UNIVERSITY OF SOUTHAMPTON

SYNTHESIS OF TRIPHENYLENE BASED MACROCYCLES

by

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Doctor of Philosophy

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ABSTRACT

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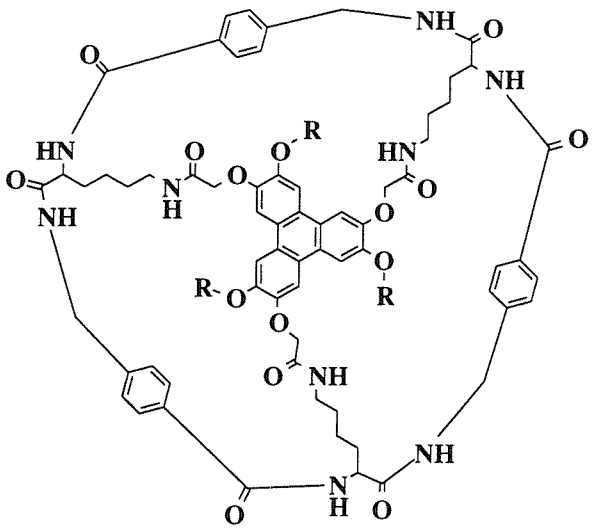
This thesis is concerned with the synthesis of large macrocyclic structures based on the triphenylene system. The eventual aim of the project was to use the macrocycles to bind saccharides in water.

The first stage was to suitably functionalise the triphenylene system to give a base unit for the macrocycles. The first macrocycle (**100**) was built onto the base unit and obtained by cyclisation under high dilution conditions in very good yield as two isomers which could be separated by HPLC. Binding studies showed that a simple aromatic guest (1, 3, 5-benzene triol) would bind to the macrocycle in organic solvents.

In an attempt to make the macrocycle water soluble, a second version (**101**) was synthesised where the pentyl chains of **100** had been replaced by benzyl groups which could be removed after cyclisation and replaced by more hydrophilic groups.

Problems with the cyclisation of **101** and it's poor solubility in organic solvents lead to the development of a third macrocycle with methyl ester side-chains (**118a**). Hydrolysis of the methyl esters of **118a** gave a water soluble derivative (**118b**) which was studied for binding interactions with a range of saccharides and other organic molecules but no binding was observed.



100 R = C_5H_{11}

101 R = Bn

118a R = CH_2CO_2Me

118b R = CH_2CO_2H

Contents

Chapter Four - The Second Macrocycle

Chapter Five - The Third Macrocycle

Chapter Six - Experimental

Preface

The research described in this thesis was carried out under the supervision of Dr. Jeremy D. Kilburn at the University of Southampton between October 1994 and October 1997. No part of this thesis has been submitted at this or any other university except where specific acknowledgement has been made.

Acknowledgements

Three years is a long time and you end up owing to a lot of people.

Firstly I have to thank my supervisor Dr. Jeremy Kilburn for all his help and support, also my industrial supervisor Dr. Iain Gillies for his help while on my CASE placement and for his supply of ideas throughout the project.

On the technical side: in Southampton I would like to thank Mrs. Joan Street for running NMR's and Dr. John Langley for running and processing mass spectra (and for organising the Christmas dinners!). At Dartford: Paul Mace for his help with the HPLC work and John Warren for doing exotic NMR experiments.

I am grateful to EPSRC and Wellcome for funding the work in this thesis.

I need to thank everybody in the Kilburn group and the rest of the chemistry department for making work what it was for the last three years. Thanks to all the people whose houses I've lived in (and there's been a few!) plus Ella and the rest for badminton.

Finally, I would like to thank my parents for all their support during my time at university.

Abbreviations

Ac_2O	acetic anhydride
Bn	benzyl
BOC	*tert*-butyloxycarbonyl
CPK	Corey-Pauling-Koltun
DCC	*N*, *N'*-dicyclohexylcarbodiimide
DIPEA	*N*, *N*-diisopropylethylamine
DMAP	4-(*N*, *N*-dimethylamino)pyridine
DMF	*N*, *N*-dimethylformamide
DMSO	dimethyl sulfoxide
EDC	1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride
EI	Electron Impact
ES	Electrospray
FAB	Fast Atom Bombardment
IR	Infra Red
HOBt	1-hydroxybenzotriazole
HPLC	High Pressure Liquid Chromatography
MS	Mass Spectrometry
mp	melting point
NMR	Nuclear Magnetic Resonance
ROE	Rotating Frame Nuclear Overhauser Effect
ROSEY	Rotating Frame Overhauser Enhancement Spectroscopy
RT	room temperature
sat. aq.	saturated aqueous solution
TOCSY	Totally Correlated Spectroscopy
TFA	trifluoroacetic acid
TLC	Thin-Layer Chromatography
UV/VIS	Ultraviolet/Visible
Z	benzyloxycarbonyl

Chapter One - Introduction

1.1 General Introduction

A crude definition of Host-Guest chemistry might be: The synthesis of (usually) large molecules (hosts) and the study of their interactions with smaller molecules (guests). This is just one aspect of the overall field of supramolecular chemistry which includes areas such as self-assembly and self-replication.[1-5]

Why is Host-Guest chemistry worth studying ? At one level it can be used as a tool to investigate some of the fundamental interactions which occur between molecules. Alternatively it may lead to the development of novel sensing devices[6,7], new materials[8] or new catalysts for a range of chemical reactions which might even rival enzymes for their substrate selectivity.[9,10] At all levels it frequently involves challenging synthetic organic chemistry to build the hosts and can often lead to new methodology along the way making it valuable to 'mainstream' organic synthesis as well.[11] For further background information the reader is directed to several reviews.[12-14]

There are two main areas to this kind of work: the first being the construction of the host molecule, the second is to investigate it's binding abilities with guests. The synthetic aspects are dictated by the structures chosen and are more variable; the binding abilities are controlled by a range of factors and are discussed in the following sections.

1.2 Factors Affecting Binding

Any binding that occurs between a host and a guest is the result of a balance of enthalpic and entropic factors. For the simple equilibrium in Figure 1 the binding constant (K_a) reflects the concentrations of free host [H], free guest [G] and of the host-guest complex [H-G].

$$[H] + [G] \overset{K_a}{\rightleftharpoons} [H\text{-}G] \qquad K_a = \frac{[H\text{-}G]}{[H]\,[G]}$$

Figure 1

We can use K_a to obtain a free energy of binding (ΔG°) as shown in Figure 2 (R is the gas constant and T is the temperature).

$$\Delta G^\circ = -RT \ln K_a \qquad \text{and} \qquad \Delta G^\circ = \Delta H^\circ - T\Delta S^\circ$$

Figure 2

If binding occurs the free energy change must be negative and as stated has entropic (ΔS°) and enthalpic (ΔH°) contributions. These can be broken down further to give a range of factors in subtle balance which may or may not lead to binding taking place.

Entropic Factors:	Enthalpic Factors:
General entropy	Electrostatics
Preorganisation	Hydrogen bonding
Cooperativity	Van der Waals forces
Hydrophobic effects	π-π stacking interactions
	Cation-π and other interactions

1.2.1 Entropic Factors

1.2.1.1 General Entropy

Entropy is a feature of many of the interactions which will be considered in this introduction so it is covered first in a general manner, specific ways in which it applies to certain interactions will be considered where relevant.

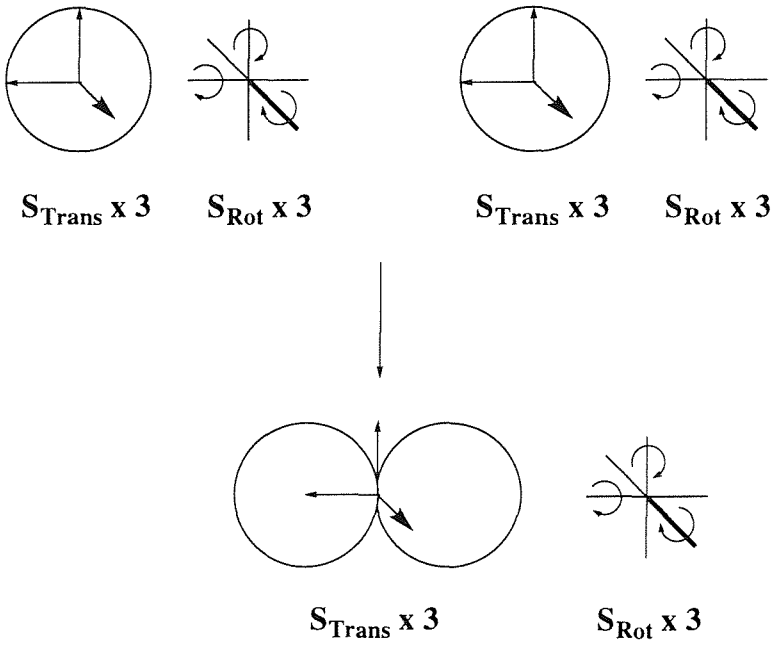
A simple definition of entropy is that it gives a measure of the degree of disorder or randomness of a system. The greater the disorder, the higher the entropy and the more favoured the system. At the molecular level entropy for a molecule is comprised of it's translational, rotational and vibrational modes.

Translational entropy is significant and has a value of approximately 40 $kJmol^{-1}$ for a solution of a small molecule at 298 K (25°C).[15] Translational entropy has only a small dependence on molecular weight but is proportional to the volume occupied by the molecule. A smaller volume means the molecule is more restricted and therefore has a lower entropy; translational entropy is inversely proportional to concentration since a greater number of molecules means a smaller average volume for each molecule.

Rotational entropy can be of a similar magnitude to translational entropy and also has a small mass dependence but is independent of concentration.

Vibrational entropy results from flexing of covalent bonds and generally only contributes a small amount (4-6 $kJmol^{-1}$) to the total entropy of a molecule.

When two molecules come together the translational and rotational entropies of the combined species are only marginally greater than those of the individual molecules (Figure 3) with an overall loss of three degrees of translational entropy and three degrees of rotational entropy which can amount to 55-70 $kJmol^{-1}$ at 298 K (for a 1 molar solution), though there is a slight offset from additional vibrational entropy in the combined species.[15,16]

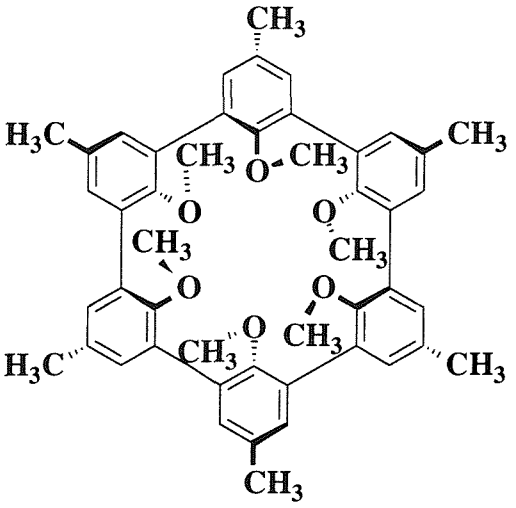


Overall: 3 degrees of translational freedom and 3 degrees of rotational freeedom are lost

Figure 3

1.2.1.2 Preorganisation

One way to reduce the entropy loss in a host-guest system is to use a host which is already in the conformation required for binding and therefore does not suffer any conformational restriction during binding. This is the principle of *preorganisation* and was introduced by Cram.[17,18] An excellent example of the power of preorganisation is the cyclic spherand **1** compared with the acyclic podand **2** shown in Figure 4.



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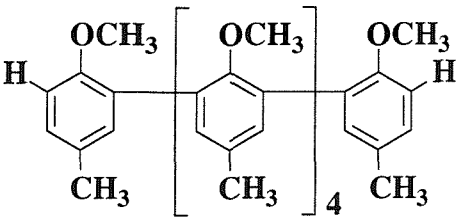
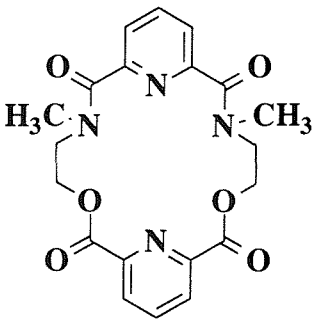


2

Figure 4

In principle the podand **2** can adopt over 1000 conformations in solution only two of which will be ideally suited to binding metal ions. The relatively low binding constant (K_a = 2.4 x 10^4 or $-\Delta G^\circ < 25$ kJmol^{-1}) reflects the entropy loss on binding. The oxygen atoms in the preorganised spherand **1** are already arranged within the cavity in a suitable manner to bind a metal ion, leading to much stronger binding (K_a = 4.5 x 10^{16} or $-\Delta G^\circ > 95$ kJmol^{-1}). The difference in binding constants (a factor of approximately 10^{12}) clearly shows the advantages of preorganisation.

A secondary effect of preorganisation is increased selectivity and can be seen by comparing macrocycles **3** and **4**, where the change from oxygen to alkylated nitrogen gives a more conformationally restricted macrocycle.[19] Macrocycle **3** is more selective for silver(I) ions than lead(I) ions by a factor of 63 but the more preorganised macrocycle **4** shows a selectivity factor of 283 because it cannot change conformation to bind the lead ions as easily as the less constrained version **3**.



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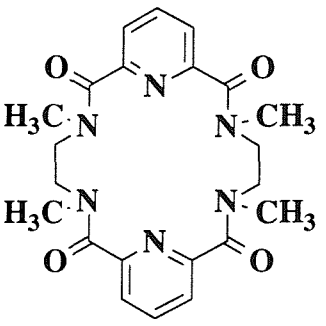


4

Figure 5

Sanders has recently introduced the concept of predisposition by using cinchonidine derived monomers to form stable covalent trimers under thermodynamic conditions. He defines predisposition as "a strong conformational or structural preference expressed by the building block once incorporated into a larger structure giving rise to a thermodynamic preference for a particular product."[20,21] The distinction between the two terms is subtle and interesting but is outside the scope of this thesis.

1.2.1.3 Cooperativity

The concept of cooperativity essentially states that in a system with more than one potential binding interaction, once the first interaction has taken place and some entropy has already been lost, the entropy loss for subsequent interactions is reduced. One might think of it as each interaction preorganising the system for the next interaction.

Hunter *et al* have plotted the stability of "molecular zipper" complexes against the number of recognition motifs (groups of interactions) and found a deviation from linearity which probably indicates a cooperative effect.[22] Figure 6 shows this graphically.

The advantage of cooperativity to the host-guest chemist is that the sum of multiple interactions can be greater than the individual parts giving more stable complexes.

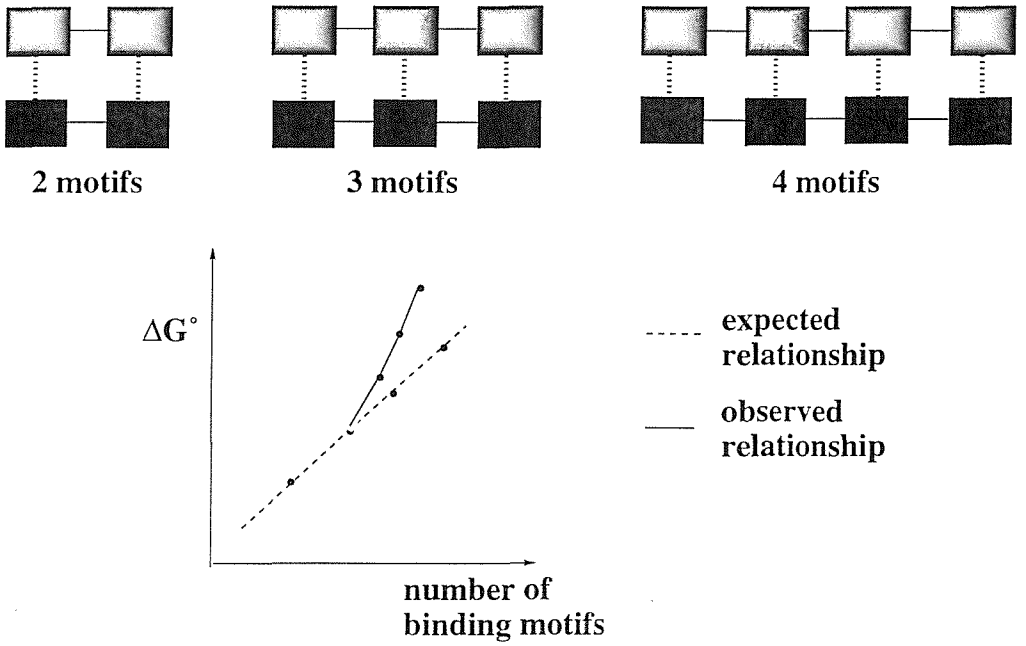


Figure 6

1.2.1.4 Hydrophobic Effects

The hydrophobic effect describes the tendency for non-polar (greasy) compounds such as hydrocarbons to aggregate in water; the classical view is that the process is largely driven by entropy.[23] In the absence of solute water forms a dynamic, loose network of hydrogen bonds where each water molecule experiences an average of four hydrogen bonds worth about 25 $kJmol^{-1}$ each.[15,24]. When a non-polar compound is present, the water molecules re-arrange themselves around the non-polar material to maintain their hydrogen bonds but in doing so they form an ice-like structure which is highly organised and has an unfavourable entropy. If two particles of non-polar material aggregate some of the ice-like water molecules can be released (Figure 7) increasing the overall entropy.

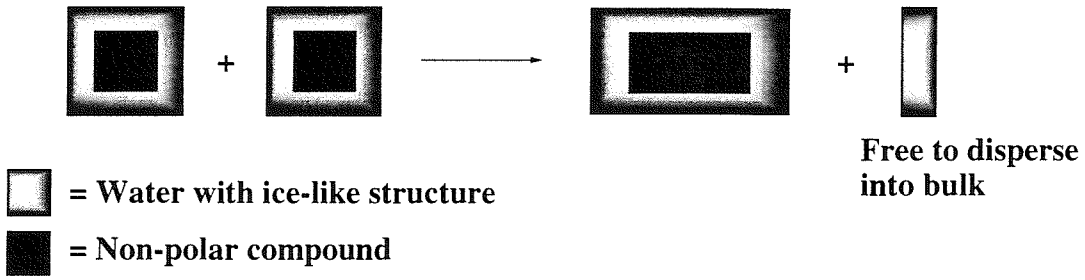
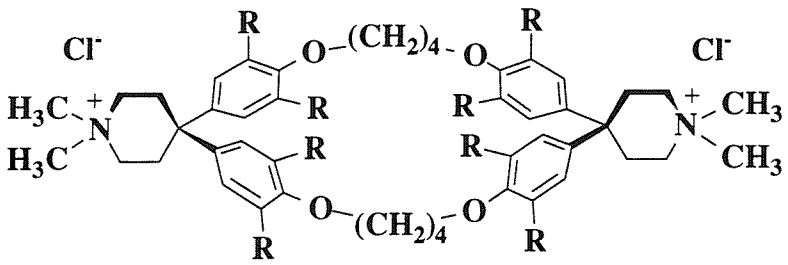


Figure 7

Another possible factor arises from the effect of van der Waals forces; as discussed later the magnitude of these forces depends on the polarisability of the local medium. Oxygen has a low polarisability so van der Waals forces tend to be weak between water and solutes. methylene groups are almost twice as polarisable as hydroxyl groups, which means that aggregated hydrocarbons will experience more significant van der Waals forces than small isolated patches of non-polar material will. This argument is invoked in a paper by Diederich for the complexation of *para*-substituted benzene derivatives by macrocycle **5**.[25]



5 R = OCH_3

Figure 8

Table 1 - Binding Data for Host 5

	ΔG kJmol^{-1}	ΔH kJmol^{-1}	–TΔS kJmol^{-1}
Complex in D_2O			
p-dimethoxybenzene	-22.5	-42.6±10.5	20.1±10.5
p-dicyanobenzene	-21.9	-39.7±4.2	18.0±4.2
Complex in d^4-methanol			
p-dimethoxybenzene	-7.8	-17.6±6.3	10.0±6.3
p-dicyanobenzene	-5.0	-18.4±6.3	13.4±6.3

Table 1 shows some entropy and enthalpy values for the complexes of **5** in deuterium oxide and d^4-methanol. The aqueous system resulted in much more stable complexes but the driving force appeared to be enthalpic with the entropy change actually being unfavourable. The authors suggest that because water has a low polarisability the van der Waals forces between the water and the organic surfaces of the free host and guest were less favourable than those between the complexed host and guest. Interestingly they make no more than a passing comment on the possibility of a contribution from π-π interactions (covered later). The effect of solvent on π-π interactions has not been studied in detail so it is difficult to comment on their possible contribution to the observed results, but a later paper from the same group which studied hosts such as **5** with various disubstituted naphthalene derivatives seemed to suggest that π-π interactions were dominant.[26] This example highlights the difficulties in separating and quantifying the contribution of individual interactions to the overall strength of binding.

1.2.2 Enthalpic Factors

1.2.2.1 Electrostatics

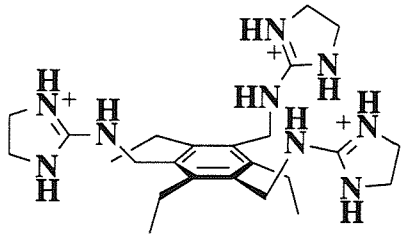
Strictly speaking all intermolecular interactions are based on electrostatic effects but here the term will be used to refer to interactions involving either a formal charge or a dipole moment. There are several different sub-categories of electrostatic forces and the strength (V) varies with the distance between the species involved (r); these are shown in Table 2.[15,27]

Table 2 - Variation of Strength with Distance for Electrostatic Interactions

Type of interaction	n in $V \propto r^{-n}$
Ion-ion	1
Ion-permanent dipole	2
Ion-induced dipole	4
Permanent dipole-permanent dipole (parallel orientation)	3
Permanent dipole-permanent dipole (free rotation/random orientation)	6
Permanent dipole-induced dipole	6

The strength of electrostatic interactions are also highly dependent on the surrounding environment: they are usually inversely proportional to solvent polarity and are generally weak in aqueous solution. An example of this effect is the bond energy between sodium and chloride ions which in an ionic lattice is calculated to be 494 $kJmol^{-1}$ but in aqueous solution falls to just 5 $kJmol^{-1}$.[27] By studying a range of host-guest complexes and comparing the number of ionic interactions with the free energy of binding, Schneider has found that the value of ΔG = -5 $kJmol^{-1}$ per ion pair is reasonably consistent in water.[28]

A similar result is obtained with a recently reported receptor for citrate.[29] The receptor **6** (shown in Figure 9) has three guanadinium cations preorganised to be complementary to the carboxylate groups of citrate. In water the receptor was found to bind to citrate with an association constant of 6.9 x 10^3 M^{-1} (ΔG = -22 $kJmol^{-1}$ at 298 K). Although this equates to 7.3 $kJmol^{-1}$ for each ion pair there is almost certainly some hydrogen bonding between the carboxylates and the guanadinium NH groups as well.



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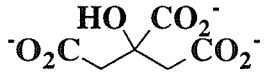


citrate

Figure 9

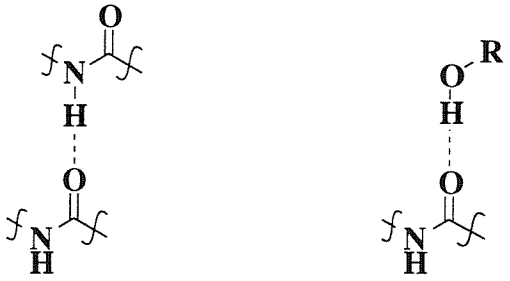
1.2.2.2 Hydrogen Bonding

The hydrogen bond is a very important interaction in biological systems and is also the main reason why water is a liquid, unlike similar small molecules (ammonia, hydrogen sulfide) which are gases. Life as we know it would probably not exist without the hydrogen bond.

A hydrogen bond consists of a proton which is bound to two electronegative atoms. The proton is located at the normal covalent bond distance from the atom it is formally bound to (the donor) but is closer to the other electronegative atom (the acceptor) than the normal van der Waals contact radius, indicating an attractive force. The electronegative atoms involved in hydrogen bonding are usually oxygen or nitrogen and are generally aligned with all three atoms in a linear fashion to maximise the hydrogen bond strength though deviations from a linear arrangement cause only small reductions in energy.[15] In addition the ideal arrangement has the proton aligned with the unshared pair of electrons on the donor atom.[27]

The strength of a hydrogen bond is difficult to quantify as it is determined by several factors including solvent, local environment, the strength of the donor and acceptor groups as well as the geometry already mentioned. Some estimates vary from 12 to 38 $kJmol^{-1}$ while others suggest it can reach 65 $kJmol^{-1}$ or even higher if there is an ionic component.[15,30]

Williams *et al* have extensively studied interactions with the vancomycin group of antibiotics and conclude that amide-amide hydrogen bonds (Figure 10) in such systems typically have a value of -1 to -7 $kJmol^{-1}$.[31] They have also estimated the energy of an amide-hydroxy hydrogen bond to be about -12 $kJmol^{-1}$ in similar systems.[32]



amide-amide hydrogn bond

amide-hydroxy hydgrogen bond

Figure 10

Schneider has compared a range of hydrogen bonded host-guest complexes and by plotting the free energy of binding (ΔG) against the number of hydrogen bonds in the complex a reasonably good correlation was obtained, indicating an average value for a hydrogen bond of $\Delta G = -5$ kJmol^{-1} in deuteriochlorform.[33] In carbon tetrachloride (a more inert solvent) the value rose to $\Delta G = -10$ kJmol^{-1} reflecting the fact that chloroform associates weakly ($K_a \approx 1$) with amides.

Recent work with the system shown in Figure 11 showed that changes to the groups R^1 and R^2 affected the binding constants observed.[34] The dominant effect was thought to be when R^1 and R^2 were electron withdrawing (CF_3 or NO_2): the reduction in electron density in the triazine ring lead to an enhancement of the positive electrostatic potential of the amide protons of **7** and consequently stronger hydrogen bonds were formed between **7** and the flavin **8**. Any effect of weakening the acceptor properties of **7** was presumably masked by the increased strength of the two donor hydrogen bonds

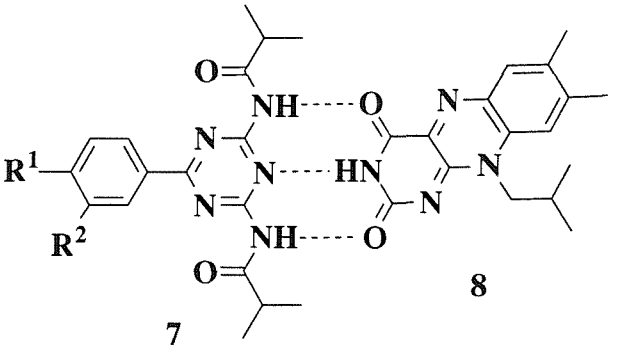
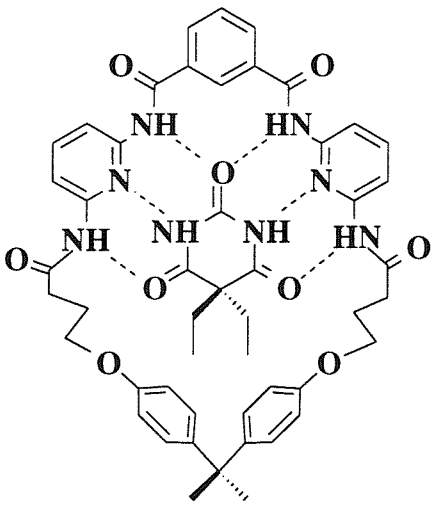


Figure 11

Two excellent examples of hosts which make extensive use of hydrogen bonding are shown in Figure 12 with the species they bind. Complex **9** has an association constant of 1.37 x 10^6 M^{-1} ($\Delta G = -35$ kJmol^{-1}at 298 K) in deuteriochloroform and consists of a barbiturate bound to the host by six hydrogen bonds.[35]

A second example of hydrogen bonding is complex **10** which shows a host that completely satisfies the hydrogen bonding potential of urea by almost completely encircling it giving a binding constant of 8 x 10^3 M^{-1} in 1:1 deuteriochloroform/d^6-DMSO ($\Delta G = -22$ kJmol^{-1}).[36] Although the number of hydrogen bonds is the same in these two cases a direct comparison is not possible due to the presence of DMSO in the case of **10** which is strongly competitive towards hydrogen bond formation.



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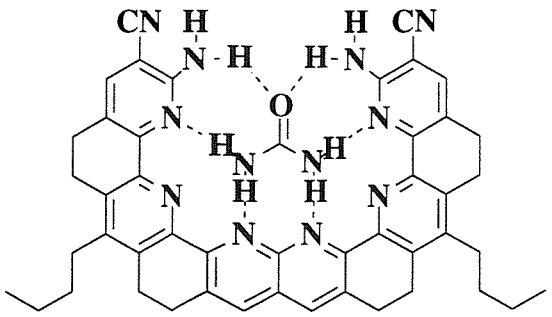
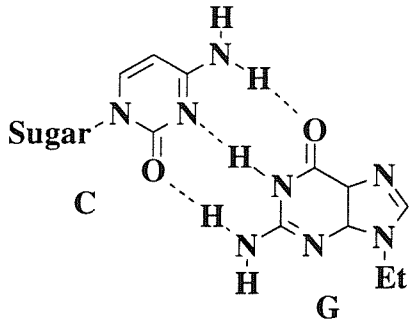


10

Figure 12

1.2.2.3 Secondary Interactions

When analysing hydrogen bond strengths Schneider observed some deviations from linearity. A theory which addresses these was put forward by Jorgenson *et al* and involves secondary interactions between the atoms involved in the hydrogen bonds.[37,38] An example of behaviour which can be explained by this theory is shown in Figure 13 where the pair of cytosine-guanine derivatives **11** has a binding constant of 10^4-10^5 M^{-1} but the uracil-purine pair **12** has a binding constant of just 170 M^{-1}.



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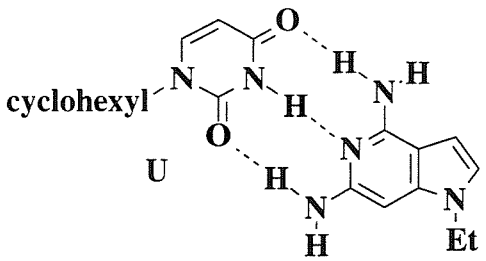

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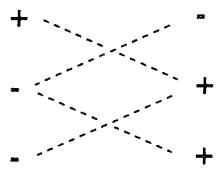


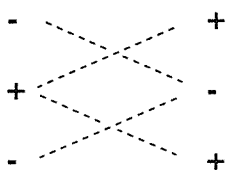


Figure 13

Both complexes have the same number and type of hydrogen bonds but they have different patterns of secondary interactions which are shown below the complexes; an NH group is taken to represent a partial positive charge while O or N represent partial negative charges. For complex **11** there are two repulsive and two attractive interactions but for complex **12** there are four repulsive interactions leading to a much less stable complex. Recent work suggests that for more flexible systems (such as peptide chains) secondary interactions between *covalently adjacent* hydrogen bonding groups may be as important as the secondary interactions discussed above even to the point of cancelling them out.[39]

1.2.2.4 Van der Waals forces

Van der Waals forces (also known as dispersion or London-Eisenschitz forces) are weak interactions arising from the effect of temporary dipoles. Averaged over time a neutral molecule has no net dipole but fluctuations in the density of it's electron clouds lead to temporary dipoles, which can induce other temporary dipoles in adjacent molecules resulting in an attractive force.

$$V = \frac{A}{r^{12}} - \frac{B}{r^{6}}$$

Figure 14

The energy between two atoms is described by the equation in Figure 14 where V is the energy, A and B are constants for particular atoms and r is the separation between the atoms. The r^{-6} term corresponds to the attractive force between induced dipoles and has the same distance dependence as two of the dipole terms in Table 2. The potential energy curve for the interatomic forces (Figure 15) is dominated by the r^{-12} term which is the strong repulsive force between atoms at small interatomic distances as their electron clouds begin to interpenetrate. The minimum point on the curve corresponds to the van der Waals contact distance and is the optimum separation between the two atoms.

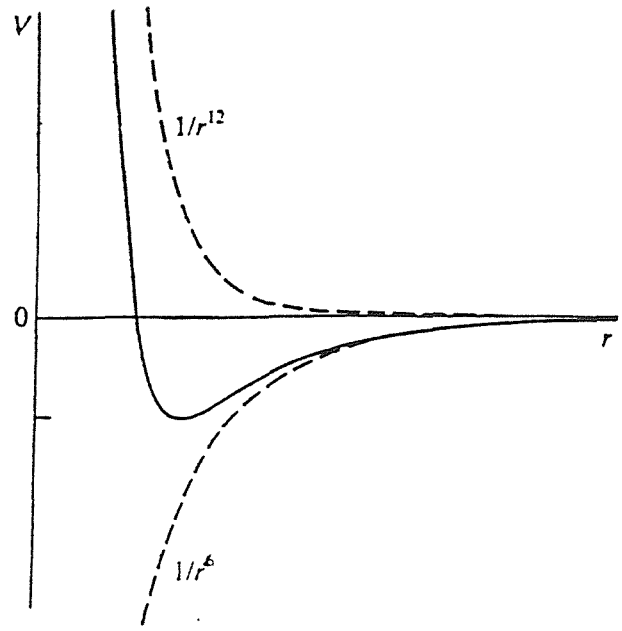


Figure 15

The term B in the equation above contains a factor for the polarisability of the atoms involved, an important factor as the temporary induction of a dipole relies on polarisation of an electron cloud. Also important is the solvent polarisability: it has already been mentioned that water has a low polarisability and only experiences weak van der Waals forces with solutes, but can effectively enhance such interactions *between* solutes by hydrophobic effects.

The magnitude of van der Waals forces is small but they are additive so become significant. At optimal separations the van der Waals energy between two hydrogen atoms is just -0.0778 $kJmol^{-1}$ and between two carbon atoms -0.284 $kJmol^{-1}$ but for benzene in it's crystalline form each CH group is found to contribute 6.7 $kJmol^{-1}$ to stabilising it's structure.[15]

Similarly the gas-phase interaction between two C-H bonds has an energy of only 0.8 $kJmol^{-1}$ but the large number of bonds in a molecule such as *n*-hexane leads to a total van der Waals attraction of 25 $kJmol^{-1}$ between molecules.[24]

Although van der Waals forces can make a significant contribution to the overall binding energy they generally do not have any effect on selectivity.

1.2.2.5 π-π Stacking Interactions

The exact nature of π-π interactions is still unresolved but there is a general consensus that face-to-face stacking of aromatic rings is unfavourable while offset stacked and T-shaped geometries experience an attractive force (Figure 16). This has been confirmed by analysis of crystal structure data though the low levels of statistical clustering reflect the weak nature of these interactions.[40,41]

Hunter and Sanders have advanced the theory that an aromatic ring may be considered as a positively charged σ-framework sandwiched between the two negatively charged π-electron clouds (Figure 16).[42,43] The hydrogens of the aromatic ring have a slightly positive charge and can interact with the π-clouds of a second ring.

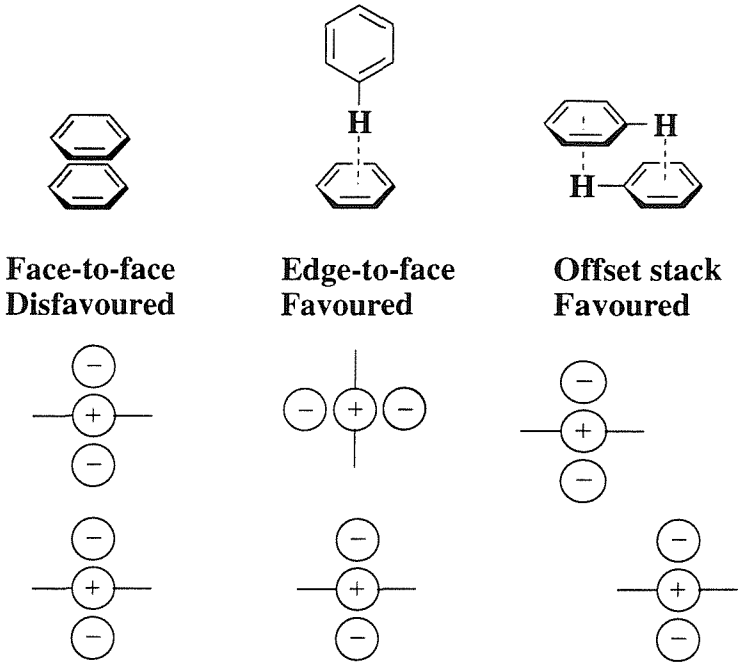
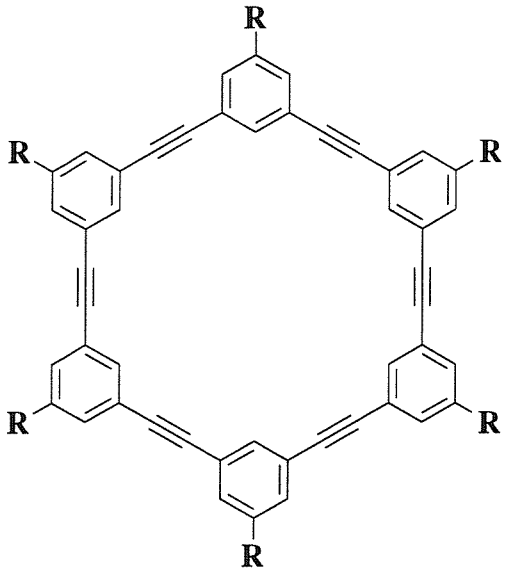
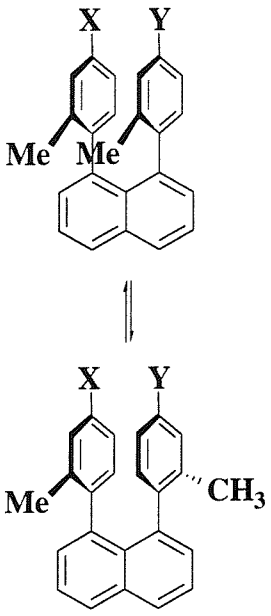


Figure 16

Quantifying these interactions is difficult because of their weak nature but some novel and elegant experiments have been carried out over the last few years. Moore *et al* observed the stacking of phenylacetylene macrocycles such as **13** and **14** in deuteriochloroform (Figure 17) and found that the strongest association occurs when the substituents are electron withdrawing, because the reduction in electron density in the aromatic rings reduces the electrostatic repulsion between the ring faces allowing the offset stacking arrangement to occur.[44,45]



13 R = $CO_2{}^nC_4H_9$ $K_a = 60\ M^{-1}$
14 R = $O^nC_4H_9$ $K_a = 0$



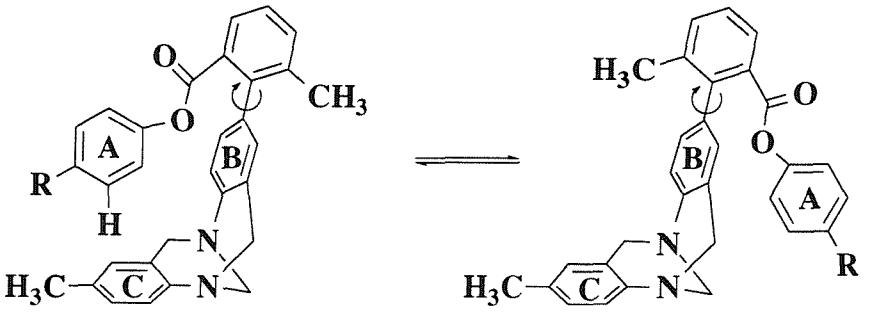
15 X, Y = H, OMe, NO_2, CO_2Me

Figure 17

Cozzi and Siegel *et al* have synthesised the compound **15** shown in Figure 17 where the two tolyl rings are held in a face-to-face arrangement by the naphthalene scaffold.[46,47] The methyl groups act as markers for measuring the equilibrium of conformational exchange. The barrier to interconversion depends on the nature of the X and Y groups and the slowest interconversion is found for electron withdrawing groups (NO_2 or CO_2Me), which indicates that the lack of electron density in the aromatic rings reduces the electrostatic repulsion between them (as for the phenylacetylene macrocycles). Conversely when X and Y were electron donating (OMe) there was a very rapid interconversion between the two forms.

A conceptually similar idea was reported by Wilcox *et al* to study the effects of T-shaped π-π interactions with a "molecular torsion balance".[48] The two conformers shown in Figure 18 result from rotation about the bond indicated. Both forms have a T-shaped interaction between rings A and B but only conformer **16a** has the additional interaction between rings A and C which should lead to a preference for that isomer. NMR spectroscopy was used to determine the ratio of isomers present at room temperature and from this the additional stabilisation free energy from the π-π interaction of rings A and C was calculated.

For R = H, ΔG° = -1.0 kJmol^{-1}; when R was electron withdrawing such as CN or NO_2 ΔG° became -2.7 kJmol^{-1} and when R was electron donating ΔG° remained at -1.0 kJmol^{-1} confirming that reduction in π-electon density favours π-π interactions. Interestingly changing the aryl ester for cyclohexyl gave a significant stabilisation (ΔG° = -1.5 kJmol^{-1}) and a *tert*-butyl ester gave the most stabilisation with ΔG° = -3.4 kJmol^{-1}. The ratio of conformers observed was not affected by changing the solvent.



16a **16b**

Figure 18

Rebek *et al* have produced a series of receptors based on Kemp's triacid incorporating several different aromatic units (benzene, naphthalene and anthracene).[49,50] On binding with 9-ethyl adenine each additional benzene ring of the host was found to contribute approximately 1.8 kJmol^{-1} of extra stabilisation energy.

Recently Hunter *et al* published a method for determining the magnitude of π-π interactions which they refer to as a chemical double mutant cycle.[51] The complexes involved are shown in Figure 19 where the principle involves changing only one functionality at a time and across the whole cycle other interactions are factored out leaving only the π-π interaction of interest.

