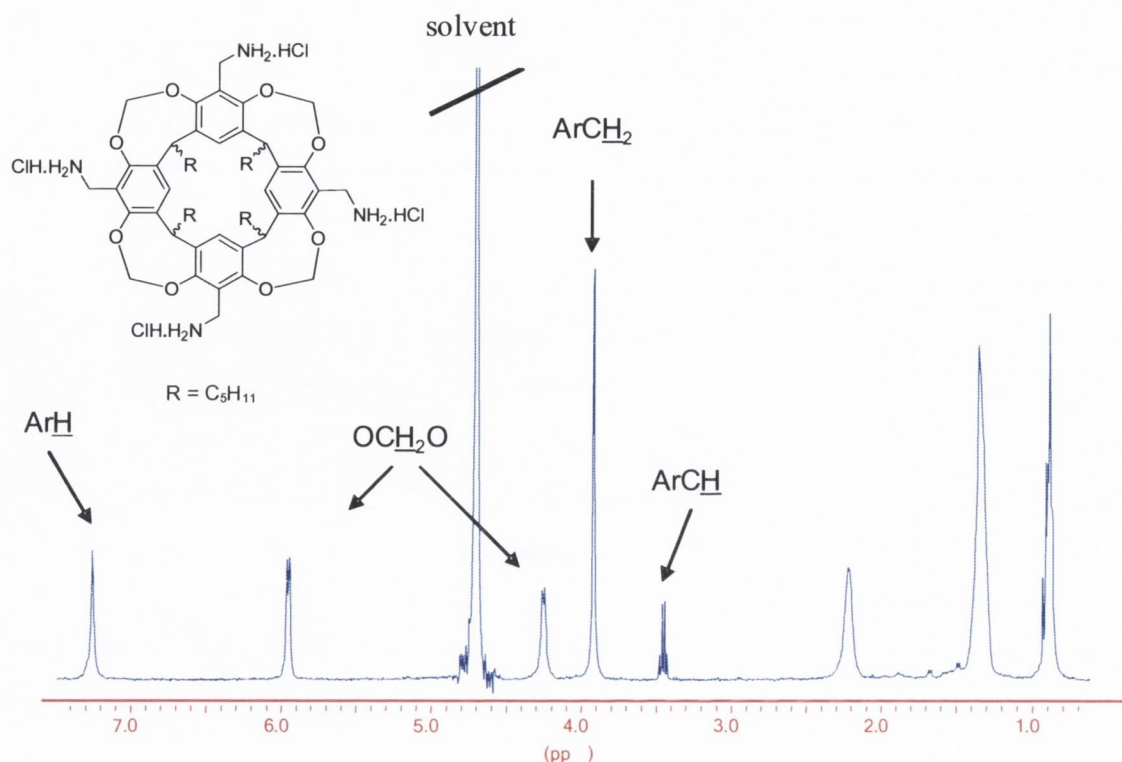
reaction of the phthalimide compounds with hydrazine monohydrate in ethanol proved to be a clean and efficient reaction yielding the desired compound in near quantitative yield (98%). However, the overall yield for these two steps, at 34%, is rather low. For this reason it was decided to investigate alternative routes to the formation of the tetraaminomethyl cavitand.

Gunnlaugsson *et al.* have published a one step synthesis for the conversion of a bromomethyl group to an amine hydrochloride and this method was applied to cavitand **296**.²²⁸ To achieve this, cavitand **296** was stirred with hexamethylenetetramine, a source of ammonia, in CHCl_3 . The resulting solid precipitate was isolated by filtration and without further purification, was heated in ethanol/HCl. The desired compound (**298**) precipitated upon cooling and did not require any further purification. The hydrochloride product can be converted to the free base, compound **290**, by stirring in an aqueous basic solution followed by extraction with CH_2Cl_2 (Scheme 5.5).



Scheme 5.5: Alternative synthesis of tetraaminomethyl cavitand **290**

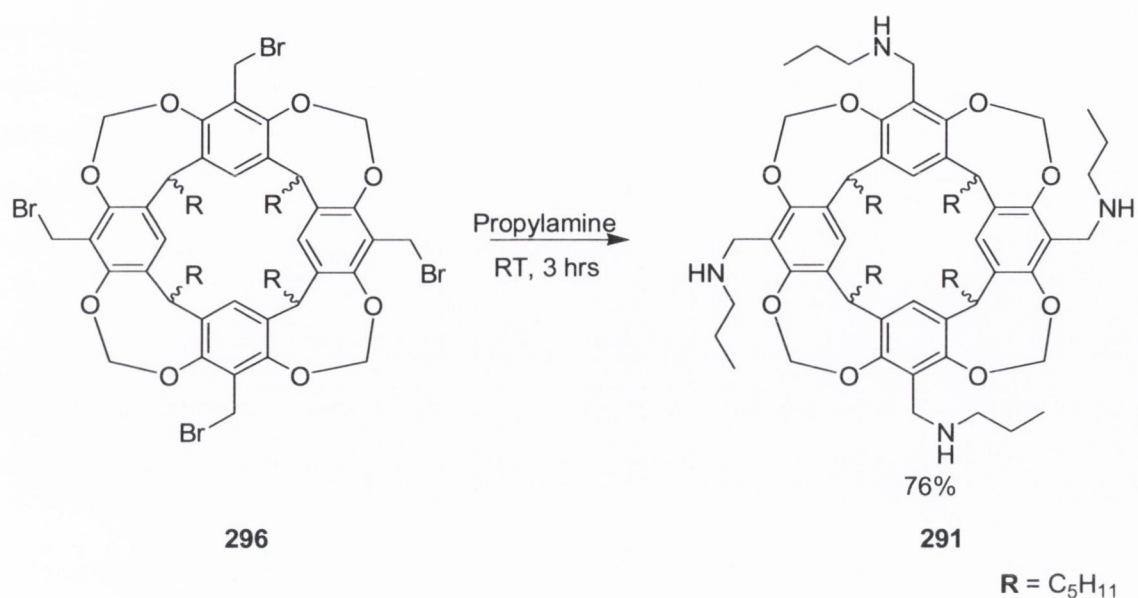
The ^1H NMR spectrum (400 MHz, D_2O) of the novel cavitand **298** is shown in Figure 5.7. The signal for the proton on the aromatic ring is observed at 7.26 ppm. The *exo* and *endo* protons of the CH_2 cavitand bridge give rise to two characteristic doublets, due to geminal coupling. These are observed at 5.95 and 4.25 ppm respectively. The signals for the alkyl chain protons, the three signals furthest upfield, are all considerably broadened in the HCl salt. The singlet corresponding to the CH_2 adjacent to the amino group was observed at 3.91 ppm.

Figure 5.7: ^1H NMR (400 MHz, D_2O) of cavitand 298

Although this transformation also involves two steps, there is no lengthy purification necessary at either step, which leads to an overall yield of *ca.* 80%, a significant improvement on the literature values. Consequently, this method was employed in all subsequent syntheses of cavitand **290**.

5.2.2 Synthesis of Propylaminomethyl Cavitand 291

The propylaminomethyl cavitand (**291**) was formed in one step from the bromomethyl cavitand (**296**) previously described. The reaction was carried out by stirring **296** at room temperature in neat propylamine. The unreacted amine was then removed by distillation, and the cavitand was isolated after a simple acid base work up in 76% yield (**Scheme 5.5**).



Scheme 5.6: Synthesis of propylaminomethyl cavitand 7

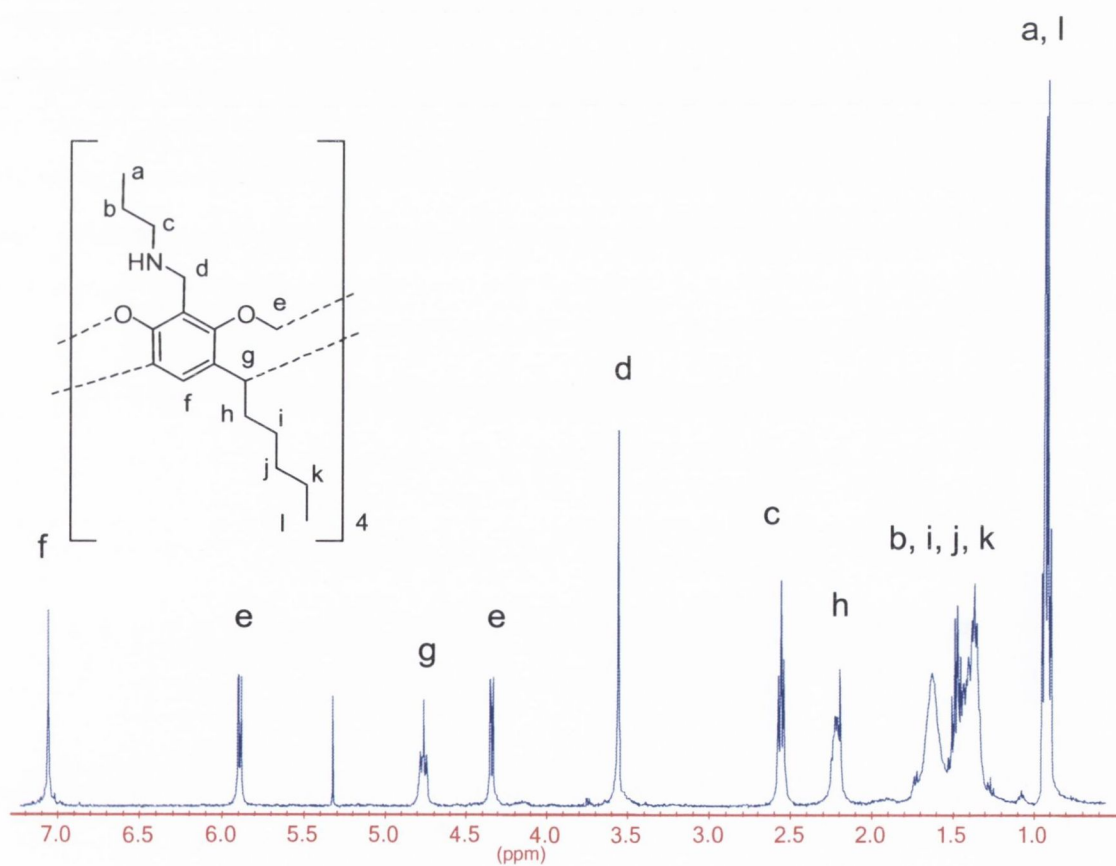


Figure 5.8: 1H NMR (400 MHz, $CDCl_3$) of cavitand 291

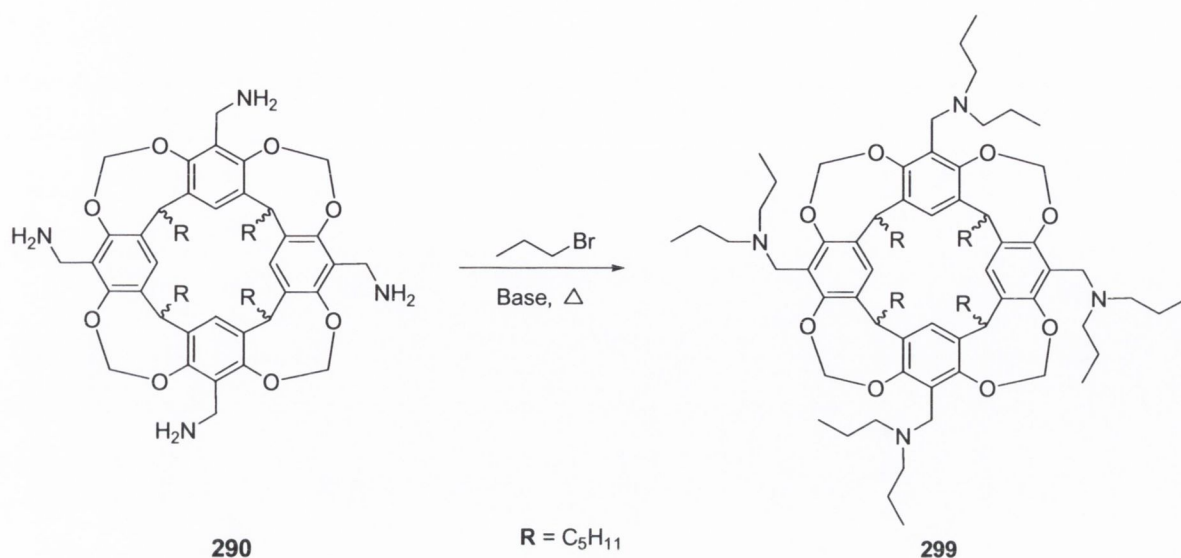
The ^1H NMR (400 MHz, CDCl_3) of cavitand **291** is shown in **Figure 5.8**. The proton *f* appears as a singlet at 7.06 ppm. The characteristic pair of doublets arising from the cavitand bridge appear at 5.89 and 4.34 ppm. The CH group, *g*, appears as a triplet at 4.76 ppm. The CH_2 group adjacent to the aromatic ring, *d*, appears as a singlet at 3.56 ppm. The remaining signals correspond to groups in the alkyl chains of the lower and upper rim of the cavitand.

5.3 Functionalisation of the Aminomethyl Cavitands

Having successfully synthesised the desired starting material cavitand, the next step was to carry out further functionalisation on these structures using pyridine based ligands. The following two sections describe our efforts towards this goal.

5.3.1 Model Studies of the Alkylation of Aminomethyl Cavitands

Initially, a few simple alkylation reactions were carried out on the aminomethyl cavitand (**290**) to see which conditions were most appropriate for the introduction of our complex ligands. The alkylating agent chosen for this purpose was bromopropane. This would give a similar product to the propylaminomethyl cavitand so the outcome of the reaction should be easy to ascertain. The reactions carried out are summarised in **Table 5.1**. The reactions were all worked up in an identical manner; the reaction solvent was evaporated and the residue was redissolved in $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$. The organic layer was then separated and dried over MgSO_4 and the solvent removed under reduced pressure.



Scheme 5.7: Alkylation of cavitand 290 with bromopropane

Table 5.1: Alkylation of cavitand 290 with bromopropane, * indicates reaction was carried out in a pressure tube

Reaction	Base	Solvent	Conditions	Yield
A	K ₂ CO ₃	MeCN	100 °C*, 16 hrs	91%
B	Cs ₂ CO ₃	MeCN	100 °C*, 16 hrs	84%
C	NaH	DMF	80 °C, 16 hrs	-

The ¹H NMR (400 MHz, CDCl₃) spectra obtained from these reactions are shown in **Figure 5.9**. The spectra clearly show that the choice of base plays an important role in the outcome of the reaction. In reaction **A**, the ¹H NMR spectrum shows the desired product (**299**) has been obtained in relatively high purity after a simple work up. The ¹H NMR, as expected, is very similar to that obtained for cavitand **291** (**Figure 5.8**), and the same assignment applies. The downfield section of the ¹H NMR shows a singlet for the proton on the aromatic ring, two doublets for the methylene cavitand bridge and a triplet for the bridging proton of the resorcarene substructure. The upfield section shows the expected singlet for the CH₂ group adjacent to the aromatic rings on the upper rim and various multiplets for the alkyl chain protons from the upper rim propyl groups and the lower rim pentyl groups.

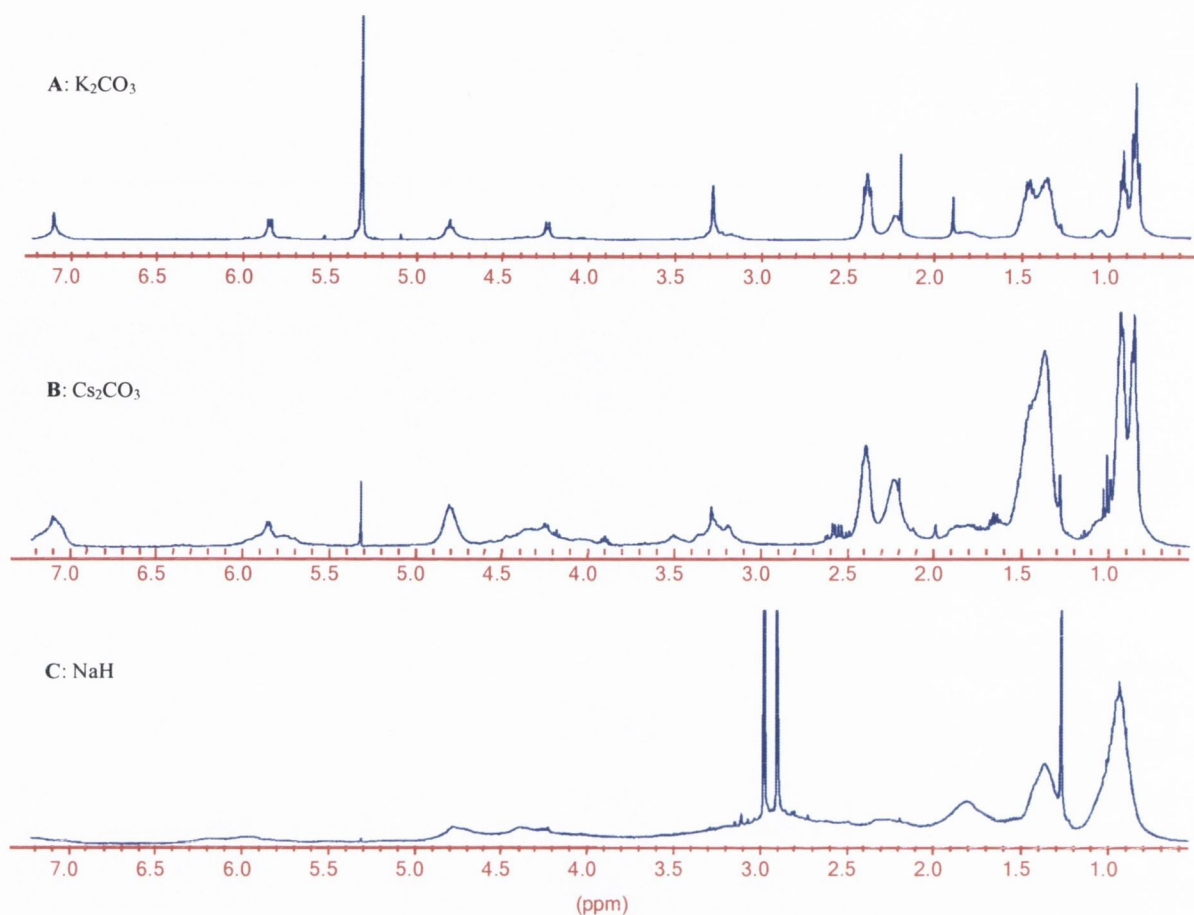


Figure 5.7: ^1H NMR (400 MHz, CDCl_3) spectra obtained from the reaction of cavitand **290** and bromopropane under different conditions

In reaction **B** the cavitand **290** has undergone alkylation, nevertheless there is still evidence of unreacted and/or partially reacted compounds in the ^1H NMR spectrum. The reaction catalysed by NaH was not successful, as neither the desired compound nor the unreacted cavitand are observed in the spectrum, perhaps indicating that this base is too strong for these compounds and has led to their decomposition.

For the alkylation of cavitand **290** with bromopropane under the conditions described in **Table 5.1** K₂CO₃ is by far the best choice of base. Although the reaction conditions in reaction **A** have proved most successful in this case, the change in ligand may mean that this may not necessarily hold true for later alkylation reactions. It does, however, show the importance of finding the right set of conditions.

5.3.2 Attempted Alkylation of Aminomethyl Cavitands with Amidopyridine Ligands

Gunnlaugsson and co-workers have previously shown that the attachment of pyridine containing amide groups to cyclen enabled the formation of La(III) and Eu(III) complexes.²²⁵ Cavitand analogues of these products were thus decided on as desirable targets, as they can be expected to display interesting metal binding properties.

The three pyridine containing ligands, differing only in the position of the amide, were synthesised in high yield by reaction of the appropriate aminopyridine with chloroacetyl chloride.²²⁹ 2-Chloro-*N*-pyridin-2-yl-acetamide (**300**) and 2-chloro-*N*-pyridin-4-yl-acetamide (**302**) were synthesised by the reaction of chloroacetyl chloride with a stirring solution of 2- or 4-aminopyridine and triethylamine in DCM at 0 °C. In the case of 2-chloro-*N*-pyridin-3-yl-acetamide (**301**) the ligand was synthesised by the addition of chloroacetyl chloride to a solution of 3-aminopyridine in acetone at 0 °C without the need for any additional base. The ligand was isolated as the HCl salt and was used in this form in further reactions.

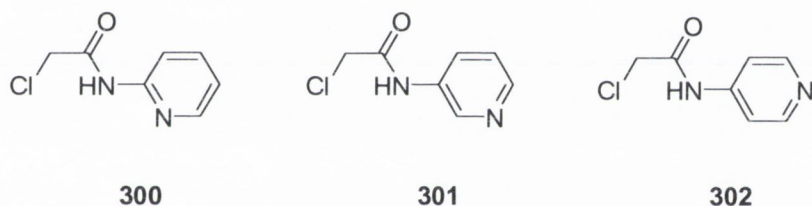


Figure 5.10: Pyridine based ligands

Following our successful alkylation of cavitand **290** using bromopropane we initially investigated the reaction of cavitand **290** with ligand **303** under the conditions described in row **A** of **Table 5.1**. However, this method proved unsuccessful, and consequently it was necessary to investigate a large range of other bases, solvents and starting materials. These attempts are summarised in **Table 5.2**. The reaction outcomes have been classified into three main categories; when the original cavitand was reisolated the reaction outcome was classified as no reaction (**NR**). When a reaction had taken place, but the desired compound was not observed by NMR spectroscopy or mass spectrometry, and could not be isolated by standard purification methods this was classified as desired product not observed (**NO**), and finally when no cavitand like compound was observed after the reaction then the outcome was classified as the decomposition of the starting materials (**D**).

Table 5.2: Attempted synthesis of amidopyridine functionalised cavitands, where iodide salts were used the cavitand was stirred with the base and salt for 1 hr prior to the addition of the ligand. *reactions carried out in a pressure tube. NR = no reaction, D = Starting materials decomposed, NO = desired product not observed

Cavitand	Ligand	Base	Solvent	Reaction Conditions	Result
290	301. HCl	Et ₃ N	DCM	40 °C, 48 hrs	NR
290	302	K ₂ CO ₃ , KI	MeCN	100 °C* 16 hrs	D
290	301.HCl	Et ₃ N	DCM	48 °C, 48 hrs	NO
298	302	Cs ₂ CO ₃ , KI	DMF	80 °C, 72 hrs	NO
298	300	K ₂ CO ₃ , NaI	Acetone	56 °C 16 hrs	D
298	302	K ₂ CO ₃ , NaI	Acetone	56 °C 16 hrs	NO
298	22.HCl	K ₂ CO ₃ , KI	MeOH	65 °C 72 hrs	NO
298	300	H ₂ KPO ₄ , KI	MeCN	72 °C, 16 hrs	NO
291	302	Cs ₂ CO ₃ , KI	DMF	80 °C 72 hrs	NO
291	302	NEt ₃	DCM	40 °C, 16 hrs	NR
291	301.HCl	Cs ₂ CO ₃ , KI	DMF	80 °C 72 hrs	NO
291	300	HK ₂ PO ₄ , KI	MeCN	82 °C 16 hrs	D
291	300	Cs ₂ CO ₃ , KI	DMF	80 °C, 72 hrs	NO
291	300	NEt ₃	DCM	40 °C, 16 hrs	NR

As can be seen from this summary, none of the reaction conditions employed led to the isolation of the desired product. Nor was any evidence of the target compounds observed from mass spectrometry analysis. One possible reason for this is that the high base equivalents used in the alkylation of cavitands is not suitable for these ligands and may have led to unwanted side reactions where the chloromethyl group of the ligand is reacting with the nitrogen of the pyridine ring. The occurrence of this side reaction has since been conclusively demonstrated within the Gunnlaugsson group and a crystal structure has been obtained of the product of the alkylation reaction between two molecules of ligand **301**.²²⁹ The structure of this possible side product is shown in **Figure 5.11**.

