Pyrogallol[4]arenes:

A Synthetic Investigation

Pauline Griffin

K. Nolan Research Group

Ph.D. Thesis

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Project Submission Form

Student Name: Pauline Griffin
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Lecturer: Dr. Kieran Nolan
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Declaration

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Signed: Pauline Griffin

Table of Contents

List of Abbreviations

%E	extent of extraction
^{1}H NMR	proton nuclear magnetic resonance
Å	angstroms
A_0	absorbance of the picrate salt solution
AcOH	acetic acid
A_e	absorbance of the picrate salt solution after extraction
Ag^+	silver ion
BF_3OEt_2	boron trifluoride diethyl etherate
Bu^n	normal butyl
Bu^t	tertiary butyl
$Ca(OH)_2$	calcium hydroxide
Ca^{2+}	calsium ion
$CaCl_2$	calcium chloride
Cd^{2+}	cadmium ion
$CDCl_3$	deuterated chloroform
CH_2Cl_2	dichloroethane
$CHCl_3$	chloroform
CMPO	carbamoylmethylphosphine oxide
CO_2	carbon dioxide
Co^{2+}	cobalt ion
COSY	correlation spectroscopy
CPK	Corey-Pauling-Koltun
Cs^+	caesium ion
CsCl	caesium chloride
Cu^{2+}	copper ion
D_2O	deuterium oxide
DCM	dichloromethane
DMF	dimethylformamide
DMSO	dimethyl sulphoxide
DMSO-d6	deuterated dimethyl sulphoxide

e.g.	for example
EI-MS	electrospray ionisation mass spectroscopy
equiv.	equivalents
et al.	and others
EtOH	ethanol
FAB-MS	fast atom bombardment mass spectrometry
g	gram
$Ga(NO_3)_3$	gallium nitrate
Gp-120	glycoprotein-120
H^+	hydrogen ion
H_2O	water
H-bonding	hydrogen bonding
HCHO	formaldehyde
HCl	hydrochloric acid
Hg^{2+}	mercury ion
HIV	human immunodeficiency virus
hrs	hours
i.e.	that is
IPA	isopropyl alcohol
IR	infra red
ISE	ion selective electrode
IUPAC	International Union of Pure and Applied Chemistry
J	Coupling Constant
K^+	potassium ion
K_2CO_3	potassium carbonate
KBr	potassium bromide
KOH	potassium hydroxide
LC/MS	liquid chromatography mass spectroscopy
Li^+	lithium ion
LiCl	lithium chloride
m-	meta
M	molar (mol/litre)
m	multiplet
m/z	mass to charge ratio

MeI	methyl iodide
MeOH	methanol
$Mg(OH)_2$	magnesium hydroxide
Mg^{2+}	magnesium ion
$MgCl_2$	magnesium chloride
mls	millilitres
mmol	millimoles
mol	mole
N	normal
Na^+	sodium ion
NaCl	sodium chloride
$NaOCD_3$	deuterated sodium methoxide
NaOH	sodium hydroxide
$NiCl_2$	nickel chloride
nm	nanometres
NMR	nuclear magnetic resonance
NO_2	nitro group
OEt	ethoxy
OH	hydroxy group
OMe	methoxy
osc/min	oscillations per minute
p-	para
Pb^{2+}	lead ion
Ph	phenyl
ppm	parts per million
Rb^+	rubidium ion
rccc	reference, *cis, cis, cis*
rcct	reference, *cis, cis, trans*
rctc	reference, *cis, trans, cis*
rctt	reference, *cis, trans, trans*
s	singlet
S_{M+}	selectivity ratio
$SnCl_4$	tin tetrachloride (stannic chloride)
SSM	separate solutions method

t-	tertiary
t	triplet
t-butyl	tertiary butyl group
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TsOH	toluenesulphonic acid
UV	ultra violet
v/v	volume to volume ratio
W	watts
Zn^{2+}	zinc ion
$ZnCl_2$	zinc chloride
β	stability constant
µl	microlitres
µl/min	micro litres per minute
π	pi
υ	wavelength (cm^{-1})
°C	degrees Celcius

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Firstly I would like to thank my supervisor, Dr. Kieran Nolan, whose great encouragement and enthusiasm have brought me this far. Whenever I had a problem, I knew that Kieran's support and advice would get me through.

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Abstract

The first part of this work involved the study of the acid condensation of pyrogallol with acataldehyde. The product formed, pyrogallol[4]arene, is present as a mixture of two isomers, the rccc cone and the rctt flattened partial cone conformations, which could be separated using an extraction/reprecipitation procedure. A series of studies was undertaken to determine if these two isomers could be interconverted. We found that both the rctt flattened partial cone and rccc cone isomers could not be interconverted, demonstrating the high stability of the pyrogallolarene macrocycle compared to the well-documented resorcinarenes. Alkylation of the pyrogallolarene macrocyle with ethyl bromoacetate was successfully achieved and analysis of both isolated products (rccc and rctt) revealed that the original conformations are maintained and are temperature stable.

The same acidic reaction conditions were used to condense pyrogallol with a variety of ketones leading to the first ever pyrogallolarenes possessing two alkyl groups at the bridging carbons. The conformations of this new class of sterically hindered pyrogallolarene were established.

Also reported is the development of new gentle, environmentally friendly condensation conditions for the preparation of pyrogallolarenes. This work lead to the development of a new and novel metal catalysed condensation reaction. We found that these conditions are highly efficient for the preparation of pyrogallolarenes from aryl aldehydes possessing electron rich groups. Furthermore, the resulting cyclic tetramers prepared by this new methodology, are of higher purity than the cyclic tetramers prepared from the harsh acid condensation conditions that have been used to date.

The final section of this research work involved the investigation of the ion selectivity of both calix[4]arene phthalonitriles and pyrogallol[4]arenes using picrate extractions, mass spectral techniques and ion selective electrode based potentiometry.

Chapter 1

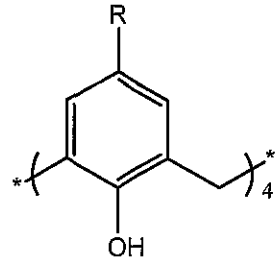
Literature Survey

I. Calixarenes

The history of calixarenes[1] extends back to the work of Adolph von Baeyer in 1872. A hard resinous non-crystalline product was formed from the reaction of aqueous formaldehyde with phenol. It was not possible to fully characterise the products at the time and it was not until decades later that the cyclic structure of these compounds was successfully determined.

A. Structure and Conformations

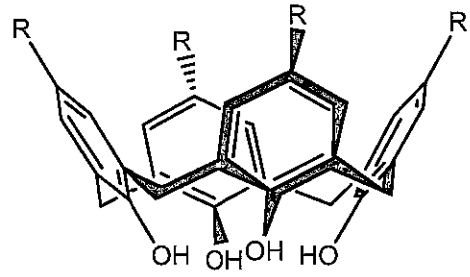
1. Structure of Free Calixarenes



1

Figure 1: *General structure of a calix[4]arene*

A calixarene (**1**) is a cyclic compound consisting of repeated phenol units. The most common stereoisomer for the calixarenes is the cone conformation (Figure 2). It is this from this structure that Gutsche *et al.*[2] derived the name calixarene, as the molecule resembles a chalice (calix) and consists of aromatic rings (arene). Calixarenes have been known by many different names such as mehrkermethylenephenolverbindungen (Zinke[3]), Zinke products, and cyclic tetranuclear novolaks[4]. *P-tert*-butylcalix[4]arene is more systematically named as 5,11,17,23-tetra-tert-butyl-25,26,27,28-tetrahydroxycalix[4]arene[1].

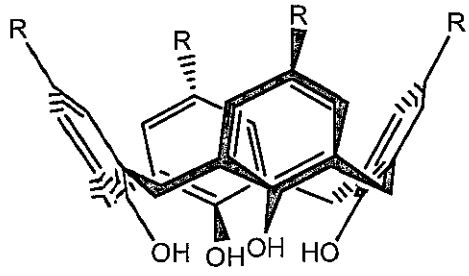


1a

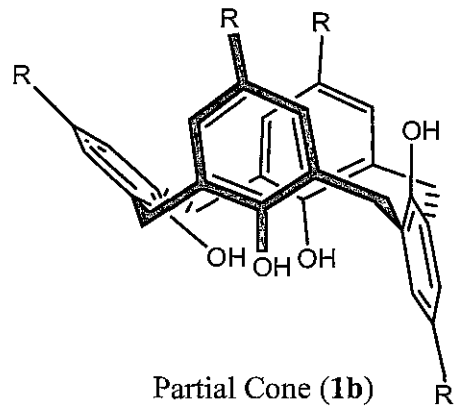
Figure 2: *Calix[4]arene in the cone conformation*

Calixarenes are known to range in size from 4 to 14 phenol units[5]. The most studied calixarene rings consist of 4, 6 or 8 phenol units. The number of phenol units in the ring is denoted by the numeral in square brackets e.g. calix[4]arene for a cyclic tetramer or calix[6]arene for a cyclic hexamer.

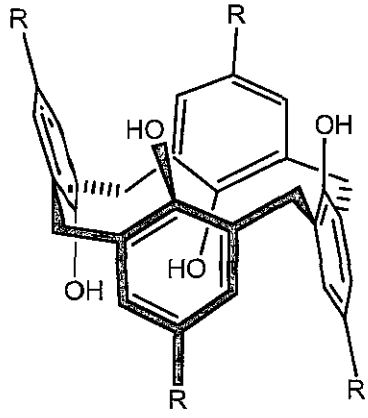
Calix[4]arenes can exist in four conformations: cone (**1a**), partial cone (**1b**), 1,2-alternate (**1c**) and 1,3-alternate (**1d**) (Figure 3).



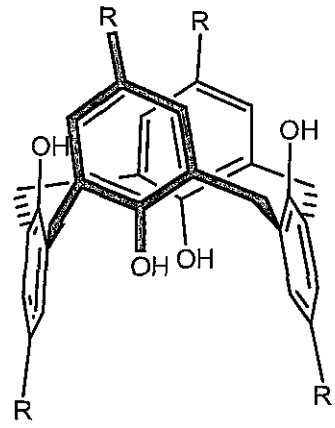
Cone (**1a**)



Partial Cone (**1b**)



1,2-alternate (**1c**)



1,3-alternate (**1d**)

Figure 3: *Conformations of calix[4]arenes*

Larger calixarenes can exist in more conformations, for example the pleated loop conformation for the calix[10]arene (Figure 4)[6].

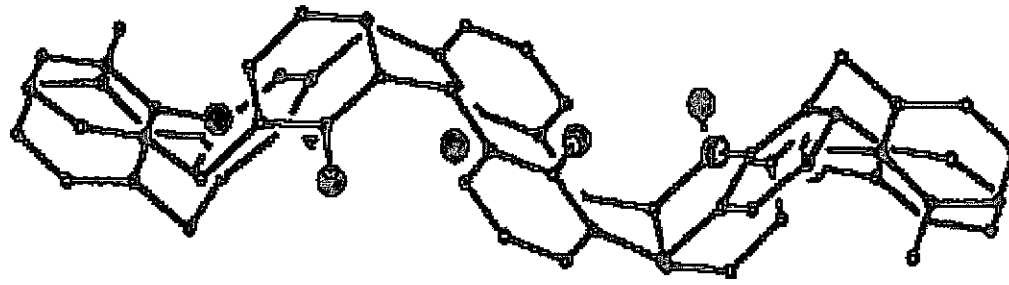


Figure 4: *The pleated loop conformation of calix[10]arene*[6]

The cone conformation is the thermodynamically favoured conformation for many calix[4]arenes. However, they are conformationally mobile at room temperature. In general, mobility increases with increased ring size[7].

The protons of the CH_2 groups that bridge the phenyl rings are in different chemical environments (axial and equatorial) but interconvert quickly on the NMR time scale to show a singlet. When the temperature is dropped sufficiently, the conformation becomes more rigid and interconversion is slower which causes the CH_2 signal to resolve into a pair of doublets[8].

The calix[8]arene shows a ^1H NMR spectrum which is almost identical to that of the calix[4]arene in non H-bonding solvents ($CDCl_3$ or bromobenzene-d_5). Both the octamer and the tetramer show resolution of the CH_2 groups into a doublet at around 5°C. This similarity disappears in pyridine-d_5 where there is no resolution of the CH_2 into a doublet in the case of the octamer, even at temperatures as low as -40°C.

The difference in NMR spectra is attributed to the H-bonding ability of pyridine, which interferes with the intramolecular H-bonding and this results in a less rigid conformation.

When a calixarene changes from one conformation to another, the OH group must pass through the centre of the macrocycle ring. Evidently when this group is larger, e.g. ether or ester, steric effects come into play and the molecule is generally locked in one conformation i.e. stabilisation of the ring occurs.

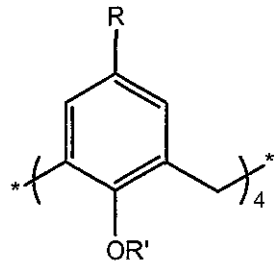


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Figure 5: *General structure of substituted calix[4]arene*

The substituents on the upper and lower rings play a part in determining the overall conformation of the macrocycle. Table 1 lists some of the different conformations formed depending on the R and R' substituents (**2**, Figure 5).

***p*-substituent (R)**	**OR' group**	**Conformation**
H	OMe	Partial Cone
t-Butyl	OMe	Partial Cone
H	OEt	Partial Cone
t-Butyl	OEt	Partial Cone
H	$OCH_2CH{=}CH_2$	Partial Cone
t-Butyl	$OCH_2CH{=}CH_2$	Cone
H	$OCH_2C_6H_5$	Cone
t-Butyl	$OCH_2C_6H_5$	Cone
t-Butyl	$OSiMe_3$	Cone
$CH_2CH{=}CH_2$	$OSiMe_3$	Cone
C_6H_5/ *t*-Butyl	$OSiMe_3$	Cone
H	OCOMe	1,3-alternate
t-Butyl	OCOMe	Partial Cone
C_6H_5/ *t*-Butyl	OCOMe	1,3-alternate + Partial Cone

Table 1: *Conformations of different substituted calix[4]arenes*[8]

2. Structure of Ion Bound Calixarenes

The majority of studies on the structure of calixarenes encapsulating metal ions has been focused on the substituted tetramers. In the ester-substituted molecules, the metal ion is situated among the oxygen atoms of the pendant groups. However, the X-ray crystal structure of the monocaesium derivative of the unsubstituted macrocyclic tetraphenol *p-tert*-butylcalix[4]arene shows that the caesium ion is not bound to the phenolic oxygens but is encapsulated within the actual macrocycle[9].

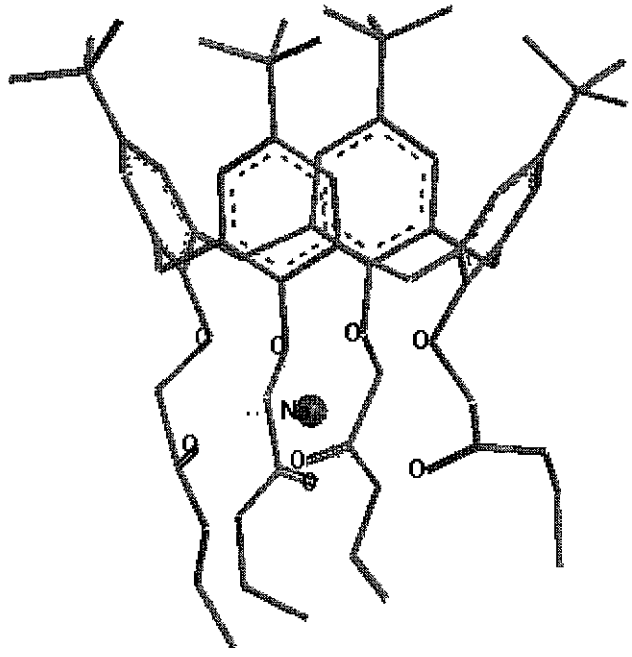


Figure 6: *Tetraethyl ester calix[4]arene with sodium bound in the cavity*[10]

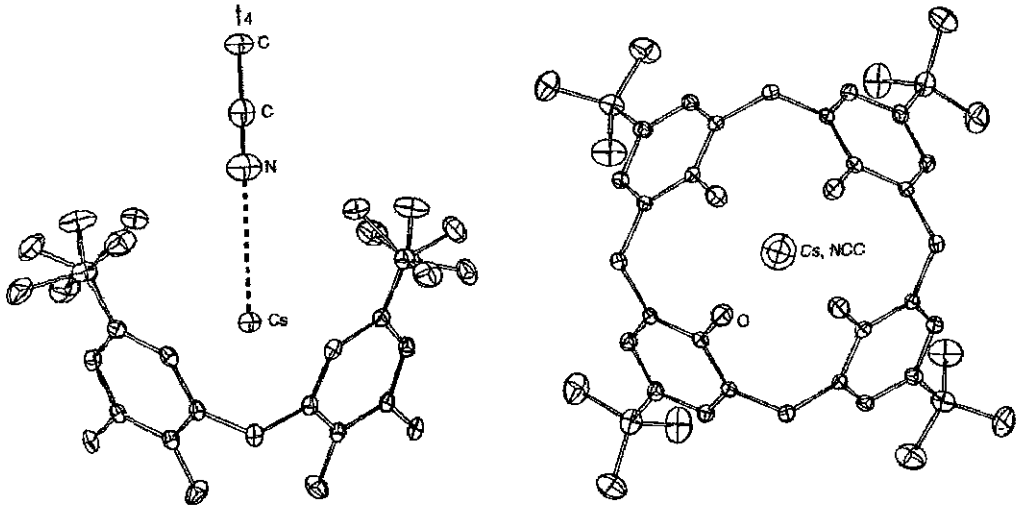
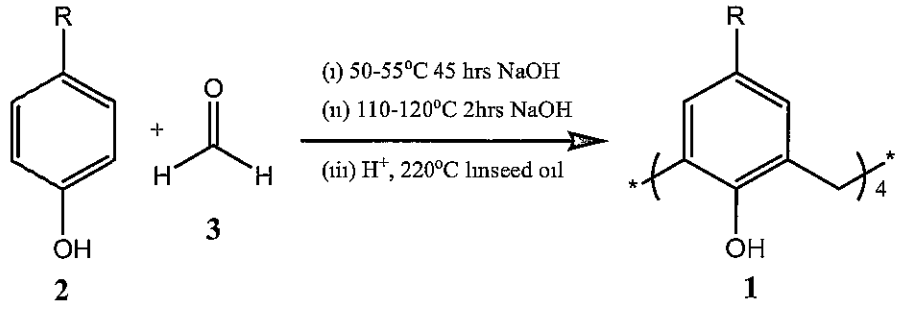


Figure 7: *Diagram of calixarene binding of caesium*[9]

B. Synthesis

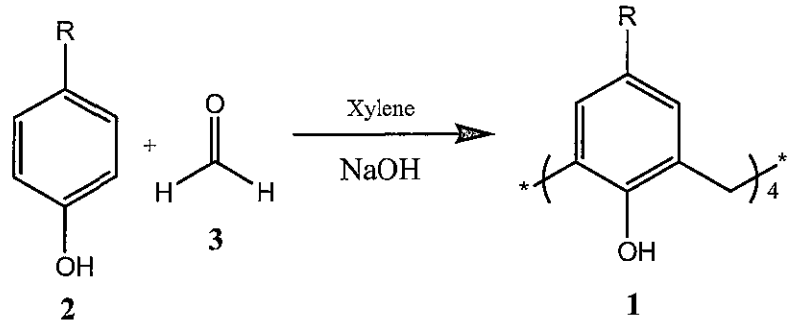
1. Base Catalysed Synthesis of Calixarenes

A three-step method to synthesise the cyclic macrocycles was developed by Zinke *et al.*[3,11-13]. This method involved heating *para*-substituted phenols (**2**) with aqueous formaldehyde (**3**) and sodium hydroxide at 50 - 55°C for 45 hours, followed by heating at an increased temperature of 110 - 120° C for a further two hours. After acidification at this stage, the resinous material is suspended in linseed oil and heated at 220°C for several hours.



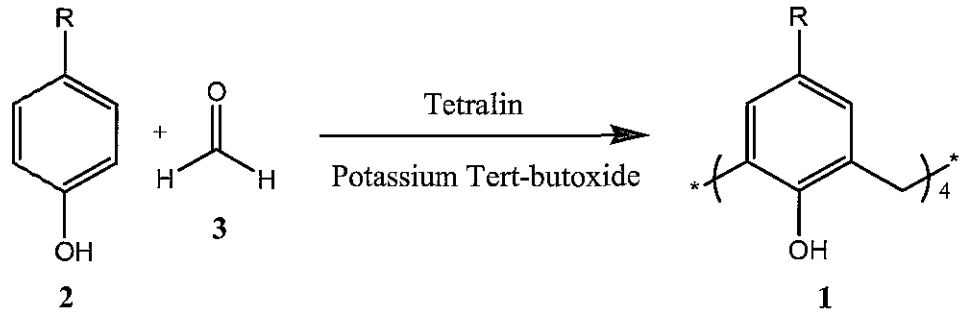
Scheme 1: *Zinke's 3-step calixarene synthesis*

Munch developed an alternative one step method for the synthesis of compounds that closely resembled those of Zinke. Munch's synthesis, which is detailed in a review by Gutsche *et al.*[13] involved the reflux of *para*-substituted phenol (**2**), paraformaldehyde (**3**) and a small amount of concentrated aqueous base (such as KOH) in a hydrocarbon solvent (xylene) for several hours.



Scheme 2: *Munch's one step calixarene synthesis*

Patrick and Egan[14] adapted the Munch method by using potassium *tert*-butoxide in place of KOH and tetralin in place of xylene. This method was found to be much more satisfactory even though limitations exist in the range of phenols that can be used successfully.



Scheme 3: *Patrick and Egan's calixarene synthesis*

Gutsche *et al.*[13] set up a study to compare the products of these various synthetic methods. The Munch and Patrick-Egan syntheses resulted in the formation of the cyclic octamer in moderate yields (37-45%) with the hexamer and tetramer being produced in lower yields. The product of the three-step Zinke reaction contained 26% octamer and 6% tetramer with no evidence of hexamer formation. When Dowtherm (a eutectic mixture of phenyl ether and diphenyl) was used in the final thermal step instead of linseed oil, the octamer and the tetramer were formed in nearly equal amounts.

Despite these results by Gutsche *et al.*[13], the yields obtained by each of these methods and even the products obtained have been known to vary greatly from one laboratory to another or even from one synthesis to another by the same chemist. For years the synthesis of these compounds seemed like a hit and miss situation. Following Zinke's method, the extent of acidification at the second step of the synthesis can greatly affect the resulting products. Complete neutralisation removes too much base, which impedes the reaction. Insufficient acidification leaves too much base, which changes the course of the reaction.

At a concentration of 0.03-0.04 equivalents of base, the yield of the cyclic tetramer is at it's highest (60%). A decrease in the base used in the reaction mixture causes the

yield of the tetramer to decrease ultimately to zero. An increase in the amount of base used also causes the yield of the tetramer to decrease. However, in this case, the formation of the cyclic hexamer increases and reaches a maximum at 0.4 equivalents. (See Figure 8)

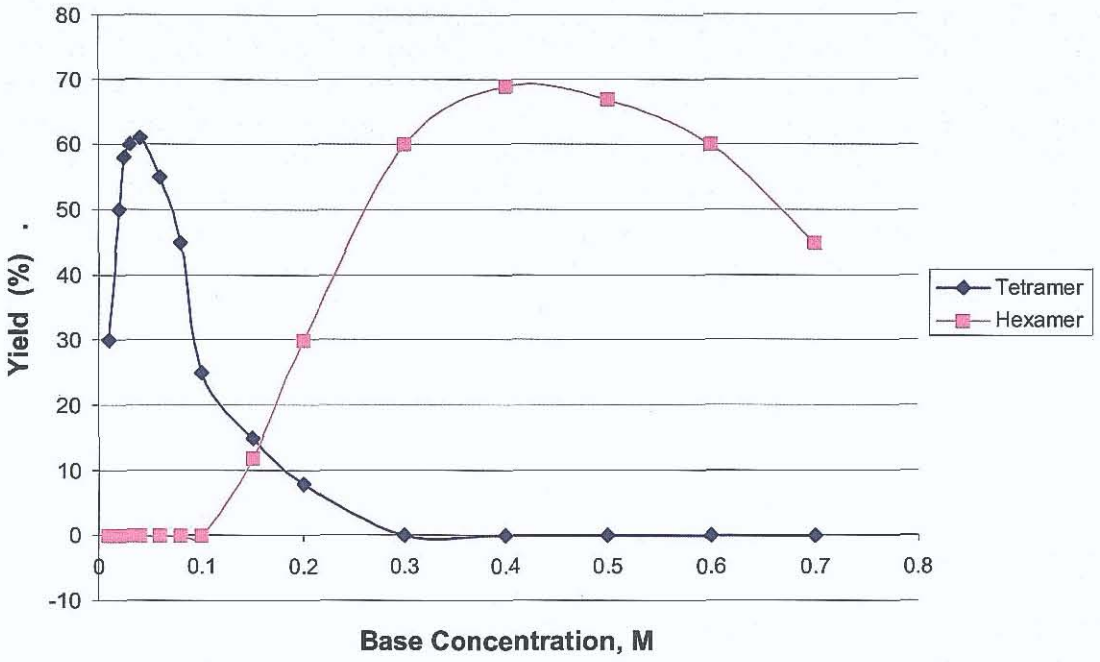


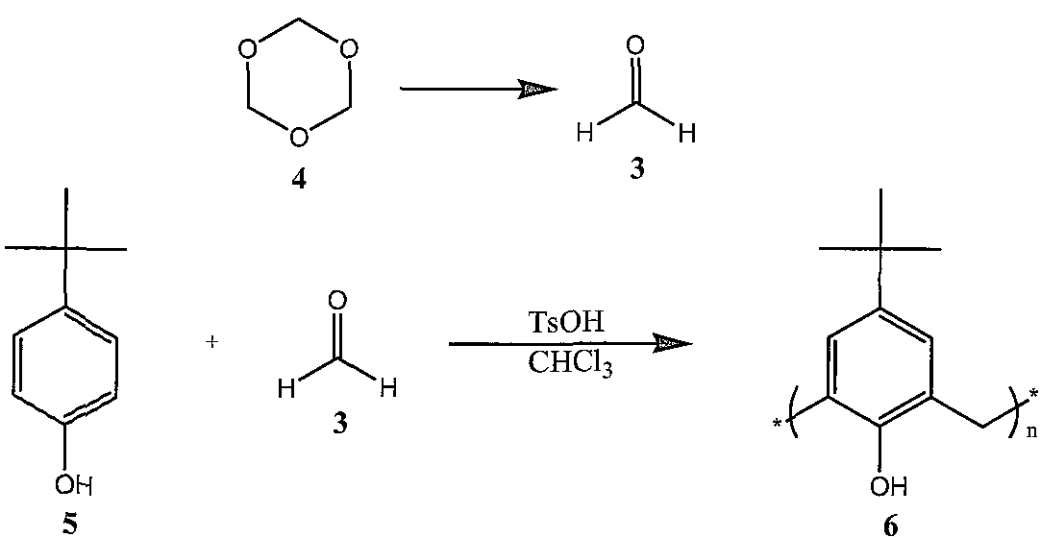
Figure 8: *Effect of base concentration on the formation of p-tert-butylcalix[4]arene and p-tert-butylcalix[6]arene*[4]

The cation that accompanies the basic anion can have a lesser but still significant effect on the outcome of the reaction[4,13]. When the base is included in the reaction mixture at a ratio of 45:1 phenol:base, the following differences are found. Lithium hydroxide as a base catalyst in the cyclisation is quite inferior to other alkali metal hydroxides. Sodium hydroxide, potassium hydroxide and caesium hydroxide have been shown to give similar reaction mixtures with the octamer being the major component. The hydroxides of alkaline earth metals magnesium and calcium ($Mg(OH)_2$ and $Ca(OH)_2$) cause a completely unsuccessful reaction, in which the starting materials are almost totally recovered. When barium hydroxide is used, a reaction occurs but yields a series of linear oligomers instead of the desired cyclic products.

However, when the concentration of base in the reaction mixture is increased to 2:1 phenol:base, the results are quite different[13]. The percentage yield of the hexamer increases with the larger alkali metal cations (K^+, Rb^+ and Cs^+) acting as catalyst, with the rubidium hydroxide producing the pure hexamer in 74% yield. It has been speculated that templation causes these effects. The tetramer is quite a rigid structure while the octamer is very flexible. The hexamer is flexible enough to accommodate a range of cations with the diameter of the ring ranging from 2.0 to 2.9Å. This cavity diameter is suitable for encompassing potassium or rubidium ions, which have cation diameters of 2.66 and 2.94Å respectively.

2. Acid Catalysed Synthesis of Calixarenes

The acid catalysed reaction of phenol and formaldehyde was for many years assumed to result in the formation of linear oligomers with the cyclic products only being formed in very small amounts, if at all[4,15]. Ludwig and Bailie[16] have also reported small amounts of calixarenes as products in the acid catalysed reaction. However, Stewart and Gutsche[15] discovered that a 25-30% yield of calixarenes could be produced by refluxing *p-tert*-butylphenol (**5**) with a slight excess of paraformaldehyde (**3**) in AcOH with a catalytic amount of HCl. A high proportion of the mixture of calixarenes consisted of "large" calixarenes (calixarenes containing more than eight aryl units[17]). A study was carried out to perfect the reaction conditions to produce the "large" calixarenes by varying the acid catalysts, the solvents, the reaction times and the reactant ratios and concentrations.



Scheme 4: *Reaction conditions used to produce "large" calixarenes*

The highest yields of "large" calixarenes were produced with a high concentration of *p-tert*-butylphenol (**5**), *s*-trioxane (**4**) (which is used as a HCHO source), $CHCl_3$ and *p*-toluenesulphonic acid (TsOH) (Scheme 4). These conditions resulted in a very high yield of calixarenes which was a mixture of the "large" calixarenes with the slightly smaller calix[7]arene.

3. Green Chemistry in the Synthesis of Calixarenes

Solvents are well known to be some of the more toxic substances that are used in the laboratory and are harmful to the environment[18]. Solvents are often used in large amounts and are recycled wherever possible. However, the reduction in the quantity of solvent used or indeed its complete elimination from a reaction pot would significantly reduce the amount of toxic waste from the laboratory. Makha *et al*[19], devised a simple and rapid solventless procedure for the synthesis of *p*-phenylcalixarenes. Previously, the synthesis of this compound involved the use of diphenyl ether but the solventless procedure, as well as avoiding the use of diphenyl ether, also uses lower reaction times, lower energy, has an easier work-up and leads to higher yields. The synthesis consists of heating, to 120°, a slurry of *p*-phenylphenol and aqueous formaldehyde. After the mixture gets to temperature, a catalytic amount of 1M NaOH or KOH was added and heating continued under a stream of nitrogen for approximately one hour until oligomerisation had occurred. The solid was then broken down and heated again for a further hour and cooled to room temperature. The solid was then suspended in a 1:1 mixture of methanol and 1M HCl and stirred vigorously for 30 minutes. After filtration and drying, the mixture of small calixarenes was triturated with acetone to yield the calix[6]arene. Successive crystallation from acetone produced the remaining calix[4] and calix[5]arenes.

C. Properties

1. Ion Extraction of Calixarenes

Arnaud-Neu *et al.*[20] studied the effects of calixarene substituents on their ion extraction. A range of calix[4], calix[6] and calix[8]arenes were synthesised with various substituents on their upper and lower rings as shown in Figure 9. The data were obtained by extraction of metal picrates from aqueous solutions into the

dichloromethane solutions of the calixarene derivatives. The equilibrium concentrations of the picrates in the organic phase were then determined spectrophotometrically. The extraction data are shown in Tables 2 and 3.

Ester Series

	Tetramers					Hexamers				Octamers			
	7	**8**	**9**	**10**	**11**	**16**	**17**	**18**	**19**	**21**	**22**	**23**	**24**
Li	15.0	1.8	6.7	1.1	27.6	11.4	4.7	1.7	2.6	1.1	0.8	0.9	0.4
Na	94.6	60.4	85.7	34.2	94.0	50.1	10.4	10.3	6.7	6.0	7.5	8.3	4.1
K	49.1	12.9	22.3	4.8	75.8	85.9	51.3	29.1	25.2	26.0	20.2	25.5	12.1
Rb	23.6	4.1	9.8	1.9	53.4	88.7	94.1	41.2	77.7	30.2	28.9	29.8	17.5
Cs	48.9	10.8	25.5	4.6	81.9	100.0	94.6	54.8	94.6	24.5	30.1	20.1	27.0

Table 2: *Percent Extraction of Alkali Metal Picrates on Calixarene Esters*[20]

Ketone Series

	Tetramers				Hexamer	Octamers		Others	
	12	**13**	**14**	**15**	**20**	**25**	**26**	**27**	**28**
Li	31.4	49.8	46.6	34.1	1.2	0.7	1.5	2.6	0
Na	99.2	94.0	92.8	94.3	6.2	9.9	21.6	3.9	0
K	84.1	72.6	81.4	47.7	12 8	25.1	7.7	5.4	0
Rb	53.7	23.4	43.7	27.1	11.6	20.8	1.7	6.8	0
Cs	83.8	17.2	31 6	50 7	13.6	15.3	4.5	7.1	0

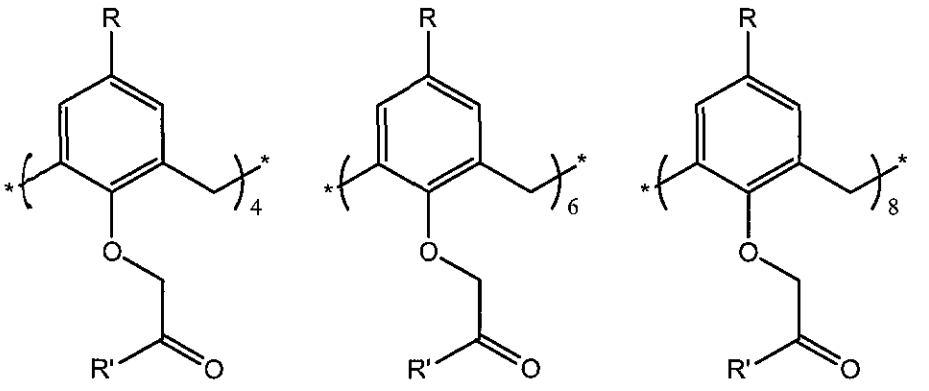
Table 3: *Percent Extraction of Alkali Metal Picrates on Calixarene Ketones*[20]

The presence of *p-tert*-butyl groups on the upper rims of the esters of all sizes generally caused an increase in the percentage extraction compared to the absence of the *p-tert*-butyl group, while not affecting the ion selectivity. However, the presence of this bulky alkyl group on the upper rim of the ketone series of calixarenes did not significantly affect the extraction. The smaller tetramers (**7-11**) showed a preference for Na^+, while the larger hexamers (**16-19**) and octamers (**21-24**) showed an affinity for the larger ions, K^+, Rb^+ and Cs^+ with little selectivity. The octamers show low

extraction and low levels of selectivity among the alkali cations[21]. The extraction ability of the hexamers was greater than that of the octamers, which is possibly due to the fact that the molecular cavity of the hexamers is larger and more uniform than that of the octamers as the octameric structure is large enough and flexible ebough to facilitate twisting[22]. While the ketone tetramers (**12-15**) show a lowered selectivity between ions, especially Na^+/K^+, these molecules possess the broadest range of extraction ability among the calixarenes tested. There is a significant increase in percentage extraction of Li^+ with the tetraketones compared to the tetraesters.

The larger cyclic compounds show minimal extraction of this small ion. The tetraketones also show a much greater affinity for the larger ions Rb^+ and Cs^+ than the tetraesters. Both the ester and ketone octamers show low levels of extraction and low selectivity between the five ions tested (Li^+, Na^+, K^+, Rb^+ and Cs^+). Evidence of macrocyclic necessity is shown by the reduced extraction of the acyclic analogue (**27**). The dihydroxy tetramer (**28**) shows no extraction of any of the ions tested, which implies that the ion requires a full encapsulation of oxygen atoms to bind successfully.

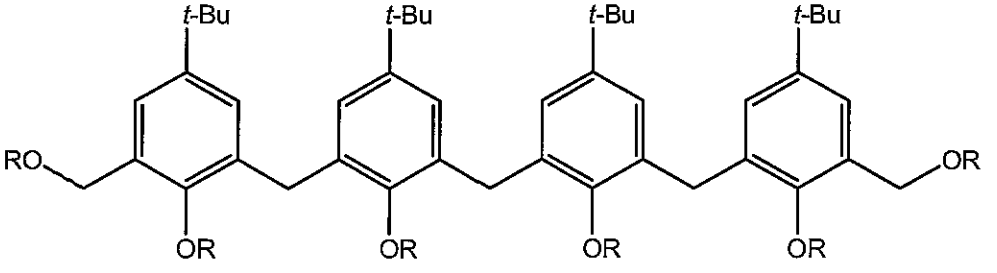
All of the cyclic tetrameric ionophores were found to exist in the cone conformation both in solution and in the solid state.



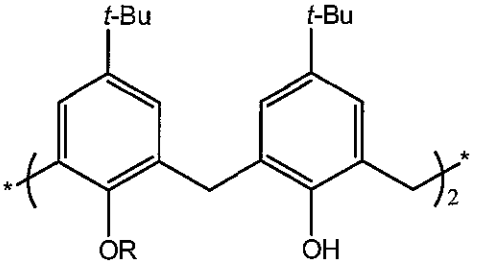
7 R=*t*-Bu R'=OEt
8 R=H R'=OEt
9 R=*t*-Bu R'=OMe
10 R=H R'=OMe
11 R=*t*-Bu R'=O*t*-Bu
12 R=*t*-Bu R'=Me
13 R=*t*-Bu R'=1-Ad
14 R=*t*-Bu R'=*t*-Bu
15 R=*t*-Bu R'=Ph

16 R=*t*-Bu R'=OEt
17 R=H R'=OEt
18 R=*t*-Bu R'=OMe
19 R=H R'=OMe
20 R=*t*-Bu R'=Me

21 R=*t*-Bu R'=OEt
22 R=H R'=OEt
23 R=*t*-Bu R'=OMe
24 R=H R'=OMe
25 R=*t*-Bu R'=Me
26 R=*t*-Bu R'=*t*-Bu



27 R=CH_2CO_2Et

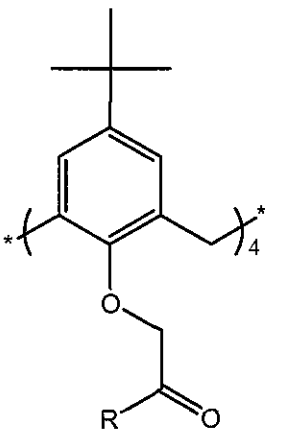


28 R=CH_2CO_2Et

Figure 9: *Substituted calix[4]arenes used in the study by Arnaud-Neu et al*[20]

In a later study, Arnaud-Neu *et al.*[23] investigated the difference between the selectivity ratio (S_{M+}) and the extent of extraction (%E) of a range of substituted calix[4]arenes as shown in Figure 10. The selectivity ratio (S_{M+}) is an expression of the preference of a receptor for one cation (M^+) relative to another (M'^+) and is shown

by the formula $S_{M+} = \beta_{M+}/\beta_{M'+}$ where β is the stability constant for complexation of each cation by the receptor. The extent of extraction (%E) refers to the ability of the receptor to transport a cation from one phase to another e.g. from water to chloroform.