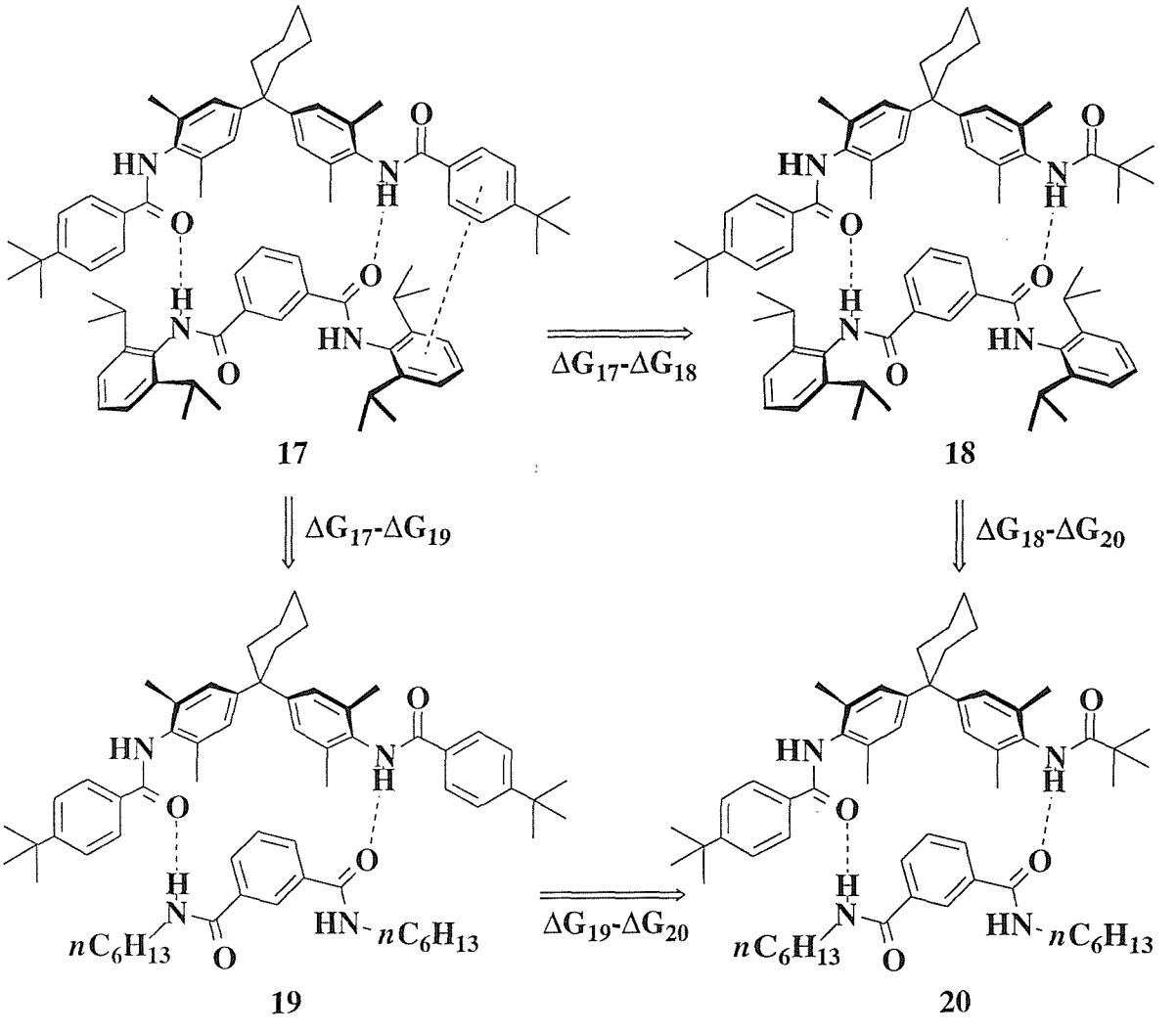
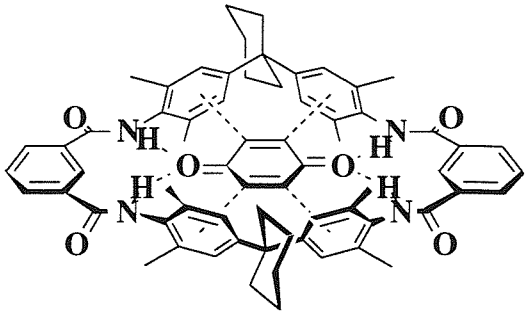


Figure 19

The value obtained from this experiment was -1.4 ± 0.8 kJmol^{-1} which is comparable to the figure obtained by Wilcox *et al* for their simplest unsubstituted system. Schneider has recently criticised some of the assumptions made in the double mutant cycle, particularly the assumption that the zipper molecules are rigid when there are actually several benzylic bonds which can rotate freely.[52]

An additional factor to be considered is the presence of heteroatom substituents on the aromatic ring. These have already been considered for their electron withdrawing effect but for further details the reader is referred to a recent review by Hunter.[53]

A good example of a host-guest complex which relies heavily on π-π interactions is shown in Figure 20.[54] The *p*-benzoquinone is bound by hydrogen bonds to the carbonyl groups and four π-π type interactions to the aromatic rings of the host with an association constant of 1.2 x 10^3 M^{-1} in deuteriochloroform (ΔG = -17.6 kJmol^{-1} at 298 K).



21

Figure 20

1.2.2.6 Cation-π and Other Interactions

There are several other interactions which are either weaker or less well investigated than the major ones covered above. The first of these is the cation-π interaction where the predominant effect is an attractive force between a positively charged species (such as quaternary ammonium) and the negatively charged π-electron cloud of an aromatic ring. A recent paper on this subject suggests a correlation between theoretical binding energies for a sodium cation and various substituted benzene rings against the electrostatic potential of the ring.[55] The same group has also reported strong binding results ($K_a \approx 10^5$) for a range of water soluble hosts and guests where one of the primary binding interactions was thought to be cation-π.[56]

Another interaction involving π-systems has recently been reported by Hunter *et al* where a double mutant cycle was used to obtain an energy value for a pyrrole NH-π hydrogen bond of $\Delta G^\circ = -4.5 \pm 0.5$ kJmol^{-1} at 298 K in chloroform).[57,58] The pyrrole was at an angle of 90° to the benzene ring π-system in the manner of a T-shaped π-π interaction (Figure 21). The N-H bond dipole is larger than the C-H dipole and interacts more strongly with the negatively charged π-electron cloud, giving a larger value for ΔG than for π-π interactions.

Pyrrole NH-π interaction

Figure 21

One final interaction is the C-H···O hydrogen bond. This is thought to have an energy up to 8 $kJmol^{-1}$ but is usually less and is influenced by much the same factors as 'normal' hydrogen bonds. Two good recent reviews have been published.[59,60]

1.2.3 Complementarity

As a final comment on the range of interactions discussed above, it is important that the host is designed to be complementary to the guest. The interactions used must be compatible (e.g. positively and negatively charged groups) and need to be arranged appropriately. It is no use having two point binding if only one interaction can occur at a time! Steric factors must not be overlooked, if a macrocyclic host with a cavity is used then it is vital to ensure that the cavity is large enough and that the guest can actually get access to it.

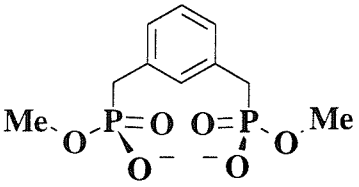
Having discussed the key interactions which occur during host guest chemistry, the binding of saccharides will be considered with a brief overview of the significant literature to date.

1.3 Saccharide Binding

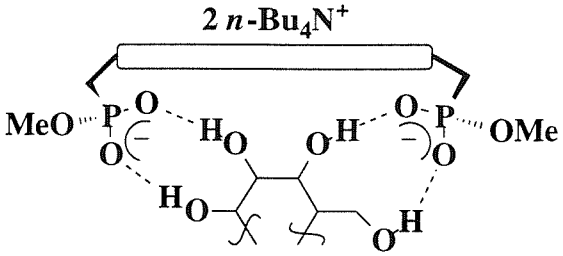
Binding saccharides presents a challenge to the host-guest chemist for several reasons: saccharides are complicated guests and are water soluble unlike many of the hosts/guests described so far; the differences between saccharides are subtle making selectivity a difficult issue, resultingly limited progress has been made in this area. The only exception is the boronic acid work of Shinkai *et al* which has steadily progressed to give structures which are reasonably simple yet can bind some saccharides with good selectivity (see later).

1.3.1 Binding of Saccharides in Organic Solvents

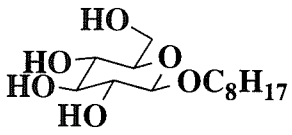
Most of the systems studied so far have been soluble in organic solvents and involved binding pyranosides functionalised with long alkyl chains. Hamilton *et al* have reported the diphosphonate receptor **22** (Figure 22) which showed strong but non-selective binding to the four octyl-pyranosides **23-26** by two point interactions between the phosphonates and two of the sugar diols (shown schematically in Figure 22).[61]



22

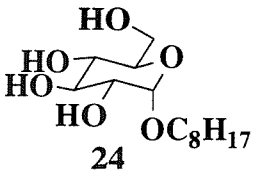


Proposed binding interactions



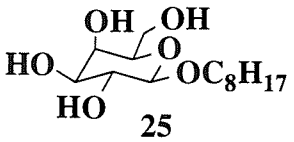
23

1-O-octyl-β-D-glucopyranoside
K_a = 4.4 x 10^3 M^{-1}



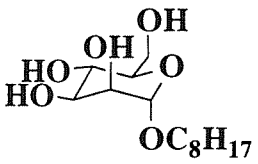
24

1-O-octyl-α-D-glucopyranoside
K_a = 4.2 x 10^3 M^{-1}



25

1-O-octyl-β-D-galactopyranoside
K_a = 3.9 x 10^3 M^{-1}



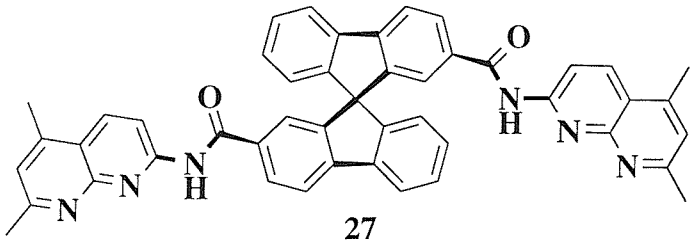
26

1-O-octyl-α-D-mannopyranoside
K_a = 4.0 x 10^3 M^{-1}

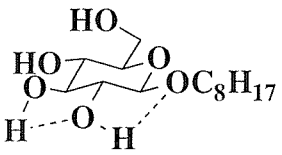
Figure 22

More complex square cyclophane-type receptors have been reported by Diederich *et al* which also utilise phosphonate anions and were found to bind either mono- or disaccharides strongly (K_a 10^4 in polar organic solvents) depending on the size of the host cavity and the separation of the phosphonate groups.[62,63]

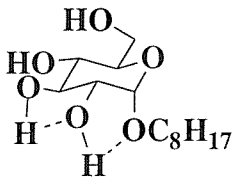
Several reports have been published where alkyl pyranosides are bound by non-ionic hydrogen bonds in organic solvents such as the molecular cleft **27** in Figure 23 reported by Diederich *et al*.[64] These hosts showed a particular affinity for the mannopyranoside **26** compared with the glucopyranosides **23** and **24** which was attributed to differences in the number and strength of intramolecular hydrogen bonds in the free pyranosides being broken when binding occurred. Aslyn *et al* had previously determined that intramolecular *trans*-hydrogen bonds were worth 8.1 ± 0.3 $kJmol^{-1}$ and *cis*-hydrogen bonds 9.3-10.5 ± 0.6 $kJmol^{-1}$ which is consistent with the observation that the mannopyranoside **26** (with only one intramolecular hydrogen bond to break) shows much stronger binding than the glucopyranosides **23** and **24** which have two such bonds to break.[65]



27



23



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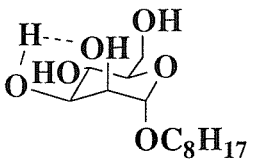


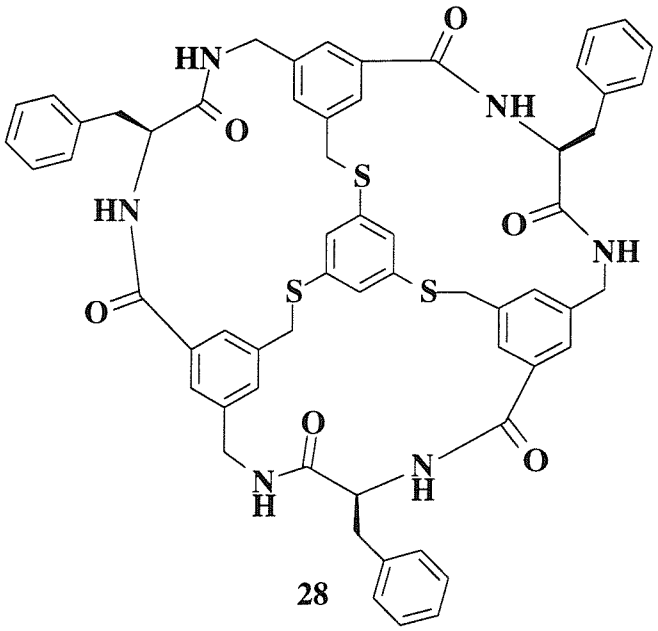
26

	23	**24**	**26**
	2 x *trans*	**1 x *trans*, 1 x *cis***	**1 x *cis***
K_a:	**600 M^{-1}**	**360 M^{-1}**	**1270 M^{-1}**
ΔG°:	**-15.9 $KJmol^{-1}$**	**-14.6 $KJmol^{-1}$**	**-18.0 $KJmol^{-1}$**

Figure 23

The preference for binding mannopyranosides over glucopyranosides was also observed by Bonar-Law *et al* with a porphyrin based host where they placed pyranosides in an order of 'stickiness' towards the host (mannoside > glucoside > galactoside).[66] The 'stickiness' was presumed to arise from the same factors described above, there were also differences between the binding of α- and β-anomers but the effect was less pronounced.

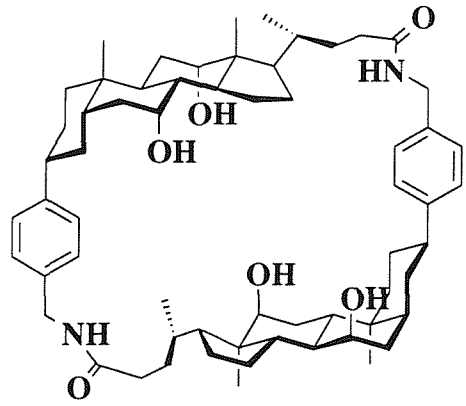
An alternative architecture was used by Still *et al* to bind saccharides in deuteriochloroform with the C3-symmetric macrocycle **28** (Figure 24).[67] No particular mode of binding was described but it is a reasonable assumption that hydrogen bonding was involved as there are a large number of potential hydrogen bond donor/acceptor sites around the rim of the macrocycle. Most monosaccharides bound with ΔG = -8.4 to -12.5 kJmol^{-1} with the exception of 1-O-octyl-α-D-mannopyranoside **26** which bound with ΔG = -21.4 kJmol^{-1}. This macrocycle is particularly relevant to the synthetic targets which will be outlined in the next chapter.



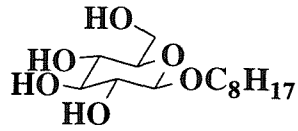
28

Figure 24

A synthetic host based on tetrahydroxycholaphane was reported by Davis *et al* and displays both diastereoselectivity and enantioselectivity (Figure 25).[68,69] The binding of **29** with four isomers of 1-O-octylglucopyranoside (**23**, **24**, **30** and **31**) in deuteriochloroform was studied and the binding constants are shown in Figure 25. There was a difference of a factor of 3 between the binding constants for enantiomers **23** and **30** while between enantiomers **24** and **31** the difference was a factor of 1.75. The diastereoselectivity factor was 5.3 between anomers **23** and **24** but there was no significant difference between **30** and **31**. The fact that selectivity is observed is reasonable as the interior of the host will be a chiral environment and the predominant interaction is probably hydrogen bonding; differences in the arrangement of hydroxyls on the sugar will lead to different patterns of hydrogen bonds with the host some of which will be more favoured than others.

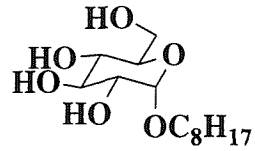


29



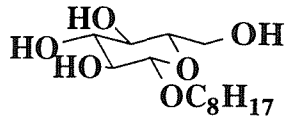
23 β-D

$K_a = 3100\ M^{-1}$



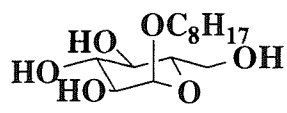
24 α-D

$K_a = 582\ M^{-1}$



30 β-L

$K_a = 1000\ M^{-1}$

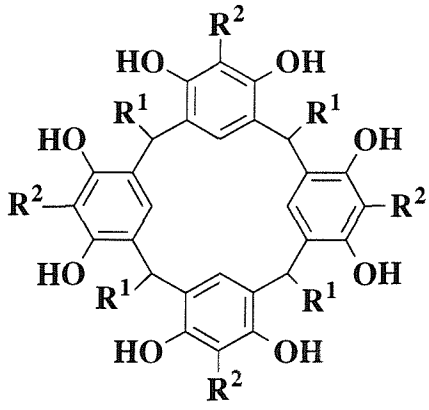


31 α-L

$K_a = 1030\ M^{-1}$

Figure 25

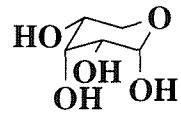
So far all the sachharides discussed have been protected at the anomeric centre, Aoyama *et al* have investigated the binding of resorcinane **32** with unprotected ribose (Figure 26).[70,71] Unprotected ribose would not normally dissolve in carbon tetrachloride but it will do so in the presence of resorcinane **32**. The ribose was bound predominantly as it's α-pyranose form (**35** in Figure 26) which is interesting since this form normally only represents approximately 22% of the sugar in aqueous solution (the β-pyranose and α-/β-furanose forms representing the remaining 78.5%). No binding constants were reported but the host was found to be fairly selective for ribose in extraction studies. The saccharide was thought to be bound by hydrogen bonding between the sugar hydroxyls and the host hydroxyls.



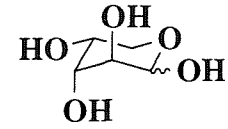
32 $R^1 = n\text{-}C_{11}H_{23}$, $R^2 = H$

33 $R^1 = (CH_2)_2SO_3Na$, $R^2 = CH_3$

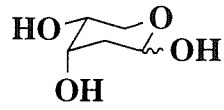
34 $R^1 = (CH_2)_2SO_3Na$, $R^2 = H$



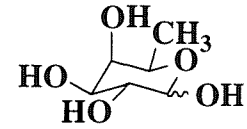
35 α-D-ribopyranose



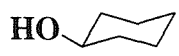
36 D-arabinose



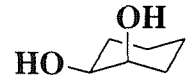
37 D-2-deoxyribose



38 D-fucose



39 cyclohexanol



40 *cis*-cyclohexanediol

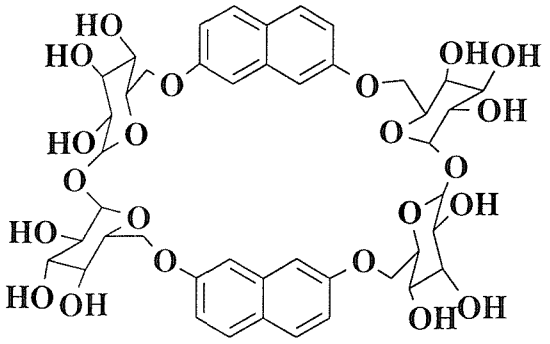
Figure 26

A second version of this host (**33**) has sulfonate groups to give solubility in water and additional methyl groups around the rim of it's cavity.[72] Binding with saccharides in water was very weak ($K_a < 10\ M^{-1}$ for arabinose **36**, 2-deoxyribose **37** and fucose **38**) but there was slightly stronger binding with cyclohexanol **39** and *cis*-cyclohexanediol **40** ($K_a = 125\ M^{-1}$ and $80\ M^{-1}$ respectively). The results strongly suggest that the main driving force for binding in this case was the hydrophobic effect because the more hydrophilic sugars showed much weaker binding. The additional methyl groups on the host probably enhanced this effect by deepening the hydrophobic cavity, as a version which lacked these methyl groups (**34**) showed even weaker binding to cyclohexanol **39** and *cis*-cyclohexanediol **40** ($K_a < 20\ M^{-1}$) and essentially no binding to the saccharides.

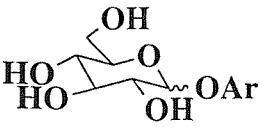
1.3.2 Binding of Saccharides in Water

The binding of sugars in water to date seems to rely heavily on hydrophobic effects as sugars are uncharged, so electrostatic forces cannot be used and hydrogen bonding is weak because water is a very competitive solvent. Solvation of sugars has been studied computationally and it was concluded that the water forms well defined first and second solvation shells around the saccharide molecules with approximately 10-12 hydrogen bonds between the saccharide and the solvent.[73] Because the saccharide is well solvated by water a large number of strong interactions between host and saccharide must be formed to balance the loss of these hydrogen bonds between saccharide and water on binding.

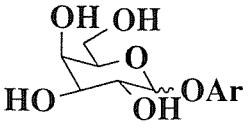
Two other examples of hosts which bind saccharides in water are shown below. The first reported by Penadés *et al* , was described as a glycophane (**41**) and showed moderate binding with *para*-nitrophenylpyranosides in water.[74] Glycophane **41** bound *para*-nitrophenol weakly ($Ka = 15\ M^{-1}$), the β-anomers of the pyranosides showed slightly stronger binding (Table 3) and the α-anomers showed stronger binding still. The implication is that there is an additional stabilisation provided by the saccharides which is stronger for the α-anomers.



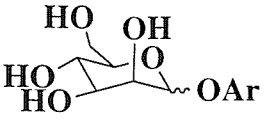
41



42 *p*-nitrophenylglucopyranoside



43 *p*-nitrophenylgalactopyranoside



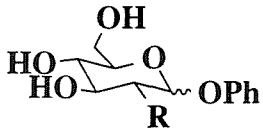
44 *p*-nitrophenylmannopyranoside

Figure 27

Table 3 - Binding Data for Host 41

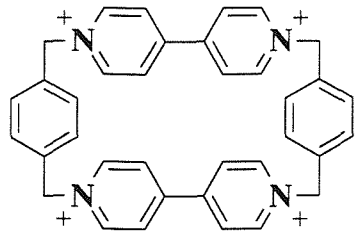
Guest	K_a (M^{-1})	$-\Delta G$ ($kJmol^{-1}$) at 303 K
p-nitrophenol	15	6.8
β-*p*-nitrophenylglucopyranoside	63	10.4
β-*p*-nitrophenylgalactopyranoside	95	11.5
β-*p*-nitrophenylmannopyranoside	72	10.8
α-*p*-nitrophenylglucopyranoside	135	12.4
α-*p*-nitrophenylgalactopyranoside	150	12.6
α-*p*-nitrophenylmannopyranoside	258	14.0

The second example of binding in water uses a host which was originally synthesised by Stoddart *et al*[75,76] and has now been reported by Smith *et al* to be capable of binding phenoxypyranosides.[77] The host **45** is shown in Figure 28 with some of the guests studied; binding was carried out in aqueous buffer at pH 7.4.

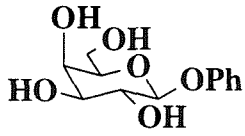


R = OH
46 D-phenylglucoside

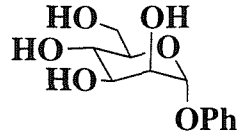
R = $NHCOCH_3$
47 D-phenyl N-acetylglucosaminide



45



48 β-D-phenylgalactoside



49 α-D-phenylmannoside

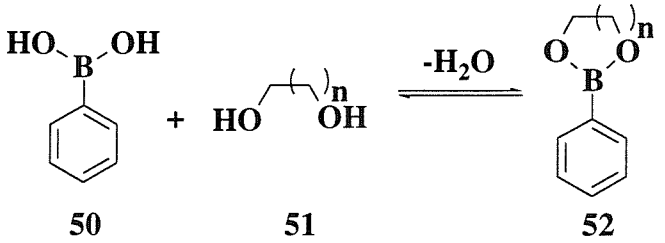
Figure 28

The authors suggest that complexation was driven by inclusion of the phenoxy group of the guests within the cavity of the host, presumably by a combination of hydrophobic effects and possibly some aromatic interactions (π-π) between host and guest. The binding was generally strong with most of the guests studied, the most noticeable selectivity was for β-phenylglucopyranosides over their α-anomers by an average of 3.0 $kJmol^{-1}$ (Table 4). The selectivity was not due to solvophobic effects as the preference was maintained when the solvent was changed to acetonitrile (though the magnitude of the binding constants was considerably reduced to 543 M^{-1} for the β-anomer and 173 M^{-1} for the α-anomer). The electron densities of the phenyl rings of both anomers were the same when compared by carbon-13 NMR chemical shifts making an electronic factor unlikely. The authors concluded that the effect was probably steric in nature which appeared to be confirmed by a molecular modelling study that predicted the β-anomer complex to be more stable by 1.7 ± 0.4 $kJmol^{-1}$ on steric grounds.[78]

Table 4 - Binding Data for Host 45

Guest	K_a (M^{-1})	-ΔG ($kJmol^{-1}$) at 295K	ΔΔG
β-D-phenylglucoside	4.1×10^3	20.5	
α-D-phenylglucoside	1.4×10^3	18.0	2.5
β-D-phenyl N-acetylglucosaminide	1.0×10^3	17.1	
α-D-phenyl N-acetylglucosaminide	0.2×10^3	13.8	3.3
β-D-phenylgalactoside	5.3×10^3	21.3	
α-D-phenylmannoside	1.5×10^3	18.0	3.3

The hosts discussed so far all bind saccharides either by hydrogen bonds (in organic solvents) or a combination of hydrophobic interactions and possibly π-π interactions. In all cases there is almost certainly some contribution from van der Waals forces, entropic effects and cooperative factors. There is one other class of saccharide binding hosts which should be mentioned: the boronic acid based hosts of Shinkai *et al.* In the presence of 1, 2- or 1, 3-diols, boronic acids can form 5- or 6-membered cyclic esters as shown in Figure 29.



50 **51** **52**

Figure 29

The vicinal *cis*-diols of saccharides form more stable cyclic esters with boronic acids than simple acyclic diols such as ethylene glycol. With simple saccharides the equilibria between the pyranose and furanose forms complicates matters, but there does seem to be a selectivity order for monosaccharides which applies to all monoboronic acids (Table 5).[79]

Table 5 - Association Constants for Diols with Monoboronic Acids

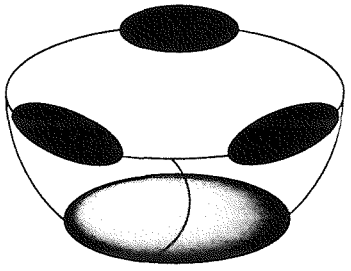
Saccharide (or diol)	K_a (M^{-1})
ethylene glycol	≈ 3
D-glucose	110
D-mannose	170
D-galactose	275
D-fructose	4365

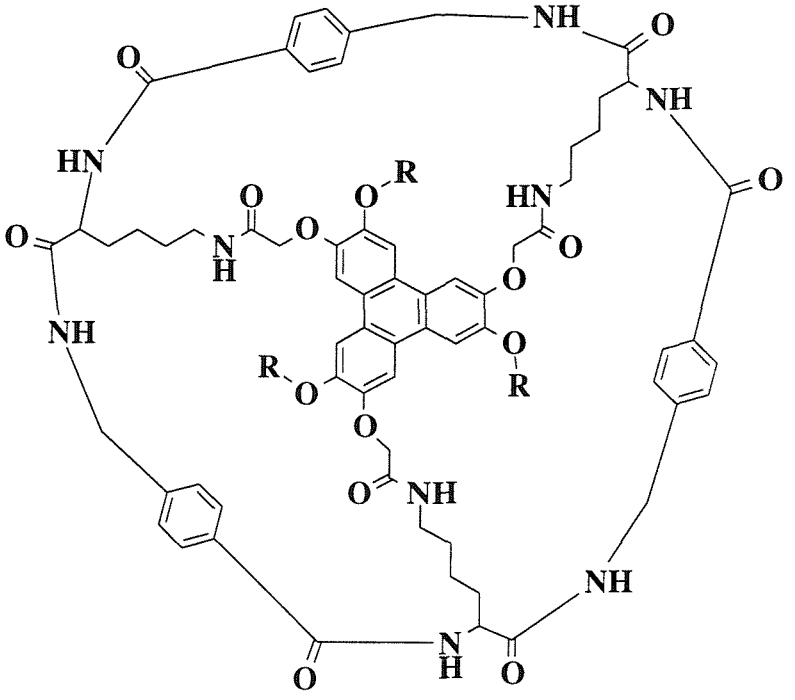
In recent years Shinkai *et al* have reported a large number of increasingly sophisticated hosts for saccharides based on the boronic acid functionality. Some of these utilise two point binding (diboronic acids) and many have involved photoelectron transfer fluorescence as a means of signalling their binding to a saccharide. To discuss these further is not appropriate here but the reader is directed to two recent reviews for further information.[80,81]

This concludes the introduction to host-guest chemistry, the next section sets out the work attempted within this field.

1.4 Programme of Work

The aim of the project was the synthesis of a variety of host molecules of the type shown in Figure 30 and to study their binding interactions with guests, particularly saccharides.





53

Figure 30

In contrast to many synthetic hosts the macrocycle **53** does not have a particular binding site. Instead it has a range of features which all have the potential to contribute to the binding of suitable guests. The macrocycle was designed to be bucket shaped (shown by the schematic in Figure 30) and have a large cavity which would be capable of accepting guests such as mono or disaccharides.

The macrocycles were built around the flat, rigid triphenylene base which can act as a scaffold for the structure, allowing the macrocycle to exist with a cavity and may also be able to provide hydrophobic interactions (in water) or take part in aromatic stacking. Space filling (CPK) models suggested that to a reasonable approximation, when saccharides adopt a chair conformation they would be fairly flat with the hydroxyls on a hydrophilic face and the methylenes on the other, hydrophobic face. Obviously this would depend on the distribution of hydroxyls around the sugar ring but it was hoped that some hydrophobic interactions between the saccharides and the triphenylene might be observed. The triphenylene could

also be used as a fluorescent probe to measure when binding occurred, as a guest located above the triphenylene would perturb it's π-electron cloud and lead to a change in it's fluorescence.[82,83]

The side walls of the macrocycle were to be based on (L)-lysine to provide a chiral environment, while benzene rings were chosen as rigid spacers (by using CPK models) to be capable of maintaining a cavity without being so rigid that they would hinder the final cyclisation.

The linkages between the base, the rigid spacers and the side walls are mostly amide bonds which it was hoped would provide a large number of potential hydrogen bond sites (both donor and acceptor) to suitable guests.

The R groups were to be varied to control the solubility of the macrocycle either in organic or aqueous solvent systems.

Finally the macrocyclic structure is C_3-symmetric which allows the complex structure to be built up relatively easily. Macrocycles of this type (such as **28** in Figure 24) are well precedented. Still *et al* have reported several variations on this theme using a smaller benzene derived base unit, one of which was shown to bind octyl-pyranosides in organic solvents as discussed earlier.[67,84-86]

CPK Models of macrocycle **53** are shown in Figures 31 and 32 where the cavity of the macrocycle is clearly visible (the R groups are represented by methyl for clarity).

Synthetic Strategy

The general macrocyclic structure **53** can be disconnected into an acyclic precursor which can be further simplified into two main sections: the triphenylene base unit **54** and the side wall/rim unit **55** (Figure 33). The side wall/rim unit may be further disconnected into two suitably protected amino acids (**56** and **57**).

The synthesis of the macrocyclic structures from these fragments will be discussed in the following chapters starting with the base unit.

Figure 31 - CPK Model of Macrocycle 53 (Side View)

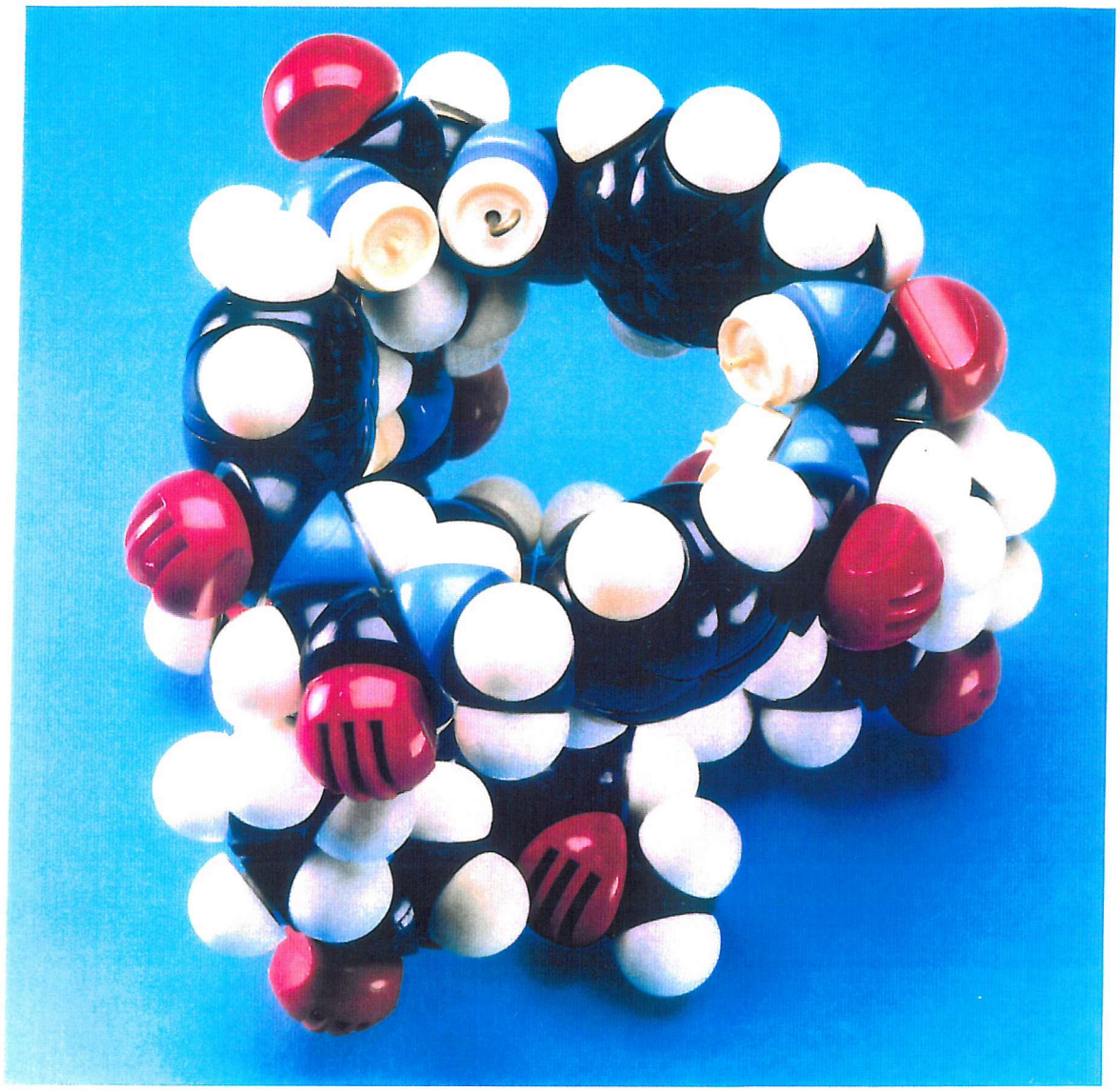
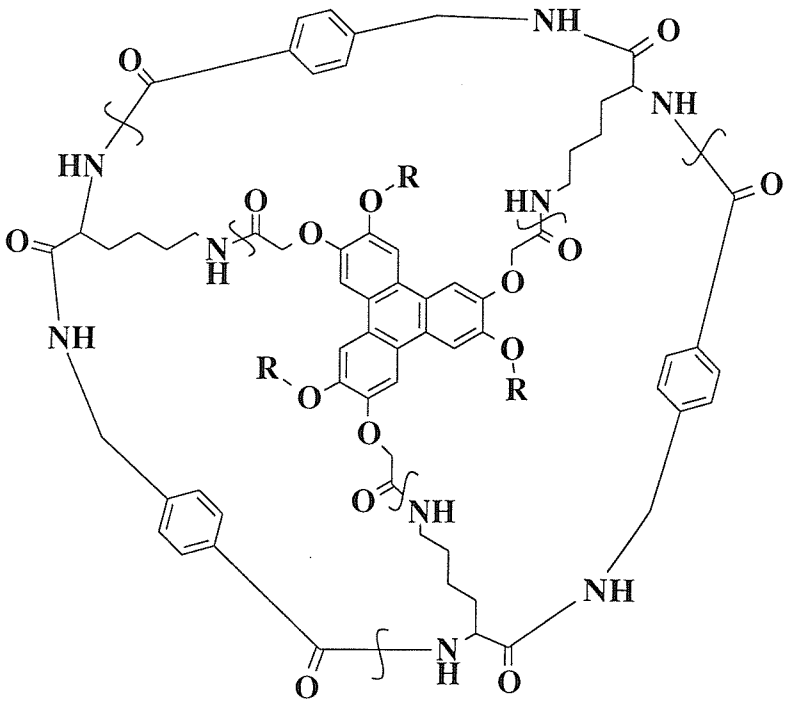
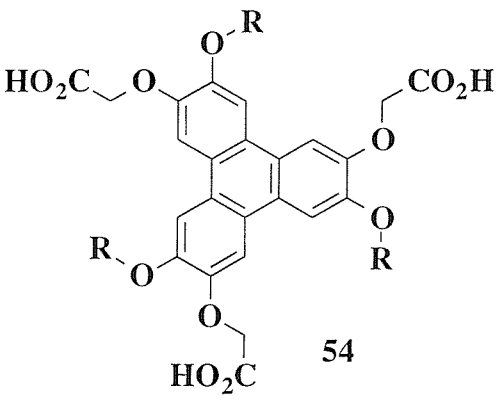


Figure 32 - CPK Model of Macrocycle 53 (Top View)



53



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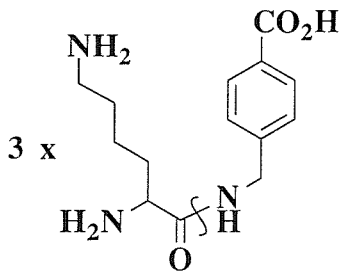
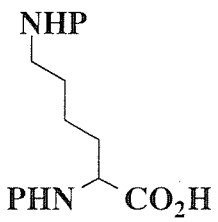


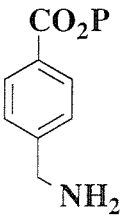
3 x

55

P = Protecting group



56



57

Figure 33

Chapter Two - Synthesis of a Triphenylene Base Unit

2.1 Requirements and Initial Strategy

The first task in the synthesis of the macrocycles was to produce the triphenylene base unit. The general form was to be that shown in Figure 34 where R^1 and R^2 are different and at least one of them would allow the attachment of the macrocycle side-wall/rim unit. Figure 34 also shows an abbreviated way of depicting the triphenylene system that will be used throughout this thesis.

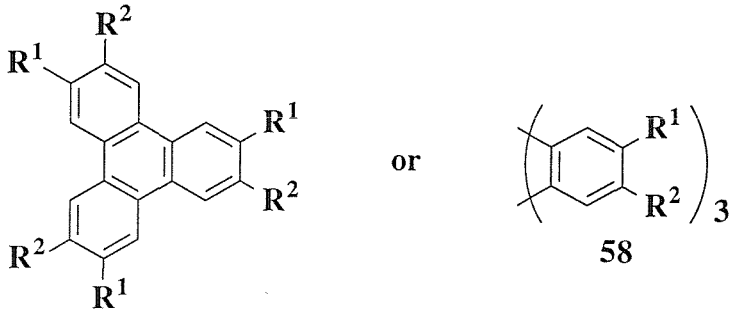
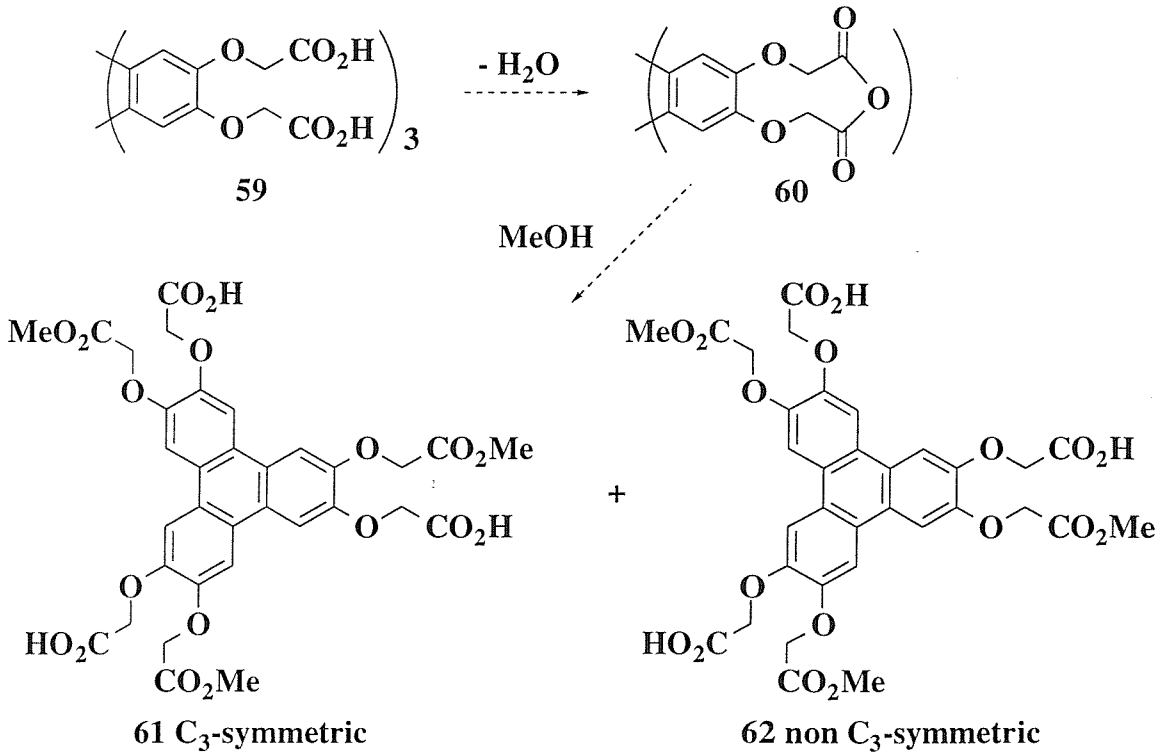


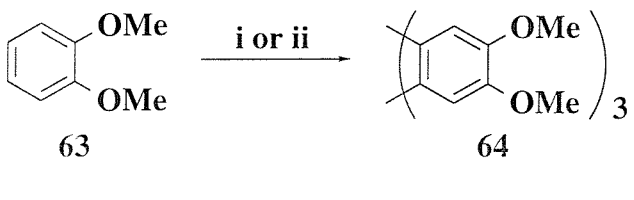
Figure 34

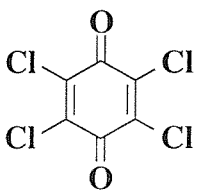
The triphenylene system can easily be synthesised with all six substituents identical (R^1=R^2) so the initial synthetic strategy was to obtain the hexakis(oxyacetic acid) triphenylene **59**, form the anhydride **60** by dehydration and then open the anhydride with methanol giving the two isomeric compounds **61** and **62** (Scheme 1). The C_3-symmetric isomer could then be used as a base for the macrocycle.



Scheme 1

The first stage was to construct the triphenylene core from a dialkoxybenzene via an oxidative trimerisation (Scheme 2). Initially the method used was to treat 1, 2-dimethoxybenzene **63** with *p*-chloranil **65** and 70% sulfuric acid for a period of 8 days.[87] Apart from the long reaction time, the yield was low (33%) and removal of the excess *p*-chloranil used was problematic. The low solubility of the hexamethoxytriphenylene **64** meant that column chromatography or recrystallisation were not effective methods for purification so an alternative method was devised: by suspending the crude product mixture in chloroform and stirring with a basic, aqueous solution of sodium dithionite the *p*-chloranil was reduced (presumably to the quinol) and passed into the aqueous phase as a salt.[88] The hexamethoxytriphenylene **64** was recovered reasonably pure from the organic phase.