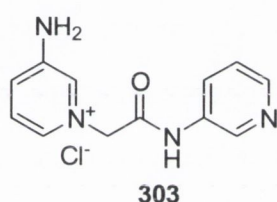
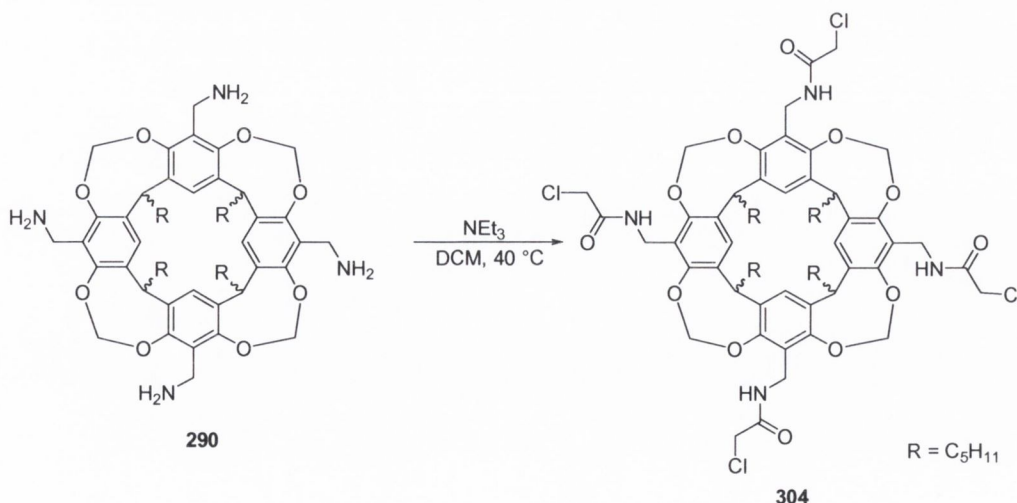


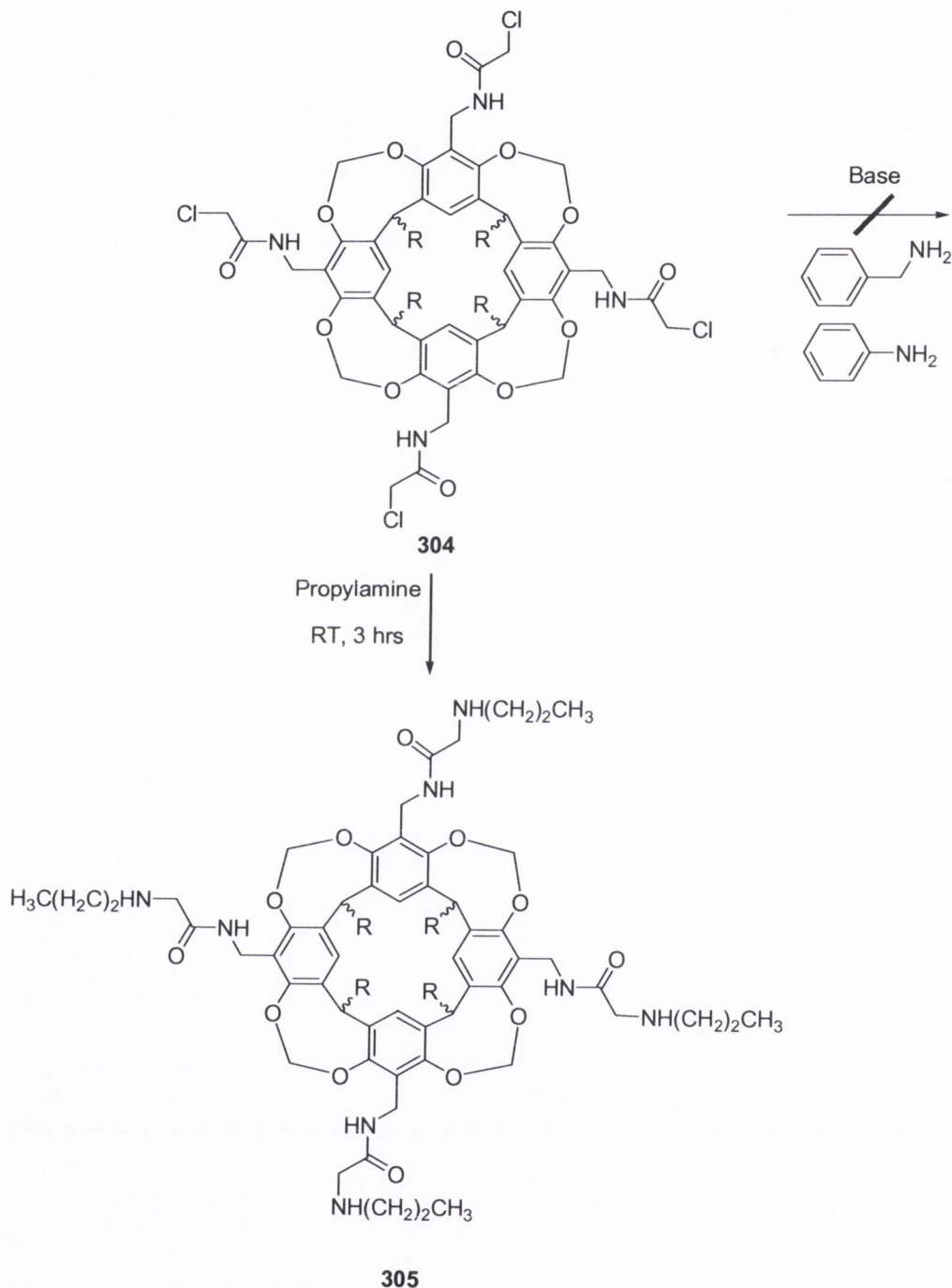
Figure 5.11: Side product obtained during reaction with ligand **301**

As the direct alkylation of the aminocavitands (**290**, **291** and **298**) with the pyridine ligands (**300-302**) was unsuccessful it was decided to further functionalise the upper rim to change its reactivity. The aminomethyl cavitand (**290**) was successfully derivitised by base catalysed reaction with chloroacetyl chloride to give compound **304**. This left a chloromethyl group on the upper rim of the cavitand making it possible to alkylate this site with amines.



Scheme 5.8: Further derivitisation of cavitand **290**

Cavitand **304** was then reacted with both aliphatic (propylamine and benzylamine) and aromatic (aniline) amines according to **Scheme 5.9**. The only product successfully isolated from these reactions was that from the reaction of **304** and propylamine. This is possibly because the propylamine is the most basic of the amines.

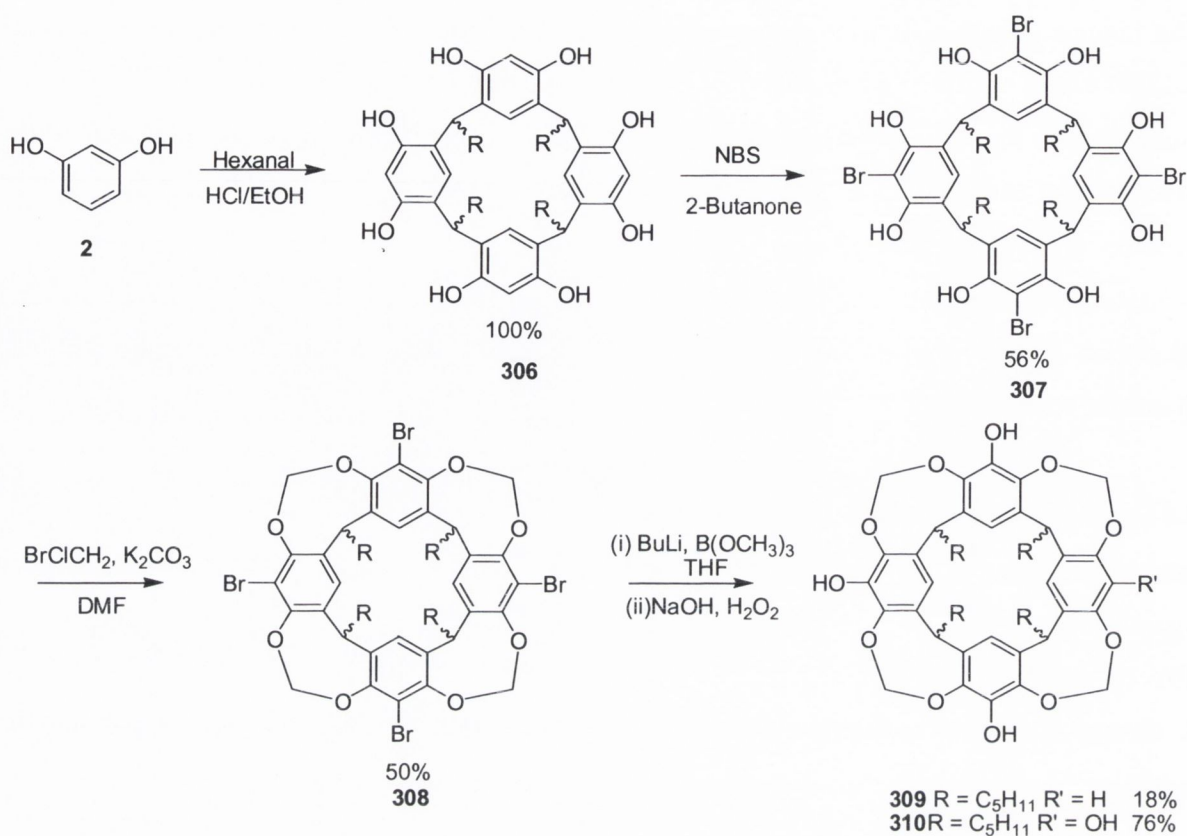


The planned functionalisation of cavitand ligands **290** and **291** with amidopyridine ligands (**21-23**) was ultimately not successful. Nor did the reaction of cavitand **304** with aromatic amines yield any of the desired products. No method has, as yet, been developed for the suitable functionalisation of these cavitands with aromatic ligands. Consequently, it was decided at this point to change strategy and to work with a different functionality for alkylation on the upper rim. The synthesis of the triol (**309**) and tetrol (**310**) cavitands, their alkylation and the preliminary studies carried out on the resulting novel cavitands will be discussed next.

5.4 Synthesis of Tetrol and Triol Cavitands

As a new approach, another type of functionalised cavitand was investigated as a platform for ligand attachment. These cavitands feature hydroxyl groups on their upper rim, which being directly attached to an aromatic ring, have acidic protons and are very amenable to alkylation. A change in ligand to the use of benzoic acid was decided upon due to the previously mentioned problem with the self-reaction of the amidopyridine ligands.

The tetrol cavitand can be formed in four steps.¹⁰⁸ In the first step, resorcinol (**2**) and hexanal undergo acid catalysed condensation to obtain the desired resorcarene. This reaction goes in near quantitative yield and only the desired boat isomer was formed. Stirring of this resorcarene with NBS gave the tetrabrominated derivative **307** in 56% yield, where the bromo groups are at the 2 position of the resorcinol subunit; a position highly activated by the adjacent hydroxyl groups. The formation of the cavitand of the bromoresorcarene was initially carried out in DMSO using Cs_2CO_3 as a base. Again in this synthesis, a large amount of the tribridged product was present at the end of the reaction. The desired tetra-bridged cavitand was however, the sole product isolated when this reaction was carried out at high temperatures in a pressure tube (75%). The use of pressure tubes allows the reaction to be put under more forcing conditions, not only shortening the reaction time, but also increasing the yield of the tetra-bridged product.²²¹



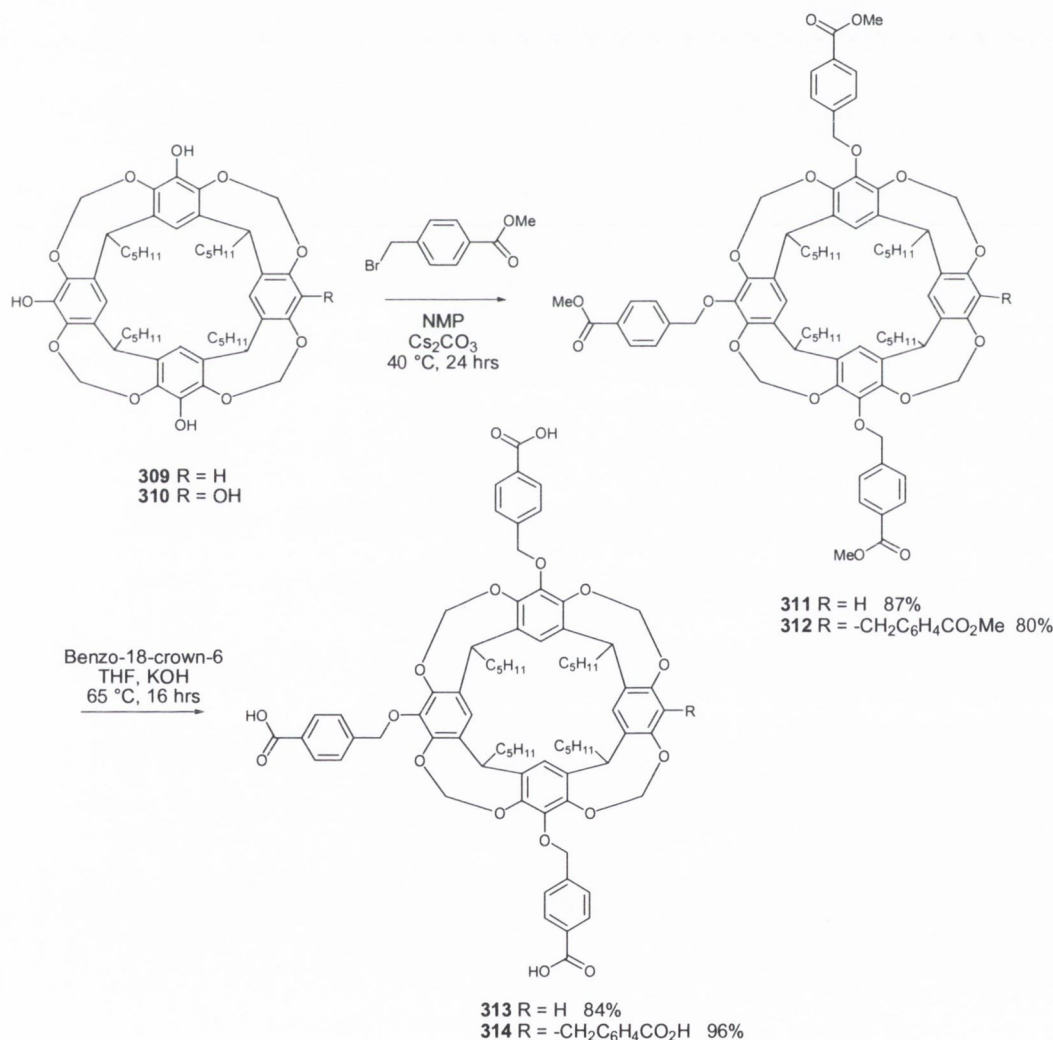
Scheme 5.10: Synthesis of the tetrol and triol cavitands

The introduction of the hydroxyl group on the upper rim was carried out by the introduction of a boronic ester, using BuLi and B(OMe)_3 , and its subsequent decomposition upon addition of an aqueous solution of H_2O_2 and NaOH (Scheme 5.10).²³⁰ This reaction can also lead to the formation of several side products where the upper rim contains less than four hydroxyl groups, the remaining positions being substituted with either hydrogen or bromine atoms. The synthesis of these side products, if desired, can be optimised by altering the conditions of the reaction, different equivalents of BuLi and reaction lengths being the most crucial factors,²³¹ an example of this has been published by Sherburn and co-workers, who found that they could functionalise alternating groups on the upper rim in reasonable yields (58% for functionalisation with hydroxyl groups) when 2.1 equivalents of $n\text{BuLi}$ were used in place of the usual two-fold excess.²³² In our hands, during the synthesis of the tetrol derivative (**310**), the main side product formed was a previously reported cavitand which contained three hydroxyl groups on the upper rim, the remaining upper rim aromatic position being substituted with a proton (**309**).

5.5 Alkylation of Tetrol and Triol Cavitands with Benzoic Acid Ligands

In this section, the successful synthesis of four novel cavitands will be discussed. The further derivitisation of these ligands to give four novel compounds with either benzoic acid or benzoic methyl ester groups on the upper rim is then detailed. In the final part of this chapter the preliminary findings on the interaction of these ligands with a range of metals is reported.

The triol and tetrol cavitands (**309** and **310**) were both successfully alkylated using the commercially available methyl-4-bromomethyl benzoate, to give the products **311** and **312** in high yields of 87 and 80%, respectively. These compounds were converted to the corresponding benzoic acid derivatives, **313** and **314**, by refluxing **311** and **312** in a 1:1 mixture of THF and 1M aqueous KOH solution with a catalytic amount of benzo-18-crown-6.



Scheme 5.11: Synthesis of benzoic acid functionalised cavitands

The ^1H NMR spectrum (400 MHz, CDCl_3) of the tri-ester cavitand (**311**) and the ^1H NMR spectrum (400 MHz, $\text{DMSO}-d_6$) of the tetra-acid cavitand (**314**) are shown in **Figures 5.12** and **5.13**, respectively. As can be seen from the spectra, the lower symmetry of the tri-functionalised compounds leads to a more complex spectrum. The protons for the methylene group of the cavitand-bridge appear as a pair of doublets in the tetra-substituted product (**314**) while in the case of the tri-substituted cavitand (**311**) these protons lead to four doublets, two of which overlap slightly. An increase in complexity in the aromatic region corresponding to the resorcarene substructure is also observed in **311** compared to that of **314**. In compound **311**, three singlets are observed, the signal at 6.88 ppm integrates for three protons and corresponds to the protons on the lower rim of the aromatic rings that bear upper rim substituents, another two singlets, observed at 7.09 and 6.52 ppm, correspond to the upper and lower rim proton of the unsubstituted aromatic ring.

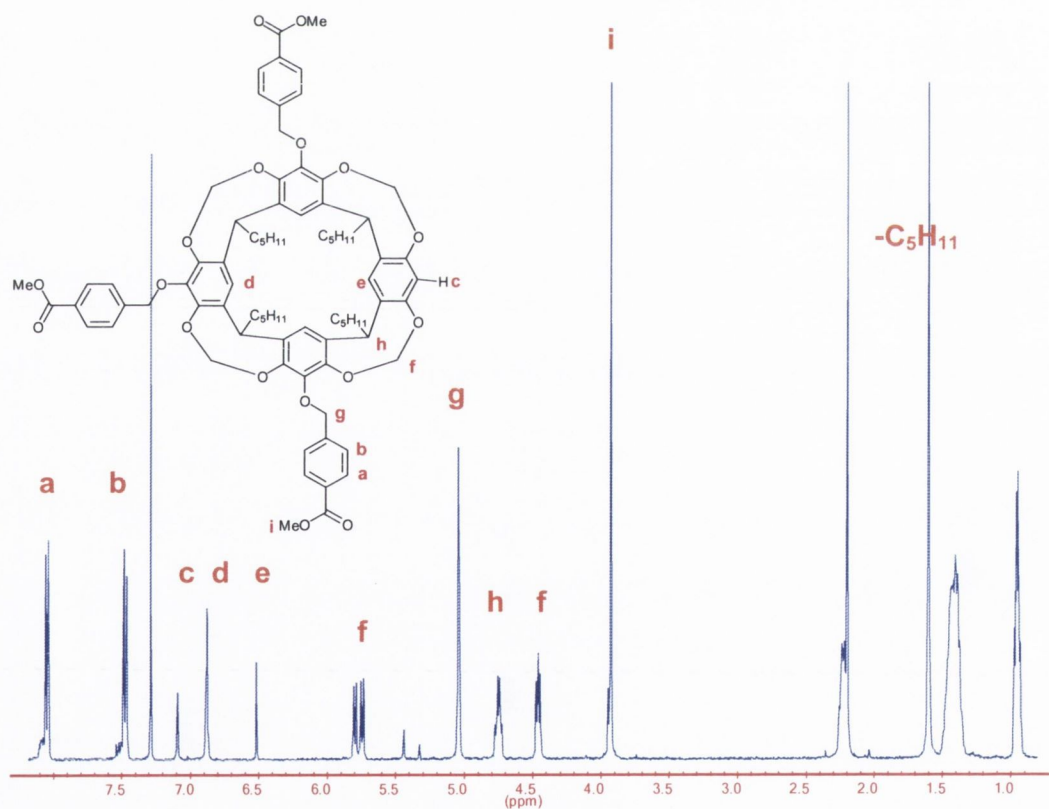


Figure 5.12: ^1H NMR (400 MHz, $\text{DMSO}-d_6$) of cavitand **311**

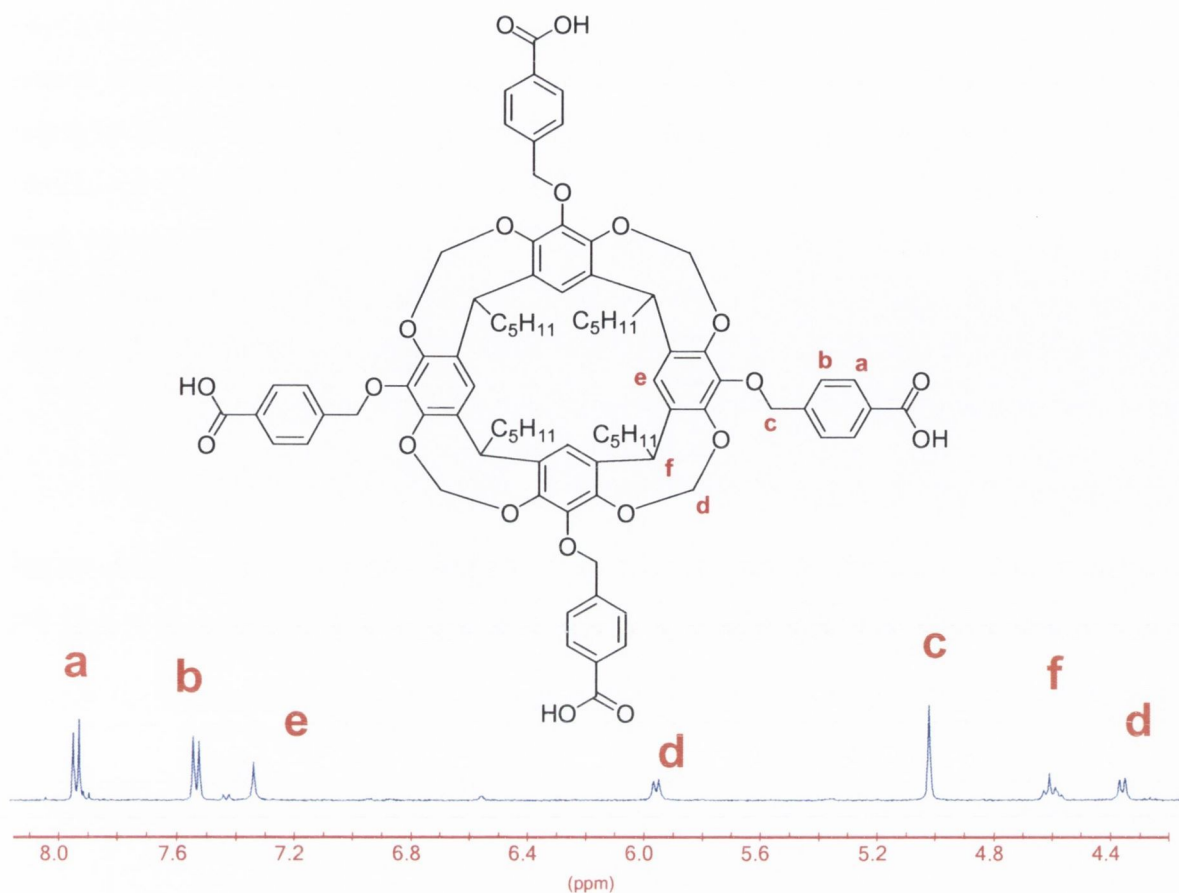


Figure 5.13: ¹H NMR (400 MHz, DMSO-*d*₆) of cavitand 314

In summary, novel cavitands with either three or four ester groups on the upper rim had been successfully synthesised in five steps. An additional step yielded two more novel cavitands (**313** and **314**), having either three or four benzoic acids groups on the upper rim. In the final part of this chapter, preliminary recognition studies carried out on these molecules will be reported. These results will be followed up by a more comprehensive investigation to be carried out within the Gunnlaugsson group.

5.6 Preliminary Binding Studies

The binding ability of the four novel compounds described above (**32-33**) was screened towards a range of metal ions. These measurements were carried out on 1×10^{-5} M solutions of the ligands in either MeCN (compounds **313** and **314**) or in a 1:1 CH₃CN:CHCl₃ mixture (compounds **311** and **312**). The change in solvent system was due to the insolubility of these

ester compounds in MeCN. Eight metal salts, chosen to include cation components from group I (NaCl, KI), group II (CaSO₄), transition (Zn(AcO)₂, NiCl₂, AgPF₆) and lanthanide metals (Eu(OTf)₃, Tb(OTf)₃), were screened in the preliminary binding studies. An excess of metal salt was added to a 3 ml solution of the ligand and the mixture was allowed to equilibrate overnight. The absorbance spectra and the fluorescence emission spectra of the ligands were recorded and compared with those obtained after the addition of the metal salts. When lanthanide salts were added the phosphorescence spectra were also recorded. The results obtained for each of the ligands will now be discussed in turn.

5.6.1 Results for Compound 311

The absorption spectrum of **311** changed on addition of most of the metal ions tested, except for Ca²⁺ as can be seen in **Figure 5.14**. In all cases apart from Ni²⁺ we see a growth in the band at 270 nm, this increase is most pronounced for Zn²⁺.