29 R=OMe
30 R=OEt
31 R=OBu^n
32 R=OBu^t
33 R=OCH_2COPh
34 R=OCH_2CF_3

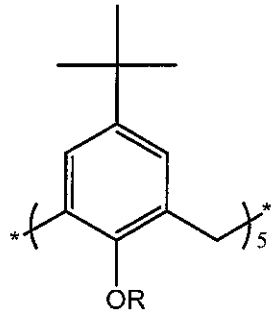
Figure 10: *Substituted calix[4]arenes used in the study by Arnaud-Neu et al.*[23]

The Arnaud-Neu group[23] found that Na^+ selectivity of the methoxy-substituted calix[4]arene (**29**) is lower than the ethoxy- (**30**) which is in turn lower than the O-*n*-butyl-substituted calix[4]arene (**31**). The *o-tert*-butyl-substituted tetramer (**32**) diminishes selectivity for Na^+ over K^+. The addition of a phenacyl ester in the R position (**33**) greatly increases the sodium selectivity, possibly due to the presence of 2 potential binding sites The trifluoroethyl ester (**34**) shows very low selectivity for sodium ions and also shows no extraction within the limits of accuracy. The X-ray crystal structure of this fluorinated compound is very similar to those of the methyl and ethyl esters suggesting that it is not the lack of preorganisation of binding sites that causes the poor extraction.

2. Calix[5]arenes

A study by Barrett *et al.*[21] investigated the difference between calix[4]arenes and calix[5]arenes. Li^+, Na^+, K^+, Rb^+ and Cs^+ all favour complexation with p-*tert*-butyl calix[5]arene in a 1:1 ratio. Both the *tert*-butyl ester and the ethyl ester pentamers show increased extraction for all ions compared to the ethyl ester tetramer and hexamer. The *tert*-butyl ester pentamer is more effective at complexation than the ethyl ester pentamer. The calix[4]arene ethyl ester in the cone conformation favours the sodium ion while the calix[5]arene ethyl ester also in the cone conformation favours larger ions with little selectivity between K^+, Rb^+ and Cs^+. The *tert*-butyl ester

pentamer also shows high extraction for larger ions with slight selectivity for K^+. The stability constants were found to reflect the extraction data.



35 R=H
36 R=CH_2CO_2Et
37 R=$CH_2CO_2Bu^t$
38 R=CH_2CO_2H

Figure 11: *Substituted calix[5]arenes used in the study by Barrett et al.*[21]

Barrett *et al.*[21] also investigated the extraction of silver ions. The ethyl pentamer (**36**) and the ethyl tetramer form equally strong complexes with Ag^+. The *tert*-butyl substituent enhances the stability of the Ag^+ complex by sterically enhancing the rigidity of the structure

For ester groups substituted onto the lower rim of a calix[4]arene, the nature of the substituent on this functional group influences the cation selectivity of the molecule[5]. The Na^+/K^+ selectivity is detrimentally affected by a decrease in the chain length of the alkyl substituent. The addition of a *tert*-butyl group causes the greatest loss in selectivity while the phenacyl group caused the molecule to show great selectivity for Na^+ over K^+. Substituents containing heteroatoms or multiple bonds can cause a significant difference in the Na^+/K^+ selectivity. The strong electron withdrawing character of the fluorine atoms in the trifluoroethylester cause the selectivity to drop dramatically.

Izatt *et al.*[24] studied the cation transport ability of a number of calixarenes of various sizes using a liquid membrane system. In all the tests, the calixarenes selectively carried Cs^+ through the H_2O-CCl_4, CH_2Cl_2-H_2O liquid membrane system. While the greatest selectivity for Cs^+ was shown by the calix[4]arene, the greatest flux of caesium ions was observed with the larger calix[6] and calix[8]arenes. It was postulated that this large ion flux effect might be due to the calixarene binding two metal ions. Low [Cs^+]-to-[Rb^+] ratio experiments were carried out which showed that the *p-tert*-butylcalix[6]arene is selective for Rb^+ under these conditions. As the concentration of caesium ions in the mixture increases in relation to the concentration

of rubidium ions, the tendency towards Cs^+ selectivity increases, suggesting that the cation flux depends, in part, on the relative concentration of the cations in the source phase.

3. Calixarene Carboxylic Acids

While calixarene esters do not complex alkaline earth metal ions[25], calixarene carboxylic acids show effective complexation with both alkali and alkaline earth metal cations[26]. *P-tert*-butylcalix[4]arenes substituted with two ether groups and two carboxylic acid groups on the lower rim (**39**, Figure 12) have been studied for their ability to extract alkaline earth ions[27]. The calix[4]arene diacid (**39**) forms a 2:1 ion-ligand stoichiometry in most cases. Calcium is preferentially extracted followed by strontium and barium. Extraction of magnesium with these compounds is very low.

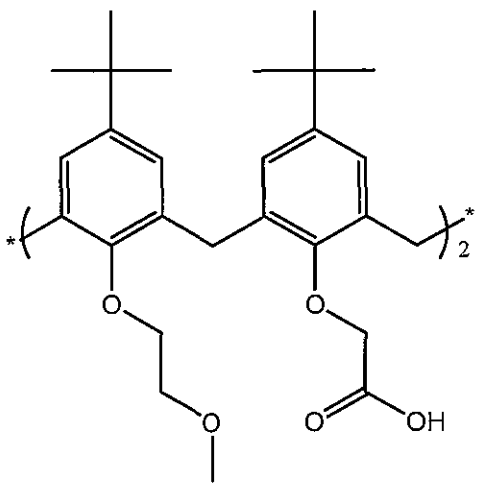


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Figure 12: *Calix[4]arene diacid*

Studies have been carried out on a variety of calixarene carboxylic acids ranging from monoacids to triacids[26]. Calixarene carboxylic acids are much better complexing agents than either the calixarene tetraesters or tetraketones. The tetraacid is also better than the equivalent tetraamides when pH is taken into account. The calixarene carboxylic acids show stronger complexation with the divalent alkaline earth ions than with monovalent alkali metal ions.

4. N- and S-containing Functional Groups

The binding of calixarene derivatives with cations tends to increase according to the order: ester < ketone < amide < carboxylic acid irrespective of the cation involved[5].

This series is also the order of increasing basicity of the carbonyl oxygen atoms. Acid and amide derivatives of calix[4]arenes show a strong affinity for alkaline earth metals, with which ester and ketone derivatives do not associate at all.

Replacement of the carbonyl groups of *p-tert*-butylcalix[4]arene tetradiethylamide by thiocarbonyls causes a significant decrease in extraction efficiency with regards to a selection of ions. An increase in extraction is observed for Cu^{2+}. The thioamide shows increased selectivity for some heavier ions even though it's efficiency is low.

Extraction of metal cations from an aqueous phase into dichloromethane was studied by Chang *et al.*[25] It was found that calixarene amides were selective for divalent cations, in particular strontium and barium, as opposed to the monovalent alkali metal cations. The higher polarity of the amide carbonyl coordinating site, compared to the ester carbonyl group ensures a stronger interaction of the ligand with divalent rather than monovalent ions of a similar size.

5. Phosphorous-containing Calixarene Derivatives

Extraction of lanthanides and actinides has been shown to occur with phosphorous substituted calixarenes[5]. Calix[4]- and [5]arenes substituted at the upper ring by a CMPO-like functionality (-NH-C(O)-CH_2-P(O)Ph_2) have been studied for their extraction ability of lanthanides and actinides[28]. These derivatives have shown increased extraction of europium, thorium, neptunium, plutonium and americium compared to the commonly used extractant, CMPO (carbamoylmethylphosphine oxide). The analogous linear compounds also showed greater extraction capabilities than CMPO. Several ligating groups are thought to cooperate to increase the extration abilities of the molecules. The exact structure and composition of the extracted complex is not yet known.

Calixarenes substituted on their lower rims with phosphorous containing derivatives have also been studied. Malone *et al.*[29] substituted a phosphorous group ($OCH_2CH_2POPh_2$) onto the lower rim of calix[4], [5] and [6]arenes (**40**), which showed a high efficiency in extraction of europium, thorium, plutonium and americium from simulated nuclear waste. Picrate extraction studies showed greater

extraction capabilities than CMPO complexes. Thorium is possibly extracted in a 2:1 complex with the substituted calixarene. *P-tert*-butyl substituents on the upper rim cause an increase in extraction of thorium. The tetravalent thorium ion shows enhanced extraction compared to the trivalent europium ion. Various different compounds in this series (n=4, 6, 8; R=H, *p-tert*-butyl) extracted plutonium and americium to greater or lesser extents.

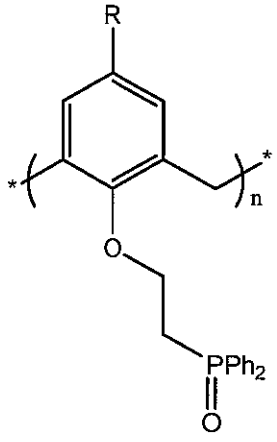

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Figure 13: *Lower rim phosphorous substituted calixarenes (R = alkyl, n =4-6)*

6. Nitrogen-containing Calixarene Derivatives

Studies have also been carried out on calixarenes substituted on the lower rim with nitrogen-containing groups[30] (Figure 14). Both derivatives studied were shown to be better at extracting alkali cations than the corresponding esters. The pyrrolidinyl amide proved to be a better carrier for Li^+, Na^+ and K^+ than the diethyl amide. Both tetraamides show selectivity for the potassium ion over the other alkali ions tested.

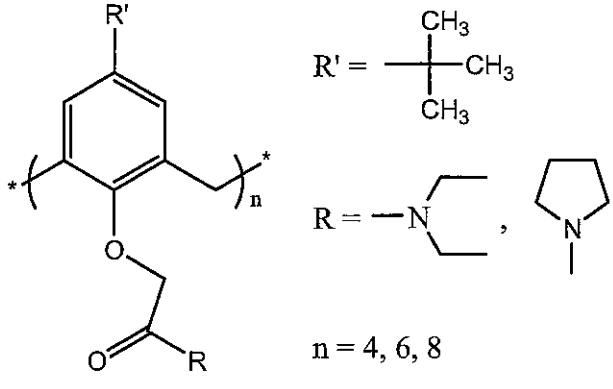

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Figure 14: *Nitrogen substituted calixarenes*

7. Unsymmetrical Calixarenes

The Arnaud-Neu[23] group studied some unsymmetrically substituted calix[4]arenes. The introduction of one methyl ester group among three ethyl esters showed no significant difference in Na^+ selectivity. There was also very little selectivity difference after the introduction of two methyl ketone groups with two ethyl ester groups.

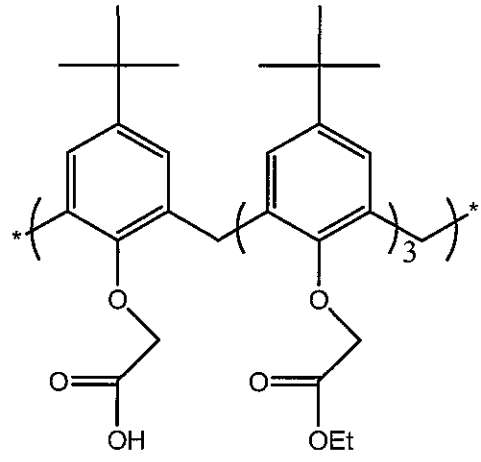

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Figure 15: *Monoacid triester substituted calix[4]arene*

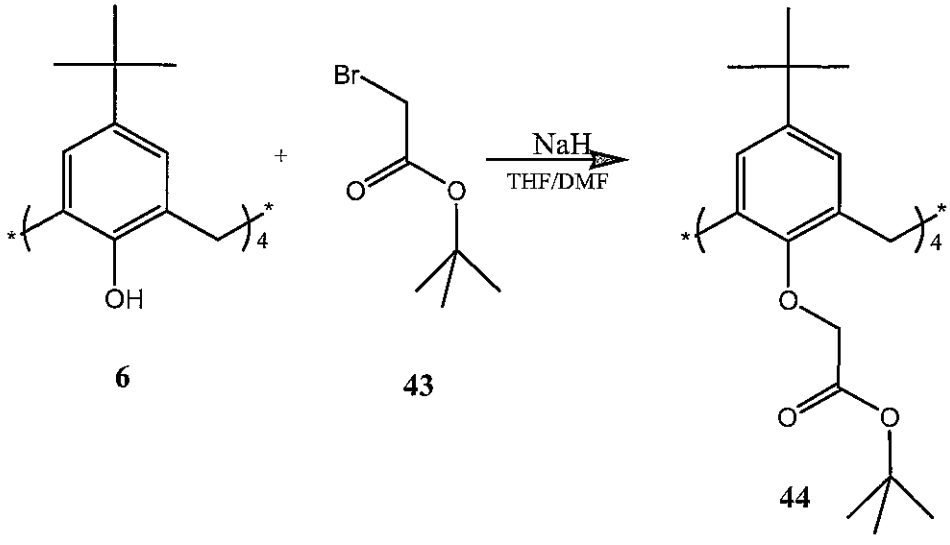
The monoacid triester (Figure 15) showed high logβ values for both Na^+ and K^+, which meant that there was low selectivity for Na^+ over K^+ (S_{Na+} was low). The percentage extraction for this compound was 0%. The authors postulated that there was a possibility of extraction of Na^+ or K^+ as a neutral complex with the calix[4]arene in a mono carboxylate anionic form.

One tertiary amide group substituted on the lower rim of the calix[4]arene with three ethyl ester groups showed strong binding of both sodium and potassium ions but again low selectivity between the two. The strong binding power of the amides is evident in extraction where selectivity still favours the Na^+ ion.

8. NMR Studies

^1H NMR studies[31] of calix[4]arene *tert*-butyl ester (Scheme 5) showed that addition of Na^+ ion (in the form of NaSCN) causes a downfield shift of aromatic protons by 0.4ppm (from 6.7 to 7.1ppm) and an upfield shift in the doublet of the axial protons by 0.7ppm (from 4.9 to 4.2ppm). The methylene protons of the acetate moieties are

shifted 0.4ppm upfield (from 4.7 to 4.3ppm) whereas all other signals shift slightly downfield. The studies of Arduini *et al.*[31] show a 1:1 complexation ratio, as the ^{1}H NMR signals do not shift further upon addition of more than one equivalent of metal ion. For ratios of ligand:metal ion lower than 1:1, a mixture of the free ligand and complex is observed, indicating that inclusion speeds are low on the NMR time scale at room temperature.



6 **43** **44**

Scheme 5: *Synthesis of calix[4]arene tert-butylester*

The same studies on this compound with KSCN also show a 1:1 complexation ratio. However, when the [K^+]/[ligand] ratio is lower than 1, the peaks in the ^{1}H NMR are broadened, indicating fast exchange rates This is probably due to the fact that K^+ is less tightly bound to the hydrophilic cavity and therefore can exchange more quickly than Na^+

9. Calixcrown Ion Binding

Crown ethers have shown the ability to separate alkali and alkaline earth metal cations. Alfieri *et al.*[32] synthesised the first calixcrown or 'crowned' calixarene as they called it (**45**, Figure 16). Corey-Pauling-Koltun (CPK) models show that when a polyethereal chain joins the two opposite hydroxy groups, a circular ring is created. The calixarene moiety is in the cone conformation and the two free hydroxy groups are positioned one to each side of this polyethereal ring. The calixcrown was synthesised in 30% yield from molar equivalents of *p-tert*-butylcalix[4]arene and

pentaethylene glycol ditoluene-*p*-sulphonate in refluxing benzene for 48 hours. Two equivalents of *t*-BuOK were added stepwise in two 1 equivalent portions. After purification, the compound was found to be in the cone conformation by X-ray crystal data (Figure 16, R = H, n = 4).

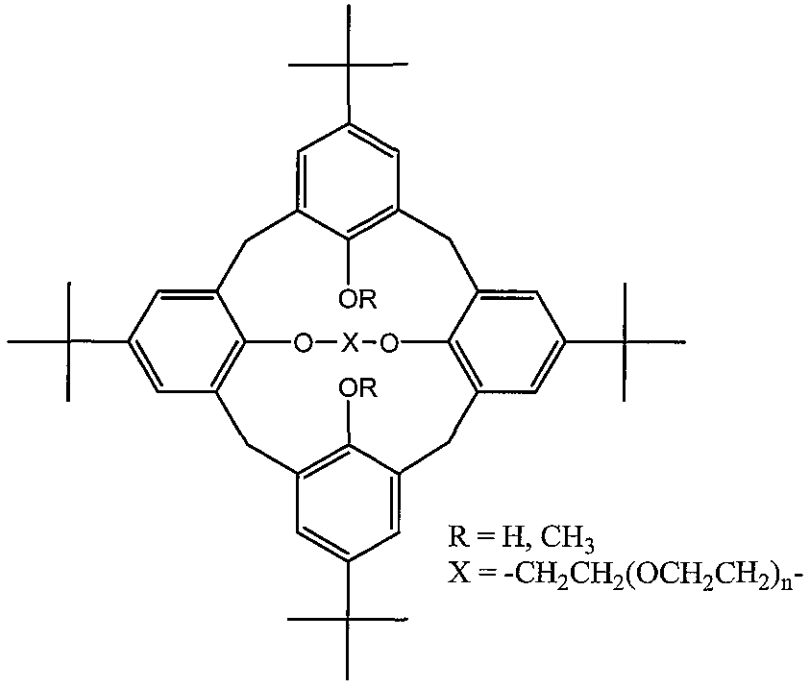


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Figure 16: *Calixcrown*

Ghidini *et al.*[33,34] used two methods to synthesise the calixcrowns. Their first method involved dialkylation of the *p-tert*-butylcalix[4]arene followed by addition of the crown ether chain. Reaction of *p-tert*-butylcalix[4]arene with diazomethane produced a complex mixture of mono-, di-, tri- and tetramethoxy substituted calixarenes. When methyl tosylate in THF was used instead of diazomethane, this produced a mixture of mono- (20%) and 1,3-dimethoxycalixarene (32%) and some unreacted starting material. Yields were increased by reacting the *p-tert*-butylcalix[4]arene with methyl tosylate in acetone and potassium carbonate. These reaction conditions improved the yield of the 1,3-dimethoxycalix[4]arene to 75%. Very high yields (95%) of 1,3-bis(benzyloxy)-p-tert-butylcalix[4]arene were produced from the reaction of benzyl tosylate with *p-tert*-butylcalix[4]arene in acetone and sodium carbonate.

Both the bis(benzyloxy) and the dimethoxy calix[4]arenes produced calixcrowns on reaction with sodium hydride and tetraethylene glycol ditosylate in 25% and 30%

yields respectively. However, it took a much longer reaction time for the 1,3-diethoxy-*p-tert*-butylcalix[4]arene to form a calix crown, even in small amounts. These results indicate that the nature of the alkoxy substituents has a direct influence on the bridging of 1,3-dialkoxy calix[4]arenes.

The second method used for the synthesis of dialkoxy calix[4]arene crown-5 was the formation of the dihydroxy calix[4]arene crown-5 followed by alkylation. The first step followed the method of Alfieri *et al.* to form the dihydroxy crown compound[32]. During the synthesis of dihydroxycalix[4]crown-5, the macrotricyclic product *p-tert*-butylcalix[4]arene bis-crown-5 was isolated (**46**, Figure 17).

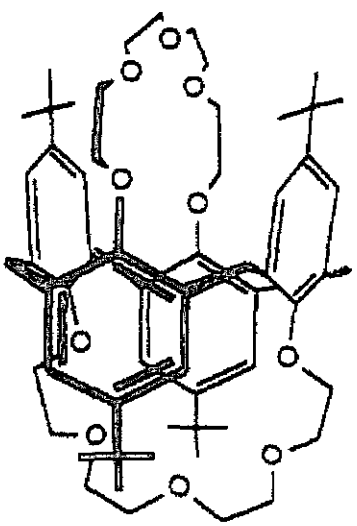

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Figure 17: *p-tert-butylcalix[4]arene bis-crown-5*

The dihydroxy compound was dialkylated with ethyl iodide in THF/DMF to give the diethoxycalix[4]arene-crown-5 in almost quantitative yield. However, the product was found by HPLC to be a mixture of three compounds with very similar retention times. After separation with TLC, the compounds were found to all have identical molecular weights (by MS) but NMR and X-ray crystallography analyses showed that the compound was formed as a mixture of the flattened cone, partial cone and 1,3-alternate conformations.

Dijkstra *et al.*[33] studied the conformational changes of calix crowns upon complexation. 1,3-dimethoxy-*p-tert*-butylcalix[4]arene-crown-5 (**47**, Figure 18) is

found in the cone conformation. However, upon complexation with potassium, the complex forms a flattened partial cone conformation. The same is true for the rubidium complex.

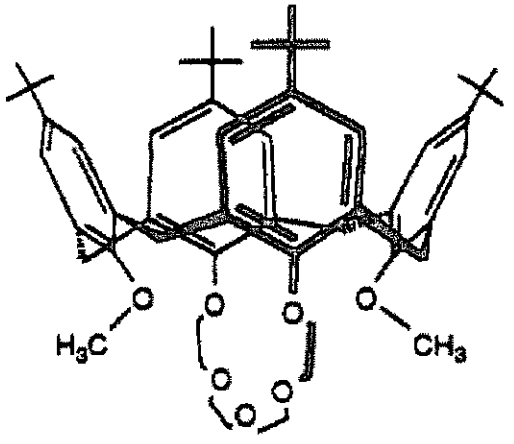

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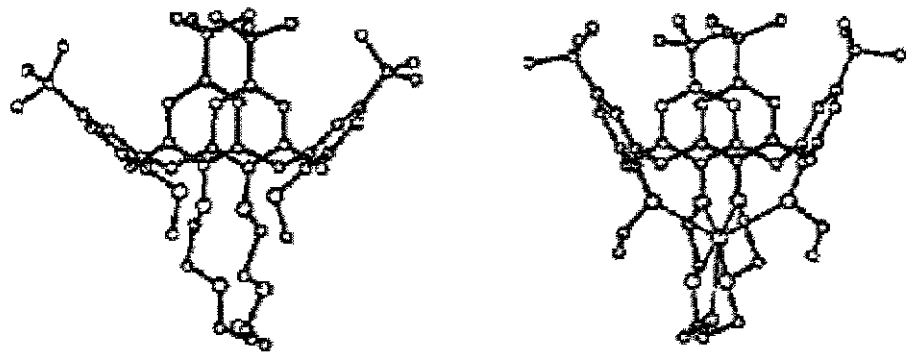
Figure 18: *1,3-dimethoxy-p-tert-butylcalix[4]arene-crown-5*[34]

Conversely, a year later, Ghidini *et al.*[34] found that the 1,3-dimethoxy-*p-tert*-butylcalix[4]arene-crown-5 showed a flattened cone conformation for the free ligand. X-ray crystal structures back up this claim (**47**, Figure 19). The same group also found that the potassium complex of 1,3-diethoxy-p-tert-butylcalix[4]arene-crown-5 (**48a**) shows a higher symmetry than the free ligand. The potassium ion is coordinated by seven oxygen atoms, five from the polyether ring and one from each of the ethoxy groups. In the uncomplexed ligand, the methoxy groups are free to move inwards into the cavity of the molecule. In the case of the partial cone configuration (**48b**), one ethoxy group is located in the hydrophobic cavity with the oxygen lone pairs pointing outwards whereas the other is beside the polyether ring. The oxygen lone pairs of both ethoxy groups are inside the hydrophobic cavity of the molecule when it is oriented in the 1,3-alternate conformation (**48c**).



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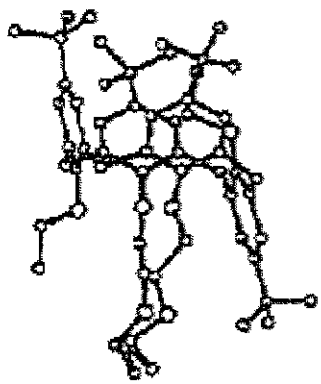
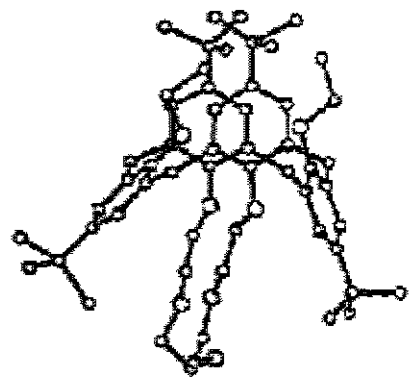
48a



48b



48c

Figure 19: *Crystal structures of 1,3-dimethoxy-p-tert-butylcalix[4]arene crown-5 (47) in the flattened cone conformation, the potassium picrate complex of 1,3-diethoxy-p-tert-butylcalix[4]arene crown-5 in the cone conformation (**48a**), 1,3-diethoxy-p-tert-butylcalix[4]arene crown-5 in the partial cone conformation (**48b**) and 1,3-diethoxy-p-tert-butylcalix[4]arene crown-5 in the 1,3-alternate conformation (**48c**)*[34]

A study was carried out by Ghidini *et al.*[34] to synthesise different conformationally stable forms of the same calix[4]arene crown ethers and to compare their complexing ability. They synthesised a range of 1,3-dialkoxycalix[4]arene crown ethers in the cone, partial cone and 1,3-alternate conformations. The study revealed that a slight difference in the geometry of the pre-organised macrocycle could dramatically affect its binding ability. In all cases the partial cone conformation showed the greatest alkali metal ion binding ability.

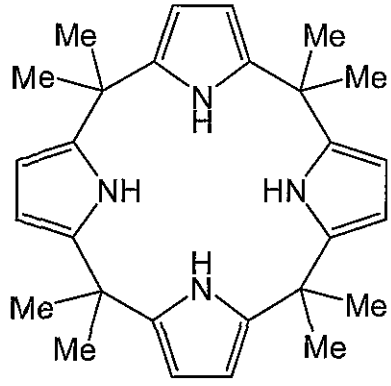
The cone conformation of the di-isopropoxycalix[4]arene crown ethers shows no extracting power towards alkali cations[5], while the 1,3-alternate conformer shows

high extraction with Cs^+ selectivity. The conformationally mobile methoxycalix[4]arene crown ether shows some extraction, again with selectivity towards the caesium ion.

The selectivity of the calix crowns is also dependant on the length of the polyether chain[5]. With 4 oxygen atoms in the polyether chain (Figure 16, n = 2) sodium is preferentially extracted but as the length of the chain increases, it is the ions with the larger ionic radii that are selectively extracted. When there are 5 ether groups on the chain (Figure 16, n = 3), this macrocycle is selective for potassium and rubidium and when this increases by one (Figure 16, n = 4), caesium is selectively extracted. The larger ring with 7 ether groups (Figure 16, n = 5) shows minimal extraction for any of the alkali metal ions tested.

II. Calixpyrroles

The first appearance of calixpyrroles in the literature is from Baeyer's work on acid catalysed condensation of pyrrole and acetone in 1886[35]. The product that Baeyer obtained was a white crystalline product and was subsequently characterised as an octamethyl substituted form of porphyrinogen[36] or *meso*-octamethyl-calix[4]pyrrole[37] (**49**, Figure 20). Porphyrinogens (**50**), macrocycles consisting of four pyrrole rings linked by the *meso*-like positions are useful porphyrin precursors and therefore have received much attention in the literature. However, substituted porphyrinogens cannot be used as porphyrin precursors and have only recently been studied in depth.



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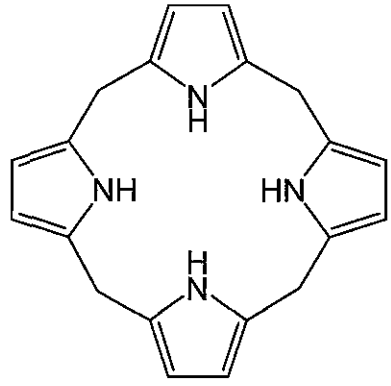
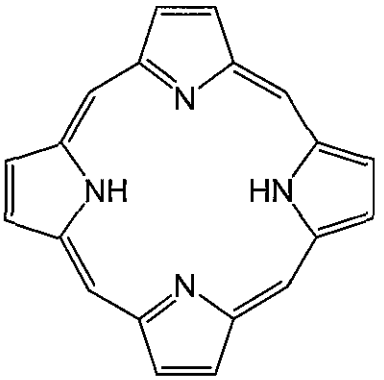


50

Figure 20: *Calix[4]pyrrole (49) and porphyrinogen (50)*

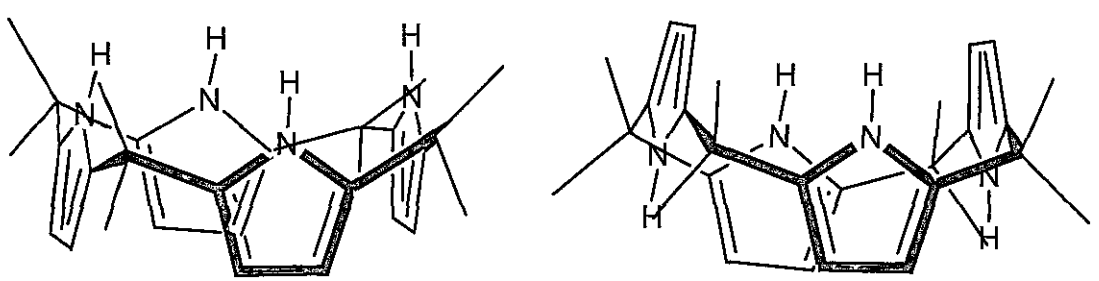


51

Figure 21: *Porphyrin*

A. Structure

Calix[4]pyrroles are flexible molecules which are similar in structure to porphyrins (**51**) However, the pyrrole rings are free to rotate in the calixpyrroles, where in the porphyrins, the sp^2 hybridisation in the porphyrin bridging carbons limits the molecule to a rigid structure. Calix[4]pyrroles are generally found to have a 1,3-alternate conformation (**52b**), which is different to calixarenes due to the inability of the calix[4]pyrroles to form hydrogen bonds between the various pyrrolic NH groups[38]. The 1,3-alternate conformation is unusual in calixarenes with only a few reports of structurally characterised examples in the literature, the first being by Beer and co-workers who reported X-ray crystallographic structural evidence of calixarene di- and tetra-esters in the 1,3-alternate conformation when complexed with K^{+}[39].



52a **52b**

Figure 22: *Calix[4]pyrrole in the cone (**52a**) and 1,3-alternate (**52b**) conformations*

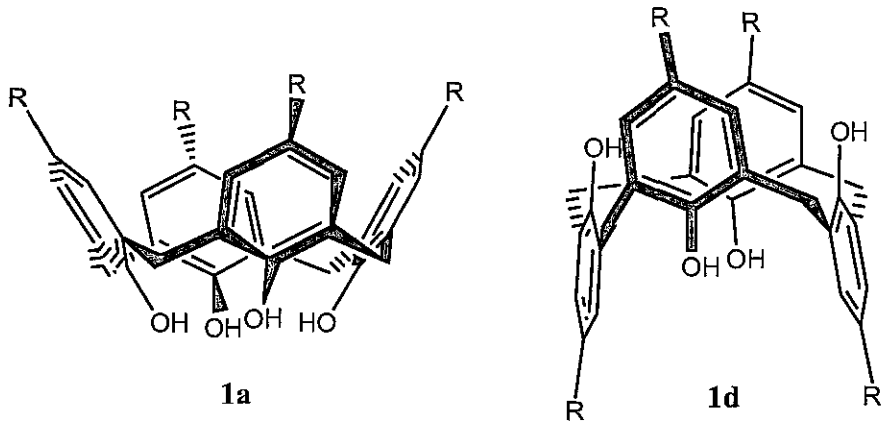
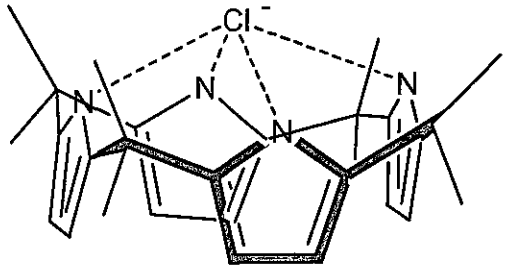


Figure 23: *Calix[4]arene in the cone (**1a**) and the 1,3-alternate (**1d**) conformations*

B. Anion Binding

Calixpyrroles have been shown to possess anion-binding properties[36]. The structure of the macrocycle changes considerably upon complexation with an anion. Slow evaporation of a dichloromethane/octamethyl calix[4]pyrrole solution containing an excess of tetrabutylammonium chloride (Bu_4NCl) produced crystals of the chloride complex.



53

Figure 24: *Calix[4]pyrrole/chloride complex*

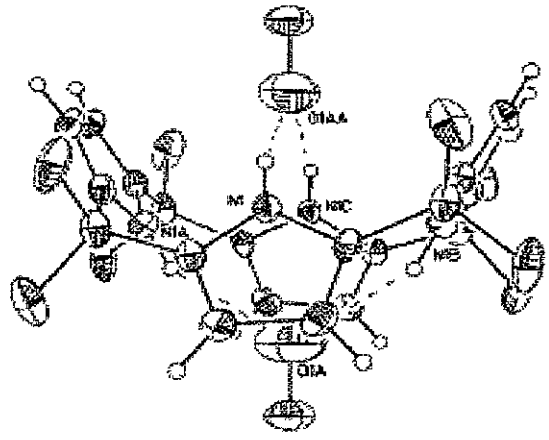
This ligand was shown to be in the cone conformation by X-ray crystal analysis (**53**, Figure 24). A similar method was used to produce crystals of a tetrabutylammonium fluoride (Bu_4NF)/tetraspirocyclohexylcalix[4]pyrrole complex. X-ray crystal analysis of this complex also showed a cone-like structure. In both cases the four NH protons form hydrogen bonds with the halide ion[38]. The structures of these two complexes are very similar, but the fluoride ion, in the solid state at least, is more tightly bound than the chloride ion. In the chloride complex, the nitrogen to ion distances are in the region of 3.264 to 3.331 Å, while the nitrogen to ion distances in the corresponding

fluoride complex are 2.970 Å. Symmetry causes the four pyrrole groups to be equivalent. Because of the differences in nitrogen to ion distances, the chloride ion resides much further above the N4 root mean square plane than the fluoride ion (2.319 and 1.499 Å respectively)[36]. In ^{19}F NMR of the fluorine complex, the bound fluorine atom produced a quintet, which implies that it is bound to the four NH protons.

C. Binding of Neutral Substrates

Due to the small number of available functionalising sites that are suitable for hydrogen bonding in neutral molecules such as short chain alcohols or simple monoamides, binding of these neutral substrates poses a problem in supramolecular chemistry. Adding to this problem is the lack of large hydrocarbon surfaces necessary for efficient hydrophobic or π-π interactions[40].

Meso-octamethylcalix[4]pyrrole (**54**, Figure 25) was investigated as a neutral substrate acceptor[40]. It adopted a 1,3-alternate conformation in the solid state upon complexation with two methanol molecules. One alcohol molecule lies above the macrocycle and one below, each doubly hydrogen bonded to the two pyrrolic NH groups. This is a similar conformation to the one formed by oxidised porphyrin when complexed with two water molecules[41]. The pyrrole groups are tilted inwards, which gives further evidence that the methanol molecules are bonded to the macrocycle and are not just occupying space in the lattice. An X-ray crystal structure of *meso*-octamethylcalix[4]pyrrole·2(DMF) (DMF = N,N-dimethylformamide) was also obtained. The calix[4]pyrrole in this case adopts a 1,2-alternate conformation with each amide hydrogen bonded to adjacent pyrroles. Each of the DMF molecules lies 3.4Å above the plane of one of the pyrrole rings to which it is not bonded. This lead to the proposal by Gale et al.[40] that the stabilization of the calix[4]pyrrole-DMF complex is due to π-π stacking interactions.

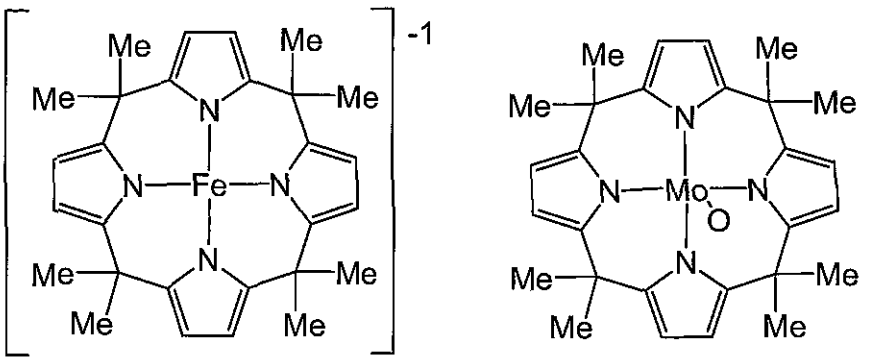


54

Figure 25: Meso-octamethylcalix[4]pyrrole bound to methanol molecules[40]

D. Transition Metal Complexation

Calix[4]pyrroles or porphyrinogens have been shown to coordinate with transition metals to form metallated porphyrin-like complexes which have been called artificial porphyrins[42]. The metallated complex was formed from octamethyl calix[4]pyrrole in a multi-step reaction[43]. Firstly, it was reacted with n-butyllithium ($LiBu^n$) in tetrahydrofuran (THF) to form the lithium salt. The salt was then reacted with $FeCl_2(THF)_{1.5}$ in a 2:1 molar ratio in THF, which produced a deep red solution. The residue formed upon evaporation of the solvent was purified by recrystallisation from toluene-acetonitrile, to yield the metallated complex, which is extremely sensitive to oxidants. Iron (III) is bonded in a planar coordination geometry to the four deprotonated nitrogens of the ligand, while the six-membered chelation rings are oriented alternatively up and down to give an *rtct* isomer (**55**, Figure 26). When the lithium salt complex is treated with $MoOCl_4$ in THF, a green solution is formed which yields a molybdenum metallated complex when recrystallised from THF-toluene. The conformation of the molybdenum macrocyclic ligand is also *rtct* but is slightly distorted due to the oxo functionality at the metal (**56**, Figure 26).

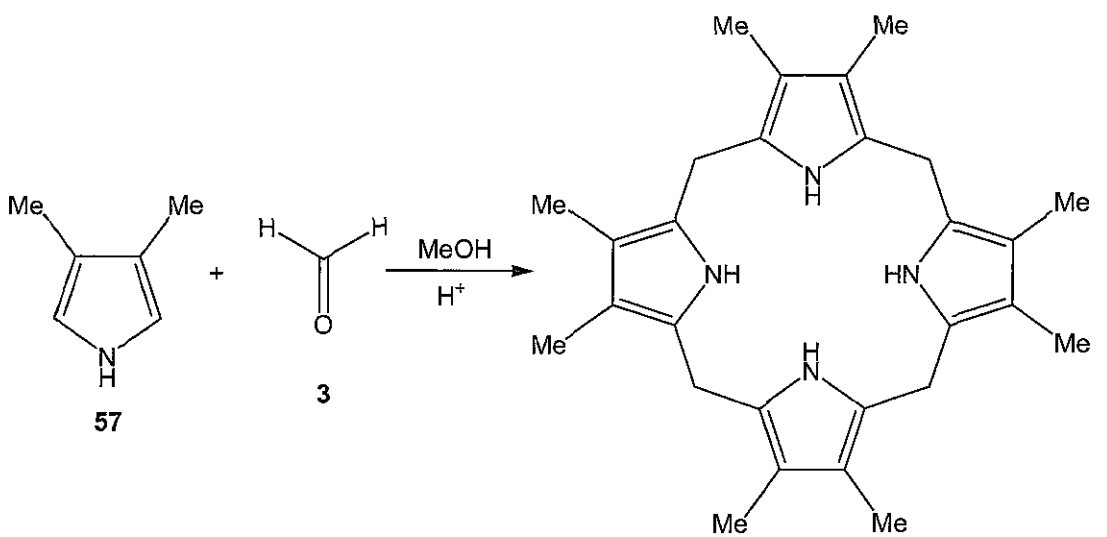


55 56

Figure 26: *Meso-octamethylcalix[4]pyrrole iron and molybdenum complexes*

E. Modification at the C-rim

It has been reported[44] that 3,4-dimethyl pyrrole (**57**) reacts with aqueous formaldehyde (**3**) in methanol with acetic acid as a catalyst without the need for high temperatures to form *meso*-octamethylcalix[4]pyrrole (**58**). This low temperature reaction produces the product in high yields (94%). Refluxing the reaction solutions in concentrated HCl or formaldehyde-diethyl acetal does not yield the desired product.