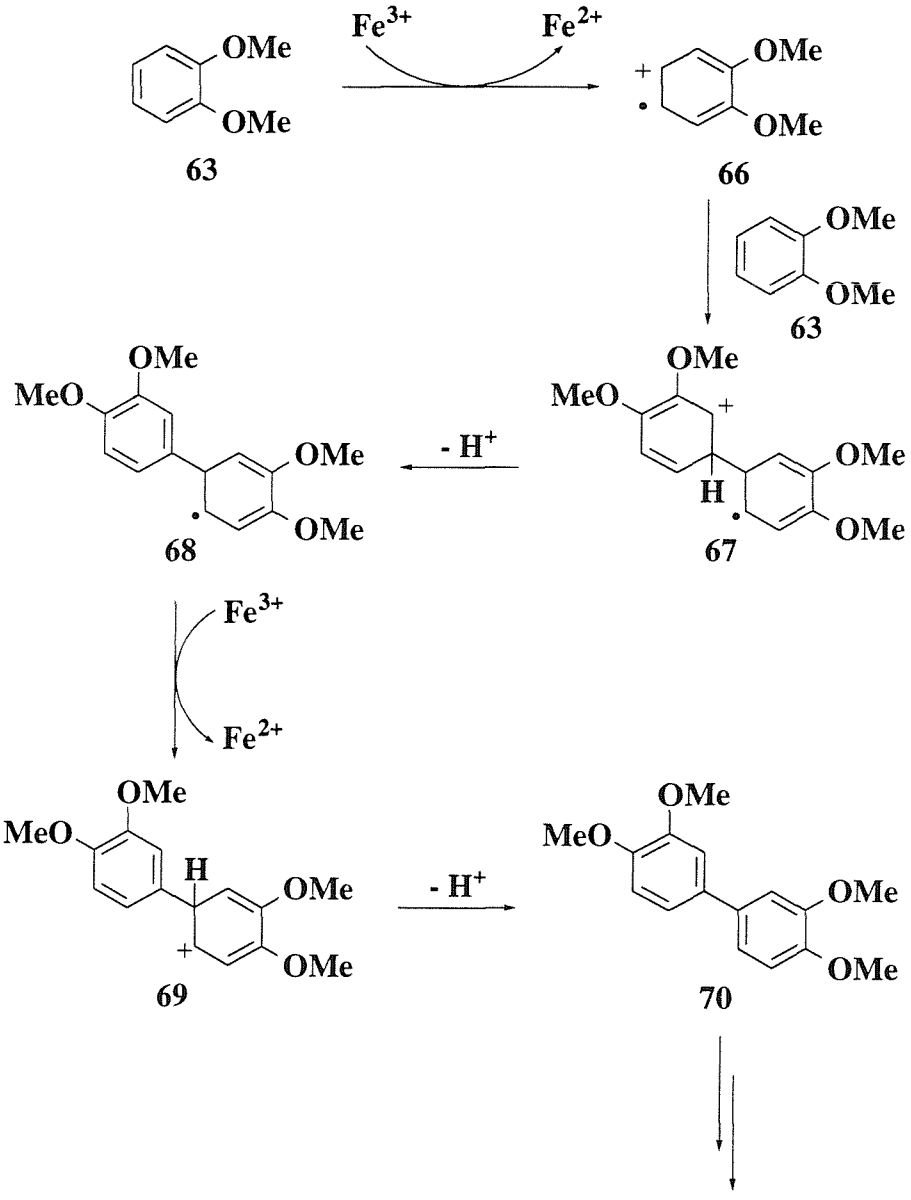
65 ***p*-chloranil**

(i) ***p*-chloranil / 70% H_2SO_4 (33% yield)**

(ii) **$FeCl_3$ / CH_2Cl_2 / H_2SO_4 (81% yield)**

Scheme 2

Even with this relatively simple purification method the yield of the reaction was still poor so a different method of trimerisation was investigated. The use of ferric chloride in dichloromethane with a catalytic quantity of sulfuric acid gave a much faster reaction (typically 3 hours in total) and an improved yield of 81%.[89] The mechanism is not specifically discussed in the literature on triphenylenes but a plausible mechanism is shown in Scheme 3 for the ferric chloride method.

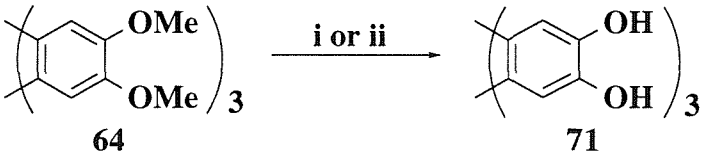


Scheme 3

Oxidation of dimethoxybenzene **63** gives a radical cation **66** which can react with a second molecule of **63** to give radical cation **67**. Loss of a proton to give the biaryl radical **68**,

followed by a second oxidation and proton loss to regain aromaticity, gives biaryl **70** which can react further in the same manner to eventually give hexamethoxytriphenylene **64**.

The next step was to cleave the methyl ethers of **64** to give hexahydroxytriphenylene **71**. This reaction could be carried out using either boron tribromide in dichloromethane[87] or a mixture of hydrobromic and acetic acids (Scheme 4).[90] Both methods gave excellent yields but the hydrobromic acid/acetic acid method has the advantage of being simpler to carry out on a large scale because it does not require anhydrous conditions.

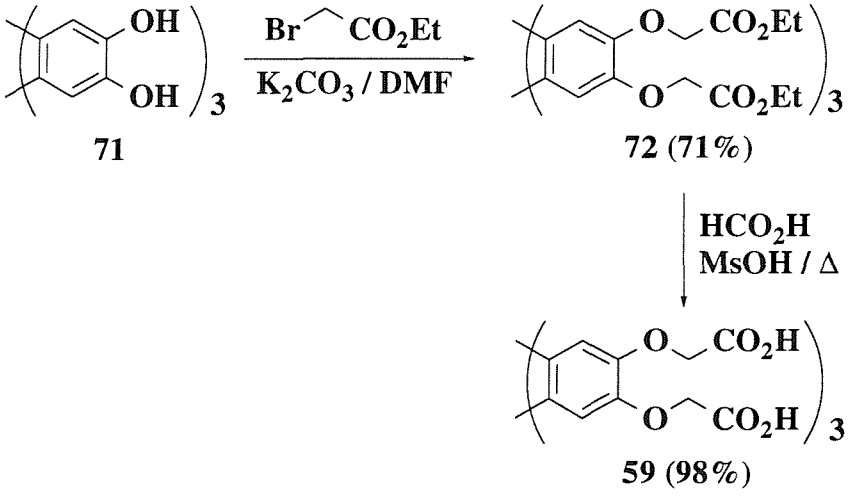


64 **71**

(i) BBr_3 / CH_2Cl_2 / -78° (98% yield)
(ii) HBr / HOAc / Δ (quant. yield)

Scheme 4

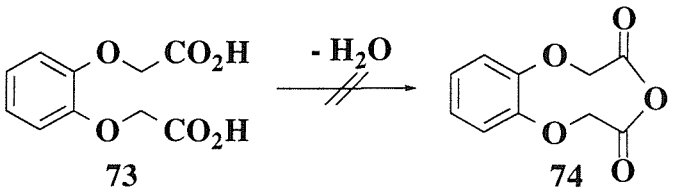
Alkylation of the hydroxy groups of **71** was straightforward using ethyl bromoacetate to give the hexakis(ethyl ester) **72** in good yield. The esters were cleaved by transesterification with refluxing formic acid/methanesulfonic acid to give the hexakis(oxyacetic acid) **59** in near quantitative yield (Scheme 5).[91]



71 **72 (71%)** **59 (98%)**

Scheme 5

Investigations into forming the required anhydride were carried out on the model compound **73** (Scheme 6) which was more soluble and less polar than the triphenylene equivalent **59**. Unfortunately no evidence for formation of the anhydride was obtained with a variety of conditions. It was anticipated that forming a 9-membered ring might be difficult as the reaction would have an unfavourable entropy change but it was still disappointing that no reaction occurred. The methods tried and some comments are shown in Table 6. If an anhydride had been formed it would have been possible to detect it by the presence of two bands in the IR spectrum in the regions 1840-1800 cm^{-1} and 1780-1740 cm^{-1}, compared with the free acid which showed a single band at 1670 cm^{-1}.



Scheme 6

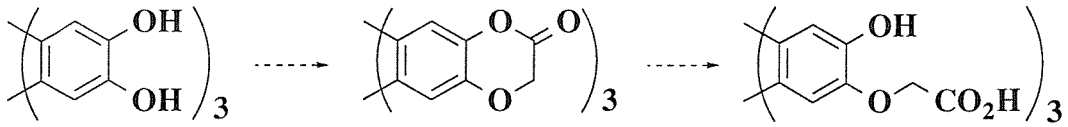
Table 6 - Conditions used for attempted formation of anhydride 74

Conditions	Reaction time	Comments
DCC (1 eqv) / DMF[92]	48 hours	No reaction
Ac_2O (neat) / reflux[93]	22 hours	Diacylated product isolated
Ac_2O (neat) / DMAP / reflux	23 hours	Unidentified mixture of products
Ac_2O (1 eqv) / DMF / reflux	22 hours	No reaction
Triphosgene / Et_3N / DMF[94]	1.5 hours	Unknown product*
Thionyl chloride (neat)	16 hours	No reaction
Thionyl chloride (1 eqv) / acetone / DIPEA / reflux	21 hours	Decomposition of starting material

* The unknown product appeared to be an anhydride by IR but the NMR contained a signal at δ 12.3 which suggested a carboxylic acid proton.

2.2 Alternative Approaches to the Base

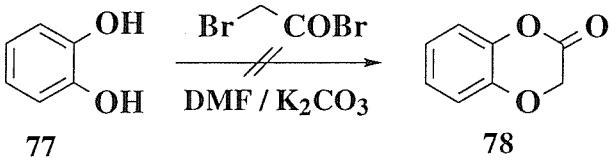
Following the failure of the anhydride approach an alternative route was considered (Scheme 7) . By forming the lactone **75** and then opening with base it would be possible to differentiate between the *ortho*-oxygens on the triphenylene ring although the C_3- and non C_3-symmetric isomers of **76** would probably both be produced and would require separation.



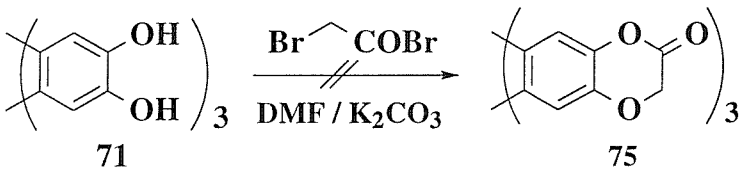
71 75 76

Scheme 7

A search of the literature for this kind of reaction did not provide any useful information so the two reactions shown in Scheme 8 were attempted. The expectation was that acylation at the carbonyl of bromoacetyl bromide would occur first followed by a fast intramolecular alkylation but in both cases the starting material decomposed during the reaction.



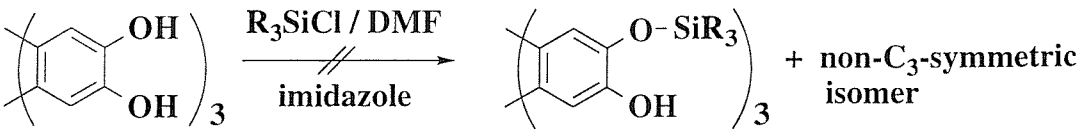
77 78



71 75

Scheme 8

The next approach studied was the use of bulky silicon groups (Scheme 9) in the hope that steric hindrance would prevent silylation of both the *ortho*-oxygens.

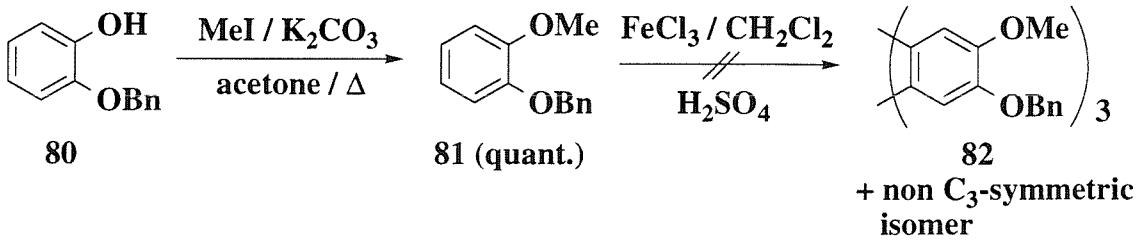


71 79

Scheme 9

Three different silicon reagents were tried: thexyldimethylchlorosilane[95], *tert*-butyldiphenylchlorosilane[96] and tri-*n*-hexylchlorosilane. In all three cases the reactions did not go to completion and the desired products could not be isolated from the reaction mixtures.

The methods described so far for obtaining a C3-symmetric triphenylene base unit all involved forming the triphenylene and then attempting to differentiate between it's *ortho*-oxygens. An alternative method involves differentiating between the oxygens *before* the trimerisation reaction is carried out (Scheme 10). Methylation of *ortho*-benzyloxyphenol **80** proceeded smoothly in quantitative yield using a literature method[97], but when the trimerisation of **81** was attempted the reaction gave a complex mixture of products. The NMR spectrum of this mixture showed the absence of a signal for the benzyl methylene ($\delta \approx$ 5.2) suggesting the benzyl groups had been removed by the reaction conditions. Ferric chloride can be used to cleave benzyl groups so this result was not unexpected.[98] The trimerisation conditions are fairly harsh with hydrogen chloride gas being generated and are incompatible with most easily removable protecting groups.

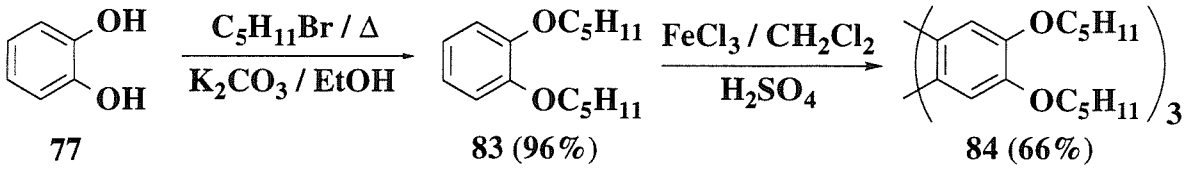


80 **81 (quant.)** **82** + non C_3-symmetric isomer

Scheme 10

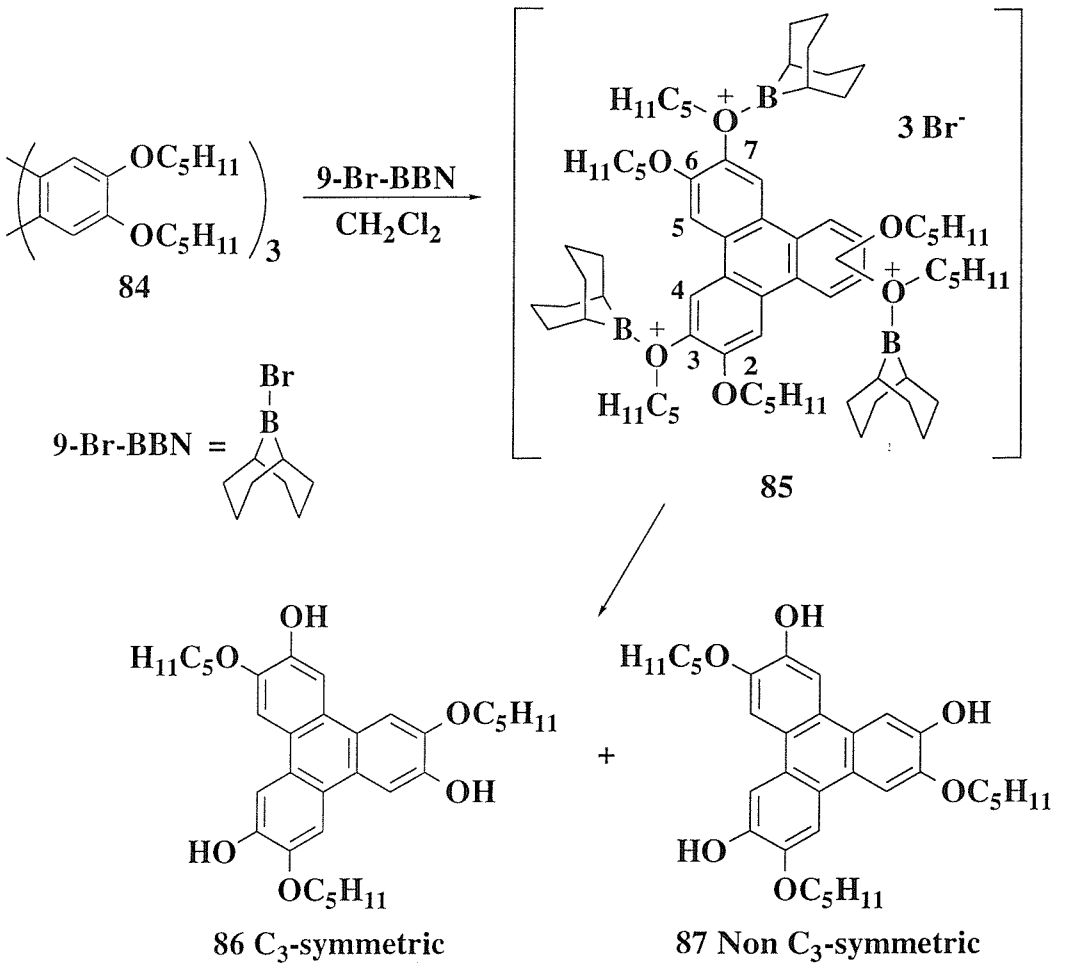
2.3 The 9-Br-BBN Method

The problem of producing a suitably functionalised triphenylene was eventually solved by using a method which appeared in the literature during the course of these investigations.[99] The hindered boron reagent 9-bromo-9-borabicyclo[3.3.1]nonane (9-Br-BBN) was used to selectively cleave three of the pentyl chains of hexapentyloxytriphenylene **84** (Scheme 12) giving a mixture of the C3-symmetric and non C3-symmetric isomers of the product, which could easily be separated by flash column chromatography. The hexapentyloxytriphenylene **84** was obtained from catechol by alkylation in near quantitative yield, followed by the ferric chloride induced trimerisation (Scheme 11).



77 **83 (96%)** **84 (66%)**

Scheme 11



Scheme 12

Table 7 shows the various conditions investigated for the reaction. On the first attempt (entry 2) the reaction proceeded according to the literature (entry 1) though the reaction was complete after only 4 hours as judged by TLC. Subsequent attempts to repeat this failed (entries 3-7) even with a fresh supply of the reagent. Refluxing the reaction mixture was tried, as was altering the workup procedure from the addition of stoichiometric quantities of ethanolamine to treatment with hydrochloric acid or sodium bicarbonate solution. In all cases consistently low yields were obtained with the non C3-symmetric isomer as the major product.

When the reaction temperature was reduced to -30°C the yields improved considerably and the desired C3-symmetric isomer became the major product. It was also important to keep the reaction time short as entries 8-11 clearly show that longer reaction times led to lower yields of both isomers. Reducing the temperature to -40°C was also investigated but the C3-symmetric isomer obtained was contaminated by an impurity with a very similar R_F (probably a triphenylene with only two pentyl groups cleaved).

The best conditions (entry 11) gave a total yield (90%) that was slightly better than the original procedure (85%) but more significantly had increased the amount of the desired C3-symmetric isomer **86** from 38% to 55% at the expense of the non C3-symmetric form **87**. Statistically one would expect to observe just 25% of the C3-symmetric isomer and 75% of the non C3-symmetric isomer. Obviously steric hindrance prevents the boron reagent from being chelated to both the 2, 3-related ethers (Scheme 12), but examination of a CPK model also shows the potential for steric clash between two equivalents of the boron reagent if bound to the 3, 6-related ethers. This is confirmed by the enhanced selectivity observed on reducing the temperature and indicates that the intermediate **85** as drawn is more stable than it's non C3-symmetric equivalent.

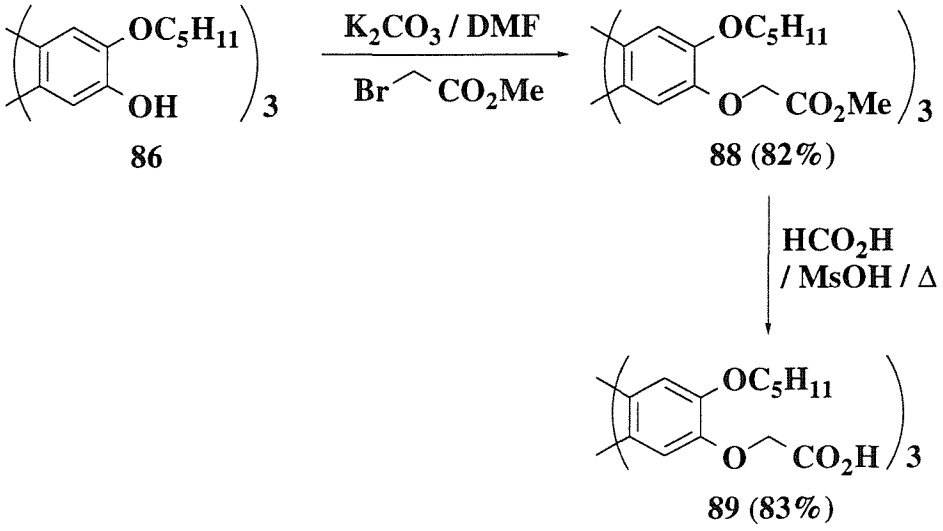
Table 7 - Reaction and Workup Procedures for Scheme 12

Entry	Scale	Temp	Time	Workup	Yield C3	Yield non C3
1	300 mg	RT	30 hrs	Ethanolamine	38%	47%
2	300 mg	RT	4 hrs	Ethanolamine	37%	49%
3	300 mg	RT	4 hrs	Ethanolamine	5%	12%
4	600 mg	RT	28 hrs	Ethanolamine	2%	18%
5	300 mg	Reflux	16 hrs	Ethanolamine	3%	12%
6	300 mg	RT	28 hrs	aq. HCl	9%	15%
7	300 mg	RT	21 hrs	$NaHCO_3$ / THF	9%	2%
8	300 mg	-30°C	15 hrs	$NaHCO_3$ / THF	42%	26%
9	600 mg	-30°C	22 hrs	$NaHCO_3$ / THF	27%	23%
10	1.5 g	-30°C	40 hrs	$NaHCO_3$ / THF	20%	8%
11	1.5 g	-30°C	4.5 hrs	$NaHCO_3$ / THF	55%	35%
12	1.5 g	-40°C	6.5 hrs	$NaHCO_3$ / THF	~63%	31%

It is also worth commenting on the workup procedures given in Table 7: the literature method (entry 1) involved adding a stoichiometric quantity of ethanolamine to the reaction mixture before adding water and extracting the products with dichloromethane. A simpler method (entries 7-12) was to cannulate the reaction mixture at -30°C directly into a well stirred mixture of saturated sodium bicarbonate and tetrahydrofuran to release the product and destroy any slight excess of 9-Br-BBN.

Although the enhanced selectivity resulting from the lower reaction temperature has been explained the reason for the increased overall yields is not clear. Probably the 9-Br-BBN reagent degrades the starting material at room temperature but this effect is minimised at lower temperatures. More than a slight excess of reagent was also found to produce considerably lower overall yields.

Having produced a suitable C3-symmetric triphenylene it was possible to functionalise it to give a base unit (Scheme 13).



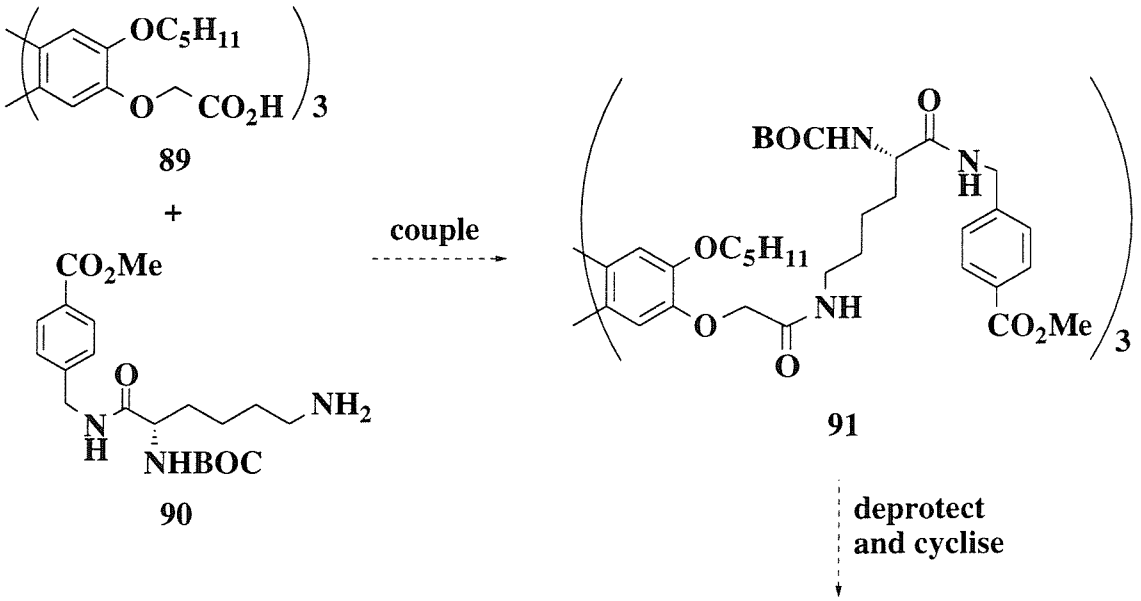
Scheme 13

Alkylation of trihydroxytriphenylene **86** with methyl bromoacetate followed by cleavage of the methyl esters of **88** in refluxing formic acid/methanesulfonic acid gave the tri-acid **89** in very good yield. The tri-acid **89** was to be used as the base for a first macrocycle (**53** where R = pentyl) without altering the pentyl chains as they could be used to provide solubility in organic solvents and the resulting macrocycle would be useful for testing the remainder of the synthetic strategy, which is the subject of the next chapter.

Chapter Three - The First Macrocycle

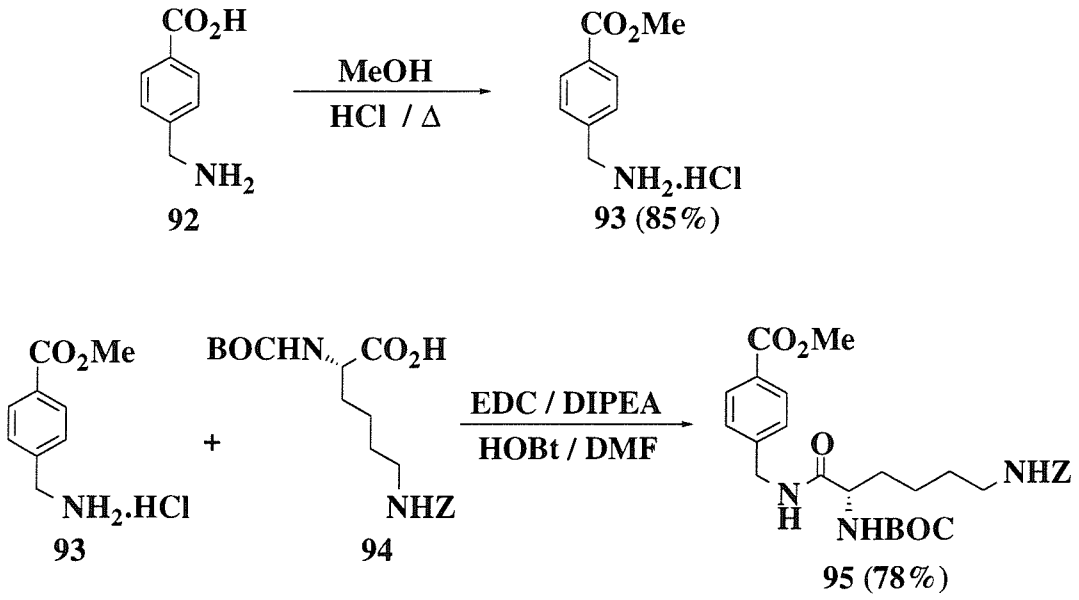
3.1 Synthesis of the Precursor

Having made a suitable base unit **89** the side-wall and rim building block had to be constructed and coupled onto the base, giving a cyclisation precursor (Scheme 14).



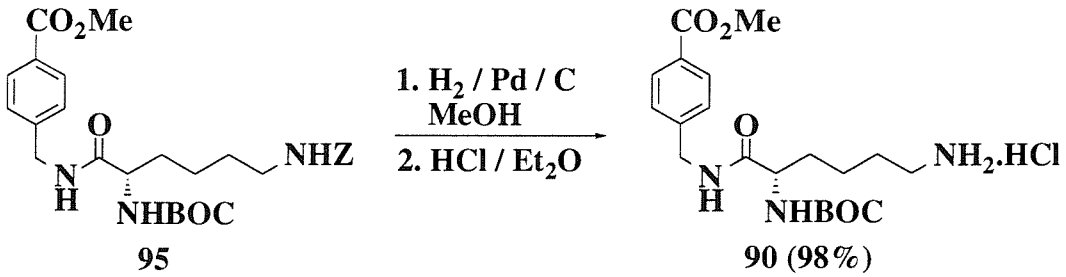
Scheme 14

To make building block **90**, 4-(aminomethyl)benzoic acid **92** was refluxed in methanol in the presence of hydrogen chloride to give **93** in very good yield as it's hydrochloride salt (Scheme 15).[100] A peptide coupling with the doubly protected (L)-lysine derivative **94** (commercially available) using EDC, gave the protected side-wall/rim unit **95** in good yield.



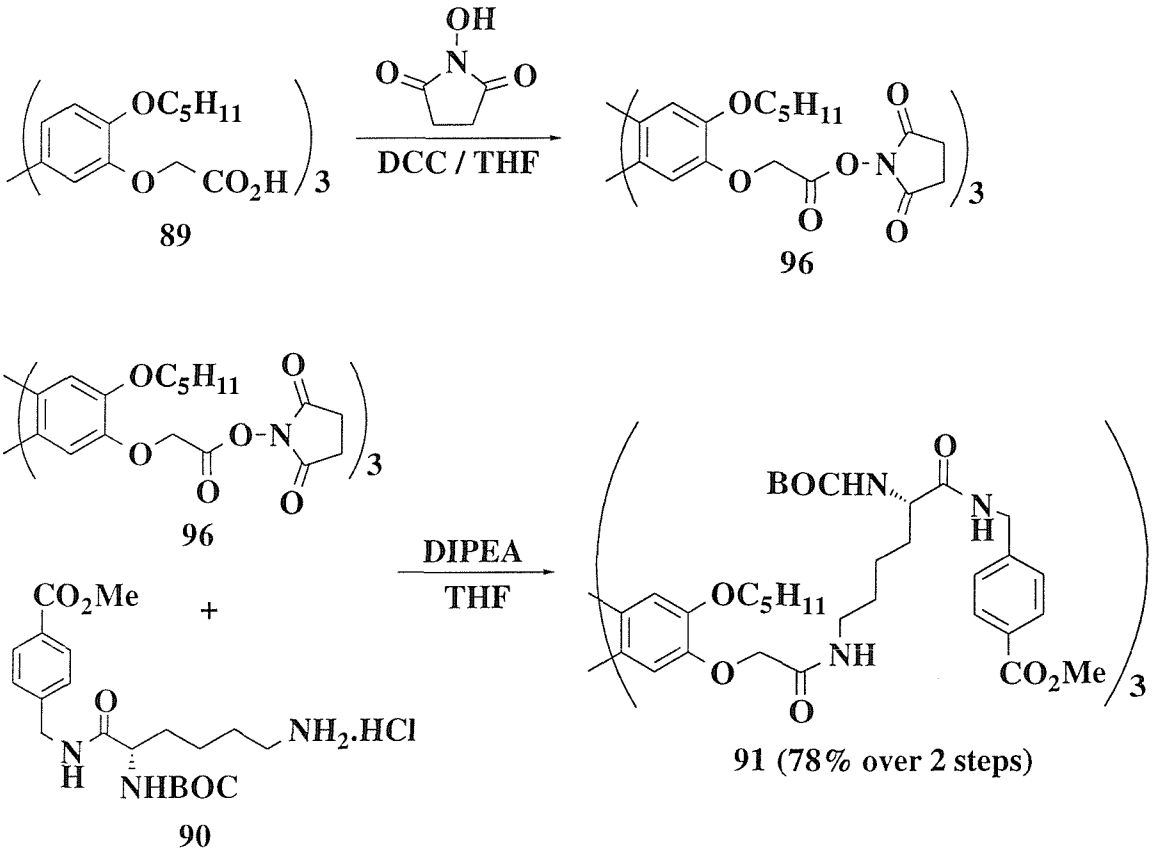
Scheme 15

Removal of the Z protecting group from **95** by catalytic hydrogenolysis, proceeded smoothly and in near quantitative yield, with the product **90** isolated as it's hydrochloride salt (Scheme 16).



Scheme 16

Having synthesised the base unit **89** and the side-wall/rim unit **90** they needed to be coupled together. Initially a direct coupling with EDC and DIPEA in DMF was tried but the reaction gave multiple products and the yield of the desired product was very low (5-10%). A much better result was obtained by forming an N-hydroxysuccinimide activated ester with the base unit, then reacting this with the side-wall/rim hydrochloride salt **90** in a second step (Scheme 17).[101] The activated ester **96** was isolated but not purified before being taken on directly to the next step, giving a yield for the triple peptide coupling of 78% over two steps

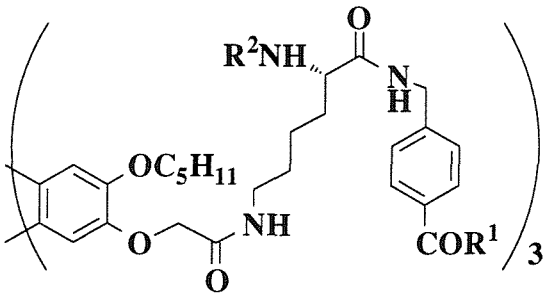


Scheme 17

3.2 Cyclisation Studies

To convert the precursor **91** into the macrocycle required the removal of the methyl esters and BOC protecting groups then the resulting free acids and amines had to be coupled together to give the macrocyclic structure. This was carried out by hydrolysis of the methyl esters and activation of the resulting acids as pentafluorophenol esters (Scheme 18). The tri-acid **97** was very polar and insoluble in most solvents so was taken on without further purification. The BOC groups were cleaved by treatment with 50% trifluoroacetic acid in dichloromethane and after removal of the solvents *in vacuo*, the residue was triturated with ether to give the tris(trifluoroacetate) salt **99**. The tris(activated ester) **98** and tris(trifluoroacetate) salt **99** were assumed to be unstable and were taken on directly without purification. Cyclisation was achieved by adding a solution of **99** in tetrahydrofuran to a solution of DIPEA in tetrahydrofuran over a period of 5 hours. Typically the activation of **97** was carried out with 100 mg of material and the tris(trifluoroacetate) salt **99** would be dissolved in 5 ml of tetrahydrofuran, then added to the DIPEA in 50 ml of tetrahydrofuran. The large volumes of solvent (relative to the amount of precursor) were used to minimise the concentration of the activated precursor **99** in the reaction vessel to prevent the formation of

dimers, trimers and higher oligomers. The addition of precursor over a period of hours reduces it's effective concentration even further promoting the intramolecular cyclisation instead of unwanted intermolecular reactions.[86]



91 $R^1 = OCH_3$, R^2 = BOC

97 R^1 = OH, R^2 = BOC (92%)

98 $R^1 = C_6F_5O$, R^2 = BOC

99 $R^1 = C_6F_5O$, $R^2 = H_2^+ CF_3CO_2^-$

100 Macrocycle

LiOH / 1, 4-dioxane

C_6F_5OH / DCC / THF

50% CF_3CO_2H / CH_2Cl_2

DIPEA / THF High dilution

Scheme 18

The hydrolysis of tris(methyl ester) **91** was attempted using several sets of conditions to establish how to cleave the esters cleanly (Table 8). The optimum conditions found were: lithium hydroxide (1.0 M) and 1, 4-dioxane at a temperature of 50°C for 3 hours. If the temperature or the reaction time was increased impurities began to appear.

Table 8 - Ester Hydrolysis Conditions

Temp	Time	Base	Co-solvent*	Yield	Comments
RT	50 hrs	LiOH (3.3 eqv)	MeOH	-	Virtually no reaction
RT to 75°C	20 hrs	KOH (3.3 eqv)	MeOH	-	No reaction then decomposed at 75°C
75°C	5 hrs	1.0M LiOH	1, 4-dioxane	-	Partial decomposition
60°C	1.5 hrs	1.0M LiOH	1, 4-dioxane	79%	Some polar impurities present
50°C	3 hrs	1.0M LiOH	1, 4-dioxane	92%	Almost single spot reaction

* Co-solvents were used in a 1:1 ratio with water.

For the macrocyclisation sequence a wide range of conditions were used to try and optimise the yield (Table 9). The activation step was carried out using pentafluorophenol and DCC in THF to give **98** except in two cases where pentafluorothiophenol was used (entries 6 and 7). The BOC cleavage step was carried out with 50% trifluoroacetic acid/dichloromethane in all cases except two, where 4.0 M hydrogen chloride in 1, 4-dioxane was used (entries 5a and 5b).

Table 9 - Macrocyclisation Conditions

Entry	Solvent	Temperature	Base (eqv.)	Addition Time	Yield (3 steps)
1	THF	50°C	DIPEA (6)	5 hrs	10%
2a	THF	RT	DIPEA (50)	5 hrs	22%
2b	THF	Reflux	DIPEA (50)	5 hrs	19%
3a	MeCN	50°C	DIPEA (50)	5 hrs	10%
3b	DMF	50°C	DIPEA (50)	5 hrs	6%
4a	THF	50°C	DIPEA (6)	5 hrs	10%
4b	THF	50°C	DIPEA (100)	5 hrs	11%
5a	THF	50°C	DIPEA (50)*	5 hrs	2%
5b	DMF	50°C	$CsCO_3$ (20)	5 hrs	2%
6**	THF	RT	DIPEA (50)	5 hrs	25%
7**	THF	RT	DIPEA (50)	8 hrs	40%

* 3 equivalents of DMAP used as well

** Pentafluorothiophenol used for activation

The yield for the cyclisation is slightly variable but it is interesting to note that the conditions used had very little effect on the yield. Apart from entries 1, 6 and 7 the experiments were run in pairs by activating and deprotecting 200 mg of tri-acid **97** and then dividing the material between two syringes for addition to two separate reaction vessels. This approach ensured a valid comparison between the two sets of conditions.

Comparing entries 2a and 2b shows that the reaction temperature does not have an effect on the macrocycle yield. Equally entries 3a and 3b show that the solvent used in the reaction

vessel (the precursor was still added as a solution in tetrahydrofuran) does not seem to influence the yield significantly.

Entries 4a and 4b indicated that the quantity of base used was unimportant while entries 5a and 5b were used to investigate whether the nature of the base had an influence. For these two entries the BOC removal step was carried out with 4.0 M hydrogen chloride in 1, 4-dioxane rather than trifluoroacetic acid/dichloromethane which may have been the cause of the abnormally low yield, but the fact that 5a and 5b show the same yield does suggest that the base used is not an important factor.

The use of pentafluorothiophenol to form an activated ester rather than pentafluorophenol was also investigated (entries 6 and 7).[102,103] Pentafluorothiophenol forms a more activated ester so should theoretically speed up the desired intramolecular cyclisation minimising the amount of uncyclised precursor in the reaction mixture at any given time. Comparing the yield of entry 6 (25%) with entry 2a (22%), which used pentafluorophenol but was otherwise identical, does not suggest a significant improvement but comparing it with what appears to be a more typical yield (~10%) indicates that pentafluorothiophenol is a more effective activated ester.

A clear effect was observed when the time taken to add the activated precursor to the reaction mixture was increased. By reducing the rate of addition of precursor, any build-up of unreacted starting material should be prevented and polymerisation reactions would be minimised. Entry 7 shows that adding the precursor over 8 hours instead of 5 hours produced a significant increase in the macrocycle yield.

It would have been interesting to study the effect of increasing the addition time further to find the upper limit for this improvement, but the supply of tri-acid **97** was exhausted so no further cyclisations were carried out. A yield of 40% over the three steps is good for this kind of system, because the cyclisation has an unfavourable entropy due to the loss of degrees of freedom when the molecule is constrained into the macrocyclic ring.

3.3 Macrocycle Isomers

On isolating the products from the macrocyclisation reaction it became obvious that there were two isomeric macrocycles being produced. The proton NMR of the mixture showed two sets of signals, which were particularly clear for the *para*-substituted benzene rings on the macrocycles rim and the methyl groups at the end of the pentyl chains. Measurement of the integrations for these signals gave an average ratio of 2.3:1 (there was a slight variation between batches of macrocycle and also whether the *para*-substituted ring or the pentyl methyl signals were measured). The macrocycles were indistinguishable by TLC and inseparable by flash column chromatography but could be separated by semi-preparative reverse-phase HPLC. Once separated the macrocycles remained as single isomers both in the HPLC eluent over a period of a few days and in d^6-DMSO over several weeks ruling out an equilibrium between the two forms. While the NMR spectrum suggested an isomer ratio of 2.3:1, integration of the HPLC peaks gave a ratio of 1.8:1 and the semi-preparative HPLC separation gave the two isomers in an isolated ratio of 2.1:1. The average of the NMR and HPLC results gives the isolated ratio but it is interesting to notice the discrepancy.

A possible explanation for the formation of the isomers is shown in Figure 35 (the aromatic rim spacers are omitted for clarity). In principle there are four distinct compounds which could be formed in the cyclisation reaction. Compound **100a** is one possible isomer of the macrocycle, the arrows to it's right represent an arbitrary 'direction of rotation'. For the base this is defined as going from the side wall to an adjacent pentyl chain in a clockwise direction, as viewed from above. In the same way the rim is defined as clockwise when going from a lysine carbonyl group through the α-carbon to the corresponding lysine nitrogen atom also as viewed from above. If isomer **100a** could be turned inside-out in the manner of an umbrella a new compound would be formed, isomer **100b** which would still have the clockwise 'rotation' at the base when going from side-wall to pentyl chain and also from lysine carbonyl to nitrogen, but the base would be above the rim. It should be made clear at this point that CPK models indicate that this 'umbrella' inversion would not be possible because the macrocyclic rim is too small for the triphenylene base to fit through. The other key difference between isomers **100a** and **100b** is that the lysine α-protons point into the macrocyclic cavity as drawn for isomer **100b** but are outside the cavity in isomer **100a**.

There is an analogous situation for isomers **100c** and **100d** where the base is kept with a clockwise rotation but the rim is drawn with an anti-clockwise rotation for isomer **100c** and although an 'umbrella' inversion would maintain these directions of rotation, the base would then be below the rim and the α-protons would point inwards for isomer **100d**.

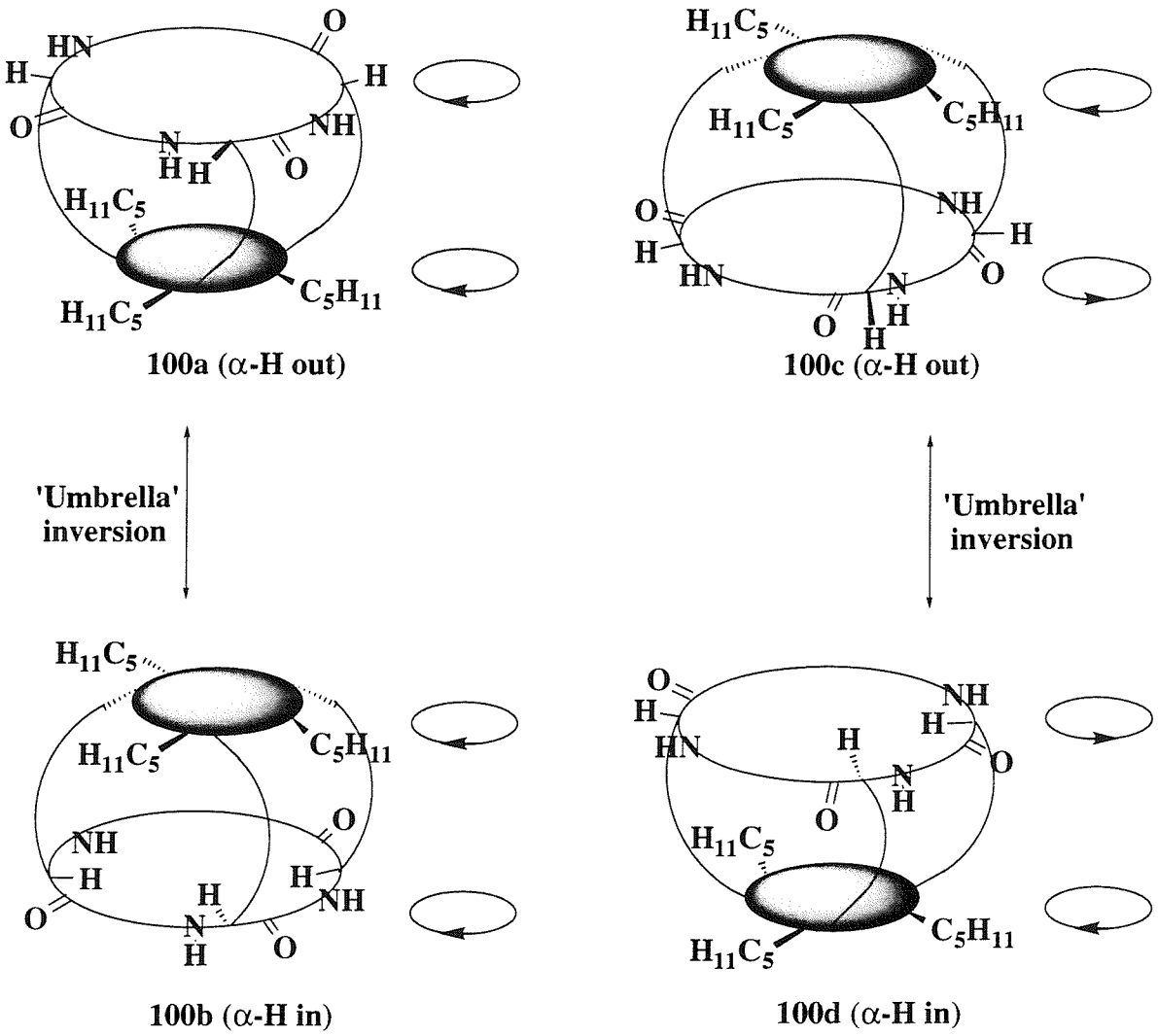
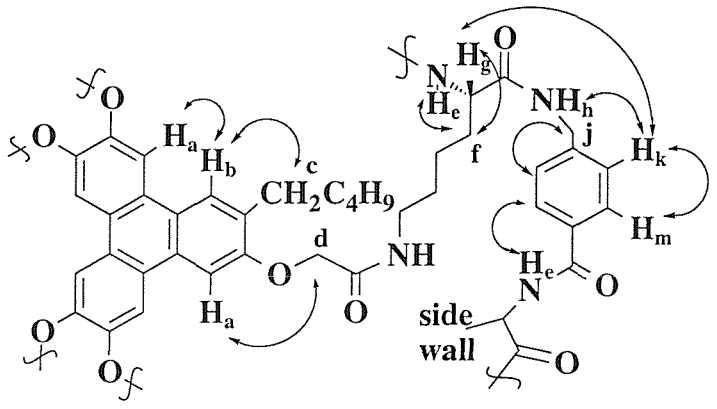


Figure 35

In principle all four isomers can be formed from the precursor **99**, the differences result from whether the rim cyclises above or below the base and whether the lysine α-protons are pointing into or out of the cavity.