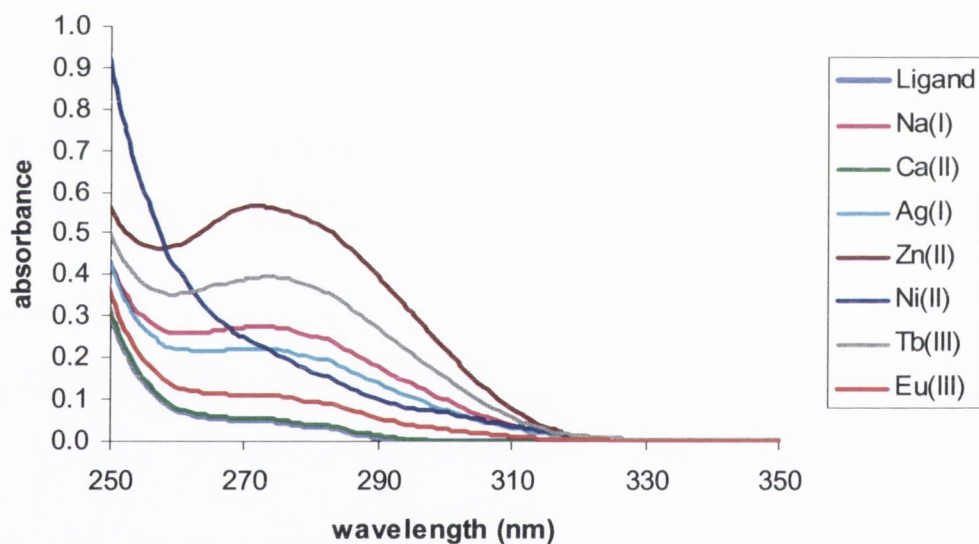


Figure 5.14: The absorbance spectra of compound 311 [1×10^{-5} M] in 1:1 CH₃CN:CHCl₃ and upon addition of an excess of various metal salts

The fluorescence emission spectrum of **311** also changes upon the addition of these metal salts (**Figure 5.15**). The spectra obtained after the addition of an excess of Zn²⁺ and Tb(III) showed the largest increase in the fluorescence intensity of the compound. These spectra are omitted from the figure below as the fluorescence intensities were out of range. All the metal ions

screened show significant changes and, after Zn^{2+} and Tb(III) , Na^+ and Ag^+ showed the largest increase in intensity. However, the emission of the ligand is completely quenched upon addition of K^+ .

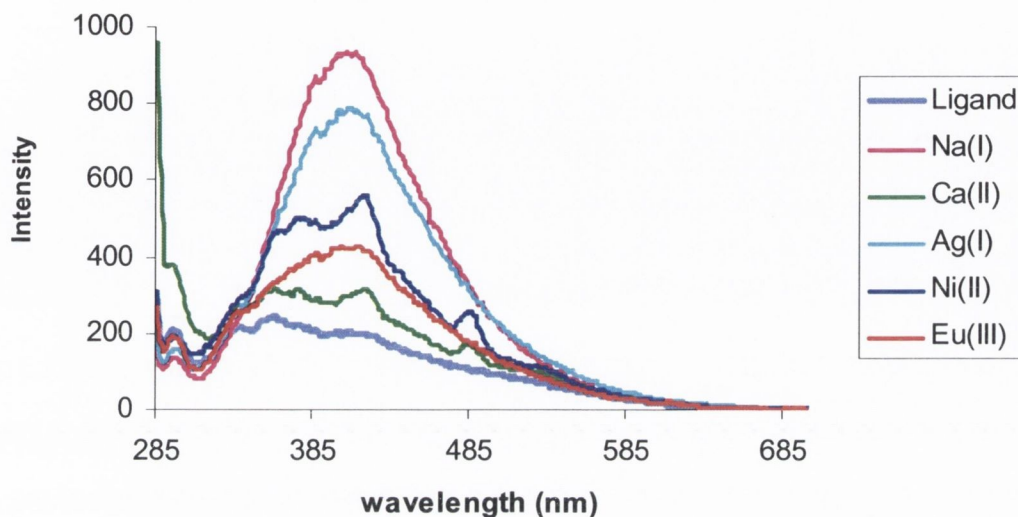


Figure 5.15: Fluorescence emission spectra of ligand 311 [1×10^{-5} M] in 1:1 $\text{CH}_3\text{CN}:\text{CHCl}_3$ and upon addition of various metal salts (exciting at 274 nm)

The binding of lanthanide ions by compound **311** was also confirmed by observing the Eu(III) and Tb(III) emission at long wavelength upon excitation at 274 nm. The spectra obtained after the addition of Eu(III) and Tb(III) are shown in **Figure 5.16a** and **Figure 5.16b**, respectively. The fine structures of the phosphorescence spectra are characteristic of Eu(III) and Tb(III) complexes. It is worth noting the difference in intensity of these spectra. Eu(III) is known to be able to quench the excited states of phenol derived antennae, which explains the low intensity in comparison to the spectrum obtained for Tb(III) .

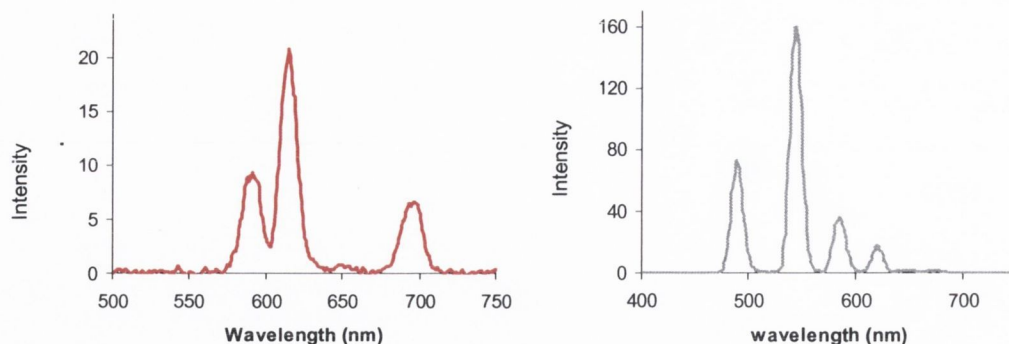


Figure 5.16: Phosphorescence spectra of ligand 311 [1×10^{-5} M] in 1:1 $\text{CH}_3\text{CN}:\text{CHCl}_3$ after addition of a) Eu^{3+} and b) Tb^{3+}

5.6.2 Results for Compound 312

The three-armed ester compound (**312**) shows slightly different behaviour than previously discussed. The spectrum, after addition of NaCl , shows little change from that of the ligand prior to any additions. A significant change was, however, observed with the addition of NiCl_2 , along with smaller changes for many other metal ions (Figure 5.17).

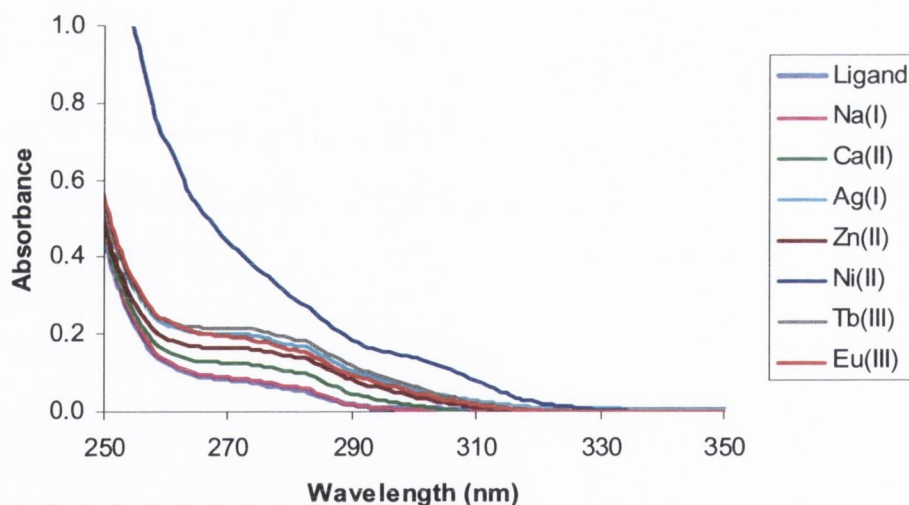


Figure 5.17: The absorbance spectra of compound 312 [1×10^{-5} M] in 1:1 $\text{CH}_3\text{CN}:\text{CHCl}_3$ and upon addition of an excess of various metal salts

The fluorescence emission spectrum of the ligand on addition of Ni^{2+} also increased significantly. The addition of Ag^+ , Zn^{2+} and Ca^{2+} also produce changes of a similar magnitude while little change is seen on addition of NaCl (**Figure 5.18**).

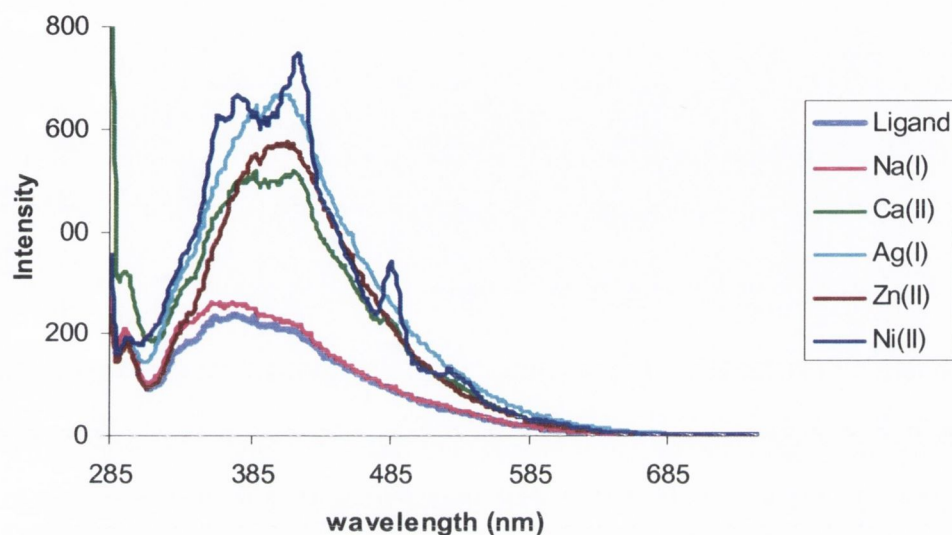


Figure 5.18: Fluorescence spectra of ligand **312** [1×10^{-5} M] in 1:1 $\text{CH}_3\text{CN}:\text{CHCl}_3$ and upon addition of various metal salts (exciting at 274 nm)

The binding of Eu^{3+} and Tb^{3+} by ligand **312** was also confirmed by the appearance of the characteristic lanthanide emission, occurring at long wavelengths, in the spectrum obtained after the addition of these salts to the ligand and excitation at 274 nm (**Figure 5.19**).

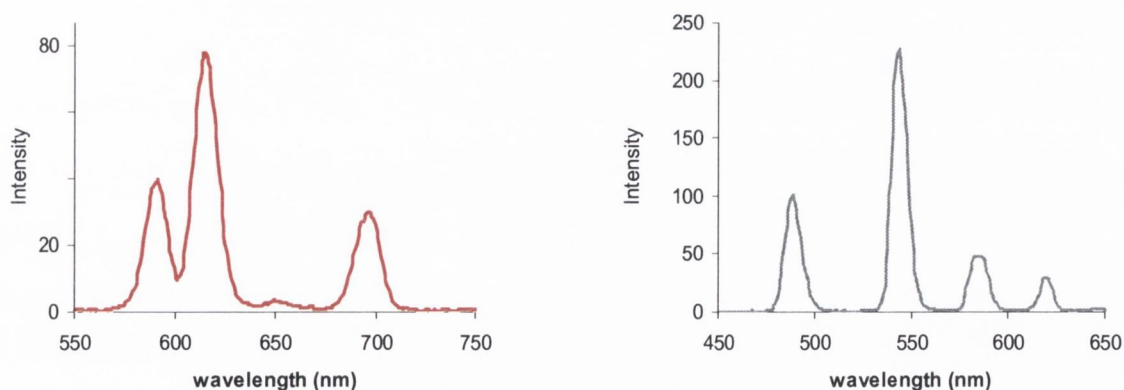


Figure 5.19: Phosphorescence spectra of ligand **312** [1×10^{-5} M] in 1:1 $\text{CH}_3\text{CN}:\text{CHCl}_3$ after addition of a) Eu^{3+} and b) Tb^{3+}

These results show that ligands **311** and **312** do have the ability to interact in some way with the salts added. A more detailed study will be carried out within the Gunnlaugsson group to determine the nature, strength and selectivity of these interactions, which cannot be fully understood on the basis of these preliminary measurements. The acid derivatives of these methyl esters were also investigated and the results for these ligands will now be discussed.

5.6.3 Results for Compound 313

The main differences noted in the band at 233 nm in the absorbance spectra of **313**, illustrated in **Figure 5.20**, are the large increase in its absorbance after the addition of Ni^{2+} and a significant decrease upon addition of Ca^{2+} . In the case of Ca^{2+} , a concomitant increase in the band at 274 nm was observed. The addition of either Na^+ or Ag^+ , resulted in a larger increase in the band at 274 nm.

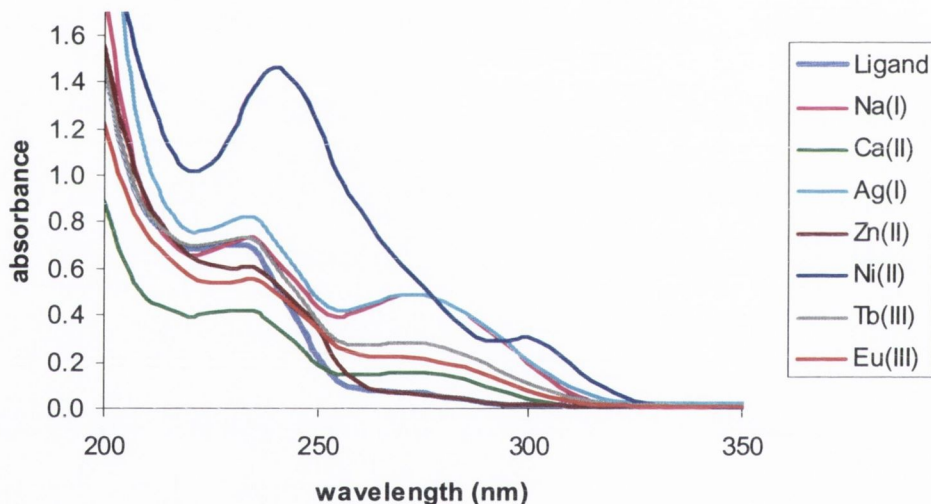


Figure 5.20: The absorbance spectra of compound **313** [1×10^{-5} M] in CH_3CN and upon addition of an excess of various metal salts

The metals that produce the most change in the fluorescence spectra of the ligand are Ca^{2+} , Zn^{2+} and Ni^{2+} . As can be seen from these spectra, there may have been some undissolved salt in these solutions, which although not visible to the naked eye, could cause scattering of the light and lead to the unexpected peaks observed (**Figure 5.21**).

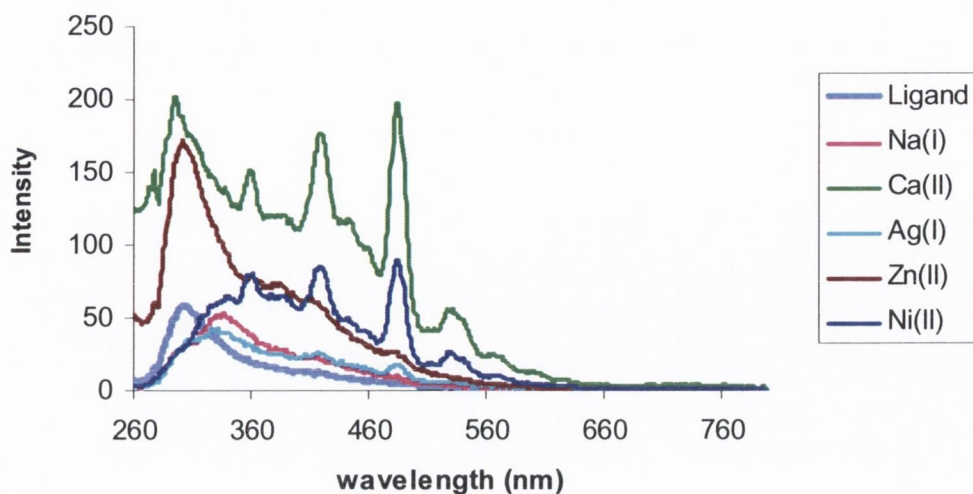


Figure 5.21: Fluorescence spectra of ligand 313 [1×10^{-5} M] in CH_3CN and upon addition of various metal salts (exciting at 233 nm)

The phosphorescence emission spectra obtained after addition of Eu^{3+} and Tb^{3+} again show that these ligands have the ability to bind lanthanides (Figure 5.22).

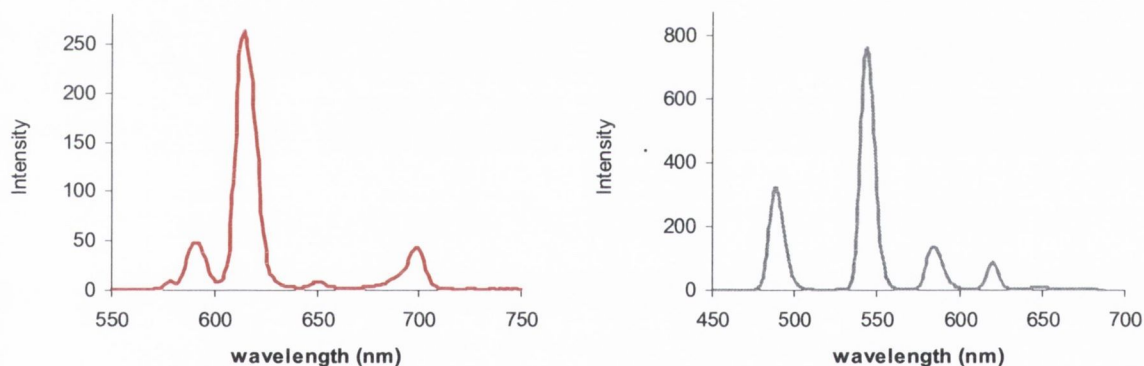


Figure 5.22: Phosphorescence spectra of ligand 311 [1×10^{-5} M] in CH_3CN after addition of a) Eu^{3+} and b) Tb^{3+}

5.6.4 Results for Compound 314

The most significant change observed in the absorbance spectra of **314** occurs after the addition of Eu^{3+} .

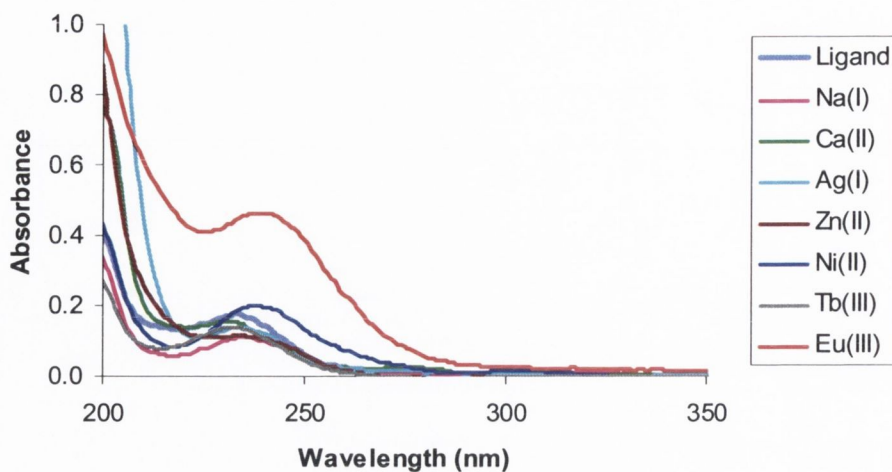


Figure 5.23: The change in absorbance of compound **314** [1×10^{-5} M] in CH_3CN and upon addition of an excess of metal salt

For **314** an increase is observed in the peak at 307 nm upon addition of Ca^{2+} and Zn^{2+} (Figure 5.24).

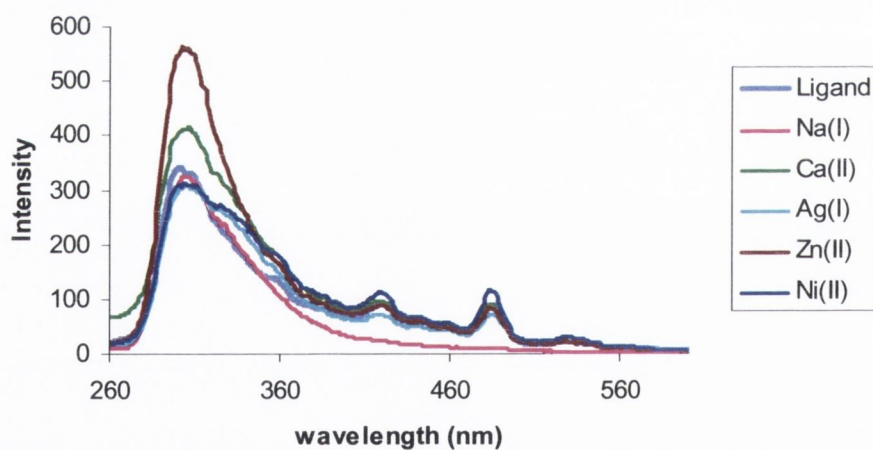


Figure 5.24: Fluorescence spectra of ligand **314** [1×10^{-5} M] in CH_3CN and upon addition of various metal salts (exciting at 233 nm)

The binding of lanthanide ions by ligand **314** is confirmed by the phosphorescence spectra recorded after the addition of Eu^{3+} and Tb^{3+} (Figure 5.25).

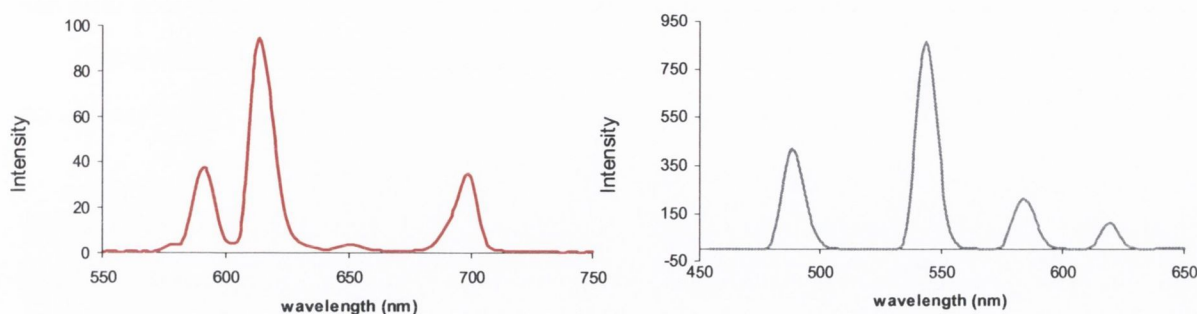


Figure 5.25: Phosphorescence spectra of ligand 314 [1×10^{-5} M] in CH_3CN after addition of a) Eu^{3+} and b) Tb^{3+}

5.6.5 Summary of the Results Obtained from Preliminary Measurements

To summarise the common trends, all the ligands tested showed an affinity for lanthanide metal ions and a change was also observed upon addition of Zn^{2+} to all compounds. For all the ligands, the intensity of the phosphorescence was higher for Tb(III) than that of Eu(III) , indicating a stronger interaction with the former. Although most spectra do show some change in the presence of the metal ions, it is difficult to draw further conclusions on this behaviour without more in depth investigation. More detailed work will thus need to be carried out on these ligands to determine the relative strength of their interactions with different metal ions and subsequently their selectivity.

5.7 Conclusions

- A number of cavitands, suitable for alkylation with ligand groups on the upper rim, were successfully synthesized (**12**, **13**, **19**, **31a** and **31b**).
- The alkylation of the amine cavitands (**12**, **13** and **19**) with the simple alkylating agent bromopropane was carried out to highlight the importance of reaction conditions and their effect on the outcome of the reaction.
- A series of pyridine ligands (**21-23**) were successfully synthesised and these were reacted with amine functionalised cavitands (**12**, **13**, **19**) under a large variety of conditions, this did not however lead to the successful isolation of the desired products.

- Cavitand **12** was successfully converted to amide functionalized cavitand **25**, which was then successfully alkylated, although this was only found to be possible with the simple and very basic amine, propylamine. No further derivitisation was successful.
- The hydroxyl functionalised cavitands (**31a** and **31b**) were successfully alkylated with methyl-4-bromomethyl benzoate to give the novel cavitands **311** and **312**.
- The upper rim methyl ester groups of cavitands **311** and **312** were successfully converted to acid groups leading to the isolation of two more novel cavitands: **313** and **314**.
- Preliminary studies were carried out on the interaction of cavitands **311**, **312**, **313** and **314** with various metal ions. The effects of ion addition were studied by UV, fluorescence and phosphorescence spectroscopy. Each ligand showed some metal binding ability with lanthanide complexes being formed in all cases.

Chapter 6

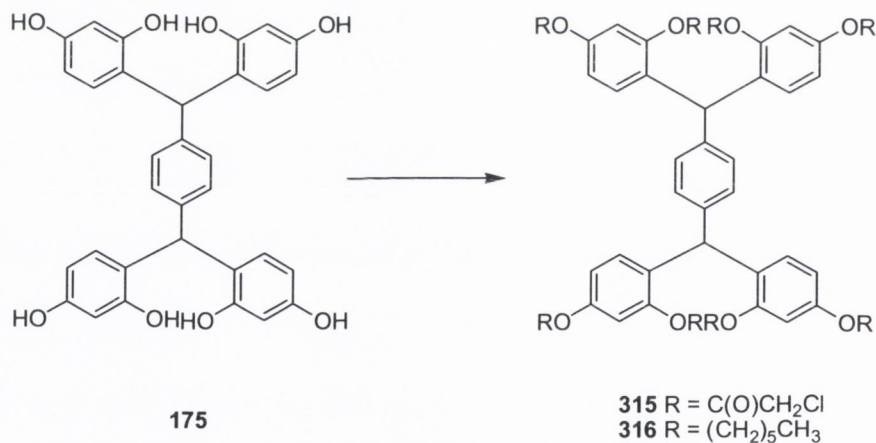
Future Work

6.1 Introduction

In each of the synthetic chapters discussed within this thesis, there is the potential for further work to be carried out and these possible future opportunities will each be outlined here in turn. In some cases, the preliminary results will also be reported. In these cases, this work was not completed due to time constraints, but will be continued in the Matthews and Gunnlaugsson research groups.