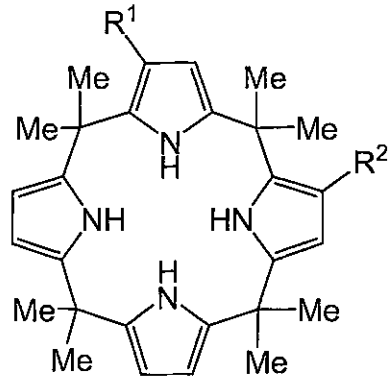
58

Scheme 6: *Formation of a meso-octamethylcalix[4]pyrrole*

Gale at al.[45] investigated the synthesis of carbon-rim or C-rim modified calix[4]pyrroles. Their first strategy involved direct synthesis from 3,4-disubstituted pyrroles and ketones. 3,4-Dimethoxy pyrrole was condensed with cyclohexanone in

glacial acetic acid. After column chromatographic purification, the product β-octamethoxy-*meso*-tetraspirocyclohexylcalix[4]pyrrole was isolated in 8% yield.

Using the second strategy, the C-rim was modified on a pre-synthesised calyix[4]pyrrole. The *meso*-octamethylcalix[4]pyrrole (**58**) was dissolved in dry THF and cooled to -78°C. A solution of n-butyllithium in hexane (4.0 equiv.) was added dropwise to the calixpyrrole followed by 4.0 equiv. of ethyl bromoacetate. The reaction was allowed to warm to room temperature after one hour stirring at -78°C. Two products were obtained after purification by column chromatography, the monoester (**59**, in 26% yield) and the diester (**60**, in 3% yield). A mixture of diesters would be expected but surprisingly, the diester is formed as a single isomer with the ester groups attached to the calixpyrrole in the 2 and 7 positions[36]. The monoester was characterised by ^{13}C NMR[37], in which the β-pyrrole carbon resonances totalled eight as opposed to a single resonance in the unsubstituted *meso*-octamethylcalix[4]pyrrole. This is due to the complete loss of symmetry upon mono esterification of the C-rim.

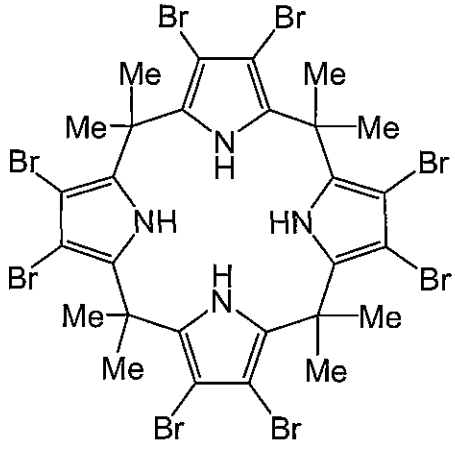


59 $R^1 = CH_2CO_2Et$, $R^2 = H$
60 $R^1 = R^2 = CH_2CO_2Et$

Figure 27: *Unsymmetrical calix[4]pyrrole*

Another C-rim modification was achieved by Gale and co-workers[36,45]. Upon reaction of *N*-bromosuccinimide with *meso*-octamethylcalix[4]pyrrole in dry THF, β-octabromo-*meso*-octamethylcalix[4]pyrrole was produced in 90% yield. X-ray crystal structure analysis showed that the octabrominated product exists in a chair-like flattened 1,2-alternate conformation in the solid state. It was found that the C-rim modifications cause a difference in anion binding properties. The octamethoxy calix[4]pyrrole shows reduced stability constants for the complexation with fluoride

and chloride when compared to the *meso*-tetraspirocyclohexylcalix[4]arene. The electron donating ability of the eight C-rim methoxy groups cause a reduction of the anion binding ability due to the decrease in the acidity of the pyrrole NH protons. In the same way, the monoester compound shows lower stability constants for the binding with chloride, fluoride and dihydrogen phosphate anions in comparison with *meso*-octamethylcalix[4]pyrrole. This is due to the presence of lone pair electrons on the oxygen atoms of the attached ester group that cause slight repulsion with the anions. However, the octabromo compound shows higher stability constants with chloride, fluoride and dihydrogen phosphate than *meso*-octamethylcalix[4]pyrrole. In this case, the change in anion-binding capacity could be due to the electron-withdrawing nature of the eight C-rim bromine atoms. This electron-withdrawing nature increases the acidity of the NH protons and therefore enhances anion-binding ability.

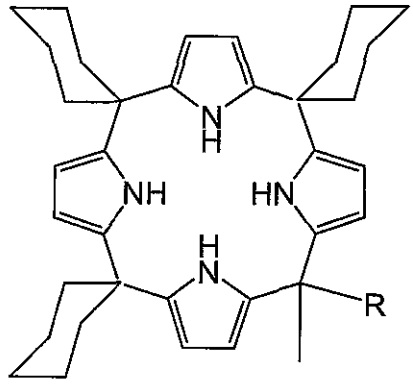


61

Figure 28: *Brominated calix[4]pyrrole*

F. Modification at the Meso-position

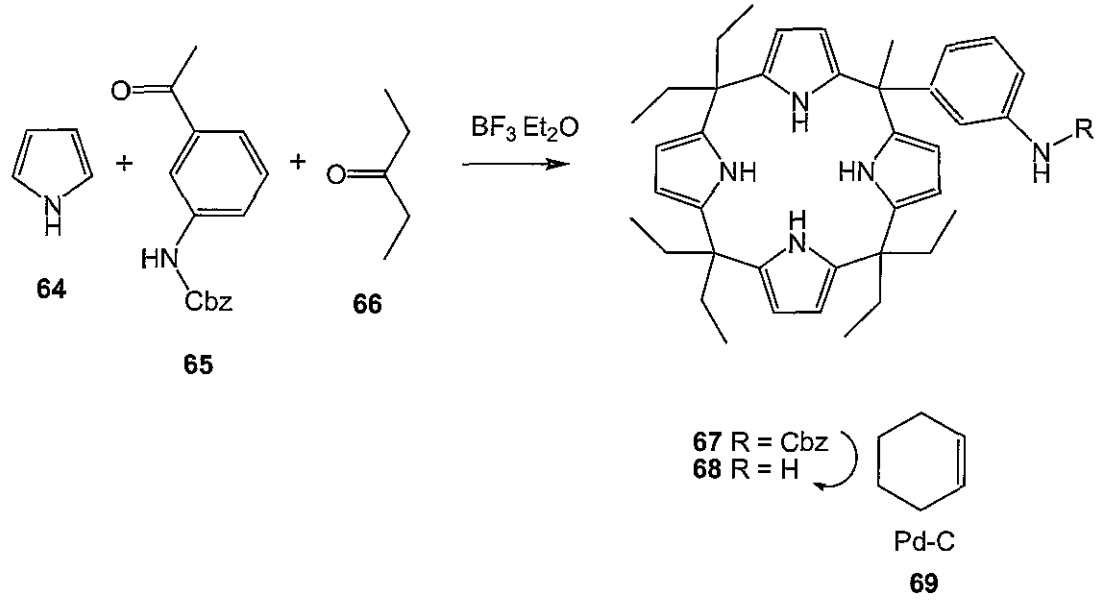
The synthesis of *meso*-functionalized calix[4]pyrroles is achieved by co condensation of pyrrole with different ketones. Sessler et al.[46] have reported the synthesis of a calixpyrrole monoacid (**62**) by the acid catalysed condensation of pyrrole with cyclohexanone and methyl 4-acetylbutyrate, followed by hydrolysis of the generated monomethyl ester.



62 R = $(CH_2)_3CO_2H$
63 R = $(CH_2)_3CO_2CH_3$

Figure 29: *Meso-modified calix[4]pyrrole*

Another *meso*-functionalized calix[4]pyrrole was synthesised by Anzenbacher et al.[47] by condensation of pyrrole with 3-pentanone and Cbz-protected 3-aminoacetophenone in the presence of BF_3:Et_2O (Scheme 7). This reaction produced the protected product **67** which when deprotected yielded **68**.



Scheme 7: *Synthesis of a meso-modified calix[4]pyrrole*

G. Modification at the N-rim

The nitrogen atoms of the calix[4]pyrrole can be modified to increase binding ability of the calix[4]pyrrole with metal ions in a low oxidation state. The Japanese group of Furusho et al.[48] have reported the synthesis of *N*-alkylated *meso*-

octaethylcalix[4]pyrroles. The methylation of the N-rim was attempted by reaction of the *meso*-octaethylcalix[4]pyrrole with four equivalents of *n*-butyllithium and methyl iodide. The ^{1}H NMR spectrum confirmed the absence of N-rim alkylation but showed the formation of a mixture of various β-methylated products. The use of sodium hydride and methyl iodide in THF in the presence of 18-crown-6 ether yielded a mixture of *N*-methylated *meso*-octaethylcalix[4]pyrrole. The mixture was purified by column chromatography and analysed by ^{1}H NMR and FAB-MS. The products were found to be a mixture of mono-, di-, tri-, and tetra-methylated *meso*-octaethylcalix[4]pyrroles with no formation of β-methylated products. The main product was the mono-methylated product when one equivalent of MeI was used. A mixture of di-, tri and tetra-methylated products were formed with two equivalents of MeI, with the opposite-*N*, *N'* di-methylated product being predominantly formed. X-ray crystal analysis of the opposite-*N*, *N'*-dimethylated *meso*-octaethylcalix[4]pyrrole revealed that the pyrrole rings are alternately pointing up and down in a 1,3-alternate conformation.

N-ethylation of *meso*-octaethylcalix[4]pyrrole was successfully achieved by reacting ethyl iodide with *meso*-octaethylcalix[4]pyrrole under similar conditions as the N-rim methylation reactions above. Only the monoethylated product was successfully isolated. Ineffective attempts to synthesise the polyethylated product involved the use of other alkyl halides such as benzyl chloride, dichloroethane and *m*-xylene dibromide. These alkyl halides caused the formation of complex mixtures, which included β-alkylated products.

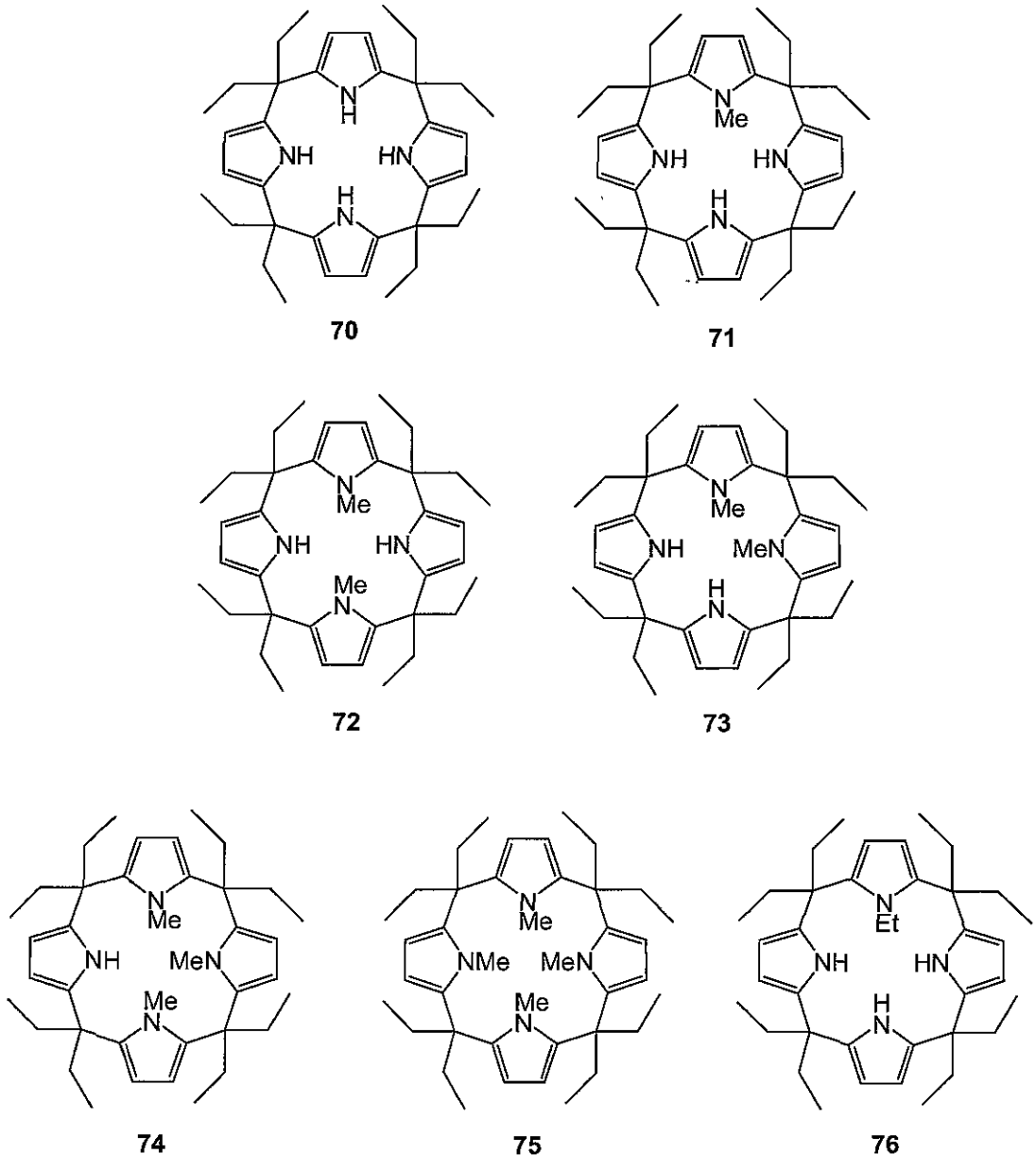
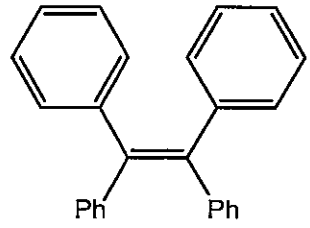


Figure 30: A selection of N-rim modified Calix[4]pyrroles

III. Resorcinarenes

The first reported synthesis of a resorcinarene type compound dates back more than 100 years. In 1872, Adolf von Baeyer[49] reported the formation of a red coloured product, which changed to violet in alkaline solution when concentrated sulphuric acid was added to a mixture of benzaldehyde and resorcinol. When this red resin was heated a crystalline product was formed which was later found to be an isomer of the resin. About 10 years later, the correct elemental composition of this sparingly soluble

high melting point product ($C_3H_{10}O_2$) was determined by Michael[50]. The elemental composition of the acetal derivative $(C_{13}H_8(OCOCH_3)_2)_n$ was also determined. Along with this information, Michael also reported that the product is formed by the combination of an equal number of benzaldehyde molecules and resorcinol molecules and the elimination of an equal number of water molecules. Michael incorrectly suggested the structure **77** for the compound (Figure 31)[51].

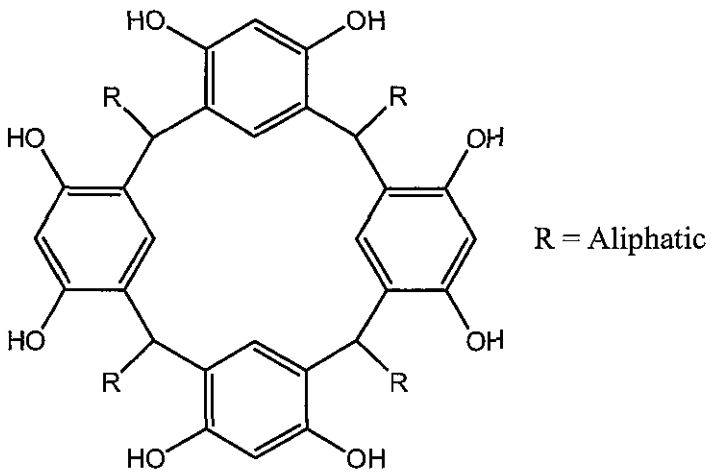


77

Figure 31: *Michael's incorrect structure for the acid catalysed product of benzaldehyde and resorcinol*[50,51]

It was not until many years later that the molecular weight of the compound was determined by Niederl and Vogel[52]. By carrying out several condensation reactions between resorcinol and various aldehydes and determining the molecular weights of the products they were able to calculate that the resorcinol molecule and the aldehyde reacted in a 4:4 ratio.

They proposed the cyclic tetrameric structure **78**, which is analogous to porphyrins, and other frequently encountered natural compounds.



78

Figure 32: *Niederl and Vogel's cyclic tetrameric structure*

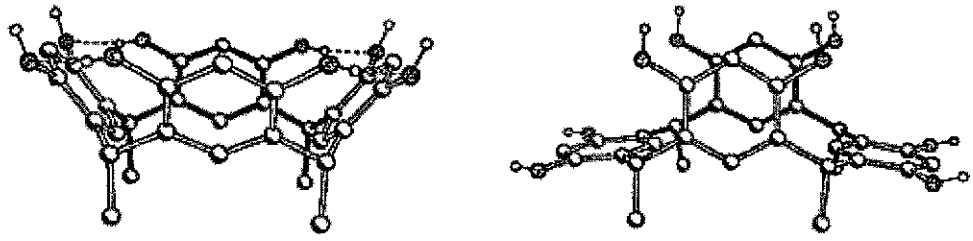
This structure was finally proven to be correct by Erdtman and co-workers in 1968 by single crystal X-ray analysis[53].

The official IUPAC name for compound **78** (R = aliphatic) is 2,8,14,20-tetra-alkylpentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19 (26),21,23-dodecaene-4,6,10,12,16,18,22,24-octol[51]. However, various names have been used in the literature to describe these compounds, for example, resorcinol-derived calix[4]arenes[4], calix[4]resorcarenes[4], octols[54], Högberg compounds[55], metacyclophanoctaols[56] or resorcinarenes[51].

A. Structure

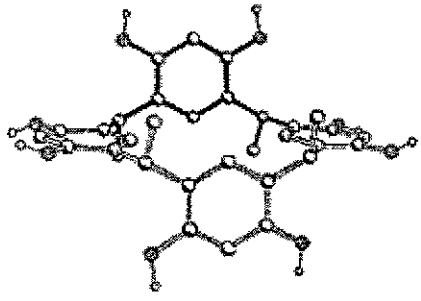
Resorcinarenes can exist in many different isomeric forms. There are three different stereochemical elements that affect the conformation of a resorcinarene molecule[51].

1) The conformation of the macrocyclic ring. The ring can adopt six different positions, which are similar to those of the calixarene macrocycle ring. The six positions are named cone, flattened cone, flattened partial cone, 1,3-alternate, (Figure 33), partial cone and 1,2-alternate (Figure 34).

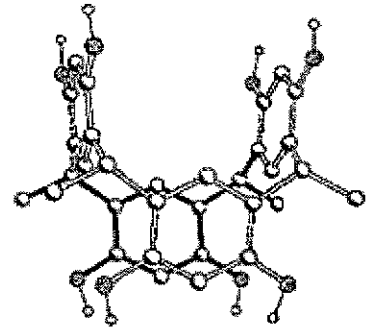


78a

78b

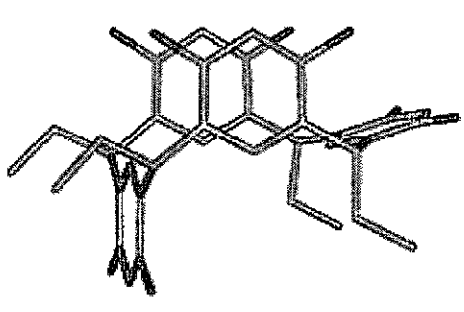


78c

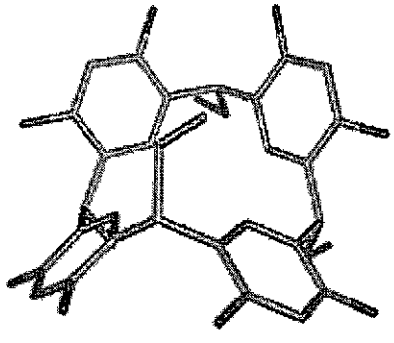


78d

Figure 33: *Conformations of resorcinarenes[57] cone (78a), flattened cone (78b), flattened partial cone (78c) and 1,3-alternate (78d)*



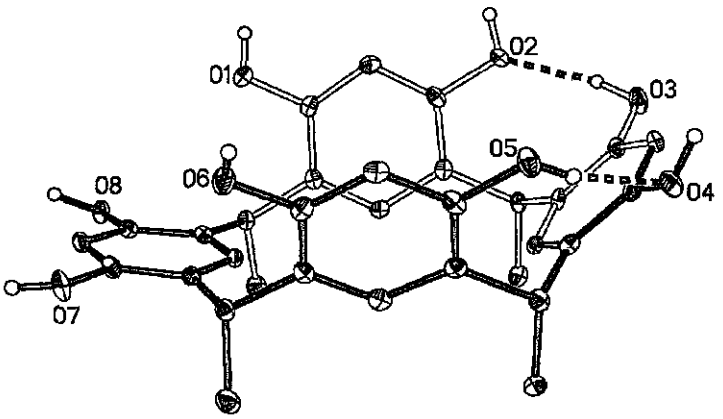
78e



78f

Figure 34: *Resorcinarene[58] in the partial cone (78e) and 1,2-alternate (78f) conformations*

Ma and Coppens[59] have more recently discovered another conformation of the resorcinarene macrocyclic ring. This new conformation, names the scoop, has been described as a hybrid of the cone and flattened cone conformations[59]. There are two hydrogen bonds between three of the resorcinol units and the fourth resorcinol unit is linked to neighbouring molecules via hydrogen bonding.



78g

Figure 35: *Resorcinarene in the scoop conformation*[59]

2) The relative configurations of the substituents on the methylene bridges. These substituents can be positioned all-cis (rccc), cis-cis-trans (rcct), cis-trans-trans (rctt) or trans-cis-trans (rtct) (Figure 36).

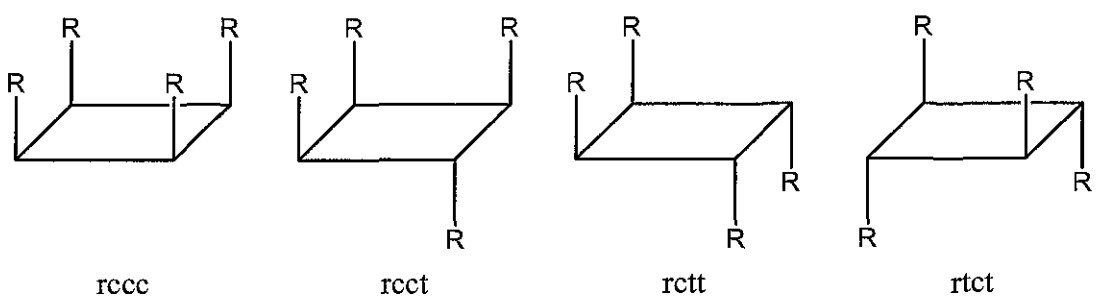


Figure 36: *Relative configurations of the substituents on methylene bridges*

3) The individual configurations of the substituents on the methylene bridges, which can be either axial or equatorial.

Resorcin[4]arenes can form large hexameric spherical structures. The structure of these capsules was deduced by NMR methods[60-62] and by X-ray crystal structure determination[50]. Six molecules of C-methylresorcin[4]arene and eight molecules of water self assemble to form a capsule held together by sixty hydrogen bonds. The capsule takes the shape of a snub cube, one of the thirteen Archimedean solids. The

square faces correspond to the resorcin[4]arene molecules and the eight triangles that adjoin three squares correspond to water molecules (Figure 37).

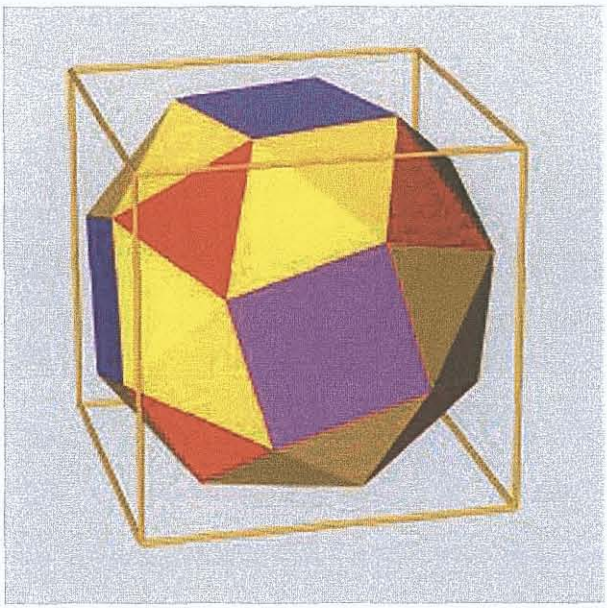


Figure 37: *The snub cube. The square faces correspond to the resorcin[4]arenes and the red triangles correspond to the water molecules*[63,64]

B. Synthesis

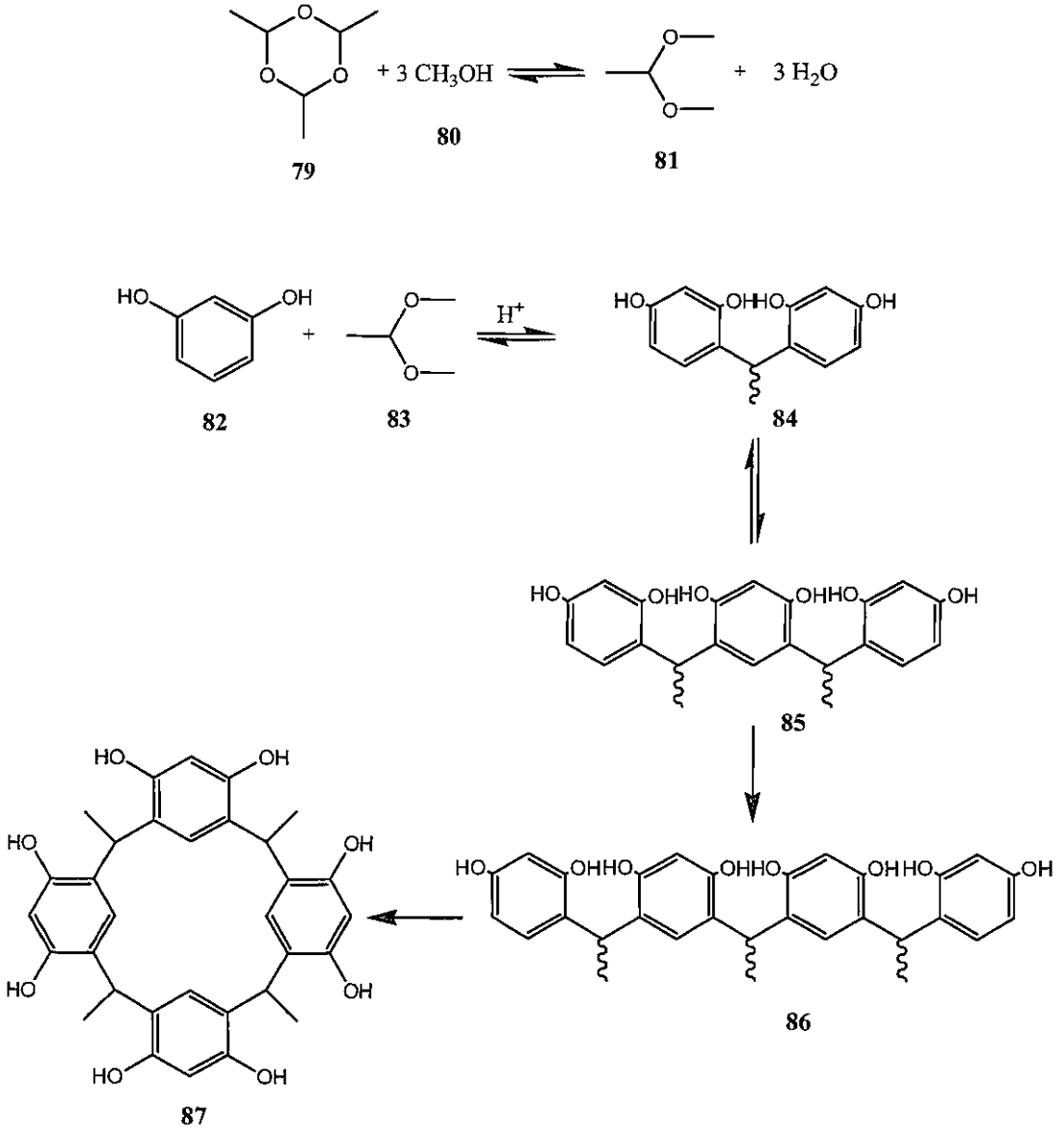
1. Acid Catalysed Synthesis

The synthesis of resorcinarenes is achieved by the reasonably simple method of acid-catalysed condensation of resorcinol with aldehydes, though the exact optimum conditions vary between aldehydes[51,65,66]. The product generally precipates out of the reaction solution but on occasion, some water is needed to aid in the crystallisation of the product. Yields are generally quite high (between 60 and 99%[51,65]) but when the resorcinol is substituted in the 2-position with electron withdrawing groups such as NO_2 or Br, the cyclic product is not formed. In this case, mixtures of oligomers or other compounds are formed. Also, when the hydroxy groups of the resorcinol are alkylated or partially alkylated, the cyclic product is not formed[67]. In this case, the possibility of formation of hydrogen bonds between the phenolic groups is reduced or eliminated altogether. Steric hindrance may also play a role in the prevention of cyclisation.

The mechanism of the acid catalysed reaction between resorcinol and acetaldehyde was studied by Weinelt and Schneider[67] using high field ^1H NMR spectroscopy (Scheme 8). It was found that resorcinol does not react directly with the aldehyde but

instead reacts with its rapidly formed dimethyl acetal. This reaction produces dimers, trimers and tetramers as well as longer chain linear polymers as reaction intermediates.

The formation of the cyclic tetramer proceeds via the coupling of the dimethyl acetal with resorcinol to form linear oligomer intermediates. The linear tetrameric intermediate is thought to be in a folded conformation, which explains its rapid conversion to the cyclic product. Due to the rapid cyclisation, this intermediate was not isolated in the reaction mixture. The smaller dimer and trimer intermediates were isolated and showed resorcinol and not methoxyethyl units at the terminal positions.



Scheme 8: *Resorcinarene Synthesis*[67]

Högberg[68] studied the reaction of resorcinol with acetaldehyde under varying concentrations of acid. Equimolar quantities of resorcinol and acetaldehyde in aqueous hydrochloric acid produced a mixture of products in the partial cone and the flattened cone comformations. The same reaction in a 4:1 (v/v) ethanol:concentrated hydrochloric acid solution yielded no product. However, when water was added to the reaction mixture, a small amount of product in the flattened cone conformation precipitated out. When a 2.2:1 (v/v) ethanol:water:concentrated hydrochloric acid solution was used as the reaction solvent, only the resorcin[4]arene in the flattened cone conformation was formed. No partial cone isomer was detected in the reaction mixture under these conditions.

It has been reported in the literature that the acid catalysed reaction of resorcinol and benzaldehyde (4:1 ethanol:concentrated hydrochloric acid) produces a tetramer of different conformations[69]. One isomer is formed in the partial cone conformation and is initially the dominant isomer in the reaction mixture. The yield of this isomer reaches a maximum after one hour and subsequently decreases. The isomer in the flattened cone conformation increases with the reaction time to an eventual yield of approximately 80%. The flattened cone isomer is the only product in the final reaction mixture. This indicates that the formation of the isomer in the partial cone conformation is reversible under the reaction conditions.

A separate set of experiments[69] was performed to confirm the reversible interconversion of isomers. The isomer in the partial cone conformation was treated under conditions similar to the condensation reaction conditions. After five hours, the product was collected in 80% yield as a 50:50 mixture of the two isomers. After ten hours, the product collected consisted of only the flattened cone isomer in 80% yield. A similar experiment was set up on the flattened cone isomer. After 20 hours of refluxing, no evidence of the partial cone isomer was detected. These experiments show that the partial cone isomer is the kinetically favoured one, which is converted into the thermodynamically more stable isomer, the flattened cone.

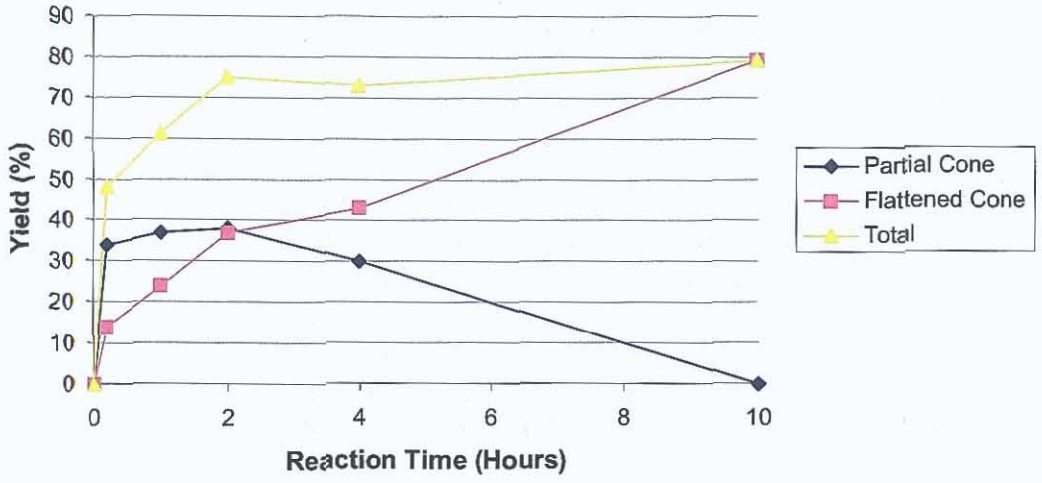


Figure 38: *Yields of resorcinarene isomers over time*[69]

Weinelt and Schneider[67] also carried out a study on the interconversion of different isomers of resorcin[4]arenes. They heated the cone isomer at 50°C in a 5% solution of HCl in methanol. The results are plotted in Figure 39. After approximately 20 minutes, equilibrium was reached where half of the original amount of cone isomer had isomerised into a mixture of the flattened cone and the partial cone isomers. Under these conditions, the cone isomer is thermodynamically the most stable isomer, followed by the flattened cone. The partial cone isomer is the least stable under these conditions and therefore is only formed in small yields.

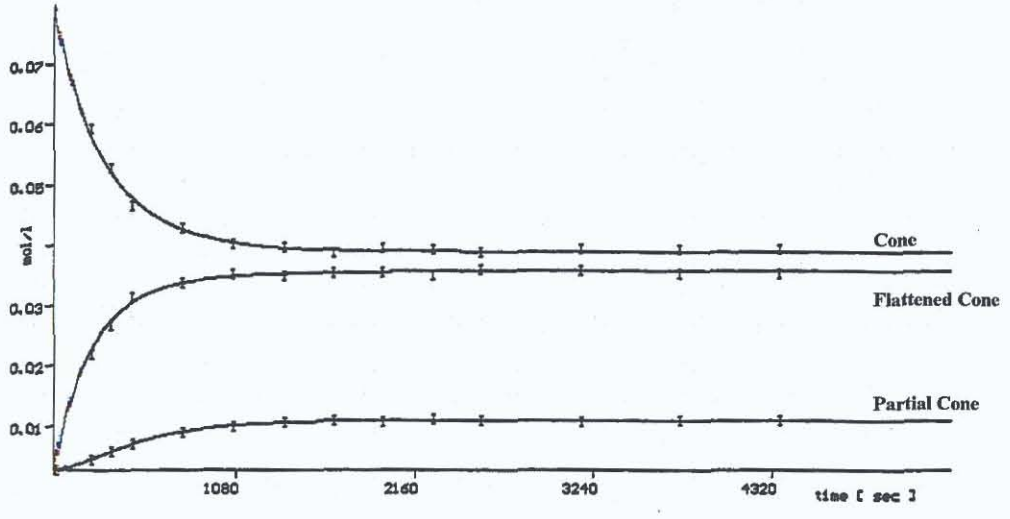
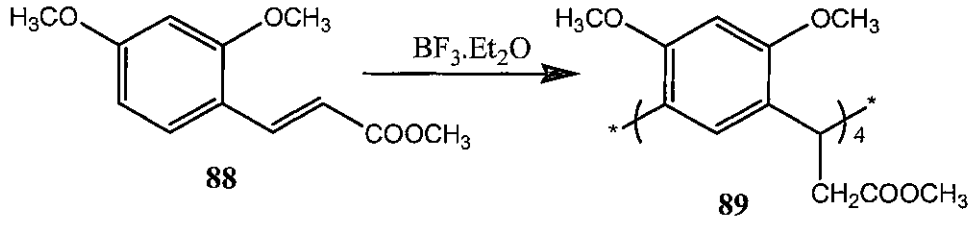


Figure 39: *Plot of Weinelt and Schneider's interconversion reaction results*[67]

2. Other Synthetic Methods

Resorcin[4]arenes can be synthesised by the treatment of (*E*)-2,4-dimethoxycinnamic acid methylester with $BF_3 \cdot Et_2O$[70]. After 15 hours, this room temperature reaction yielded a mixture of flattened cone and 1,2-alternate isomers of the resorcin[4]arene in a total of 75% yield. The flattened cone isomer was formed in slightly higher yields than the 1,2-alternate isomer. With a longer reaction time, the relative yield of the 1,2-alternate isomer decreased. After a reaction time of 48 hours, 90% of the product was found to be in the flattened cone conformation. Increasing the temperature of the reaction or increasing the ratio of $BF_3 \cdot Et_2O$ also increased the percentage of the flattened cone isomer in the reaction mixture without altering the overall yield of product.



Scheme 9: *Synthesis of resorcin[4]arene from (E)-2,4-dimethoxycinnamic acid methylester*

While the mechanism remains unresolved, the isolation of a dimeric compound (Figure 40) indicated that the reaction proceeds either by successive stepwise growth of a linear oligomeric chain before cyclisation or by direct cyclo-oligomerisation of the dimer.

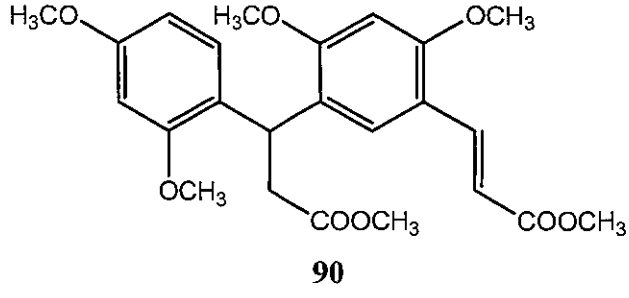
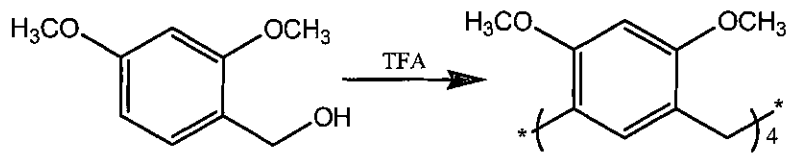


Figure 40: *Dimeric intermediate in the reaction of resorcin[4]arene from (E)-2,4-dimethoxycinnamic acid methylester*

Treatment of 2,4-methoxybenzylalcohol with trifluoroacetic acid (5% in $CHCl_3$) at room tempeature produces a resorcin[4]arene in high yields[71].



91 **92**

Scheme 10: *Synthesis of resorcin[4]arene from 2,4-methoxybenzylalcohol*

The synthesis of this simple compound by this method is significant, as the reaction of resorcinol and the very reactive aldehyde, formaldehyde under acid conditions does not form the cyclic tetramer but instead yields only polymeric products[4]. Different isomers of this compound cannot be isolated as it is extremely flexible due to the absence of alkyl chains at the methylene bridges.