Figure 35 provides a possible explanation for the formation of the isomers but conclusive proof of which isomers were formed has not been obtained. X-ray crystal structures would be desirable but it was not possible to obtain the macrocycles in a crystalline state. Various methods of growing crystals were tried: slow evaporation from solution and slow diffusion (of liquid phases or vapour) of a solvent the macrocycles were insoluble in (such as water or ether) into a solution of macrocycle (in chloroform or DMSO). In all cases the material came out of solution in an amorphous state.

NMR ROE experiments were carried out in an attempt to determine the structures of the macrocycles but were inconclusive. The significant ROE's observed for the major isomer of macrocycle **100** are shown in Figure 36 and although they are consistent with the macrocyclic structure, they give no useful details about which isomer it is. Two very weak ROE's were also observed between H_k and H_d and between H_k and H_a. These were the only interactions seen between the base of the macrocycle and the rim indicating that the macrocycle cavity is very large with the base and the rim distant from each other.



ROE's for Macrocycle 100

Figure 36

The minor isomer was not studied in this way and although it can always be argued that it might have differed from the major isomer in an informative manner, it was decided that due to the large distance between the base and the rim of the macrocycle further NMR work would not reveal anything useful.

3.4 Conclusions

A suitable C_3-symmetric triphenylene which could be used as a base unit was synthesised by the enhancement of a recently published literature method and was used in a successful synthesis of the macrocycles **100**. Conditions for the cyclisation were investigated extensively to obtain good yields of the macrocycles.

The two isomeric macrocycles obtained were separated by semi-preparative HPLC and characterised but their exact nature is still unknown as crystals could not be produced for X-ray analysis and NMR data was inconclusive. The lack of ROE contacts between the base and rim does suggest that the macrocycle existed in solution with a large cavity which was a good indication for the possibility of binding suitable guests.

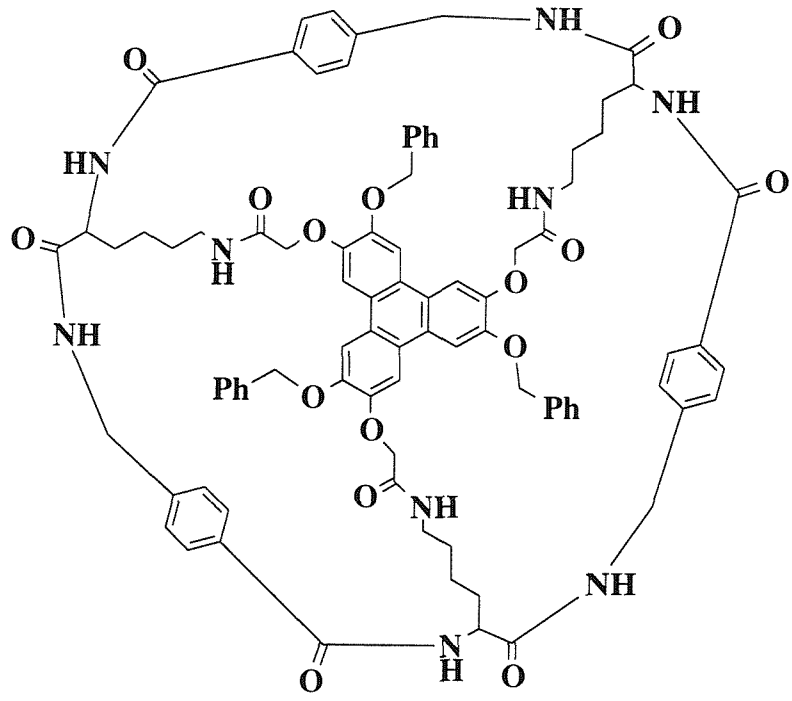
Before the isomers had been separated work had begun on a second macrocycle with benzyl groups in place of the pentyl chains. The hope was that the benzyl groups could easily be removed following cyclisation and replaced with alternative functionality (such as a carboxylic acid), which would make the macrocycle water soluble.

Binding studies were carried out on the pentyl macrocycle but this was done in conjunction with the second macrocycle so is discussed at the end of the next chapter.

Chapter Four - The Second Macrocycle

4.1 Synthesis

The first macrocycle **100** was useful for proving that the synthetic route was effective and that the cyclisation would give the desired macrocyclic product. The eventual aim of the project was to bind saccharides in water, so clearly the pentyl chains had to be replaced by more hydrophilic groups. It was decided to synthesise macrocycle **101** where the pentyl chains of macrocycle **100** had been replaced by benzyl groups (Figure 37). The intention was to remove the benzyl groups after cyclisation and replace them with functionality such as carboxylic acids (for example by alkylation with bromoacetic acid) which could be used to make the macrocycle water soluble.

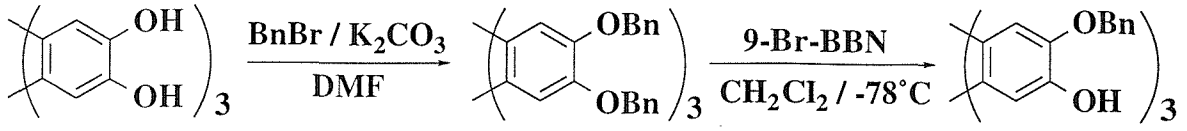


101

Figure 37

It seemed reasonable that the 9-Br-BBN methodology described earlier could be extended to the cleavage of benzyl groups instead of pentyl groups. The hexabenzyloxytriphenylene **102** was synthesised by alkylation of hexahydroxytriphenylene **71** with benzyl bromide in excellent yield before being treated with 9-Br-BBN in dichloromethane to give the new trihydroxytriphenylene **103** (Scheme 19). A more direct route to hexabenzyloxytriphenylene **102** (rather than demethylation of hexamethoxytriphenylene **64** and re-alkylation with benzyl

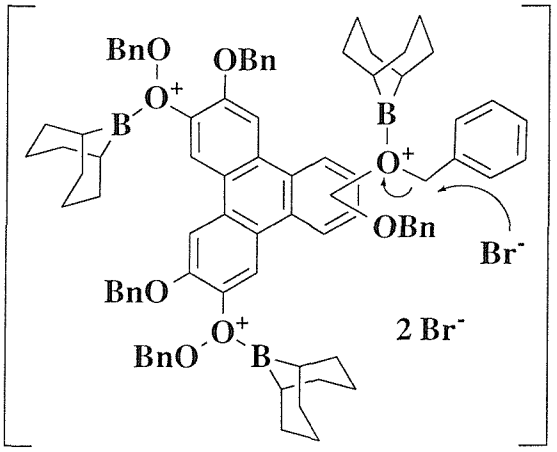
bromide) would be to trimerise 1, 2-dibenzyloxybenzene but the benzyl groups are unstable to the reaction conditions as discussed earlier.



71 **102 (92%)** **103 (49%)**

Scheme 19

Initially the conditions used for the debenzylation of **102** were the same as for the pentyl version of the reaction but very low yields were obtained (<10%), so the reaction temperature was reduced to -78°C increasing the yield of the C3-symmetric isomer to 49%. The optimal reaction time was even shorter than for the pentyl version and was generally less than 1 hour. As before if the reaction was left for too long or an excess of reagent was used, the yields were considerably lower and large quantities of insoluble black material (presumably degraded triphenylene) were obtained during the workup. The faster reaction time is understandable: the intermediate **104** (Figure 38) is attacked at the benzylic carbon by bromide anion and a benzylic carbon will be more reactive than the equivalent carbon of a pentyl chain.

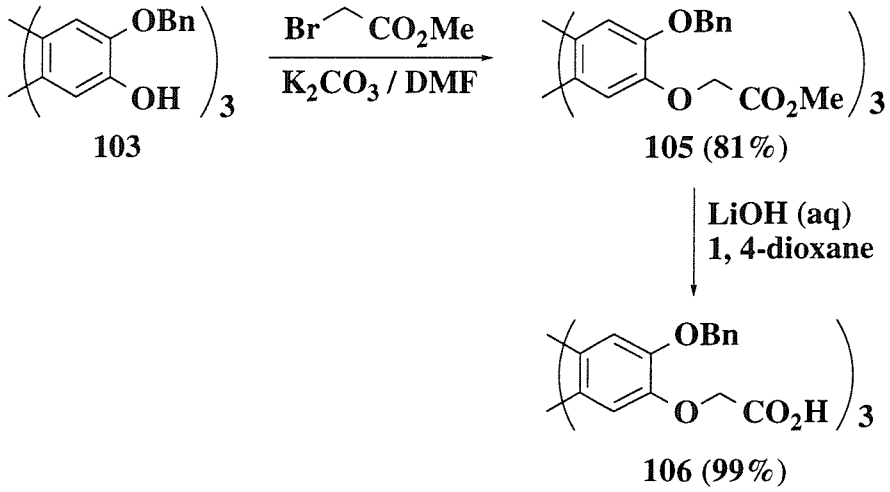


104

Figure 38

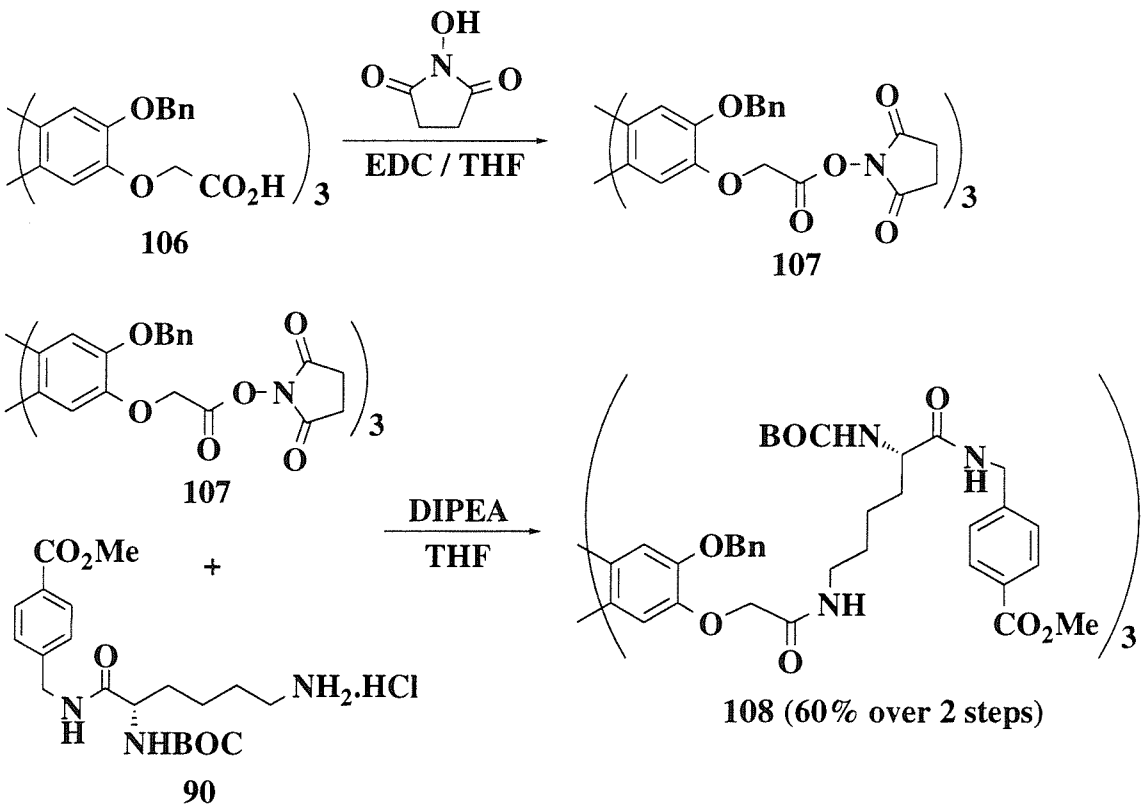
The new C3-symmetric triphenylene **103** was elaborated into the second macrocycle in a very similar manner to the pentyl analogue. Alkylation of **103** with methyl bromoacetate followed by ester hydrolysis (both in very good yield) gave the new base unit **106** (Scheme 20). Lithium hydroxide and 1, 4-dioxane were used for the ester hydrolysis rather than the

formic acid/methanesulfonic acid method used on the pentyl version. The latter method was tried but the conditions were too harsh and partial cleavage of the benzyl groups occurred.



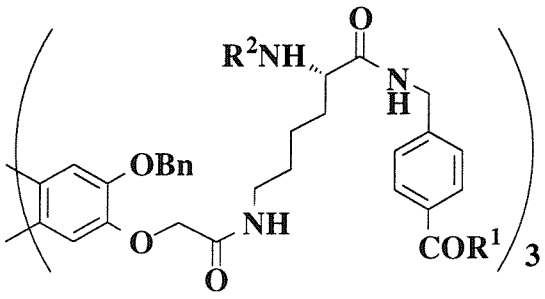
Scheme 20

The side-wall/rim building block was coupled onto the base using N-hydroxysuccinimide activated ester methodology (Scheme 21), although the yield was slightly lower for the resulting precursor **108** at 60% over the two steps instead of 78% for the pentyl version **91**.



Scheme 21

Once the new precursor had been made some cyclisations were carried out. The general procedure was the same as for the pentyl analogue: beginning with hydrolysis of the methyl esters of the precursor **108** then activation, deprotection and cyclisation (Scheme 22). As in the case of the pentyl analogue the tri-acid **109** was very polar and was insoluble in most organic solvents making purification difficult so it was taken on directly. Following the improved yields obtained for the pentyl macrocycle **100** the pentafluorothiophenol activated ester was used instead of the pentafluorophenol version.



108 $R^1 = OCH_3$, R^2 = BOC

LiOH / 1, 4-dioxane

109 R^1 = OH, R^2 = BOC (84%)

C_6F_5SH / DCC / THF

110 $R^1 = C_6F_5S$, R^2 = BOC

50% CF_3CO_2H / CH_2Cl_2

111 $R^1 = C_6F_5S$, $R^2 = H_2^+ CF_3CO_2^-$

DIPEA / THF High dilution

101 Macrocycles

Scheme 22

Three cyclisations were carried out to give the benzyl macrocycles with the results summarised in Table 10. Initially the conditions used were based on the most successful pentyl macrocycle cyclisation: room temperature, 50 equivalents of DIPEA and addition of the precursor solution over a 10 hour period (entry 1). The yield was disappointingly low at 15% so the addition time was increased to 18 hours (entry 2) but the yield did not improve. Increasing the volume of solvents used (for the precursor and DIPEA solutions) and hence lowering the concentration of precursor in the reaction mixture, did not lead to an increase in yield either (entry 3).

Table 10 - Cyclisation Conditions for Macrocycle 101

Entry	Scale	Addition Time	Theoretical Final Concentration	Yield
1	100 mg	10 hrs	0.98 μmol ml^{-1}	15%
2	100 mg	18 hrs	0.98 μmol ml^{-1}	10%
3	350 mg	10 hrs	0.34 μmol ml^{-1}	16%

In all cases the base used was DIPEA (50 equivalents), the solvent was THF and the reactions were carried out at room temperature.

The macrocycle **101** was obtained as a mixture of isomers which could not be separated by flash column chromatography as before. The ratio by NMR (based on integrals of the *para*-substituted ring signals) was 5.0:1 while the HPLC output suggested a ratio of 3.5:1.

It is interesting to note that the pentyl macrocycle isomers were formed in a ratio of approximately 2:1 but there seemed to be a greater selectivity between the isomers of the benzyl macrocycles (3.5-5.0:1). It is difficult to suggest why this difference occurs without knowing the exact structures of the isomers. The difference between the isomers results from the relative arrangements of the base and the rim but the lack of significant ROE interactions (in the case of the pentyl macrocycles) suggests that the base and the rim are distant from each other. Another point to consider is the lower yield of the benzyl macrocycles compared to the pentyl version, the effect is probably steric in nature and may be that the bulk of the benzyl groups makes it more difficult for all three side arms to come together on the same side of the triphenylene system hindering the cyclisation.

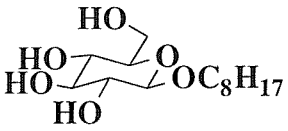
Attempts were made to cleave the benzyl groups from the mixture of macrocycles **101** by catalytic hydrogenolysis but no reaction occurred with gaseous hydrogen or ammonium formate in the presence of 10% palladium on carbon catalyst. These conditions were used to remove benzyl groups from compounds similar to the tribenzyloxytriphenylene **105** without difficulty (Chapter 5) so it was disappointing to observe no reaction with the benzyl macrocycles **101**.

At this point several factors had to be considered: the failure to remove the benzyl groups from macrocycles **101** under mild conditions, poor separation of the isomers by HPLC and the low yield of the cyclisation step sequence. It was decided that in view of these problems it was not worth continuing with the benzyl macrocycles **101** and an alternative functional group to replace benzyl would be necessary to achieve the aim of water solubility.

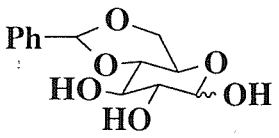
Although the benzyl macrocycles were not going to be converted into a water soluble derivative, they had some solubility in organic solvents so their binding with simple guests was studied.

4.2 Preliminary Binding Studies

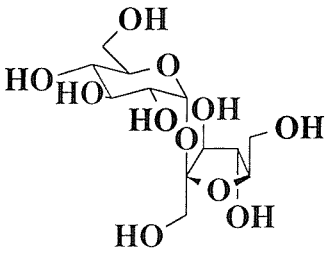
Discovering what class of compounds a synthetic host will bind can require relatively large quantities of material. Only small quantities of the pentyl macrocycles **100** were available after separation by HPLC so the mixture of isomers of the benzyl macrocycles **101** was used in preliminary binding studies. Several different types of guest were tried: two monosaccharides, a disaccharide, two C3-symmetric guests and two protected dipeptides (Figure 39).



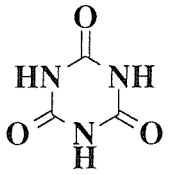
23 1-O-octyl-β-D-glucopyranoside



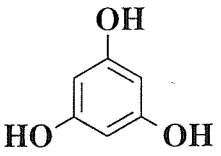
112 4, 6-O-benzylidene-D-glucose



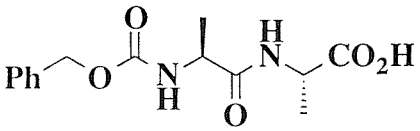
113 sucrose



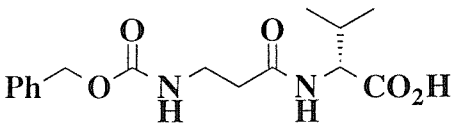
114 cyanuric acid



115 1, 3, 5-benzene triol



116 N-Z-L-Ala-L-Ala



117 N-Z-β-Ala-D-Val

Figure 39

The initial investigations into the binding properties of the benzyl macrocycles **101** were carried out in deuteriochloroform. Guests which were sufficiently soluble in deuteriochloroform (**23**, **112**, **116**, **117**) were studied as a 1:1 mixture in solution with the macrocycle (typical quantities of material used were 3 mg of macrocycle with 1 equivalent of guest in 700 μl of $CDCl_3$). The NMR spectra of the macrocycle, the guest and the mixture were all compared to look for changes in either the macrocycle or guest proton signals. Guests which were insoluble in deuteriochloroform (**113**, **114**, **115**) were shaken with a solution of macrocycle (typically 3 mg of macrocycle in 700 μl of $CDCl_3$ shaken with 3 equivalents of guest for 1 hour or longer), which was then filtered and the NMR spectrum studied for any signals corresponding to the guest which would indicate solubilisation by the macrocycle and therefore binding. In the case of cyanuric acid **114** which only has NH protons, the NMR spectrum of the host was examined for changes.

Negative results were obtained for all the guests in Figure 39 except for benzene triol **115**, where several changes in the NMR spectrum of the macrocycles were observed, particularly the disappearance of the signal at δ 8.00 and the loss of structure in the signals at δ 5.50-5.20 (Figure 40).

To study the binding in more detail a titration experiment was carried out using the major isomer of pentyl macrocycle **100**. At this point a brief discussion of the NMR titration method for determining binding constants is appropriate.

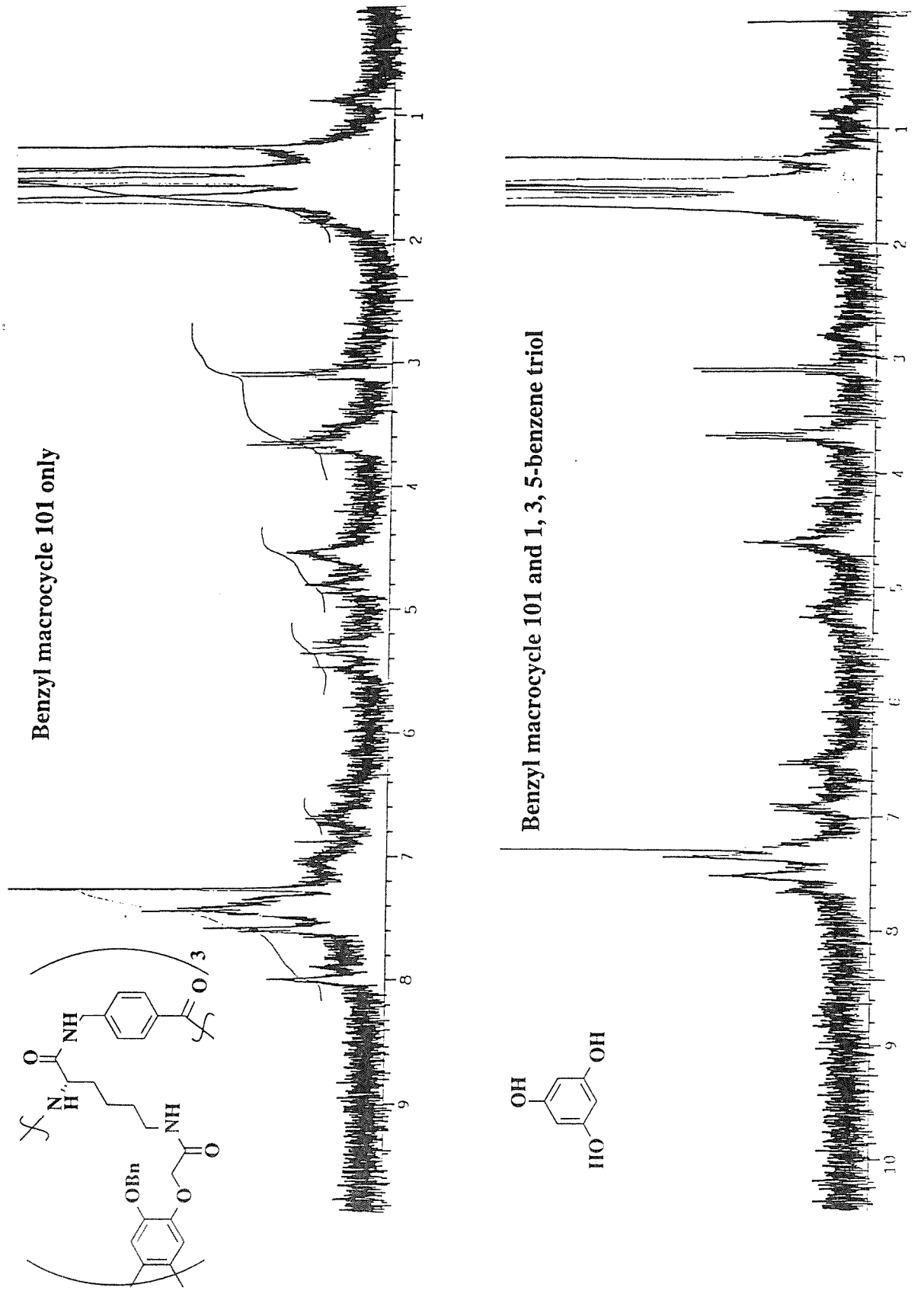


Figure 40 - Macrocycle 101 only and with benzene triol at 270 MHz in $CDCl_3$

4.3 Background to NMR Titration Experiments

NMR is generally a useful technique to use for investigating binding interactions as it can provide a large amount of data for relatively little effort. When a host-guest complex forms, the equilibrium between free host, free guest and the complex is usually rapid on the NMR timescale, so an NMR spectrum of the mixture represents the average environment of the species involved. In practice this means that by taking a solution of host and acquiring it's NMR spectrum in the free state and after repeated additions of a guest, it is possible to monitor the changes which result from formation of the complex by following one or more suitable peaks in the NMR spectra. Equally this approach can be reversed and a solution of guest can be monitored while small quantities of host are added. The peaks chosen for observation are frequently NH's which show significant changes in chemical shift if they become hydrogen bonded.

For the simple 1:1 equilibrium in Figure 41 it can reasonably be assumed that when the half the macrocycle is involved in binding (half saturation) the concentrations of free host and bound host are equal so the equation for K_a simplifies to $K_a = 1/[G]_{1/2}$

By plotting the chemical shift of a given host signal (δ_{host}) against the concentration of the guest added and measuring the value of the guest concentration at the half saturation point (which can be read from the graph as the halfway point between δ_{free} and $\delta_{saturated}$) it is possible to find K_a for the binding equilibrium.

$$[H] + [G] \overset{K_a}{\rightleftharpoons} [H\text{-}G]$$

$$K_a = \frac{[H\text{-}G]}{[H]\,[G]}$$

at half saturation [H] = [H-G] so:

$$K_a = \frac{1}{[G]_{1/2}}$$

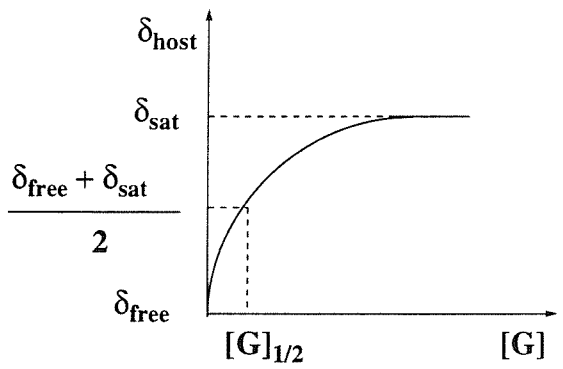


Figure 41

In practice computational methods are used to find values for K_a from the experimental data and although the mathematics is more sophisticated the basic principle is still the same. The binding data in this thesis was analysed using HOSTEST 5 developed by Wilcox and was available on the University of Oxford VAX mainframe (vax@ox.ac.uk).[104]

The concentrations of host and guest chosen for a binding experiment are important for determining binding constants accurately. Figure 42 shows two possible binding curves: for high concentration (or strong binding), saturation is achieved quickly so most of the data points will lie on the horizontal portion of the curve. The most useful data lies between 20% and 80% saturation with the important value of $[G]_{1/2}$ being between these two limits at 50% saturation. The second curve represents an example of a binding experiment with suitable concentrations of the species involved.

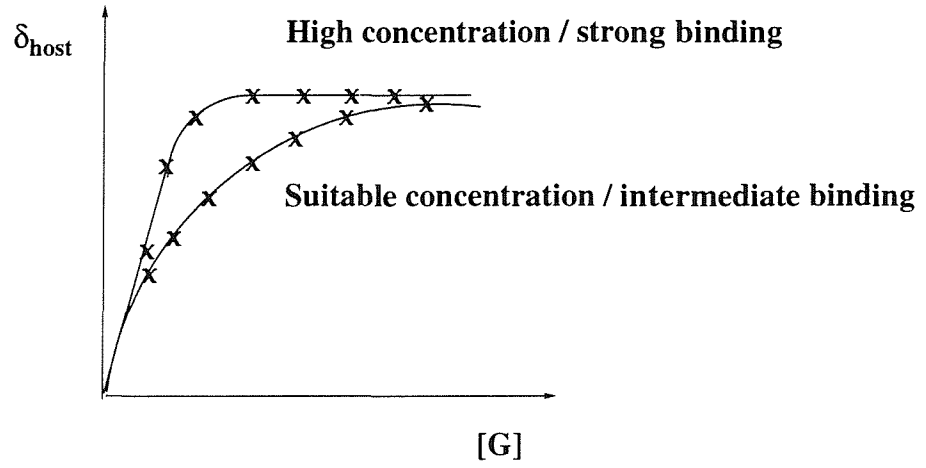


Figure 42

Suitable concentrations for measuring binding constants are generally in the region of $1/K_a$. For the pentyl macrocycle **100** (with a relative molecular mass of 1439) assuming a binding constant of approximately 10^3 dm^3mol^{-1} would require the use of 1 mg of macrocycle which would produce very poor quality NMR spectra. A binding constant of 10^2 dm^3mol^{-1} would ideally require the use of 10 mg of macrocycle to give good results but this is a lot of macrocycle to use up for one experiment. A compromise of 3-4 mg of macrocycle gives reasonable NMR spectra and data of acceptable quality.

Other factors which must be considered are whether the binding being observed really is 1:1 (the simple model above will not be valid for other cases) and the effects of reducing the concentration of host by repeated additions of guest solution. For the former case computer programs such as HOSTEST can account for more complex binding stoichiometries and for the latter it is possible to do a dilution experiment where aliquots of solvent are added to a host solution and the NMR spectra examined for changes which can be accounted for if necessary.

4.4 Measurement of a Binding Constant

Having used benzyl macrocycle **101** to discover that binding of 1, 3, 5-benzene triol could occur the major isomer of the pentyl macrocycle **100** was used to determine a value for the binding constant.

The binding study was carried out in 5% d^6-dimethyl sulfoxide/deuteriochloroform because the guest was insoluble in deuteriochloroform alone. The NMR spectrum of a solution of 3 mg of pentyl macrocycle **100** (major isomer) in 600 µl of solvent (3.5 mM) was acquired then repeated aliquots of guest solution were added and the NMR spectrum acquired after each addition. The dihydrate of benzene triol was used in solution at a concentration of 17.0 mM. Initially aliquots containing 1/6 equivalent of guest were added, the volume of the aliquots was increased at intervals through the experiment with 7 equivalents of guest being added in total.

Six signals were monitored: the two triphenylene singlets (A - δ 7.95 and B - δ 7.84), the three NH's (C - δ 7.54, D - δ 7.43 and E - δ 6.87) and one of the *para*-substituted benzene ring doublets (F - δ 6.77). Figure 43 shows the first and last spectra recorded during the binding study, the appearance of the benzene triol peaks at δ 5.80 and δ 8.12 is obvious (for free benzene triol the aromatic peak occurs at δ 5.85).

It would be reasonable to expect large changes in chemical shift (typically +1 ppm) of the NH signals if they were involved in hydrogen bonding but in this case the largest change observed experimentally was just +0.12 ppm for NH C. This suggests that there were no strong hydrogen bonding interactions occurring (possibly the d^6-dimethyl sulfoxide used was competing too strongly) or that some other effect (such as a conformational change in the macrocycle) was masking them in the NMR spectra.

The data sets for signals C, D (NH's) and F (*para*-substituted benzene ring) gave very poor curve fits when processed using HOSTEST with any of the possible modes of binding (1:1, 1:2 and 2:1) and were discarded. The data for signals A, B (triphenylene) and E (NH) gave reasonable curve fits when processed as 1:1 binding and values for K_a that were consistent with each other: A: 148, B: 116 and E: 162 dm^3mol^{-1} (Figures 44 and 45). When these signals were processed as 1:2 binding the curve fits appeared reasonable once again but there were no similarities between the K_a values obtained suggesting this mode of binding was not being observed.

Combining the data for signals A, B and E (as 1:1 binding - Figure 45) gave a value for K_a = 149 ± 33 dm^3mol^{-1} (standard deviation calculated using the error option in HOSTEST) which equates to $\Delta G = -12.2 \pm 0.5$ $kJmol^{-1}$ at 20°C (293 K). This level of binding is fairly weak but is not unreasonable given the presence of d^6-dimethylsulfoxide and water (the dihydrate of benzene triol **115** was used) which will compete strongly with the guest for hydrogen bonding sites.

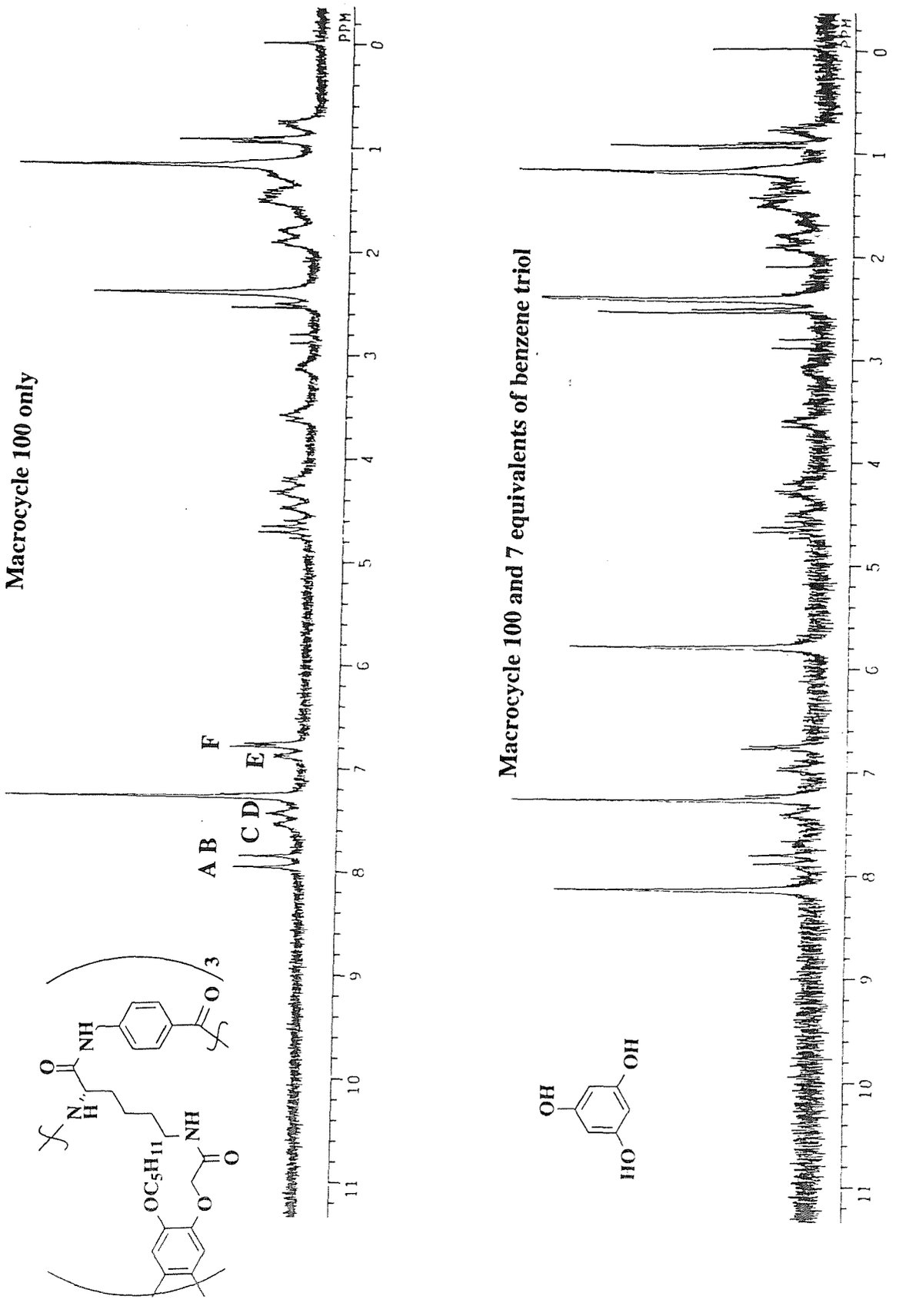
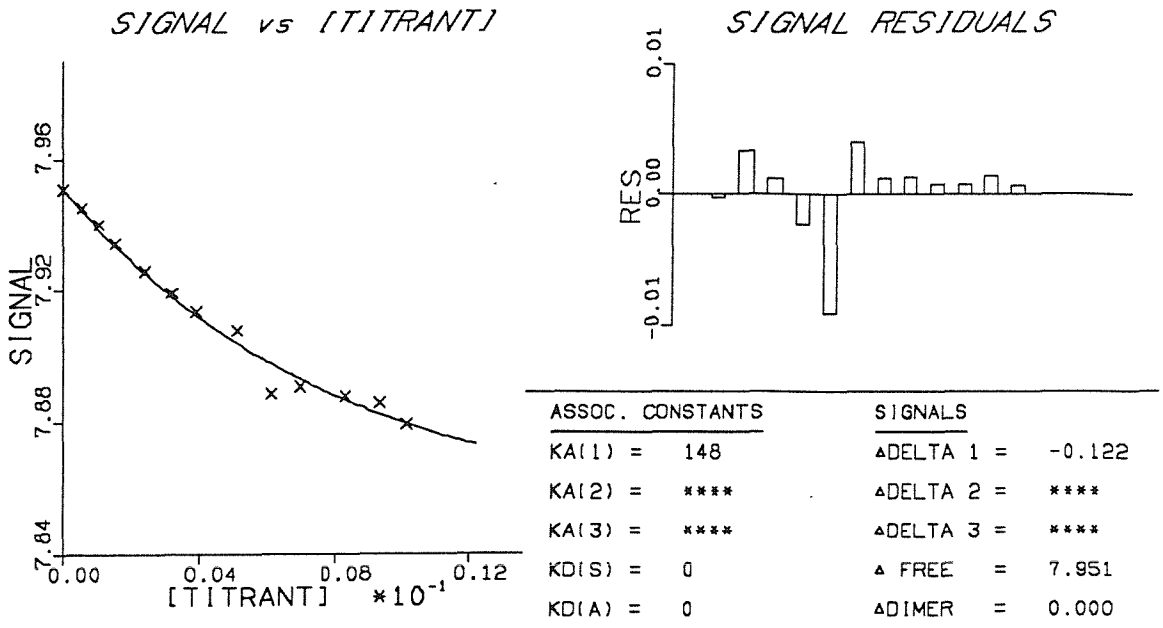


Figure 43 - Spectra from binding study at 270 MHz in 5% d^6-DMSO/$CDCl_3$

NMR titration curve for signal A



NMR titration curve for signal B

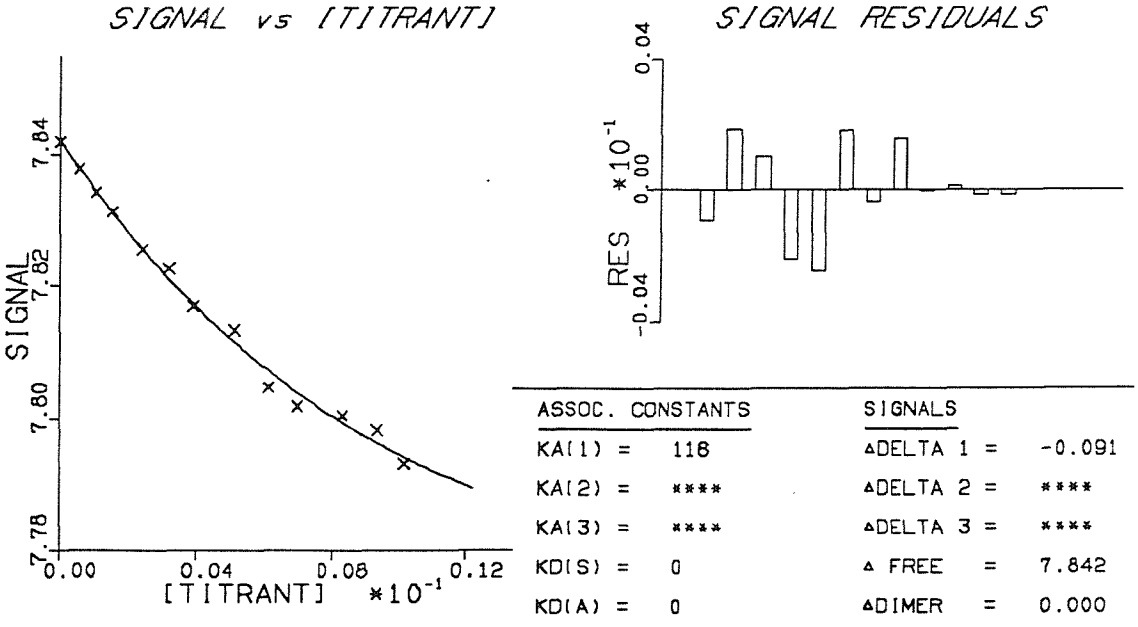
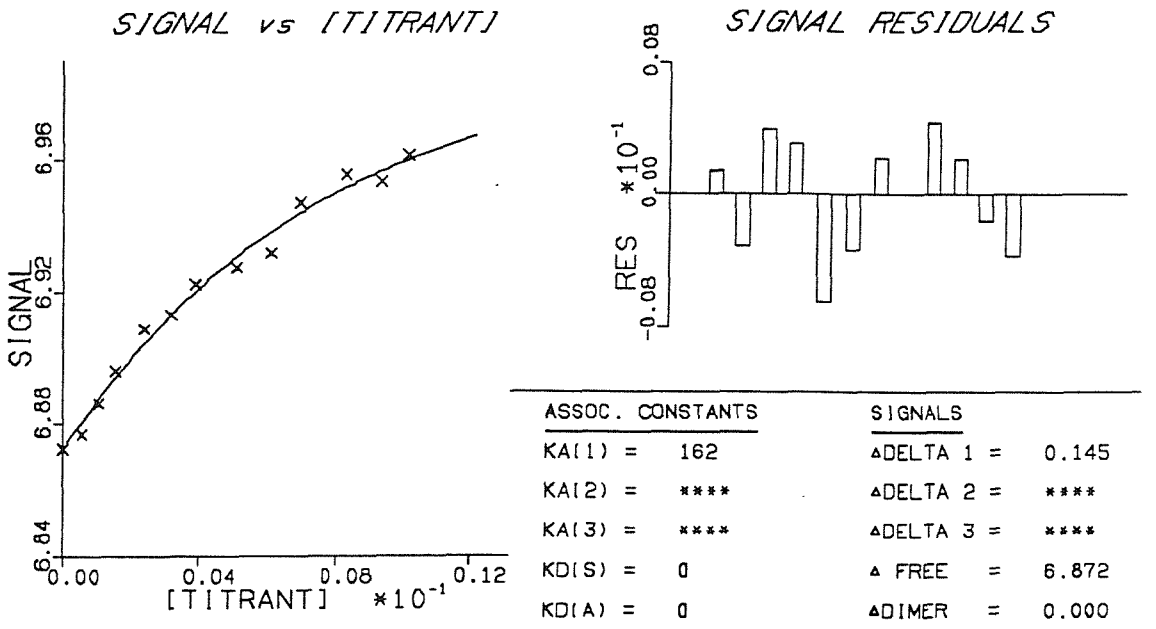


Figure 44 - NMR Titration Curves

NMR titration curve for signal E



NMR titration curve for signals A, B and E combined

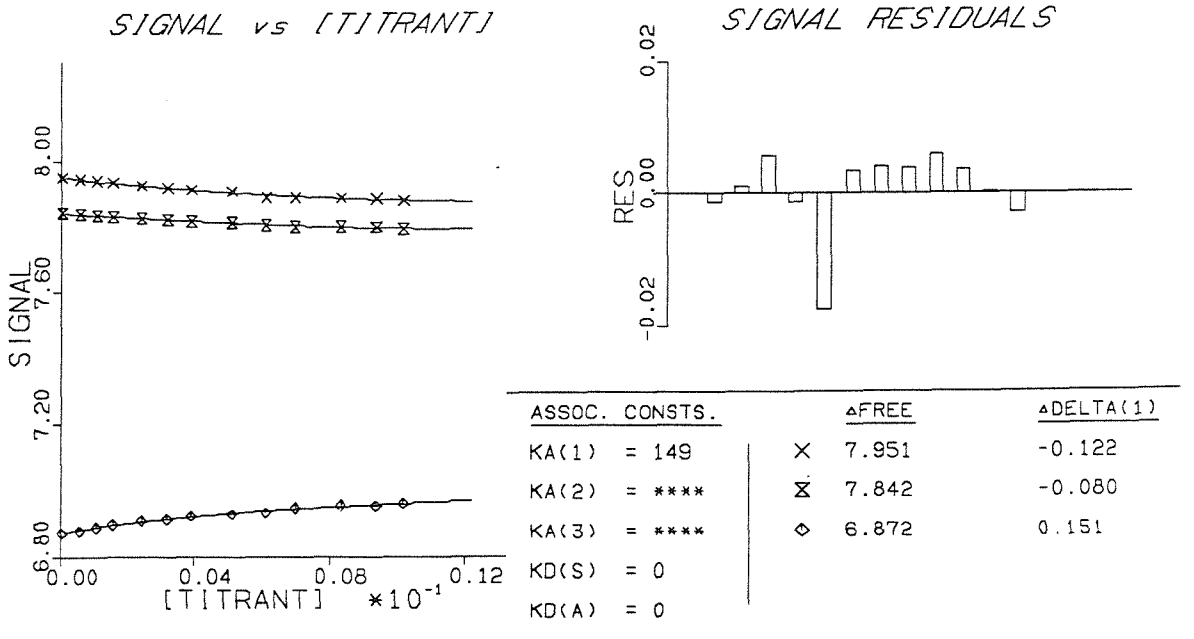


Figure 45 - NMR Titration Curves

It is interesting to speculate how the benzene triol might be binding with the macrocycle. CPK models show that if it was located in the cavity just above the triphenylene base it could potentially form hydrogen bonds to the amide linkages adjacent to the triphenylene ring and possibly π-π stacking interactions with the triphenylene. Equally the models suggest that the guest could fit within the top rim of the macrocycle adopting a T-shaped orientation with all three aromatic spacers simultaneously and having the potential for hydrogen bonds to the amide linkages of the rim. The only signals that show meaningful changes in the NMR spectrum during the binding study were the ones analysed, there were no changes to the lysine derived side-walls or the pentyl chains. The signals which were used to generate the binding curves (A, B and E) correspond to the triphenylene and the NH adjacent to the lysine α-carbon which unfortunately does not resolve the question of where the guest was being bound and in fact hints more at a 1:2 binding stoichiometry.