6.2 Future Work Arising from Chapter 2

In **Chapter 2** a number of acyclic resorcinol dimers were generated. These dimers, especially those with eight hydroxyl groups, show some possibilities as a dendrimer core. Preliminary work towards this end was carried out on these dimers by exploring the reactivity of the eight hydroxyl groups. The molecules proved amenable to functionalisation, **175** was successfully alkylated in all eight positions using either bromoalkanes or chloroacetylchloride. Hence, by incorporating other groups in these positions a new central core can be developed. Such work will be undertaken shortly.



Scheme 6.1: Alkylation of resorcinol dimer **175**

6.3 Future Work Arising from Chapter 3

Chapter 3 is perhaps the most interesting chapter in terms of future work. The OMRA compound **209b** (**Figure 6.1**), from which most of the results in this chapter stemmed from, possesses very interesting characteristics. The phenol groups of its lower rim should prove

amenable to either further functionalisation with various electrophiles, to make it a potential host or to further derivitisation to change the functionality.

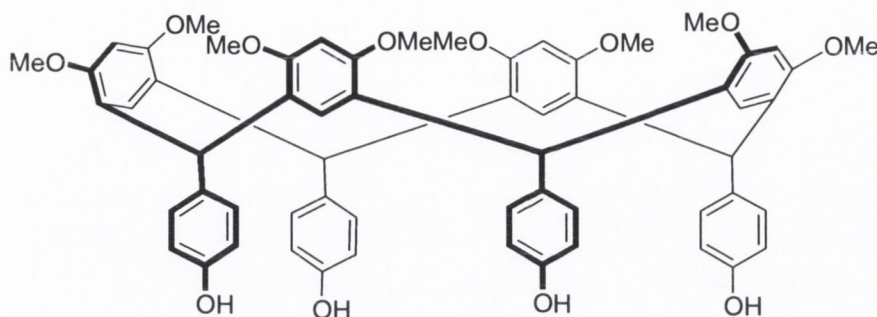


Figure 6.1: Structure of 209b

6.3.1 Results from a Preliminary Spectroscopic Study of 209b

Quite apart from the very interesting synthetic possibilities of this molecule, some intriguing spectroscopic properties were also noticed. The compound itself was a purple powder. However, in certain solvents, dependant on the concentration of **209b**, the solution changed colour. This is illustrated in **Figure 6.2**, where 1.65×10^{-4} M solutions of compound **209b** are made up in different solvents; the compound itself is also included in the photograph for comparison.

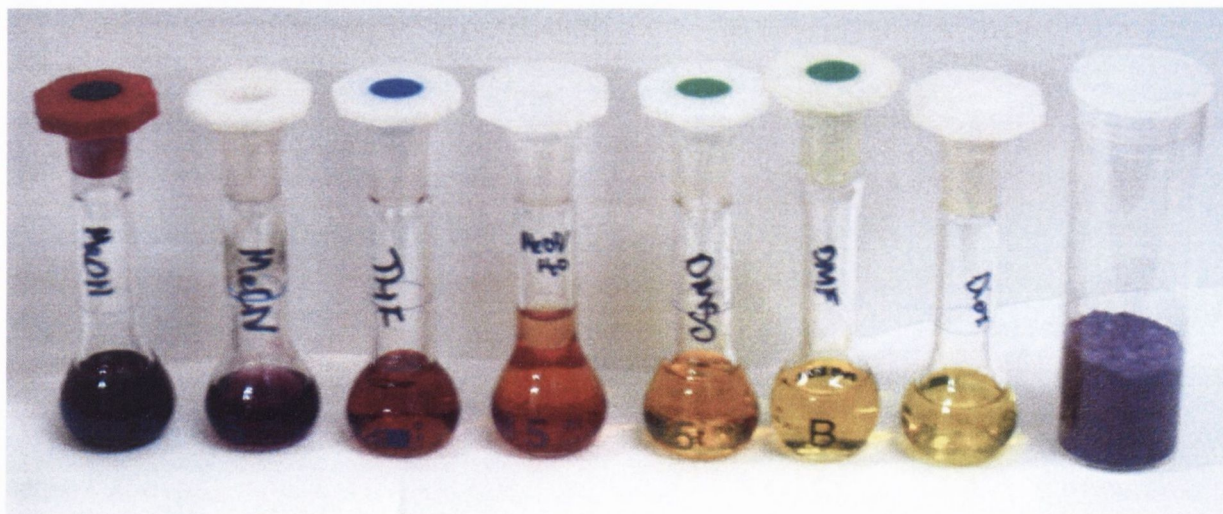


Figure 6.2: Colour change of compound 209b in various solvents (l→r MeOH, MeCN, THF, 1:1 MeOH:H₂O, DMSO, DMF, Dioxane) at $[1.65 \times 10^{-4}$ M] and the compound 209b, a purple powder

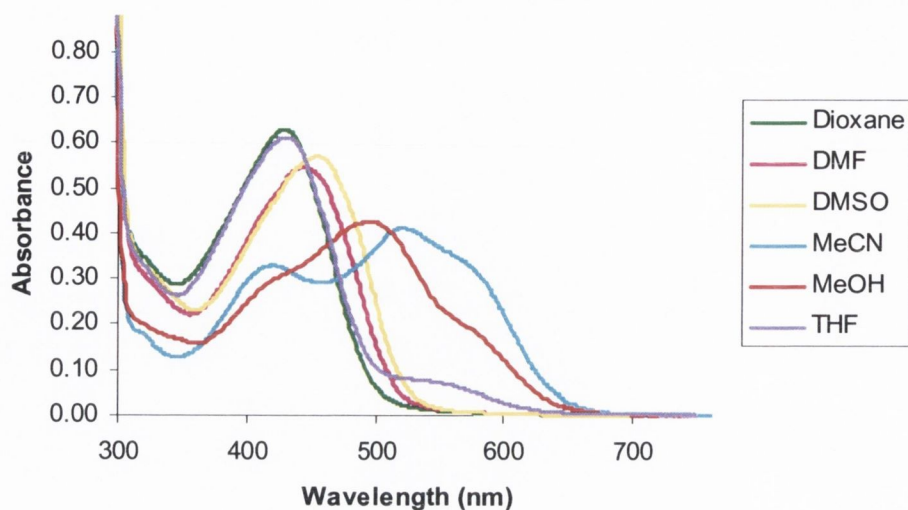


Figure 6.3: Absorbance spectra of **209b** in various solvents at 1.65×10^{-4} M concentration

The absorbance spectra of each of these solutions shown in **Figure 6.2** are illustrated in **Figure 6.3**. In the case of dioxane, a single band at 427 nm was observed, while in THF this band is also visible, but additionally a smaller band centred at *ca.* 552 nm is also observed. Solutions of **209b** in DMF and DMSO give rise to a single absorption band, which is somewhat shifted from that previously observed band in THF and now appears at *ca.* 446 nm. The absorbance spectra of **209b** in MeOH and MeCN are more complex, with three bands being observed in both solvents, although their λ_{max} occurs at different wavelengths; in MeOH, these three bands are observed at 416, 499 and 570 nm, while in MeCN they appear at 410, 516 and 570 nm. The increased complexity of the absorbance spectra in the case of MeOH and MeCN may indicate a stacking of the molecules at high concentration in solution, this has previously been reported in polar solvents.²³³ It has also been reported that π -stacking of molecules can play a role in their anion selectivity.²³⁴ This could also be due to aggregation of the molecules.

To investigate if the molecules are indeed stacking, the absorbance spectra of **209b** in MeCN were recorded at a series of ligand concentrations, from 1.65×10^{-4} to 1.65×10^{-5} M. The results obtained are shown in **Figure 6.4**. The expected overall decrease in the absorption spectrum is accompanied by the disappearance of the bands at 516 and 570 nm. At the lowest

concentration only the band originally at 410 nm remains and this has shifted to *ca.* 450 nm. The decrease in concentration is also accompanied by a purple to yellow colour change in the solution.

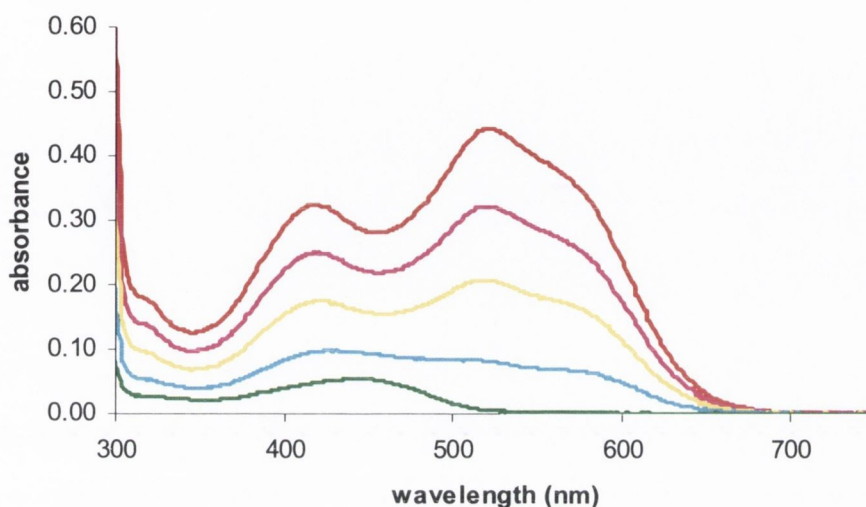


Figure 6.4: Change in the absorbance spectra of compound **209b** in MeCN as the concentration decreases from $[1.65 \times 10^{-4}]$ to $[1.64 \times 10^{-5}]$

In addition to the solvent effects discussed above, the effects of various anions on a $[1.65 \times 10^{-4}]$ solution of **209b** in MeCN were also investigated. The tetrabutylammonium (TBA) salts of the various anions, Cl^- , Br^- , I^- , F^- , OAc^- , were used to minimise the effect of the counter ion. The results obtained using TBA salts were also reproduced when potassium salts were used, indicating that the changes shown below are down to interaction with anions and that the counterion does not interfere. The structurally similar calixarenes have previously been shown to interact with anions.²³⁵ Interestingly, although the 1,3-alternate conformer bound dicarboxylates, the cone conformer was deprotonated.

When the TBA salts of bromide and chloride were added to the solution a gradual decrease in the band at 410 nm was observed, accompanied by a slightly larger decrease in the bands at 516 and 570 nm. The Br^- titration was halted at just over 80 equivalents of TBABr (**Figure 6.5**) while the chloride titration was halted after the addition of just over 90 equivalents

(Figure 6.6). No significant colour change was observed over the course of these titrations that were visible to the naked eye.

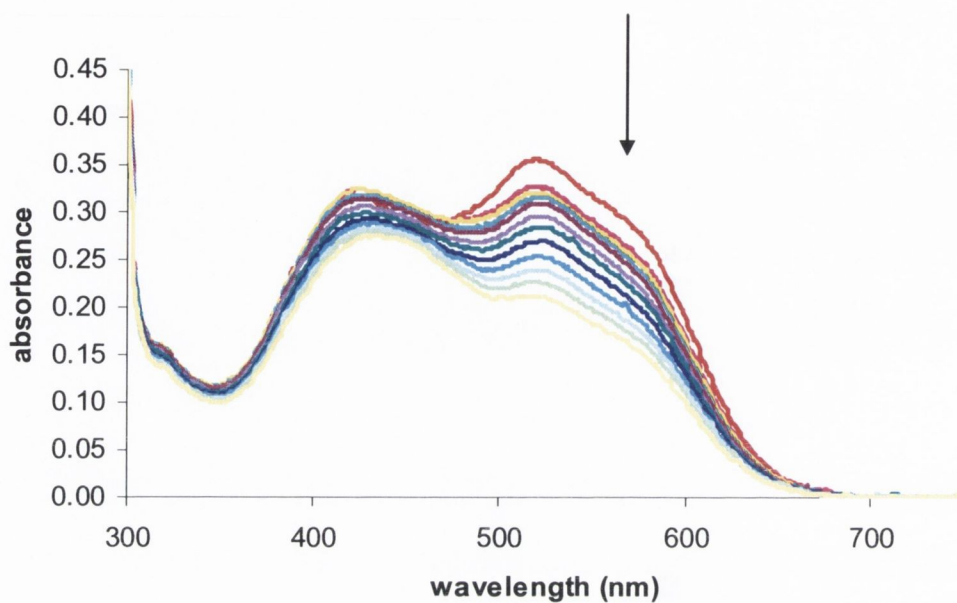


Figure 6.5: Change in the absorbance spectrum of 209b in MeCN [1.65×10^{-4}] upon addition of TBABr

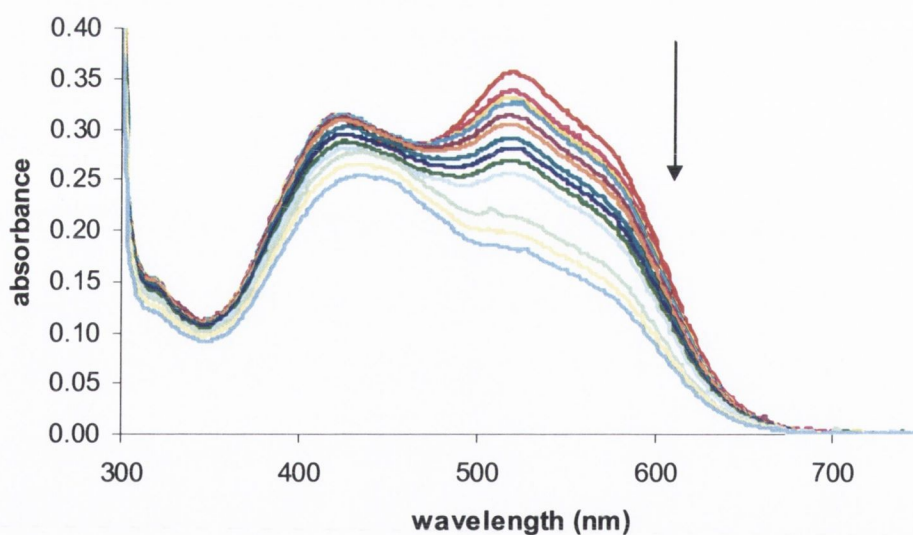


Figure 6.6: Change in the absorbance spectrum of 209b in MeCN [1.65×10^{-4}] upon addition of TBACl

The addition of TBAI to the 1.65×10^{-4} M solution of **209b** in MeCN caused a purple to yellow colour change after only two equivalents. After the addition of 10 equivalents, no

further changes were observed (**Figure 6.7**). This result implies that the iodide is interacting with compound **209b** much more strongly than was seen for chloride and bromide, which is extremely interesting.

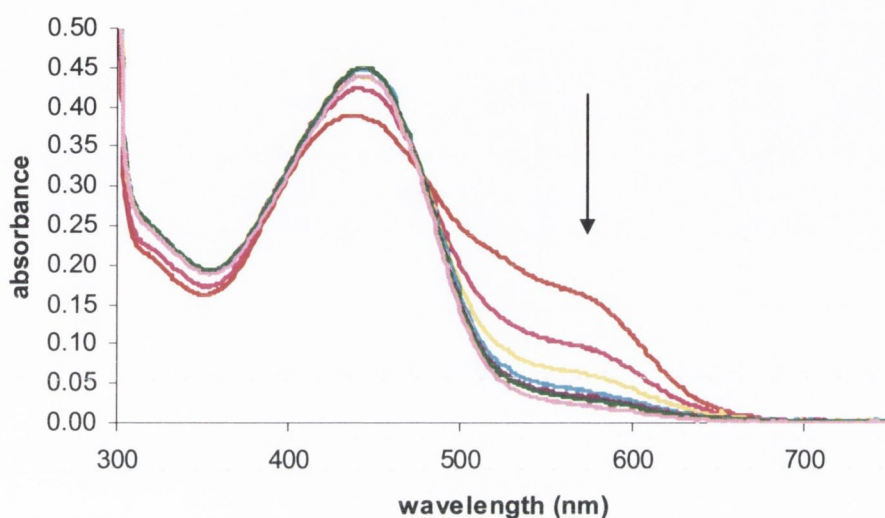


Figure 6.7: Change in the absorbance spectrum of 209b in MeCN [1.65×10^{-4}] upon addition of TBAI

The change observed upon addition of either TBAF or TBAOAc were similar and in fact, much more dramatic than that observed for any of the ions described above. In the case of TBAOAc, the solution turns to yellow after the addition of 0.5 equivalents of the salt. When **209b** is titrated with TBAF, this colour change takes place after the addition of one equivalent of the TBAF salt, when the bands at 516 and 570 nm disappeared. Upon additions of either the fluoride or acetate ions, the appearance of a new band, centred at 350 nm or 343 nm respectively, was observed.

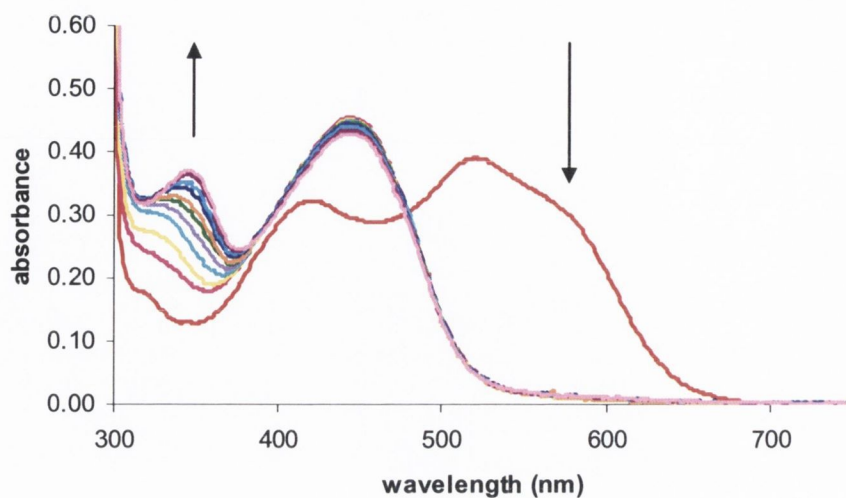


Figure 6.8: Change in the absorbance spectrum of 209b in MeCN [1.65×10^{-4}] upon addition of TBAOAc

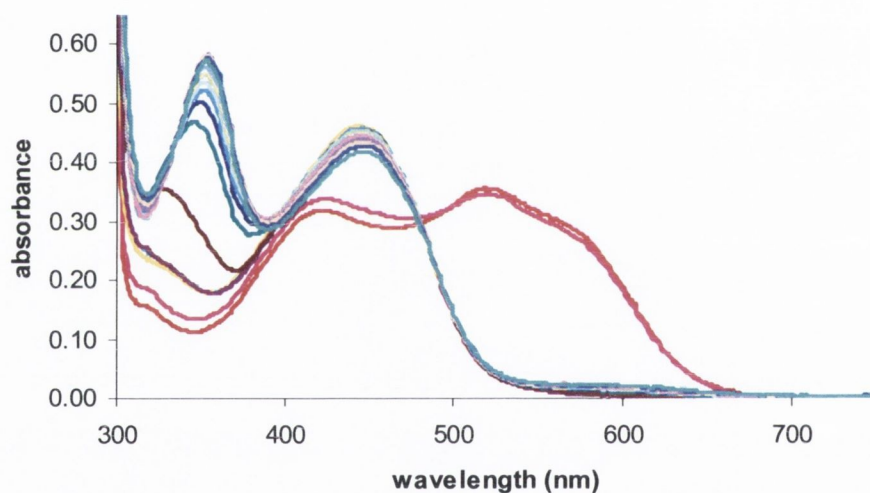


Figure 6.9: Change in the absorbance spectrum of 209b in MeCN [1.65×10^{-4}] upon addition of TBAF

When these titrations are carried out at with a 1.65×10^{-5} M solution of **209b** in MeCN no change in the absorption spectra was observed. This is very interesting and suggests that stacking or aggregation of the molecules at higher concentrations may be the reason for the changes observed.

All this data may be attributable to the stacking of the molecules of **209b** at high concentrations in polar solvents. Two of the possible many ways of stacking these molecules

are illustrated in **Figure 6.10**. In **Figure 6.10a** the stacking is due to a π - π stacking interaction between the aromatic groups on the lower rim, while in **Figure 6.10b** the stacking is due to hydrogen bonding of the hydroxyl groups on the lower between molecules of **209b**. When the molecules are in the non-polar dioxane the solution is yellow in colour, regardless of the concentration, indicating the molecules are not stacking or aggregating. This is also supported by the appearance of only a single band in the absorption spectrum. Although DMF and DMSO are highly polar solvents, molecules of these solvents have previously been shown to reside as guests in molecules similar to **209b**.^{99,198} The most plausible explanation in this case would therefore be that the solvent molecules are guests in the host **209b** and disrupt the molecules ability to stack.

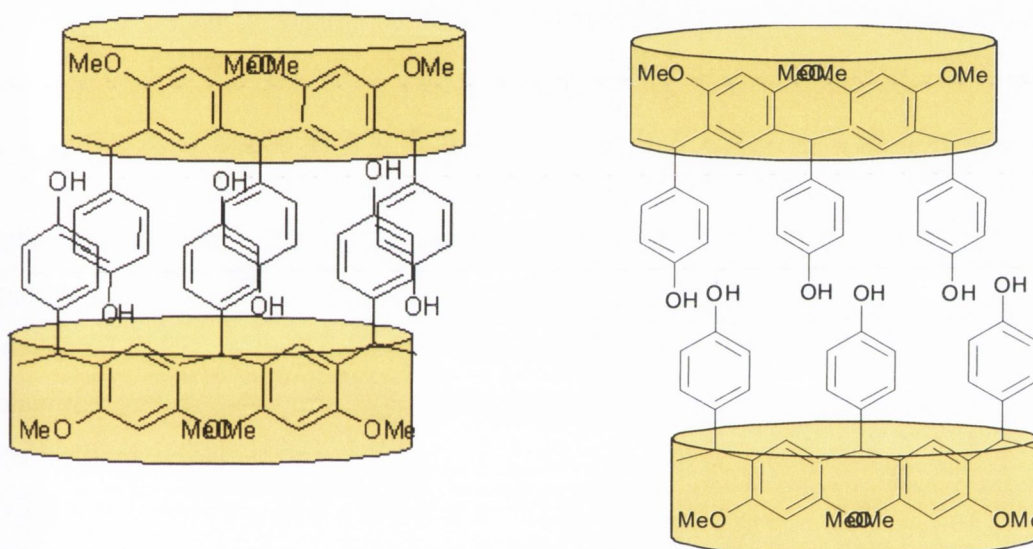


Figure 6.10: Possible modes of stacking for **209b**: a) aromatic π stacking and b) hydrogen bonding between lower rim hydroxyl groups of adjacent molecules

Upon the addition of an anion it is believed that this stacking is disrupted due to some interaction of the anion with the lower rim of the molecule. This is illustrated in **Figure 6.11**.

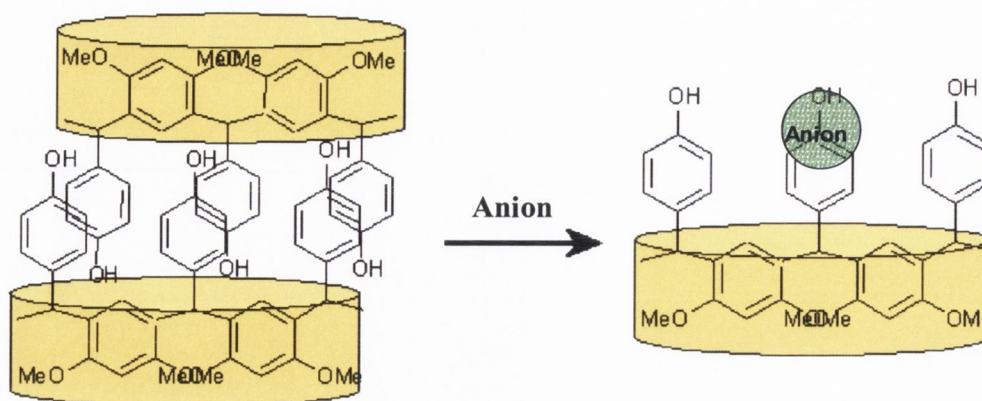


Figure 6.11: Disruption in stacking on interaction with an anion

The ability of the ions studied to disrupt these interactions follows the trend:



The size of the various ions provides a possible explanation for this. Bromide and chloride ions may be too small to interact with the lower rim of **209b**. While iodide, which is significantly larger may prove a better fit. The changes seen for $(\text{OAc})^-$ appear to be the “best” fit and cause the largest disruption in the absorption spectrum, even at low equivalents. Fluoride also has a strong effect, which is surprising considering this is the smallest of the anions studied. This may indicate that the fluoride is acting in a different way, that it is in fact deprotonating the lower rim of **209b** and it is the deprotonation that leads to a disruption in the stacking.

It must be stressed that, at this stage in our investigation, these discussions are only hypothetical and no definitive explanation for the behaviour has yet been found. This work will be continued within the Gunnlaugsson group.