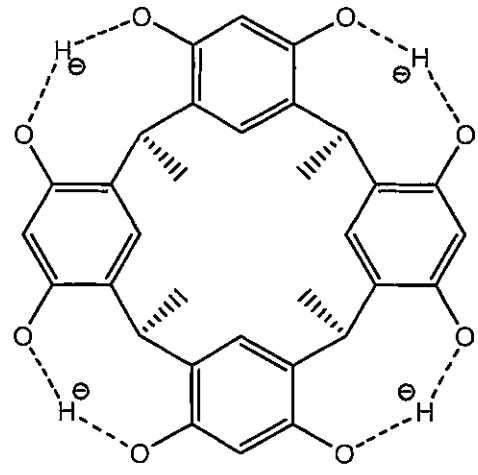
C. Solvent-Free Synthesis

Resorcin[4]arenes can be synthesised in high yields by a solvent-free method which involves the room temperature reaction of resorcinol with benzaldehyde derivatives in the presence of a solid acid catalyst[72]. The starting materials are simply ground together in equimolar quantities. Even if the reagents are solids, the mixture turns to a paste or a viscous liquid[72,73]. Washing with water to remove the excess acid and recrystallisation from hot methanol purifies the crude product. Roberts *et al.*[72] suggest that the reaction proceeds in a similar manner to the mechanism known for the reaction involving the dissolution of reagents in a solvent prior to the reaction. The reaction by the traditional solvent synthesis generally occurs on a time scale of a few hours to many days. However, the solvent-free reaction only requires a few minutes to ensure substantial conversion of starting materials to products. This method also proceeds without the need for external heating and the mixing of products is achieved during the grinding process and subsequent formation of the viscous liquid or paste.

D. Resorcin[4]arene Ion Binding

Resorcin[4]arenes are soluble in aqueous basic solutions due to the deprotonation of phenolic hydroxy groups[51]. The deprotonoated resorcin[4]arene (Figure 41) is

stabilized by hydrogen bonding and the delocalisation of the negative charge. Further studies showed that even a strong base such as $NaOCD_3$ does not remove the remaining four hydroxy protons[74].



93

Figure 41: *Deprotonated resorcin[4]arene*

The intra-molecular hydrogen bonding in resorcinarenes has been likened to the 'flip flop' H-bonding of cyclodextrins[75,76]. Mäkinen *et al.* carried out a study on the complexation of ammonium ions by resorcinarenes. The two resorcinarenes they used in the study were tetraethylresorcin[4]arene (**94**) in the cone conformation and the octamethylated derivative (**95**) of the same compound in the flattened cone conformation (Figure 42). A variety of alkyl ammonium ions were tested for their complexing ability (Figure 43).

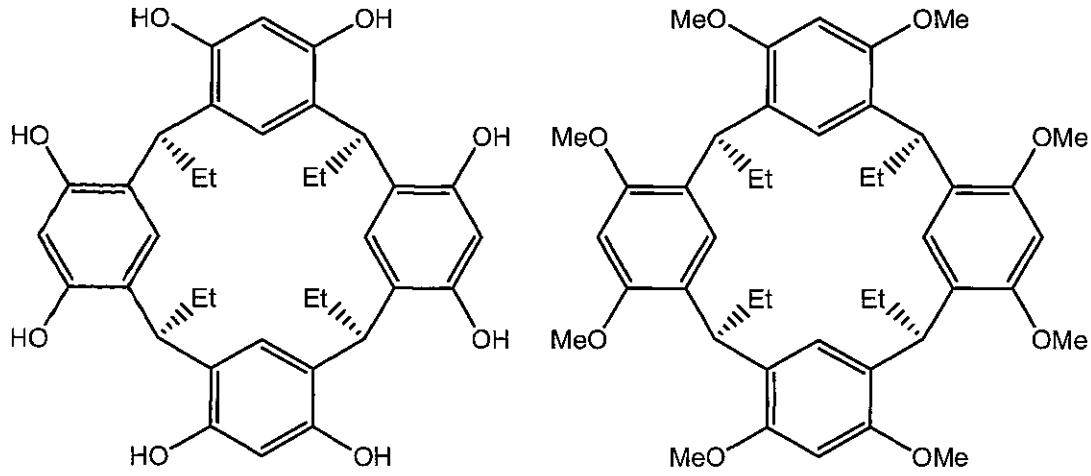
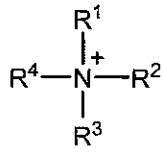


Figure 42: *Tetraethylresorcin[4]arene **94** and octamethylated tetraethylresorcin[4]arene **95***



96. $R^1=R^2=R^3=R^4=CH_3$
97: $R^1=R^2=R^3=CH_3$, $R^4=H$
98: $R^1=R^2=CH_3$, $R^3=R^4=H$
99: $R^1=CH_3$, $R^2=R^3=R^4=H$
100. $R^1=R^2=R^3=R^4=CH_2CH_3$
101: $R^1=R^2=R^3=CH_2CH_3$, $R^4=H$
102: $R^1=R^2=CH_2CH_3$, $R^3=R^4=H$
103· $R^1=CH_2CH_3$, $R2=R^3=R^4=H$
104: $R^1=CH_2CH_2CH_3$, $R^2=R^3=R^4=H$
105: $R^1=R^2=R^3=R^4=CH_2CH_2CH_3$

Figure 43: *The alkyl ammonium ions used by Mäkinen et al.*[75]

Monomeric and dimeric complexes were formed from **94** and the tetramethyl ammonium ion **96**. A low concentration of the guest ion resulted in the formation of a high percentage of dimers. An increase in the concentration of guest ion caused an increase in the percentage of monomer formed although the dimeric capsule formation didn't drop below 50% in solutions up to a 1:10 ratio of host:guest.

In the dimeric complex, the guest ion is thought to be encapsulated inside a closed cavity between two resorcinarene units whereas in the monomer, the guest is located in the cavity of the resorcinarene but is still reactive to outside reagents. To test this theory, a host exchange from trimethyl ammonium to dimethyl ammonium ion experiment was attempted[75]. Exchange occurred from the cavity of the monomeric

complex but no exchange occurred in the dimeric capsule. This confirms the capsule structure of the dimer. An X-ray crystal structure of a triethyl ammonium ion encapsulated by two resorcinarene units has been published by Shivanyuk *et al.*[77] which also corroborates this capsule structure.

No capsule dimer is formed upon complexation of tetramethyl ammonium ion **96** and **95**. Only monomers are formed in this instance. Mäkinen *et al.*[75] published an X-ray crystal structure of the tetramethyl ammonium ion **96** and **94** (Figure 44).

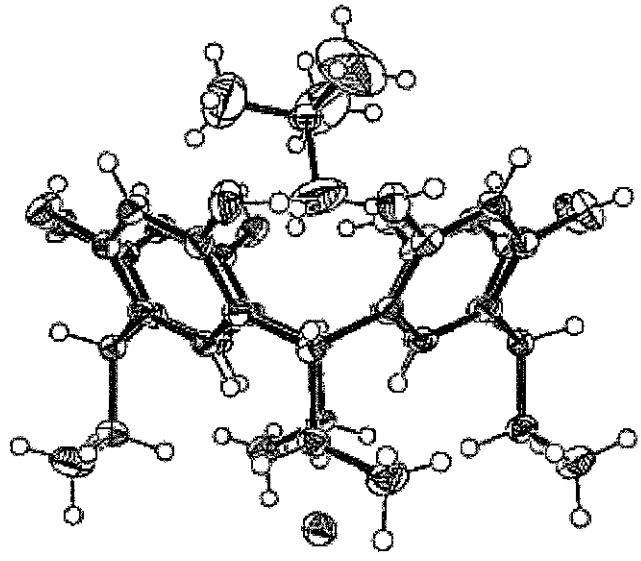


Figure 44: *X-ray crystal structure of the tetramethyl ammonium bromide complex of tetraethylresorcin[4]arene*

The free tetraethylresorcin[4]arene is in the slightly distorted cone conformation but the symmetry of the ligand is increased upon complexation with the tetramethyl ammonium ion. The cation is situated in the cavity of the host while the bromine ion is found at the lower rim. The bromine anion is linked via weak CH-Br hydrogen bonds between the ethyl chains. Ligand **94** forms monomers with all the methyl ammonium guests tested but only forms dimers with the tri and tetramethylated species. The order of complexation is tetra>tri>di≈mono. Mäkinen *et al.*[75] suggest that minimum energy is achieved when one methyl group is pointing towards the cavity. A possible explanation for the complex formation series is that statistically, a tetra-substituted compound is more likely to have one group oriented towards the

cavity. This possibility is reduced in the case of mono- or di-substituted compounds and therefore the probability of interaction decreases.

Complexation of ammonium ions with the flattened cone octamethylated compound **95** follows a different order. In this case the order of complexation is tri>di>tetra>mono. The different conformation of the host plays a major role in the complexation of cations. The mono-substituted ammonium ion is too small to interact with the paralled resorcinol units and steric hindrance prevents the inclusion of the tetra-substituted compound in the complex. The tri and di methyl ammonium ions however, are small enough to fit inside the cavity but also elongated enough to interact with the resorcinol units. Complexation of the methylated host **95** is still much weaker than that of the unmethylated host **94** for each of the methyl ammonium cations.

Complexation of **94** with ethyl ammonium ions decreases compared to the methyl ammonium ions, which is as expected due to the steric effects of the ethyl groups. The tetraethyl ammonium ion mainly forms dimers while the complexation of the monoethyl ammonium ion increased with respect to the monomethyl ammonium ion due to its relatively small size. It was shown that steric factors hinder complexation with **91**. The monoethylated ammonium ion complexes to a much greater extent than the more highly substituted ammonium ions.

The length of the carbon chain also affects complexation. Overall binding becomes stronger as the length of the alkyl chain on the monoalkylated ammonium ion increases. The tetra propyl ammonium ions failed to form complexes at all, probably due to steric hindrance.

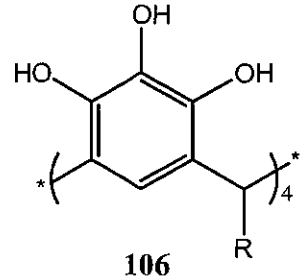
Resorcin[4]arenes have shown selective binding for caesium ions over other alkali metal cations[78]. The caesium ion is thought to be located in the hydrophobic cavity in this molecule. Sodium and potassium ions have been shown to complex with resorcinarenes, if only in small amounts[75].

IV. Pyrogallolarenes

A. Synthesis and Structure

Pyrogallol[4]arenes are easily synthesised by the acid catalysed condensation of pyrogallol with aldehydes in aqueous media[79]. The cone conformation is generally precipitated out of the reaction mixture but the partial cone is formed under kinetic conditions.

Pyrogallol[4]arenes are formed under similar reaction conditions to resorcinol[4]arenes. The synthesis of the resorcinol[4]arenes requires a longer reaction time, which indicates that pyrogallol is considerably more reactive than resorcinol[80].



106

Figure 45: *General structure of a pyrogallol[4]arene*

Under reflux conditions, the tetra-*isobutyl*-pyrogallol[4]arene tetramer is formed with a simple conformation and high symmetry[79]. However, when the reaction is performed at room temperature, the product is a large spherical hexameric macrocyclic 'supermolecule'. The ^{1}H NMR of this molecule is complicated with broad bands but the X-ray crystal structure analysis revealed a self-organised structure with six pyrogallolarenes, each occupying the edge of an octahedron. The pyrogallol[4]arenes are arranged to give the octahedron a polar interior (the hydroxy groups are pointing into the sphere) and an apolar exterior, with the alkyl chains directed outwards. The octahedron is very large on a molecular scale with the diameter ranging from 14.1 to about 19Å.

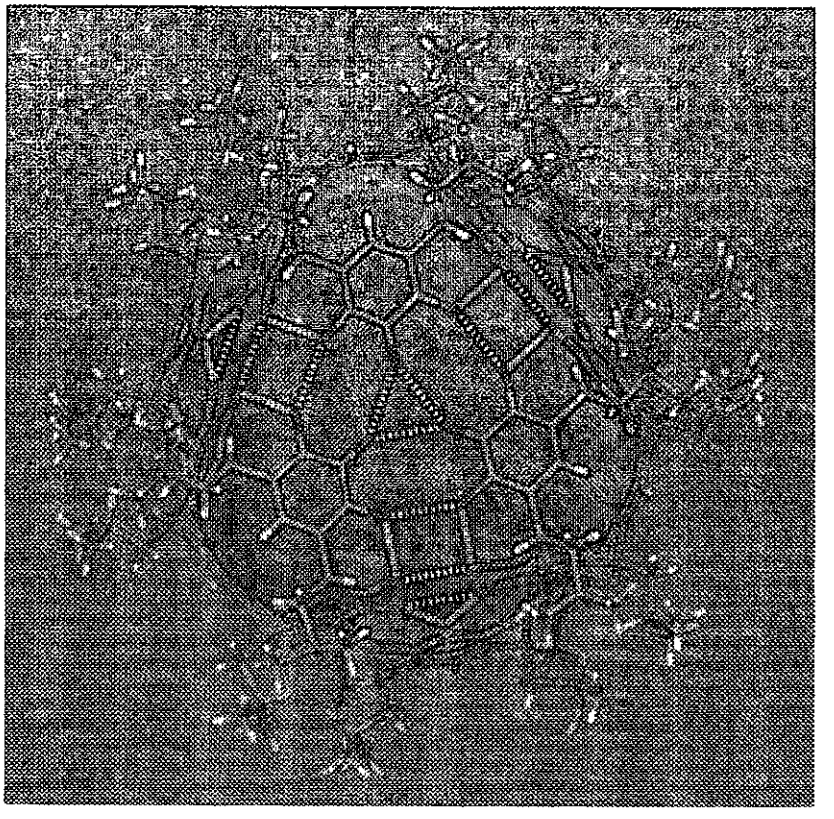
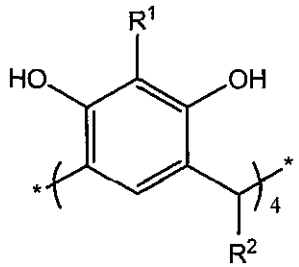


Figure 46: *The octahedral 'supermolecule' formed from six pyrogallolarene molecules (intermolecular hydrogen bonds are shown in yellow)*[81]

The solvent can cause an effect in the formation of the supermolecule as more polar solvents can compete for hydrogen bond acceptor/donor sites. This hexameric superstructure is very fragile, due to the weakness of the intramolecular hydrogen bonds holding the structure together. The synthesis of this large hexameric molecule as opposed to the layer structure was at first thought to be coincidental[79] but it has since been reproduced[80]. The molecule, when compared to [(C-methylresorcin[4]arene)$_6$(H_2O)$_8$] is very unstable. This is surprising as there are 48 intermolecular hydrogen bonds holding the 6 pyrogallol[4]arene moieties together as opposed to the resorcin[4]arene hexamer which is only held together by 36 intermolecular hydrogen bonds[81].

Avram and Cohen[62] published a comparative study of the hexameric capsules of two resorcinol[4]arenes and two pyrogallol[4]arenes (Figure 47).



107 $R^1 = H$, $R^2 =$ isobutyl
108 $R^1 = H$, $R^2 = C_{11}H_{23}$
109 $R^1 = OH$, $R^2 =$ isobutyl
110 $R^1 = OH$, $R^2 = C_{11}H_{23}$

Figure 47: *The resorcinol[4]arenes and pyrogallol[4]arenes used in the study by Avram and Cohen*[62]

All four capsules spontaneously self-assemble in deuterated chloroform solutions, which is reflected in their low diffusion coefficients. Addition of deuterated methanol increases the diffusion coefficients in all four cases. This is due to the fact that alcohols can disrupt the hydrogen bonding, causing a decrease in aggregation.

More methanol was required to disrupt the pyrogallol[4]arene capsules than the resorcinol[4]arene capsules which implies that the pyrogallol[4]arene capsules are more stable than the resorcinol compounds. The substituents on the methylene bridges also appear to play a role in the stability of the hexameric spheres. The stability difference between the undecyl substituted capsules is much greater than that of the isobutyl substituted capsules.

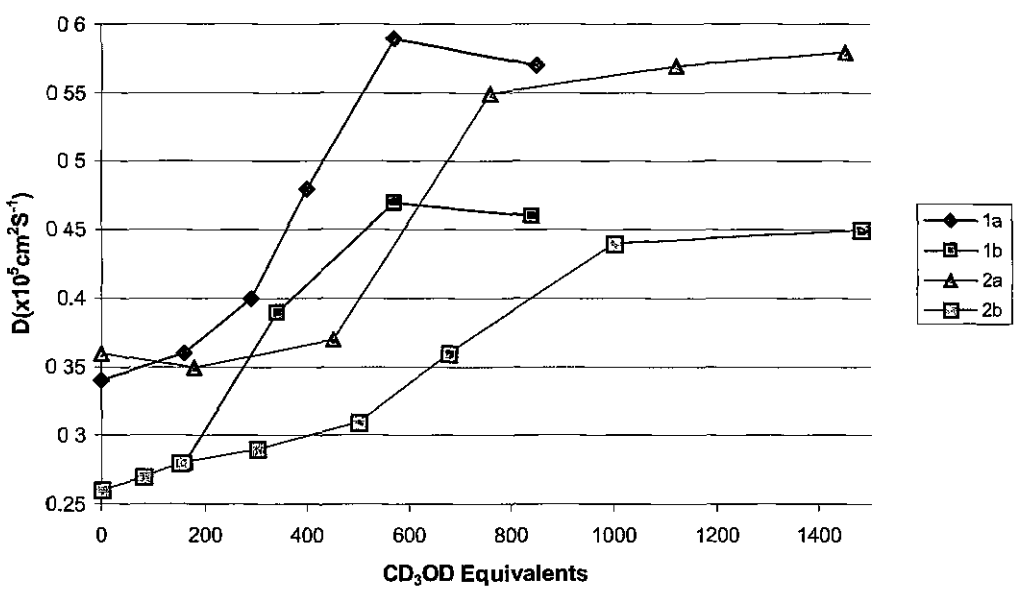


Figure 48: *Graph of diffusion coefficients with respect to addition of CD_3OD equivalents*[62]

It was also found that in all cases, exchange of encapsulated chloroform molecules takes place before complete break-down of the hexameric structure[62]. It is possible that dissociation of one resorcinol[4]arene or pyrogallol[4]arene subunit occurs to form a pentameric intermediate where exchange of encapsulated chloroform with bulk solvent chloroform can take place[82].

^{1}H NMR titration studies on the hexamer[81] show that there are methanol molecules trapped inside the sphere, which do not exchange with the methanol molecules in the bulk solvent. The hexameric sphere, with methanol as a guest has been shown to be stable in deuterated acetone up to 150°C.

Tests have shown[83] that the c-isobutylpyrogallol[4]arene hexameric sphere is insoluble in water and even after sonication for 30 minutes in water, the spherical hexameric structure is not degraded.

Atwood *et al.*[81] have synthesised a range of stable pyrogallol[4]arene hexamers with differing R groups (Figure 1, R = *n*-propyl to *n*-tridecyl). For the smaller alkyl groups, R = methyl or ethyl, there is no evidence for the formation of hexameric spheres. Pyrogallol[4]arenes with short chain alkyl groups show low solubility in apolar solvents while those with long chain alkyl groups show low solubility in polar solvents. Therefore, the choice of R groups on the molecule can determine the solubility in polar or apolar solvents.

The synthesis of tetraethylpyrogallol[4]arene has been reported by Shivanyuk *et al.*[84] After the acid catalysed synthesis of the tetramer, crystallisation from a methanol solution of quinuclidine hydrochloride (1-azabicyclo[2.2.2]octane hydrochloric acid), a dimeric molecular capsule was formed which surrounded one disordered quinuclidinium cation (Figure 49).

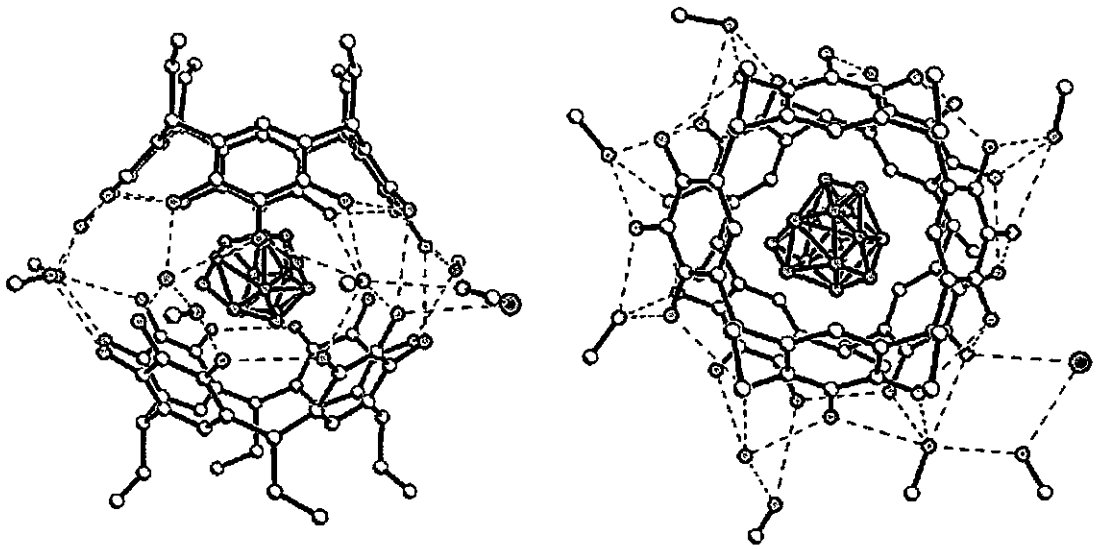
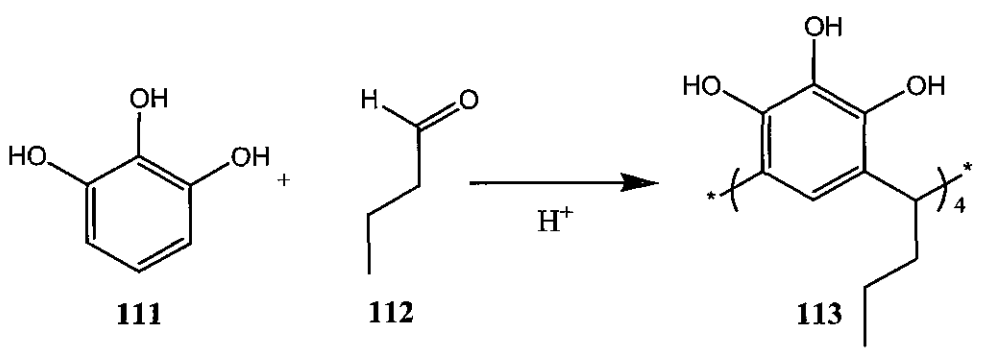


Figure 49: *Single crystal X-ray structure of the dimeric tetraethylpyrogallol[4]arene moiety encapsulating a quinuclidinium ion*[84] *(side view and top view)*

At room temperature, the acid catalysed reaction between butyraldehyde and pyrogallol (Scheme 11) yields C-propylpyrogallol[4]arene as a white precipitate[83]. Addition of water to the purification filtrate yields a second batch of the pyrogallol[4]arene. Reasonable yields of the pyrogallol[4]arenes can be produced using aqueous hydrochloric acid as the solvent or even just from mixing the aldehyde with pyrogallol in the presence of a small amount of concentrated hydrochloric acid.



Scheme 11: *Acid catalysed reaction of pyrogallol and butyraldehyde*

Shivanyuk and Rebek[85] have reported studies on this tetrapropyl pyrogallol[4]arene (**113**). This molecule adopts a slightly distorted cone conformation due to the stabilizing effect of the intramolecular hydrogen bonds. Two molecules of this compound can form a dimer linked by hydrogen bonds through sixteen water molecules and can encapsulate four acetonitrile molecules (Figure 50).

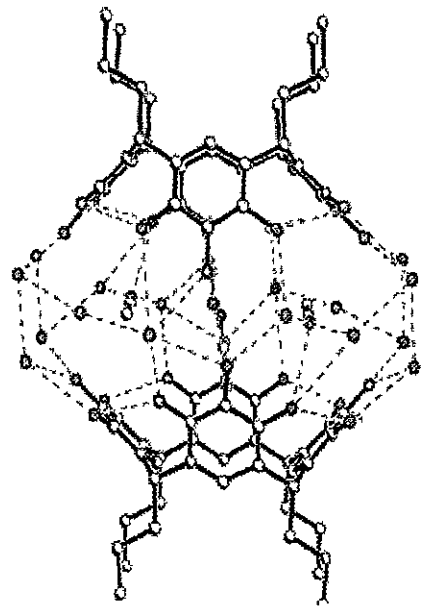


Figure 50: *X-ray crystal structure of tetrapropylpyrogallol[4]arene showing the hydrogen bonding through water molecules and encapsulated acetonitrile molecules*[85]

Recently, McKinlay *et al.*[86] reported the formation of a metal coordinated pyrogallol[4]arene capsule. They treated C-propan-3-ol pyrogallol[4]arene with copper(II) nitrate hydrate in aqueous acetone. This procedure resulted in the self-assembly of a large neutral coordination capsule. Single crystal X-ray analysis of the capsule showed that the molecule consists of 6 pyrogallol[4]arene ligands and 24 copper ions. The structure of this capsule is very similar to that of the hydrogen bonded pyrogallol[4]arenehexameric capsule, discussed previously. Figure 51 shows the similarities in structure of the two related hexameric capsules.

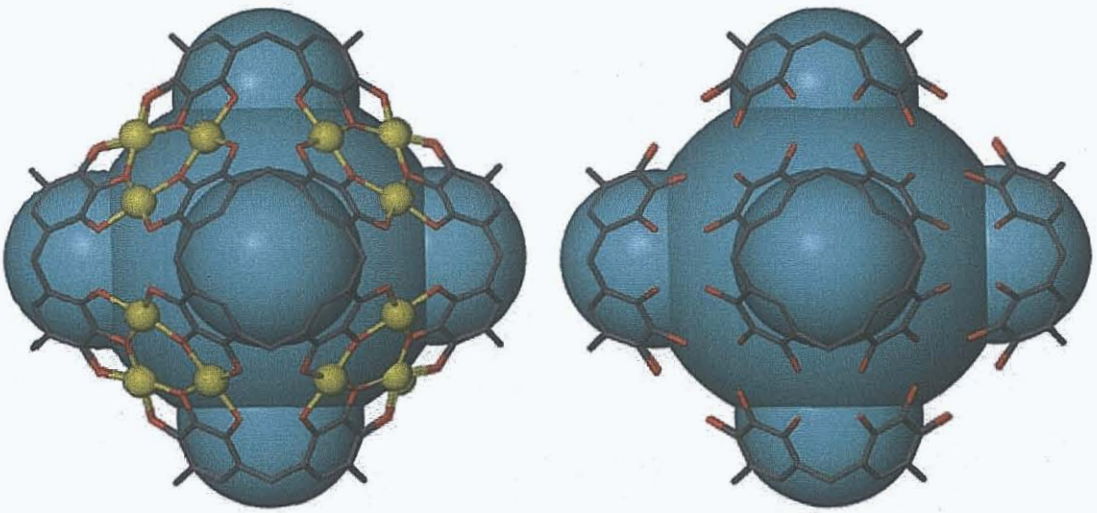


Figure 51: *Structures of the metal coordinated (left) and the hydrogen bound (right) pyrogallol[4]arene capsules (hydrogen atoms and alkyl tails are omitted for clarity)*[86]

The pyrogallol[4]arene units in the capsule are held together by eight planar Cu_3O_3 arrays (Figure 52). Oxygen atoms occupy all four of the equatorial positions on the copper centres. As there are also 24 pyrogallol phenol groups remaining, there are 24 intramolecular hydrogen bonds in addition to the 96 Cu-O coordination bonds attaching the six pyrogallol[4]arene moieties together.

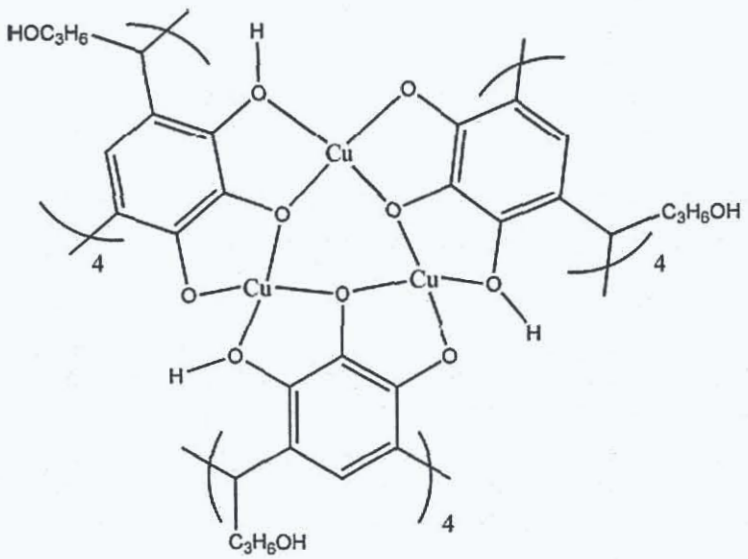


Figure 52: *The copper-oxygen framework coordinating the pyrogallol[4]arene capsule*[86]

A gallium-coordinated pyrogallol[4]arene hexameric capsule has also been reported[87, 88]. Treatment of C-pentylpyrogallol[4]arene in acetone or acetonitrile with two equivalents of $Ga(NO_3)_3$ yielded the pyrogallol[4]arene hexamer as shown in Figure 53. This molecule consists of 6 C-pentylpyrogallol[4]arene moieties, 12 Ga^{3+} ions and 4 water molecules.

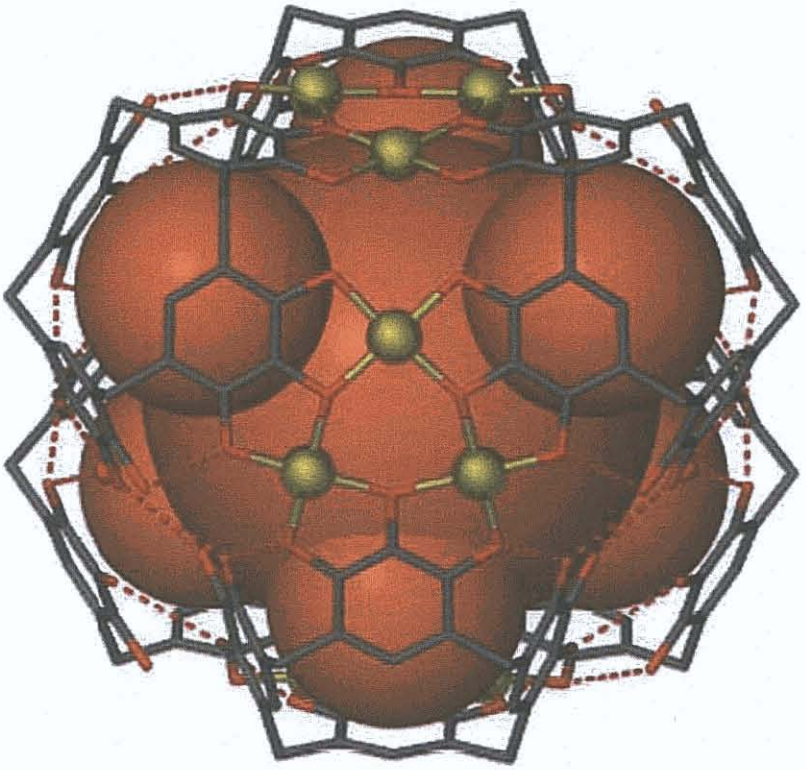
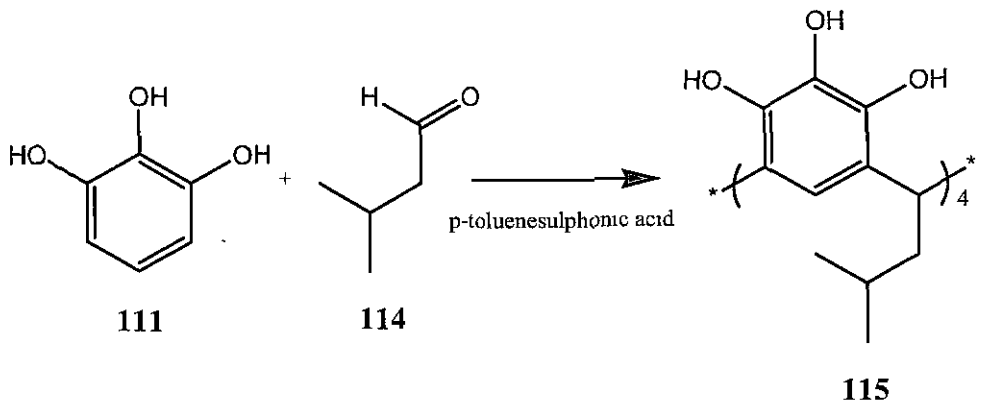


Figure 53: *Ga_{12}(C-pentylpyrogallol[4]arene)$_6$ (Ga^{3+} ions are gold, red spheres are water molecules)*[87]

B. Solvent-free Pyrogallol[4]arene Synthesis

Solvent-free syntheses are also possible for the formation of pyrogallol[4]arenes. Antesberger *at al.*[89] reported the high yield synthesis of C-isobutyl-calix[4]pyrogallolarenes (Scheme 12). Reaction of equimolar amounts of pyrogallol and isovaleraldehyde with catalytic quantities of solid p-toluenesulphonic acid produced the tetramer after five minutes of constant grinding using a mortar and pestle. Recrystallisation of the product from methanol yields the bilayer structure while recrystallisation from chloroform results in the formation of the hexameric nano-capsules.



111 **114** **115**

Scheme 12: *Solvent-free synthesis of pyrogallol[4]arene*

C. Cation complexes of Pyrogallol[4]arenes

Tetra-*isobutyl*-pyrogallol[4]arene forms monomeric and dimeric complexes with alkali metal cations[79].

Letzel *et al.*[90] studied the differences between resorcinol[4]arene and pyrogallol[4]arene ion binding. They proposed two different binding mechanisms, one for the smaller Li^+ and Na^+ ions, and another for the larger K^+, Cs^+ and Rb^+ ions. The first binding mechanism involves the small alkali metal ion binding near to the oxygen atoms in the upper rim of the tetramer Competitive studies showed that pyrogallol[4]arenes with their 12 upper rim OH groups bind these small ions much better then the resorcinol[4]arenes which possess only 8 OH groups on the upper rim.

However, the number of hydroxy groups in the tetramer does not influence the binding of larger alkali metal cations such as K^+, Cs^+ and Rb^+. These ions are situated in the cavity of the tetramer, where they fit well and are in closer contact with the aromatic ring systems.

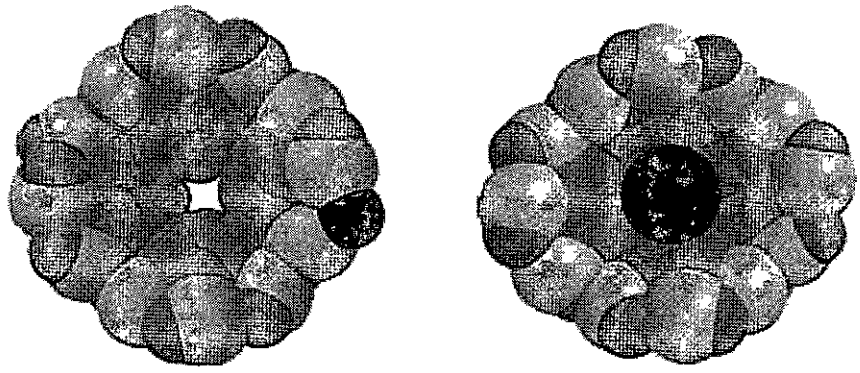
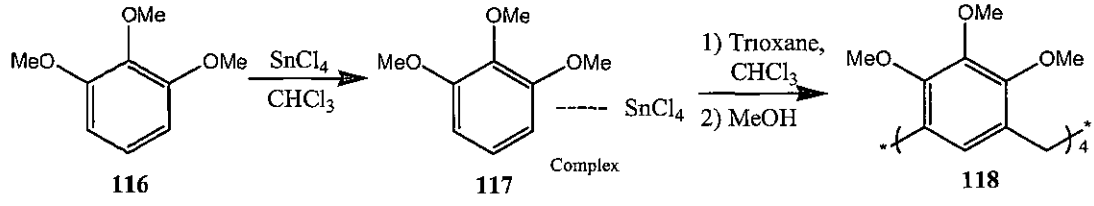


Figure 54: *Pyrogallol[4]arene complexed with Li^+(left) and K^+(right)*[90]

D. Synthesis of Methoxypyrogallol[4]arene

Iwanek et al.[91] reported the synthesis of methoxypyrogallol[4]arene from 1,2,3-trimethoxybenzene and trioxane, using $SnCl_4$ as a catalyst.



Scheme 13: *Synthesis of methoxypyrogallol[4]arene*[91]

Due to its similarity to a crown ether (presence of 12 OMe groups), the Iwanek group[91] chose to test this compound for complexation with alkali metal cations. Electrospray ionisation mass spectral results show that the caesium ion is strongly complexed while Li^+ is least complexed of the 5 alkali metal cations tested.

V. Thesis Proposal

Aryl pyrogallolarenes, which are all in the rctt conformation, show good bioactivity, especially the partially alkylated pyrogallolarenes, which are lower in charge density and contain free phenol groups. These compounds bind to the gp-120 receptors by electrostatic interactions. We believe that these latter compounds may also be redox active.

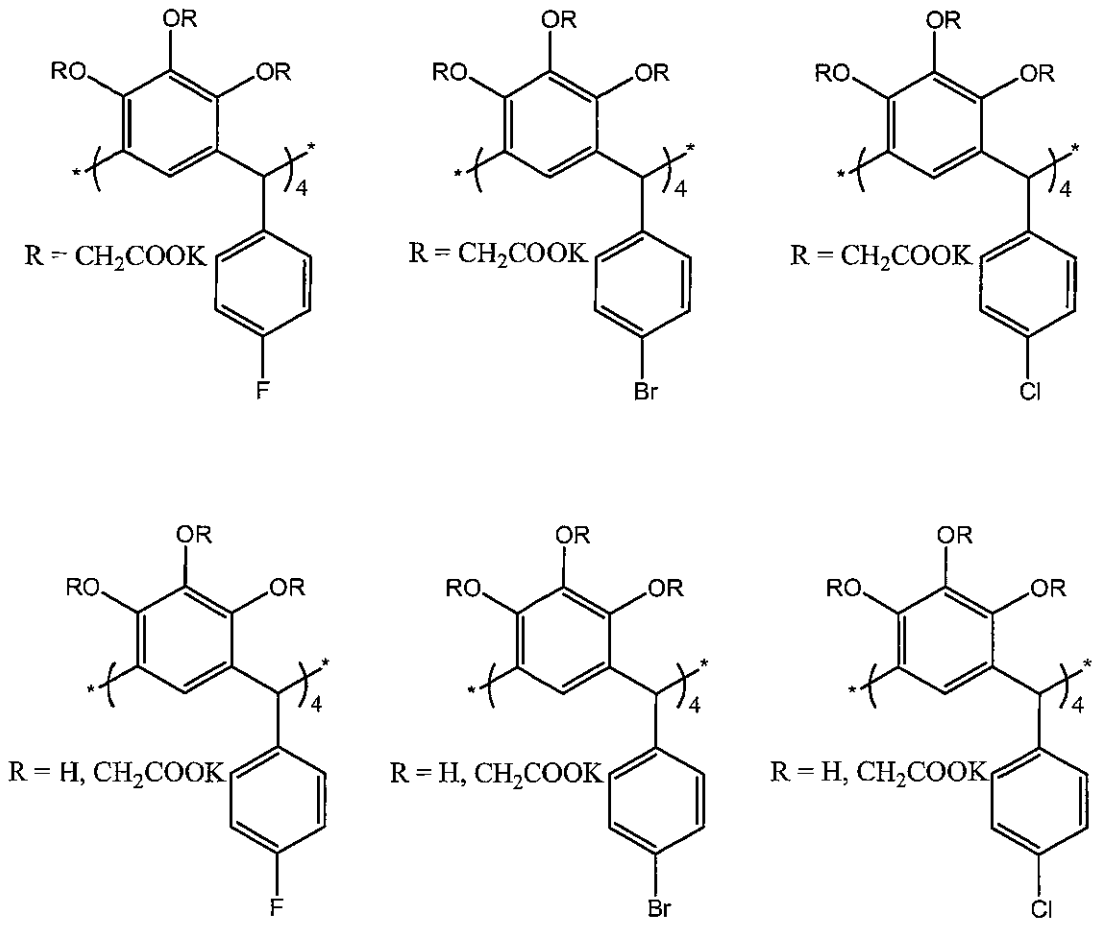


Figure I: *A selection of pyrogallol[4]arenes which were tested for GP120 inhibition activity*

Compound	EC-50	TC-50	Selectivity Index
Tetra-4-fluorophenyl pyrogallol[4]arene dodeca acetate potassium salt	8.683	2812	334.33
Tetra-4-bromophenyl pyrogallol[4]arene dodeca acetate potassium salt	0.494	195.6	400 89
Tetra-4-chlorophenyl pyrogallol[4]arene dodeca acetate potassium salt	2.65	868.19	335.54
Tetra-4-fluorophenyl pyrogallol[4]arene partially alkylated acetate potassium salt	12.01	1131.09	88.49
Tetra-4-bromophenyl pyrogallol[4]arene partially alkylated acetate potassium salt	2.64	1375.65	526.72
Tetra-4-chlorophenyl pyrogallol[4]arene partially alkylated acetate potassium salt	0.247	1015	4158.4

Table I: *GP120 inhibition results for a selection of pyrogallol[4]arenes*

However, a recent SAR study of an rccc alkyl pyrogallolarene, carried out by Carey in our research group, showed poor bioactivity against the HIV-1 virus. This compound was the tetradecylpyrogallol[4]arene tetramer, made from the condensation of decanal with pyrogallol. We would like to find out whether the bioactivity of a pyrogallolarene is due to the stereoisomer or to the presence of the alkyl groups on the lower rim.