After carrying out these experiments, a report of a cage-type host which bound benzene triol was published but owing to the low solubility of the guest in deuteriochloroform a binding constant was not measured.[105]

The binding study described above was carried out using the major isomer of pentyl macrocycle **100**, it might have been interesting to repeat the experiment with the minor isomer but it was felt it would be very unlikely that there would be a difference in the binding constants any larger than the experimental error. Although the calculated error in the binding constant is acceptable (22%), the small changes in chemical shift measured mean that the figures should be treated with some caution.

4.5 Conclusions

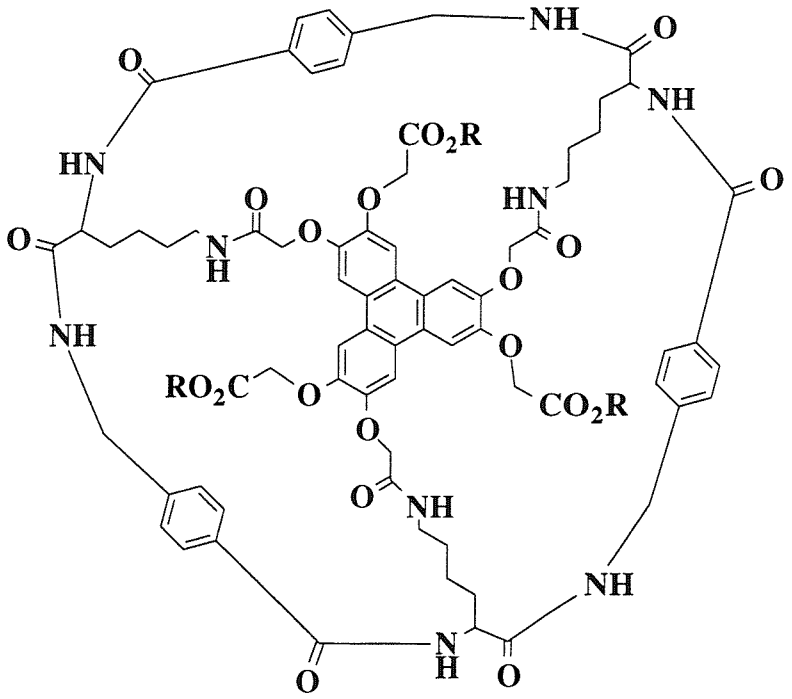
A second macrocycle was synthesised by elaborating a new base unit produced by extending the 9-Br-BBN methodology described in Chapter 2. The ratio of the isomers obtained was different when compared with the pentyl macrocycle but there was no obvious reason for this fact. Unfortunately the problems with separating the isomers and the difficulties with removing the benzyl groups under mild conditions prevented conversion of macrocycle **101** into a water soluble variant.

The benzyl macrocycle was useful for screening possible guests one of which was found to bind and was studied further with the major isomer of the pentyl macrocycle. Although the exact mode of binding was not established it was felt that the benzene triol was reasonably comparable to the simple approximation of a saccharide outlined in the Programme of Work (flat, with several hydroxyls and with a hydrophobic face) and it suggested there was potential for the macrocycles to bind saccharides. With this in mind it was decided that rather than investigate the binding in organic solvents any further, the benzyl macrocycle would be abandoned and efforts made to create a new version of the macrocycle which could be made water soluble and it's interactions with saccharides studied.

Chapter Five - The Third Macrocycle

5.1 Synthesis of a Water Soluble Macrocycle

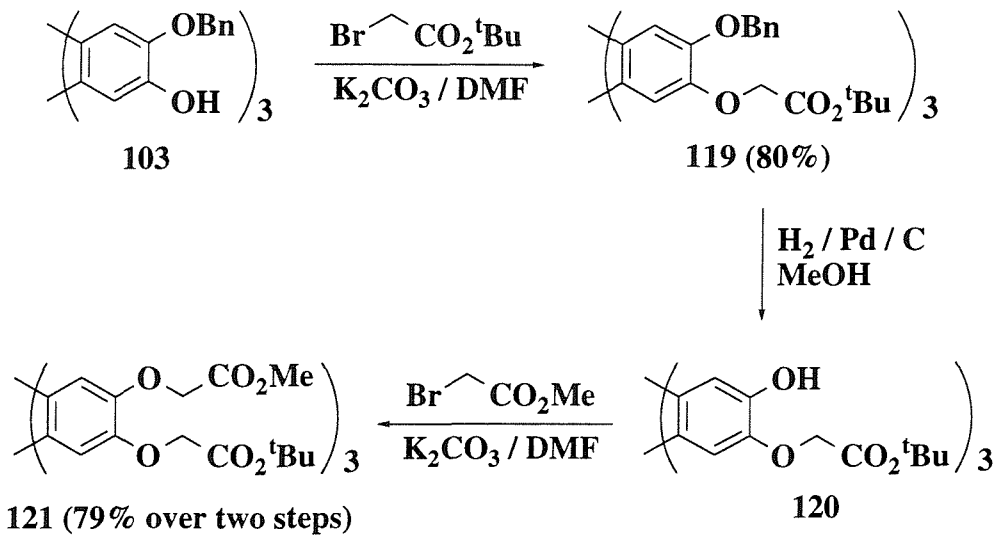
The benzyl macrocycle **101** from the previous chapter was abandoned for several reasons described previously and it was decided to replace the benzyl groups with an alternative functional group to achieve water solubility. The resulting new macrocycles **118** are shown in Figure 46 where the side chains are now CH_2CO_2H (**118b**) to obtain water solubility as their salts.



118a R = Me
118b R = H

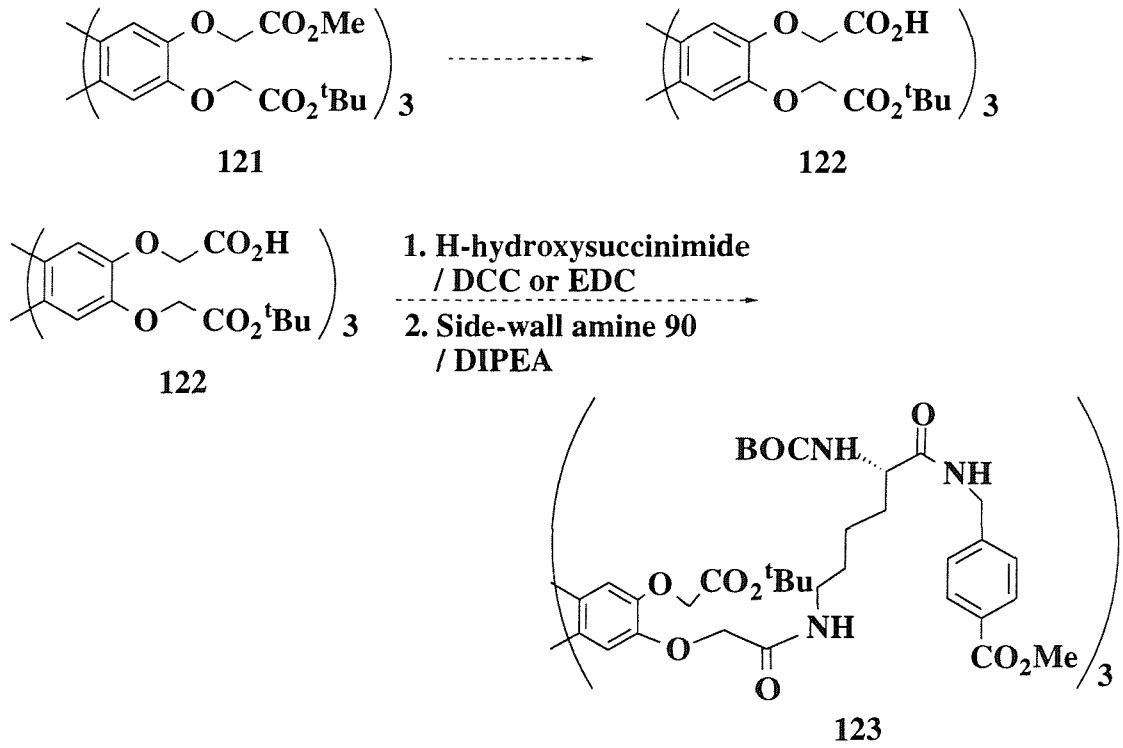
Figure 46

The route used began from the tribenzyloxytriphenylene **103** in Scheme 23 which was alkylated with *tert*-butyl bromoacetate to give the tris(*tert*-butyl ester) **119** in very good yield. The benzyl groups were removed by hydrogenolysis to give the intermediate **120**, which was insoluble in most organic solvents so was isolated but not purified. Taking **120** on directly by alkylation with methyl bromoacetate/potassium carbonate in dimethylformamide gave the triphenylene **121** in good yield over the two steps (79%).



Scheme 23

The planned route was to selectively hydrolyse the methyl esters of **121** then couple on the side-wall/rim as shown in Scheme 24 to give precursor **123**. During the cyclisation sequence it was hoped that the *tert*-butyl esters would be cleaved by the acidic conditions used for removal of the BOC groups and after cyclisation the macrocycle would be obtained in it's free acid form **118b**.



Scheme 24

Selective hydrolysis of the methyl esters of **121** proved to be more difficult than anticipated. A range of conditions was tried but the results seemed to be either no reaction, no selectivity (with all the esters being hydrolysed) or partial reaction of both types of ester (Table 11).

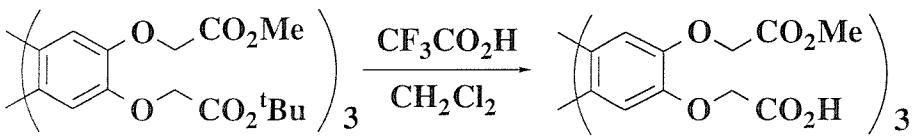
Table 11 - Ester Hydrolysis Conditions

Entry	Reaction Conditions	Temperature	Results
1	NaOH (3.6 eqv) / MeOH	RT, 50°C, 75°C	No reaction
2	LiOH (1.0 M) / 1, 4-dioxane	50°C	No selectivity
3	LiOH (1.0 M) / 1, 4-dioxane	RT	No selectivity
4	LiOH (0.5 M) / 1, 4-dioxane	RT	No selectivity
5	LiOH (0.1 M) / 1, 4-dioxane	RT	No reaction
6	KO^{t}Bu / DMSO[106]	RT	Partially cleaved both esters
7	LiI / DMF[107]	RT, 75°C, Reflux	No reaction at RT or 75°C, partial cleavage of both esters at reflux

The last two entries in Table 11 (6 and 7) are worth commenting on: they were reported in the literature as methods for cleaving hindered methyl esters but interestingly they also partially cleaved the *tert*-butyl esters of triphenylene **121**.

It might have been possible to find conditions suitable for selective cleavage of the methyl esters (possibly at room temperature with somewhere between 0.1 and 0.5 M lithium hydroxide), but even if this had been the case it would then be necessary to carry out another selective hydrolysis on the methyl esters of **123**. In view of the apparent lability of the *tert*-butyl esters it was decided that this might be very difficult, so the synthetic strategy was altered.

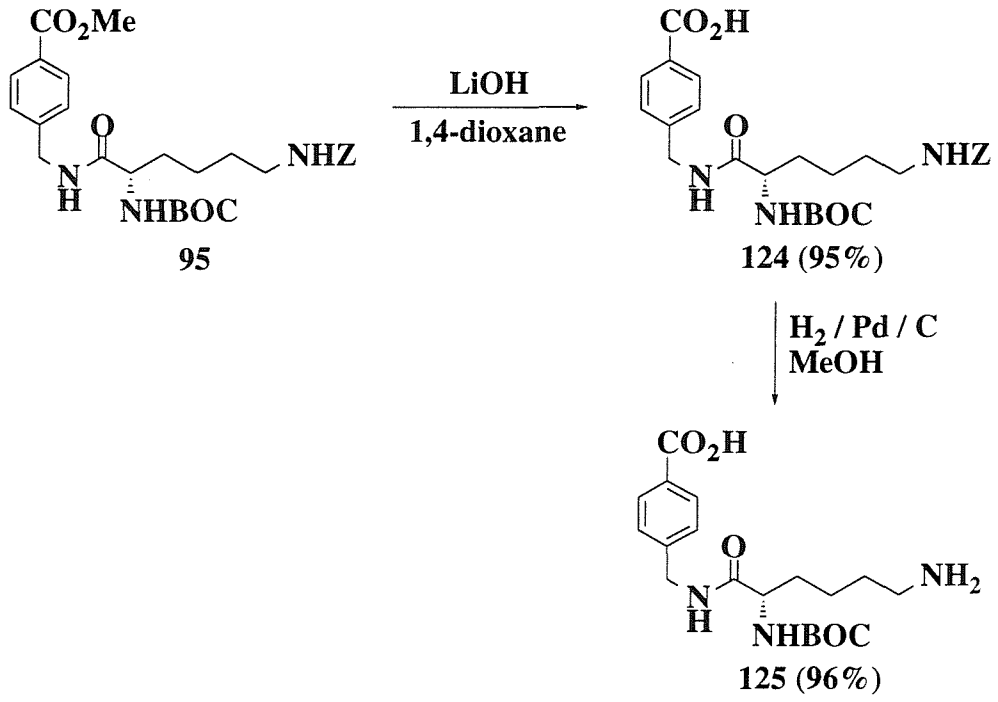
Trifluoroacetic acid induced cleavage of the *tert*-butyl esters of **121** was achieved in near quantitative yield with no reaction of the methyl esters (Scheme 25).



121 **61 (99%)**

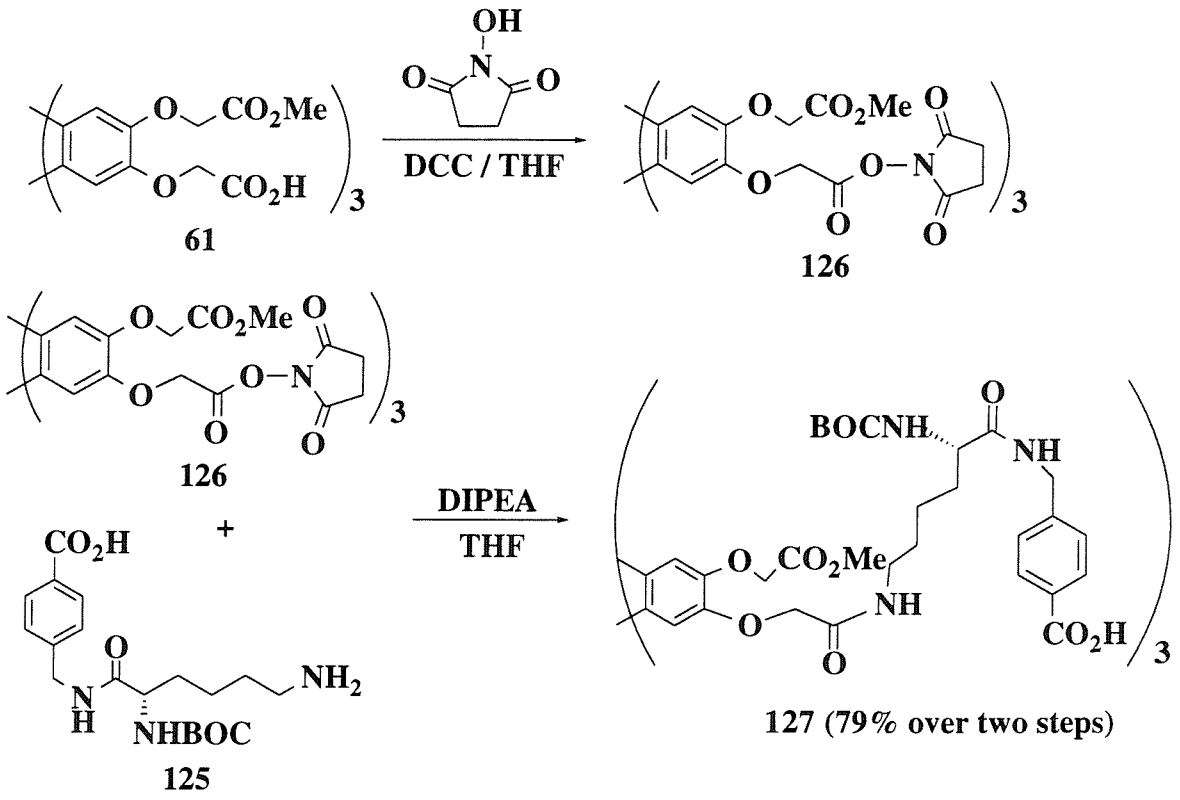
Scheme 25

The side-wall/rim building block was modified slightly before being coupled to the base unit **61**. The methyl ester was removed prior to the coupling reaction to avoid the problem of having two different methyl ester groups in the resulting precursor **127**. Hydrolysis of the methyl ester was easily accomplished with lithium hydroxide and removal of the Z protecting group was carried out by hydrogenolysis as before (Scheme 26). This order of steps was chosen, because if reversed it would have been very difficult to isolate the amino acid **125** from the aqueous reaction mixture used for the ester hydrolysis.



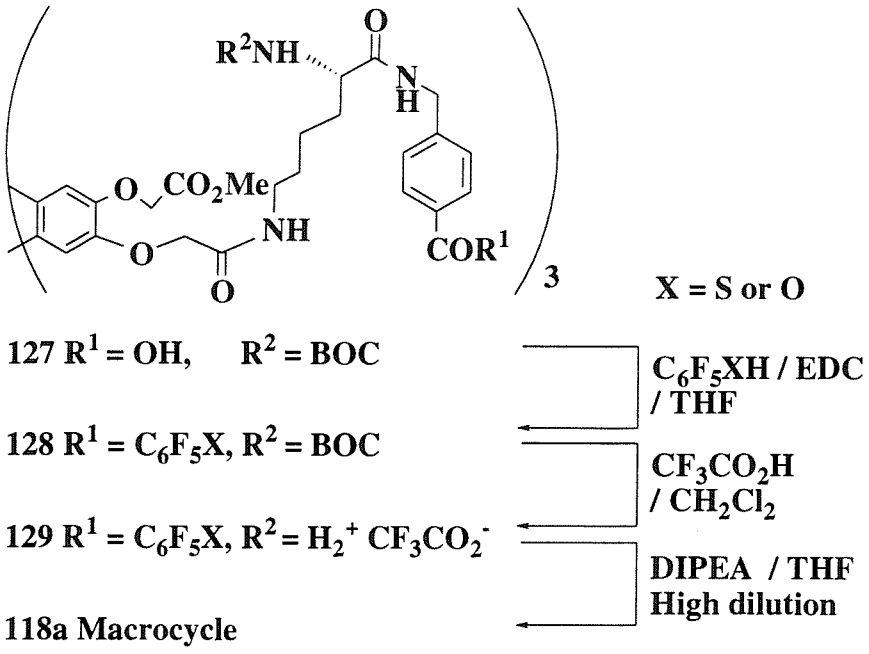
Scheme 26

Coupling the side-wall/rim unit to the base was carried out by using the activated ester methodology described for the first two macrocycles (Scheme 27); the only difference was the use of the side-wall/rim building block **125** with the unprotected acid functionality. The addition of a stoichiometric quantity of DIPEA gave the carboxylate salt and allowed the side-wall/rim amine to attack the activated ester carbonyl. The reaction proceeded smoothly and gave the precursor **127** in excellent yield comparable to that obtained with the original pentyl analogue.



Scheme 27

The final stages in the synthesis of the third macrocycle were the activation, deprotection and cyclisation (Scheme 28).



Scheme 28

The initial conditions used for the cyclisation sequence are summarised in Table 12; the yields obtained were consistently lower than for the pentyl version. Comparing entries 1 and 2 shows that increasing the time used for addition of the solution of activated precursor to the reaction vessel did not have a significant effect on the yield. Similarly changing the reaction temperature to 50°C (entry 3) or increasing the dilution of the reaction (entry 4) did not give better results.

Table 12 - Initial Cyclisation Conditions

Entry	Temperature	Addition Time	Yield	Dilution
1	RT	7 hrs	8%	50 ml
2	RT	19 hrs	11%	50 ml
3	50°C	10 hrs	9%	50 ml
4	RT	10 hrs	6%	250 ml

All reactions were carried out at 100 mg scale in THF and used DIPEA as a base except entry 3 which used DMAP. Pentafluorothiophenol esters were used.

Following these disappointing results the individual reactions in the cyclisation sequence were investigated in more detail. If the initial activation step did not proceed efficiently the resulting precursor would have one or more unactivated sites and would be unable to cyclise during the final step, leading to a build up of unreacted material that would promote polymerisation reactions. Formation of the pentafluorothiophenol ester causes a small change in the chemical shift of the aromatic protons *ortho* to the carboxylic acid of **127** (unactivated δ 7.35 ppm, activated δ 7.48 ppm in d^6-DMSO), so the degree of activation can be estimated from the relative integrals in the proton NMR spectrum. Several different conditions were studied for the activation and workup (Table 13).

Table 13 - Conditions for Activated Ester Formation.

Entry	Reaction Conditions	Workup procedure	Activation
1a	EDC / THF	Removed solvent	80%
1b		Removed solvent, triturated with water	75%
2	DCC / DMF	Chloroform / 2.0 M HCl partition	80%
3a	EDC / DMF / DMAP	Precipitated by adding water	90%
3b		Chloroform / 2.0 M HCl partition	95%
4a	DCC / DMF / DMAP	Chloroform / sat. Na_2CO_3 partition	90%
4b		Chloroform / 1.0 M NaOH partition	70%
5	EDC / THF / DMAP	Removed solvent, triturated with water	85%

Entries 1a and 1b of Table 13 show the conditions used for the activation for the cyclisations in Table 12: EDC and THF. The workup involved removal of the solvent *in vacuo* and trituration of the residue with water to remove any excess coupling reagent or pentafluorothiophenol. The integrals corresponding to the activated and unactivated sites showed 80% activation where the workup was just removal of the solvent and much the same result when triturated with water. It should be noted that this does not mean 80% of the molecules were fully activated (at all three acids) but that 80% of the free acids had formed activated esters.

Changing the activation conditions to DCC / DMF was tried (entry 2) and the workup involved partitioning the reaction mixture between chloroform and hydrochloric acid. The activation achieved was comparable to that in entry 1. The use of DMAP was investigated and a good level of activation was observed (entries 3a and 3b) with either of the workup procedures used. The conditions used in entries 4a and 4b gave good activation when partitioning the reaction mixture between chloroform and saturated sodium carbonate solution but a poor result when sodium hydroxide solution was used. Finally entry 5 (compared with entry 3a) shows that no significant improvement in activation was achieved by using DMF as solvent in place of THF. The recovery of material was best when the workup involved precipitation or trituration of the product with water. Partitioning the product between organic and aqueous phases tended to give a partial emulsion resulting in low recovery of material from the organic phase.

The conditions chosen for further work were: EDC / DMF / DMAP with precipitation of the product from the reaction mixture by adding water, but using these conditions and carrying

out the last two steps of the cyclisation sequence gave virtually no macrocycle (≈ 1 mg). An insoluble white material was observed when removing the BOC groups and when attempting to dissolve the precursor in THF for the cyclisation. This solid had not been seen before and it's NMR spectrum showed peaks which were at the same chemical shifts as the activated and deprotected precursor **129** but were very broad suggesting some kind of polymer though it is difficult to see how polymeric material could have been formed.

It seemed a reasonable assumption that the cause of the problems with this insoluble material was the DMAP used in the activation step so the original activation conditions were returned to (EDC / THF no DMAP) and changes made to the other steps in the cyclisation sequence. Rather than using 50% trifluoroacetic acid in dichloromethane the concentration was reduced to 10% and the reaction time increased from 1 hour to 3 hours. It was considered that some of the macrocycle might be being retained on the chromatography column used for purification after the cyclisation, so a small quantity of pure macrocycle (5 mg) was subjected to preparative TLC with 4 mg being recovered. The good level of recovery led to the use of preparative TLC for purification of the remaining cyclisation reactions (Table 14) and 10% trifluoroacetic acid / dichloromethane for the deprotection.

Table 14 - Cyclisation Conditions

Entry	Scale	Activated ester	Cyclisation Conditions	Overall yield
1	100 mg	C_6F_5SH	DIPEA / THF	5%
2a	100 mg	C_6F_5SH	DIPEA / THF / benzene triol	14%
2b	100 mg	C_6F_5SH	DIPEA / THF / H_2O	9%
3	100 mg	C_6F_5OH	DIPEA / THF	15%
4a	100 mg	C_6F_5OH	DIPEA / THF / benzene triol	14%
4b	100 mg	C_6F_5OH	DIPEA / THF / H_2O	14%
5a	100 mg	C_6F_5OH	DIPEA / THF	11%
5b	100 mg	C_6F_5OH	K_2CO_3 / H_2O	0%
6	400 mg	C_6F_5OH	DIPEA / THF	5%
7	1 g	C_6F_5OH	DIPEA / THF	22%
8	1.7 g	C_6F_5OH	DIPEA / THF	21%

All activations were carried out on a 100 mg scale with EDC / THF followed by trituration with water to workup. Yields are over 3 steps.

Using EDC / THF for the activation, 10% trifluoroacetic acid / dichloromethane for deprotection and preparative TLC for purification after cyclisation with DIPEA in THF, gave a 5% yield of macrocycles (entry 1). Templating the macrocycle's formation with benzene triol (used as it's dihydrate) was studied, with water present in a second cyclisation as a control (entries 2a and 2b). The difference between the yields obtained (14% and 9%) is probably not significant in view of the apparent variability of the yield from these reactions.

Pentafluorophenol was used in place of pentafluorothiophenol and gave a slightly improved yield of 15% (entry 3) which was counter-intuitive when compared with the formation of the pentyl macrocycles where the best yields were obtained with the more active pentafluorothiophenol. The improvement is small but seemed to be reasonably consistent for the remaining cyclisations carried out.

The templating experiment was repeated with the pentafluorophenol activated esters (entries 4a and 4b) but no difference in yield was obtained, although the result was consistent with the previous entry in suggesting a better yield for the use of pentafluorophenol rather than pentafluorothiophenol.

A final experiment was to attempt the cyclisation reaction in water (entry 5b) but no macrocycle was obtained from this reaction.

At this point in the project it was decided that further investigation of the cyclisation conditions was not justified so the scale was increased to generate more material. On a 400 mg scale of tri-acid **127** the activation and deprotection steps appeared to proceed as before but after the cyclisation only a 5% yield of macrocycle was obtained. The low yield could have resulted from the variability that seemed to be inherent in the cyclisation reaction or it could have been a result of the increased scale. To avoid any further loss of material through low yields, further scale-up reactions were carried out by activating and deprotecting on a large scale (entries 7 and 8, Table 14) then the activated precursor material was split into nine portions which were cyclised in three batches of three individual reactions over a period of several days, storing the activated precursor at low temperature until required. Interestingly the yields obtained were relatively high for both entries which was unexpected as the volume of solvent used for the cyclisation (particularly in the case of entry 8) was not increased in proportion to the scale of the reaction (for reasons of convenience) and the reaction mixtures were actually more concentrated than normal.

Once again two isomeric forms of the macrocycle **118a** were obtained; the ratio was slightly variable but on average it was 3.5:1 as measured by NMR comparing the integrals of the *para*-substituted benzene ring. Comparing this with the earlier macrocycles where the ratio for pentyl was 2.1:1 (isolated) and for benzyl 5.0:1 (by NMR) the third macrocycle **118a** lies between the two at 3.5:1. The effect is most likely to be steric rather than electronic but as stated earlier, without knowing the exact structure of the isomers and in view of the fact that

the base seems to be distant from the rim it is difficult to suggest any specific reason for the effect.

The isomers of macrocycle **118a** could not be separated by HPLC so alternative methods were considered. During one of the first attempts at making the macrocycle some separation of the macrocycles was obtained on the flash chromatography column: the major isomer was obtained pure and the minor isomer was obtained as a 1:1 mixture with the major isomer. Unfortunately this success was never repeated either on a column or by TLC (even with multiple elutions of the plate). Fractional recrystallisation from *iso*-propanol was tried following the method shown in Figure 47 in the hope that one of the isomers would crystallise more readily but NMR analysis of the material at the fourth level showed no change in the ratio of isomers.

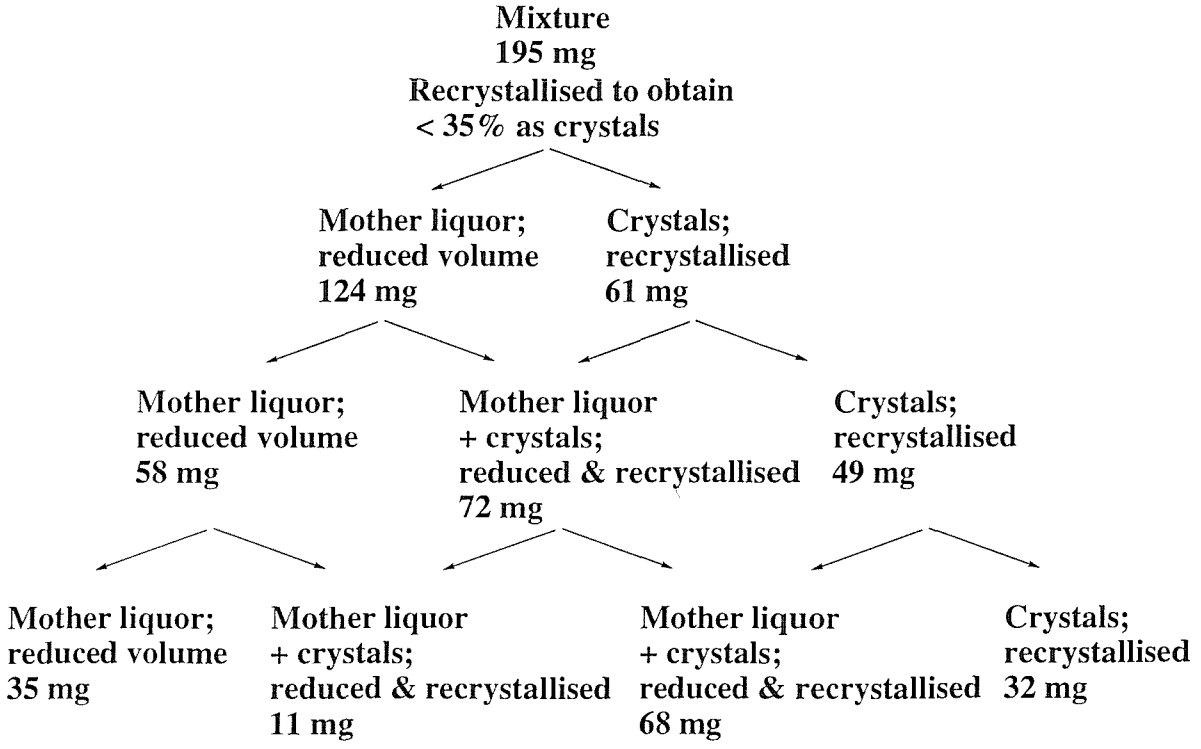
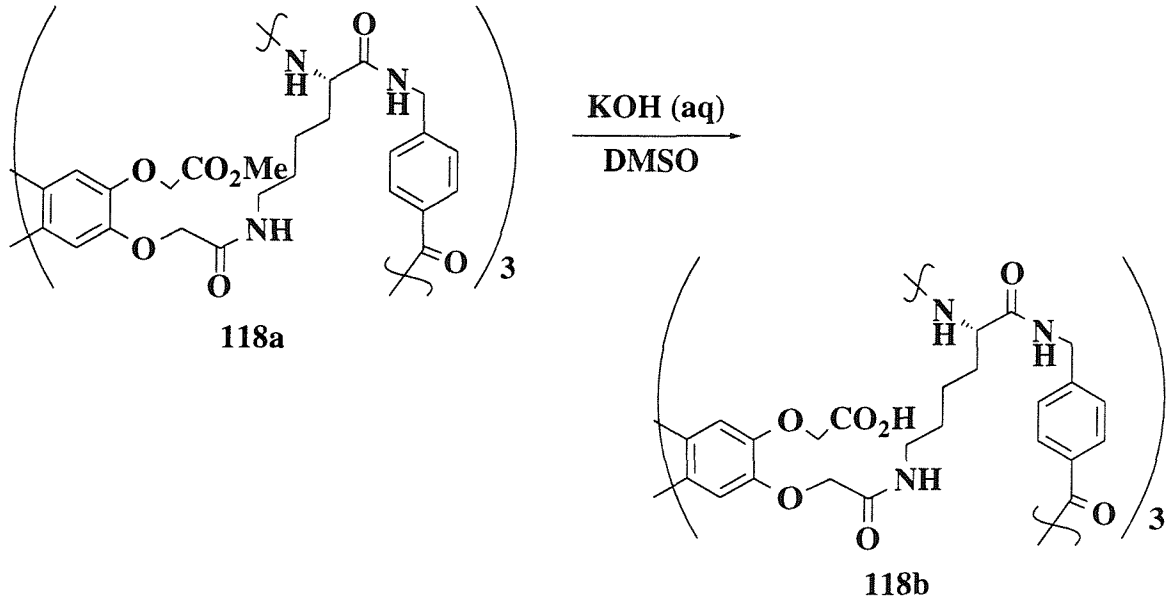


Figure 47

Initial attempts at hydrolysis of the methyl esters of macrocycle **118a** to give the free acid version **118b** was problematic. The main difficulty was following the reaction as the macrocycles are very polar and run poorly on TLC. A sample of the macrocycle was dissolved in d^6-DMSO and NaOD in D_2O added until the methyl ester peak had disappeared and the aromatic region of the NMR was clean (indicating a C_3-symmetric product had formed). Suitable conditions were found to be five equivalents of base and just a few minutes reaction time at room temperature.

In practice the ester hydrolysis was carried out by treating a solution of the macrocycle **118a** in DMSO, with aqueous potassium hydroxide solution and an acidic workup to give the free acid form of the macrocycle in 78% yield (Scheme 29).



Scheme 29

Once the free acid form of the macrocycle had been isolated it was pleasing to discover that it would dissolve in water as a salt, by adding a stoichiometric quantity of sodium (or potassium) hydroxide or in phosphate buffer (pH 7).

The proton NMR of the macrocycles **118b** did not show peaks corresponding to the minor isomer but the some signals could be seen in the carbon-13 NMR. Comparison of the peak heights between major and minor isomers for certain signals gave an average ratio of 3.1:1 which is comparable with the ratio of 3.5:1 observed in the proton NMR of the methyl ester version **118a**.

Separation of the isomers by HPLC could not be achieved at this stage; the free acid form was too insoluble in the eluents (acetonitrile/water) to elute from the column and the lithium or potassium salts of **118b** were washed off the column too rapidly to give a separation.

5.2 Binding Studies

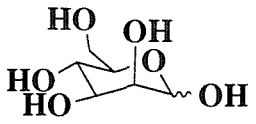
The fluorescence of the triphenylene unit was referred to in the Programme of Work section as a possible means of studying binding between the macrocycles and guests. Some initial investigations were carried out using 10^{-5} M solutions of macrocycle in borate buffer (10^{-4} M).[108,109] Borate buffer was chosen to provide a constant pH of 9, eliminating the possibility of changes in the spectra due to pH effects and also because it can easily be prepared in a deuterated form and might have been useful if NMR studies were required for further information on binding. Solutions of D-mannose (0, 1, 10, 50 and 100 equivalents) were added to the macrocycle and the fluorescence spectra (λ_{ex} = 308 nm, λ_{em} = 398 nm) were recorded but the results did not show a clear pattern and were not consistent with binding occurring. The fluorescence of a sample of macrocycle was recorded several times and the intensity of the fluorescence was found to be quite variable making it inappropriate for use in studying binding.

Some investigations into the possibility of studying binding by UV/VIS spectra were carried out with D-mannose using the same solutions as above but recording the UV/VIS spectrum between additions of guest solution. None of the absorbance peaks monitored showed a consistent rise or fall in intensity which would have indicated that binding was occurring.

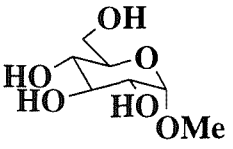
It was felt that studying binding by NMR might provide more information, so some reverse titrations were performed by adding solutions of macrocycle (0, 0.5 and 1 equivalent) to solutions of guests and recording the NMR spectra. The solutions used were made up in deuterated borate buffer and the quantity of macrocycle used was 4 mg (in 400 µl of buffer solution) with a corresponding 1 equivalent of D-mannose in each case (in 600 µl of buffer). No changes were seen in the NMR spectrum of the saccharide on adding the macrocycle. It was considered that the borate buffer might be interacting with the saccharides in a competitive manner and preventing binding; not an unreasonable idea considering that boronic acids have been used to bind saccharides as discussed in the introduction to this thesis.

There were no obvious deuterated alternatives to the borate buffer which were cheap and readily available so it was decided to continue reverse titration experiments without a buffer and if any effects which might indicate binding were observed the experiment would need to be repeated in the presence of buffer at constant pH.

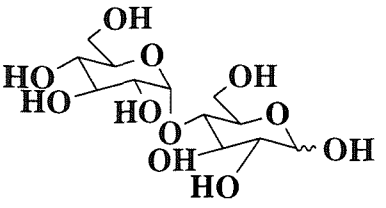
The macrocycle was dissolved in D_2O by shaking with 3 equivalents of sodium deuteroxide solution and then added to the guest solution in portions (0, 0.5 and 1 equivalents) as before. The saccharides investigated are shown in Figure 48; in the cases of D-mannose **130**, methyl α-D-glucopyranoside **131**, D-maltose **132** and mannosamine **133** there were no significant changes in the NMR spectra of either the saccharide or the macrocycle.



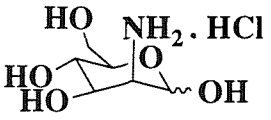
130 D-mannose



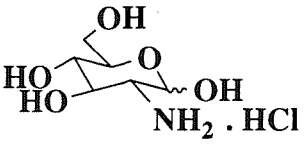
131 methyl α-D-glucopyranoside



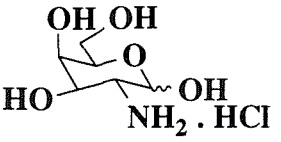
132 D-maltose



133 D-mannosamine hydrochloride



134 D-glucosamine hydrochloride

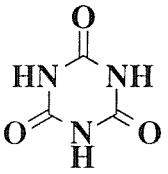


135 D-galactosamine hydrochloride

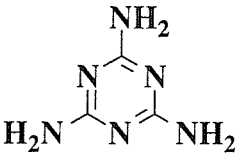
Figure 48

There were some slight changes in the NMR spectra of D-glucosamine **134** and D-galactosamine **135** (used as their hydrochloride salts) on adding the macrocycle, but when the titrations were repeated in deuterated borate buffer no changes were seen, suggesting that the effect observed in the absence of buffer was pH based. The titrations without buffer were repeated adding just 0.1 and 0.3 equivalents of macrocycle and although some slight changes were seen they were not considered to be significant being of the order of 0.02 ppm. It was felt that if a guest was being bound anywhere in the region of the triphenylene base or the aromatic rings of the macrocycle rim there would be a change in chemical shift of the order of 1.0 ppm due to shielding effects from the aromatic ring currents.[110]

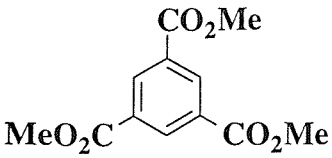
The disappointing conclusion drawn from the experiments outlined above was that the macrocycle was not capable of binding saccharides in an aqueous environment. A range of other substrates was studied (Figure 49) in an attempt to discover something about the potential binding properties of the macrocycles.