6.4 Future Work Arising from Chapter 4

The tetra alkylation of calixarene with the bromoaldehydes synthesised for **Chapter 4** should be possible and is only a matter of finding the right synthetic conditions. These molecules, once synthesised, will hopefully yield the elusive dimer. The monoaldehyde, if generated in

larger quantities, may also yield an interesting dendrimer type structure should it undergo a condensation reaction with resorcinol.

6.5 Future Work Arising from Chapter 5

Chapter 5 shows only the results of the preliminary investigation into the metal binding ability of the four novel cavitands synthesised. The lanthanide ions screened, Eu(III) and Tb(III), show particular promise and full titrations will be carried out within the Gunnlaugsson group shortly, to better determine the nature of the interaction of lanthanide ions with compounds **311**, **312**, **313** and **314**.

Chapter 7

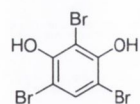
Experimental

7.1 General Experimental Details

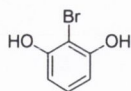
Melting points were determined using IA9000 digital melting point apparatus. Infrared spectra were recorded on a Perkin Elmer Spectrum 1 FTIR fitted with an ATR sampling accessory. ^1H NMR spectra were recorded at 400 MHz using a Bruker Spectrospin DPX-400 instrument. Tetramethylsilane (TMS) was used as an internal reference standard, with chemical shifts expressed in parts per million (ppm or δ) downfield from the standard and coupling constants (J) expressed in Hz. ^{13}C NMR were ^1H decoupled and were recorded at 100 MHz using a Bruker Spectrospin DPX-400 instrument. Mass spectra were determined by detection using Electrospray on a Micromass LCT spectrometer, using Waters 9360 to pump solvent, controlled by MassLynx 3.5 on a Compaq Deskpro workstation. Accurate mass was determined relative to a standard of Leucine Enkephaline (Tyr-Gly-Gly-Phe-Leu) and all accurate mass calculated to ≤ 5 ppm. Elemental Analysis was performed in the Microanalytical Laboratory, University College, Dublin. Accurate masses were determined by a peak-matching method using leucine enkephalin as the standard reference. Starting materials were obtained from Sigma-Aldrich, Fluka and Lancaster and used as received. Thin Layer Chromatography (TLC) was carried out using silica gel plates (60, F₂₅₄). These plates were visualised by 253 nm ultraviolet light. Column chromatography was run using silica gel 600 (230-400 mesh ASTM). Solvents were purified and dried using standard laboratory procedures.

7.2 Synthesis

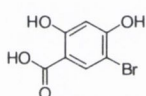
2,4,6-Tribromoresorcinol (166)¹⁴⁵



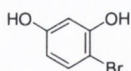
Bromine (4.32 g, 1.4 ml, 27.03 mmol) in DCM (20 ml) was added dropwise to a suspension of resorcinol (1 g, 9.08 mmol) in DCM (20 ml). The reaction mixture was heated at reflux until HBr ceased to be evolved. Decolourising charcoal was added and the reaction mixture was filtered whilst still hot. The solvent was removed under reduced pressure from the filtrate to yield a cream crystalline solid (2.47 g, 79 %). m.p. 111 °C (lit. 109-111 °C); ^1H NMR (400 MHz, CDCl_3) δ 7.63 (s, 1H, H), 5.95 (s, 2H, OH); ^{13}C NMR (100 MHz, CDCl_3) δ 149.8, 133.0, 100.4, 98.3.

2-Bromoresorcinol (153)¹⁴⁵

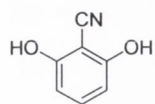
Tribromoresorcinol (1.5 g, 4.3 mmol) was added to a solution of Na₂SO₃ (8 g, 46.5 mmol) in distilled water (30 ml) and left to stir for three hours. The reaction mixture was then acidified with conc. HCl and gently warmed to expel sulphur dioxide. The product was extracted with toluene (2 x 10 ml) and the solvent was removed under reduced pressure from the filtrate to yield an off white powder (0.576 g, 71 %). m.p. 100 – 102 °C (lit. 100-102 °C); ¹H NMR (400 MHz, CDCl₃) δ 7.12 (t, *J* = 8.16 Hz, 1H, CHCHCH), 6.62 (d, *J* = 8.2 Hz, 2H, CHC(OH)), 5.56 (s, 2H, OH).

2,4-Dihydroxy-5-bromobenzoic acid (169)¹⁴⁸

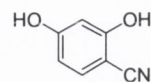
2,4-Dihydroxybenzoic acid (5 g, 32.46 mmol) was dissolved in acetic acid (40 ml) and heated to 45 °C. Once the solid had dissolved the solution was cooled to 30 °C and a solution of bromine (5.19 g, 1.6 ml, 32.46 mmol) in acetic acid (25 ml) was added dropwise. The solution was left to stir for fifteen minutes at 30 °C and was then poured into distilled water (500 ml) and cooled to 4 °C overnight. The white precipitate that formed was isolated by filtration, washed with ice-cold distilled water and dried (4.83 g, 64 %). m.p. 210-212 °C (lit. 204 -212 °C); ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.24 (s, 1H, COOH), 7.83 (s, 1H, CHCBr), 6.48 (s, 1H, CHCOH); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 170.8, 162.1, 160.1, 134.0, 106.0, 103.3, 99.7.

4-Bromoresorcinol (159)¹⁴⁸

2,4-Dihydroxy-5-bromobenzoic acid (4.5 g, 19.4 mmol) was heated at reflux in distilled water (50 ml) for twenty-four hours. The solution was then filtered, cooled and extracted with ether (2 x 20 ml). The solvent was removed under reduced pressure and the product was left to stand at 4 °C overnight to crystallise. The product was isolated as a cream powder (2.4 g, 66 %). m.p. 98-100 °C (lit. 100 – 102 °C); ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.01 (s, 1H, C(OH)CBr), 9.49 (s, 1H, OH), 7.18 (d, *J* = 8.8 Hz, 1H, CHCBr), 6.42 (d, *J* = 2.5 Hz, 1H, CHC(OH)CH), 6.18 (dd, *J* = 8.76 Hz, 2.5 Hz 1H, CHCHC(OH)); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 157.8, 154.6, 132.7, 108.2, 103.6, 98.1.

Synthesis of 2-Cyanoresorcinol (154) and 4-Cyanoresorcinol (160)¹⁵⁰

A 1M solution of BCl_3 in DCM (12 ml, 12 mmol) was cooled to 0°C . Resorcinol (1.1 g, 10 mmol) in DCM (10 ml), CH_3SCN (0.88 g, 0.82 ml, 12 mmol) and AlCl_3 (1.33 g, 10 mmol) were



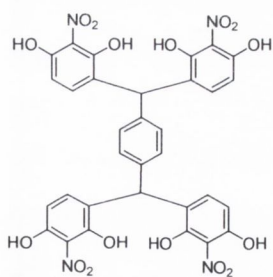
added sequentially. After the additions were complete the reaction mixture was heated at reflux for 4 hrs. Water (20 ml) was added and the organic layer was extracted, dried over MgSO_4 and the solvent removed at reduced pressure. The crude product was purified by column chromatography (silica, hexane: ethyl acetate 4:6) to give 2-cyanoresorcinol and 4-cyanoresorcinol, both as off white powders, in 11 and 19% yield respectively.

2-Cyanoresorcinol

m.p. $189-191^\circ\text{C}$ (lit. 209°C); ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.15 (s, 2H, OH), 6.91 (t, $J = 7.5$ Hz, 1H, CHCHCH), 6.17 (d, $J = 7.5$ Hz, 2H, CHCHCH); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ 162.8, 117.8, 108.1, 102.4, 64.9

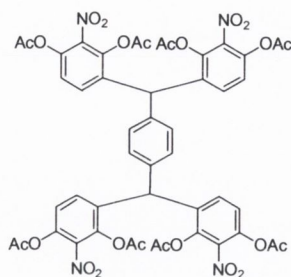
4-Cyanoresorcinol

m.p. $176-178^\circ\text{C}$ (lit. $175-179^\circ\text{C}$); ^1H NMR (400 MHz, CDCl_3) δ 10.65 (bs, 2H, OH), 7.36 (d, $J = 8.2$ Hz, 1H, CNCCH), 6.41 (s, 1H, OHCCH), 6.31 (d, $J = 6.1$ Hz, 1H, CNCCHCH); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ 161.9, 158.4, 134.3, 129.7, 106.2, 102.3, 89.5

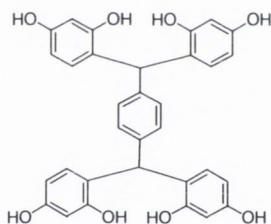
Compound 171

Nitroresorcinol (2 g, 13 mmol) and terephthalaldehyde (0.87 g, 6.5 mmol) were dissolved in ethanol (80 ml) and conc. HCl (20 ml). The reaction was heated at reflux for three days. The product was isolated by filtration as an orange powder (1.54 g, 66 %).

m.p. 220°C (dec.); ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.61 (s, 4H, OH_{in}), 9.95 (s, 4H, OH_{ex}), 6.91 (s, 4H, ArH), 6.60 (d, $J = 8.52$ Hz, 4H, C(OH)CHCH), 6.45 (d, $J = 8.52$ Hz, 4H, C(OH)CH), 5.98 (s, 2H, ArCH); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ 148.7, 146.9, 140.3, 132.0, 131.3, 128.8, 123.1, 107.1, 41.2; ν_{max} 1698, 1616, 1549, 1168 cm^{-1} .

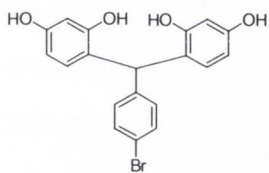
Compound 171a

Compound **22** (1 g, 1.4 mmol) was dissolved in a hot mixture of acetic anhydride (30 ml) and a catalytic amount of pyridine (1 ml). The reaction mixture was left to stir at 110 °C for three hours and then allowed to cool. Water was added to encourage precipitation and the reaction vessel was left in the fridge overnight. The product was isolated by filtration and purified by column chromatography (silica, hexane: ethyl acetate 1:1) to yield a yellow powder (0.3 g, 20 %). m.p. 250 °C (dec.); ^1H NMR (400 MHz, CDCl_3) δ 7.44 (d, $J = 8.52$ Hz, 4H, (AcO)CCHCH), 7.24 (d, $J = 9$ Hz, 4H, (AcO)CCH), 7.20 (s, 4H, ArCH), 2.29 (s, 12H, OCH₃), 2.11 (s, 12H, OCH₃); ^{13}C NMR (100 MHz, CDCl_3) δ 168.0, 167.3, 141.8, 140.5, 137.5, 133.4, 133.2, 129.7, 122.4, 59.4, 44.9, 20.3, 19.7; ν_{max} 1782, 1542, 1168, 1040 cm^{-1} .

Compound 175

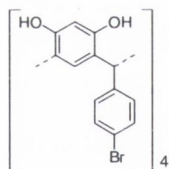
Terephthalaldehyde (1.35 g, 10 mmol) was dissolved in DMF (10 ml) and added dropwise to a solution of resorcinol (13.2 g, 120 mmol) in ethanol (30 ml) and conc. HCl (11.25 ml). The reaction mixture was stirred for one hour at 0 °C and then poured into ice-cold water (500 ml). The ethanol was removed under reduced pressure and the residual aqueous solution extracted with ethyl acetate (2 x 100 ml). The organic phase was dried over MgSO_4 and the solvent was removed under reduced pressure from the filtrate. The resultant oily residue was purified by column chromatography (silica, hexane: ethyl acetate 5:5, then ethyl acetate) to give a yellow powder (0.94 g, 17.5 %). m.p. 210 °C (dec.); Calculated for $\text{C}_{32}\text{H}_{26}\text{O}_8 \cdot \text{H}_2\text{O}$: C: 64.86, H: 5.44; Found: C: 64.70, H: 5.17; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.97 (s, 4H, OH_{in}), 8.94 (s, 4H, OH_{ex}), 6.78 (s, 4H, ArH), 6.41 (d, $J = 8.2$ Hz, 4H, C(OH)CHCH), 6.22 (s, 4H, C(OH)CHC(OH)), 6.07 (d, $J = 6.16$ Hz, 4H, C(OH)CH), 5.73 (s, 2H, ArCH); ^{13}C NMR (100 MHz, CDCl_3) δ 156.1, 155.3, 142.0, 130.0, 128.2, 121.6, 105.3, 102.3, 40.7; ν_{max} 1782, 1542, 1168, 1039 cm^{-1} .

Compound 178

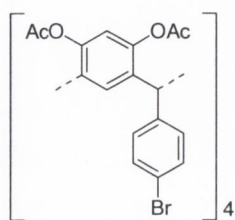


Bromobenzaldehyde (3.7 g, 20 mmol) was dissolved in DMF (10 ml) and added dropwise to a solution of resorcinol (13.2 g, 120 mmol) in ethanol (30 ml) and conc. HCl (11.25 ml). The reaction mixture was stirred for one hour at 0 °C and then poured into ice-cold water (500

ml). The ethanol was removed under reduced pressure and the residual aqueous solution extracted with ethyl acetate (2 x 100 ml). The organic phase was dried over MgSO₄ and removed under reduced pressure. The resultant oily residue was purified by column chromatography (silica, hexane: ethyl acetate 5:5, then hexane: ethyl acetate 1:9) to give a dark brown viscous oil (2.5 g, 32 %). ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.07 (s, 2H, OH_{in}), 9.01 (s, 2H, OH_{ex}), 7.38 (d, *J* = 8.2 Hz, 2H, CHCBr), 6.87 (d, *J* = 8.2 Hz, 2H, CHCHCBr), 6.37 (d, *J* = 8.2 Hz, 2H, C(OH)CHCH), 6.25 (d, *J* = 2 Hz, 2H, C(OH)CHC(OH)), 6.09 (dd, *J* = 8 Hz, 2.8 Hz, 2H, C(OH)CHCH), 5.72 (s, 1H, HArCH); ¹³C NMR (100 MHz, CDCl₃) δ 156.4, 155.4, 145.1, 131.0, 130.6, 130.0, 120.7, 118.2, 105.5, 102.4, 41.1; ν_{max} 3300, 972 cm⁻¹

Compound 181¹²

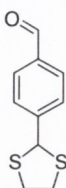
Resorcinol (5 g, 45.4 mmol) and bromobenzaldehyde (8.4 g, 45.4 mmol) were dissolved in ethanol (50 ml). Conc. HCl (5 ml) was added and the reaction mixture was heated at reflux for three days. The reaction mixture was allowed to cool and the product was isolated by filtration as an orange powder (7.69 g, 61 %). m.p. >300 °C (lit. > 390 °C); ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.19 (d, *J* = 8.52 Hz, 8H, CHCBr), 6.61 (d, *J* = 8 Hz, 8H, CHCHCBr), 6.21 (s, 4H, C(OH)CHC(OH)), 6.10 (vbs, 4H, CH), 5.66 (s, 4H, ArCH).

Compound 182²³

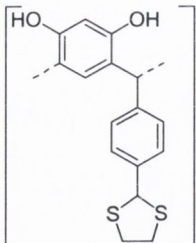
Compound 11 (6.8 g, 6.16 mmol) was dissolved in a mixture of acetic anhydride (30 ml) and a catalytic amount of pyridine (1 ml) heated to 60 °C. The reaction mixture was stirred at 110 °C for three hours and then allowed to cool. Methanol was added to encourage precipitation and the reaction vessel was left in the freezer overnight. The product was isolated

by filtration and recrystallised from chloroform to give a white powder (7 g, 79 %). m.p. > 300 °C (no lit. value reported); ^1H NMR (400 MHz, CDCl_3) δ 7.43 (d, $J = 8.2\text{ Hz}$, 8H, CHCBr), 7.08 & 6.99 (s, 4H, C(OAc)CHC(OAc)), 6.72 (vbs, 8H, CHCHCBr), 6.04 (s, 2H, CH), 5.92 (s, 2H, CH), 5.39 (s, 4H, ArCH), 2.07 & 2.01 (s, 24H, OCH_3)

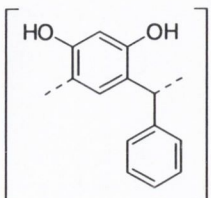
4-(1,3-dithiolan-2-yl)benzaldehyde (184)²³⁶

 Ethanedithiol (6.84 ml, 7.68 g, 81.54 mmol) was added to terephthaldialdehyde (10 g, 74.55 mmol) in DCM (170 ml). The reaction mixture was cooled to 0 °C and $\text{BF}_3(\text{Et}_2\text{O})$ (10 ml) was added. The reaction mixture was allowed to rise to room temperature and left to stir overnight. The reaction mixture was washed with water (3 x 100 ml) and dried over MgSO_4 . The solvent was removed under reduced pressure from the filtrate and the crude product was purified by column chromatography (silica, hexane: ethyl acetate, 4:1 v/v) to give a pale yellow solid (3.1 g, 20 %). m.p. 36 – 38 °C (lit. 38-40 °C); ^1H NMR (400 MHz, CDCl_3) δ 9.99 (s, 1H, CHO), 7.83 (d, $J = 8.52\text{ Hz}$, 2H, ArH), 7.67 (d, $J = 8.52\text{ Hz}$, 2H, ArH), 5.65 (s, 1H, CH), 3.51 (m, 2H, CH_2), 3.38 (m, 2H, CH_2); ^{13}C NMR (100 MHz, CDCl_3) δ 193.1, 130.0, 129.7, 128.5, 54.5, 39.9, 39.8.

Compound 185

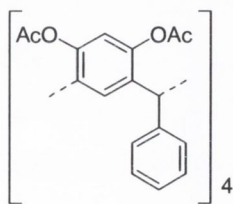
 4-(1,3-dithiolan-2-yl)benzaldehyde (1.5 g, 7.13 mmol) and resorcinol (0.78 g, 7.13 mmol) were heated at reflux together in ethanol (40 ml) and conc. HCl (4 ml) for one week. The reaction mixture was filtered to yield a light brown powder (1.6 g, 74 %). m.p. 200 °C (dec.); ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.59 (s, 4H, ArH), 8.45 (s, 4H, ArH), 7.01 (d, $J = 8\text{ Hz}$, 8H, ArH), 6.53 (d, $J = 8\text{ Hz}$, 8H, ArH), 6.32 (s, 2H, ArH), 6.28 (s, 2H, ArH), 6.09 (s, 2H, ArH), 5.68 (s, 2H, ArH), 5.61 (s, 4H, CH), 5.47 (s, 4H, CHS), 3.40 (m, 16H, CH_2); ν_{max} 1756, 1602, 1169 cm^{-1} .

Compound 190¹²

 Resorcinol (2 g, 18 mmol) and freshly distilled benzaldehyde (1.82 ml, 1.91 g, 18 mmol) were dissolved in a stirred solution of ethanol (80 ml) and conc. HCl (20 ml). The reaction mixture was heated at reflux

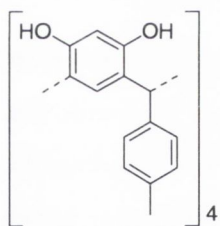
overnight. After cooling the product was isolated by filtration as an orange solid (4.08 g, 100%). m.p. 220-230 °C dec. (no lit. value reported); ^1H NMR (400 MHz, DMSO – d_6) δ 8.57 (bs, 8H, OH), 6.94 (m, 12H, ArH), 6.73 (m, 8H, ArH), 6.32 (bs, 4H, ArH), 6.13 (s, 4H, ArH), 5.63 (s, 4H, ArCH); ^{13}C NMR (100 MHz, DMSO – d_6) δ 152.5, 145.7, 128.6, 127.1, 124.5, 120.4, 120.0, 102.0, 41.4.

Compound 192⁵



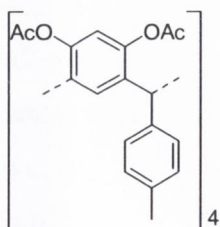
DM187 (2 g, 2.52 mmol) was dissolved in a hot stirring mixture of acetic anhydride (30 ml) and pyridine (1 ml). The reaction mixture was heated at 110 °C for four hours. After cooling MeOH (60 ml) was added and the product was isolated by filtration as a yellow powder (2.24g, 79%). m.p. 357-359 °C (lit. 351 °C or 401-405 °C); ^1H NMR (400 MHz, CDCl_3) δ 7.28 (m, 8H, ArH), 7.01-7.07 (m, 12H, ArH), 6.71 (bs, 4H, ArH), 6.13 (s, 2H, ArH), 5.91 (s, 2H, ArH), 5.40 (s, 4H, ArCH), 2.08 (s, 12H, CCH_3), 1.96 (s, 12H, CCH_3).

Compound 191¹²



Resorcinol (5 g, 45.0 mmol) and p-tolualdehyde (5.4 g, 5.32 ml, 45 mmol) were dissolved in a stirred solution of ethanol (80 ml) and conc. HCl (20 ml). The reaction mixture was heated at reflux overnight. After cooling the product was isolated by filtration as a brown powder (9.41 g, 98%) m.p. 375-380 °C (lit. >304°C); ^1H NMR (400 MHz, DMSO – d_6) δ 8.50 (s, 8H, OH), 6.76 (d, $J = 7.6$ Hz, 8H, ArH), 6.58 (d, $J = 7.6$ Hz, 8H, ArH), 6.21 (bs, 4H, ArH), 6.12 (s, 4H, ArH), 5.58 (s, 4H, ArCH).

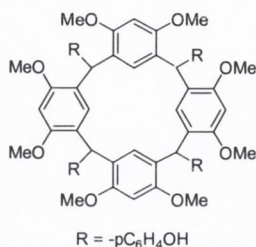
Compound 193²³⁷



191 (2 g, 2.36 mmol) was dissolved in a hot stirring mixture of acetic anhydride (30 ml) and pyridine (1 ml). The reaction mixture was heated at 110 °C for four hours. After cooling MeOH (60 ml) was added and the product was isolated by filtration as a tan coloured solid (2.33g, 90%). m.p. >350 °C dec. (lit. >315°C); ^1H NMR (400 MHz, CDCl_3) δ 7.12 (s,

2H, ArH), 6.88 (d, $J = 8.5$ Hz, 8H, ArH), 6.84 (s, 2H, ArH), 6.60 (bs, 8H, ArH), 6.11 (s, 2H, ArH), 5.96 (s, 2H, ArH), 5.35 (s, 4H, ArCH).

Compound 209



The synthesis of the compound shown was carried out a number of times to study the effect of different acids, solvents and temperatures on the ratio of isomers obtained.

Method 1: Control

1,3-Dimethoxybenzene (0.5 ml, 0.528 g, 3.82 mmol) and p-hydroxybenzaldehyde (0.466 g, 3.82 mmol) were stirred together in acetic acid (20 ml) at room temperature overnight. Distilled water (50 ml) was added to the reaction mixture to aid precipitation. When no precipitate appeared the reaction mixture was extracted with ethyl acetate (2 x 20 ml), dried over MgSO₄ and the solvent removed at reduced pressure. An NMR of the residue isolated showed only unreacted starting materials.

Method 2: HCl Catalyst, 80 °C

1,3-Dimethoxybenzene (0.5 ml, 0.528 g, 3.82 mmol) and p-hydroxybenzaldehyde (0.466 g, 3.82 mmol) were stirred together in acetic acid (20 ml). Conc. HCl (1 ml, 0.0102 mmol) was added dropwise and the reaction mixture was heated at 80 °C overnight. After cooling the precipitate was isolated by filtration and washed with ether to yield a purple powder which NMR showed to be the desired product in the chair conformation (0.497 g, 54%).

Method 3: H₂SO₄ Catalyst, 80 °C

1,3-Dimethoxybenzene (0.5 ml, 0.528 g, 3.82 mmol) and p-hydroxybenzaldehyde (0.466 g, 3.82 mmol) were stirred together in acetic acid (20 ml). Conc. H₂SO₄ (0.227 ml, 0.0102 mmol) was added dropwise and the reaction mixture was heated at 80 °C overnight. After cooling the precipitate was isolated by filtration and washed with ether to yield a purple powder which NMR showed to be the desired product in the chair conformation (0.458 g, 50%).

Method 4: HNO₃ Catalyst, 80 °C

1,3-Dimethoxybenzene (0.5 ml, 0.528 g, 3.82 mmol) and p-hydroxybenzaldehyde (0.466 g, 3.82 mmol) were stirred together in acetic acid (20 ml). HNO_3 (0.99 ml, 0.0102 mmol) was added dropwise and the reaction mixture was heated at 80 °C overnight. After cooling, distilled water was added to aid precipitation. When no precipitate appeared the reaction mixture was extracted with ethyl acetate (2 x 20 ml), dried over MgSO_4 and the solvent removed at reduced pressure. An NMR of the residue isolated did not indicate the presence of the desired product.

Method 5: TFA Catalyst, 80 °C

1,3-Dimethoxybenzene (0.5 ml, 0.528 g, 3.82 mmol) and p-hydroxybenzaldehyde (0.466 g, 3.82 mmol) were stirred together in acetic acid (20 ml). TFA (1.03 ml, 0.0102 mmol) was added dropwise and the reaction mixture was heated at 80 °C overnight. After cooling, distilled water was added to aid precipitation. When no precipitate appeared the reaction mixture was extracted with ethyl acetate (2 x 20 ml), dried over MgSO_4 and the solvent removed at reduced pressure. An NMR of the residue isolated showed only unreacted starting materials.