Following on from this work on pyrogallol[4]arenes, a number of issues were raised which we wished to explore.

1) Can we control the stereochemistry of the reactions?

Pyrogallol[4]arenes have been shown to have biological activity against HIV, to date only the rctt chair stereoisomer has been evaluated since this is the sole product from the condensation of aromatic aldehydes with pyrogallol. We wish to develop methods

that may favour the production of the rccc cone isomer in these condensations. If this is achieved, then a complete SAR with respect to stereoisomerism will be completed.

We wish to achieve this goal by carrying out a series of studies to determine whether we can interconvert the stereoisomers of the actual macrocycle post condensation.

2) Can we increase the scope of the reaction?

Pyrogallolarenes have, to date, only been synthesised using aldehydes. We are interested in expanding the scope of this reaction to include ketones. If successful, not only would this be the first demonstration of condensing ketones in calixarene/resorcinarene/pyrogallolarene chemistry, but it will also give us further structural diversification for our HIV-1 SAR studies. We believe that this goal is possible since pyrogallol is far more electron-rich than either phenol or recorcinol and we believe its reactivity should be comparable to that of pyrrole, which on condensation with ketones gives the cyclic tetramer, calix[4]pyrrole.

3) Can we prepare pyrogallol[4]arenes using less harsh conditions?

We are interested in preparing pyrogallolarenes of the following structure:

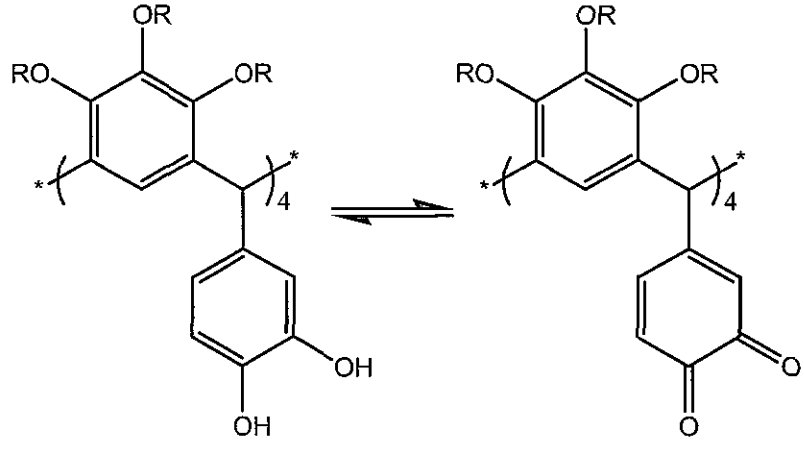


Figure II: *Potential redox active pyrogallolarene structures*

We believe that these compounds will solve a present problem with respect to the biological activity of the partially alkylated pyrogallolarenes. It is possible that the

partially alkylated pyrogallolarenes, which have been shown to be more active against HIV-1 than completely alkylated pyrogallolarenes, are acting as redox agents. To prove this, it is ideal to prepare a completely alkylated pyrogallolarene, which possesses redox active moieties as, shown in Figure II. However, to prepare such a molecule will require using protected aldehydes, this will allow for the selective alkylation of the pyrogallol phenoxy groups of the pyrogallolarene, followed by cleavage of the protection groups to give the target compounds. The problem in achieving this goal is that any protection group used to date (acetate, benzyl) is cleaved during the condensation reaction as a result of the strong acid conditions.

Our group recently explored the possibility of using weaker acid conditions for the preparation of pyrogallolarenes, however all of these attempts failed. It is the goal of this work to try and develop gentler reaction conditions. If achieved then this will open the door for the preparation of not only redox active pyrogallolarenes, but also other novel derivatives.

4) The last aspect of this work involves validating mass spectrometry as a tool for screening the ionophoric properties of the pyrogallol[4]arenes.

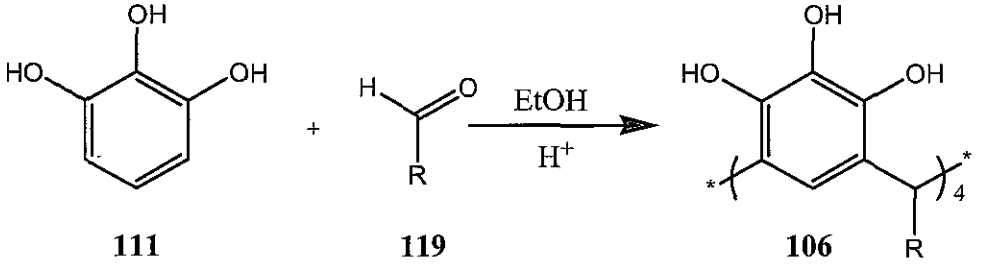
To investigate a potential alternative application for the pyrogallol[4]arenes, we decided to explore their capability for ion selectivity. We wish to compare the results from mass spectrometry with established ion selective electrode methods and liquid/liquid extraction methods (picrate salts). If successful then we can confidently screen the ionphore ability of new macrocycles in a few minutes instead of a few days or weeks.

Chapter 2

Pyrogallol/Aldehyde Reactions

I. Introduction

Condensation of pyrogallol with acetaldehyde under acidic conditions produces a cyclic tetramer, called a pyrogallolarene. We discovered that the acetaldehyde pyrogallolarene exists in two conformations, the cone *rccc* isomer and the flattened partial cone *rctt* isomer. The cone *rccc* isomer is made in higher yields than the flattened partial cone *rctt* isomer in the condensation reaction of pyrogallol with acetaldehyde under acidic conditions. Previous studies[92] showed that each tetramer is formed in only one conformation, usually the flattened partial cone conformation. We were interested in examining the reaction conditions in order to isolate each of the isomers. We were also curious as to whether there was interconversion from one conformation to another. In this case, both isomers were found to be extremely stable, neither showing interconversion of conformation by temperature ^{1}H NMR studies (temperatures up to 110°C in DMSO).

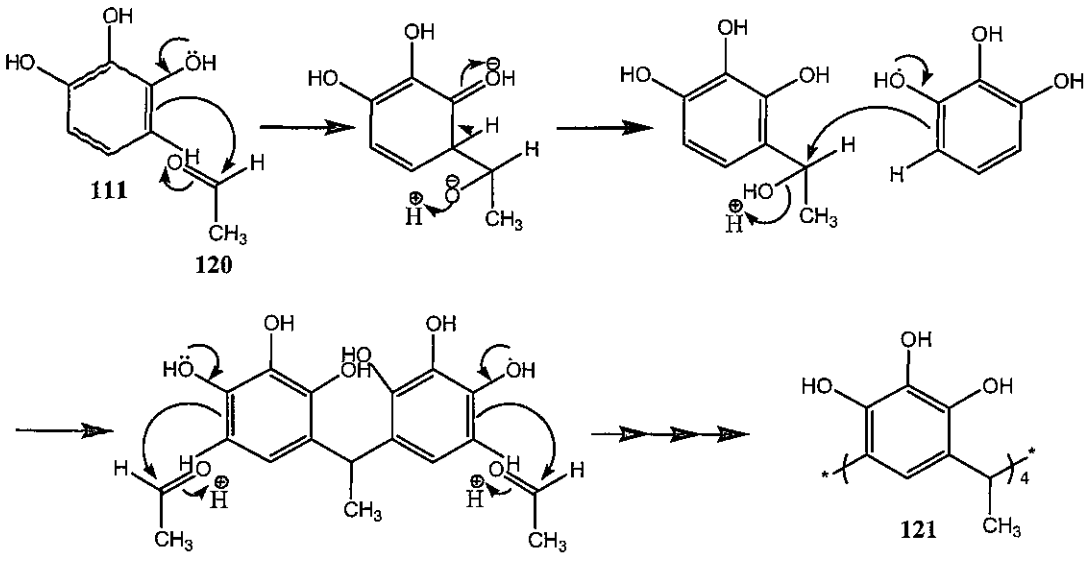


111 **119** **106**

R=Alkyl, aryl

Scheme 14: *General reaction scheme of the synthesis of pyrogallol[4]arenes*

The proposed mechanism of formation of the pyrogallol[4]arenes is shown in Scheme 15. This mechanism involves the cyclisation of a linear tetramer, formed by successive electrophilic substitutions. The linear tetramer cyclises to form the thermodynamically stable cyclic tetramer.



Scheme 15: *Mechanism of formation of tetramethylpyrogallol[4]arene*

II. Results and Discussion

A. Time Study

We were interested in optimising the yields of each of the isomeric products. Yield optimising experiments have already been carried out by Carey[92] regarding the concentrations of starting materials. A time study was carried out to discover the optimum reaction time to give the greatest yield of products. The yields of the two different isomers were also studied over time.

The time study of the tetramethylpyrogallol[4]arene synthesis showed that no initial precipitate was formed when the starting materials were refluxed for less than 5 hours. However, with the addition of ice to the reaction mixture, a precipitate did form, which was filtered and washed with ice water. This compound was found to be a mixture of two conformers, the cone and the flattened partial cone isomers.

In a second reaction, a precipitate formed after 5 hours reaction time. This resulting precipitate was filtered and washed with a 4:1 solution of ethanol: water. Addition of ice to the filtrate yielded a second precipitate, which was filtered and washed with ice water. The first precipitate was found to be a mixture of the cone and flattened partial cone conformations of the tetramer whereas the second precipitate was found to be the pure cone isomer.

The mixture of compounds was purified by repeated extraction in ethanol. The mixture was heated in ethanol and the insoluble solids were filtered off. The filtrate was evaporated under reduced pressure to yield the cone isomer. This process was repeated to eliminate all the cone isomer from the mixture and isolate the flattened partial cone isomer. Both precipitates were analysed by ^{1}H NMR spectroscopy. The ^{1}H NMR data of the precipitates show high purity of the compounds formed. Many condensation products of macrocycles give a complicated mixture of products, which can be very difficult to separate (e.g. calixarenes). The yields of each of the two isomers formed, along with the total yields for the time study, are shown in Table 4.

As can be seen in Table 4, the yield of the cone isomer and the total yield progressively increases with an increase in time up to 48 hours, and then slightly decreases. The yield of the flattened partial cone isomer is very low for reaction times up to 5 hours. The yield of the flattened partial cone isomer increases with time but does not achieve a moderate yield even after a reaction time of one week. The optimum yield was obtained after 48 hours but as there was only a slight increase in yield from 24 to 48 hours, it was decided to use a 24-hour time frame for the remainder of the experiments.

	Time (Hours)	Cone Isomer Yield (%)	Flattened Partial Cone Isomer Yield (%)	Total Yield (%)
2-A	1	7	0	7
2-B	2	17	1	18
2-C	3	19	3	22
2-D	4	20	3	23
2-E	5	23	3	26
2-F	24	30	7	37
2-G	48	36	8	44
2-H	168	31	13	44

Table 4: *Results including initial precipitate and slurry products*

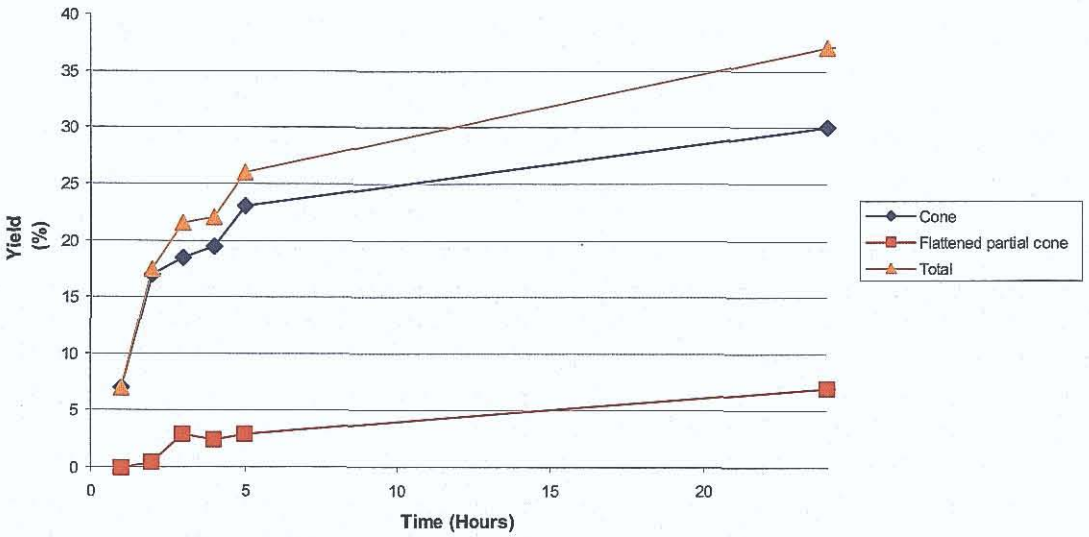


Figure 55: *Results including initial precipitate and slurry products*

B. Dilute Acid Time Study

A second time study was undertaken, this time using dilute acid conditions. Equimolar amounts of pyrogallol and acetaldehyde were reacted under acidic ethanolic conditions (12.5% acid) for times varying from one hour to one week. No product was formed for all reactions up to and including 24 hours. Only the 48-hour and weeklong reactions produced a product, and even then in low yields. The product was formed solely in the cone conformation after the reaction mixture was poured onto ice.

Reaction	Time (Hours)	Cone Isomer Yield (%)	Flattened Partial Cone Isomer Yield (%)	Total Yield (%)
3-A	1	0	0	0
3-B	2	0	0	0
3-C	3	0	0	0
3-D	4	0	0	0
3-E	5	0	0	0
3-F	24	0	0	0
3-G	48	13	0	13
3-H	168	15	0	15

Table 5: *Dilute acid time study*

C. Room Temperature Time Study

A third time study was carried out which involved the reaction of equimolar amounts of pyrogallol and acetaldehyde in acidic ethanol (37% acid) at room temperature. No product was formed within a day but a very small amount of the cone isomer was formed after 24 hours. After one week of reaction at room temperature, a mixture of isomers was formed. Both the cone and the flattened partial cone isomers were formed in low yields with the cone isomer being predominant.

	Time (Hours)	Cone Isomer Yield (%)	Flattened Partial Cone Isomer	Total Yield (%)
4-A	3	0	0	0
4-B	24	1	0	1
4-C	168	8	5	13

Table 6: *Room temperature time study results*

D. ^{1}H NMR Analysis

1. Cone rccc Isomer:

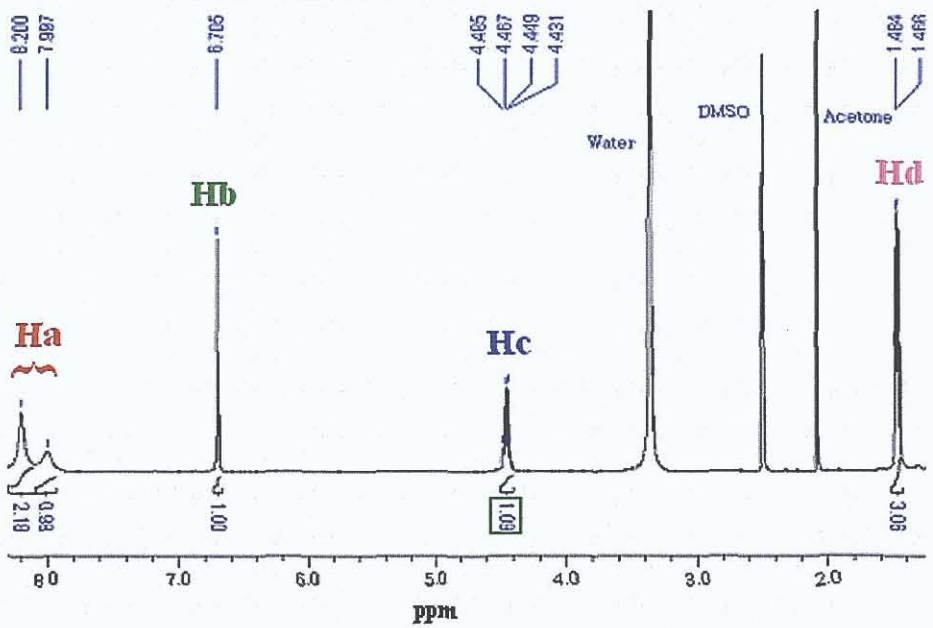


Figure 56: *^{1}H NMR of the acetaldehyde pyrogallol[4]arene in the cone conformation*

The cone isomer is the more symmetrical of the two, with the simpler ^{1}H NMR spectrum. The pyrogallol hydroxy groups (Ha) show up as a broad peak at 8.2ppm. The appearance of a broad peak for the OH groups in DMSO-d6 is attributed to the exchange of D_2O, which is present in the solvent, with the OH protons. Hb, the free

proton on the lower rim of the pyrogallol units appears as a singlet at 6.7ppm. The bridging protons, Hc, appear as a quartet at 4.5ppm and the acetaldehyde methyl group, Hd, is seen as a doublet at 1.5ppm.

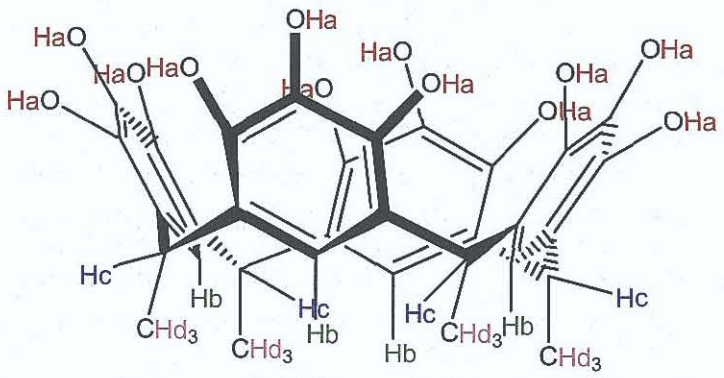


Figure 57: *Pyrogallol[4]arene in the cone conformation*

2. Flattened Partial Cone rctt Isomer:

The ^{1}H NMR spectrum of the flattened partial cone isomer is more complicated due to its relative lack of symmetry compared to the cone isomer. The main difference in the spectra shows up in the region between 5.5 and 7ppm (Figure 58).

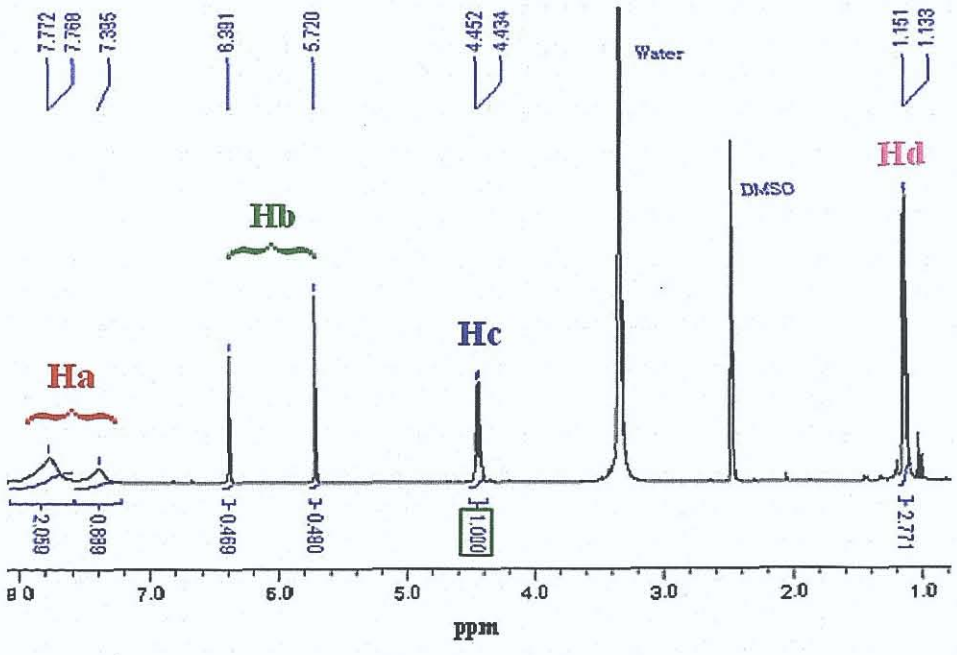


Figure 58: *^{1}H NMR of the acetaldehyde pyrogallol[4]arene in the flattened partial cone conformation*

The aromatic pyrogallol protons, Hb, show up in the aromatic region but appear as two singlets of equal integration. In this conformation, the aromatic pyrogallol protons are in two different chemical environments (Figure 59). Two of the protons are pointing directly into the macrocycle ring while one is pointing upwards and the other is pointing downwards. The two pointing upwards and downwards are more deshielded as they are each lying parallel to a benzene ring. This deshielding causes them to appear more upfield on the ^{1}H NMR spectrum.

The hydroxyl protons appear at 7.4 and 7.8ppm. Depending on the purity of the solvent, DMSO, these protons can appear as distinct singlets of broad peaks in the ^{1}H NMR spectrum. The 4 protons on the methylene bridges are all in the same chemical environment and therefore appear as a quartet at 4.5ppm. The methyl groups appear as a doublet at 1.2ppm.

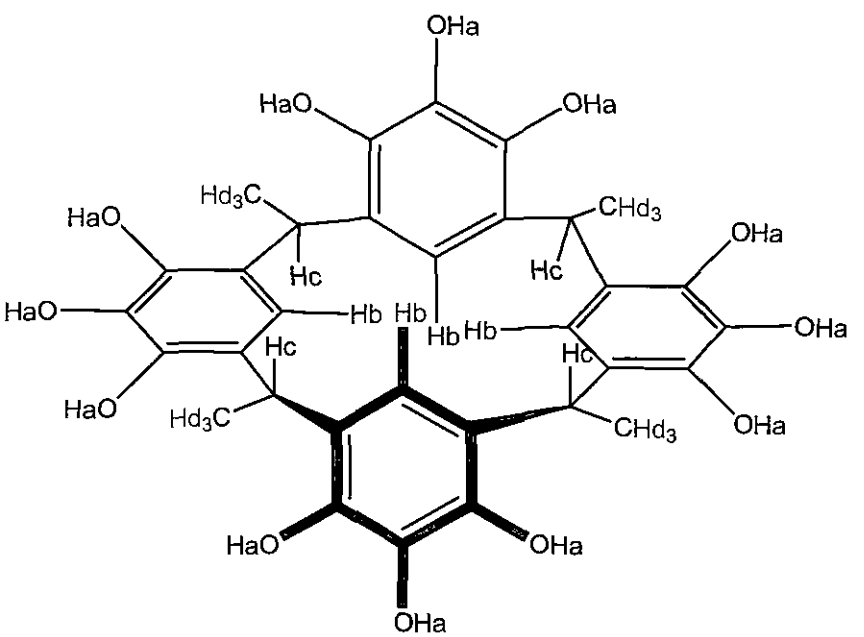


Figure 59: *Pyrogallol[4]arene in the flattened partial cone conformation*

E. Interconversion Reactions

It has been reported in the literature that the acid catalysed reaction of resorcarene and aldehydes produces a tetramer of different conformations[69]. The kinetically favoured isomer is formed in the partial cone conformation and reaches a maximum yield after one hour and subsequently decreases as the reaction time is extended (Figure 60). The

isomer in the flattened cone conformation, which is the thermodynamically favoured isomer, increases with the reaction time to an eventual yield of approximately 80%. This indicates that the formation of the isomer in the partial cone conformation is reversible under the reaction conditions. A separate set of experiments was performed to confirm this. The isomer in the partial cone conformation was treated under conditions similar to the initial reaction conditions (Refluxing for 24 hours in acidic ethanolic solution). After five hours, the product was collected in 80% yield as a 50:50 mixture of the two isomers. After ten hours, the product collected consisted of only the flattened cone isomer in 80% yield.

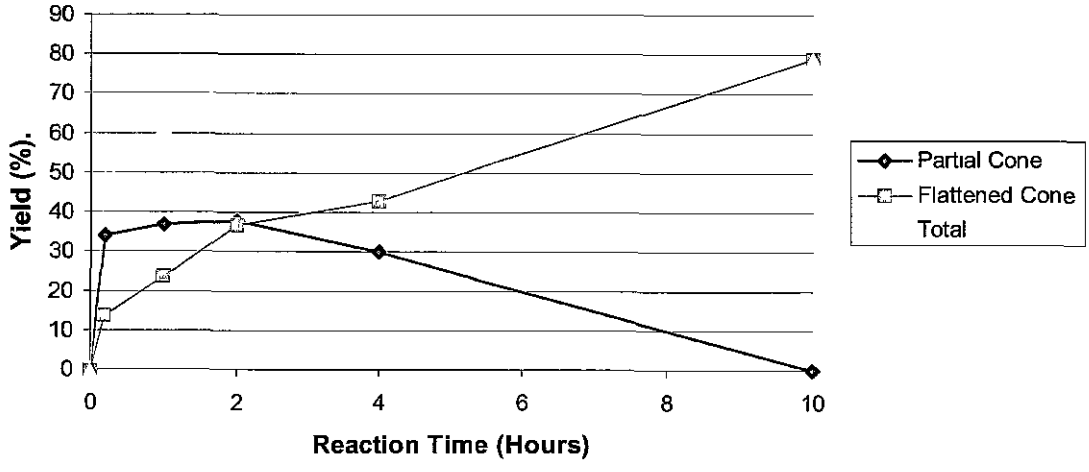


Figure 60: *Yields of resorcin[4]arene isomers over time*[69]

The similar reaction using pyrogallol and acetaldehyde under acidic conditions also produces two different isomers, which are recovered from the reaction mixture, the cone isomer and the flattened partial cone isomer. The results of the time study discussed earlier indicate that there is no interconversion between isomers. The yields of both pyrogallol[4]arene isomers gradually increase with time, unlike the yields of resorcin[4]arenes.

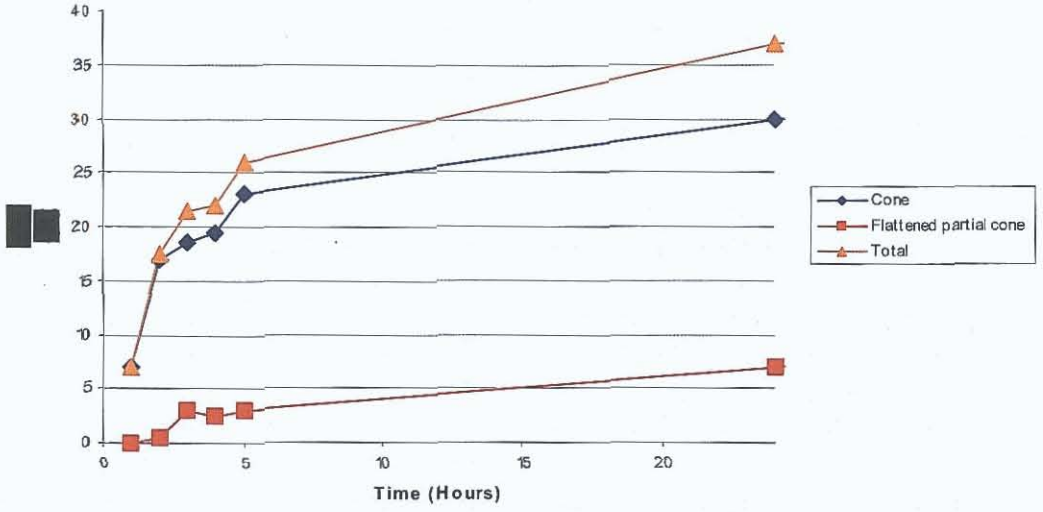


Figure 61: *Yields of pyrogallol[4]arene isomers over time*

Two control reaction were completed to verify our suspicions that there is no interconversion between isomers of the pyrogallol[4]arene. A pure sample of each isomer was treated under acidic ethanolic conditions at 80°C overnight and the product was analysed. In each case, only the starting material was recovered. In the case of the cone isomer, the product was recovered in 26% yield and was found to be the tetramer purely in the cone conformation. The attempted interconversion reaction of the flattened partial cone isomer yielded only 12% product, which when analysed was found to be the unchanged tetramer. In both cases, no interconversion occurred and the tetramer was recovered in low yields in its original conformation.

We have reported the synthesis of the flattened partial cone rctt conformation due to the similarity of the ^{1}H NMR spectrum of our product with that of the tetra-4-fluorophenylpyrogallol[4]arene synthesised by Carey[92]. The crystal structure of this compound showed that the compound is in the flattened partial cone conformation with the pyrogallol rings at an angle of 87.62° from each other with two pyrogallol units lying in the plane.

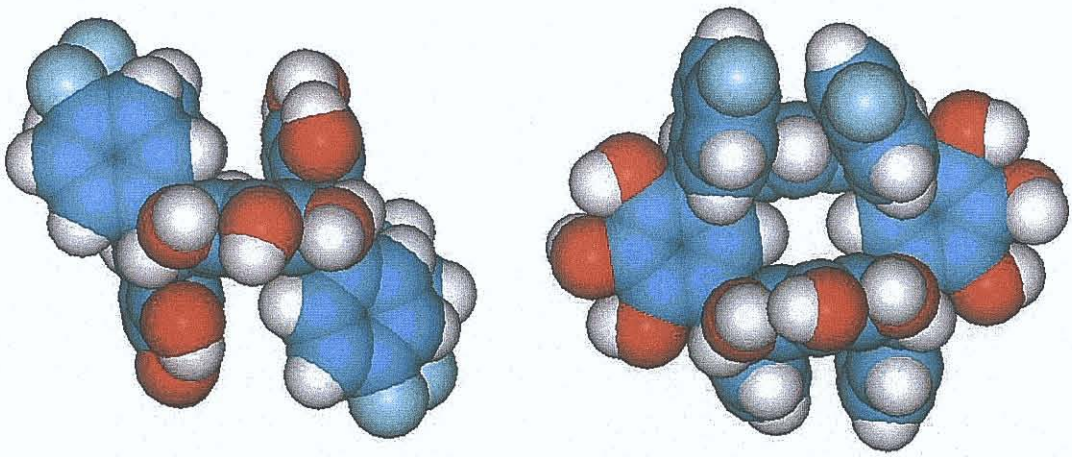


Figure 62: *The crystal structure of 4-fluorophenylpyrogallol[4]arene in the flattened partial cone conformation*

However, there is another conformation, which may result in the ^{1}H NMR spectrum shown in Figure 58. The flattened cone conformation (Figure 63) could also show 2 different peaks for the aromatic pyrogallol protons, with two protons pointing into the macrocyclic ring and two pointing downwards. Both the flattened partial cone and the flattened cone are unlikely to interconvert with the cone conformation. Interconversion of the flattened partial cone would require the breakage of C-C bonds, which is unlikely. The flattened cone is held in that conformation by three H-bonds across the macrocycle between the hydroxy groups of opposite pyrogallol rings. These bonds must be broken in order for the compound to convert to the cone conformation. Both of these interconversions require high energy to break the bonds necessary so interconversion is improbable.

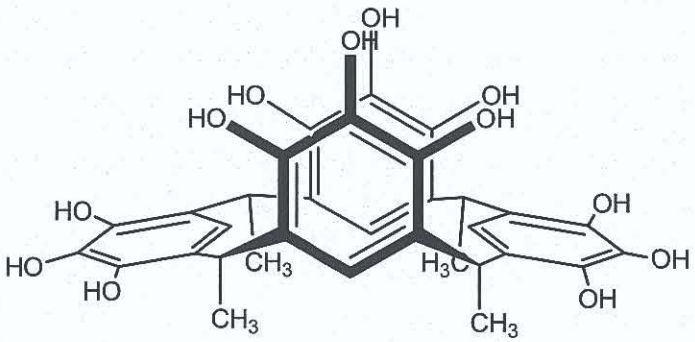


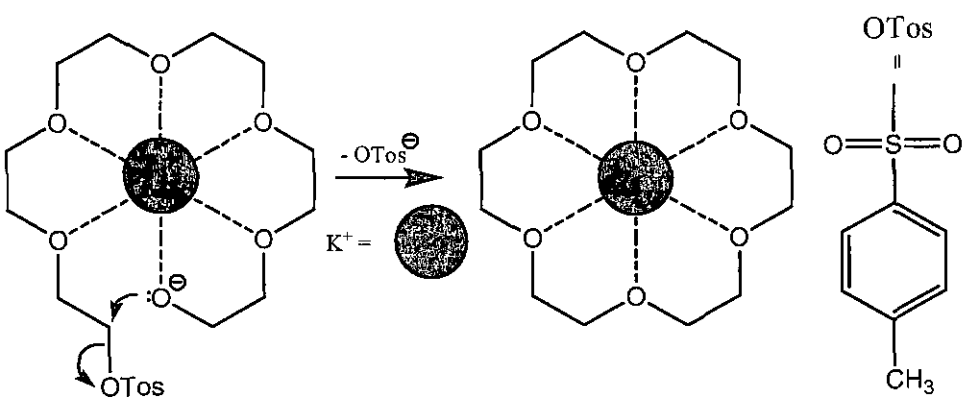
Figure 63: *Methylpyrogallol[4]arene in the flattened cone conformation*

We can rule out the possibility of a mixture of flattened partial cone and flattened cone isomers in the reaction due to the sharpness of the peaks in the ^{1}H NMR spectrum. Referring again to Högberg's data on resorcin[4]arenes[69], there is a $\Delta\delta$ of between 0.7ppm and 0.13ppm for the bridging proton and aromatic proton between the flattened partial cone and the flattened cone isomers. A mixture of isomers would result in an increase in the number of peaks or a broadening of the existing peaks in the ^{1}H NMR spectrum.

F. Metal Templation Studies

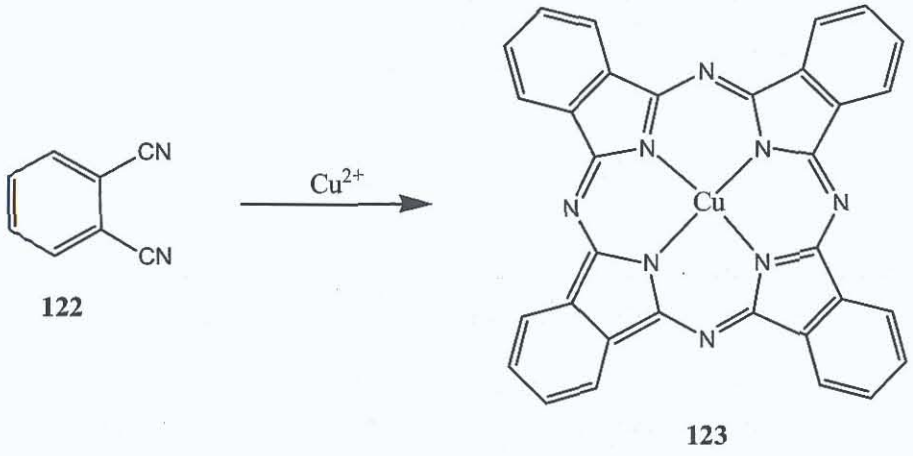
Busch[93] defined the chemical template as follows: "A chemical template organises an assembly of atoms, with respect to one or more geometric loci, in order to achieve a particular linking of the atoms. Templates are distinguished from reagents because they affect the macroscopic geometry of the reaction and not the intrinsic chemistry."

Kinetic templation effects occur when the template causes the preorganisation of the reactants, which wrap around the template. This brings the reactive sites into close proximity and therefore increases the formation of this predominant product.[94]



Scheme 16: *Metal templation synthesis of 18-crown-6*[94]

Scheme 16 shows the metal templation of 18-crown-6 around a potassium ion. The K^+ ion acts as a template for the synthesis of the 18-crown-6 by binding to the acyclic polyether and prearranging it into a conformation that brings the reactive ends together to allow for efficient covalent bond formation. Another example[95] of the kinetic template effect is the synthesis of phthalocyanines formed spontaneously on heating 1,2-dicyanobenzenes in the presence of metal ions such as Cu^{2+} (Scheme 17).



122 123

Scheme 17: *Phthalocyanine synthesis using metal templation*[95]

A metal templation study was carried out previously[92] to compare the yields of two different pyrogallol[4]arenes under the influence of a variety of different metal salts. In the case of the tetra-4-fluoropyrogallol[4]arene, sodium, potassium, zinc and nickel all gave enhanced yields of the tetramer whereas only the potassium ion gave some enhancement of the yield in the condensation of pyrogallol and acetaldehyde.

We decided to reinvestigate the metal templation effects on the synthesis of tetramethyl pyrogallol[4]arene (**121**, Scheme 15), this time focusing on the yield ratios of the cone isomer to the flattened partial cone isomer. We were interested to see if metal templation would increase the formation of the cone isomer. This isomer possesses a very symmetrical central cavity into which metal ions may possibly coordinate. The lithium ion coordinates to the hydroxy groups on the pyrogallol moieties, which are then preorganised into the cone conformation. In this way, the presence of the lithium ion, aids in the formation of the product in the cone conformation.

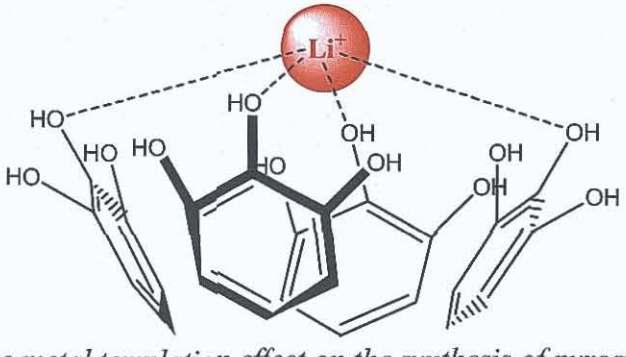


Figure 64: *The metal templation effect on the synthesis of pyrogallol[4]arenes*

The six salts tested and the resulting cone:flattened partial cone isomer ratios are shown in Table 7 along with the ratios from the metal-free synthesis.

Salt	Cone:Flattened Partial Cone Isomer Ratio	Ionic Radius (pm)
LiCl	55:1	90
NaCl	23:1	116
$MgCl_2$	58:1	86
$CaCl_2$	49:1	114
CsCl	5:1	181
KBr	11:3	152
Control	4:1	n/a

Table 7: *Salts and the resulting cone:flattened partial cone isomer ratios*

None of the salts produced a significantly enhanced overall yield of tetramer, which follows previous results. Four metal ions, namely lithium, sodium, calcium and magnesium increased the cone:flattened partial cone isomer ratio. The smallest ion, Li^+, possibly fits neatly into the cavity and therefore causes a templation effect and an increase in the amount of the cone isomer that is formed. Na^+ is a slightly bigger ion but results suggest that this ion also fits into the pyrogallol[4]arene tetrameric cavity.

As can be seen from the graph in Figure 65, the salts with the metal ions of smaller ionic radii produce a much higher proportion of the cone rccc isomer compared to the flattened partial cone rctt isomer. The lithium and magnesium ions give a very similar response in the isomer ratios. This is because they both have very similar ionic radii. Although the magnesium ion has an extra valence shell compared to the lithium ion, it has a greater positive charge, which decreases the ionic radius.