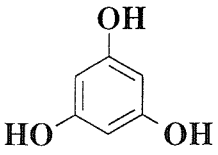
114 cyanuric acid



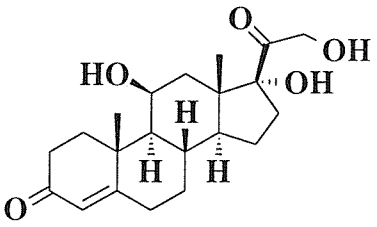
136 melamine



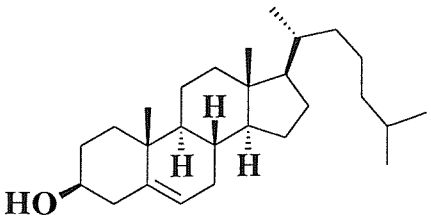
137 trimethyl 1, 3, 5-benzenetricarboxylate



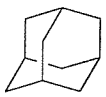
115 1, 3, 5-benzene triol



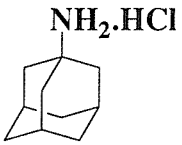
138 hydrocortisone



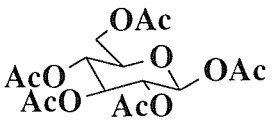
139 cholesterol



140 adamantane



141 1-adamantanamine hydrochloride



142 β-D-glucose pentaacetate

Figure 49

As described in the previous chapter, compounds which were soluble in water (melamine **136**, benzene triol **115** and 1-adamantanamine hydrochloride **141**) were studied as 1:1 mixtures with the macrocycle but no significant changes in the spectra of the macrocycle or (for benzene triol and 1-adamantanamine) the spectra of the guest were observed.

Guests which were not soluble in water were shaken with a solution of 4 mg of macrocycle **118b** (and 3 equivalents of NaOD) in 600 μl of D_2O for 1-2 hours, filtered, then the NMR spectrum was recorded and examined for evidence of binding. In all cases except that of β-D-glucose pentaacetate **142** there were no changes to the macrocycle spectrum and no obvious indication of any new signals which might have been due to guest being solubilised by the macrocycle.

For the case of β-D-glucose pentaacetate, peaks corresponding to the guest were observed in the NMR spectrum, so a control experiment was carried out by shaking the guest in D_2O in the absence of macrocycle then filtering and recording the NMR spectrum. By using D_2O containing 0.017% DMSO as an internal standard it was possible to estimate the amount of guest dissolved in the presence and absence of macrocycle. Comparing the integrals of the anomeric proton of the guest with the DMSO peak suggested that 16% more guest was

solubilised in the presence of macrocycle. This figure is small and could have arisen from experimental errors.

A reverse titration was carried out using a solution of β-D-glucose pentaacetate (0.45 mg) in D_2O (700 μl) and adding aliquots of macrocycle **118b** as it's sodium salt (a stock solution of 8 mg of macrocycle with 3 equivalents of NaOD in 1 ml of D_2O was used). A total of five equivalents of macrocycle were added to the guest solution and a series of NMR spectra recorded. Although there were some changes in the chemical shift of some of the guest signals the maximum change in chemical shift was at the guest anomeric proton and was just 0.07 ppm; as discussed earlier it was felt that if a guest was being bound within the cavity of the macrocycle much larger changes in chemical shift would be observed.

500 MHz NMR studies in H_2O (rather than D_2O) comparing a 1:1 mixture of macrocycle and β-D-glucose pentaacetate with macrocycle only and guest only, showed that although the small (< 0.1 ppm) change in the guest anomeric proton was still present there were no changes to the macrocycle signals including the NH's so it was concluded that binding was not occurring.

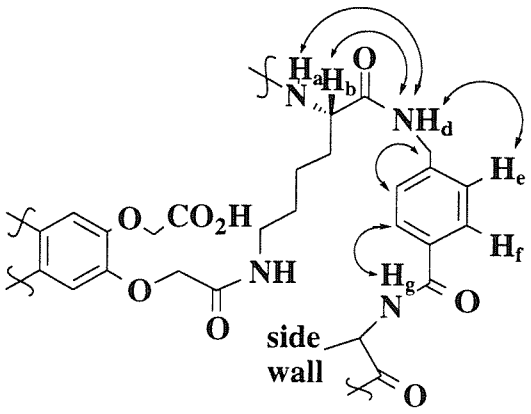
To establish the reason for the changes in the NMR spectrum of β-D-glucose pentaacetate a dilution experiment was carried out. Aliquots of D_2O were added to a solution of β-D-glucose pentaacetate in D_2O (0.45 mg in 700 μl) and the chemical shifts of the β-D-glucose pentaacetate signals were monitored. There were no changes in chemical shift which indicates that the effect seen when adding macrocycle solution to the guest was not caused by dilution of the guest solution. The effect was most likely to have been caused by small pH changes occurring as the macrocycle solution was added.

5.3 Attempts to Determine the Structure/Conformation of Macrocycle 118

While an X-ray crystal structure would probably answer questions about the nature of the isomers formed in the cyclisation it proved impossible to obtain crystals from the third macrocycle. In the same manner as for the pentyl macrocycles a range of conditions were tried for growing crystals: slow evaporation, liquid-liquid and liquid-vapour diffusion between solvents. Although the macrocycle **118a** was readily soluble in DMSO and insoluble in water or diethyl ether no combination of these solvents in the above conditions was effective. Similarly the free acid version **118b** could readily be dissolved in water as it's salt but diffusion of acetone or tetrahydrofuran into this solution or slow evaporation did not produce any crystals.

One possible reason for the lack of binding observed could be the collapse of the macrocyclic cavity which might occur in an aqueous environment to minimise the number of hydrophobic surfaces exposed to the solvent. A sample of macrocycle in phosphate buffer at

pH 6.5 (0.1 M buffer[108]) was studied by ROESY[111] and TOCSY[112] spectroscopy at 500 MHz in an attempt to establish whether the cavity of the macrocycle remained open in an aqueous environment. The interactions recorded are shown in Figure 50, only correlations which existed on the ROESY spectrum and not the TOCSY spectrum are shown. Only interactions which would be expected were observed though they are consistent with those shown for pentyl macrocycle **100** (Figure 36). As before no interactions between the base and the rim of the macrocycle were observed, suggesting that the cavity was open and had not collapsed in the aqueous solution.



ROE's for Macrocycle 118b

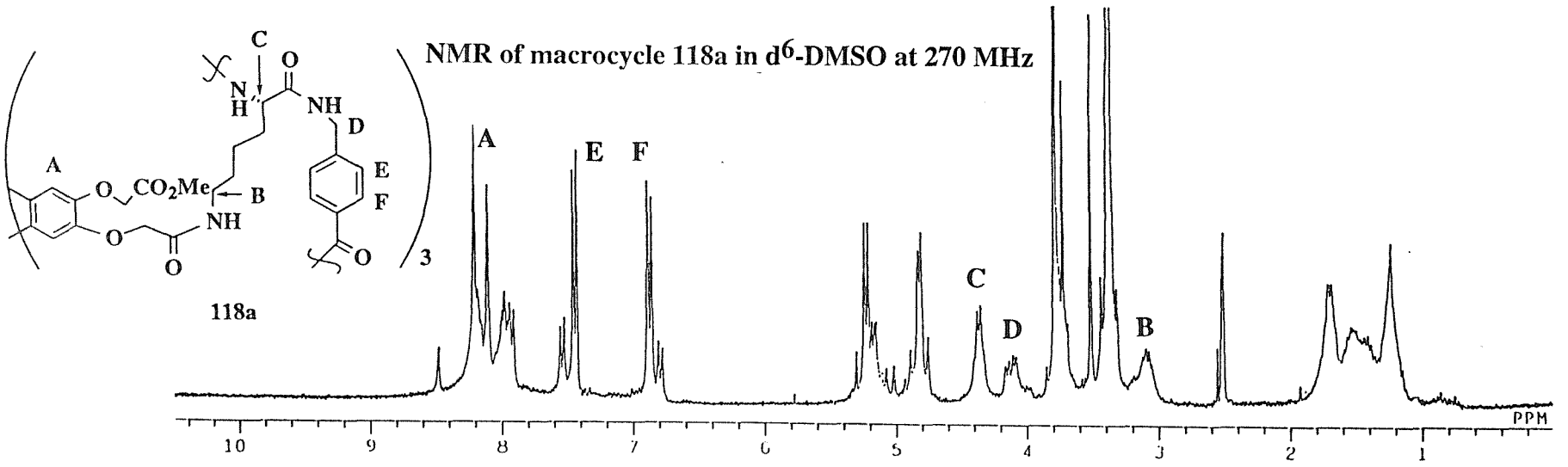
Figure 50

Comparing the NMR spectra of the macrocycle **118a** and the acyclic compound **143** in d^6-DMSO shows that the cyclisation only leads to a small number of changes (Figure 51). The triphenylene singlets (A) do not change their chemical shift and although the *para*-substituted benzene ring protons (E and F) move, this may be due to the formation of amide bonds. The methylenes protons B and D become diastereotopic, but most significantly the lysine α-proton (C) moves from δ 3.90 in the acyclic compound to δ 4.38 in the macrocycle, a change of 0.48 ppm. In addition the remaining lysine methylene signals become more spread out changing from δ 1.70-1.20 to δ 1.90-1.05.

It is perhaps more interesting to consider the effect of solvent on the NMR spectra (Figure 52). Comparing the spectra of **143** in d^6-DMSO and water (dissolved by adding 6 equivalents of sodium deuteroxide) shows that the triphenylene signals (A) move upfield by 0.55 ppm while the signal for methylene D moves by 0.30 ppm (Table 15). A change of similar magnitude is seen for the lysine methylenes which move from δ 1.70-1.20 to δ 1.55-0.90. The lysine α-proton (C) moves from δ 3.90 but it's position in the D_2O spectrum could not be established with certainty.

Table 15 -Chemical Shifts for Compound 143 in d^6-DMSO and D_2O

Signal	δ in d^6-DMSO (ppm)	δ in D_2O (ppm)	Δ δ (ppm)
triphenylene (A)	8.20, 8.10	7.60 (br)	- 0.55
Ar$C\underline{H}_2$NH (D)	4.35	4.05	- 0.30
lysine α-proton (C)	3.90	Could not be assigned	N/A
lysine methylenes	1.70-1.20	1.55-0.90	-


NMR of macrocycle 118a in d6-DMSO at 270 MHz
118a
A
E
F
C
D
B
3
PPM
10
9
8
7
6
5
4
3
2
1

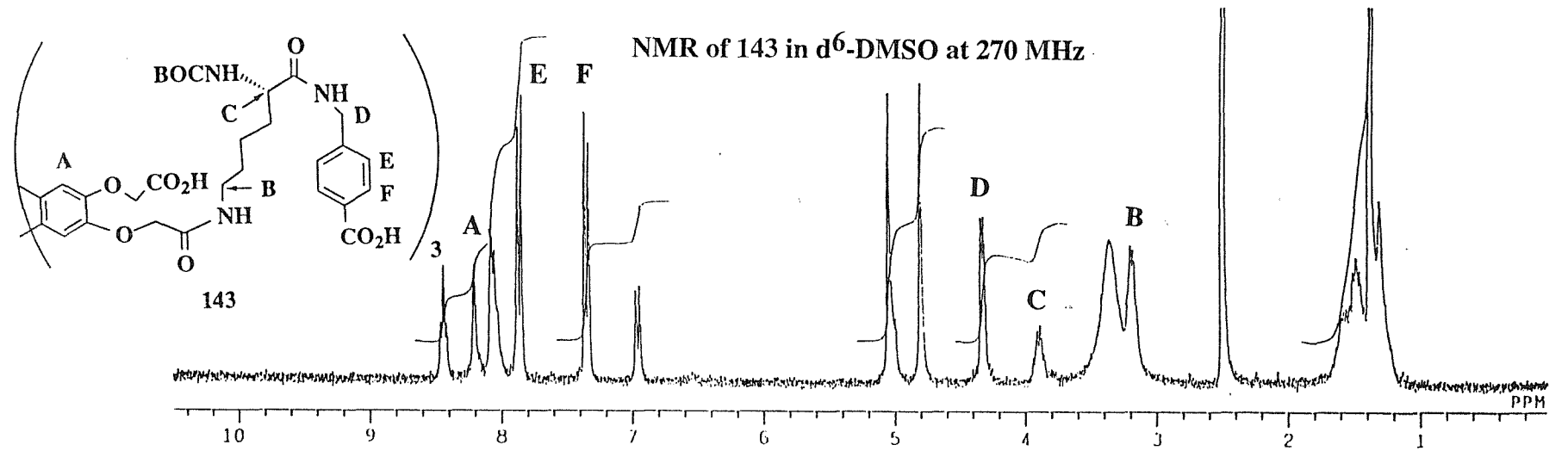

NMR of 143 in d6-DMSO at 270 MHz
143
BOCNH
A
E
F
D
C
B
3
PPM
10
9
8
7
6
5
4
3
2
1

Figure 51

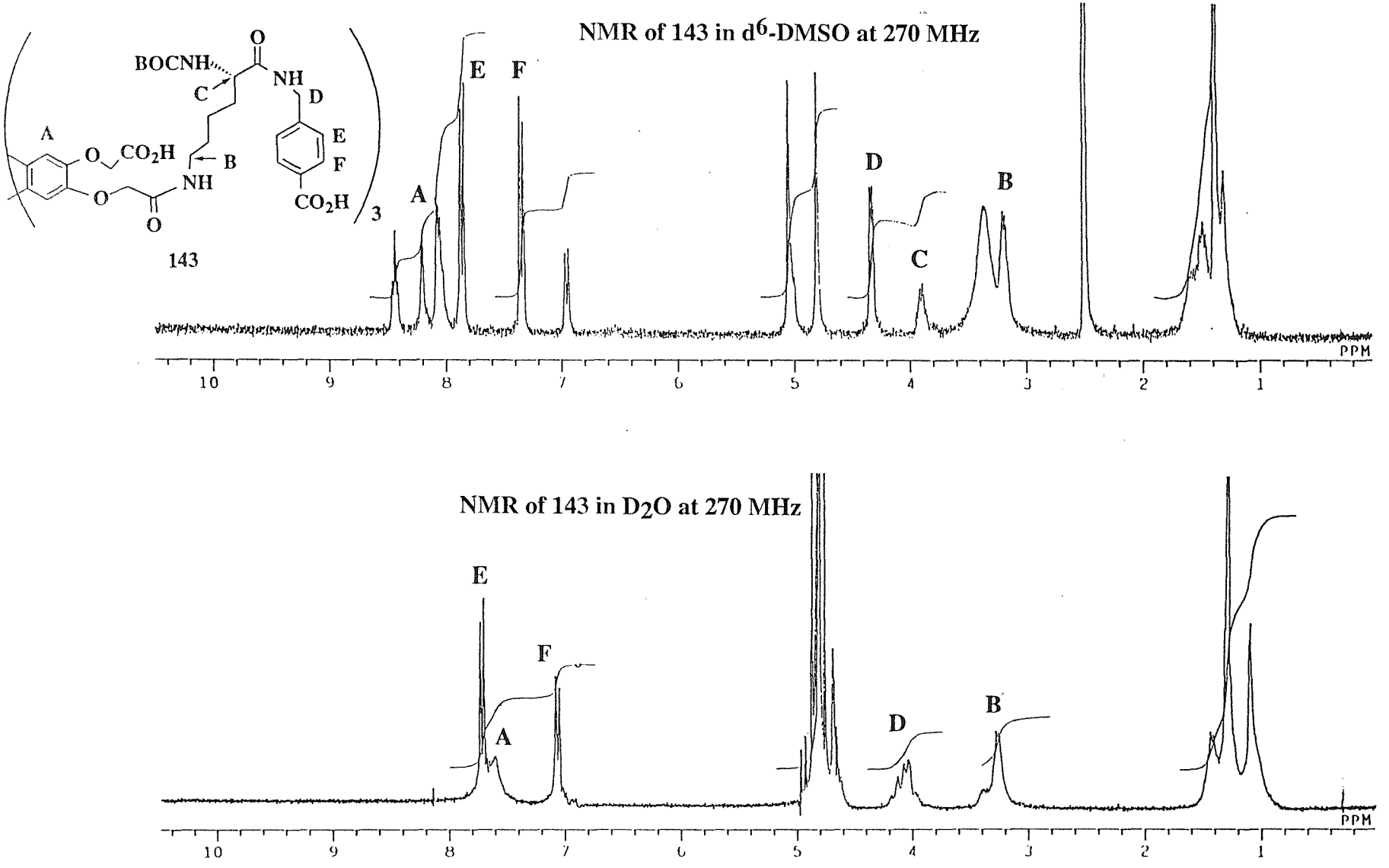

BOCNH
C
O
NH
D
A
O
CO2H
B
E
F
NH
CO2H
O
O
3
143
NMR of 143 in d6-DMSO at 270 MHz
E
F
A
D
C
B
PPM
10
9
8
7
6
5
4
3
2
1
NMR of 143 in D2O at 270 MHz
E
F
A
D
B
PPM
10
9
8
7
6
5
4
3
2
1

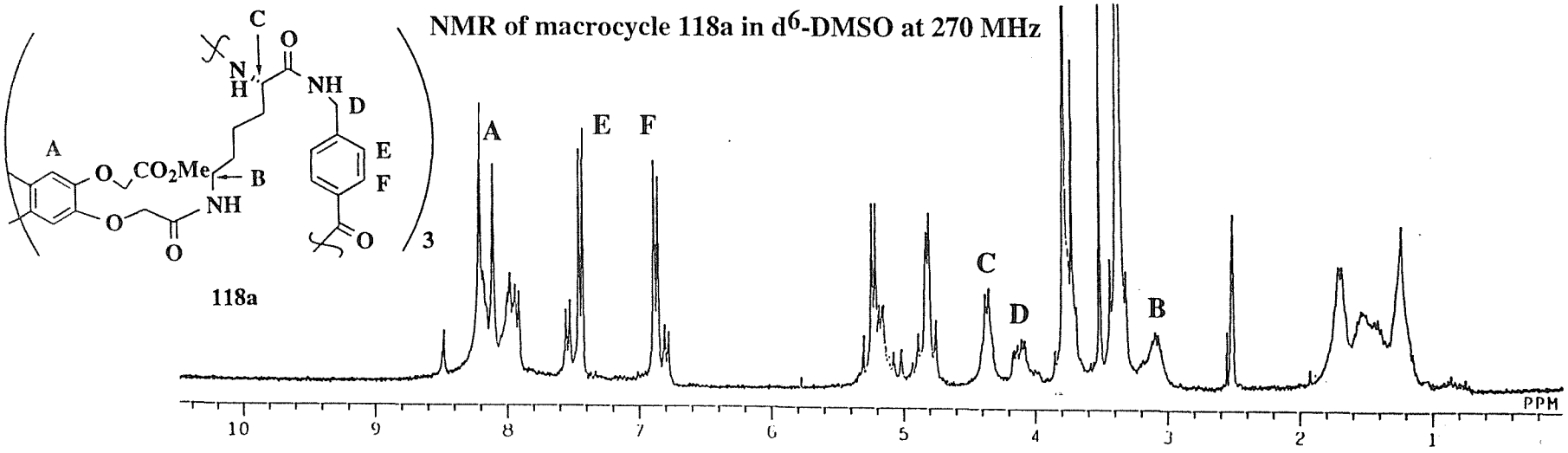
Figure 52

A different pattern of changes is seen in the NMR spectra when comparing the third macrocycle in it's methyl ester form **118a** in d^6-DMSO and the free acid form **118b** as it's sodium salt in D_2O (Table 16). The triphenylene signals move upfield by 1.00 ppm although the *para*-substituted ring signals (E and F) are virtually unchanged. The lysine α-proton (C) is also virtually unchanged and the methylenes B, D and those of the lysine chain show relatively small changes in chemical shift (Figure 53).

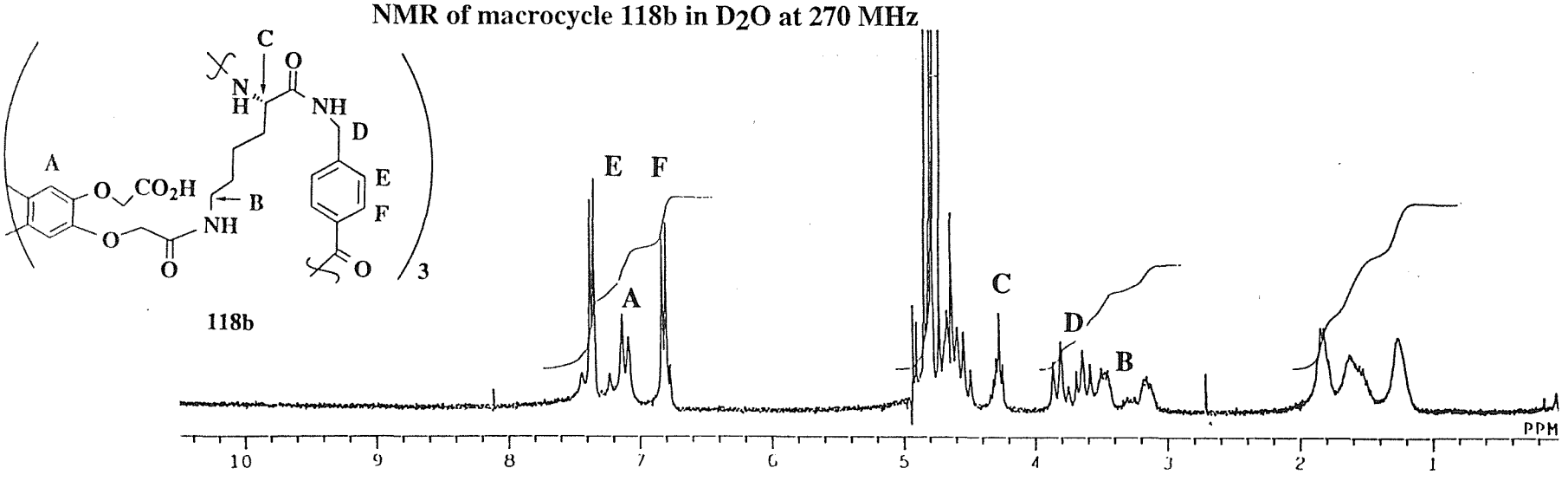
Table 16- Chemical Shifts for Macrocycle 118 in d^6-DMSO and D_2O

Signal	δ in d^6-DMSO (ppm)	δ in D_2O (ppm)	Δ δ (ppm)
triphenylene (A)	8.20, 8.10	7.16, 7.10	- 1.04, - 1.00
p-substituted ring (E and F)	7.44, 6.88	7.38, 6.82	- 0.06, - 0.06
lysine α-proton (C)	4.38	4.30	- 0.08
$ArC\underline{H}_2NH$ (D)	4.10, ≈ 3.75	3.80, 3.66	- 0.30, - 0.09
lysine methylenes	1.90-1.05	1.95-1.05	-

Although the results discussed above are interesting they do not provide any further information about the conformation of the macrocycles **118** in solution.



118a



118b

Figure 53

5.4 Molecular Modelling

In a final attempt to discover why the macrocycle **118b** did not show any binding ability some simple molecular modelling was carried out. The modelling was carried out using MacroModel 5.0 running on a Silicon Graphics Workstation. The AMBER[113] force field was used and the solvent was set as water. All non-bonded interactions were included in the calculations. A sequence of ten simulated annealing molecular dynamics simulations were carried out, each consisted of 1 ns of slow cooling from 600 K to 0.01 K using a time step of 1.5 fs . The compound was entered into the program as macrocycle **118a** (the methyl ester).

It should be stated that aim of this modelling was solely to give an indication as to whether the macrocycle might tend towards having an open or collapsed cavity in an aqueous environment.

The last three simulations from the set of ten were compared (Figure 54) and it can be seen that there is a good degree of consistency between the structures, with an open cavity clearly visible, although the side chains ($OCH_2CO_2CH_3$) are flexible and do not adopt a particular conformation. The structure from the tenth simulation is also shown on it's own (Figure 55) for clarity.

The structure generated from the tenth simulation was subjected to a room temperature molecular dynamics simulation, recording 150 structures which were then played back as an animated movie within MacroModel. It appeared that there was only a small amount of flexing of the macrocyclic structure, the triphenylene base remained reasonably rigid as expected and there appeared to be no tendency for the structure to collapse.

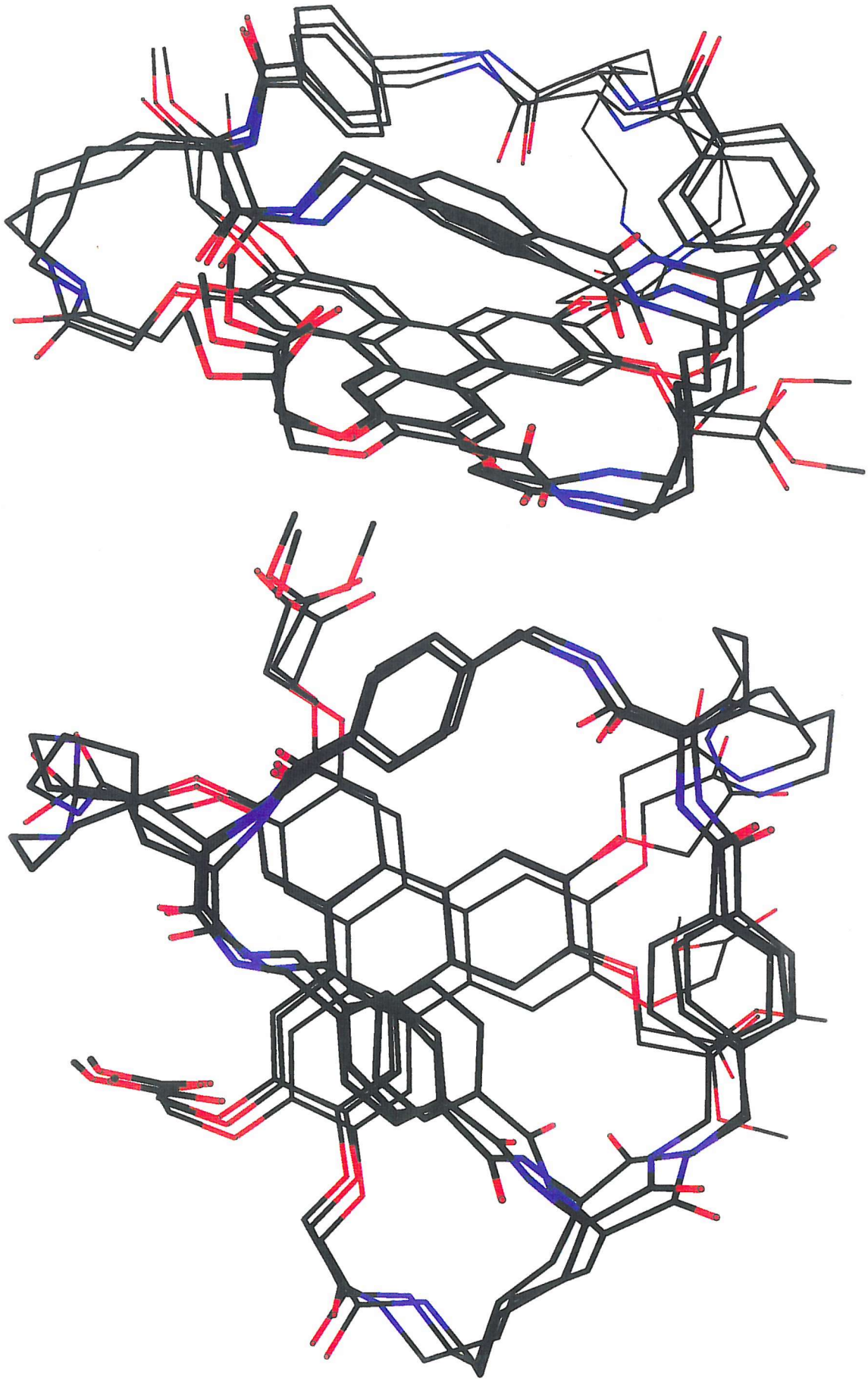


Figure 54 - Last three molecular dynamics simulation structures (side and top views)

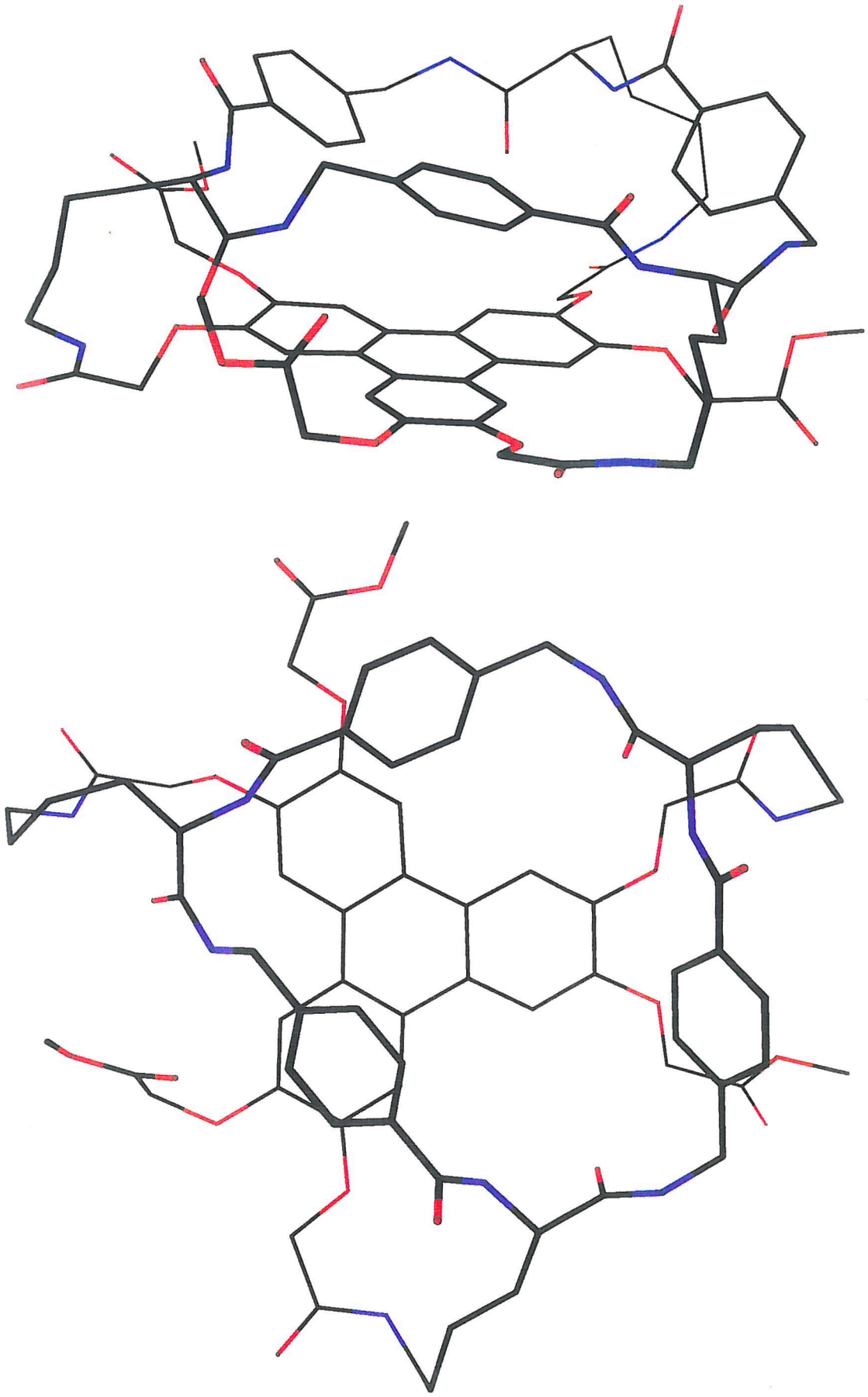


Figure 55 - Tenth molecular dynamics simulation structure (side and top views)

5.5 Conclusions

The third macrocycle was successfully synthesised by extending the methodology developed in the earlier chapters and was made soluble in water by hydrolysis of the methyl esters to give a free acid form. As with the first two macrocycles the third version **118** was formed as a mixture of two isomers.

Extensive binding studies were carried out but all proved negative, even with a guest (benzene triol **115**) which was found to bind to an earlier version of the macrocycle. NMR studies suggested that the macrocyclic cavity remained open but did not provide any more information on the problem of the two isomeric forms of the macrocycle. Some simple molecular modelling studies also suggested that the cavity remained open in aqueous media.

5.6 Overall Conclusions

Some existing methodology for the functionalisation of the triphenylene system was improved and extended to new substrates allowing the synthesis of a range of novel triphenylene derivatives. These were used in the synthesis of three novel macrocyclic structures with the aim of binding saccharides in water. The first and second macrocycles showed binding to a simple guest (benzene triol) in organic solvents while the third macrocycle did not appear to display any binding in aqueous solution. All three macrocycles were formed as a mixture of two isomers during the final cyclisation step, probably resulting from the relative orientation of the triphenylene base unit to the macrocyclic rim. The ratio of the isomers varied with the different macrocycles.

It is interesting to speculate on why the third macrocycle did not show any binding in water: NMR and molecular modelling studies suggested that the macrocyclic cavity had not collapsed, which would have prevented potential guests from gaining access to the inside of the macrocycle to bind. It is possible that the cavity was too large for the guests studied and although they could get inside the macrocycle, once there the potential hydrogen bonding sites of the macrocycle were too distant preventing the formation of hydrogen bonds (which would be weak in water anyway). Even with this problem the large, hydrophobic triphenylene base was still present so it was disappointing not to see some kind of interaction particularly with the more hydrophobic guests such as adamantane **140**.

If further work was to be conducted using the triphenylene system as a scaffold for a synthetic host it would probably be worthwhile simplifying the structure of the host. Replacing the (L)-lysine with an achiral building block and removing the benzylic methylene from the rim unit would prevent the formation of isomeric structures during the cyclisation. Changing the lysine chain for a more rigid unit might also help to minimise the entropy loss on cyclisation and improve the yield.

Chapter 6 - Experimental

6.1 General Methods and Instrumentation

General Experimental

Reactions requiring anhydrous conditions were carried out in flame-dried glassware under an atmosphere of dry nitrogen or argon. Where possible reagents were purified according to the procedures in: Purification of Laboratory Chemicals, D.D. Perrin, W. L. F. Armarego, Pergamon Press, Oxford, 3rd Edition (1988).

Thin Layer Chromatography was performed on Camlab aluminium backed sheets coated with silica (0.25mm) containing fluorescent indicator UV_{254}. Column chromatography was performed with Camlab Silica Gel 60 (0.04-0.063mm/230-400 mesh).

Petrol refers to the fraction boiling between 40-60°C.

Instrumentation

Melting points were determined in open capillary tubes using a Gallenkamp Electrothermal Melting Point Apparatus and are uncorrected.

Infrared spectra were recorded on a Perkin-Elmer 1600 series Fourier Transform Spectrophotometer. Solids were supported as Nujol mulls, liquid samples as thin films on sodium chloride plates and solutions contained in sodium chloride cells.

Proton NMR spectra at 270 MHz were obtained on a JEOL GX 270, at 300 MHz on a Bruker AC 300 and at 500 MHz on a Varian VRX 500 spectrometer. Peak positions are quoted against the δ scale relative to the residual solvent signal ($CHCl_3$ δ 7.27, DMSO δ 2.50, MeOH δ 3.35, H_2O δ 4.80) using the following abbreviations: s, singlet, d, doublet, t triplet, q quartet, m multiplet, br broad, bs broad singlet, bd broad doublet, bq broad quartet.

Carbon-13 NMR spectra were recorded at 68 MHz on the JEOL, 75.5 MHz on the Bruker AC 300, at 90.5 MHz on the Bruker AM 360 and at 125.7 MHz on the Varian. The multiplicities of carbon-13 signals were elucidated using distortionless enhancement by polarisation transfer (DEPT) experiments and are indicated in parenthesis.

Two-dimensional NMR correlation experiments were obtained on the Bruker AM 360 and Varian machines.

Electrospray mass spectra were recorded on a Micromass Platform quadrupole mass analyser. Fast Atom Bombardment and Electron Impact spectra were recorded on a VG Analytical 70-250-SE normal geometry double focusing mass spectrometer.

Ultraviolet/Visible spectra were recorded on a Hewlett Packard 8452A diode array spectrophotometer.

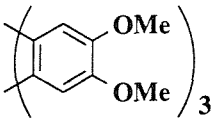
Fluorescence spectra were recorded on a Perkin-Elmer LS-3 fluorescence spectrometer.

Optical rotations were measured on an Optical Activity AA-100 polarimeter and are calculated according to the following formula: $[\alpha]_D = 100\alpha/(lc)$ where α is the observed rotation, l is the path length (0.5 dm), c is the concentration in g 100 ml^{-1}. The units of $[\alpha]_D$ are 10^{-1} deg cm^2 g^{-1}.

Microanalysis data was obtained from GlaxoWellcome, Dartford.

6.2 Experimental For Chapter Two

2, 3, 6, 7, 10, 11-Hexamethoxytriphenylene (64)



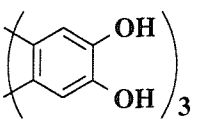
By the *p*-chloranil method of Beattie *et al*[87]

1, 2-Dimethoxybenzene **63** (10g, 72 mmol) was added to a suspension of *p*-chloranil (44.5g, 181 mmol) in sulfuric acid (70%, 140 ml) and the colour changed from yellow to dark blue. The mixture was stirred overnight then left to stand for 8 days before being poured into water. A precipitate was recovered by filtration and washed with water to give 46 g of purple solid. The crude product was suspended in chloroform (500 ml) and vigorously stirred with a solution of sodium dithionite (48 g, 276 mmol) in aq. sodium hydroxide (0.5 M, 500 ml). After 10 minutes the layers were separated, the organic layer was dried with magnesium sulfate and the solvent was removed *in vacuo*. The resulting material was recrystallised from chloroform/ethanol to give hexamethoxytriphenylene **64** as a light purple powder (3.28 g, 33%); mp 308-309°C (lit[87]. mp 314.5-316°C);
δ_H (270 MHz, $CDCl_3$): 7.71 (6 H, s, ArH), 4.12 (18 H, s, OCH_3).

By the ferric chloride method of Boden *et al*[89]

1, 2-Dimethoxybenzene **63** (15 g, 109 mmol) was added to a well stirred suspension of anhydrous ferric chloride (53 g, 327 mmol) and sulfuric acid (1.06 g, 10.9 mmol) in dichloromethane (330 ml) over a period of 50 minutes. The mixture was stirred for a further 2 hours during which time acidic fumes were evolved and a precipitate formed. The reaction mixture was filtered and the residue washed with methanol (heat and gas evolved) to give hexamethoxytriphenylene **64** as a light grey powder (11.94 g, 81%).

2, 3, 6, 7, 10, 11-Hexahydroxytriphenylene (71)



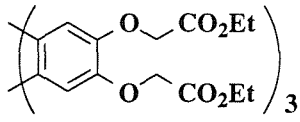
By the boron tribromide method of Beattie *et al*[87]

Boron tribromide (1.0 M in dichloromethane, 14 ml, 14 mmol) was added to a suspension of 2, 3, 6, 7, 10, 11-hexamethoxytriphenylene **64** (750 mg, 1.84 mmol) in dichloromethane (100 ml) at -78°C over a period of 10 minutes; the mixture was then allowed to reach room temperature over 18 hours under a nitrogen atmosphere. Water (5 ml) was added, the dichloromethane was removed *in vacuo* and the product recrystallised from water to give hexahydroxytriphenylene **71** as a dark green solid (586 mg, 98%); mp. > 310°C (lit.[87] >310°C);
δ_H (300 MHz, d^6-DMSO): 9.30 (6 H, bs, ArOH), 7.62 (6 H, s, ArH).

By the hydrobromic acid/acetic acid method of Piattelli *et al*[90]

A suspension of 2, 3, 6, 7, 10, 11-hexamethoxytriphenylene **64** (7.85 g, 19 mmol) in 48% hydrobromic acid (200 ml) and glacial acetic acid (200 ml) was refluxed for 17 hours under a nitrogen atmosphere to give a black solution; on cooling to room temperature a solid precipitated was observed. After removal of the solvents *in vacuo* the residue was heated in boiling water (150 ml) and cooled to room temperature. A black solid was recovered by filtration and washed well with water before being dried under vacuum in the presence of phosphorus pentoxide to give hexahydroxytriphenylene **71** as a black solid (6.32 g, quant.).

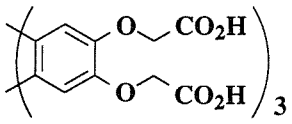
2, 3, 6, 7, 10, 11-Hexakis(ethyl 2-oxyacetate) triphenylene (72) by the method of Schiodt[91]



A mixture of 2, 3, 6, 7, 10, 11-hexahydroxytriphenylene **71** (0.5 g, 1.5 mmol), potassium carbonate (2.89 g, 20.9 mmol) and ethyl bromoacetate (1.68 g, 10.1 mmol) in dimethylformamide (40 ml) was stirred at room temperature for 65 hours under a nitrogen atmosphere. The mixture was poured into hydrochloric acid (4.0 M, 50 ml) and the precipitate recovered by filtration. Recrystallisation from ethanol gave the hexakis(ethyl ester) **72** as an off-white solid (0.93 g, 71%); mp 119-120°C (dec.); υ_{max} (Nujol)/cm^{-1}: 1748, 1621, 1511;
δ_H (300 MHz, $CDCl_3$): 7.75 (6 H, s, ArH), 4.90 (12 H, s, $ArOCH_2$), 4.32 (12 H, q, J = 7 Hz, $OC\underline{H}_2CH_3$), 1.34 (18 H, t, J = 7 Hz, CH_3);
δ_C (75.5 MHz, $CDCl_3$): 169.1, 147.4, 124.2, 108.6 (1), 66.9 (2), 61.5 (2), 14.4 (3);
MS (FAB): 840 [M^+];

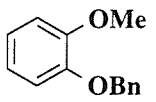
Found: C, 59.60; H, 6.00. $C_{42}H_{48}O_{18}$ requires C, 60.00; H, 5.75 %.

2, 3, 6, 7, 10, 11-Hexakis(oxyacetic acid) triphenylene (59) by the method of Schiodt[91]



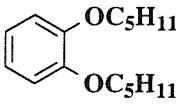
A mixture of 2, 3, 6, 7, 10, 11-hexakis(ethyl 2-oxyacetate) triphenylene **72** (400 mg, 0.48 mmol) and methanesulfonic acid (71 mg, 0.74 mmol) in formic acid (7 ml) was refluxed for 2 hours under a nitrogen atmosphere; a white precipitate was formed. The mixture was cooled, water was added (10 ml) and the precipitate was recovered by filtration then washed with water, ethanol and diethyl ether. Drying under vacuum gave the hexa-acid **59** as an off-white solid (312 mg, 98%); mp 233-234°C (dec.); υ_{max} (Nujol)/cm^{-1}: 1738, 1619, 1521;
δ_H (300 MHz, d^6-DMSO): 13.25 (6 H, s br, CO_2H), 7.99 (6 H, s, ArH), 5.00 (12 H, s, OCH_2);
δ_C (75.5 MHz, d^6-DMSO): 170.5, 147.7, 123.5, 108.1 (1), 65.9 (2);
MS (FAB): 672 [M^+];
Found: C, 50.14; H, 4.16. $C_{30}H_{24}O_{18}.3H_2O$ requires C, 49.59; H, 4.16 %.