Method 6: HCl Catalyst, Room Temperature

1,3-Dimethoxybenzene (0.5 ml, 0.528 g, 3.82 mmol) and p-hydroxybenzaldehyde (0.466 g, 3.82 mmol) were stirred together in acetic acid (20 ml). Conc. HCl (1 ml, 0.0102 mmol) was added dropwise and the reaction mixture was stirred at room temperature overnight. After cooling the precipitate was isolated by filtration and washed with ether to yield a purple powder which NMR showed to be the desired product in 2:1 ratio of chair to boat conformation (0.51 g, 55%).

Method 7: H_2SO_4 Catalyst, Room Temperature

1,3-Dimethoxybenzene (0.5 ml, 0.528 g, 3.82 mmol) and p-hydroxybenzaldehyde (0.466 g, 3.82 mmol) were stirred together in acetic acid (20 ml). Conc. H_2SO_4 (0.227 ml, 0.0102 mmol) was added dropwise and the reaction mixture was stirred at room temperature overnight. After cooling the precipitate was isolated by filtration and washed with ether to yield a purple

powder which NMR showed to be the desired product desired product in 1:1.3 ratio of chair to boat conformation (0.467 g, 50%).

Method 8: HNO₃ Catalyst, Room Temperature

1,3-Dimethoxybenzene (0.5 ml, 0.528 g, 3.82 mmol) and p-hydroxybenzaldehyde (0.466 g, 3.82 mmol) were stirred together in acetic acid (20 ml). HNO₃ (0.99 ml, 0.0102 mmol) was added dropwise and the reaction mixture was heated at 80 °C overnight. After cooling, distilled water was added to aid precipitation. . When no precipitate appeared the reaction mixture was extracted with ethyl acetate (2 x 20 ml), dried over MgSO₄ and the solvent removed at reduced pressure. An NMR of the residue isolated did not indicate the presence of the desired product.

Method 9: TFA Catalyst, Room Temperature

1,3-Dimethoxybenzene (0.5 ml, 0.528 g, 3.82 mmol) and p-hydroxybenzaldehyde (0.466 g, 3.82 mmol) were stirred together in acetic acid (20 ml). TFA (1.03 ml, 0.0102 mmol) was added dropwise and the reaction mixture was stirred at room temperature overnight. After cooling, distilled water was added to aid precipitation. When no precipitate appeared the reaction mixture was extracted with ethyl acetate (2 x 20 ml), dried over MgSO₄ and the solvent removed at reduced pressure. An NMR of the residue isolated showed only unreacted starting materials.

The yields for each method used in this synthesis are detailed in **Chapter 4**.

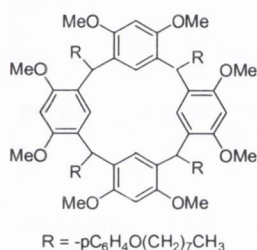
209a – Chair

m.p. 320 °C (dec.); ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.79 (s, 4H, OH), 6.60 (s, 2H, ArH), 6.46 (s, 2H, ArH), 6.36 (m, 16H, ArH), 6.17 (s, 2H, ArH), 5.97 (s, 2H, ArH), 5.49 (s, 4H, ArCH), 3.64 (s, 12H, OCH₃), 3.59 (s, 12H, OCH₃); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 185.5, 178.6, 155.6, 154.8, 132.6, 129.7, 125.1, 123.5, 114.1, 55.7, 55.6; ν_{max} 1609, 1582, 1504, 1452, 1437, 1199, 1093, 1030 cm⁻¹.

209b – Boat

m.p. 280-285 °C; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.4 (s, 4H, OH), 6.53 (d, $J = 8.5$ Hz, 8H, ArH), 6.47 (d, $J = 8.5$ Hz, 8H, ArH), 6.36 (s, 4H, ArH), 6.13 (s, 4H, ArH), 5.45 (s, 4H, ArCH), 3.60 (s, 12H, OCH_3); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ 154.9, 154.8, 133.5, 129.5, 129.4, 114.4, 114.3, 114.2, 55.7, 41.6; ν_{max} 1611, 1582, 1509, 1499, 1542, 1438, 1200, 1095 cm^{-1} .

Compound 216



Method 3 and 7 were applied to 1,3-Dimethoxybenzene (0.5 ml, 3.82 mmol) and 4-octyloxybenzaldehyde (0.89 g, 3.82 mmol). The crude products of these reactions were isolated by filtration as blue powders.

Method 3: 0.89 g, 54% overall yield, Chair isomer 100%

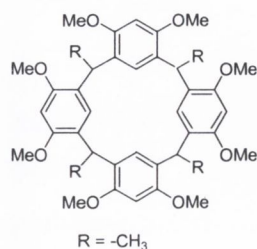
Method 7: 0.35 g, 21% overall yield, Chair:Boat 5:1

m.p. 245-250 °C; Calculated for $\text{C}_{92}\text{H}_{120}\text{O}_{12}$: C: 77.80, H: 8.45; Found: C: 77.93, H: 8.53; ^1H NMR (400 MHz, CDCl_3) δ 6.58 (d, $J = 8.0$ Hz, 8H, ArH), 6.49 (d, $J = 8.0$ Hz, 8H, ArH), 6.46 (s, 2H, ArH), 6.41 (s, 2H, ArH), 6.21 (s, 2H, ArH), 5.83 (s, 2H, ArH), 5.69 (s, 4H, ArCH), 3.84 (t, $J = 6.5$ Hz, 8H, OCH_2), 3.71 (s, 12H, OCH_3), 1.75 (m, 8H, OCH_2CH_2), 1.2-1.5 (m, 40H, $(\text{CH}_2)_5\text{CH}_3$), 0.91 (t, $J = 7$ Hz, 12H, CH_3); ^{13}C NMR (100 MHz, CDCl_3) δ 183.0, 156.3, 155.5, 155.1, 134.5, 129.5, 127.8, 125.0, 124.2, 112.9, 96.1, 94.9, 67.3, 55.9, 55.4, 41.5, 31.4, 29.2, 29.1, 28.9, 25.7, 22.4, 13.7; ν_{max} 2929, 2852, 1609, 1584, 1508, 1202, 1038 cm^{-1}

Boat (not isolated)

^1H NMR (400 MHz, CDCl_3) δ 6.72 (d, $J = 8.5$ Hz, 8H, ArH), 6.59 (d, $J = 8.5$ Hz, 8H, ArH), 6.15 (s, 4H, ArH), 5.98 (s, 4H, ArH), 5.68 (s, 4H, ArCH), 3.92 (t, $J = 7.5$ Hz, 8H, OCH_2), 3.69 (s, 12H, OCH_3), 3.65 (s, 12H, OCH_3), 1.80 (m, 8H, OCH_2CH_2), 1.2-1.5 (m, 40H, $(\text{CH}_2)_5\text{CH}_3$), 0.91 (t, $J = 7$ Hz, 12H, CH_3).

Compound 217¹⁵



Method 3 and 7 were applied to 1,3-Dimethoxybenzene (0.5 ml, 3.82 mmol) and acetaldehyde (0.21 ml, 0.168 g, 3.82 mmol). The crude products of these reactions were isolated by filtration as blue powders.

Method 3: 0.44 g, 70% 100% Chair

Method 7: Total Yield 0.5713 g, 91%; Boat:Chair 3:2

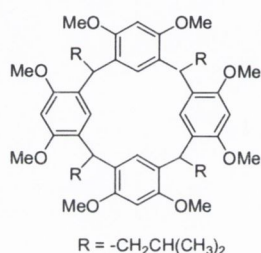
Chair

m.p. 320 °C (lit. 326-328 °C); ^1H NMR (400 MHz, CDCl_3) δ 7.12 (s, 2H, ArH), 6.55 (s, 4H, ArH), 6.41 (s, 4H, ArH), 6.11 (s, 4H, ArH), 4.59 (q, $J = 7.0$ Hz, 4H, ArCH), 3.96 (s, 12H, OCH_3), 3.66 (s, 12H, OCH_3), 1.45 (d, $J = 7.50$ Hz, 12H, CHCH_3).

Boat (not isolated)¹⁵

^1H NMR (400 MHz, CDCl_3) δ 6.40 (s, 4H, ArH), 6.35 (s, 4H, ArH), 4.65 (q, $J = 7.0$ Hz, 4H, ArCH), 3.61 (s, 24H OCH_3), 1.31 (d, $J = 7.0$ Hz, 12H, CHCH_3).

Compound 218¹⁴



Method 3 and 7 were applied to 1,3-Dimethoxybenzene (0.5 ml, 3.82 mmol) and isovaleraldehyde (0.329 g, 0.41 ml, 3.82 mmol). The crude products of these reactions were isolated by filtration as off-white powders.

Method 3: 0.24 g, 30.5% overall yield, 100% chair isomer

Method 7: 0.694 g, 88.1% overall yield, chair 52%, boat 48%

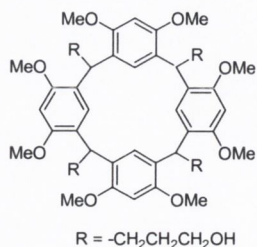
Chair

m.p. 290-300 °C; ^1H NMR (400 MHz, CDCl_3) δ 6.96 (s, 2H, ArH), 6.51 (s, 2H, ArH), 6.43 (s, 2H, ArH), 6.27 (s, 2H, ArH), 4.69 (m, 4H, ArCH), 3.91 (s, 12H, OCH_3), 3.65 (s, 12H, OCH_3), 1.62 (m, 8H, CH_2), 1.43 (m, 4H, CH), 0.85 (d, $J = 6.0$ Hz, 24H, $\text{CH}(\text{CH}_3)_2$); ^{13}C NMR (100 MHz, CDCl_3) δ 156.1, 154.9, 127.1, 127.0, 126.3, 123.0, 96.9, 95.7, 55.8, 55.7, 43.7, 32.8, 25.4, 23.1, 21.6

Boat (not isolated)

^1H NMR (400 MHz, CDCl_3) δ 6.61 (s, 4H, ArH), 6.35 (s, 4H, ArH), 4.61 (t, $J = 7.6$ Hz, 4H, ArCH), 3.63 (s, 24H, OCH_3), 1.69 (m, 8H, CH_2), 1.55 (m, 4H, CH), 0.92 (d, $J = 6.0$ Hz, 24H, $\text{CH}(\text{CH}_3)_2$).

Compound 219



Method 1

1,3-Dimethoxybenzene (0.5 ml, 3.82 mmol) and 2,3-dihydrofuran (0.289 ml, 3.82 mmol) were stirred together in acetic acid (20 ml) and conc. HCl (1 ml) was added dropwise. The reaction mixture was then heated at 60 °C overnight. After cooling the product was isolated by

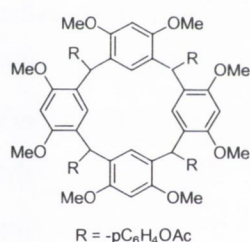
filtration and washed with Et₂O to yield a white powder (0.489 g, 61.4%).

Method 2

1,3-Dimethoxybenzene (0.5 ml, 3.82 mmol) and 2,3-dihydrofuran (0.289 ml, 3.82 mmol) were stirred together in acetic acid (20 ml) and conc. HCl (1 ml) was added dropwise. The reaction mixture was then stirred at room temperature overnight. After cooling the product was isolated by filtration and washed with Et₂O to yield a white powder (0.107 g, 17.4%).

m.p. 210-220 °C; Calculated for C₄₈H₆₄O₁₂·3CH₃COOH: C: 64.01, H: 7.56; Found: C: 64.60, H: 6.99; ¹H NMR (400 MHz, CDCl₃) δ 6.89 (s, 2H, ArH), 6.50 (s, 2H, ArH), 6.41 (s, 2H, ArH), 6.30 (s, 2H, ArH), 4.57 (t, *J* = 7.5 Hz, ArCH), 4.01 (t, *J* = 6.5, 8H, CH₂OH), 3.90 (s, 12H, OCH₃), 3.68 (s, 12H, OCH₃), 1.74 (m, 8H, CHCH₂), 1.54 (m, 8H, CH₂CH₂OH); ¹³C NMR (100 MHz, CDCl₃) δ 156.1, 155.3, 126.5, 126.3, 125.8, 122.6, 96.2, 95.3, 64.3, 55.6, 55.5, 34.7, 30.5, 30.3, 26.5; ν_{max} 2940, 2837, 1735, 1608, 1578, 1496, 1439, 1243, 1203, 1027, 889 cm⁻¹

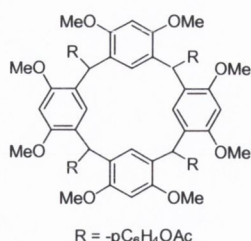
Compound 223a (Chair)



209a (1 g, 1.03 mmol) was stirred in acetic anhydride (20 ml) and a catalytic amount of pyridine (1 ml) was added. The reaction mixture was then heated at reflux for three hours. After complete cooling, MeOH (30 ml) was slowly added to aid precipitation. The precipitate was isolated by filtration and washed with MeOH (70 ml) to yield the desired product

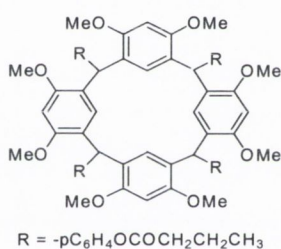
as a white powder (0.98 g, 93%). m.p. 350-360 °C; Calculated for C₆₈H₆₄O₁₆·2CH₃CO₂COCH₃: C: 68.05, H: 5.71; Found: C: 67.79, H: 5.43; ¹H NMR (400 MHz, CDCl₃) δ 6.71 (d, *J* = 8.5 Hz, 8H, ArH), 6.65 (d, *J* = 8.5 Hz, 8H, ArH), 6.45 (s, 2H, ArH), 6.41 (s, 2H, ArH), 6.18 (s, 2H, ArH), 5.76 (s, 4H, ArCH), 5.64 (s, 2H, ArH), 3.72 (s, 12H, OCH₃), 3.69 (s, 12H, OCH₃), 2.29 (s, 12H, OCCH₃); ¹³C NMR (100 MHz, CDCl₃) δ 168.7, 155.6, 155.4, 147.9, 141.5, 140.2, 131.2, 129.4, 128.0, 123.8, 119.7, 95.5, 94.6, 55.6, 55.4, 41.6, 30.5; ν_{max} 2943, 2837, 1733, 1609, 1583, 1503, 1463, 1291, 1200, 1033 cm⁻¹.

Compound 223b (Boat)



209 (0.467 g, 0.48 mmol) was stirred in acetic anhydride (20 ml) and a catalytic amount of pyridine (0.5 ml) was added. The reaction mixture was then heated at reflux for three hours. After complete cooling, MeOH (20 ml) was slowly added to aid precipitation. The precipitate was isolated by filtration and washed with MeOH (50 ml) to yield the acylated mixture of conformers as a white powder. This crude product was then purified by column chromatography (silica, ethyl acetate: chloroform, 1:4 v/v) to give both the crude boat isomer as a white powder (0.07 g, 15%). 1H NMR (400 MHz, $CDCl_3$) δ 6.78 (dd, $J = 9$ Hz, 16H, ArH), 6.43 (s, 2H, ArH), 6.22 (s, 2H, ArH), 6.22 (s, 2H, ArH), 6.07 (s, 2H, ArH), 5.79 (s, 2H, ArH), 5.73 (s, 4H, ArCH), 3.66 (s, 12H, OCH_3), 3.52 (s, 12H, OCH_3), 2.33 (s, 12H, $OCCH_3$).

Compound 224



209 (1 g, 1.03 mmol) was stirred in $CHCl_3$ (20 ml) with butyric anhydride (3 g, 16 mmol). A catalytic amount of pyridine (0.5 ml) was added. The reaction mixture was heated at reflux overnight. After cooling MeOH (30 ml) was added slowly. The precipitate was collected by filtration and washed with ether (40 ml) to give the chair isomer as a light purple powder (0.43 g, 31%). The filtrate was evaporated to dryness and the residue stirred in ether. This was the filtered and the powder isolated was further purified by column chromatography ($CHCl_3$:EtOAc 95:5) to give the boat isomer as a yellow powder (0.37 g, 26%).

224a (Chair)

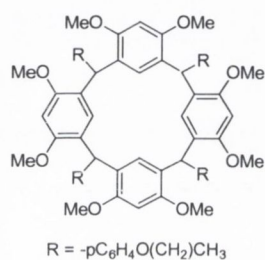
m.p. 334-337 °C; Calculated for $C_{76}H_{80}O_{16}$: C: 73.06, H: 6.45; Found: C: 73.08, H: 6.47; 1H NMR (400 MHz, $CDCl_3$) δ 6.70 (d, $J = 8.5$ Hz, 8H, ArH), 6.65 (d, $J = 8.5$ Hz, 8H, ArH), 6.44 (s, 2H, ArH), 6.41 (s, 2H, ArH), 6.19 (s, 2H, ArH), 5.76 (s, 4H, ArCH), 5.69 (s, 2H, ArH), 3.71 (s, 12H, OCH_3), 3.69 (s, 12H, OCH_3), 2.52 (t, $J = 7.0$ Hz, 8H, $COCH_2$), 1.80 (m, 8H, $CH_2CH_2CH_3$), 1.06 (t, $J = 7.5$ Hz, 12H, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 155.6, 155.4, 147.9, 140.1, 131.1, 129.4, 128.0, 123.9, 123.6, 119.7, 95.5, 94.7, 55.6, 55.4, 41.6, 35.9, 18.0, 13.3; ν_{max} 2966, 2935, 2878, 2832, 1751, 1612, 1586, 1502, 1451 cm^{-1} .

224b (Boat)

m.p. 255-265 °C; Calculated for C₇₆H₈₀O₁₆: C: 73.06, H: 6.45; Found: C: 72.56, H: 6.42

¹H NMR (400 MHz, CDCl₃) δ 6.78 (??), 6.42 (s, 2H, ArH), 6.23 (s, 2H, ArH), 6.10 (s, 2H, ArH), 5.82 (s, 2H, ArH), 5.73 (s, 4H, ArCH), 3.62 (s, 12H, OCH₃), 3.51 (s, 12H, OCH₃), 2.55 (t, *J* = 7.5 Hz, 8H, COCH₂), 1.83 (sextet, 8H, CH₂CH₂CH₃), 1.09 (t, *J* = 7 Hz, CH₂CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 171.5, 155.8, 155.5, 148.0, 140.9, 132.3, 129.2, 127.9, 123.9, 123.6, 120.0, 95.9, 95.6, 55.6, 41.9, 35.9, 18.1, 13.3;

Compound 225a



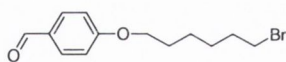
209a (0.5 g, 0.52 mmol) and bromopropane (0.37 ml, 0.51 g, 4.12 mmol) was stirred together with K₂CO₃ (1.15 g, 8.32 mmol) in DMF (15 ml) at 65 °C overnight. After this time the solvent and any remaining unreacted bromopropane were removed at reduced pressure.

The residue was dissolved in DCM (20 ml) and washed with 0.1M HCl (20 ml) and brine (20 ml). The organic layer was dried over MgSO₄ and the solvent removed at reduced pressure to yield the desired product as a yellow powder (0.422 g, 72%).

Alternative Synthesis of Compound 225a

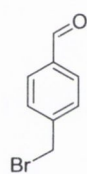
209a (0.5 g, 0.52 mmol) and bromopropane (0.37 ml, 0.51 g, 4.12 mmol) was stirred together with Cs₂CO₃ (2.71 g, 8.32 mmol) in DMF (15 ml) at 65 °C overnight. After this time the solvent and any remaining unreacted bromopropane were removed at reduced pressure. The residue was dissolved in DCM (20 ml) and washed with 0.1M HCl (20 ml) and brine (20 ml). The organic layer was dried over MgSO₄ and the solvent removed at reduced pressure to yield the desired product as a yellow powder (0.300 g, 51%). m.p. 279-282 °C; ¹H NMR (400 MHz, CDCl₃) δ 6.59 (d, *J* = 8.5 Hz, 8H, ArH), 6.50 (d, *J* = 8.6 Hz, 8H, ArH), 6.46 (s, 2H, ArH), 6.40 (s, 2H, ArH), 6.22 (s, 2H, ArH), 5.85 (s, 2H, ArH), 5.69 (s, 4H, ArCH), 3.82 (t, *J* = 6.5 Hz, 8H, OCH₂), 1.78 (m, 8H, CH₂CH₂CH₃), 1.03 (t, *J* = 7.5 Hz, 12H, CH₂CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 156.3, 155.5, 155.1, 134.6, 131.2, 129.5, 127.8, 125.1, 124.2, 112.9, 96.1, 94.9, 68.8, 55.9, 55.4, 41.6, 22.3, 10.1; ν_{max} 2960, 2934, 2876, 1608, 1582, 1503, 1462, 1451, 1436, 1201, 1096, 924, 820 cm⁻¹

4-(6-Bromo-hexyloxy)-benzaldehyde (226)²³⁸



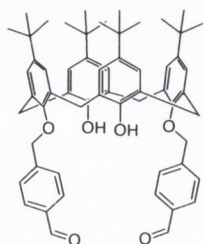
4-Hydroxybenzaldehyde (1 g, 81.9 mmol) and 1,6-dibromohexane (12.5 ml, 81.9 mmol) were stirred at reflux overnight in acetone (50 ml) with K_2CO_3 (11.3 g, 81.9 mmol). After cooling the acetone was removed at reduced pressure and the residue was dissolved in DCM (50 ml) and water (50 ml). The organic layer was separated, dried over MgSO_4 and the solvent removed at reduced pressure to give the crude product as a pale yellow liquid. This was purified by column chromatography (silica, hexane: ethyl acetate, 8:2 v/v) to give the desired product as a crystalline solid (1.369 g, 59%). m.p. 37-39 °C (no lit. value given); ^1H NMR (400 MHz, CDCl_3) δ 9.90 (s, 1H, CHO), 7.85 (d, $J = 9$ Hz, 2H, ArH), 7.01 (d, $J = 9$ Hz, 2H, ArH), 4.07 (t, $J = 6.5$ Hz, 2H, OCH_2), 3.45 (t, $J = 6.5$ Hz, 2H, CH_2Br), 1.89 (m, 4H, $\text{OCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{Br}$), 1.55 (m, 4H, $\text{OCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{Br}$); ^{13}C NMR (100 MHz, CDCl_3) δ 190.3, 163.7, 131.5, 129.3, 114.3, 67.7, 33.3, 32.1, 28.4, 27.4, 24.7

4-Bromomethyl-benzaldehyde (249)²³⁹



4-Bromomethyl-benzonitrile (2 g, 10.2 mmol) was stirred in freshly distilled DCM (6 ml). The suspension was cooled to 0 °C and stirred under nitrogen. DiBAL (10.2 ml, 1.0 M in DCM) was added slowly *via* a syringe. The reaction mixture was allowed to rise to room temperature and then heated at 45 °C for 4 hrs. The reaction was then quenched by the addition of 10% H_2SO_4 until the mixture had reached pH 3. The aqueous solution was extracted with DCM (2 x 20 ml). The organic layers were combined, dried over MgSO_4 and the solvent removed at reduced pressure. The crude product was then recrystallised from hexane to give white needle like crystals (1.3 g, 64%). m.p. 90-94 °C (lit. 92-103 °C); ^1H NMR (400 MHz, CDCl_3) δ 10.04 (s, 1H, CHO), 7.89 (d, $J = 8$ Hz, 2H, ArCH), 7.58 (d, $J = 8$ Hz, 2H, ArCH), 4.54 (s, 2H, CH_2); ^{13}C NMR (100 MHz, CDCl_3) δ 233.6, 191.1, 182.3, 129.7, 129.2, 31.5.

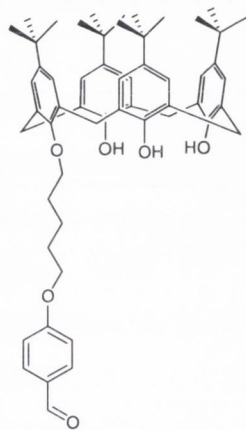
Compound 250²⁰⁴



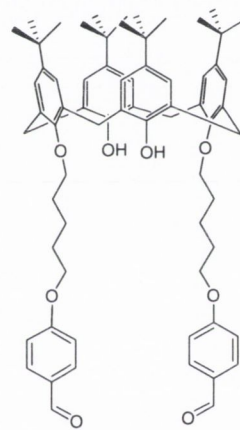
t-Butyl calixarene (0.5 g, 0.77 mmol) and K_2CO_3 (0.85 g, 6.16 mmol) were stirred together in MeCN (20 ml) and 4-bromomethylbenzaldehyde (0.3 g, 1.54 mmol) was added. The reaction mixture was then heated at reflux overnight. After cooling, the solvent was removed at reduced pressure and

the remaining residue was partitioned between DCM (20 ml) and H₂O (20 ml). The organic layer was separated, washed with 0.1 M HCl (10 ml), dried over MgSO₄ and the solvent removed at reduced pressure to give the desired product as an off-white crystalline solid (0.57 g, 76.6%). m.p. 119 °C (lit. 226-228 °C); ¹H NMR (400 MHz, CDCl₃) δ 10.07 (s, 2H, CHO), 7.92-7.88 (m, 8H, ArH), 7.09 (s, 4H, ArH), 6.83 (s, 4H, ArH), 5.15 (s, 4H, OCH₂), 4.39 (d, *J* = 13 Hz, 4H, ArCH₂), 3.35 (d, *J* = 13 Hz, 4H, ArCH₂), 1.31 (s, 18H, C(CH₃)₃), 0.97 (s, 18H, C(CH₃)₃); ¹³C NMR (100 MHz, CDCl₃) δ 191.5, 150.1, 148.9, 147.0, 143.5, 141.3, 135.5, 131.9, 129.7, 127.0, 127.0, 125.2, 124.7, 76.6, 33.5, 33.5, 31.3, 31.2, 30.5; *ν*_{max} 3407, 2954, 2865, 1699, 1609, 1578, 1482, 1205, 1015 cm⁻¹.