Potassium and caesium have the largest atomic radii of all the metal ions shown and they cause an increase in the formation of the more unsymmetrical rctt isomer. However, none of the ions tested caused the formation of the rctt isomer in greater yields than the rccc cone isomer.

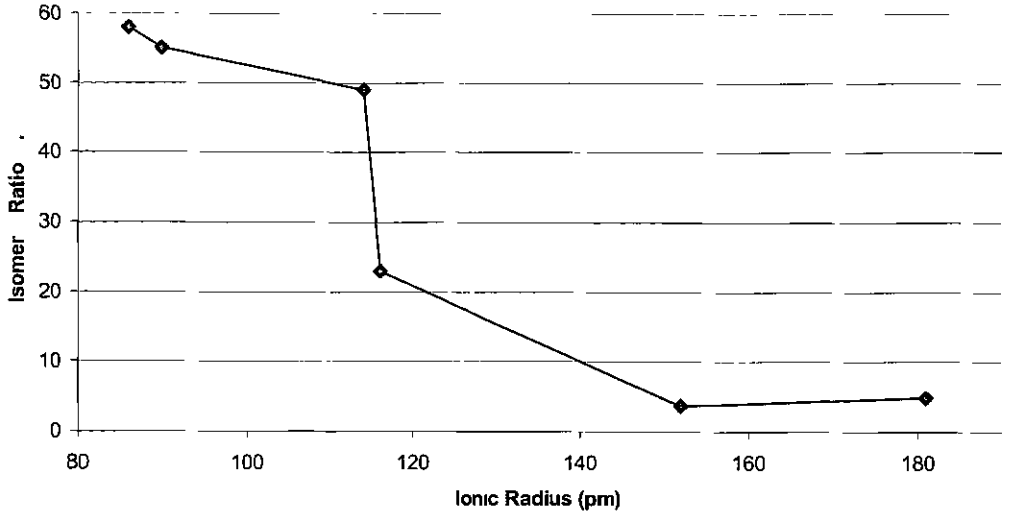


Figure 65: *Graph of cone:flattened partial cone isomer ratio with respect to ionic radii*

The metal ion coordinates to the hydroxy groups of the pyrogallol and if the ion is small enough, four pyrogallol groups can approach the ion for coordination. In this way, they prearrange into the cone conformation.

Caesium ions had very little effect on the yield ratios compared to the control reaction but the results from the KBr experiment were interesting. K^+ was the only ion to decrease the cone:flattened partial cone isomer ratio. This relatively large monovalent ion is possibly too big to fit into the cone shaped cavity and inhibits complete cyclisation in this conformation.

These results are contradictory to the results of Letzel *et al.*[90] who used Calotte model calculations (obtained using the Montecarlo method) to show diagrammatically the position of the alkali metal ions with regard to the pyrogallolarenes (see Chapter 1). They suggest that the Li^+ ion is situated close to the hydroxy groups on the rim of the tetramer but cannot specify if the ion if located inside or outside the cavity. Our results suggest that the small metal ion is located within the cavity as otherwise, templation would not occur.

III.Experimental

A. General procedure for the synthesis of pyrogallol[4]arenes

1.0g (8mmol) of pyrogallol and 0.44mls (8mmol) of acetaldehyde were mixed in 10mls of ethanol. To this solution 3.5mls of concentrated (37%) hydrochloric acid was added and the reaction was stirred at 80°C for 24 hours. The resulting pink reaction mixture was filtered and washed with 4:1 ethanol:water. The filtrate was poured onto ice and a light pink precipitate formed, which was filtered and washed with ice-cold water. The precipitates were found to be a mixture of isomers, which were separated by repeated extraction in hot ethanol. Total yield of cone isomer = 0.39g (32%); total yield of flattened partial cone isomer = 0.10g (8%).

Cone isomer: ^{1}H NMR (DMSO-d6): δ [ppm] 8.2 (s, 12H, O**H**), 6.7 (s, 4H, Ar-**H**), 4.5 (q, J=7.2Hz, 4H, Ar-C**H**-CH_3), 1.5 (d, J=7.2Hz, 12H, CH-C**H**$_3$).
Mass Spec: $C_{32}H_{32}O_{12}$ Expected: *m/z* 608
Found: *m/z* 631 (M+23)

Flattened partial cone isomer: ^{1}H NMR (DMSO-d6): δ [ppm] 7.8 (s, 4H, O**H**), 7.7 (s, 4H, O**H**), 7.4 (s, 4H, O**H**), 6.4 (s, 2H, Ar-**H**), 5.7 (s, 2H, Ar-**H**), 4.5 (q, J=7.2Hz, 4H, Ar-C**H**-CH_3), 1.2 (d, J=7.2Hz, 12H, CH-C**H**$_3$).
Mass Spec: $C_{32}H_{32}O_{12}$ Expected: *m/z* 608
Found: *m/z* 631 (M+23)

B. Tetramethylpyrogallol[4]arene synthesis time study

The general procedure was followed with refluxing for periods varying from one hour to one week.

Yields are shown in Table 4 (Page 68). ^{1}H NMR analysis was used to determine the structures of the products.

C. Tetramethylpyrogallol[4]arene synthesis dilute acid time study

The general procedure was followed using dilute (12.5%) hydrochloric acid with refluxing for periods varying from one hour to one week.

Yields are shown in Table 5 (Page 69). ^{1}H NMR analysis was used to determine the structures of the products. ^{1}H NMR analysis showed that solely the cone isomer was formed.

D. Tetramethylpyrogallol[4]arene synthesis room temperature time study

The general procedure was followed with refluxing for periods varying from three hours to one week at room temperature.

Yields are shown in Table 6 (Page 70). ^{1}H NMR analysis was used to determine the structures of the products.

E. Tetramethylpyrogallol[4]arene cone isomer attempted interconversion

0.5g (0.82mmol) of the tetramethylpyrogallol[4]arene in the cone conformation was heated to reflux in 5mls of ethanol and 1.75mls of hydrochloric acid overnight. The product was analysed by ^{1}H NMR and found to consist totally of the cone conformation.

F. Tetramethylpyrogallol[4]arene flattened partial cone isomer attempted interconversion

0.25g (0.41mmol) of the tetramethylpyrogallol[4]arene in the flattened partial cone conformation was heated to reflux in 5mls of ethanol and 1.75mls of hydrochloric acid overnight. The product was analysed by ^{1}H NMR and found to consist totally of the starting material in the flattened partial cone conformation.

G. Tetramethylpyrogallol[4]arene synthesis metal templation study

The general procedure was followed with refluxing for 24 hours with 8mmol of various metal salts.

Yields are shown in Table 7 (Page 78). ^{1}H NMR analysis was used to determine the structures of the products.

Chapter 3

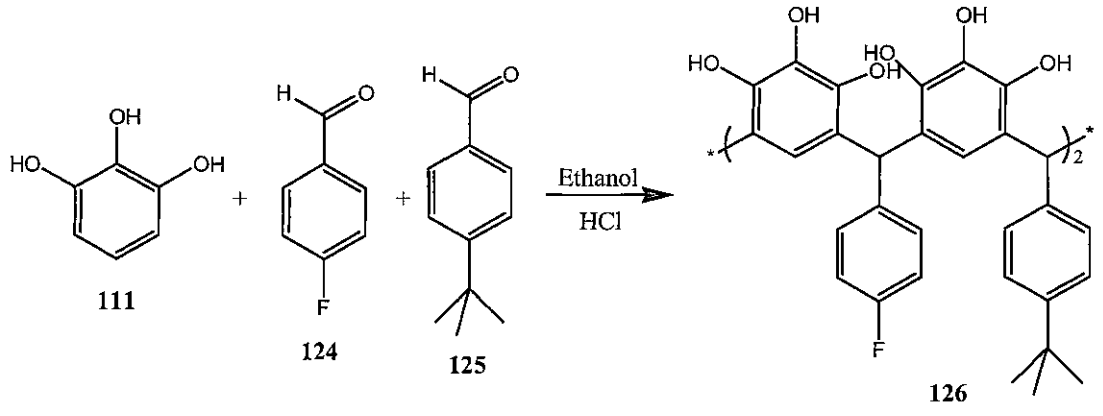
Unsymmetrical Pyrogallol/Aldehyde Tetramer Reactions

IV. Results and Discussion

It has been shown that partially alkylated pyrogallolarenes are more biologically active compared to the fully substituted tetramers[92]. These molecules are unsymmetrical about the upper rim. It is not known whether symmetry at the bridging groups influences biological activity.

A mixture of substituents causes a decrease in the symmetry of the molecule around the bridging groups. We were interested in studying the effects of this reduction in symmetry on the biological activity of the compounds.

For this reason, a study was carried out to investigate the possibility of synthesizing unsymmetrical pyrogallol[4]arenes using two different aldehydes. Scheme 18 shows the reaction of pyrogallol with 4-fluorobenzaldehyde and 4-*tert*-butylbenzaldehyde to yield a tetramer.



Scheme 18: *Synthesis of a mixed condensation pyrogallol[4]arene*

A mixture of products was expected. 6 products could be produced as shown in Figure 66.

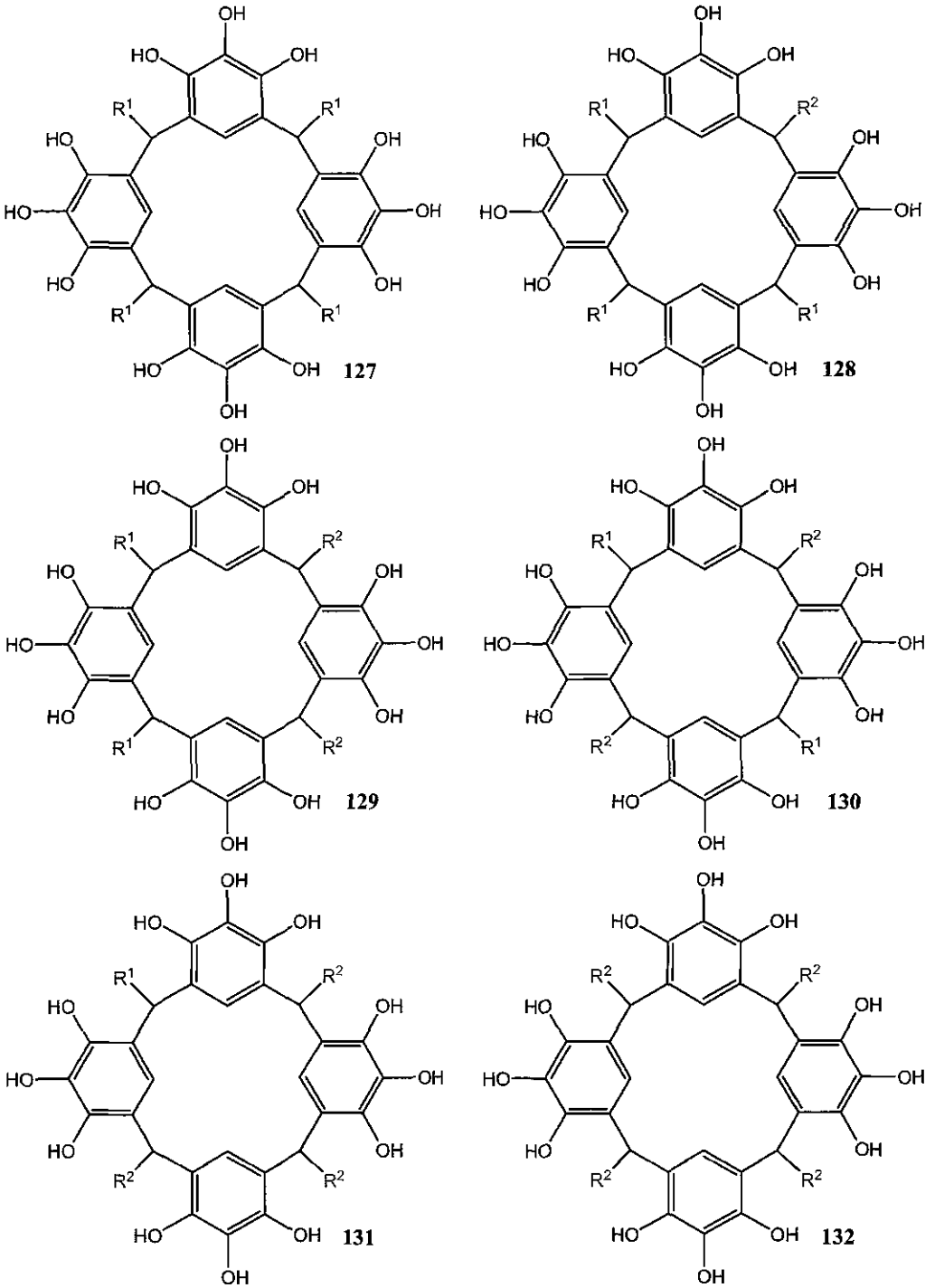


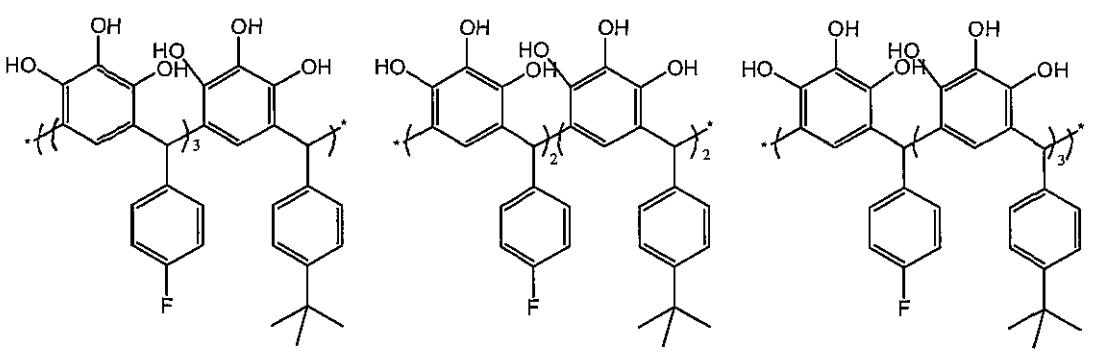
Figure 66: *Potential products of unsymmetrical condensation using 2 different aldehydes*

A. Mixed Condensation Synthesis of Pyrogallol[4]arenes Using 2 Different Aldehydes

Two aldehydes were chosen that have been proven to produce tetramers in good yield, 4-fluorobenzaldehyde and 4-*tert*-butylbenzaldehyde. 4-*Tert*-butylbenzaldehyde was also chosen in the hope that the solubility of the resulting tetramer would be increased by the presence of pendant alkyl groups on the substituent. The reaction conditions used were the same as for pyrogallol[4]arene synthesis using a single aldehyde. The amounts of each aldehyde used are shown in Table 12.

Reaction	Pyrogallol	4-fluoro benzaldehyde	4-*tert*-butyl benzaldehyde	Ethanol	Hydrochloric acid
8-A	0.5g (4mmol)	0.107mls (1mmol)	0.501mls (3mmol)	5mls	1.75mls
8-B	0.5g (4mmol)	0.214mls (2mmol)	0.334mls (2mmol)	5mls	1.75mls
8-C	0.5g (4mmol)	0.321mls (3mmol)	0.167mls (1mmol)	5mls	1.75mls

Table 12: *Amounts of different aldehydes used in the unsymmetrical reactions*



133 **134** **135**

Figure 67: *Desired products from reaction of pyrogallol with 4-fluorobenzaldehyde and 4-tert-butylbenzaldehyde*

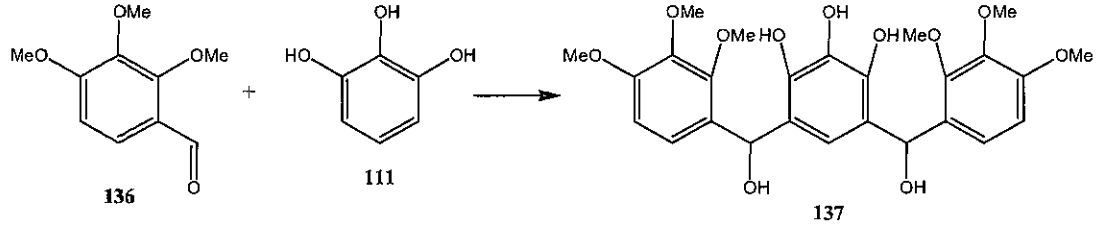
After stirring at reflux overnight, the light pink precipitates of reactions **8-A** and **8-B** were filtered. No precipitate formed in the reaction mixture of reaction **8-C**. The

filtrates from reactions **8-A** and **8-B**, and the reaction mixture from reaction **8-C** were poured onto ice and the resulting dark pink precipitates were isolated.

^{1}H NMR of the precipitates showed a complex mixture of products, especially for the slurry precipitates. A portion of the slurry product of reaction **8-B** was analysed by thin layer chromatography in 100% ethyl acetate and showed 2 spots. Column chromatography proved difficult as the polar nature of the pyrogallol[4]arene causes it to streak along the column. Successful separation was not achieved even after numerous columns. Reverse phase chromatography also proved unsuccessful.

B. Reaction of Pyrogallol with 2,3,4-Trimethoxybenzaldehyde

An attempt was made to prepare a pyrogallolarene, which is unsymmetrically substituted on the upper rim. A stepwise synthesis was undertaken by the formation of a trimer, which would then be reacted with a monomer to form the desired tetramer.



Scheme 19: *Attempted trimer synthesis*

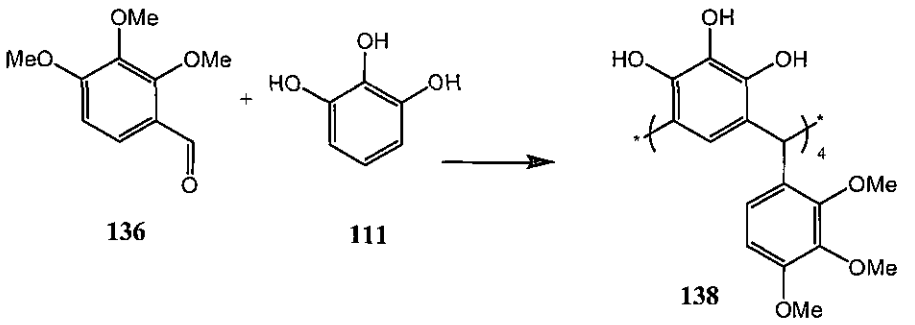
It was hoped that the trimer would be formed so the reaction was carried out under differing concentrations of acid (Table 13).

Reaction	Pyrogallol	2,3,4-trimethoxy benzaldehyde	Ethanol	Hydrochloric Acid	Yield (%)
11	0.5g (4mmol)	1.57g (8mmol)	15mls	5.5mls	18
12	0.5g (4mmol)	1.57g (8mmol)	15mls	2.5mls	24
13	0.5g (4mmol)	1.57g (8mmol)	15mls	0.5mls	32

Table 13: *Amounts of acid used in the unsymmetrical reactions*

Three reactions were performed. Each reaction involved refluxing pyrogallol with twice the excess of 2,3,4-trimethoxybenzaldehyde in 15mls of ethanol. The amount of hydrochloric acid added to the reactions varied from 5.5mls to 0.5mls. Unfortunately, the trimer was not formed in any of the three reactions. A pyrogallol tetramer was formed in all cases, with yields increasing with decreasing concentrations of acid. Each of the three reactions formed the cone and the flattened partial cone isomers in a 2:1 ratio. This result is interesting as previous work by Carey[92] showed that most aromatic aldehydes produce the tetramer solely in the *rctt* flattened partial cone conformation. The only aromatic aldehyde to form the tetramer in another conformation was the highly sterically hindered 4-*t*-butylbenzaldehyde. This aldehyde formed the cyclic tetramer in a mixture of conformations, consisting of the *rccc* cone conformation in 27% yield and also the *rctt* flattened partial cone conformation in 66% yield.

The 2,3,4-trimethoxybenzaldehyde is remarkably electron donating, which deactivates the aldehyde. This results in the formation of the tetramer as opposed to polymerisation, which occurs with more reactive aldehydes. The steric effects of the three methoxy groups possibly contribute to the formation of the *rccc* cone isomer.



Scheme 20: Tetramer synthesis using 2,3,4- trimethoxybenzaldehyde

We believe that the cyclic tetrameric compound was formed but the product produced a complicated ^{1}H NMR spectrum, which indicates that a mixture of isomers was formed.

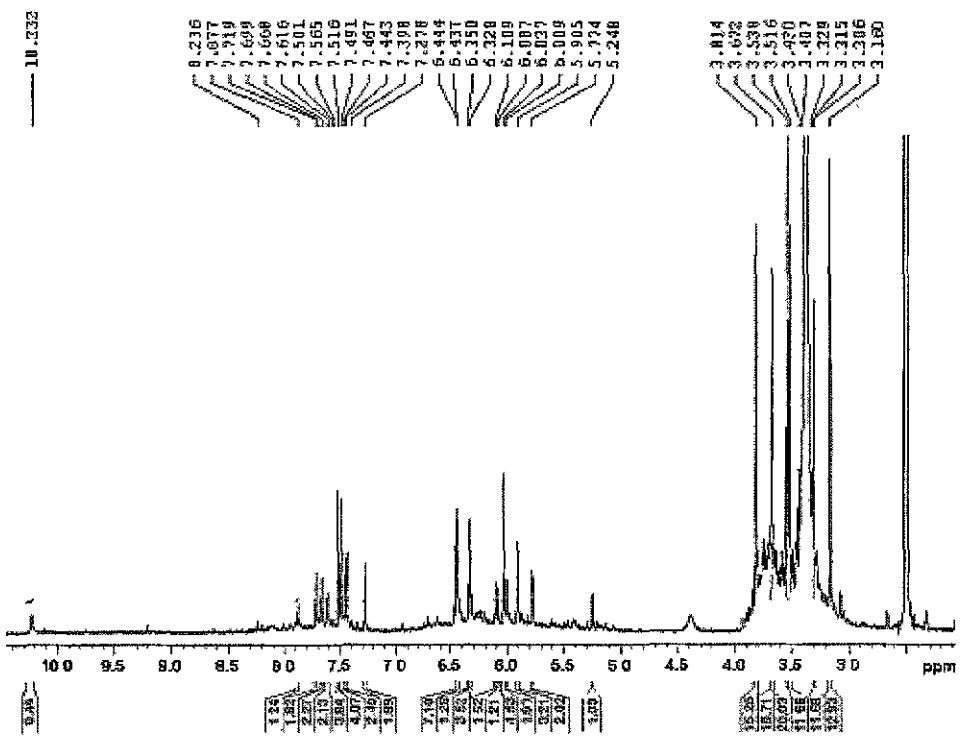


Figure 68: *^{1}H NMR spectrum of 2,3,4-trimethoxyphenyl pyrogallol[4]arene*

On initial inspection, it appeared that the product was formed in the flattened partial cone *rctt* and the cone *rccc* conformations. We came to this conclusion based on the presence of two singlets of nearly equal integration at 5.25 and 5.77ppm, and the larger singlet at 5.91ppm. The two peaks at 5.25 and 5.77ppm could be assigned to

the pyrogallol aromatic protons of the flattened partial cone *rctt* isomer. In this conformation, two of the pyrogallol protons are pointing between the trimethoxy rings of the pyrogallol[4]arene and are therefore shifted upfield by the anisotropic effect to 5.25ppm. The other two pyrogallol protons are not as greatly affected by these anisotropic effects and therefore appear slightly downfield at 5.77ppm. This spectrum would appear to be a typical spectrum for the *rctt* conformation.

However, the integration of the peak at 5.91ppm does not correspond to this conformation. Also, when the other peaks in the region between 5 and 7ppm were taken into account, it became clear that the flattened partial cone isomer was not present.

We decided to carry out a series of ^{1}H NMR experiments. The first involved the addition of D_2O. The resulting spectrum is shown in Figure 69.

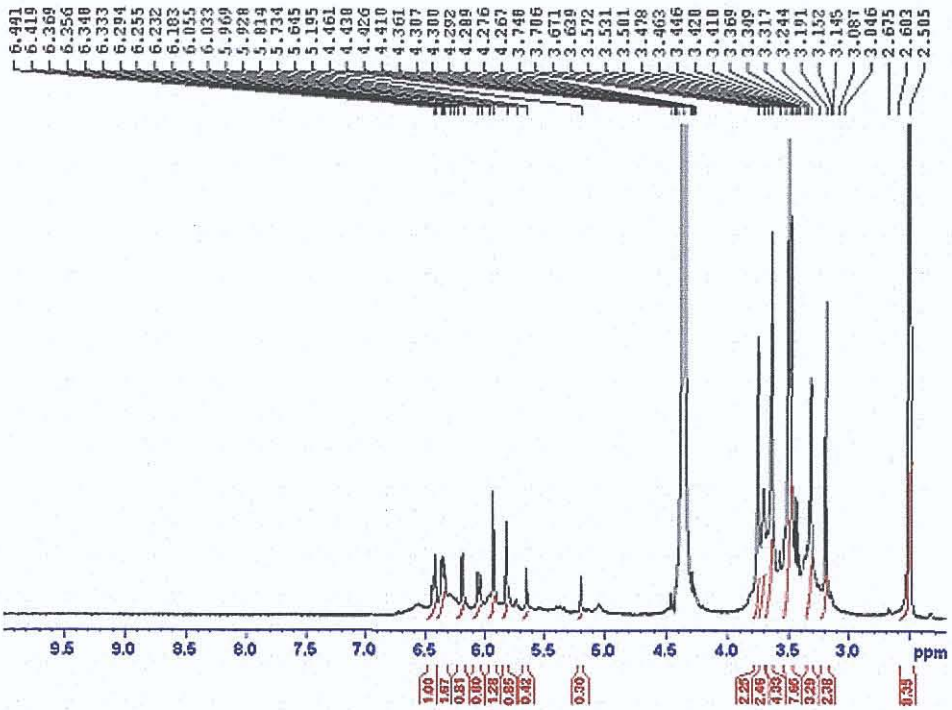


Figure 69: *^{1}H NMR spectrum of 2,3,4-trimethoxyphenyl pyrogallol[4]arene in DMSO with D_2O*

It is evident that all peaks beyond 7 ppm are due to the macrocycle hydroxy protons. A temperature experiment in DMSO-d_6 was then carried out and the results are shown in Figure 70. Upon heating the sample there is a change in the spectrum. The main significant change is the disappearance of the peak at 5.77ppm. If the flattened partial cone *rctt* isomer was present, this peak would be unaffected. Temperature NMR experiments have previously been carried out on the tetra-4-fluorophenyl pyrogallol[4]arene and the ^{1}H NMR spectrum remains unaffected.

The peaks at 6.33 and 6.35ppm appear to be two singlets of differing integration at room temperature. However, on heating, it becomes clear that there had been a singlet merging with one of the peaks of a doublet.

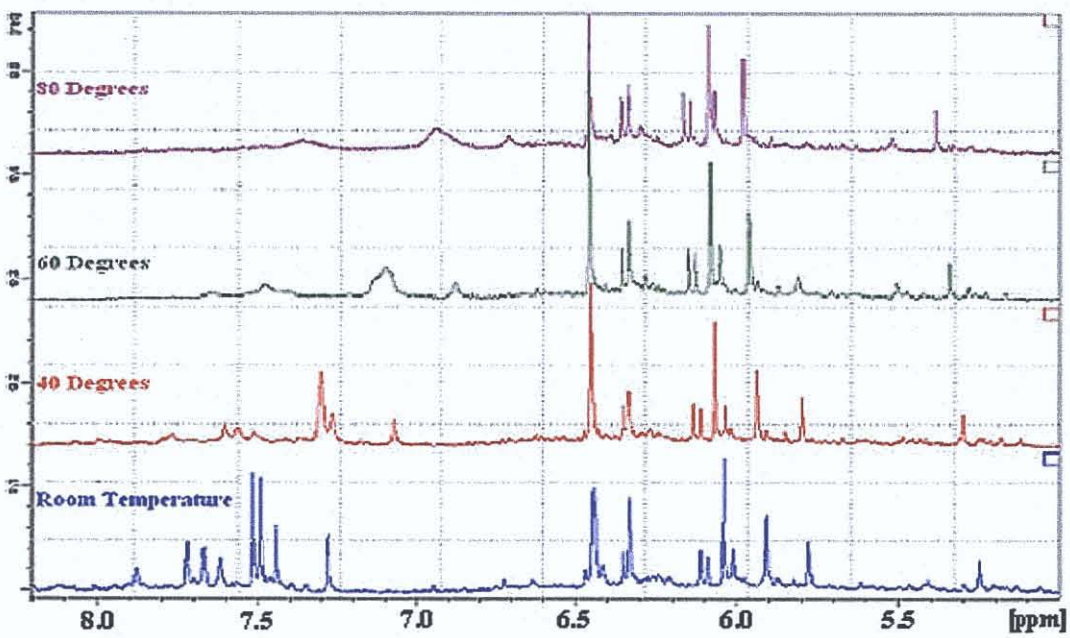


Figure 70: *^{1}H NMR temperature study of 2,3,4-trimethoxyphenyl pyrogallol[4]arene*

The only known isomers that we could possibly have are the cone, the flattened cone and the 1,3-alternate conformations. Both the cone and the 1,3-alternate conformations should only have one signal for the pyrogallol proton and one for the bridging proton. The flattened cone isomer possesses two kinds of pyrogallol protons and should therefore show two signals for these protons.

The ^{1}H-^{1}H COSY spectrum of 2,3,4-trimethoxyphenyl pyrogallol[4]arene (Figure 71) shows that the two doublets at 6.09ppm and 6.34ppm are coupled, and they can be

assigned to the protons of the trimethoxyphenyl rings of the macrocycle. It should also be noted that there are two sets of singlets for the methyl groups of the trimethoxyphenyl substiutents indicating that these substituents exist in two separate environments. It is possible that the substituents exist in an axial or equatorial environment, so the bridging protons of the macrocycle are either axial or equatorial. It is possible that atropisomers may exist, where the methoxy groups point either into the macrocycle or out of the macrocycle. It is possible for atropisomers to form since the ortho methoxy substituent can sterically block rotation of the trimethoxyphenyl substitutent.

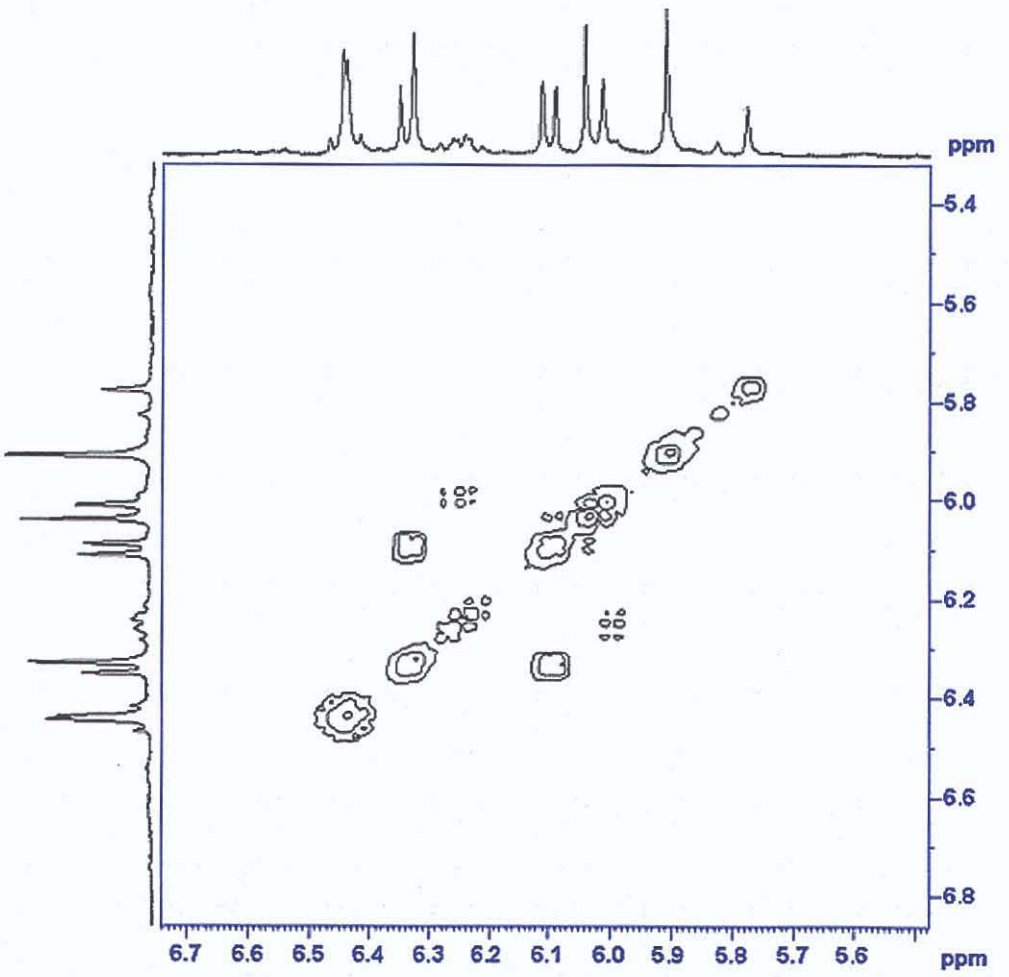


Figure 71: *^{1}H-^{1}H COSY spectrum of 2,3,4-trimethoxyphenyl pyrogallol[4]arene*

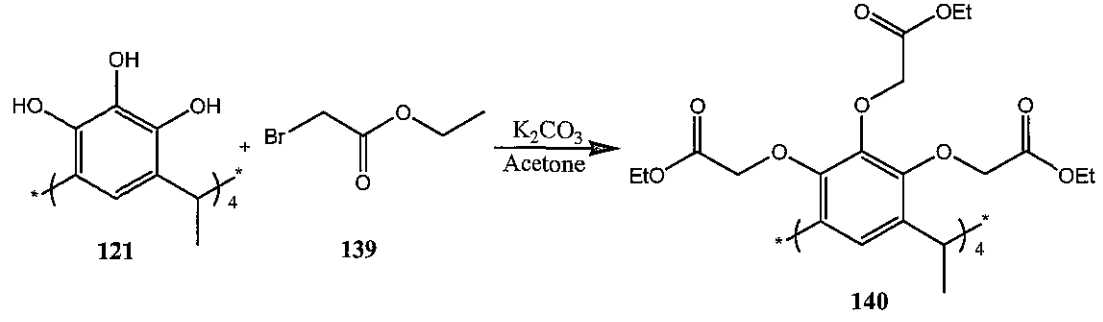
It is impossible to unambiguously allocate a structure to the compound we have made without obtaining a crystal structure. Unfortunately, a pure sample is needed to grow

crystals for X-ray crystal analysis and due to the nature of the mixture we have, separation and purification are not possible.

C. Complete Alkylation of Tetramethylpyrogallol[4]arene

Complete alkylation of the upper rim of the tetramethylpyrogallol[4]arene was attempted. Previous work on similar compounds[92] showed that a large excess of alkylating agent is required and the reaction needs to be forced to completion over 5 days. For this reason, tetramethylpyrogallol[4]arene in both the cone and the flattened partial cone conformations was reacted with 16 equivalents of ethylbromoacetate and 25 equivalents of potassium carbonate in dry acetone. Extra equivalents of ethylbromoacetate and potassium carbonate were added each day over a five-day period to increase the likelihood of complete alkylation.

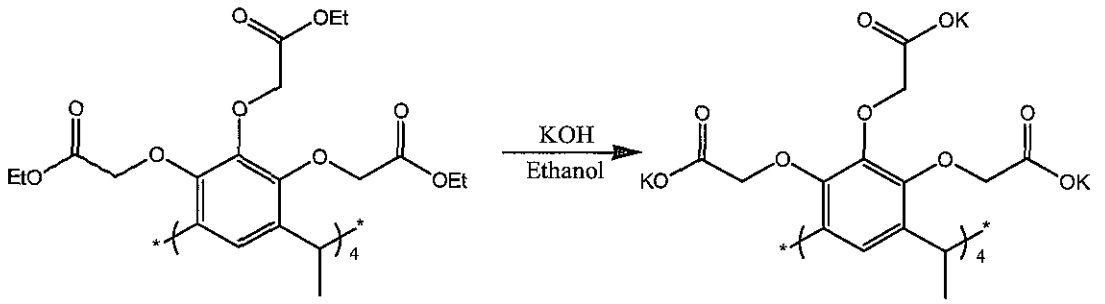
Analysis of the products showed that only partial alkylation of the cone isomer was achieved. The product obtained was a mixture of partially alkylated tetramers. We believe this is due to two factors. The steric hindrance in the upper rim of the pyrogallol[4]arene in the cone conformation prevents easy access of the reagents to the upper rim hydroxyl groups. Also, the upper rim of the pyrogallol[4]arene in the cone conformation possesses many hydrogen bonds which must be broken if alkylation is to occur.



Scheme 21: *Complete alkylation of tetramethylpyrogallol[4]arene*

However, in the case of the flattened partial cone isomer, full alkylation was achieved. ^{1}H NMR analysis showed that the impurities were still present even after repeated recrystallisation. The presence of a single dodeca-substituted product was identified by mass spectrometry. The dodeca-acetate ester derivatives were then hydrolysed into

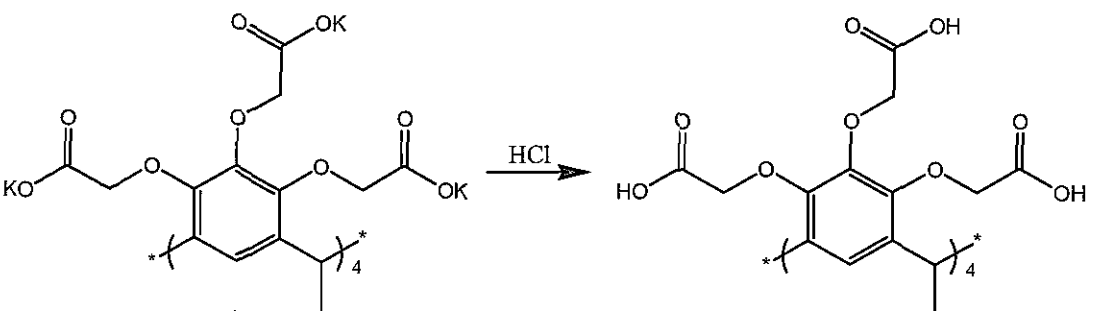
the corresponding dodeca-acetate potassium salts by reacting with potassium hydroxide in ethanol for 3 hours.



140 **141**

Scheme 22: *Base catalysed hydrolysis of tetramethylpyrogallol[4]arene dodeca-acetate ester to the corresponding acetate potassium salt*

Final purification was achieved by simple precipitation of the water-soluble salts from hydrochloric acid. This resulted in the formation of the corresponding dodeca-acetate acid.