2-Benzyloxyanisole (81) based on the method of Mackenzie et al[97]



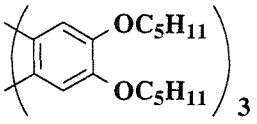
A mixture of 2-(benzyloxy)phenol **80** (0.5 g, 2.5 mmol), methyl iodide (3.54 g, 24.9 mmol) and potassium carbonate (1.73 g, 12.5 mmol) in acetone (20 ml) was refluxed for 17 hours under a calcium chloride drying tube. The mixture was cooled, filtered and the acetone removed *in vacuo*. The residue was taken into ethyl acetate (20 ml) and was washed with water (2 x 10 ml) and brine (1 x 10 ml) then dried with magnesium sulfate before removing the solvent *in vacuo* to give 2-benzyloxyanisole **81** as a yellow oil (0.53 g, quant.);
R_F = 0.4 (10% ethyl acetate/hexane);
δ_H (270 MHz, $CDCl_3$): 7.49-7.32 (5 H, m, ArH), 6.96-6.84 (4 H, m, ArH), 5.18 (2 H, s, OCH_2), 3.91 (3 H, s, OCH_3);
δ_C (75.5 MHz, $CDCl_3$): 149.9, 148.4, 137.4, 128.7 (1), 128.0 (1), 127.4 (1), 121.6 (1), 121.0 (1), 114.4 (1), 112.1 (1), 71.2 (2), 56.1 (3);
Known compound: mp 54-55°C[114]

1, 2-Dipentyloxybenzene (83) based on the method of Boden *et al*[89]



A mixture of catechol **77** (5 g, 45 mmol), pentyl bromide (25.7 g, 170 mmol) and potassium carbonate (28.2 g, 204 mmol) in ethanol (250 ml) was refluxed for 17 hours under a nitrogen atmosphere. The mixture was cooled, filtered through Celite and the ethanol removed *in vacuo*. The residue was taken into ethyl acetate (50 ml), washed with water (3 x 25 ml) and the combined aqueous layers back-extracted with ethyl acetate (2 x 25 ml). The combined organic layers were dried with magnesium sulfate and the solvent was removed *in vacuo* to give a yellow oil. Filtration through silica washing with 10% ethyl acetate/petrol and removal of the solvents *in vacuo* gave dipentyloxybenzene **83** as an almost colourless oil (10.88 g, 96%); R_F (20% ethyl acetate/petrol) 0.6;
υ_{max} (Thin film)/cm^{-1}: 2931, 2870, 1592, 1504;
δ_H (300 MHz, $CDCl_3$): 6.91 (4 H, s, ArH), 4.01 (4 H, t, J = 7 Hz, OCH_2) 1.84 (4 H, tt, J = 7, 7 Hz, $OCH_2C\underline{H}_2$), 1.53-1.33 (8 H, m, $(CH_2)_2$), 0.94 (6 H, t, J = 7 Hz, CH_3);
δ_C (75.5 MHz, $CDCl_3$): 149.2, 121.0 (1), 114.0 (1), 69.2 (2), 29.0 (2), 28.2 (2), 22.5 (2), 14.1 (3);
Known compound: bp[160] 225°C[115]

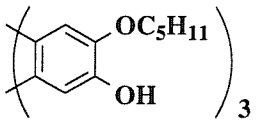
2, 3, 6, 7, 10, 11-Hexapentyloxytriphenylene (84) based on the method of Boden et al[89]



1, 2-Dipentyloxybenzene **83** (5 g, 20 mmol) was added over a ten minute period to a vigorously stirred suspension of anhydrous ferric chloride (9.72 g, 60 mmol) and sulfuric acid (0.2 g, 2 mmol) in dichloromethane (75 ml) cooled in ice. The mixture was stirred for 45 minutes at room temperature (acidic fumes were evolved) before being quenched by the addition of methanol (75 ml). The solvents were removed *in vacuo*, the residue was suspended in water and the desired product recovered by filtration. Recrystallisation from ethanol gave hexapentyloxytriphenylene **84** as an off-white solid (3.28 g, 66%); mp (cryst-meso phase) 60°C, (meso-liquid phase) 110°C (lit.[116] 69°C, 122°C respectively); υ_{max} (Nujol)/cm^{-1}: 1617, 1518;
δ_H (300 MHz, $CDCl_3$): 7.84 (6 H, s, ArH), 4.24 (12 H, t, J = 7 Hz, OCH_2), 1.96 (12 H, tt, J = 7, 7 Hz, $OCH_2C\underline{H}_2$), 1.63-1.40 (24 H, m, $(CH_2)_2$), 0.99 (18 H, t, J = 7 Hz, CH_3);

δ_C (75.5 MHz, $CDCl_3$): 148.9, 123.6, 107.3 (1), 69.7 (2), 29.1 (2), 28.4 (2), 22.6 (2), 14.1 (3);
IR and ^1H data in accordance with literature.[116]

2, 6, 10-Trihydroxy-3, 7, 11-tripentyloxytriphenylene (86) and 2, 6, 11-Trihydroxy-3, 7, 10-tripentyloxytriphenylene (87) based on the method of Closs *et al.*[99]



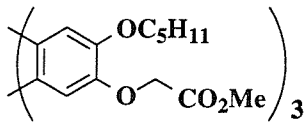
+ non C_3-symmetric isomer

9-Bromo-9-borabicyclo[3.3.1]nonane (9 ml of a 1.0 M solution in dichloromethane) was pre-cooled to -30°C and added to a solution of 2, 3, 6, 7, 10, 11-hexapentyloxytriphenylene **84** (1.5 g, 2.0 mmol) in dichloromethane (15 ml) at -30°C. The mixture was stirred at -30°C for 4.5 hours under an argon atmosphere and then cannulated directly into a vigorously stirred mixture of sat. aq. sodium bicarbonate solution (25 ml) and tetrahydrofuran (50 ml) at room temperature. The organic solvents were removed *in vacuo* and the aqueous residue extracted with dichloromethane (3 x 25 ml). The combined organic extracts were dried with magnesium sulfate and the solvent was removed *in vacuo* to give a yellow oil. Flash column chromatography eluting with 60% dichloromethane/petrol then dichloromethane gave the C_3-symmetric isomer **86** (596 mg, 55%) and the non C_3-symmetric isomer **87** (373 mg, 35%).
C_3-symmetric isomer:
mp 157-158°C (MeOH) (lit.[99] mp 140°C);
R_F (60% dichloromethane/petrol) 0.5; υ_{max} (Nujol)/cm^{-1}: 3540, 3417, 1632, 1592;
δ_H (270 MHz, $CDCl_3$): 7.92 (3 H, s, ArH), 7.78 (3 H, s, ArH), 5.92 (3 H, bs, OH), 4.25 (6 H, t, J = 7 Hz, OCH_2), 1.94 (6 H, tt, J = 7, 7 Hz $OCH_2C\underline{H}_2$), 1.61-1.39 (12 H, m, $(CH_2)_2$), 0.99 (9 H, t, J = 7 Hz, CH_3);
δ_C (75.5 MHz, $CDCl_3$): 145.9, 145.4, 124.0, 123.0, 107.1 (1), 104.6 (1), 69.1 (2), 29.1 (2), 28.4 (2), 22.7 (2), 14.2 (3).
NMR and IR data are in accordance with the literature.[99]

Non-C_3-symmetric isomer:
mp 119-120°C (MeOH) (lit.[99] mp 146°C);
R_F (60% dichloromethane/petrol) 0.2; υ_{max} (Nujol)/cm^{-1}: 3550, 3384, 1630, 1514;
δ_H (270 MHz, $CDCl_3$): 7.94, 7.93, 7.77, 7.70, 7.69 (6 H, 5 x s, ArH), 5.90 (3 H, br, OH), 4.27, 4.26, 4.25 (6 H, 3 x t, J = 6, 6, 7 Hz, OCH_2), 2.01-1.84 (6 H, m, $OCH_2C\underline{H}_2$), 1.65-1.35 (12 H, m, $(CH_2)_2$), 1.00, 0.99 (9 H, t x 2, J = 7, 7, CH_3);
IR data in accordance with literature.

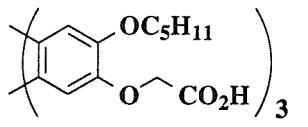
Literature NMR data shows only two OCH_2 triplets at δ 4.26 and δ 4.23 and only one CH_3 triplet at δ 0.96 (recorded at 200 MHz in $CDCl_3$).[99]

2, 6, 10-Tris(methyl 2-oxyacetate)-3, 7, 11-tripentyloxytriphenylene (88)



A mixture of 2, 6, 10-trihydroxy-3, 7, 11-tripentyloxytriphenylene **86** (1.80 g, 3.4 mmol), methyl bromoacetate (2.01 g, 13.1 mmol) and potassium carbonate (3.63 g, 26.3 mmol) in dimethylformamide (30 ml) was stirred at room temperature for 40 hours under a nitrogen atmosphere. The mixture was poured into hydrochloric acid (2.0 M, 100 ml) and a light yellow solid recovered by filtration. Recrystallisation from ethanol gave the tris(methyl ester) **88** as a light brown solid (2.08 g, 82%); mp 152-153°C;
υ_{max} (Nujol)/cm^{-1}: 1752, 1618, 1511;
δ_H (300 MHz, $CDCl_3$): 7.94 (3 H, s, ArH), 7.79 (3 H, s, ArH), 4.88 (6 H, s, $OC\underline{H}_2CO$), 4.25 (6 H, t, J = 7 Hz, $OC\underline{H}_2CH_2$), 3.85 (9 H, s, CO_2CH_3), 1.98 (6 H, tt, J = 7, 7 Hz, $OCH_2C\underline{H}_2$), 1.66-1.41 (12 H, m, $(CH_2)_2$), 1.00 (9 H, t, J = 7 Hz, $CH_2C\underline{H}_3$);
δ_C (75.5 MHz, $CDCl_3$): 169.8, 149.6, 147.1, 125.5, 122.8, 111.1 (1), 106.3 (1), 69.1 (2), 68.0 (2), 52.2 (3), 29.0 (2), 28.3 (2), 22.5 (2), 14.1 (3);
MS (ES): 774 $[M+Na]^+$, 1149 $[3M+2Na]^+$, 1524 $[2M+Na]^+$;
Found: C, 67.50; H, 7.34. $C_{42}H_{54}O_{12}$ requires C, 67.18; H, 7.25 %.

2, 6, 10-Tripentyloxy-3, 7, 11-tris(oxyacetic acid)triphenylene (89)

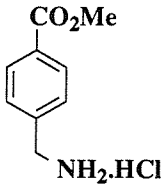


A suspension of 2, 6, 10-tri(methyl 2-oxyacetate)-3, 7, 11-tripentyloxytriphenylene **88** (145 mg, 0.19 mmol) and methanesulfonic acid (14 mg, 0.15 mmol) in formic acid (2 ml) was refluxed for 4.5 hours; the starting material dissolved on heating and after approximately 1 hour a precipitate began to form. The mixture was cooled, water was added (5 ml) and a grey solid was recovered by filtration, washed with water, ethanol and diethyl ether then recrystallised from tetrahydrofuran/water to give the tri-acid **89** as a grey solid (114 mg, 83%); mp 246-247°C (dec.); υ_{max} (Nujol)/cm^{-1}: 1739, 1619, 1518;

δ_H (300 MHz, d^6-DMSO): 7.93 (3 H, s, ArH), 7.92 (3 H, s, ArH), 4.99 (6 H, s, $OC\underline{H}_2CO$), 4.25 (6 H, t, J = 6 Hz, $OC\underline{H}_2CH_2$), 1.85 (6 H, tt, J = 7, 7 Hz, $OCH_2C\underline{H}_2$), 1.56-1.36 (12 H, m, $(CH_2)_2$), 0.94 (9 H, t, J = 7 Hz, CH_3);
δ_C (75.5 MHz, d^6-DMSO): 170.4, 148.3, 147.3, 123.3, 122.4 , 107.2 (1), 106.8 (1), 68.6 (2), 65.7 (2), 28.5 (2), 27.8 (2), 21.9 (2), 13.9 (3);
MS (ES): 821 $[M+TFA-H]^-$;
Found: C, 62.23; H, 7.15. $C_{39}H_{48}O_{12}.2H_2O$ requires C, 62.89; H, 7.04 %.

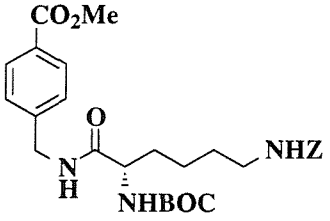
6.3 Experimental For Chapter Three

Methyl 4-(aminomethyl)benzoate (93), HCl salt by the method of Nair *et al*[100]



Gaseous hydrogen chloride was bubbled through a suspension of 4-(aminomethyl)benzoic acid **92** (10 g, 66 mmol) in methanol (220 ml) until a clear solution was obtained (1 hour); which was refluxed for 18 hours under a nitrogen atmosphere. The methanol was removed *in vacuo* and diethyl ether (200 ml) added to the residue. A white solid was recovered by filtration, washed with diethyl ether and dried under vacuum. Recrystallisation from methanol gave methyl ester **93** as white needles (11.29 g, 85%); mp 248-248.5°C (lit.[100] 225°C); υ_{max} (Nujol)/cm^{-1}: 1726, 1598, 1285;
δ_H (300 MHz, d^6-DMSO): 8.65 (3 H, br, NH_3^+), 7.99 (2 H, d, J = 8 Hz, ArH), 7.66 (2 H, d, J = 8 Hz, ArH), 4.11 (2 H, bq, J = 6 Hz, CH_2), 3.87 (3 H, s, CH_3);
δ_C (75.5 MHz, d^6-DMSO): 165.9, 139.4, 129.4, 129.21 (1), 129.18 (1), 52.2 (3), 41.6 (2);
MS (ES): 166 $[M+H]^+$.

Methyl 4-({[(2S)-2-*N*-BOC-amino-6-*N*-Z-aminohexanoyl]amino}methyl)benzoate (95)



EDC (1.90 g, 9.9 mmol) was added in three portions to a solution of methyl 4-(aminomethyl)benzoate, hydrochloride salt **93** (2.0 g, 9.9 mmol), α-N-*tert*-butyloxycarbonyl-ε-N-carboxybenzyl lysine **94** (3.77 g, 9.9 mmol), HOBt (1.52 g, 9.9 mmol) and DIPEA (1.28 g, 9.9 mmol) in dimethylformamide (90 ml) at 5°C then stirred at room temperature for 16 hours under a nitrogen atmosphere. The mixture was taken into ethyl acetate (100 ml) and washed with hydrochloric acid (2.0 M, 2 x 50 ml), sat. aq. sodium bicarbonate solution (2 x 50 ml) and brine (1 x 50 ml) then dried with magnesium sulfate and the solvent removed *in vacuo*. Recrystallisation from acetone/diethyl ether gave the dipeptide **95** as white fluffy

crystals (4.08 g, 78%); mp 123-123.5°C; υ_{max} (Nujol)/cm^{-1}: 3313, 1724, 1682, 1657, 1538, 1276;

δ_H (300 MHz, $CDCl_3$): 7.96 (2 H, d, J = 8 Hz, ArH), 7.35-7.28 (7 H, m, ArH), 6.91 (1 H, br, NH), 5.30 (1 H, d, J = 8 Hz, NHBOC), 5.08 (2 H, s, OCH_2Ph), 4.97 (1 H, t, J = 6 Hz, NH), 4.46 (2 H, d, J = 5 Hz, $ArCH_2NH$), 4.11 (1 H, br, CH(NHBOC)), 3.90 (3 H, s, CH_3), 3.16 (2 H, t, J = 6 Hz, CH_2NHZ), 1.90 (2 H, m, CH_2), 1.72-1.30 (13 H, m, CH_2 x 2, $C(CH_3)_3$);

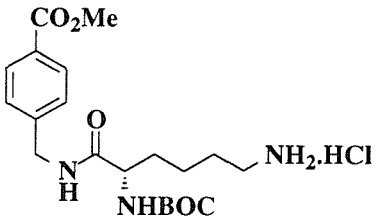
δ_C (75.5 MHz, $CDCl_3$): 172.4, 166.8, 156.7, 155.8, 143.4, 136.5, 129.9 (1), 129.2, 128.5 (1), 128.11 (1),128.09 (1), 127.3 (1), 80.2, 66.7 (2), 54.5 (1), 52.1 (3), 42.9 (2), 40.3 (2), 31.5 (2), 29.5 (2), 28.3 (3), 22.5 (2);

MS (FAB) 528 [M+H];

Found: C, 63.59; H, 6.89; N, 7.87. $C_{28}H_{37}N_3O_7$ requires C, 63.74; H, 7.07; N, 7.96 %;

$[\alpha]_D^{20}$ -8.4 ± 0.2 (c = 1.0, $CHCl_3$).

Methyl 4-({[(2S)-2-*N*-BOC-amino-6-aminohexanoyl]amino}methyl)benzoate, hydrochloride salt (90)



A mixture of Z-protected dipeptide **95** (7.0 g, 13.3 mmol) and 10% palladium on carbon (500 mg) in methanol (140 ml) was stirred at room temperature for 19 hours under atmospheric pressure of hydrogen. The catalyst was removed by filtration through Celite and the volume of solvent reduced *in vacuo*. A solution of hydrogen chloride in diethyl ether was added (1.0 M, 14 ml, 14.0 mmol) and after 10 minutes the solvents were removed *in vacuo*. The resulting solid was triturated with ether to give the hydrochloride salt **90** as a white powdery solid (5.61 g, 98%); mp 139-140°C;

υ_{max} (CH_2Cl_2)/cm^{-1}: 1715, 1670;

δ_H (300 MHz, d^6-DMSO): 8.55 (1 H, t, J = 6 Hz, NH), 7.89 (5 H, d, J = 8 Hz, ArH, br, NH_3^+), 7.39 (2 H, d, J = 8 Hz, ArH), 6.97 (1 H, d, J = 8 Hz, NH), 4.35 (2 H, d, J = 6 Hz, $ArCH_2NH$), 3.89 (1 H, br, CH(NHBOC)), 3.84 (3 H, s, CH_3), 2.72 (2 H, br, $CH_2NH_3^+$), 1.60-1.50 (2 H, m, CH_2), 1.45-1.20 (13 H, m, CH_2 x 2, $C(CH_3)_3$);

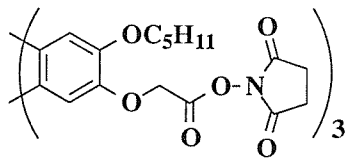
δ_C (75.5 MHz, d^6-DMSO): 172.5, 166.1, 155.4, 145.3, 129.0 (1), 127.9, 127.1 (1), 78.0, 54.4 (1), 52.0 (3), 41.7 (2), 38.5 (2), 30.9 (2), 28.1 (3), 26.4 (2), 22.4 (2);

MS (ES): 394 $[M+H]^+$;

Found: C, 55.57; H, 7.25; N, 9.68. $C_{20}H_{31}N_3O_5$ requires C, 55.87; H, 7.27; N, 9.77 %;

$[\alpha]_D^{20}$ -2.4 ± 0.2 (c=1.0, $CHCl_3$).

2, 6, 10-Tripentyloxy-3, 7, 11-tris(oxyacetic acid N-hydroxysuccinimide ester)triphenylene (96) based on the method of Anderson *et al*[101]



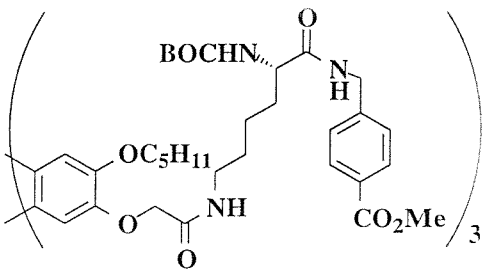
DCC (0.815 g, 3.95 mmol) in tetrahydrofuran (3 ml) was added to a solution of 2, 6, 10-tris(oxyacetic acid)-3, 7, 11-tripentyloxytriphenylene **89** (0.70 g, 0.99 mmol) and N-hydroxysuccinimide (0.375 g, 3.26 mmol) in tetrahydrofuran (7 ml) at 5°C over a five minute period. The reaction was stirred at 5°C for 1 hour then at room temperature for 19 hours under a nitrogen atmosphere. The solution was cooled in ice, filtered through Celite and the solvent was removed *in vacuo* to give the activated ester **96** as a white solid which was used directly (1.40 g, > quantitative yield). A sample was recrystallised from acetone/ether for analysis;

mp 159-160°C; υ_{max} (Nujol)/cm^{-1}: 1825, 1784, 1737, 1614, 1514;

δ_H (300 MHz, $CDCl_3$): 7.90 (3 H, s, ArH), 7.75 (3 H, s, ArH), 5.22 (6 H, s, OCH_2CO), 4.27 (6 H, t, J = 7 Hz, $OC\underline{H}_2CH_2$), 2.84 (12 H, s, CH_2CON), 1.97 (6 H, tt, J = 7, 7 Hz, $OCH_2C\underline{H}_2$), 1.68-1.40 (12 H, m, $(CH_2)_2$), 0.99 (9 H, t, J = 7 Hz, CH_3);

δ_C (75.5 MHz, $CDCl_3$): 168.7, 165.1, 149.6, 146.3, 126.1, 122.5, 111.7 (1), 106.3 (1), 69.0 (2), 65.9 (2), 29.0 (2), 28.3 (2), 25.6 (2), 22.5 (2), 14.1 (3).

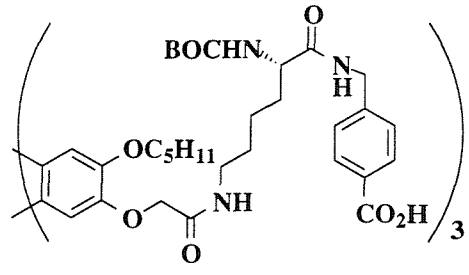
2, 6, 10-Tripentyloxy-3, 7, 11-tris(methyl 4-({[(2S)-2-*N*-BOC-amino-6-*N*-(2-oxyacetamido)hexanoyl]amino}methyl)benzoate)triphenylene (91) based on the method of Anderson *et al*[101]



A mixture of the crude tris(activated ester) **96** (theoretical 1.03 g, 0.99 mmol), the side-wall/rim hydrochloride salt **90** (1.40 g, 3.26 mmol) and DIPEA (570 µl, 3.27 mmol) in tetrahydrofuran (15 ml) was stirred at room temperature for 3 hours under a nitrogen atmosphere. The tetrahydrofuran was removed *in vacuo*, water (40 ml) was added and an

off-white solid was recovered by filtration. Flash column chromatography eluting with 0-6% methanol/dichloromethane and recrystallisation from ethanol/dichloromethane gave the protected precursor **91** as a white powder (1.41 g, 78% over 2 steps); mp 162-163°C;
υ_{max} (Nujol)/cm^{-1}: 3284, 1719, 1655;
δ_H (300 MHz, d^6-DMSO): 8.41 (3 H, t, *J* = 6 Hz, NH), 8.11 (3 H, s, ArH triphen.), 8.05-7.93 (6 H, m, ArH triphen., NH), 7.87 (6 H, d, *J* = 8 Hz, ArH rim), 7.36 (6 H, d, *J* = 8 Hz, ArH rim), 6.93 (3 H, d, *J* = 7 Hz, NHBOC), 4.74 (6 H, s, OCH_2CO), 4.33 (6 H, d, *J* =6 Hz, $ArCH_2NH$), 4.27 (6 H, t, *J* = 6 Hz, OCH_2CH_2), 3.90 (3 H, dt, *J* = 7, 6 Hz, CH(NHBOC)), 3.82 (9 H, s, CO_2CH_3), 3.18 (6 H, br, $NHCH_2CH_2$), 1.86 (6 H, tt, *J* = 7, 7 Hz, OCH_2CH_2), 1.66-1.20 (57 H, m, CH_2 x 5, $C(CH_3)_3$)), 0.93 (9 H, t, *J* = 7 Hz, CH_2CH_3);
δ_C (75.5 MHz, $CDCl_3$): 172.4, 168.8, 167.0, 156.1, 149.0, 146.9, 143.6 130.0 (1), 129.3, 127.3 (1), 124.8, 122.7, 108.4 (1), 105.6 (1), 80.3, 69.3 (2), 69.0 (2), 54.6 (1), 52.3 (3), 43.1 (2), 38.8 (2), 34.1 (2), 31.9 (2), 29.4 (2), 28.5 (3), 25.8 (2), 25.1 (2), 22.9 (2), 14.3 (3);
MS (ES): 940 $[M+2Na]^{2+}$;
Found: C, 64.37; H, 7.29; N, 6.29. $C_{99}H_{135}N_9O_{24}$ requires C, 64.79; H, 7.41; N, 6.87 %;
$[\alpha]_D^{20}$ -10.0 ± 0.2 (c=1.0, $CHCl_3$).

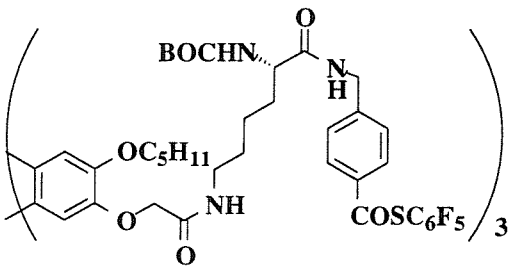
2, 6, 10-Tripentyloxy-3, 7, 11-tris(4-({[(2S)-2-*N*-BOC-amino-6-*N*-(2-oxyacetamido)hexanoyl]amino}methyl)benzoic acid)triphenylene (97)



A suspension of the tri-ester **91** (1.0 g, 0.5 mmol) in 1, 4-dioxane (25 ml) and lithium hydroxide solution (1.0 M, 25 ml, 25 mmol) was stirred at 50°C for three hours under a nitrogen atmosphere giving a clear solution. The mixture was acidified to pH 1 with hydrochloric acid (2.0 M), a solid was recovered by filtration then washed with water, ethanol and ether to give the tri-acid **97** as an off-white solid (0.90 g, 92%); mp 163-165°C (dec.);
υ_{max} (Nujol)/cm^{-1}: 3328, 1712, 1659, 1518;
δ_H (300 MHz, d^6-DMSO): 12.87 (3 H, bs, CO_2H), 8.41 (3 H, t, *J* = 6 Hz, NH), 8.12 (3 H, s, ArH triphen.), 8.05-7.95 (6 H, m, ArH triphen., NH), 7.86 (6 H, d, *J* = 8 Hz, ArH rim), 7.34 (6 H, d, *J* = 8 Hz, ArH rim), 6.93 (3 H, d, *J* = 8 Hz, NHBOC), 4.75 (6 H, s, OCH_2CO), 4.33 (6 H, d, *J* = 6 Hz, $ArCH_2NH$), 4.27 (6 H, t, *J* = 6 Hz, OCH_2CH_2), 3.90 (3 H, dt, *J* = 8, 5 Hz,

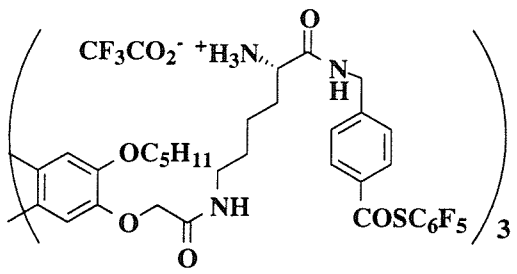
C<u>H</u>(NHBOC)), 3.19 (6 H, br, CONHC<u>H</u>$_2$CH$_2$), 187 (6 H, br, OCH$_2$C<u>H</u>$_2$), 1.60-1.30 (57 H, m, CH$_2$ x 5, C(CH$_3$)$_3$), 0.93 (9 H, t, J = 7 Hz, CH$_3$);
MS (ES): 1693 $[M\text{-}BOC+H]^+$, 1815 $[M + Na]^+$.

Typical procedure for forming 2, 6, 10-tripentyloxy-3, 7, 11-tris(pentafluorophenyl 4-({[(2S)-2-*N*-BOC-amino-6-*N*-(2-oxyacetamido)hexanoyl]amino}methyl)benzoate) triphenylene (98)



A solution of DCC (46 mg, 223 μmol) in dimethylformamide (1 ml) was added to a solution of tri-acid **97** (100 mg, 56 μmol) and pentafluorothiophenol (45 mg, 225 μmol) in dimethylformamide (1 ml) at 5°C. The mixture was stirred at 5°C for 1 hour then at room temperature for 42 hours. Additional DCC (24 mg, 116 μmol) in dimethylformamide (0.5 ml) and pentafluorothiophenol (22 mg, 110 μmol) were added after 18 hours. The mixture was filtered through Celite and the solvent was removed *in vacuo* to give the tris(pentafluorothiophenol ester) as a yellow gum (198 mg, theory 130 mg) which was taken on directly.

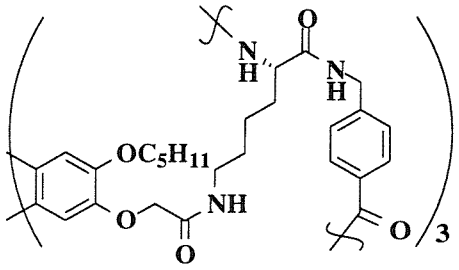
Typical procedure for cleaving *tert*-butyloxycarbonyl groups to give 2, 6, 10-tripentyloxy-3, 7, 11-tris(pentafluorophenyl 4-({[(2S)-2-amino-6-*N*-(2-oxyacetamido) hexanoyl]amino}methyl)benzoate)triphenylene, tris(trifluoroacetic acid) salt (99)



A solution of tris(pentafluorophenol ester) **98** (198 mg, from above) in 50% trifluoroacetic acid/dichloromethane (1 ml) was stirred at room temperature for 1 hour under a nitrogen atmosphere. The solvents were removed *in vacuo* to give the tris(trifluoroacetic acid) salt as

a yellow oil which was triturated with ether to give a white solid (155 mg, theory 133 mg) and was taken on directly.

Typical procedure for cyclisation to give tripentyloxy macrocycles (100)



A solution of tris(trifluoroacetic acid) salt **99** (155 mg, from above) in tetrahydrofuran (5 ml) was added to a solution of DIPEA (489 µl, 2.81 mmol) in tetrahydrofuran (50 ml) temperature over a period of 8 hours; the mixture was stirred at room temperature for a further 15 hours under a nitrogen atmosphere. The tetrahydrofuran was removed *in vacuo*, the residue was taken into dichloromethane (15 ml) and was washed with hydrochloric acid (2.0 M, 2 x 15 ml). The aqueous washes were back-extracted with dichloromethane (2 x 10 ml), the organic layers were combined, dried with magnesium sulfate and the solvent was removed *in vacuo* to give a white gum (120 mg). Flash column chromatography eluting with 0-8% methanol/dichloromethane gave the mixture of macrocycles **100** (ratio 2.3:1 by NMR) as a white solid (32 mg, 40% over three steps); R_F (10% methanol/dichloromethane) 0.4;
The two isomers could be separated by semi-preparative HPLC (see below).
Spectral data for major isomer:
υ_{max} ($CDCl_3$)/cm^{-1}: 3690, 3365, 2930, 1667, 1602, 1508, 1426;
δ_H (500 MHz, d^6-DMSO): 8.18 (3 H, s, ArH triphen.), 8.03 (6 H, br, ArH triphen., $ArCH_2N\underline{H}$), 7.97 (3 H, br, $N\underline{H}CH_2CH_2$), 7.92 (3 H, d, $CH(N\underline{H})$, J = 8 Hz), 7.46 (6 H, d, J = 8 Hz, ArH rim), 6.92 (6 H, d, J = 8 Hz, ArH rim), 4.80 (3 H, d, J = 14 Hz, $OC\underline{H}_AH_BCO$), 4.75 (3 H, d, J = 14 Hz, $OCH_A\underline{H}_BCO$), 4.39-4.27 (9 H, m, $C\underline{H}(NH)$, $OC\underline{H}_2CH_2$), 4.05 (3 H, dd, J = 14, 8 Hz, $ArC\underline{H}_AH_BNH$), 3.74 (3 H, bd, J = 14 Hz, $ArCH_A\underline{H}_BNH$), 3.35 (3 H, m, $NHC\underline{H}_AH_BCH_2$)*, 3.12 (3 H, m, $NHCH_A\underline{H}_BCH_2$), 1.89 (6 H, m, $OCH_2C\underline{H}_2$), 1.71 (6 H, br, $CH(NH)C\underline{H}_2$), 1.55 (9 H, m, $O(CH_2)_2C\underline{H}_2$, $NHCH_2C\underline{H}_AH_B$), 1.42 (9 H, m, $C\underline{H}_2CH_3$, $NHCH_2CH_A\underline{H}_B$), 1.24 (6 H, br, $NH(CH_2)_2C\underline{H}_2$), 0.95 (9 H, t, J = 8 Hz, CH_3);
* partially obscured by H_2O peak;
δ_C (125.7 MHz, d^6-DMSO): 127 (1), 126 (1), 108 (1), 107 (1), 69 (2), 68 (2), 53 (1), 42 (2), 38 (2), 31 (2), 29 (2), 28 (2), 22 (2), 22 (2), 22 (2), 14 (3);
All ^{13}C chemical shift values taken from ^1H-^{13}C correlation;
MS (ES): 754 $[M+2Cl]^{2-}$, 1473 $[M+Cl]^-$;
λ_{max} (CH_2Cl_2, 10^{-5} M)/nm: 235, 270, 278, 308;

Fluorescence (CH_2Cl_2, 10^{-5} M)/nm: λ_{ex} 230, λ_{em} 395; λ_{ex} 290, λ_{em} 387; λ_{ex} 310, λ_{em} 389;
Satisfactory microanalysis data could not be obtained.
$[\alpha]_D^{17}$ +3.5 ± 0.2 (c=0.25, 15% CH_3OH/CH_2Cl_2);

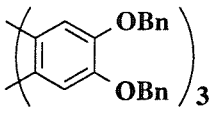
Spectral data for minor isomer:
υ_{max} ($CDCl_3$)/cm^{-1}: 3692, 3413, 3307, 2928, 2861, 1666, 1642, 1602, 1524, 1427;
δ_H (500 MHz, d^6-DMSO): 8.34 (3 H, s, ArH triphen.), 8.11 (3 H, br, $ArCH_2N\underline{H}$), 8.08 (3 H, s, ArH triphen.), 7.93 (3 H, d, J = 8 Hz, $CH(N\underline{H})$), 7.90 (3 H, br, $N\underline{H}CH_2CH_2$), 7.50 (6 H, d, J = 8 Hz, ArH rim), 6.88 (6 H, d, J = 8 Hz, ArH rim), 4.95 (3 H, d, J = 16 Hz, $OC\underline{H}_AH_BCO$), 4.71 (3 H, d, J = 16 Hz, $OCH_A\underline{H}_BCO$), 4.40-4.26 (6 H, m, $C\underline{H}(NH)$, $OC\underline{H}_AH_BCH_2$), 4.25-4.14 (6 H, m, $OCH_A\underline{H}_BCH_2$, $ArC\underline{H}_AH_BNH$), 3.78 (3 H, d, J = 14 Hz, $ArCH_A\underline{H}_BNH$), 3.30 (3 H, m, $NHC\underline{H}_AH_BCH_2$)*, 3.16 (3 H, br, $NHCH_A\underline{H}_BCH_2$), 1.85 (6 H, br, $OCH_2C\underline{H}_2$), 1.79-1.62 (6 H, br, $CH(NH)C\underline{H}_2$), 1.48 (12 H, br, $O(CH_2)_2C\underline{H}_2$, $NHCH_2C\underline{H}_2$), 1.39 (6 H, m, $C\underline{H}_2CH_3$), 1.24 (6 H, br, $NH(CH_2)_2C\underline{H}_2$), 0.92 (9 H, t, J = 8 Hz, CH_3);
* Obscured by H_2O peak, chemical shift value taken from ^1H-^1H correlation;
δ_C (125.7 MHz, d^6-DMSO): 127 (1), 126 (1), 111 (1), 107 (1), 71 (2), 69 (2), 53 (1), 42 (2), 38 (2), 30 (2), 29 (2), 28 (2), 22 (2), 22 (2), 22 (2), 14 (3);
All ^{13}C chemical shift values taken from ^1H-^{13}C correlation;
MS (ES): 754 $[M+2Cl]^{2-}$, 1473 $[M+Cl]^-$;
Satisfactory microanalysis data could not be obtained.
$[\alpha]_D^{18}$ +80.5 ± 0.2 (c=0.25, 15% CH_3OH/CH_2Cl_2);

HPLC separation of macrocycle 100 isomers

The macrocycles **100** were separated by semi-preparative HPLC injecting 1 mg of mixture (in 50 µl of DMSO) at a time and cutting the fractions by hand to give the two isomers and a small amount of mixed material which was recycled. The initial amount of macrocycle mixture was 60 mg, recovery was 21 mg for the major isomer and 10 mg for the minor isomer.
Instrumentation: Shimadzu LC-6A pump, SPD-6A UV detector, SCL-6B system controller.
Column: Supelcosil ABZ+ Plus 25 cm x 10 mm containing base deactivated silica, 5 µm pore size.
Mobile phase: 65% acetonitrile/water.
Flow rate: 5 ml/min.
Detection wavelength: 230 nm.

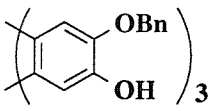
6.4 Experimental For Chapter Four

2, 3, 6, 7, 10, 11-Hexabenzyloxytriphenylene (102)



A mixture of 2, 3, 6, 7, 10, 11-hexahydroxytriphenylene **71** (9.45 g, 25 mmol), benzyl bromide (32.5 g, 190 mmol) and anhydrous potassium carbonate (55 g, 398 mmol) in dimethylformamide (230 ml) was stirred at room temperature for 20 hours under a nitrogen atmosphere. The mixture was poured into hydrochloric acid (2.0 M, 500 ml), a light brown solid was recovered by filtration and washed with water before being recrystallised from dichloromethane/ether to give the hexabenzyloxytriphenylene **102** as an off-white solid (19.82 g, 92%); mp 196-196.5°C; υ_{max} (Nujol)/cm^{-1}: 1616, 1509;
δ_H (300 MHz, $CDCl_3$): 7.69 (6 H, s, ArH triphen.), 7.57 (12 H, d, J = 7 Hz, ArH benzyl), 7.43 (12 H, dd, J = 7, 7 Hz, ArH benzyl), 7.34 (6 H, t, J = 7 Hz, ArH benzyl), 5.31 (12 H, s, OCH_2);
δ_C (75.5 MHz, $CDCl_3$): 148.5, 137.4, 128.7 (1), 128.0 (1), 127.4 (1), 123.6, 108.1 (1), 71.6 (2);
MS (ES): 865 $[M+H]^+$;
Found: C, 83.12; H, 5.55. $C_{60}H_{48}O_6$ requires C, 83.31; H, 5.59 %;

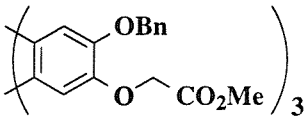
2, 6, 10-Tribenzyloxy-3, 7, 11-trihydroxytriphenylene (103)



9-Bromo-9-borabicyclo[3.3.1]nonane (8.3 ml of a 1.0 M solution in dichloromethane) was pre-cooled to -78°C and added by cannula to a solution of 2, 3, 6, 7, 10, 11-hexabenzyloxytriphenylene **102** (2.0 g, 2.3 mmol) in dichloromethane (36 ml) at -78°C. The reaction was stirred at -78°C for 40 minutes under an argon atmosphere and then cannulated directly into a vigorously stirred mixture of sat. aq. sodium bicarbonate solution (60 ml) and dichloromethane (60 ml). The aqueous phase was extracted with dichloromethane (2 x 50 ml), the combined organic extracts were shaken with brine (1 x 50 ml), dried with magnesium sulfate and the solvent was removed *in vacuo* to give an orange gum (3.9 g). Flash column chromatography eluting with dichloromethane gave the C_3-symmetric triphenylene **103** as a light brown solid (0.67 g, 49%); mp 221°C (dec.);

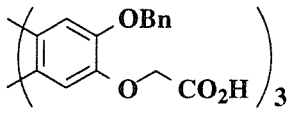
R_F (dichloromethane) 0.4;
υ_{max} (Nujol)/cm^{-1}: 3520, 1618, 1597, 1516;
δ_H (300 MHz, d^6-DMSO): 9.34 (3 H, s, OH), 7.90 (3 H, s, ArH triphen.), 7.89 (3 H, s, ArH triphen.), 7.62 (6 H, d, J = 7 Hz, ArH benzyl), 7.44 (6 H, dd, J = 7, 7 Hz, ArH benzyl), 7.35 (3 H, t, J = 7 Hz, ArH benzyl), 5.38 (6 H, s, OCH_2);
δ_C (75.5 MHz, d^6-DMSO): 146.6, 146.5, 137.3, 128.3 (1), 127.8 (1), 127.7 (1), 123.5, 121.2, 108.5 (1), 106.5 (1), 69.7 (2);
MS (ES): 630 $[M+Cl]^-$, 1224 $[2M+Cl]^-$;
Found: C, 77.68; H, 5.03. $C_{39}H_{30}O_6.0.5H_2O$ requires C, 77.60; H, 5.18 %;

2, 6, 10-Tribenzyloxy-3, 7, 11-tris(methyl 2-oxyacetate)triphenylene (105)



A mixture of 2, 6, 10-tribenzyloxy-3, 7, 11-trihydroxytriphenylene **103** (2 g, 3.4 mmol), methyl bromoacetate (2 g, 13.1 mmol) and anhydrous potassium carbonate (3.62 g, 26.2 mmol) in dimethylformamide (30 ml) was stirred at room temperature for 18 hours under a nitrogen atmosphere. The mixture was poured into hydrochloric acid (2.0 M, 4 ml), a light brown solid was recovered by filtration and washed with water before being recrystallised from dichloromethane/ethanol to give the tris(methyl ester) **105** as an off-white solid (2.22 g, 81%); mp 171-172°C; υ_{max} (Nujol)/cm^{-1}: 1752,1617,1517;
δ_H (300 MHz, $CDCl_3$): 7.68 (3 H, s, ArH triphen.), 7.62 (3 H, s, ArH triphen.), 7.59 (6 H, d, J = 7 Hz, ArH benzyl), 7.43 (6 H, dd, J = 7, 7 Hz, ArH benzyl), 7.35 (3 H, t, J = 7 Hz, ArH benzyl), 5.34 (6 H, s, OCH_2Ph), 4.86 (6 H, s, OCH_2CO_2), 3.84 (9 H, s, OCH_3);
δ_C (75.5 MHz, $CDCl_3$): 169.6, 148.5, 147.3, 137.1, 128.7 (1), 128.1 (1), 127.5 (1), 124.0, 123.1, 109.0 (1), 107.8 (1), 71.4 (2), 67.2 (2), 52.3 (3);
MS (ES): 828 $[M+NH_4]^+$, 833 $[M+Na]^+$, 1638 $[2M+NH_4]^+$, 1643 $[2M+Na]^+$;
Found: C, 69.69; H, 4.97. $C_{48}H_{42}O_{12}.H_2O$ requires C, 69.56; H, 5.35 %.

2, 6, 10-Tribenzyloxy-3, 7, 11-tris(oxyacetic acid)triphenylene (106)



A suspension of 2, 6, 10-tribenzyloxy-3, 7, 11-tri(methyl 2-oxyacetate)triphenylene **105** (2.21 g, 2.7 mmol) in 1, 4-dioxane (55 ml) and lithium hydroxide (1.0 M, 55 ml) was stirred

at 50°C for 3 hours under a nitrogen atmosphere to give a clear solution. The solvents were removed *in vacuo*, water was added (100 ml) and the solution acidified to pH 1 with hydrochloric acid (2.0 M). A white precipitate was recovered by filtration, washed with water and dried under vacuum at 40°C to give the tri-acid **106** as a white powder (2.07 g, 99%); mp 213-214°C;

υ_{max}(Nujol)/cm^{-1}: 1712, 1636, 1616, 1518;

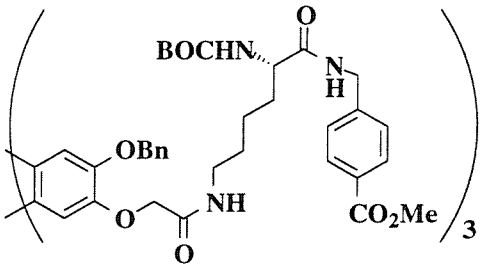
δ_H (300 MHz, d^6-DMSO): 13.11 (3 H, br, CO_2H), 8.07 (3 H, s, ArH triphen.), 7.92 (3 H, s, ArH triphen.), 7.64 (6 H, d, J = 7 Hz, ArH benzyl), 7.45 (6 H, dd, J = 7, 7 Hz, ArH benzyl), 7.37 (3 H, t, J = 7 Hz, ArH benzyl), 5.41 (6 H, s, OCH_2Ph), 5.04 (6 H, s, OCH_2CO_2);

δ_C (75.5 MHz, d^6-DMSO): 170.4, 147.8, 147.6, 137.2, 128.6 (1), 128.2 (1), 128.1 (1), 123.1, 122.8, 107.8 (1), 106.8 (1), 70.4 (2), 65.4 (2);

MS (ES): 767 $[M-H]^-$, 1151 $[3M-2H]^{2-}$;

Found: C, 68.93; H, 4.72. $C_{45}H_{36}O_{12}.H_2O$ requires C, 68.70; H, 4.87 %.