Compounds 251 and 252



t-Butyl calixarene (0.57 g, 0.88 mmol) and 4-(6-Bromo-hexyloxy)- benzaldehyde (0.5 g, 1.76 mmol) were stirred in MeCN (20 ml) with K₂CO₃ (2.42 g, 17.54 mmol) for 16 hrs at 82 °C. The MeCN was removed at reduced pressure and the residue was partitioned between DCM (20 ml) and H₂O (20 ml). The organic layer was separated and dried over MgSO₄. Evaporation of the DCM led to the



isolation of the crude product as white solid. This was purified by column chromatography (silica, DCM) to give **252** and **251**, both as white powders. (0.07 g, 9.5% and 0.63 g, 70%)

252

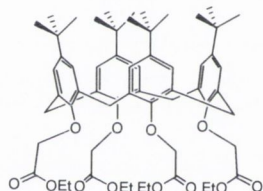
m.p. 180 °C; ¹H NMR (400 MHz, CDCl₃) δ 10.12 (s, 1H, CHO), 9.88 (s, 1H, OH), 9.57 (s, 2H, OH), 7.82 (d, *J* = 9.0 Hz, 2H, ArH), 7.13 (s, 2H, ArH), 7.09 (s, 2H, ArH), 7.08 (s, 2H, ArH), 7.04 (d, *J* = 8.5 Hz, 2H, ArH), 7.02 (s, 2H, ArH), 4.37 (d, *J* = 12.5 Hz, 2H, OCH₂O), 4.27 (d, *J* = 13.5 Hz, 2H, OCH₂O), 4.18 (t, *J* = 6.5 Hz, 4H, OCH₂CH₂), 3.47 (d, *J* = 2.5 Hz, 4H, OCH₂O), 2.22 (m, 2H, CH₂), 2.01 (m, 2H, CH₂), 1.85 (m, 2H, CH₂), 1.75 (m, 2H, CH₂), 1.25 (s, 9H, C(CH₃)₃), 1.24 (s, 18H, C(CH₃)₃), 1.22 (s, 9H, C(CH₃)₃); ¹³C NMR (100 MHz, CDCl₃) δ 190.5, 163.8, 148.9, 148.0, 147.7, 147.1, 143.4, 142.8, 133.0, 131.6, 129.3, 127.9,

127.6, 127.2, 126.0, 125.3, 125.2, 114.4, 76.5, 67.8, 52.9, 33.8, 33.6, 33.5, 32.5, 31.8, 31.0, 30.8, 30.5, 29.4, 28.5, 25.4, 25.1; MS (MeCN ES⁺) m/z 875.51 (M + Na⁺)

251

m.p. 145-151 °C; Calculated for C₆₈H₈₄O₈: C: 79.34, H: 8.22; Found: C: 78.91, H: 8.36; ¹H NMR (400 MHz, CDCl₃) δ 9.89 (s, 2H, CHO), 8.00 (s, 2H, OH), 7.82 (d, J = 9.0 Hz, 4H, ArH), 7.11 (s, 4H, ArH), 6.98 (d, J = 9.0 Hz, 4H, ArH), 6.96 (s, 4H, ArH), 4.33 (d, J = 12.5 Hz, OCH₂O) 4.11 (t, J = 6.5 Hz, 4H, OCH₂CH₂), 4.03 (t, J = 6.0 Hz, 4H, OCH₂CH₂), 3.75 (d, J = 13.0 Hz, 4H, OCH₂O), 2.10 (m, 4H, CH₂), 1.96 (m, 4H, CH₂), 1.87 (m, 4H, CH₂), 1.70 (m, 4H, CH₂), 1.32 (s, 18H, C(CH₃)₃), 1.10 (s, 18H, C(CH₃)₃); ¹³C NMR (100 MHz, CDCl₃) δ 190.4, 163.8, 150.3, 149.4, 146.6, 141.1, 132.3, 131.6, 129.3, 127.2, 125.2, 124.8, 114.3, 75.7, 67.8, 52.7, 33.6, 33.4, 31.5, 31.3, 30.7, 29.6, 28.7, 25.3, 25.2; MS (MeCN, ES⁺) m/z : 1079.63 (M + Na⁺); $\nu_{\max}$ 3373, 2945, 2867, 1690, 1600, 1578, 1509, 1392, 1362, 1257, 1160 cm⁻¹.

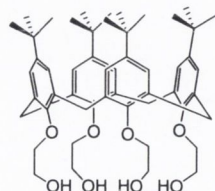
Compound 255²⁴⁰



^tBu-calixarene (10 g, 15 mmol) and K₂CO₃ (10.4 g, 75 mmol) were stirred together in MeCN (40 ml) at 82 °C for 2 hrs. After this time ethyl bromoacetate (12.52 g, 8.6 ml, 75 mmol) was added and the reaction was heated at reflux overnight. After cooling the solvent was removed at reduced pressure and the residue redissolved in DCM (100 ml) and water (100 ml).

The organic layer was separated, dried over MgSO₄ and the solvent removed at reduced pressure to give a yellow oil. This oil was then stirred in EtOH for 2 hrs. After this time the product was isolated by filtration as a white powder 10.5 g, 70%. m.p. 125-128 °C (lit. 154-205 °C); ¹H NMR (400 MHz, CDCl₃) δ 6.80 (s, 8H, ArH), 4.87 (d, J = 13 Hz, 4H, ArCH₂), 4.82 (s, 8H, OCH₂), 4.22 (q, J_L = 7.5 Hz, J_B = 6.8 Hz, 8H, CH₂CH₃), 3.21 (d, J = 13 Hz, ArCH₂), 1.31 (t, J = 7.5 Hz, 12H, CH₂CH₃), 1.09 (s, 36H, C(CH₃)₃); ¹³C NMR (100 MHz, CDCl₃) δ 170.1, 152.5, 144.7, 133.0, 124.9, 70.9, 59.9, 33.4, 31.4, 30.9, 13.8.

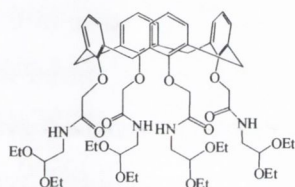
Compound 256²⁴¹



255 (3 g, 3.02 mmol) in dry ether (30 ml) was added dropwise to LiAlH₄ (1 g, 26.35 mmol) in dry ether (30 ml) at 0 °C and left to stir overnight. To quench the reaction 10% HCl (100 ml) was slowly added, this was followed by the addition of CHCl₃ (100 ml) and the reaction mixture was

left to stir for 2 hrs. The organic layer was then separated and the aqueous layer was extracted with CHCl_3 (2 x 70 ml). The organic layers were combined, dried over MgSO_4 and the solvent was removed at reduced pressure. The solid obtained was recrystallised from EtOH to give the desired product as a white powder (1.73 g, 69%). m.p. 286-288 °C (lit. 283-285 °C); ^1H NMR (400 MHz, CDCl_3) δ 6.87 (s, 8H, ArH), 4.37 (d, $J = 13$ Hz, 4H, ArCH₂), 3.9-4.1 (m, 16H, OCH₂CH₂), 3.25 (d, $J = 12.5$ Hz, 4H, ArCH₂), 1.11 (s, 36H, C(CH₃)₃); ^{13}C NMR (100 MHz, CDCl_3) δ 151.9, 145.2, 133.0, 125.1, 77.4, 61.3, 33.5, 31.0, 30.0.

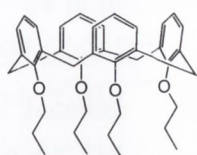
Compound 260



255 (0.25 g, 0.32 mmol) was stirred together with aminoacetaldehyde diethyl acetal (1 ml, 6.87 mmol) in ethanol (5 ml) at 78 °C overnight. The solvent was removed at reduced pressure and the residue was stirred in ether (5 ml) for 2 hrs. The product was

isolated as white powder by filtration (0.19 g, 53%). m.p. 180-182 °C; Calculated for $\text{C}_{60}\text{H}_{84}\text{N}_4\text{O}_{16}$: C: 64.50, H: 7.58, N: 5.01; Found: C: 64.41, H: 7.53, N: 4.76; ^1H NMR (400 MHz, CDCl_3) δ 7.58 (bs, 4H, NH), 6.75-6.40 (m, 12H, ArH), 4.63 (m, 4H, CH(OEt)₂), 4.60 (d, $J = 14.0$ Hz, ArCH₂), 4.51 (s, 8H, OCH₂), 3.69 (m, 8H, NHCH₂), 3.52 (m, 16H, CH₂CH₃), 3.28 (d, $J = 14.0$ Hz, ArCH₂), 1.19 (t, $J = 6.8$ Hz, 24H, CH₃); ^{13}C NMR (100 MHz, CDCl_3) δ 169.1, 133.8, 128.5, 122.8, 99.8, 73.4, 61.7, 41.1, 30.6, 30.5, 14.9; Accurate mass: Calc: 1139.5780, found 1139.5759 (M+Na); ν_{max} 3273, 2972, 2889, 1682, 1659, 1546, 1438, 1191, 1131, 1087, 1057, 760 cm^{-1} .

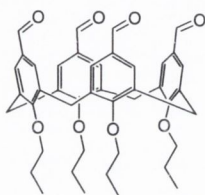
Compound 262²⁴² (synthesis of propyl calix)



Calixarene (1 g, 2.36 mmol) and NaH (1.92 g, 0.08 mmol) were stirred together in dry DMF (50 ml) at 80 °C for 1 hr. Bromopropane (3.15 g, 2.33 ml, 25.66 mmol) was added and the reaction mixture was stirred at 80 °C overnight under Ar. After cooling MeOH was added dropwise to quench the reaction and the solvent was removed at reduced pressure. The remaining residue was redissolved in DCM/H₂O and the organic layer was separated, washed with water (50 ml), brine (50 ml) and dried over MgSO_4 . The crude product was then obtained by removal of the solvent at reduced pressure and was purified by recrystallisation from DCM/MeOH to give the

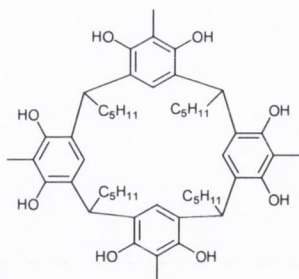
desired product as a white powder (0.95 g, 68%). m.p. 183-185 °C (lit. values range from 154.8-252.2); ^1H NMR (400 MHz, CDCl_3) δ 6.59 (m, 12H, ArH), 4.47 (d, $J = 13$ Hz, 4H, ArCH₂), 3.86 (t, $J = 7.5$ Hz, OCH₂), 3.17 (d, $J = 13.5$ Hz, ArCH₂), 1.94 (m, 8H, OCH₂CH₂), 1.01 (t, $J = 7.5$ Hz, 12H, CH₃); ^{13}C NMR (100 MHz, CDCl_3) δ 134.7, 127.6, 121.4, 32.9, 30.5, 22.8, 9.9.

Compound 263²⁴³

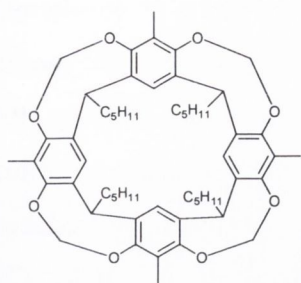


Propylcalix (0.2 g, 0.34 mmol) in dry CHCl_3 (10 ml) and TiCl_4 (1.61 g, 0.93 ml, 8.5 mmol) in dry CHCl_3 (10 ml) were simultaneously added *via* dropping funnels to a stirred solution of 1,1-dichlorodimethyl ether in dry CHCl_3 (10 ml) over 10 mins at 40 °C. The reaction mixture was stirred for an additional 20 mins at this temperature. It was then cooled and the reaction quenched with water (10 ml). The organic layer was separated, washed with water (2 x 20 ml), dried over MgSO_4 and the solvent removed at reduced pressure. The residue was triturated with EtOH to give the desired product as a white powder. (0.21 g, 87%). m.p. 290-293 °C (lit. 289-290 °C); ^1H NMR (400 MHz, CDCl_3) δ 9.61 (s, 4H, CHO), 7.18 (s, 8H, ArH), 4.53 (d, $J = 13.5$ Hz, ArCH₂), 3.96 (t, $J = 8$ Hz, 8H, OCH₂), 3.35 (d, $J = 14$ Hz, 4H, ArCH₂), 1.93 (m, 8H, CH₂CH₃), 1.03 (t, $J = 7.5$ Hz, 12H, CH₃); ^{13}C NMR (100 MHz, CDCl_3) δ 270.5, 266.5, 129.8, 111.3, 30.5, 22.9, 18.2, 11.1

Compound 293¹²

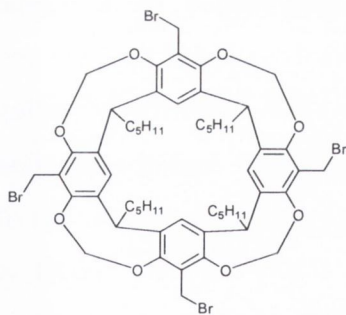


2-Methylresorcinol (5 g, 40.27 mmol) and hexanal (4.03 g, 4.83 ml, 40.27 mmol) were stirred together in EtOH (30 ml) and conc. HCl (5 ml) was added dropwise. The reaction mixture was heated at 80 °C overnight. The reaction mixture was then allowed to cool and distilled water (30 ml) was added. The product was isolated by filtration as a dark yellow powder (8.3 g, 100 %). m.p. 270 °C (lit. 260 °C); ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.67 (s, 8H, OH), 7.27 (s, 4H, ArH), 4.19 (t, $J = 7.52$ Hz, 4H, ArCH), 2.22 (m, 8H, CHCH₂), 1.94 (s, 12H, ArCH₂), 1.25 (m, 24H, (CH₂)₃), 0.86 (t, $J = 7.04$ Hz, 12H, CH₂CH₃); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ 166.9, 142.9, 130.5, 129.7, 129.5, 129.1, 40.1, 39.9, 39.1, 38.9, 33.3.

Compound **294**²²⁷

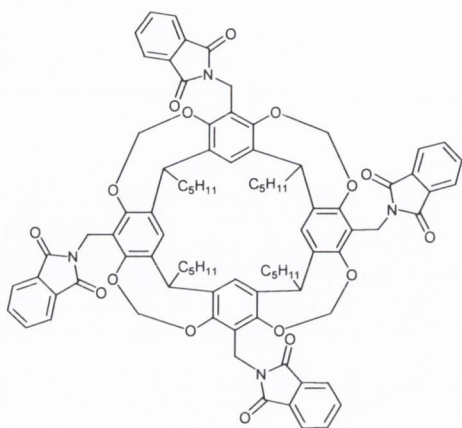
Compound **293** (8.27 g, 9.92 mmol) was dissolved in DMF (300 ml). K_2CO_3 (29.19 g, 0.21 mol) and bromochloromethane (10.75 ml, 21.39 g, 0.16 mol) were added and the reaction mixture was heated at 60 °C overnight. The DMF was removed at reduced pressure. The residue was dissolved in 1M HCl (100 ml) and DCM (100 ml). The organic layer was separated and washed with 1M HCl (2 x 100 ml)

and distilled water (100 ml) before being dried over $MgSO_4$, filtered and evaporated to give the crude product as a brown crystalline solid. This was further purified by column chromatography (DCM) to give **294** as a white crystalline solid (2.42 g, 28 %). m.p. 220 °C (lit. 135-137 °C); 1H NMR (400 MHz, $CDCl_3$) δ 6.99 (s, 4H, ArH), 5.90 (d, $J = 7.04$ Hz, 4H, OCH_2O), 4.77 (t, $J = 8.56$, 4H, ArCH), 4.28 (d, $J = 7$ Hz, 4H, OCH_2O), 2.21 (m, 8H, $CHCH_2$), 1.99 (s, 12H, $ArCH_3$), 1.42-1.35 (m, 24H, $(CH_2)_3$), 0.93 (t, $J = 7.04$ Hz, 12H, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.8, 137.5, 123.2, 117.1, 98.1, 36.6, 31.6, 29.6, 27.2, 22.3, 13.7, 9.9.

Compound **296**²²⁷

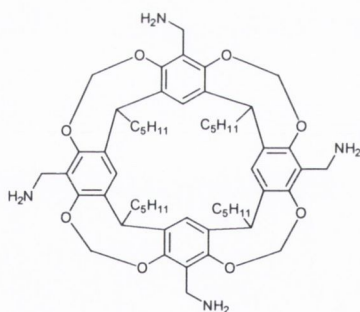
Compound **294** (3.19 g, 3.65 mmol) was dissolved in CCl_4 (150 ml). NBS (3.25 g, 18.25 mmol) and benzoyl peroxide (0.13 g, 0.55 mmol) were added and the reaction mixture was heated at 80 °C overnight. The precipitate formed was removed by filtration and the solvent was removed at reduced pressure. The residue was then dissolved in DCM and washed with distilled water (100 ml). The DCM was evaporated and the crude product

recrystallised from DCM/EtOH to give **296** as a pale yellow powder (3.59 g, 83 %). m.p. 263-266 °C (lit. 278-279 °C); 1H NMR (400 MHz, $CDCl_3$) δ 7.15 (s, 4H, ArH), 6.05 (d, $J = 6.52$ Hz, OCH_2O), 4.80 (t, $J = 7.56$ Hz, 4H, ArCH), 4.58 (d, $J = 6.52$ Hz, 4H, OCH_2O), 4.45 (s, 8H, $ArCH_2$), 2.22 (m, 8H, $CHCH_2$), 1.43-1.35 (m, 24H, $(CH_2)_3$), 0.93 (t, $J = 7$ Hz, 12H, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.5, 138.1, 124.5, 120.9, 99.1, 36.8, 31.9, 30.0, 27.5, 23.0, 22.6, 14.1.

Compound **297**²²⁷

A solution of compound **296** (1.5 g, 1.26 mmol), phthalimide, potassium derivative (1.63 g, 8.82 mmol) and hexadecyltributylphosphonium bromide (0.3g, 0.6 mmol) in toluene (75 ml) were heated at reflux overnight. The solvent was removed at reduced pressure and the residue dissolved in DCM (30 ml), washed with 1M NaOH (3 x 25 ml) and dried over MgSO₄. The solvent was removed at reduced pressure and the crude product was purified by column

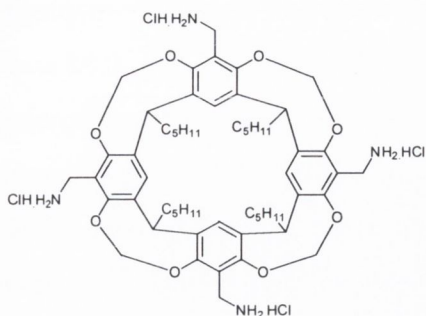
chromatography (hexane:ethyl acetate 1:1) to give pure **297** as a white solid. (0.65 g, 35 %). m.p. 210-212 °C (no lit. value reported); ¹H NMR (400 MHz, CDCl₃) δ 7.87-7.82 (m, 8H, ArH), 7.76-7.72 (m, 8H, ArH), 7.09 (s, 4H, ArH), 5.79 (d, *J* = 7.52, 4H, OCH₂O), 4.70 (t, *J* = 8.52, 4H, ArCH), 4.68 (s, 8H, ArCH₂), 4.43 (d, *J* = 7.52, 4H, OCH₂O), 2.17 (m, 8H, CHCH₂), 1.38-1.26 (m, 24H, (CH₂)₃), 0.89 (t, *J* = 7 Hz, 12H, CH₃).

Compound **290**⁸⁰

Hydrazine monohydrate (2 ml) was added to a stirred suspension of **297** (0.65 g, 0.45 mmol) in EtOH (45 ml) and THF (5 ml). The reaction mixture was heated at reflux overnight. Conc. HCl (3 ml) was added and the reaction mixture refluxed for a further 90 mins. After cooling the pH of the reaction mixture was adjusted to ~ 10 using conc. NaOH. A

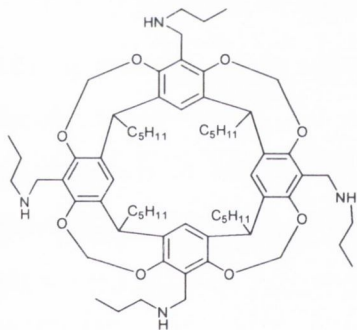
white solid precipitated and was isolated by filtration to give **290** as a white powder. (0.41 g, 98 %). m.p. 173-177 °C (lit. 175-177 °C); ¹H NMR (400 MHz, CDCl₃) δ 7.06 (s, 4H, ArH), 5.93 (d, *J* = 6.52 Hz, 4H, OCH₂O), 4.77 (t, *J* = 7.52 Hz, 4H, ArCH), 4.37 (d, *J* = 7.04, 4H, OCH₂O), 3.63 (s, 8H, ArCH₂), 2.23-2.19 (m, 8H, CHCH₂), 1.41-1.36 (m, 24H, (CH₂)₃), 0.91 (t, *J* = 7 Hz, 12H, CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 152.6, 137.8, 128.7, 98.9, 36.6, 35.8, 31.6, 29.7, 27.2, 22.3, 13.7.

Compound 298



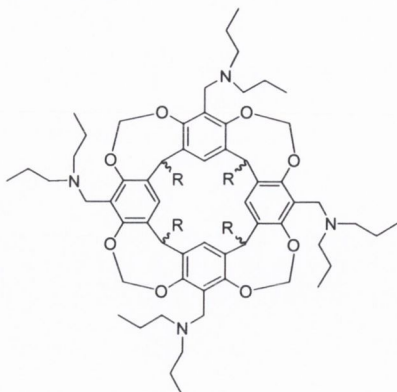
296 (0.58 g, 0.49 mmol) was dissolved in anhydrous CHCl_3 (15 ml) and added dropwise to a solution of hexamethylenetetramine (0.34 g, 2.45 mmol) in anhydrous CHCl_3 . The reaction mixture was heated at reflux overnight with vigorous stirring. The reaction mixture was allowed to cool and the precipitate that formed was removed by filtration and washed several

times with water. The resulting white solid was then suspended in a mixture of EtOH (20 ml), distilled water (4 ml) and conc. HCl (5 ml) and stirred at 70 °C overnight. After cooling the precipitate the formed was isolated by filtration to give the desired product as a white powder (0.37 g, 69 %). m.p. >350 dec.; ^1H NMR (400 MHz, D_2O) δ 7.37 (s, 4H, ArH), 5.94 (d, $J = 7.5$ Hz, 4H, OCH_2O), 4.20 (d, $J = 7.0$ Hz, 4H, OCH_2O), 3.90 (s, 8H, ArCH₂), 2.26 (bs, 8H, CHCH₂), 1.40-1.20 (m, 24H, $(\text{CH}_2)_3$), 0.83 (t, $J = 7.0$ Hz, 12H, CH₃)

Compound 291⁸⁰

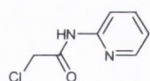
A solution of compound **296** (0.5 g, 0.42 mmol) in *n*-propylamine (10 ml) was stirred for one hour at room temperature. The amine was removed at reduced pressure and the remaining residue was dissolved in DCM (25 ml) and washed with 0.5 % aq. NaHCO_3 and dried over MgSO_4 . The solvent was removed at reduced pressure to give the product as a brown crystalline solid (0.35 g, 76 %). m.p. 250 °C (dec.) (lit.

68-70 °C); ^1H NMR (400 MHz, CDCl_3) δ 7.06 (s, 4H, ArH), 5.89 (d, $J = 6.62$ Hz, OCH_2O), 4.76 (t, $J = 8$ Hz, 4H, ArCH), 4.34 (d, $J = 7$ Hz, 4H, OCH_2O), 3.56 (s, 8H, ArCH₂), 2.53 (t, $J = 7.52$, 8H, NHCH_2CH_2), 2.21 (m, 8H, CHCH₂), 1.62-1.35 (m, 8H + 24H, $\text{NHCH}_2\text{CH}_2 + (\text{CH}_2)_3$), 0.95-0.89 (m, 12H + 12H, $\text{NHCH}_2\text{CH}_2\text{CH}_3 + (\text{CH}_2)_4\text{CH}_3$); ^{13}C NMR (100 MHz, CDCl_3) δ 153.0, 137.5, 125.8, 118.8, 98.9, 51.2, 42.8, 36.5, 31.5, 29.6, 27.1, 22.7, 22.2, 13.6, 11.3.