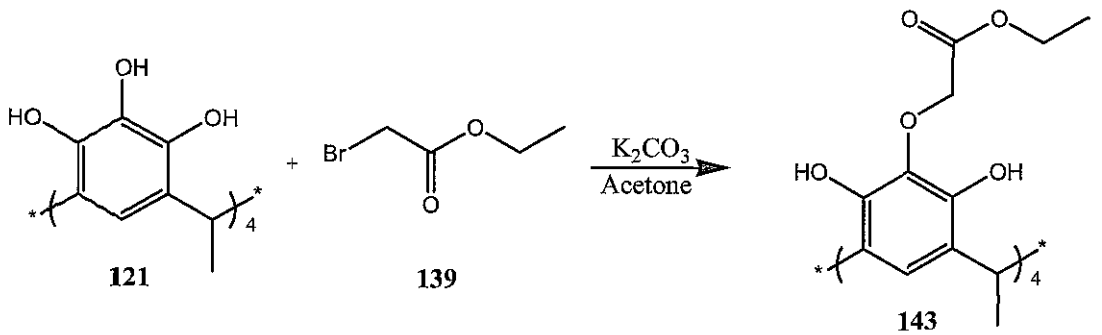


141 **142**

Scheme 23: *Acid catalysed precipitation of tetramethylpyrogallol[4]arene doceca-acetate acid from the corresponding acetate salt*

D. Partial Alkylation of Tetramethylpyrogallol[4]arene

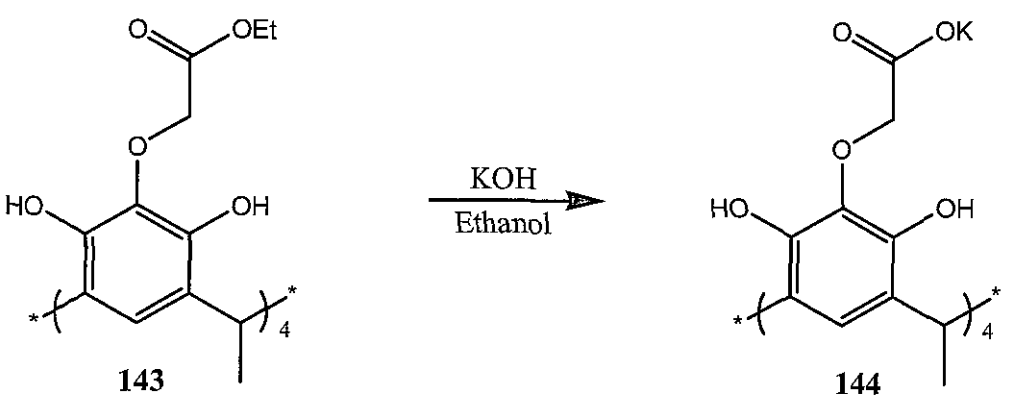
Partial alkylation of the tetramethylpyrogallol[4]arene by stoichiometric control was attempted. Previous work on similar compounds[92] showed that anything under 10 equivalents of ethylbromoacetate yielded little or no alkylated product. For this reason, 10 equivalents of ethylbromoacetate and 16 equivalents of potassium carbonate were used.



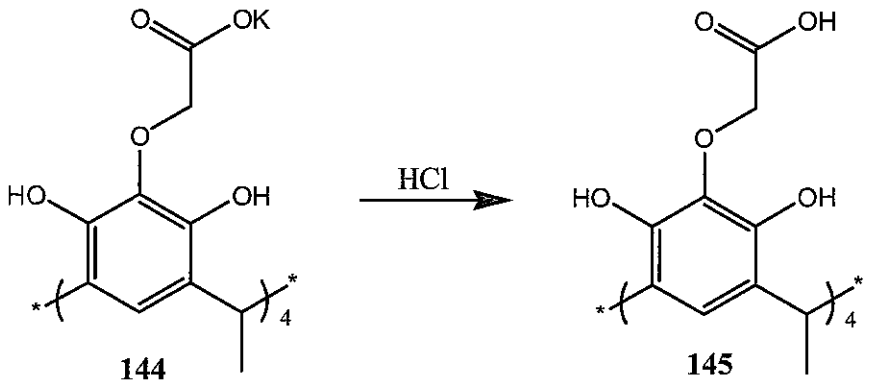
Scheme 24: *Partial alkylation of tetramethylpyrogallol[4]arene*

Analysis of the product from the cone conformation showed that alkylation did not occur. In the case of the flattened partial cone conformation, alkylation did occur but it appears that a mixture of partially alkylated products was formed. This is not surprising as alkylation may occur on more than one hydroxy group.

The partially alkylated esters were converted into the corresponding potassium salts and acids as outlined in Schemes 25 and 26. ^{1}H NMR of the resulting acids showed a complicated mixture of products. Separation of these products by column chromatography proved unsuccessful due to the high polarity of the compounds.



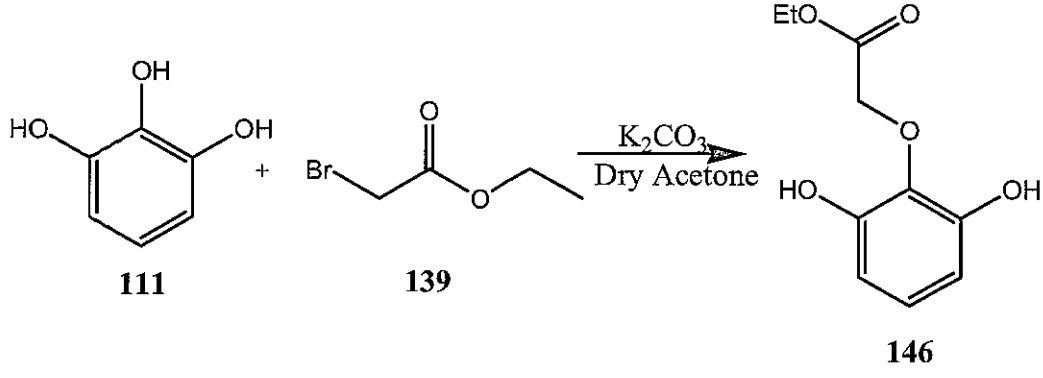
Scheme 25: *Base catalysed hydrolysis of tetramethylpyrogallol[4]arene tetra-acetate ester to the corresponding tetra-acetate potassium salt*



144 145

Scheme 26: *Acid catalysed precipitation of tetramethylpyrogallol[4]arene tetra-acetate acid from the corresponding tetra-acetate salt*

Another attempt was made at the synthesis of a partially alkylated pyrogallol[4]arene. This method involved the partial alkylation of pyrogallol and then tetramerisation of this compound. Equimolar amounts of pyrogallol and ethylbromoacetate were reacted with potassium carbonate in DMF to yield the partially alkylated pyrogallol which could then be condensed into the tetramer. The hydrogen on the central hydroxy group of the pyrogallol is the most acidic hydroxyl proton and therefore should be displaced more readily that the other two. With stoichiometric control, it was hoped that we could selectively alkylate this central hydroxy group. ^{1}H NMR analysis of the black product showed that the partially alkylated pyrogallol product was not formed. A second attempt was made using acetone as the solvent.

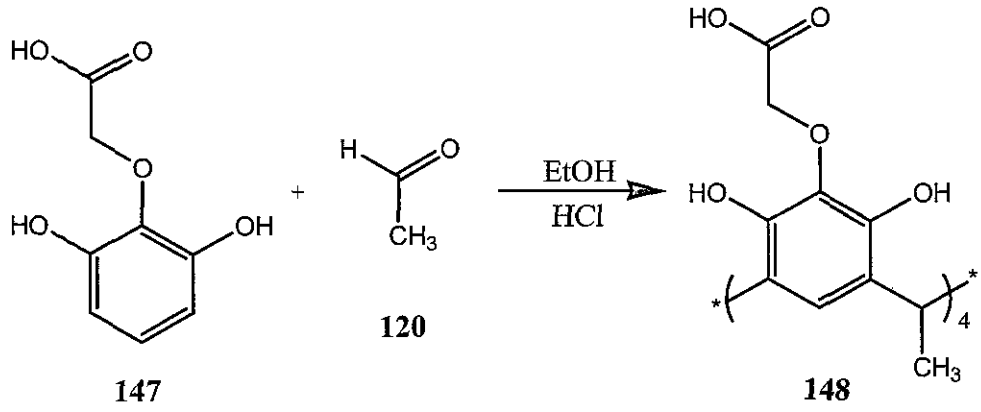


111 139 146

Scheme 27: *Partial alkylation of pyrogallol*

^{1}H NMR analysis of this product suggests that the partially alkylated product was successfully formed. No hydroxy groups appeared as the sample was run in D_2O. The aromatic protons appeared as a triplet at 6.78ppm and a doublet at 6.36ppm. The CH_2

group appeared as a singlet at 4.24ppm. We can conclude that the acid was formed by the absence of ethyl group protons in the ^{1}H NMR spectrum. The presence of a small broad peak between 10.4 and 10.5ppm is also indicative of the presence of acid groups.

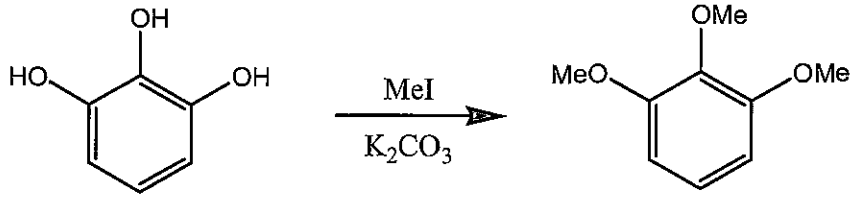


Scheme 28: *Attempted tetramerisation of partially alkylated pyrogallol*

The product from the previous reaction was treated with acetaldehyde under the normal cyclisation reaction conditions but the desired product was not formed. It is thought that the acetate groups have been cleaved off under the acidic conditions. This phenomenon is seen in calixarenes when a calix[4]arene substituted with acetate groups undergoes a reaction in harsh acidic conditions, the acetate groups can be cleaved off the molecule[96].

E. Methyl Iodide Methylation of Pyrogallol

We wanted to investigate the role of the upper rim hydroxy groups in the mechanism of formation of the pyrogallol tetramer. We decided to methylate the hydroxy groups on the pyrogallol and then use this tri-methylated molecule in the reaction with acetaldehyde. Methyl iodide was employed in the methylation process, which was carried out under basic conditions. An excess of methyl iodide and potassium carbonate was used, as this methylation reaction was known to be difficult. To achieve full alkylation, the reaction needs to be driven to completion by the use of a large excess of the methylating agent over a number of days.

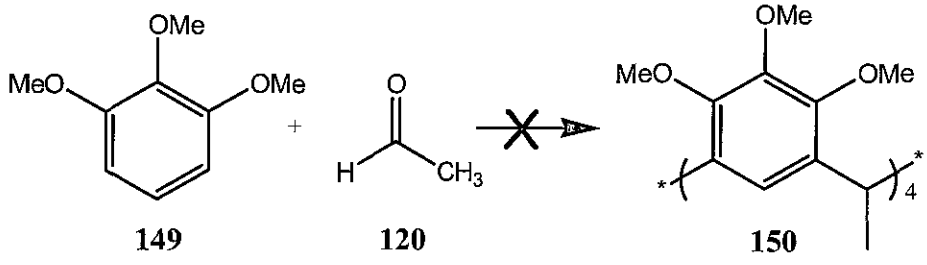


111 **149**

Scheme 29: *Methyl iodide methylation of pyrogallol*

F. Attempted Tetramerisation of Methylated Pyrogallol

1,2,3-Trimethoxybenzene (methylated pyrogallol) was reacted with acetaldehyde in equimolar amounts under identical acidic ethanolic conditions to the condensation reaction of unmethylated pyrogallol. After numerous attempts at this reaction, no product was formed. This implies that the free hydroxy groups are essential for the formation of a cyclic tetramer, which corresponds to the mechanism given in the previous chapter.



149 **120** **150**

Scheme 30: *Attempted tetramerisation of methylated pyrogallol*

V. Experimental

A. General procedure for the synthesis of pyrogallol[4]arenes with unsymmetrical bridging groups

0.5g (4mmol) of pyrogallol was reacted with varying amounts of 4-fluorobenzaldehyde and 4-*tert*-butylbenzaldehyde (Table 12) in 5mls ethanol containing 1.75mls hydrochloric acid. After 24 hours stirring at 80°C, a light pink precipitate formed in reactions 8-A and 8-B. These precipitates were filtered and washed with 4:1 ethanol:water to produce 0.16g and 0.03g of the tetramer respectively. The filtrates were poured onto ice and the resulting precipitates were filtered and washed with ice water to produce 0.80g and 1.02g of dark pink solid (for reactions 8-A and 8-B respectively). No precipitate formed in reaction 8-C. The reaction mixture (8-C) was poured onto ice and a precipitate formed which was filtered and washed with ice water to yield 0.97g of a light pink solid. The ^{1}H NMR analysis of each of the solids showed a complex mixture of products. Separation of the products was unsuccessful even after numerous passes through silica columns. Yield calculation was not possible due to the complex mixtures of products.

B. Reaction of pyrogallol with 2,3,4-trimethoxybenzaldehyde

0.5g (4 mmol) of pyrogallol was dissolved in 15mls of ethanol to which was added 5.5mls of hydrochloric acid. 1.568g (8 mmol) of 2,3,4-trimethoxybenzaldehyde was then added to the clear colourless solution, which turned red upon addition of the aldehyde. The reaction was heated at 40°C overnight. The precipitate was filtered and washed with 4:1 ethanol:water. The filtrate was recrystallised in ethanol to yield a brown solid. ^{1}H NMR of the compound showed the presence of the tetramer.
Yields are shown in Table 13 (Page 88)

Conformation 1:

^{1}H NMR (DMSO-d6): δ [ppm] 7.87 (s, 4H, O**H**), 7.71 (s, 2H, O**H**), 7.66 (s, 2H, O**H**), 7.60 (s, 4H, O**H**), 6.47 (q, J=8.2Hz, 4H, Ar-**H**), 6.44 (d, J=8.2Hz, 4H, Ar-**H**), 6.04 (s, 4H, bridging **H**), 6.01 (s, 4H, Ar-**H**), 3.82 (s, 12H, OC**H**$_3$), 3.56 (s, 12H, OC**H**$_3$), 3.17(s, 12H, OC**H**$_3$)

Conformation 2:

^{1}H NMR (DMSO-d6): δ [ppm] 7.52 (s, 2H, O**H**), 7.49 (s, 2H, O**H**), 7.45 (s, 4H, O**H**), 7.28 (s, **H**, O**H**), 6.34 (d, J=8.8Hz, 4H, Ar-**H**), 6.11 (d, J=8.8Hz, 4H, Ar-**H**), 5.91, (s, 4H, bridging **H**), 5.77 (s, 2H, Ar-**H**), 5.25 (s, 2H, Ar-**H**), 3.69 (s, 12H, OC**H**$_3$), 3.52 (s, 12H, OC**H**$_3$), 3.31 (s, 12H, OC**H**$_3$)

C. Complete alkylation of tetramethylpyrogallol[4]arene

0.5g (0.82mmol) of tetramethylpyrogallol[4]arene was reacted with 2.20g (13.16mmol, 1.46ml) ethylbromoacetate and 2.84g (20.6mmol) of potassium carbonate in 30mls of dry acetone at 60°C for 5 days. The reaction was driven to completion by the addition of 0.2 equivalents of ethylbromoacetate and potassium carbonate each day. On cooling to room temperature, all volatiles were removed under reduced pressure. The residue was treated with 5mls of dilute HCl and filtered to yield a fine yellow powder. The crude ester was purified by recrystallisation from hot methanol to give 0.6g (0.66mmol, 80% yield) of tetramethylpyrogallol[4]arene dodeca-acetate ethyl ester.

D. Base hydrolysis of tetramethylpyrogallol[4]arene dodeca-acetate ester

0.3g (0.33mmol) of tetramethylpyrogallol[4]arene dodeca-acetate ester was treated with 0.56g (9.9mmol) of potassium hydroxide under reflux in ethanol for 20 hours. The precipitate was filtered and washed with ethanol to give 0.32g (0.31mmol, 95% yield) of tetramethylpyrogallol[4]arene dodeca-acetate potassium salt.

E. Acid hydrolysis of tetramethylpyrogallol[4]arene dodeca-acetate potassium salt

0.15g (0.26mmol) of tetramethylpyrogallol[4]arene dodeca-acetate potassium salt was dissolved in distilled water. Concentrated hydrochloric acid was added dropwise, until a white precipitate formed. The reaction mixture was allowed to stand overnight and the tetramethylpyrogallol[4]arene dodeca-acetate acid was isolated by centrifugation and washed with distilled water to give 0.12g (0.21mmol, 80% yield) of tetramethylpyrogallol[4]arene dodeca-acetate acid.

^{1}H NMR (DMSO-d6): δ [ppm] 6.9 (s, 2H, Ar-**H**), 5.5 (s, 2H, Ar-**H**), 4.7 (multiplet, 16H, Ar-O-C**H**$_2$-COOH), 4.5 (d, J=8.4Hz, 8H, Ar-O-C**H**$_2$-COOH), 4.3 (s, 4H, Ar-C**H**-CH$_3$), 1.3 (s, 12H, C**H**$_3$)

Mass Spec: $C_{56}H_{56}O_{36}$ Expected: *m/z* 1304

Found: *m/z* 1327 (M+Na), 1343 (M+K)

F. Partial alkylation of tetramethylpyrogallol[4]arene

The general procedure for the complete alkylation of tetramethylpyrogallol[4]arene was followed using 0.4g (0.66mmol) of tetramethylpyrogallol[4]arene, 1.1g (6.6mmol) of ethylbromoacetate and 1.46g (10.56mmol) of potassium parbonate to give 0.11g of tetremethylpyrogallol[4]arene tetraacetate ester. Yield values are not possible to calculate, as exact molecular masses are not known.

G. Base hydrolysis of tetramethylpyrogallol[4]arene partially alkylated acetate ester

The general procedure for the base hydrolysis of tetramethylpyrogallol[4]arene dodeca-acetate ester was followed using 0.1g of tetramethylpyrogallol[4]arene tetra-acetate ester and 0.05g (0.9mmol) of potassium hydroxide, to give 0.05g of tetremethylpyrogallol[4]arene tetra-acetate potassium salt. Yield values are not possible to calculate, as exact molecular masses are not known.

H. Acid hydrolysis of tetramethylpyrogallol[4]arene partially alkylated acetate potassium salt

The general procedure for the acid hydrolysis of tetramethylpyrogallol[4]arene dodeca-acetate potassium salt was followed using 0.05g of tetramethylpyrogallol[4]arene tetra-acetate potassium salt, to give 0.05g of tetremethylpyrogallol[4]arene tetra-acetate acid. Yield values are not possible to calculate, as exact molecular masses are not known

^{1}H NMR (DMSO-d6): δ [ppm] 6.7 (broad s, 2H, Ar-**H**), 5.2 (broad s, 2H, Ar-**H**), 4.5-4 7 (multiplet, 8H, Ar-O-C**H**$_2$-COOH), 4.4-4.5 (multiplet, 4H, Ar-O-C**H**$_2$-COOH), 4.0-4.2 (multiplet, 4H, Ar-C**H**-CH$_3$), 1.3 (broad s, 12H, C**H**$_3$)

Splitting is poor due to the presence of a mixture of similar compounds.

I. Partial alkylation of progallol (first attempt)

0.5g (4mmol) of pyrogallol was mixed with 0.55g (4mmol) of potassium carbonate in 20mls of DMF. 0.44mls (4mmol) ethylbromoacetate was added and the reaction was stirred at 60°C for 24 hours. The reaction mixture was filtered and washed with acetone to give a black solid in 5% yield. ^{1}H NMR analysis showed that the desired product was not made.

J. Partial alkylation of progallol (second attempt)

0.5g (4mmol) of pyrogallol was mixed with 0.55g (4mmol) of potassium carbonate in 20mls of acetone. 0.44mls (4mmol) ethylbromoacetate was added and the reaction was stirred at 60°C for 24 hours. The reaction mixture was filtered and washed with acetone to give 0.66g of light brown solid in 90% yield.

^{1}H NMR (D_2O): δ [ppm] 10.4-10.5 (broad s, 1H, COO**H**) 6.78 (t, J=8Hz, 1H, Ar-**H**), 6.36 (d J=8.4Hz, 2H, Ar-**H**), 4.24 (s, 2H, C**H**$_2$)

K. Attempted tetramerisation of partially alkylated pyrogallol

0.5g (2.7mmol) of partially alkylated pyrogallol (2-monosubstituted pyrogallol acetate acid) was reacted with 0.12g (2.7mmol) of acetaldehyde in 8mls of ethanol and 3mls of hydrochloric acid at 80°C for 24 hours. A white solid was formed but on analysis by ^{1}H NMR was found not to be the desired product.

L. Methylation of pyrogallol

1g (8mmol) of pyrogallol was stirred in 20mls of acetone and 6.6g (48mmol) of potassium carbonate was added. 2.97mls (48mmol) of methyl iodide was added and the reaction was heated at 60°C for 48 hours. After 24 hours, another aliquot of K_2CO_3 and MeI was added. The reaction was filtered and washed with acetone and the filtrate was evaporated under reduced pressure. The residue was then recrystallised from chloroform to yield an off-white solid, which was isolated in 49% yield.

^{1}H NMR (DMSO-d6): δ [ppm] 6.60 (t, J=8Hz, 1H, Ar-**H**), 6.22 (d, J=8Hz, 2H, Ar-**H**), 3.73 (s, 9H, C**H**$_3$)

M. Attempted tetramerisation of methylated pyrogallol

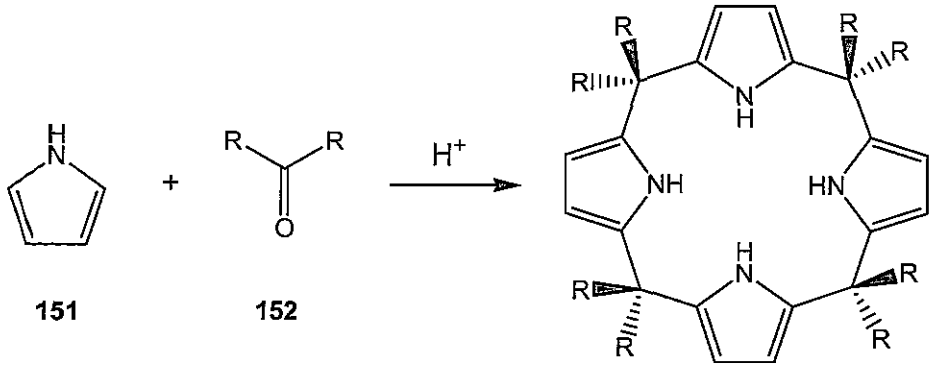
1g (12mmol) of 1,2,3-trimethoxybenzene and 0.66mls (12mmol) of acetaldehyde were mixed in 10mls of ethanol. 3.5mls of hydrochloric acid was added and the reaction was stirred at reflux for 24 hours. The reaction mixture turned dark brown/black and no product was formed.

Chapter 4

Pyrogallol/Ketone Reactions

I. Introduction

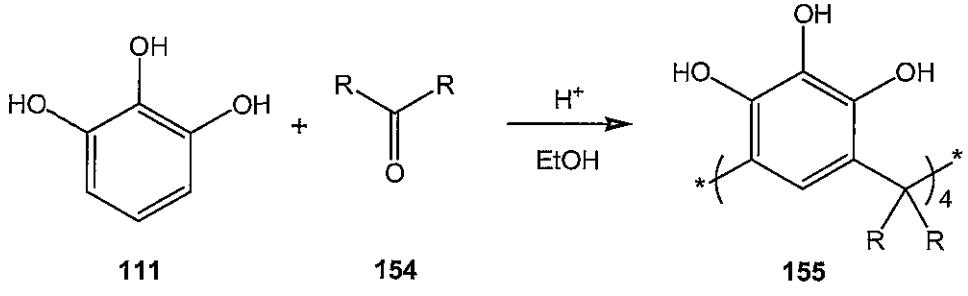
The synthesis of pyrogallol-aldehyde tetramers has been extensively studied by members of our research group[92]. Following this work, we were interested in diversifying these reactions. We investigated the synthesis of pyrogallol[4]arenes from pyrogallol and ketones. This reaction is similar to the formation of calix[4]pyrroles as reported by Gale *et al.*[36].



151 152 153

Scheme 31: Calix[4]pyrrole synthesis

The aim of this research was to optimise the conditions for the formation of the tetramer from pyrogallol and ketones. The first ketone used was the simplest ketone, acetone.



111 154 155

Scheme 32: *General synthesis of octa-substituted pyrogallol[4]arenes*

II. Results and Discussion

A. Pyrogallol/Acetone Reaction

Pyrogallol and acetone were condensed under the same conditions as the pyrogallol/acetaldehyde condensation reaction i.e. equimolar amounts of pyrogallol and acetone were reacted in acidic ethanol. There was no evidence of the formation of the more sterically hindered product with reaction times less than one week. The

tetramer was formed in low yields after refluxing for 7 days. A time and concentration study was carried out to find the optimal conditions for the reaction.

Reactions were refluxed for 3 hours, 24 hours, 6 days and one week with differing concentrations of acid. The conditions for each reaction are shown in Table 16.

Reaction	Pyrogallol	Acetone	Ethanol	HCl	Time	%Yield Conf 1	%Yield Conf 2
22-A	0.5g (4mmol)	0.5mls (6.8mmol)	5mls	1.75mls	3hrs	____	____
22-B	0.5g (4mmol)	0.5mls (6.8mmol)	2.5mls	1.75mls	3hrs	____	____
22-C	0.5g (4mmol)	0.5mls (6.8mmol)	0mls	1.75mls	3hrs	42%	____
22-D	0.5g (4mmol)	0.5mls (6.8mmol)	5mls	1.75mls	24hrs	____	____
22-E	0.5g (4mmol)	0.5mls (6.8mmol)	2.5mls	1.75mls	24hrs	____	____
22-F	0.5g (4mmol)	0.5mls (6.8mmol)	0mls	1.75mls	24hrs	72%	____
22-G	0.5g (4mmol)	0.5mls (6.8mmol)	5mls	1.75mls	6 days	____	3%
22-H	0.5g (4mmol)	0.5mls (6.8mmol)	2.5mls	1.75mls	6 days	____	9%
22-I	0.5g (4mmol)	0.5mls (6.8mmol)	0mls	1.75mls	6 days	95%	____
22-J	0.5g (4mmol)	0.5mls (6.8mmol)	5mls	1.75mls	1week	____	6%
22-K	0.5g (4mmol)	0.5mls (6.8mmol)	2.5mls	1.75mls	1week	____	9%
22-L	0.5g (4mmol)	0.5mls (6.8mmol)	0mls	1.75mls	1week	98%	____

Table 16: *Pyrogallol/acetone time and concentration study yields*

We were interested in analyzing the conformations of these more sterically hindered molecules. It was found that two products were formed during this reaction.

Isomer 1: A lack of ethanol in the reaction mixture causes the formation of the isomer in the cone conformation after precipitation of the reaction filtrate onto ice. This isomer is highly symmetrical as shown by the simple ^{1}H NMR spectrum.

Isomer 2: An unsymmetrical isomer is precipitated in low yields in the reaction with ethanol as a solvent. Due to the fact that growth of a crystal failed, we can only hypothesize over the exact conformation of this isomer. There is only one peak in the ^{1}H NMR between 4.0 and 7.6ppm, which suggests that all of the pyrogallol protons are in equal chemical environments. This rules out the possibility of the presence of many of the known isomers of pyrogallol[4]arenes and resorcin[4]arenes. The partial cone, flattened cone and flattened partial cone isomers can all be ruled out, as they would show more than one pyrogallol peak in the ^{1}H NMR spectrum.

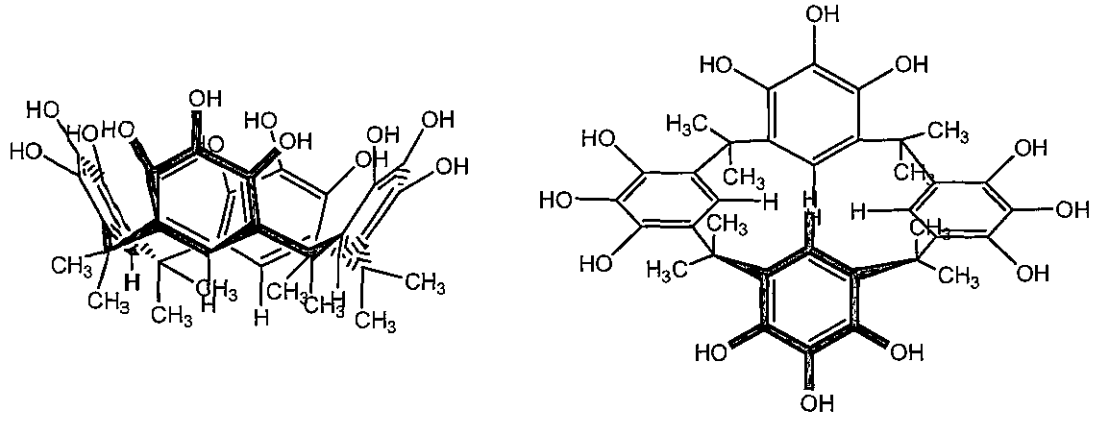


Figure 72: *Octamethylpyrogallol[4]arene in the cone and flattened partial cone conformations*

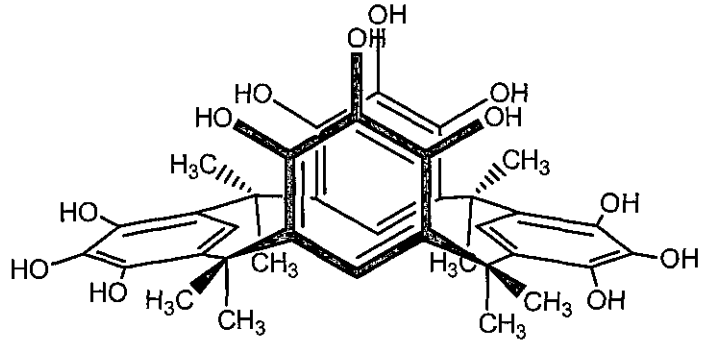
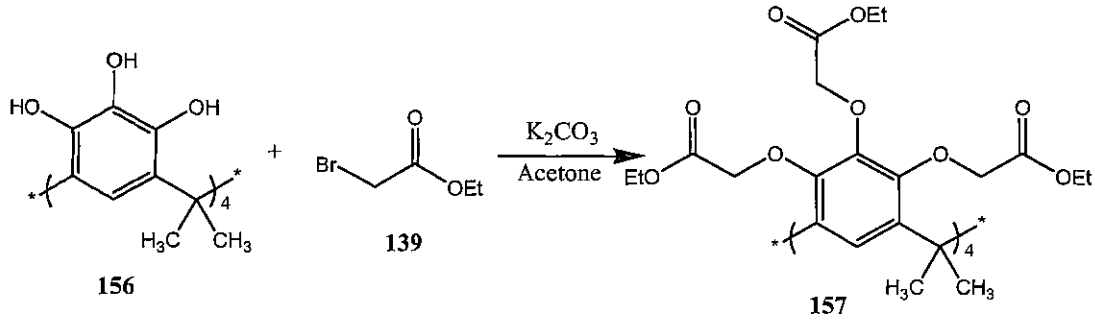
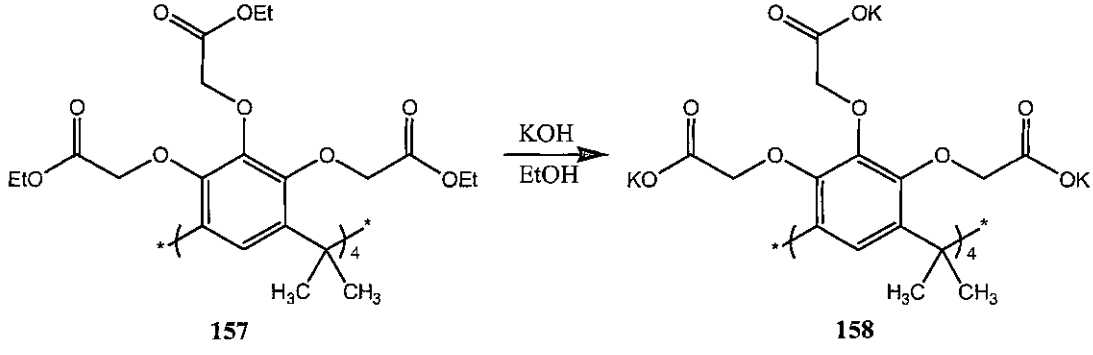


Figure 73: Octamethylpyrogallol[4]arene in the flattened cone conformation

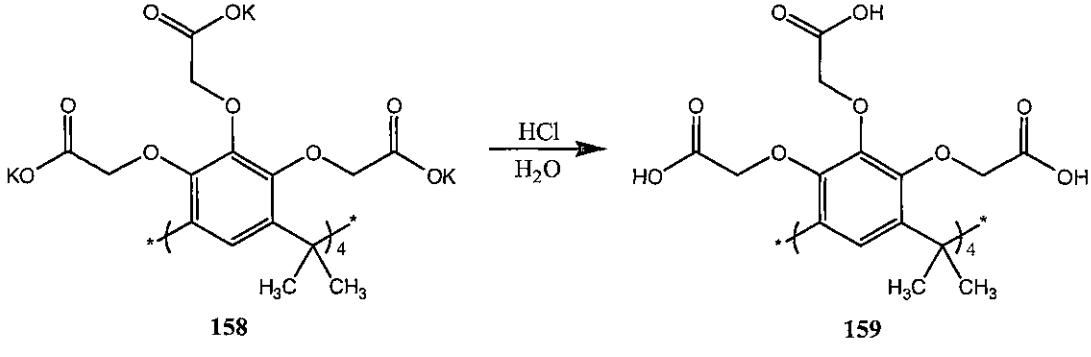
Alkylation of both isomers by the introduction of ethyl acetate groups into the hydroxy positions of the macrocycles was carried out to see whether these conformations could be locked. Alkylation was successfully achieved by treating the isomers with excess ethylbromoacetate. The alkylated products were converted into their respective acids, as the ^{1}H NMR spectra are cleaner for the acids. This reaction was carried out on the pyrogallol[4]arenes derived from both the aldehyde and from the ketone. ^{1}H NMR analysis of the isolated products showed that the original conformations are maintained.



Scheme 33: *Alkylation of octamethylpyrogallol[4]arene*



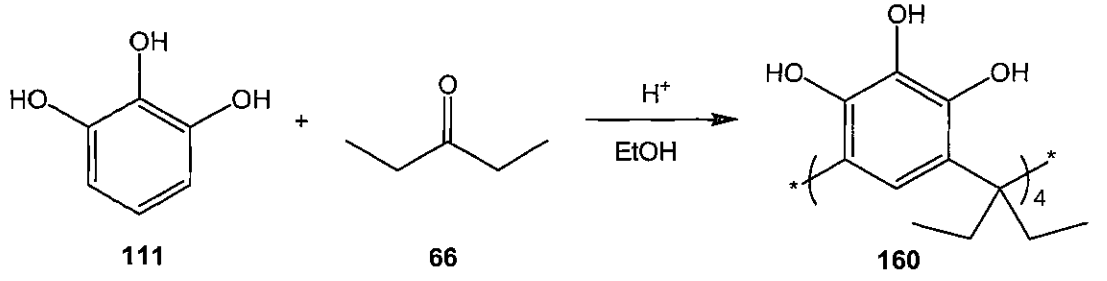
Scheme 34: *Preparation of octamethylpyrogallol[4]arene potassium salt*



Scheme 35: *Preparation of octamethylpyrogallol[4]arene acid*

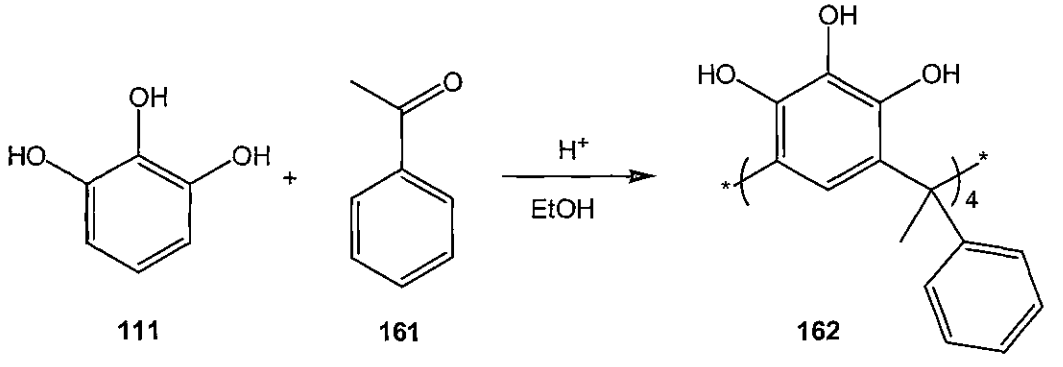
B. Attempted Condensation of Pyrogallol with Other Ketones

After the synthesis of the pyrogallol/acetone tetramer was successfully achieved, the synthesis of other tetramers was attempted with the use of different ketones. Acetophenone and pentan-3-one were reacted with pyrogallol under similar conditions to yield tetramethyltetraphenylpyrogallol[4]arene and octaethylpyrogallol [4]arene respectively. Both products were formed in low yields. This may be due to the fact that the ketones are significantly more sterically hindered than the corresponding aldehydes. Another factor that may have prevented the formation of products in high yields is the presence of a mixture of similar compounds, which needed to be separated using column chromatography.



111 66 160

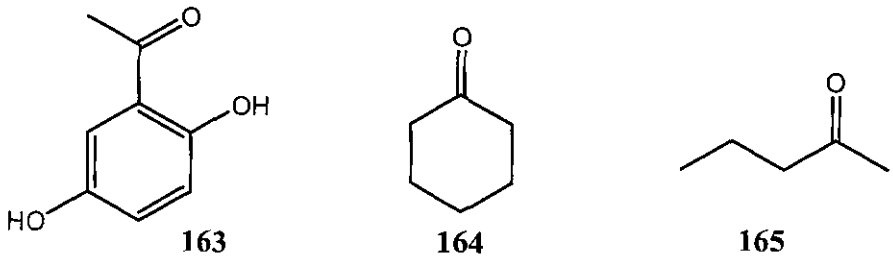
Scheme 36: *Synthesis of octaethylpyrogallol[4]arene*



111 161 162

Scheme 37: *Synthesis of tetramethyltetraphenylpyrogallol[4]arene*

The condensation of pyrogallol with a variety of other ketones was attempted. Each reaction was attempted with and without ethanol in the reaction mixture. The ketones that were condensed with pyrogallol are shown in Figure 74 below.



163 **164** **165**

Figure 74: *2,5-dihydroxyacetophenone, cyclohexanone and pentan-2-one*

In the case of 2,5-dihydroxyacetophenone, only the starting material was recovered in both cases. The reaction of cyclohexanone and pyrogallol was unsuccessful and no product was isolated. When pyrogallol was reacted with pentan-2-one, a complex mixture of products appeared to have been formed. Separation proved unsuccessful.

III.Experimental

A. Pyrogallol/acetone condensation

0.5g (4mmol) of pyrogallol was reacted with 0.29mls acetone (4mmol) in 5mls ethanol containing 1.75mls hydrochloric acid. After one week stirring at 80°C, a white precipitate formed. This precipitate was filtered and washed with 4.1 ethanol:water to produce the tetramer in 4% yield (0.02g, 0.04mmol).

^{1}H NMR (DMSO): δ [ppm] 8.17 (s, 1H, O**H**), 7.86 (s, 1H, O**H**), 6.22 (s, 1H, Ar-**H**), 1.51 (s, 3H, C**H**$_3$), 0 97 (s, 3H, C**H**$_3$), 0.26 (s, 3H, C**H**$_3$).

Mass Spec: $C_{36}H_{44}O_{12}$ Expected *m/z* 668

Found: *m/z* 687 (M+23)

B. Pyrogallol/acetone time and concentration study

The pyrogallol/acetone condensation reaction was repeated with 5mls, 2.5mls and 0mls of ethanol for 3 hours, 24 hours, 6 days and a week. When a precipitate formed in the reaction mixture, it was found to be conformation 2. When a precipitate formed from crashing the reaction mixture onto ice, conformation 1 was formed.

Yields are shown in Table 16 (page 106).

Conformation 1

^{1}H NMR (DMSO): δ [ppm] 8.71 (s, 4H, O**H**), 7.93 (s, 4H, O**H**), 7.91 (s, 4H, O**H**), 5.69 (s, 4H, Ar-**H**), 1.41 (s, 12H, C**H**$_3$), 1 29 (s, 12H, C**H**$_3$).

Conformation 2

H NMR (DMSO): δ [ppm] 8.18 (s, 4H, O**H**), 7.82 (s, 4H, O**H**), 6.24 (s, 4H, Ar-**H**), 1.50 (s, 12H, C**H**$_3$), 0.99 (s, 12H, C**H**$_3$), 0.26 (s, 12H, C**H**$_3$).

C. Alkylation of octamethylpyrogallol[4]arene

0.25g (0.38mmol) Pyrogallol/acetone tetramer was dissolved in 25mls of dry acetone. 1 31g (9.5ml) potassium carbonate (K_2CO_3) was added followed by 1.02g (6.08mmol) bromoethylacetate. The reaction was stirred at 60°C under argon for 5 days with aliquots of potassium carbonate and bromoethylacetate added on days 2 and 4.