2, 6, 10-Tribenzyloxy-3, 7, 11-tris(methyl 4-({[(2S)-2-*N*-BOC-amino-6-*N*-(2-oxyacetamido)hexanoyl]amino}methyl)benzoate)triphenylene (108) via N-hydroxy succinimide ester (107) based on the method of Anderson *et al*[101]



EDC (494 mg, 2.57 mmol) was added to a solution of 2,6,10-tribenzyloxy-3,7,11-tri(oxyacetic acid)triphenylene **106** (600 mg, 0.78 mmol) and N-hydroxysuccinimide (296 mg, 2.57 mmol) in dimethylformamide (7 ml) at 5°C. The mixture was stirred at 5°C for 1 hour and then at room temperature for 16 hours under a nitrogen atmosphere. The side-wall/rim hydrochloride salt **90** (1.10 g, 2.56 mmol) and DIPEA (450 µl, 2.56 mmol) were added and the reaction mixture was stirred at room temperature for a further 2 hours. Water (30 ml) was added, a white precipitate was recovered by filtration and washed with water. Flash column chromatography eluting with 0-8% methanol/dichloromethane gave the protected precursor **108** as an off-white powder (0.89 g, 60%); mp 195-7°C (dec.);

υ_{max}(Nujol)/cm^{-1}: 3332, 1718, 1657, 1510;

δ_H (300 MHz, d^6-DMSO): 8.43 (3 H, t, J = 6 Hz, NH), 8.16 (3 H, s, ArH triphen.), 8.14 (3 H, s, ArH triphen.), 7.96 (3 H, br, NH), 7.87 (6 H, d, J = 8 Hz, ArH rim), 7.63 (6 H, d, J = 7 Hz, ArH benzyl), 7.45 (6 H, dd, J = 7, 7 Hz, ArH benzyl), 7.41-7.33 (9H, m, ArH rim, ArH benzyl), 6.95 (3 H, d, J = 8 Hz, NHBOC), 5.42 (6 H, s, OCH_2Ph), 4.79 (6 H, s, OCH_2CO),

4.34 (6 H, d, J = 6 Hz, ArC$\underline{H}_2$NH), 3.89 (3 H, br, C$\underline{H}$(NHBOC)), 3.83 (9 H, s, CO_2CH_3), 3.12 (6H, br, NHC$\underline{H}_2CH_2$), 1.60-1.20 (45 H, m, CH_2 x 3, $C(CH_3)_3$);

δ_C (75.5 MHz, d^6-DMSO): 172.6, 167.8, 166.2, 155.5, 148.4, 147.7, 145.4, 137.1, 129.1 (1), 128.6 (1), 128.1 (1), 127.2 (1)*, 124.0, 122.9, 109.1 (1), 107.3 (1), 78.1, 70.5 (2), 69.3 (2), 54.6 (1), 52.1 (3), 41.8 (2), 38.3 (2), 31.4 (2), 28.9 (2), 28.2 (3), 23.1 (2);

* Appears to be two ArCH signals on 500 MHz ^1H-^{13}C correlation

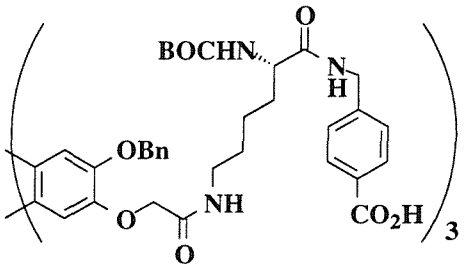
The carbon spectrum is missing one aromatic quaternary carbon signal, a similar situation exists in the spectrum of (CO_2Me) precursor **127** (see later) where a resolution enhanced 360 MHz spectrometer spectrum shows a quaternary peak (129.25 ppm) on the shoulder of an ArCH peak (129.18). The key spectral differences between **108** above and **127** are a methyl ester carbonyl and a benzyl quaternary carbon, the missing peak is neither of these therefore it is a reasonable assumption that the missing peak in the above data is similarly obscured.

MS (ES): 1929 $[M+Cl]^-$, 982 $[M+2Cl]^{2-}$;

Found: C, 64.64; H, 6.45; N, 6.36. $C_{105}H_{123}N_9O_{24}.3H_2O$ requires C, 64.70; H, 6.67; N, 6.47 %.

$[\alpha]_D^{16}$ -7.8 ± 0.2 (c = 1.0, DMF).

2, 6, 10-Tribenzyloxy-3, 7, 11-tris(4-({[(2S)-2-*N*-BOC-amino-6-*N*-(2-oxyacetamido) hexanoyl]amino}methyl)benzoic acid)triphenylene (109)



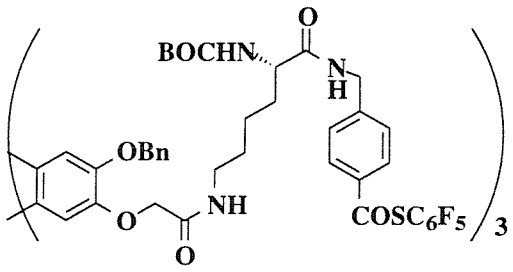
A suspension of protected precursor **108** (750 mg, 0.40 mmol) in 1, 4-dioxane (20 ml) and lithium hydroxide (1.0 M, 20 ml) was stirred at 50°C for 4 hours under a nitrogen atmosphere to give a clear solution. The mixture was acidified to pH 1 with hydrochloric acid (2.0 M), a white precipitate was recovered by filtration, washed with water and dried under vacuum at 40°C to give the tri-acid **109** (619 mg, 84%); mp 157-158°C (to foam) 184-188°C (to liquid);

υ_{max}(Nujol)/cm^{-1}: 3321, 1711, 1655, 1518;

δ_H (300 MHz, d^6-DMSO): 12.82 (3 H, s, CO_2H), 8.42 (3 H, t, J = 6 Hz, NH), 8.16 (3 H, s, ArH triphen.), 8.14 (3 H, s, ArH triphen.), 7.98 (3 H, br, NH), 7.86 (6 H, d, J = 8 Hz, ArH rim), 7.63 (6 H, d, J = 7 Hz, ArH benzyl), 7.45 (6 H, dd, J = 7, 7 Hz, ArH benzyl), 7.40-7.30 (9H, m, ArH rim, ArH benzyl), 6.94 (3 H, d, J = 8 Hz, NH), 5.42 (6H, s, OCH_2Ph), 4.79

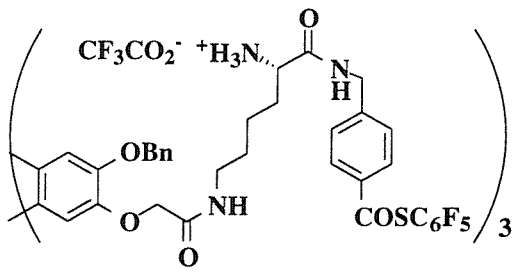
(6H, s, OCH_2CO), 4.33 (6 H, d, J = 6 Hz, $ArCH_2NH$), 3.89 (3 H, br, CH(NHBOC)), 3.12 (6 H, br, $NHCH_2CH_2$), 1.65-1.17 (45 H, m, CH_2 x 3, $C(CH_3)_3$);
δ_C (75.5 MHz, d^6-DMSO): 172.6, 167.8, 167.3, 155.5, 148.4, 147.6, 144.8, 137.1, 129.4 (1), 129.3 (1), 128.6 (1), 128.1 (1), 127.0 (1), 124.0, 122.9, 109.0 (1), 107.4 (1), 78.1, 70.5 (2), 69.2 (2), 54.6 (1), 41.8 (2), 38.3 (2), 31.4 (2), 28.9 (2), 28.2 (3), 23.1 (2); missing 1 quaternary signal as for previous compound (**108**);
MS (ES): 961 $[M+2Cl]^{2-}$;

2, 6, 10-Tribenzyloxy-3, 7, 11-tris(pentafluorophenyl 4-({[(2S)-2-*N*-BOC-amino-6-*N*-(2-oxyacetamido)hexanoyl]amino}methyl)benzoate) triphenylene (110)



A solution of tri-acid **109** (350 mg, 0.19 mmol), pentafluorothiophenol (151 µl, 1.13 mmol) and DCC (234 mg, 1.13 mmol) in dimethylformamide (7 ml) was stirred at room temperature for 23 hours. A white precipitate was recovered by filtration, washed with dichloromethane and the solvents removed from the filtrate *in vacuo* to give the tris(pentafluorothiophenol ester) **110** as a yellow oil which was taken on directly (1.01 g, theory 452 mg).

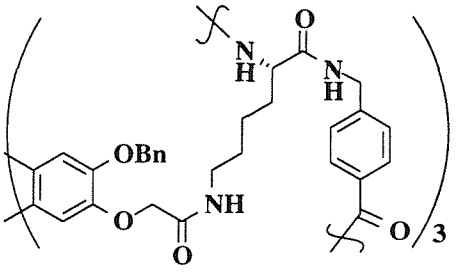
2, 6, 10-Tribenzyloxy-3, 7, 11-tris(pentafluorophenyl 4-({[(2S)-2-amino-6-*N*-(2-oxyacetamido) hexanoyl]amino}methyl)benzoate)triphenylene, tris(trifluoroacetic acid) salt (111)



A solution of tris(activated ester) **110** (1.01 g, from above) in 50% trifluoroacetic acid/dichloromethane was stirred at room temperature for 90 minutes under a nitrogen atmosphere. The solvents were removed *in vacuo* to give a yellow oil which was triturated

with ether to give the tris(trifluoroacetic acid) salt **111** as a white solid and was taken on directly (678 mg, theory 462 mg).

Typical procedure for cyclisation to give tribenzyloxy macrocycles (101)



A solution of tris(trifluoroacetate salt) **111** (678 mg, from above) in tetrahydrofuran (50 ml) was added to a solution of DIPEA (1.65 ml, 9.44 mmol) in tetrahydrofuran (500 ml) over a period of 10 hours. The mixture was stirred at room temperature for a further 8 hours under a nitrogen atmosphere. The solvent was removed *in vacuo*, the residue was taken into dichloromethane (100 ml), washed with hydrochloric acid (2.0 M, 2 x 40 ml) and sat. aq. sodium bicarbonate solution (2 x 40 ml). Both sets of aqueous washes were back-extracted with dichloromethane (30 ml each). The combined organic extracts were dried with magnesium sulfate and the solvent was removed *in vacuo* to give a yellow gum (329 mg). The gum solidified on standing, was re-dissolved in 20% methanol/dichloromethane and a yellow solid was removed by filtration. The solvents were removed from the filtrate *in vacuo* to give the macrocycles as a white solid which was a single spot by TLC (195 mg, 69%). Flash column chromatography on 97 mg of this product eluting with 0-10% methanol/dichloromethane gave the mixture of macrocycles **101** (ratio 5:1 by NMR) as a white solid (23 mg, 16% over 3 steps - assumes the remainder of the 195 mg would have given a similar amount of pure product);
R_F (10% methanol/dichloromethane) 0.3;
The macrocycles could not be separated by HPLC methods.
$\upsilon_{max}(CDCl_3)/cm^{-1}$: 3627, 2942, 2836, 2252, 1669, 1507, 1436;
MS (ES): 784 $[M+2Cl]^{2-}$, 1533 $[M+Cl]^-$;
Satisfactory microanalysis data could not be obtained for the mixture of isomers.
$[\alpha]_D^{20}$ +4.5 ± 0.2 (c=0.6, 15% CH_3OH/CH_2Cl_2).
Optical rotation measured on mixture of the two isomers.

Spectral data for major isomer:
δ_H (270 MHz, d^6-DMSO): 8.21 (6 H, br, ArH triphen.), 8.09 (3 H, t, J = 6 Hz, $ArCH_2N\underline{H}$), 7.97 (3 H, d, J = 9 Hz, $CH(N\underline{H})$), 7.88 (3 H, t, J = 6 Hz, $N\underline{H}CH_2CH_2$), 7.66 (6 H, d, J = 7 Hz, ArH benzyl), 7.55-7.38 (15 H, m, ArH), 6.91 (6 H, d , J = 8 Hz, ArH rim), 5.45 (6 H, s,

OCH_2Ph), 4.86 (3 H, d, J = 15 Hz, $OC\underline{H}_AH_BCO$), 4.76 (3 H, d, J = 15 Hz, $OCH_A\underline{H}_BCO$), 4.34 (3 H, br, $C\underline{H}(NH)$), 4.10 (3 H, dd, J = 15, 6 Hz, $ArC\underline{H}_AH_BNH$), 3.78 (3H, d, J = 15 Hz, $ArCH_A\underline{H}_BNH$), 3.30 (3 H, $NHC\underline{H}_AH_BCH_2$)*, 2.91 (3 H, br , $NHCH_A\underline{H}_BCH_2$), 1.80-1.10 (18 H, m, CH_2 x 3);

* Obscured by H_2O peak

δ_C (68.0 MHz, d^6-DMSO): 171.3, 168.1, 166.4, 148.5, 148.0, 142.9, 137.2, 132.7, 128.7 (1), 128.2 (1), 127.3 (1), 127.0 (1), 124.2, 123.2, 109.1 (1), 107.3 (1), 70.7 (2), 69.3 (2), 53.3 (1), 41.8 (2), 37.6 (2), 30.7 (2), 28.8 (2), 21.8 (2);

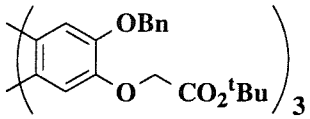
Missing one aromatic CH as for precursor **108** where it can be seen on CH correlation;

HPLC showed the presence of two isomers (ratio 3.5:1) but the resolution was too poor for a semi-preparative separation. The HPLC conditions used were the same as for the separation of macrocycle **100** isomers but the eluent was 65% acetonitrile/water. Retention times for presumed macrocycle peaks: 17.6 and 19.5 minutes.

As the isomers were not separated no specific data could be collected for the minor isomer.

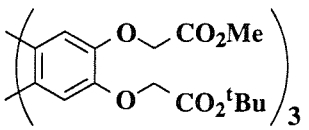
6.5 Experimental For Chapter Five

2, 6, 10-Tribenzyloxy-3, 7, 11-tris(*tert*-butyl 2-oxyacetate)triphenylene (119)



A mixture of 2, 6, 10-tribenzyloxy-3, 7, 11-trihydroxytriphenylene **103** (3.16 g, 5.3 mmol), *tert*-butyl bromoacetate (3.72 g, 19.1 mmol) and potassium carbonate (5.87 g, 42.0 mmol) in dimethylformamide (50 ml) was stirred for at room temperature for 16 hours under a nitrogen atmosphere then poured into hydrochloric acid (2.0 M, 120 ml). The resulting yellow precipitate was recovered by filtration and partitioned between ethyl acetate (50 ml) and water (50 ml). The aqueous phase was extracted with ethyl acetate (2 x 25 ml), the combined organic extracts were dried with magnesium sulfate and the solvent was removed in vacuo to give a yellow solid (5.1 g). Recrystallisation from ethanol gave the tri-ester **119** as a pale yellow solid (4.43 g, 80%); mp 103-104°C;
υ_{max}(Nujol mull)/cm^{-1}: 1746, 1642, 1509;
δ_H(300 MHz, $CDCl_3$): 7.81 (3 H, s, ArH triphen.), 7.66 (3 H, s, ArH triphen.), 7.62 (6 H, d, J = 7 Hz, ArH benzyl), 7.45 (6 H, dd, J = 7, 7 Hz, ArH benzyl), 7.37 (3 H, t, J = 7 Hz, ArH benzyl), 5.37 (6 H, s, OCH_2Ph), 4.76 (6 H, s, OCH_2CO_2), 1.52 (27 H, s, CH_3);
δ_C(75.5 MHz, $CDCl_3$): 168.1, 148.4, 147.8, 137.2, 128.7 (1), 128.1 (1), 127.5 (1), 124.2, 123.5, 108.3 (1), 107.9 (1), 82.4, 71.7 (2), 67.3 (2), 28.2 (3);
MS (ES): 954 $[M+NH_4]^+$, 959 $[M+Na]^+$, 1423 $[3M+2NH_4]^{2+}$, 1891 $[2M+NH_4]^+$, 1896 $[2M+Na]^+$;
Found C, 73.18; H, 6.20. $C_{57}H_{60}O_{12}$ requires C, 73.06; H, 6.45 %.

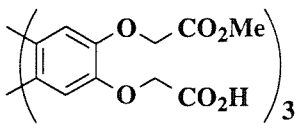
2, 6, 10-Tris(*tert*-butyl 2-oxyacetate)-3, 7, 11-tris(methyl 2-oxyacetate)triphenylene (121)



A mixture of 2, 6, 10-tribenzyloxy-3, 7, 11-tris(*tert*-butyl 2-oxyacetate)triphenylene **119** (3.70 g, 3.9 mmol) and 10% palladium on carbon (350 mg) in methanol (80 ml) was stirred at room temperature for 18 hours under atmospheric pressure of hydrogen. Dichloromethane (240 ml) was added, the mixture was filtered through Celite and the solvents were removed *in vacuo* to give a grey solid (2.72 g, theory 2.63 g). The trihydroxytriphenylene **120** was

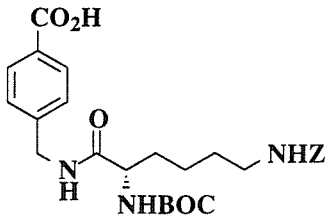
dissolved in dimethylformamide (40 ml) and stirred with methyl bromoacetate (2.17 g, 14 mmol) and potassium carbonate (4.26 g, 31 mmol) at room temperature for 4 hours under a nitrogen atmosphere. The reaction mixture was poured into hydrochloric acid (2.0 M, 150 ml), a white precipitate was recovered by filtration, washed with water and recrystallised from acetone/petrol to give triphenylene **121** as a white solid (2.74 g, 79% over two steps); mp 176.5-177°C; υ_{max}(Nujol)/cm^{-1}: 1753, 1621, 1511;
δ_H(300 MHz, $CDCl_3$): 7.83 (3 H, s, ArH), 7.72 (3 H, s, ArH), 4.93 (6 H, s, OCH_2), 4.80 (6 H, s, OCH_2), 3.87 (9 H, s, OCH_3), 1.51 (27 H, s, $C(CH_3)_3$);
δ_C(75.5 MHz, $CDCl_3$): 169.4, 167.7, 148.1, 147.4, 124.7, 123.9, 109.9 (1), 107.7 (1), 82.5, 67.4 (2), 66.9 (2), 52.3 (3), 28.1 (3);
MS (ES): 905 $[M+Na]^+$;
HRMS (FAB): found 882.3239 calcd. 882.3310 for $C_{45}H_{54}O_{18}$.

2, 6, 10-Tris(methyl 2-oxyacetate)-3, 7, 11-tris(oxyacetic acid)triphenylene (61)



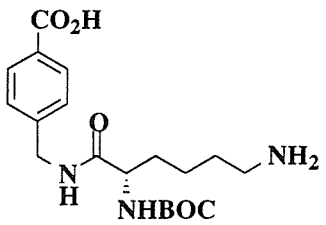
A solution of 2, 6, 10-tris(*tert*-butyl 2-oxyacetate)-3, 7, 11-tris(methyl 2-oxyacetate)triphenylene **121** (1.0 g, 1.1 mmol) in 50% trifluoroacetic acid/dichloromethane (20 ml) was stirred at room temperature for 1 hour under a nitrogen atmosphere. The solvents were removed *in vacuo* and the residue was triturated with ether to give the tri-acid **61** as a white solid (799 mg, 99%); mp 165-168°C (dec.); υ_{max}(Nujol)/cm^{-1}: 1746, 1620, 1518;
δ_H(300 MHz, d^6-DMSO): 13.09 (3 H, br, CO_2H), 7.98 (3 H, s, ArH), 7.96 (3 H, s, ArH), 5.11 (6 H, s, OCH_2), 5.03 (6 H, s, OCH_2), 3.79 (9 H, s, CH_3);
δ_C(75.5 MHz, d^6-DMSO): 170.2, 169.2, 147.4, 147.0, 123.4, 122.9, 108.0 (1), 107.3 (1), 65.7 (2), 65.3 (2), 51.8 (3);
MS (ES): 713 $[M-H]^-$, 1427 $[2M-H]^-$;
Found C, 53.21; H, 4.10. $C_{33}H_{30}O_{18}$.0.5TFA requires C, 52.93; H, 3.98 %;
HRMS (FAB): found 714.1439 calcd. 714.1432 for $C_{33}H_{30}O_{18}$.

4-({[(2S)-2-*N*-BOC-Amino-6-*N*-Z-aminohexanoyl]amino}methyl)benzoic acid (124)



A suspension of protected dipeptide **95** (7.12 g, 13.5 mmol) in lithium hydroxide (1.0 M, 180 ml) and 1, 4-dioxane (180 ml) was stirred at room temperature for 2.5 hours under a nitrogen atmosphere to give a slightly cloudy solution. The reaction mixture was filtered then acidified to pH 2 with hydrochloric acid (2.0 M) and extracted with ethyl acetate (1 x 300 ml, 2 x 150 ml). The combined organic extracts were dried with magnesium sulfate and the solvent was removed *in vacuo*. The resultant gum was triturated with ether to give the side-wall/rim acid **124** as a white solid (6.61 g, 95 %); mp 153-154°C;
υ_{max}(Nujol mull)/cm^{-1}: 3319, 1686, 1650, 1613, 1538, 1521;
δ_H(300 MHz, d^6-DMSO): 12.82 (1 H, br, CO_2H), 8.43 (1 H, t, J = 6 Hz, NH), 7.88 (2 H, d, J = 8 Hz, ArH), 7.40-7.31 (7 H, m, ArH), 7.25 (1 H, t, J = 6 Hz, NH), 6.93 (1 H, d, J = 8 Hz, NHBOC), 5.01 (2 H, s, OCH_2Ph), 4.35 (2 H, d, J = 6 Hz, $ArCH_2NH$), 3.90 (1 H, br, CH(NHBOC)), 2.98 (2 H, br, CH_2), 1.57 (2 H, br, CH_2), 1.45-1.19 (13 H, m, CH_2 x 2, $C(CH_3)_3$);
δ_C(90.5 MHz, d^6-DMSO): 172.4, 167.1, 156.0, 155.4, 144.7, 137.2, 129.2, 129.1 (1), 128.2 (1), 127.6 (1)*, 126.9 (1), 78.0, 65.0 (2), 54.5 (1), 41.7 (2), 40.0 (2), 31.3 (2), 29.0 (2), 28.1 (3), 22.8 (2);
*Two coincident ArCH signals.
MS (ES): 548 $[M+Cl]^-$, 626 $[M+TFA-H]^-$, 1025 $[2M-H]^-$;
Found C, 63.22; H, 6.78; N, 8.10. $C_{27}H_{35}N_3O_7$ requires C, 63.14; H, 6.87; N, 8.18 %;
$[\alpha]_D^{22}$ -9.4 ± 0.2 (c = 1.0, CH_3OH).

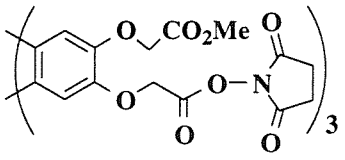
4-({[(2S)-2-*N*-BOC-Amino-6-aminohexanoyl]amino}methyl)benzoic acid (125)



A mixture of protected side-wall acid **124** (3.8 g, 7.4 mmol) in methanol (75 ml) and 10% palladium on carbon (350 mg) was stirred at room temperature for 21 hours under

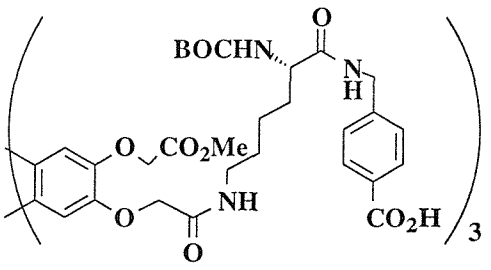
atmospheric pressure of hydrogen. A further 500 ml of methanol was added, the mixture was filtered through Celite and the solvent was removed *in vacuo* to give the amino acid **125** as a white solid (2.70 g, 96%); mp 212-213°C. Due to the very polar and insoluble nature of this compound it was used without further purification.
R_F (methanol) 0.5;
υ_{max}(Nujol)/cm^{-1}: 3237, 1713, 1670, 1598, 1520;
δ_H(300 MHz, d^4-methanol): 7.93 (2 H, d, J = 8 Hz, ArH), 7.32 (2 H, d, J = 8 Hz, ArH), 4.52 (1 H, d, J = 15 Hz, ArC$\underline{H}_A H_B$), 4.38 (1 H, d, J = 15 Hz, ArC$H_A\underline{H}_B$), 4.08 (1 H, t, J = 7 Hz, C$\underline{H}$(NHBOC)), 2.88 (2 H, t, J = 8 Hz, $NH_2C\underline{H}_2$), 1.85-1.58 (4 H, m, CH_2 x 2), 1.55-1.30 (11 H, m, CH_2, $C(CH_3)_3$);
MS (ES): 380 $[M+H]^+$, 759 $[2M+H]^+$.

2, 6, 10-Tris(methyl 2-oxyacetate)-3, 7, 11-tris(oxyacetic acid N-hydroxysuccinimide ester)triphenylene (126) based on the method of Anderson *et al*[101]



EDC (2.31 g, 12.0 mmol) was added to a solution of tri-acid **61** (2.15 g, 3.0 mmol) and N-hydroxysuccinimide (1.39 g, 12.0 mmol) in dimethylformamide (30 ml) at 5°C and stirred for 30 minutes. After stirring at room temperature for 15 hours under an argon atmosphere the reaction mixture was poured into water (150 ml) and acidified to pH 2 with hydrochloric acid (2.0 M). A white precipitate **126** was recovered by filtration, washed with water and dried under vacuum in the presence of phosphorus pentoxide before being used directly;
mp (acetonitrile) 195-196°C; υ_{max}(Nujol)/cm^{-1}: 1817, 1788, 1739, 1621, 1512;
δ_H(300 MHz, d^6-DMSO): 8.13 (3 H, s, ArH), 8.10 (3 H, s, ArH), 5.64 (6 H, s, $OC\underline{H}_2CO_2N$), 5.16 (6 H, s, $OC\underline{H}_2CO_2CH_3$), 3.76 (9 H, s, CH_3), 2.86 (12 H, s, $(CH_2)_2$);
δ_C(75.5 MHz, d^6-DMSO): 170.0, 169.0, 165.5, 147.3, 146.4, 124.0, 123.0, 108.8 (1), 107.7 (1), 65.4 (2), 64.1 (2), 51.9 (3), 25.5 (2);

2, 6, 10-Tris(4-({[(2S)-2-*N*-BOC-amino-6-*N*-(2-oxyacetamido)hexanoyl]amino}methyl) benzoic acid)-3, 7, 11-tris(methyl 2-oxyacetate)triphenylene (127) based on the method of Anderson *et al*[101]



The side-wall/rim amino acid **125** (4.45 g, 12.0 mmol) was added to a solution of the activated ester **126** (theoretical 3.03 g, 3.0 mmol) and DIPEA (1.52 g, 12.0 mmol) in dimethylformamide (45 ml) to give a suspension. After stirring at room temperature for 2 hours under an argon atmosphere, the reaction mixture was poured into water (200 ml) and acidified to pH 2 with hydrochloric acid (2.0 M). A white precipitate was recovered by filtration, washed with water and recrystallised from dimethylformamide/water to give the precursor **127** as an off-white solid (4.28g, 79% over two steps);

mp 180-181°C (dec.); υ_{max}(Nujol)/cm^{-1}: 3302, 1755, 1711, 1657, 1518;

δ_H(300 MHz, d^6-DMSO): 8.42 (3 H, t, J = 6 Hz, NH), 8.17 (3 H, s, ArH triphen.), 8.07 (3 H, s, ArH triphen.), 8.03 (3 H, br, NH), 7.87 (6 H, d, J = 8 Hz, ArH rim), 7.35 (6 H, d, J = 8 Hz, ArH rim), 6.96 (3 H, d, J = 7 Hz, CH(N<u>H</u>)), 5.16 (6 H, s, OCH_2), 4.82 (6 H, s, OCH_2), 4.34 (6 H, d, J = 6 Hz, Ar<u>CH</u>$_2$NH), 3.92 (3 H, br, <u>CH</u>(NHBOC)), 3.77 (9 H, s, CH_3), 3.21 (6 H, br, CONHC<u>H</u>$_2$$CH_2$), 1.65 (15 H, m, CH_2 x 3, $C(CH_3)_3$);

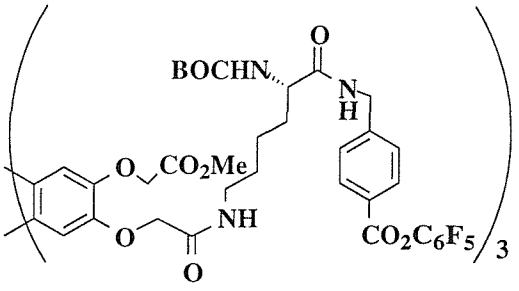
δ_C(90.5 MHz, d^6-DMSO): 172.5, 169.2, 167.6, 167.2, 155.4, 147.59, 147.57, 144.7, 129.3, 129.2 (1), 126.9 (1), 123.8, 123.5, 109.4 (1), 108.0 (1), 78.0, 69.2 (2), 65.9 (2), 54.5 (1), 51.9 (3), 41.8 (2), 38.3 (2), 31.4 (2), 28.8 (2), 28.1 (3), 23.0 (2);

MS (ES): 898 $[M-2H]^{2-}$, 1796 $[M-H]^-$;

Found C, 58.48; H, 6.04; N, 6.72. $C_{90}H_{111}N_9O_{30}.3H_2O$ requires C, 58.34; H, 6.36; N, 6.80 %;

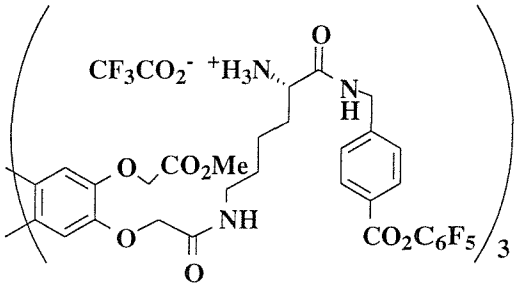
$[\alpha]_D^{17}$ -1.5 ± 0.2 (c = 1.0, DMF).

Typical procedure for forming 2, 6, 10-tris(methyl 2-oxyacetate)-3, 7, 11-tris (pentafluorophenyl 4-({[(2S)-2-*N*-BOC-amino-6-*N*-(2-oxyacetamido)hexanoyl]amino} methyl)benzoate)triphenylene (128)



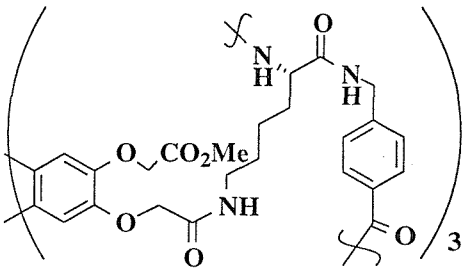
EDC (64 mg, 330 μmol) was added to a suspension of tri-acid precursor **127** (100 mg, 56 μmol) and pentafluorophenol (62 mg, 330 μmol) in tetrahydrofuran (4 ml) at 5°C and stirred for 1 hour. The mixture was stirred at room temperature for a further 16 hours under an argon atmosphere. The tetrahydrofuran was removed *in vacuo* and water added to the residue, a white solid was recovered by filtration, washed with water and dried under vacuum in the presence of phosphorus pentoxide to give the tris(pentafluorophenol ester) **128** as a white solid which was taken on directly (131 mg, theory 128 mg).

Typical procedure for cleaving *tert*-butyloxycarbonyl groups to give 2, 6, 10-tris(methyl 2-oxyacetate)-3, 7, 11-tris(pentafluorophenyl 4-({[(2S)-2-amino-6-*N*-(2-oxyacetamido) hexanoyl]amino}methyl)benzoate)triphenylene, tris(trifluoroacetic acid) salt (129)



A solution of tris(pentafluorophenol ester) **128** (131 mg, from above) in 10% trifluoroacetic acid/dichloromethane (5 ml) was stirred at room temperature for 2 hours under an argon atmosphere. The solvents were removed *in vacuo* and the resulting oil triturated with ether to give the tris(trifluoroacetic acid) salt **129** as a white powder which was taken on directly (111 mg, theory 130 mg).

Typical procedure for cyclisation to give tris(methyl 2-oxyacetate) macrocycles (118a)



A solution of tris(trifluoroacetate salt) **129** (111 mg, from above) in tetrahydrofuran (10 ml) was added to a solution of DIPEA (500 µl, 2.9 mmol) in tetrahydrofuran (50 ml) over a period of 10 hours and the mixture was stirred at room temperature for a further 6 hours under an argon atmosphere. The solvent was removed *in vacuo* and water added to the residue; a yellow solid was recovered by filtration and washed with water (53 mg) then taken into 20% methanol/dichloromethane and filtered. The solvents were removed from the filtrate *in vacuo* to give a white solid (29 mg) which was purified by preparative TLC eluting with 15% methanol/dichloromethane to give the mixture of macrocycles **118a** (ratio 3.5:1 by NMR) as an off-white solid (12 mg, 15% over three steps); mp 241°C (dec.); R_F (15% methanol/dichloromethane) 0.5;

The macrocycles could not be separated by HPLC methods.

υ_{max}(Nujol)/cm^{-1}: 3372, 1752, 1656, 1509;

MS (ES): 723 $[M+2H]^{2+}$, 1445 $[M+H]^+$, 1467 $[M+Na]^+$;

λ_{max} (CH_2Cl_2, 10^{-5} M)/nm: 240, 268, 276, 304;

Satisfactory microanalysis data could not be obtained for the mixture of isomers.

$[\alpha]_D^{23}$ -1.6 ± 0.2 (c=1.0, d^6-DMSO) measured on mixture of the two isomers.

Spectral data for major isomer:

δ_H(500 MHz, d^6-DMSO): 8.20 (3 H, s, ArH triphen.), 8.16 (3 H, br, $ArCH_2N\underline{H}$), 8.08 (3 H, s, ArH triphen.), 7.96 (3 H, br $N\underline{H}CH_2CH_2$), 7.88 (3 H, d, J = 8 Hz, $CH(N\underline{H})$), 7.42 (6 H, d, J = 8 Hz, ArH rim), 6.86 (6 H, d, J = 8 Hz, ArH rim), 5.24 (3 H, d, J = 15 Hz, $OC\underline{H}_AH_BCO_2CH_3$), 5.18 (3 H, d, J = 15 Hz, $OCH_A\underline{H}_BCO_2CH_3$), 4.82 (3 H, d, J = 15 Hz, $OC\underline{H}_AH_BCON$), 4.78 (3 H, d, J = 15 Hz, $OCH_A\underline{H}_BCON$), 4.35 (3 H, d, J = 7 Hz, $C\underline{H}(NH)$), 4.12 (3 H, br, $ArC\underline{H}_AH_BNH$), 3.77 (9 H, s, $C\underline{H}_3$), 3.72 (3 H, br, $ArCH_A\underline{H}_BNH$), 3.40 (3 H, $NHCH_2C\underline{H}_AH_B$)*, 3.08 (3 H, br, $NHCH_2CH_A\underline{H}_B$), 1.69 (6 H, br, $CH(NH)C\underline{H}_2$), 1.55 (3 H, br, $C\underline{H}_AH_B$), 1.40 (3 H, br, $CH_A\underline{H}_B$), 1.23 (6 H, br, CH_2);

*Obscured by H_2O peak.

δ_C(68 MHz, d^6-DMSO): 171.3, 169.6, 168.1, 166.3, 147.9, 147.7, 143.0, 132.6, 127.3 (1), 127.0 (1), 124.1, 123.8, 109.4 (1), 107.8 (1), 70.0 (2), 66.0 (2), 53.2 (1), 52.1 (3), 41.8 (2), 38.0 (2), 30.8 (2), 28.8 (2), 21.8 (2);

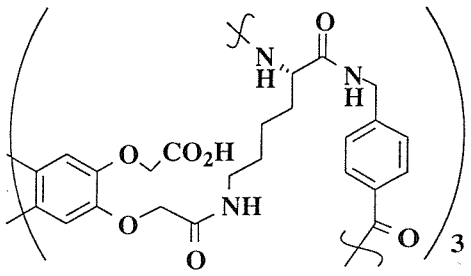
As the isomers could not be separated only limited data could be collected for the minor isomer:

Only the aromatic rim protons could be clearly seen by ^{1}H NMR:

δ_H(270 MHz, d^6-DMSO): 7.53 (6 H, d, J = 9 Hz), 6.78 (6 H, d, J = 9 Hz);

δ_C(68 MHz, d^6-DMSO): 171.5, 169.4, 168.3, 166.2, 148.2, 148.0, 143.2, 132.5, 126.8 (1), 124.7, 124.0, 111.4 (1), 108.4 (1), 69.4 (2), 66.2 (2), 53.8 (1), 52.0 (3), 41.6 (2), 37.5 (2), 30.5 (2), remaining two CH_2 signals inconclusive, one ArCH signal missing/obscured by major isomer peaks;

Tris(oxyacetatic acid) macrocycles 118b



Potassium hydroxide (1.25 ml, 0.5 M, 0.62 mmol) was added to a solution of macrocycles **118a** (180 mg, 0.12 mmol) in DMSO (1.25 ml) and the mixture stirred at room temperature for 15 minutes. Water was added (5 ml) and the mixture acidified to pH 2 with hydrochloric acid (2.0 M). A white precipitate was recovered by filtration, washed with water and dried under vacuum in the presence of phosphorus pentoxide to give the macrocyclic tri-acid **118b** as a mixture of isomers (ratio 3.1:1 by ^{13}C NMR) as an off-white solid (136 mg, 78%); mp > 270°C; υ_{max}(Nujol)/cm^{-1}: 3350, 1729, 1650, 1510;

MS (ES): 700 $[M-2H]^{2-}$, 1401 $[M-H]^-$;

λ_{max} (CH_2Cl_2, 10^{-5} M)/nm: 200, 238, 268, 276, 308;

Fluorescence (CH_2Cl_2, 10^{-5} M)/nm: λ_{ex} 308, λ_{em} 398;

Satisfactory microanalysis data could not be obtained for the mixture of isomers.

$[\alpha]_D^{23}$ 44.3 ± 0.2 (c=0.25, d^6-DMSO) measured on mixture of the two isomers.

NMR data collected on sodium salt;

Spectral data for major isomer:

δ_H(300 MHz, D_2O): 7.37 (6 H, d, J = 8 Hz, ArH rim), 7.14 (3 H, s, ArH triphen.), 7.09 (3 H, s, ArH triphen.), 6.82 (6 H, d, J = 8 Hz, ArH rim), 4.69-4.62 (6 H, m, OCH_2), 4.62 (3 H, d, J = 15 Hz, $OC\underline{H}_AH_B$), 4.52 (3 H, d, J = 15 Hz, $OCH_A\underline{H}_B$), 4.27 (3 H, t, J = 6 Hz, $C\underline{H}$(NH), 3.83 (3 H, d, J = 16 Hz, $ArC\underline{H}_AH_BNH$), 3.60 (3 H, d, J = 16 Hz, $ArCH_A\underline{H}_BNH$), 3.47 (3 H,

br, $NHC\underline{H}_AH_BCH_2$), 3.14 (3 H, br, $NHCH_A\underline{H}_BCH_2$), 1.82 (6 H, m, $CH(NH)C\underline{H}_2$), 1.70-1.40 (6 H, m, $NHCH_2C\underline{H}_2$), 1.24 (6 H, br, $CH(NH)CH_2C\underline{H}_2$);
δ_C(125.7 MHz, D_2O-phosphate buffer): 175.3, 173.8, 170.8, 170.3, 146.9, 146.4, 141.9, 131.5, 127.3 (1), 127.2 (1), 123.4, 122.4, 105.8 (1), 105.0 (1), 67.6 (2), 67.1 (2), 54.7 (1), 42.3 (2), 38.8 (2), 29.9 (2), 27.8 (2), 21.4 (2);

Spectral data for minor isomer:
Minor isomer peaks not clearly visible in ^1H NMR
δ_C(125.7 MHz, D_2O-phosphate buffer): 175.1, 173.6, 171.2, 170.3, 147.4, 146.5, 141.6, 131.6, 127.4 (1), 124.4, 122.6, 109.3 (1), 105.4 (1), 69.5 (2), 42.4 (2), 38.8 (2), 30.2 (2), 21.6 (2);
Signals for ArCH, OCH_2, CH(NH) and alkyl CH_2 missing or obscured by major isomer peaks.

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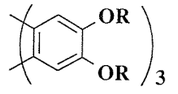
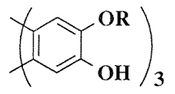
Structures of Selected Compounds



64 R = Me
71 R = H
72 R = CH_2CO_2Et
59 R = CH_2CO_2H
84 R = C_5H_{11}
102 R = Bn



86 R = C_5H_{11}
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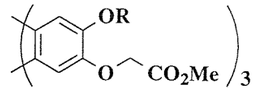
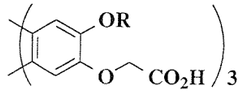
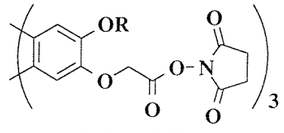


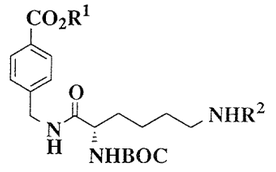
88 R = C_5H_{11}
105 R = Bn



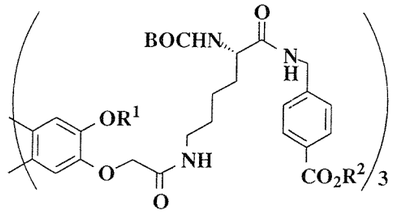
89 R = C_5H_{11}
106 R = Bn
61 R = CH_2CO_2Me



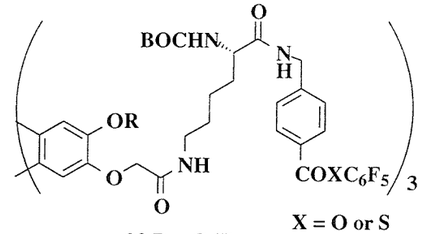
96 R = C_5H_{11}
107 R = Bn
126 R = CH_2CO_2Me



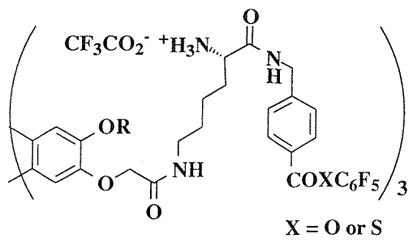
95 R^1 = Me, R^2 = Z
90 R^1 = Me, R^2 = H.HCl
124 R^1 = H, R^2 = Z
125 R^1 = H, R^2 = H



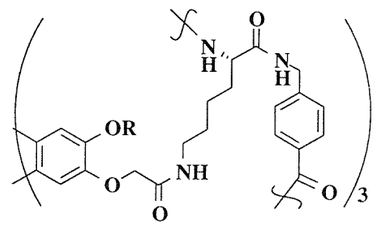
91 R^1 = C_5H_{11}, R^2 = Me
97 R^1 = C_5H_{11}, R^2 = H
108 R^1 = Bn, R^2 = Me
109 R^1 = Bn, R^2 = H
127 R^1 = CH_2CO_2Me, R^2 = H



X = O or S
98 R = C_5H_{11}
110 R = Bn
128 R = CH_2CO_2Me



X = O or S
99 R = C_5H_{11}
111 R = Bn
129 R = CH_2CO_2Me



100 R = C_5H_{11}
101 R = Bn
118a R = CH_2CO_2Me
118b R = CH_2CO_2H