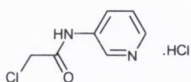
Compound 299

Aminomethyl cavitand (0.04 g, 0.043 mmol), bromopropane (0.1 ml, 0.07 g, 0.57 mmol) and K_2CO_3 (0.12 g, 0.85 mmol) were stirred together in MeCN (10 ml) in a pressure tube at 100 °C for 16 hrs. After cooling the MeCN was evaporated at reduced pressure and the residue was dissolved in DCM (10 ml) and washed with water (2 x 10 ml). The organic layer was dried over Na_2SO_4 and the solvent removed at reduced pressure to give a yellow solid (0.043 g, 91%). 1H

NMR (400 MHz, $CDCl_3$) δ 7.10 (s, 4H, ArH), 5.85 (d, J = 7.0 Hz, 4H, OCH_2O), 4.81 (t, J = 8.5 Hz, 4H, ArCH), 4.23 (d, J = 7.0 Hz, 4H, OCH_2O), 3.28 (s, 8H, $ArCH_2N$), 2.38 (t, J = 7.5 Hz, 16H, NCH_2CH_2), 2.23 (m, 8H, $CHCH_2$), 1.5-1.25 (m, 36H, $(CH_2)_3CH_3$ & $NCH_2CH_2CH_3$), 0.91 (t, J = 7.0 Hz, 12H, $(CH_2)_3CH_3$), 0.84 (t, J = 7.0 Hz, 24H, $NH(CH_2)_2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.9, 137.4, 119.5, 99.0, 55.0, 46.4, 36.4, 31.4, 29.8, 29.3, 27.0, 22.3, 18.8, 13.6, 11.5.

Synthesis of 2-Chloro-N-pyridin-2-yl-acetamide (300)²⁴⁴

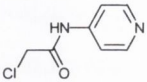
2-Aminopyridine (2 g, 21.2 mmol) and triethylamine (2.32 ml, 1.68 g, 15.9 mmol) were dissolved in DCM (50 ml) and cooled to 0 °C. Chloroacetylchloride was added gradually over 1 hr. The reaction mixture was then allowed to rise to room temperature and stirred overnight (2.14 g, 59%). m.p. 195-198 °C (lit. 119-122 °C); 1H NMR (400 MHz, $CDCl_3$) δ 10.82 (s, 1H, NH), 8.34 (d, J = 4.0 Hz, 1H, Ar-H₃), 8.05 (d, J = 8.5 Hz, 1H, Ar-H₆), 7.80 (t, J = 6.5 Hz, 1H, Ar-H₄), 7.14 (t, J = 6.5 Hz, 1H, Ar-H₅), 4.36 (s, 2H, CH₂)

Synthesis of 2-Chloro-N-pyridin-3-yl-acetamide.HCl Salt (301)²⁴⁵

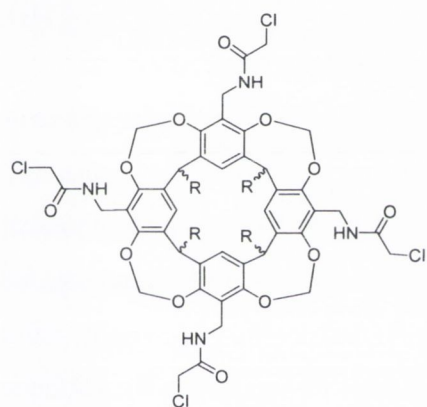
3-Aminopyridine (2 g, 21.2 mmol) was dissolved in acetone (100 ml). The solution was cooled to 0 °C and chloroacetylchloride (1.68 ml, 2.36 g, 21.2 mmol) was added gradually over 1 hr. The resulting reaction mixture was left to stir at RT for 2 hrs. The product was isolated by filtration and washed with hot acetone to give **301** as a white powder (3.84 g, 87%). m.p. 175 °C (lit. 135-137 °C) 1H NMR (400 MHz, D_2O) δ 9.16 (s, 1H, Ar-H₂), 8.45 (d, J = 6.0 Hz, 1H, Ar-H₆), 8.40 (d, J = 9.0 Hz, 1H, Ar-H₆), 7.93 (dd, J =

6.0 Hz, 3.0 Hz, 1H, Ar-H₅), 4.27 (s, 2H, CH₂); ¹³C NMR (100 MHz, D₂O) δ 165.8, 134.8, 134.4, 134.3, 130.4, 125.0, 40.1.

Synthesis of 2-Chloro-N-pyridin-4yl-acetamide (302)²⁴⁴

 4-Aminopyridine (2 g, 21.2 mmol) and triethylamine (2.32 ml, 1.68 g, 15.9 mmol) were dissolved in DCM (50 ml) and cooled to 0 °C. Chloroacetylchloride was added gradually over 1 hr. The reaction mixture was then allowed to rise to room temperature and stirred overnight (1.76 g, 48%). m.p. 240-242 °C (no lit. value reported); ¹H NMR (400 MHz, CDCl₃) δ 8.58 (d, *J* = 3.5 Hz, 2H, Ar-H₃, Ar-H₅), 7.57 (d, *J* = 6 Hz, 2H, Ar-H₂, Ar-H₆), 4.24 (s, 2H, CH₂)

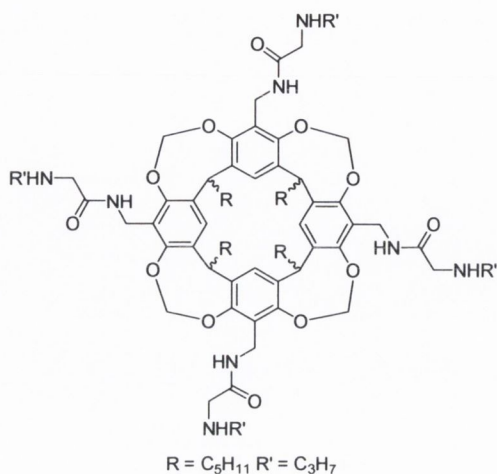
Compound 304



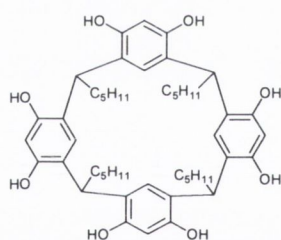
Chloroacetyl chloride (0.24 ml, 0.34 g, 3.01 mmol) was added to a stirring solution of aminomethyl cavitand (0.236 g, 0.253 mmol) and Et₃N (0.56 ml, 4.02 mmol) in DCM (20 ml) and heated at 40 °C for 16 hrs. After cooling, the solution was washed with 1M HCl (2 x 5 ml), H₂O (2 x 15 ml) and 2M NaOH (3 x 15 ml). The organic layer was dried over MgSO₄ and the solvent was removed at reduced pressure to give the desired product as a brown

powder (0.179 g, 57%). m.p. 150-153 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.12 (s, 4H, ArH), 6.99 (t, *J* = 6.0 Hz, 4H, NH), 6.01 (d, *J* = 7.0 Hz, 4H, OCH₂O), 4.78 (t, *J* = 8.0 Hz, 4H, ArCH), 4.42 (d, *J* = 7.0 Hz, 4H, OCH₂O), 4.35 (d, *J* = 5.5 Hz, 8H, CH₂NH), 4.05 (s, 8H, C(O)CH₂), 2.22 (m, 8H, ArCHCH₂), 1.5-1.3 (m, 24H, (CH₂)₃CH₃), 0.95 (t, *J* = 7.0 Hz, 12H, CH₃).

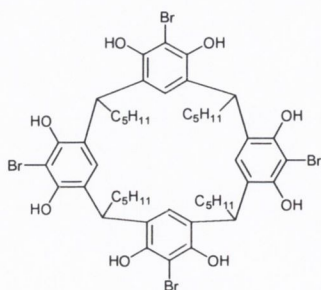
Compound 305



304 (0.033 g, 0.027 mmol) was stirred in propylamine (5 ml) at RT for 2 hrs. The unreacted propylamine was evaporated at reduced pressure and the remaining residue was dissolved in DCM (10 ml) and washed with 10% $NaHCO_3$ (10 ml). The organic layer was dried over $MgSO_4$ and the solvent removed at reduced pressure to yield a brown solid (0.028 g, 78%). m.p. >300 °C dec.; 1H NMR (400 MHz, $CDCl_3$) δ 7.64 (s, 4H, NH), 7.08 (s, 4H, ArH), 5.98 (d, $J = 7.0$ Hz, 4H, OCH_2O), 4.77 (t, $J = 8.0$ Hz, 4H, $ArCH$), 4.40 (d, $J = 7.5$ Hz, 4H, OCH_2O), 4.32 (d, $J = 6.0$ Hz, 8H, $C(O)CH_2$), 3.19 (s, 8H, $ArCH_2N$), 2.54 (t, $J = 7.0$ Hz, 8H, $NHCH_2$), 2.22 (m, 8H, $CHCH_2$), 1.5-1.2 (m, 32H, $(CH_2)_3CH_3$ & $NH(CH_2)_2CH_3$), 0.93 (t, $J = 7.0$ Hz, 12H, $(CH_2)_3CH_3$), 0.86 (t, $J = 7.5$ Hz, 12H, $N(CH_2)_2CH_3$)

Compound 306¹²

Resorcinol (5 g, 45.4 mmol) and hexanal (5.45 ml, 4.55 g, 45.4 mmol) were stirred together in EtOH (30 ml) and conc. HCl (5 ml) was added dropwise. The reaction mixture was heated at reflux overnight. After cooling distilled water (30 ml) was added to precipitate the product. Filtration gave ?? as a yellow powder (8.49 g, 97 %). m.p. 320-322 °C (lit. 330 °C); 1H NMR (400 MHz, $DMSO-d_6$) δ 8.88 (s, 8H, OH), 7.15 (s, 4H, ArH , meta to OH), 6.14 (s, 4H, ArH , ortho to OH), 4.21 (t, $J = 7.5$ Hz, 4H, $ArCH$), 2.01 (m, 8H, $CHCH_2$), 1.26-1.16 (m, 24H, $(CH_2)_3$), 0.83 (t, $J = 6.5$ Hz, 12H, CH_2CH_3); ^{13}C NMR (100 MHz, $DMSO-d_6$) δ 151.7, 123.0, 102.3, 34.0, 31.5, 27.5, 22.3, 14.0.

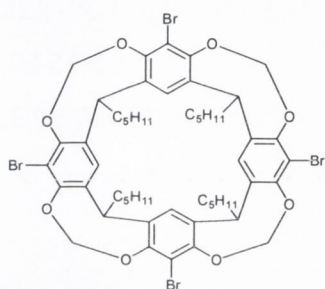
Compound 307⁹²

306 (12.4 g, 16.12 mmol) was dissolved in 2-butanone (60 ml) and NBS (17.11 g, 96 mmol) was added gradually with stirring. The reaction mixture was left to stir overnight at room temperature. The product was isolated by filtration and washed with a small

amount of ice-cold 2-butanone to give the desired product as an off-white powder (9.6 g, 56 %).

m.p. 308 °C (no lit. value reported); ^1H NMR (400 MHz, DMSO- d_6) δ 9.11 (s, 8H, OH), 7.35 (s, 4H, ArH), 4.35 (t, $J = 7.5$ Hz, 4H, ArCH), 2.15 (m, 8H, CHCH₂), 1.31-1.18 (m, 24H, (CH₂)₃), 0.86 (t, $J = 12$ Hz, 12H, CH₂CH₃); ^{13}C NMR (100 MHz, DMSO- d_6) δ 206.5, 179.4, 148.6, 125.5, 123.7, 101.3, 33.4, 31.3, 30.7, 29.5, 27.3, 22.3, 14.0

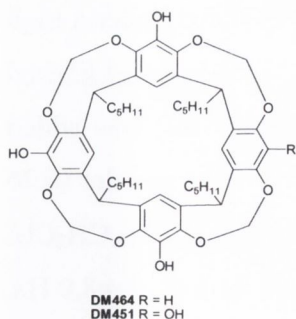
Compound 308⁹²



307 (1 g, 0.92 mmol) was stirred with K₂CO₃ (3.75 g, 27.15 mmol) and BrCH₂Cl (1.25 ml, 2.49 g, 0.018 mmol) in DMF (20 ml) in a pressure tube. The tube was sealed and the reaction was stirred overnight at 175 °C. After cooling, the DMF was removed at reduced pressure and the residue was redissolved in DCM (20 ml) and 0.01M HCl (20 ml). The DCM layer was separated, dried

over MgSO₄ and the solvent was then removed at reduced pressure to yield the crude product. The crude product was purified by column chromatography (Silica, 100% DCM) to yield the desired products as a cream powder (0.80 g, 77%). m.p. 302-303 °C (no lit. value reported); ^1H NMR (400 MHz, CDCl₃) δ 7.05 (s, 4H, ArH), 5.98 (d, $J = 7$ Hz, 4H, OCH₂O), 4.87 (t, $J = 8$ Hz, 4H, ArCH), 4.41 (d, $J = 7$ Hz, 4H, OCH₂O), 2.21 (q, $J = 8$ Hz, 8H, CHCH₂), 1.44-1.33 (m, 24H, (CH₂)₃), 0.93 (t, $J = 7$ Hz, 12H, CH₃); ^{13}C NMR (100 MHz, CDCl₃) δ 151.6, 138.8, 118.6, 113.1, 98.0, 37.2, 31.4, 29.4, 27.0, 22.2, 13.6.

Compounds 309²³² and 310¹⁰⁸



308 (1.52 g, 1.34 mmol) was dissolved in dry THF (200 ml) and stirred at -78 °C under Ar. 2.5M *n*-BuLi in hexanes (4.26 ml, 25 mmol) was added over 15 min and the reaction mixture was allowed to stir for 1 min. B(OCH₃)₃ (1.63 g, 1.75 ml, 15.65 mmol) was then added over 2 hr. The solution was warmed to 25 °C and stirred for 1 hr. It was then cooled to -78 °C and a 1.5M NaOH solution in 15% aqueous H₂O₂ (40 ml) was added over 10 min. The solution was then

warmed to 25 °C and stirred at this temperature for 15 hr. The addition of sodium

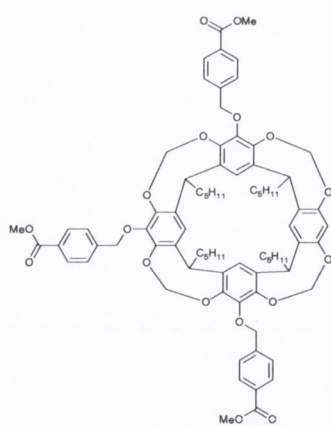
metabisulfite (6.7 g, 35.24 mmol) and the removal of THF at reduced pressure led to the isolation of the crude product by filtration as a yellow solid. This was then purified by column chromatography (ethyl acetate:chloroform 2:1) to give pure **tetrol** and **triol** as off-white powders (0.987 g, 76% and 0.208 g, 18%).

309

m.p. 250-253 °C (lit. 268-275 °C); ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 8.85 (s, 2H, OH), 8.83 (s, 1H, OH), 7.47 (s, 1H, ArH), 6.94 (s, 2H, ArH), 6.92 (s, 1H, ArH), 6.45 (s, 1H, ArH), 5.75 (d, $J = 7.5$ Hz, 2H, OCH_2O), 5.70 (d, $J = 7.5$ Hz, 2H, OCH_2O), 4.50 (m, 4H, ArCH), 4.34 (d, $J = 7.5$ Hz, 2H, OCH_2O), 4.13 (d, $J = 7.5$ Hz, 2H, OCH_2O), 2.26 (m, 8H, CHCH_2), 1.39-1.28 (m, 24H, $(\text{CH}_2)_3$), 0.89 (t, $J = 14.0$ Hz, 12H, CH_3); ^{13}C NMR (100 MHz, CDCl_3) δ 154.0, 142.3, 142.12, 142.06, 142.03, 142.0, 138.4, 138.3, 138.1, 122.6, 116.7, 110.2, 109.9, 99.3, 99.1, 36.7, 36.5, 31.51, 31.48, 28.9, 27.4, 22.3, 14.1.

310

m.p. 245 °C (dec.) (lit. 240 °C); ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 8.76 (s, 4H, OH), 6.91 (s, 4H, ArH), 5.73 (d, $J = 7.5$ Hz, 4H, OCH_2O), 4.49 (t, $J = 8$ Hz, 4H, ArCH), 4.19 (d, $J = 7.5$ Hz, 4H, OCH_2O), 2.25 (m, 8H, CHCH_2), 1.36-1.27 (m, 24H, $(\text{CH}_2)_3$), 0.88 (t, $J = 7.0$ Hz, 12H, CH_3); ^{13}C NMR (100 MHz, CDCl_3) δ 142.2, 142.0, 138.1, 110.1, 99.3, 36.7, 31.5, 29.0, 27.4, 22.3, 14.0.

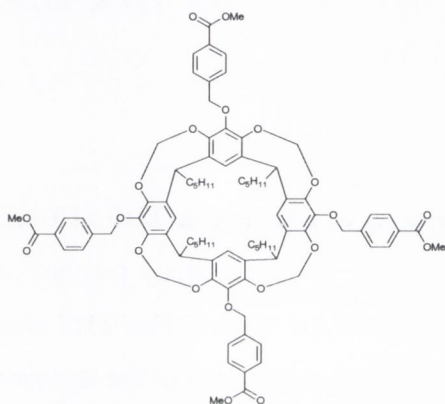
Compound 311

309 (0.20 g, 0.23 mmol), methyl-4-bromomethyl benzoate (0.84 g, 3.70 mmol) and Cs_2CO_3 (1.87 g, 5.75 mmol) were stirred together in *N*-methylpyrrolidinone (20 ml) at 40 °C for 48 hrs. The reaction mixture was filtered and the solvent was evaporated under a high vacuum. The residue was redissolved in DCM (50 ml) and filtered before being concentrated to ~ 5 ml. MeOH (60 ml) was added and the product was isolated by filtration as a white powder (0.26 g, 87%).m.p. 165-168 °C; Calculated for $\text{C}_{79}\text{H}_{88}\text{O}_{17} \cdot \text{CH}_2\text{Cl}_2$:

C:68.90, H: 6.51; Found: C: 68.29, H: 6.21; ^1H NMR (400 MHz, CDCl_3) δ 8.04 (d, $J = 8.0$ Hz, 6H, ArH), 7.47 (d, $J = 8.0$ Hz, 6H, ArH), 7.09 (s, 1H, ArH), 6.88 (s, 3H, ArH), 6.52 (s, 1H, ArH), 5.79 (d, $J = 7.5$ Hz, 2H, OCH_2O), 5.74 (d, $J = 7.0$ Hz, 2H, OCH_2O), 5.04 (s, 6H, OCH_2),

4.75 (m, 4H, ArCH), 4.46 (m, 4H, OCH₂O), 3.93 (s, 12H, OCH₃), 2.23 (m, 8H, CHCH₂), 1.41-1.37 (m, 24H, (CH₂)₃CH₃), 0.96 (m, 12H, CH₂CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 166.5, 166.0, 155.5, 154.4, 148.0, 147.7, 147.6, 143.5, 142.7, 138.7, 138.6, 138.5, 137.8, 129.2, 129.0, 126.60, 126.57, 126.50, 74.2, 74.1, 51.6, 36.6, 36.2, 31.6, 30.5, 29.4, 27.2, 27.1, 22.3, 13.7; ν_{max} 2929, 1721, 1614, 1575, 1470, 1440, 1277 cm⁻¹

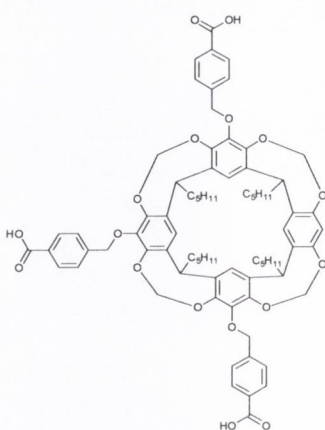
Compound 312



310 (0.19 g, 0.21 mmol), methyl-4-bromomethyl benzoate (1.04 g, 5.52 mmol) and Cs₂CO₃ (2.14 g, 6.60 mmol) were stirred together in *N*-methylpyrrolidinone (20 ml) at 40 °C for 48 hrs. The reaction mixture was filtered and the solvent was evaporated under a high vacuum. The residue was redissolved in DCM (50 ml) and filtered before being concentrated to ~ 5 ml. MeOH (60 ml) was added and the product was isolated by

filtration as a white powder (0.25 g, 80%). m.p. 200-203 °C; Calculated for C₈₈H₉₆O₂₀: C: 71.72, H: 6.57; Found: C: 71.51, H: 6.51; ¹H NMR (400 MHz, CDCl₃) δ 8.04 (d, *J* = 8.6 Hz, 8H, ArH), 7.47 (d, *J* = 8.0 Hz, 8H, ArH), 6.87 (s, 4H, ArH), 5.78 (d, *J* = 7.0 Hz, 4H, OCH₂O), 5.03 (s, 8H, OCH₂), 4.75 (t, *J* = 8.0 Hz, 4H, ArCH), 4.48 (d, *J* = 7.0 Hz, 4H, OCH₂O), 3.93 (s, 12H, OCH₃), 2.23 (m, 8H, CHCH₂), 1.46-1.36 (m, 24H, (CH₂)₃CH₃), 0.96 (t, *J* = 7.50 Hz, 12H, CH₂CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 166.5, 147.7, 143.9, 142.6, 138.6, 129.2, 129.0, 126.6, 114.0, 99.1, 74.1, 51.7, 36.5, 31.6, 29.4, 27.2, 22.3, 13.7; ν_{max} 2929, 2864, 1721, 1615, 1576, 1277, 1106, 839, 813 cm⁻¹

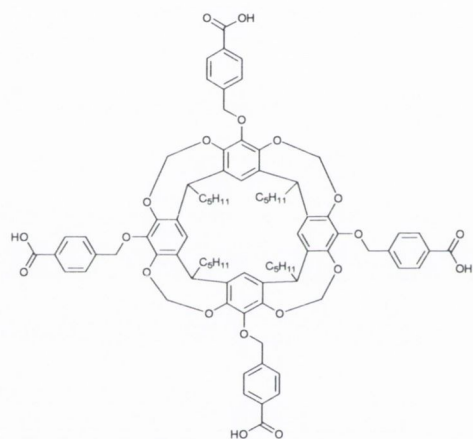
Compound 313



311 (0.1 g, 0.076 mmol) was stirred in THF (10 ml) and 1M aq. KOH (10 ml) with a catalytic amount of benzo-18-crown-6 at 65 °C for 16 hrs. The THF was removed at reduced pressure and the pH of the aqueous layer was adjusted to ~pH 1 using 1M HCl. The product was extracted from the aqueous layer with EtOAc (2x10 ml), the organic layer was dried over MgSO₄ and the solvent was

removed at reduced pressure to yield the desired product as a white powder (0.081 g, 84%). m.p. 146-148 °C; Calculated for $C_{76}H_{82}O_{17} \cdot 3H_2O$: C: 69.07, H: 6.71; Found: C: 68.90, H: 6.56; 1H NMR (400 MHz, $DMSO-d_6$) δ 7.93 (d, $J = 8.0$ Hz, 8H, ArH), 7.54 (m, 8H, ArH), 7.34 (s, 3H, ArH), 6.55 (s, 1H, ArH), 5.94 (d, $J = 7.0$ Hz, 2H, OCH_2O), 5.80 (d, $J = 7.5$ Hz, 2H, OCH_2O), 5.02 (s, 8H, $ArCH_2$), 4.60 (d, $J = 8.0$ Hz, 2H, OCH_2O), 4.57 (d, $J = 7.5$ Hz, 2H, OCH_2O), 4.36 (t, $J = 6.5$ Hz, 4H, $ArCH$), 2.33 (m, 8H, $CHCH_2$), 1.5-1.2 (m, 24H, $(CH_2)_3CH_3$), 0.88 (t, $J = 7.5$ Hz, 12H, CH_3); ^{13}C NMR (100 MHz, $DMSO-d_6$) 170.4, 167.2, 154.1, 147.32, 147.29, 143.8, 142.6, 139.0, 138.9, 138.8, 138.1, 138.0, 130.0, 129.3, 129.2, 127.4, 127.3, 74.0, 59.8, 36.9, 36.6, 31.4, 28.9, 27.3, 22.3, 21.1, 20.8, 14.1, 14.0.

Compound 314



312 (0.1 g, 0.068 mmol) was stirred in THF (10 ml) and 1M aq. KOH (10 ml) with a catalytic amount of benzo-18-crown-6 at 65 °C for 16 hrs. The THF was removed at reduced pressure and the pH of the aqueous layer was adjusted to ~pH 1 using 1M HCl. The product was extracted from the aqueous layer with EtOAc (2x10 ml), the organic layer was dried over $MgSO_4$ and the solvent was removed at reduced pressure to yield the desired product as a white solid

(0.086 g, 96%). m.p. 247-250 °C; Calculated for $C_{84}H_{88}O_{20} \cdot 3H_2O$: C: 68.56, H: 6.44; Found: C: 68.67, H: 6.41; 1H NMR (400 MHz, $DMSO-d_6$) δ 7.94 (d, $J = 7.0$ Hz, 8H, ArH), 7.53 (d, $J = 7.5$ Hz, 8H, ArH), 7.34 (s, 4H, ArH), 5.95 (d, $J = 6.0$ Hz, 4H, OCH_2O), 5.02 (s, 8H, $ArCH_2$), 4.61 (t, $J = 8.0$ Hz, 4H, $ArCH$), 4.35 (d, $J = 6.0$ Hz, 4H, OCH_2O), 2.33 (m, 8H, $CHCH_2$), 1.5-1.2 (m, 24H, $(CH_2)_3CH_3$), 0.88 (t, $J = 6.5$ Hz, CH_3); ^{13}C NMR (100 MHz, $DMSO-d_6$) δ 167.1, 147.4, 143.8, 142.6, 138.9, 130.0, 129.3, 127.4, 116.1, 74.0, 36.9, 31.4, 30.7, 29.0, 27.3, 22.3, 14.0.

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