After the reaction was finished, the solvent was blown off and dilute hydrochloric acid (HCl) was added. The resulting yellow crude product was purified by recrystallation in methanol (8% Yield).

D. Base hydrolysis of octamethylpyrogallol[4]arene dodeca-acetate ester

0.04g (0.02mmol) of the alkylated ester was heated at 80°C with 0 02g (0.4mmol) of potassium hydroxide in 5mls of ethanol. The product was filtered and washed with ethanol to produce the salt (90% Yield).

E. Acid hydrolysis of octamethylpyrogallol[4]arene dodeca-acetate potassium salt

The salt was dissolved in water and dilute hydrochloric acid was added. The acid presipitated in a fine suspension, which was centrifuged and washed with water (25% Yield).

Salt from tetramer in conformation 2

^{1}H NMR (DMSO): δ [ppm] 7.00 (broad s, 12H, O**H**), 6.39 (s, 4H, Ar-**H**), 4.72 (d, J=8Hz, 4**H**, C**H**$_2$), 4.38 (q, J=7.8Hz, 12H, C**H**$_2$), 4.19 (d, J=8Hz, 8H, C**H**$_2$), 1.26 (s, 12H, C**H**$_3$), 0.81 (s, 12H, C**H**$_3$), 0.01 (s, 12H, C**H**$_3$).

F. Pyrogallol/acetophenone condensation

0.5g (4mmol) of pyrogallol was reacted with 0.5mls acetophenone (4mmol) in 5mls ethanol containing 1.75mls hydrochloric acid. After 6 days stirring at 80°C, no precipitate formed. The red solution was poured onto ice, which produced an orange solution and red oily globules. The product was extracted with chloroform and dried over magnesium sulphate. The solvent was evaporated under reduced pressure and a dark red solid was obtained. The product was purified by column chromatography using silica gel with hexane/ethyl acetate (75:25) as eluent and collected in low yields as a red solid.

^{1}H NMR (DMSO): δ [ppm] 9.06 (s, 4H, O**H**), 8.54 (s, 4H, O**H**), 7.52 (t, J=6Hz, 4H, Ar-**H**), 7.28 (t, J=6.1Hz, 4H, Ar-**H**), 7.16 (t, J=6.1Hz, 4H, Ar-**H**), 6.49 (d, J=6Hz, 4H, Ar-**H**), 6.38 (d, J=6Hz, 4H, Ar-**H**), 5.72 (s, 4H, Ar-**H**), 1.80 (s, 12H, C**H**$_3$).

G. Pyrogallol/pentan-3-one condensation

0.5g (4mmol) of pyrogallol was reacted with 0.84mls (8mmol) pentan-3-one in 1.75mls hydrochloric acid. After 2 days stirring at 80°C, no precipitate formed. The reaction mixture was extracted with ethyl acetate, dried and the solvent was evaporated under reduced pressure. The purple product was obtained in low yields after column chromatography using silica gel with hexane/ethyl acetate (70:30) as eluent.

^{1}H NMR (DMSO): δ [ppm] 8.50 (s, 2H, O**H**), 7.81 (s, 2H, O**H**), 6.19 (s, 4H, Ar-**H**), 2.04 (q, J=6.7Hz, 8H, C**H**$_2$), 1.39 (q, J=6.5Hz, 8H, C**H**$_2$), 0.85 (t, J=6.7Hz, 12H, C**H**$_3$), 0.28 (t, J=6.5Hz, 12H, C**H**$_3$)

H. Pyrogallol/Pentan-2-one Condensation

1g (8mmol) of pyrogallol was reacted with 0.84mls (8mmol) pentan-2-one in 3.5mls ethanol for 3 days. No precipitate formed in the dark red reaction mixture but a light brown precipitate formed after adding the reaction mixture to ice. The brown solid was filtered and washed with ice water. The ^{1}H NMR spectrum of the resulting solid showed a complex mixture of products, which could not be separated.

Chapter 5

New Environmentally Friendly Approaches to Pyrogallol[4]arene Synthesis

I. Introduction

We would like to be able to introduce hydroxyl groups into the phenyl substituents of the pyrogallolarene. These hydroxyl groups can then be selectively functionalised relative to the pyrogallol hydroxyl groups on the upper rim of the pyrogallol[4]arene (Figure 75). Such an achievement would allow us to prepare:

1) Redox active pyrogallolarenes for HIV applications
2) Larger supramolecular structures capable of self-assembly in aqueous media.
3) A new generation of water-soluble phthalocyanines.

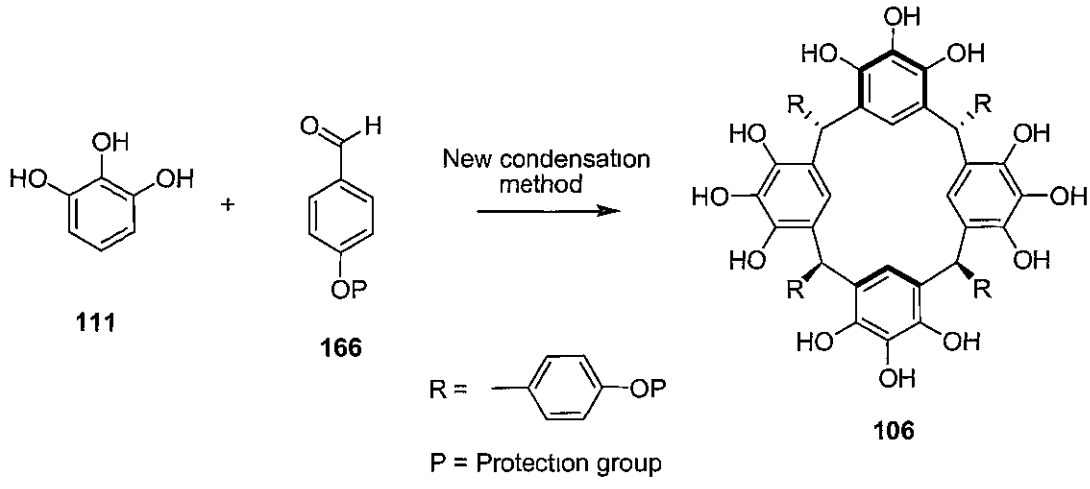


Figure 75: *Synthesis of pyrogallol[4]arene with a protection group.*

A proposed stepwise procedure to achieve this goal is outlined in Figures 76 and 77. However, the methods used to date for the synthesis of pyrogallol[4]arenes use harsh acidic conditions, which results in the cleavage of the protected phenoxy groups of the aryl aldehyde (benzyl groups). As a result the creation of new and novel derivatives of pyrogallolarene has not been achieved to date.

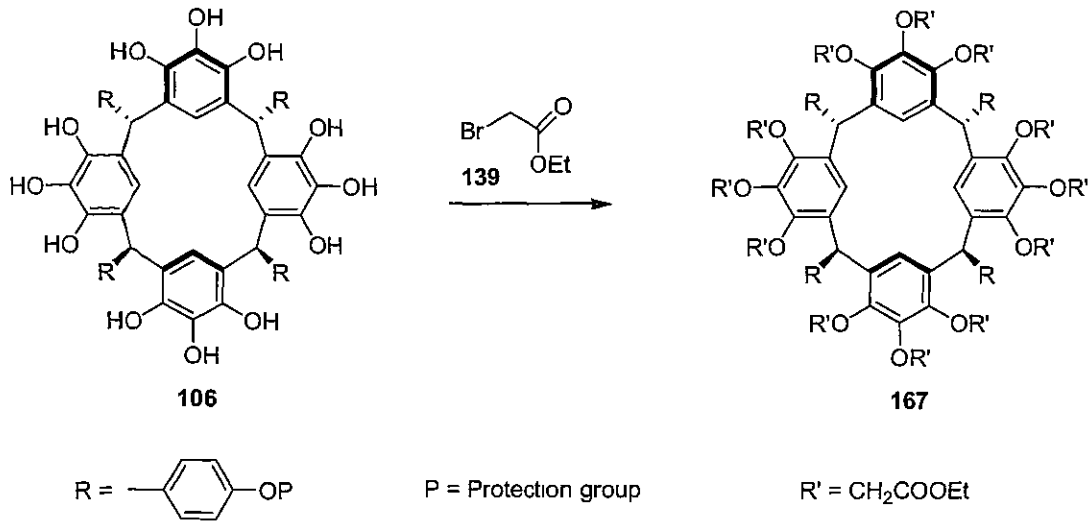


Figure 76: *Alkylation of the pyrogallol phenol groups of the pyrogallol[4]arene.*

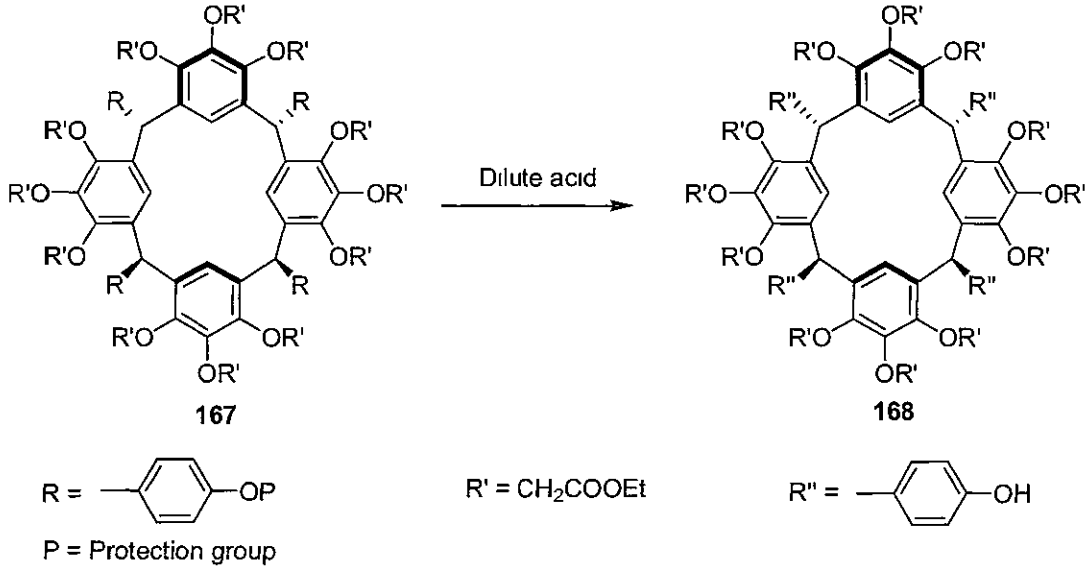


Figure 77: *Cleavage of the protection group of the phenyl substituents of the pyrogallol[4]arene*

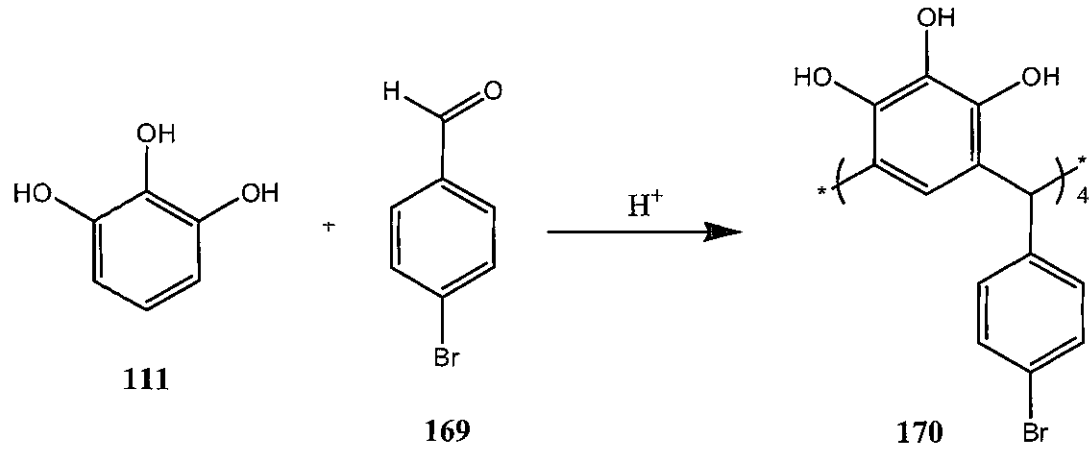
We believe that to solve this problem we must invent a new condensation methodology using alternative reaction conditions. Ideally, we would like to either eliminate or at least reduce the amount of acid required for successful condensation. Previous work carried out by Carey[92] in the Nolan group attempted condensations using diluted acid, base and alternative acids to HCl, however all attempts failed to produce the cyclic tetramer. In this work we wish to explore other alternatives specifically microwave assisted synthesis, and non-protic acids.

II. Microwave Assisted Synthesis

Microwave assisted synthesis is a relatively new concept in organic chemistry but it is proving to be a very useful tool. The excitation of molecules by microwave radiation causes them to heat efficiently and this can result in shorter reaction times, less quantity of solvent and 'gentler' reagents for many syntheses[97]. Reactions that require hours under thermal conditions can be completed within a matter of minutes in a microwave oven/reactor.

A. Microwave-Assisted Synthesis of Tetra-4-Bromophenylpyrogallol[4]arene

To explore the possibility of preparing pyrogallolarenes using microwave assisted synthesis we needed to select a suitable aldehyde, preferably a solid. 4-Bromobenzaldehyde was selected as it is a non-volatile, solid aldehyde and it gave respectable yields under acid thermal synthesis. For these reasons it was deemed safe for the microwave-assisted synthesis under atmospheric pressure.



Scheme 38: *Acid catalysed synthesis of tetra-4-bromophenylpyrogallol[4]arene*

All microwave-assisted syntheses were conducted in a domestic microwave oven at atmospheric pressure. We were first interested to see if the reactions could be carried out in the absence of solvent. Both pyrogallol and 4-bromobenzaldehyde were ground together and subsequently irradiated for ten minutes at maximum energy. No reaction occurred, only starting materials were recovered. We decided to modify the conditions by adding drops of HCl acid to the ground reagents to prepare pastes. The

first reaction attempted used two drops of concentrated HCl, which was enough to give a paste. This paste was then irradiated and we found that product formed within a minute at high power. The optimum time was found to be 4-5 minutes. The yield of this reaction was only 15%, which is markedly lower than the HCl thermal synthesis. Four more pastes were prepared using 1N, 0.1N, 0.01N HCl and water, as we wished to determine the effect of acid concentration on this reaction and to determine if the condensation can be carried out in the absence of acid. The results are listed in Table 17 below.

Reaction	Pyrogallol	4-Bromo benzaldehyde	Acid	Yield
29-A	0.65mmol (0.08g)	0.65mmol (0.12g)	3 drops 1N HCl	16%
29-B	0.65mmol (0.08g)	0.65mmol (0.12g)	3 drops 0.1N HCl	12%
29-C	0.65mmol (0.08g)	0.65mmol (0.12g)	3 drops 0.01N HCl	Trace
29-D	0.65mmol (0.08g)	0.65mmol (0.12g)	3 drops Water	-

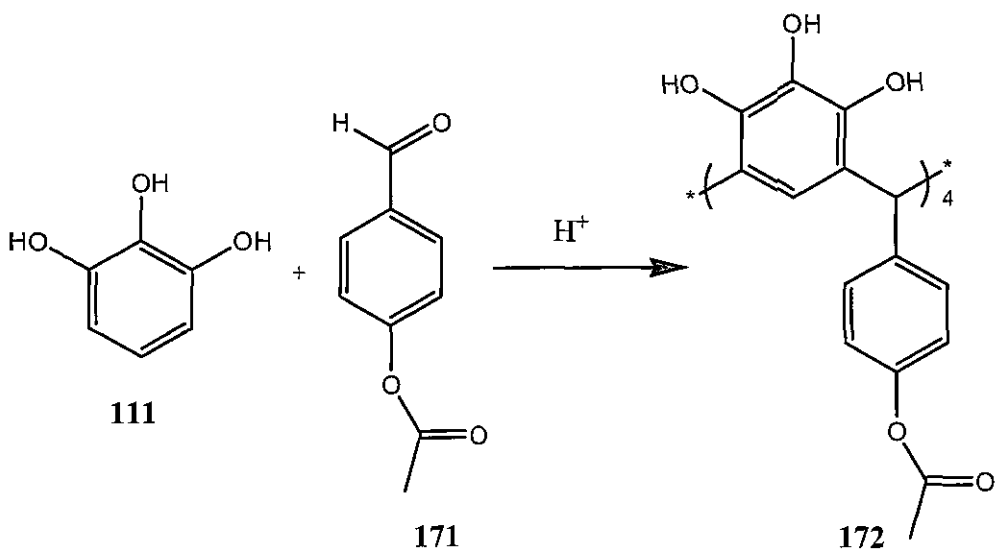
Table 17: *Concentrations of acid used in the microwave synthesis of tetra-4-bromophenylpyrogallol[4]arene*

We found that pyrogallolarene can be prepared with 0.1N HCl in modest yield, however in the absence of any acid no product was obtained. Furthermore, the purity of the crude products from these reactions showed the presence of a higher level of impurities as shown by the ^{1}H NMR of each reaction with impurities owing to the presence of unreacted aldehyde at δ10.15 (s, C**H**O) and at δ7.73 (d, Ar-**H**).

Although the yields are modest, we have demonstrated that pyrogallolarenes can be prepared in the presence of dilute HCl with a short reaction time. Previous work with acid concentration studies using thermal synthesis showed that pyrogallolarenes can only be prepared using acid concentration of 6N or higher. Thus it may be possible to apply these techniques with aryl aldehydes possessing protection groups. More optimisation of the reaction conditions is necessary using a more accurate microwave reactor system to achieve the optimal yields.

B. Microwave-Assisted Synthesis of Tetra-4-Acetoxyphenyl Pyrogallol[4]arene

The microwave-assisted methods that were developed above were applied to aryl aldehydes possessing a protection group in the 4- position of the benzyl ring, 4-acetoxybenzaldehyde was chosen. Pyrogallol and 4-acetoxybenzaldehyde were reacted with varying concentrations of acid in the microwave oven according to Table 18.



Scheme 39: *Acid catalysed synthesis of tetra-4-acetoxyphenylpyrogallol[4]arene*

Reaction	Pyrogallol	4-Acetoxy benzaldehyde	Acid	Yield
30-A	1mmol (0.12g)	1mmol (0.14mls)	3 drops 1N HCl	Trace
30-B	1mmol (0.12g)	1mmol (0.14mls)	3 drops 0.1N HCl	-
30-C	1mmol (0.12g)	1mmol (0.14mls)	3 drops 0.01N HCl	-

Table 18: *Concentrations of acid used in the microwave synthesis of tetra-4-acetoxyphenylpyrogallol[4]arene*

Each reaction was washed and centrifuged with 4:1 ethanol:water. The reaction with 0.1N HCl did not produce any solid. A red solid was formed in the reaction with 0.01N HCl but ^{1}H NMR analysis showed the presence of many impurities and was

inconclusive in determining if the desired product was formed. Purification of the crude product proved unsuccessful.

When 1N HCl was used, the reaction produced a red solid, which was analysed by ^1H NMR and found not to be the desired product, but the 4-hydroxyphenyl product as shown in Figure 78. The acetyl group was cleaved off under these conditions. It would appear that the 'superheating' of the reaction mixture in the presence of dilute acid is enough to cleave the acetyl group.

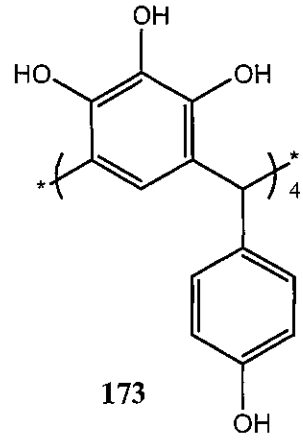


Figure 78: *The product of the reaction between 4-acetoxybenzaldehyde and pyrogallol*

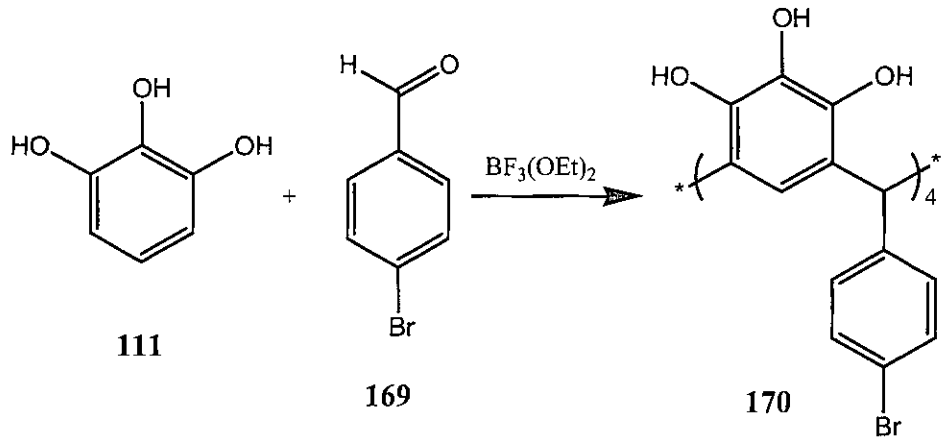
III.Environmental Thermal Synthesis

Following on from the microwave-assisted reactions, an investigation into an alternative thermal synthesis was carried out. This involved the elimination of protic-acid in the reaction mixture. We turned our attention to the use of both 'strong' and 'weak' Lewis acids.

For the 'strong' Lewis acid catalysed reaction we chose to condense pyrogallol and 4-bromobenzaldehyde using boron trifluoride diethyl etherate ($BF_3{\cdot}OEt_2$).[98-100]

Boron trifluoride diethyl etherate was added to a mixture of pyrogallol and the aldehyde in dichloromethane and stirred at room temperature for four hours. The product precipitated out upon addition of water to the reaction mixture.

The precipitate obtained was light brown in colour with a trace of pink. Attempts to purify this product were unsuccessful, and the product could not be isolated in high purity. However the ^{1}H NMR of the crude product confirmed that trace amounts of pyrogallol[4]arene **170** were indeed formed, as the rctt flattened partial cone isomer.



111 **169** **170**

Figure 79: *The Lewis acid synthesis of tetra-4-bromophenyl pyrogallol[4]arene*

In an attempt to improve yields the reaction was repeated to examine the effect of temperature on the reaction. The Lewis acid and starting materials were dissolved in anhydrous DCM at 0°C for three hours and then heated to 40°C overnight, however no improvement in yield or purity was observed, only trace amounts of impure macrocycle were obtained.

To investigate the scope of the reaction, the Lewis acid catalysis method was also employed in the condensation of pyrogallol with decanal. The isolated product was a deep red paste. However no cyclic tetramer was present as determined by both ^{1}H NMR and mass spectrometry.

A. Acid-free Thermal Synthesis of Tetra-4-Ethoxyphenyl Pyrogallol[4]arene

After evaluating the results obtained earlier in the group[92], we realised that it might be possible to prepare pyrogallol[4]arenes in the absence of acid. Earlier metal studies demonstrate that nickel chloride can triple the yields of pyrogallolarene under HCl conditions. Furthermore, it was also discovered that aryl aldehydes possessing electron-donating groups gave the best yields of pyrogallolarene under HCl conditions (in the absence of metal salts). Would it be possible to condense an alkoxy benzaldehyde with pyrogallol in the presence of a metal salt under weak acid conditions?

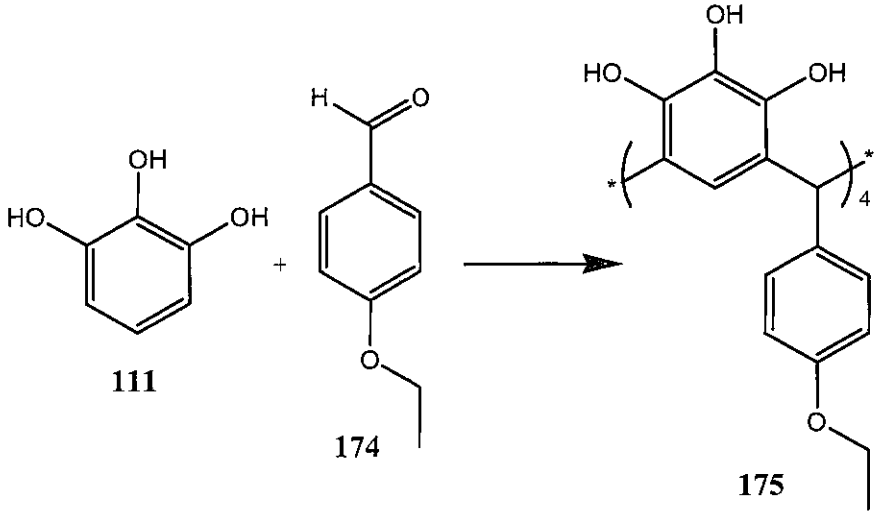
We decided to initiate a series of studies using 4-ethoxybenzaldehyde and pyrogallol in the presence of $NiCl_2$. Initially four reactions were set-up as follows:

1) stoichiometric quantity of $NiCl_2$, with 6N HCl in ethanol
2) stoichiometric quantity of $NiCl_2$, with 0.6N HCl in ethanol
3) stoichiometric quantity of $NiCl_2$, with 0.06N HCl in ethanol
4) stoichiometric quantity of $NiCl_2$, with water in ethanol.

All reactions yielded product with the neutral reaction giving the pyrogallolarene product in 22% yield. This study proves that the pyrogallolarene can be prepared under very gentle acid-free conditions. It should be noted that the formation of pyrogallolarene was fastest in the control reaction. The first reaction gave a yield of 60%. When 0.6N HCl was used, the product was formed in 40% but only 20% yield was obtained for the most dilute and the acid-free reactions.

To examine the scope of this new synthetic methodology a series of studies were undertaken. The first study was to determine if the role of $NiCl_2$ was stoichiometric or catalytic. This was achieved by setting up a series of reactions using different stoichiometries of the metal salt. In each of the reactions with varying stoichiometries of metal salts, the yield of product obtained did not vary. It is apparent from these results that this reaction is indeed catalytic with respect to the salt; however, the reaction times were slightly longer for the 10% stoichiometric reactions.

Our next study involved screening the performance of other metal-salts in place of $NiCl_2$ in this reaction. We know from previous studies that $MgCl_2$, NaCl and $CaCl_2$ also enhanced the yields of pyrogallolarene under acid conditions. Reactions were set up using these metal salts (equal stoichiometric ratio) with pyrogallol and 4-ethoxybenzaldehyde (Table 19). We found that $MgCl_2$ produced the desired product in 44% yield, which is higher than for $NiCl_2$ (22% Yield). Both $ZnCl_2$ and $CaCl_2$ gave cyclic tetramer in 28% and 16% yield respectively.



Scheme 40: *Synthesis of tetra-4-ethoxyphenylpyrogallol[4]arene*

Reaction	Pyrogallol	4-Ethoxy benzaldehyde	Ethanol	Salt	Yield (%)
33	0.12g (1mmol)	0.1mls (1mmol)	1.5mls	**$NiCl_2$** 0.14g (1mmol)	24
34	0.12g (1mmol)	0 1mls (1mmol)	1.5mls	**$CaCl_2$** 0.10g (1mmol)	16
35	0.12g (1mmol)	0.1mls (1mmol)	1.5mls	**$MgCl_2$** 0.11g (1mmol)	44
36	0.12g (1mmol)	0.1mls (1mmol)	1.5mls	**$ZnCl_2$** 0.13g (1mmol)	28
37	0.12g (1mmol)	0.1mls (1mmol)	1.5mls	**KCl** 0.07g (1mmol)	-

Table 19: *Amounts of various salts used in the acid-free metallated synthesis of pyrogallol[4]arenes*

The monovalent potassium chloride was unsuccessful at forming the tetramer. It is apparent that divalent metals are essential for the formation of pyrogallol[4]arene under these conditions.

It should also be noted that each of these reactions produced a very clean product, with minimal impurities as shown by the ^{1}H NMR of the tetra-4-ethoxyphenylpyrogallol[4]arene in Figure 80, compared to thermal protic-acid conditions.

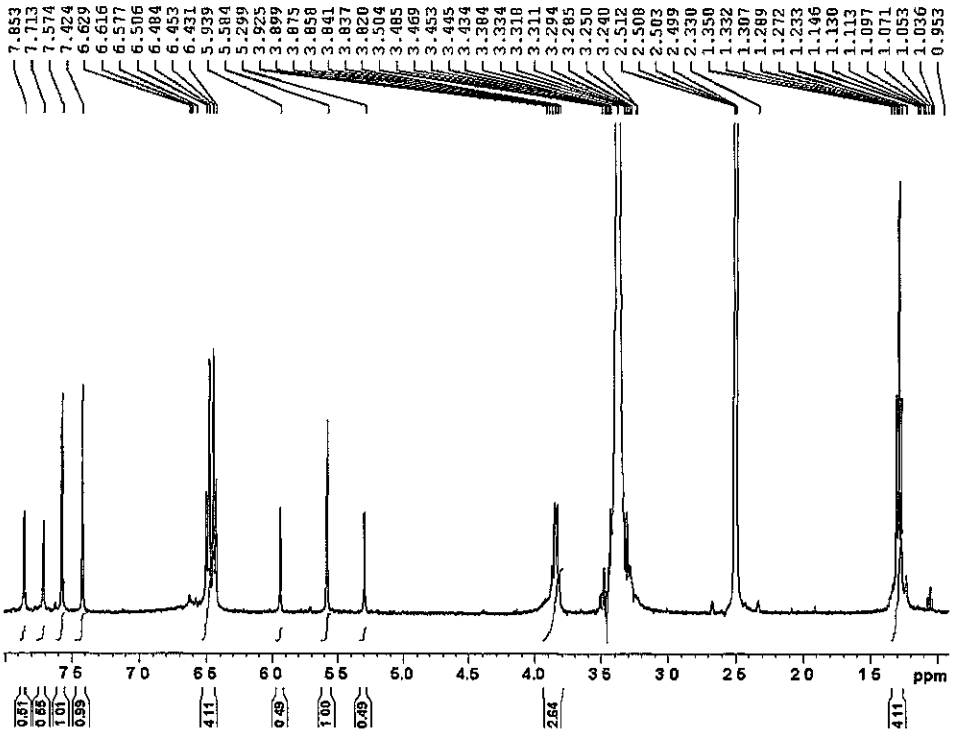


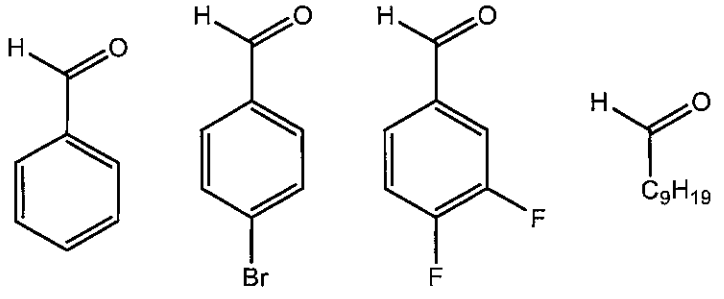
Figure 80: *^{1}H NMR of tetra-4-ethoxyphenylpyrogallol[4]arene*

We also set-up a single reaction using magnesium sulphate in place of $MgCl_2$, to determine if there was an anion effect. This reaction yielded the tetramer in the same yield as $MgCl_2$ reactions.

We then performed a solvent study on the reaction. For this study we used $NiCl_2$ (for consistency) and the reactions were carried out in MeOH, CH_2Cl_2, 1,4-dioxane and IPA (1.5mL). We found that both MeOH and IPA gave product in similar yields to ethanol, however CH_2Cl_2 and 1,4-dioxane gave no product.

B. Reaction of Pyrogallol with Various Aldehydes to Form the Tetramer Under Acid-free Conditions

The acid-free synthesis of pyrogallol[4]arene was repeated using a variety of aldehydes to investigate the effect of differing substituents on the yields of tetramer. The four aldehydes chosen were 4-bromobenzaldehyde (**169**), 3,4-difluorobenzaldehyde (**177**), benzaldehyde (**176**) and decanal (**178**) (as shown in Figure 81) and they were reacted with pyrogallol and $MgCl_2$ in ethanol.



176 **169** **177** **178**

Figure 81: *Aldehydes used in the acid free synthesis of pyrogallol[4]arenes*

The alkyl aldehyde, decanal did not produce a product in this reaction. Of the aryl aldehydes only benzaldehyde and 4-bromobenzaldehyde gave products. The reaction with benzaldehyde produced a product, which judging by the ^1H NMR is possibly a mixture of isomers. If this is the case then this is quite significant because no other method we have tried to date has yielded any other isomer with aryl aldehydes. There was some evidence of unreacted aldehyde by the presence of a small peak at 10.02ppm. The unresolved multiplets in the ^1H NMR spectrum for this compound indicate the presence of a mixture of isomers. The electron withdrawing aldehyde 177 did not give any product even after extended reaction times.

It is possible that the 3,4-difluorobenzaldehyde is too strongly deactivated by the presence of two fluorine substituents in the phenyl ring, which may destabilise the carbocation intermediate formed during the reaction. These results correspond to studies carried out by Carey[92] under 6N HCl conditions where he found that aryl aldehydes possessing electron donating groups gave higher yields of pyrogallol[4]arenes.

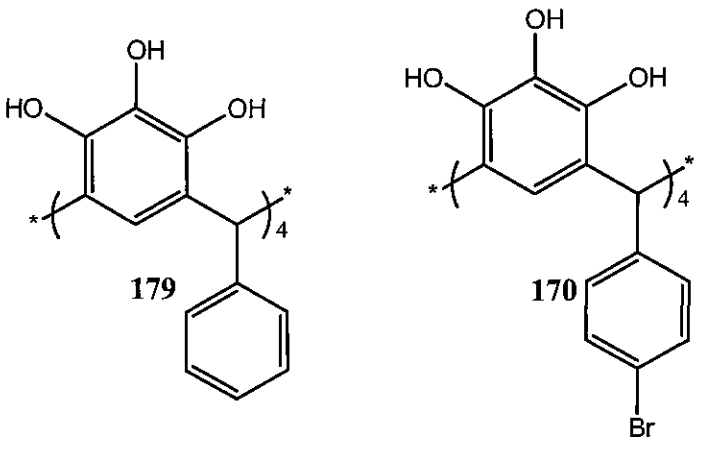


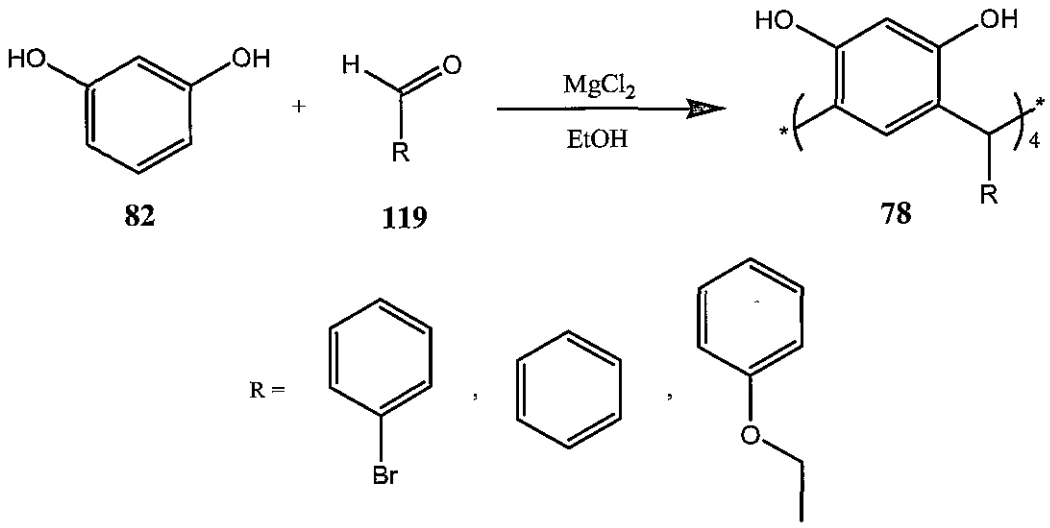
Figure 82: Condensation products from the acid-free synthesis of pyrogallol[4]arenes, tetraphenylpyrogallol[4]arene **179** and tetra-4-bromophenylpyrogallol[4]arene **170**

Aldehyde Used	Electronic Effect	Yield (%)
4-Ethoxybenzaldehyde	Electron Withdrawing	44
Benzaldehyde	Neutral Aryl	32
4-Bromobenzaldehyde	Electron Donating	12
3,4-Difluorobenzaldehyde	Electron Donating	-
Decanal	Alkyl	-

Table 20: *Results of the study of the acid-free metal catalysed synthesis of a variety of pyrogallol[4]arenes*

C. Acid-free Synthesis of Resorcinarenes

In order to further investigate the mechanism for this acid-free reaction, a series of experiments was carried out using resorcinol in place of pyrogallol. Resorcinol can be condensed with aldehyde under strong acid conditions (including strong Lewis acid conditions) to yield the cyclic tetramer resorcinarene. This compound possesses one less hydroxy group than pyrogallol and therefore, when cyclised, forms an octahydroxy tetramer, with eight OH groups on the upper rim.



Scheme 41: *Acid-free synthesis of resorcinarenes*

We decided to attempt our newly developed condensation methods with resorcinol and the aldehydes shown in Scheme 41. The 4-ethoxybenzaldehyde formed a tetramer in reasonable yields (16%), although the ^{1}H NMR spectrum of the product shows the possibility of various isomers due to the presence of broad peaks.

The 4-bromobenzaldehyde product produced a clean ^{1}H NMR spectrum, which implies an unsymmetrical system in very low yields (1%). This spectrum is similar to that shown in the literature for the *rctt* flattened partial cone isomer of tetra-4-butoxyphenylresorcin[4]arene[72].

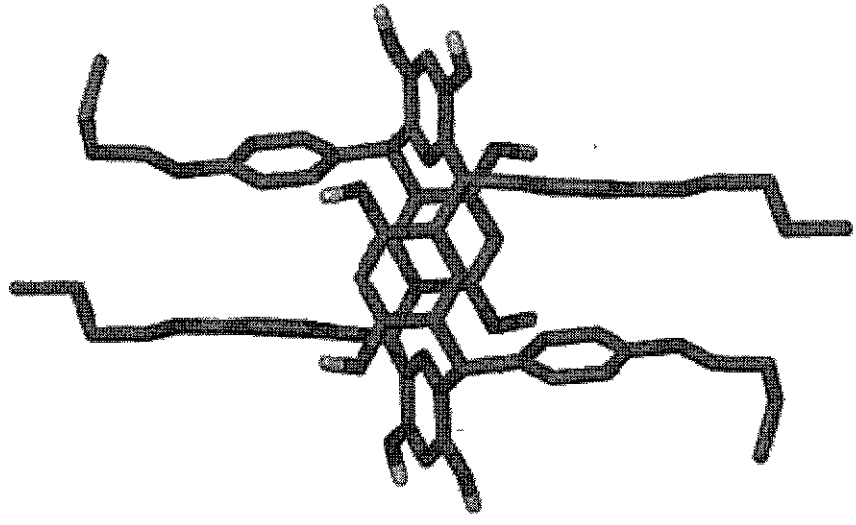


Figure 83: *The flattened partial cone rctt isomer of tetra-4-butoxyphenylresorcin[4]arene*[72]

The benzaldehyde tetramer formed a pink powder but also a large red lump formed in the reaction mixture. ^{1}H NMR analysis of both of these products showed a "dirty" spectrum. The product was washed with hot methanol and the solution was filtered. The methanol was left to evaporate and the residue was analysed by ^{1}H NMR. Neither the recrystallisation filtrate nor the residue gave a clean ^{1}H NMR spectrum of the target macrocycle.

Again, the electron-donating 4-ethoxybenzaldehyde produced the tetramer in the highest yields, although all yields for the resorcin[4]arenes were significantly lower than for the pyrogallol[4]arenes.

IV. The Mechanism of the Reaction

We initialised metal studies in the acid condensation to determine whether we could control the stereochemical outcome of the condensation under 6N HCl conditions. We found, as described previously in Chapter 2, that alkyl aldehydes are indeed affected by the presence of metal salts since the ratio of rccc:rctt changed significantly. We can explain this as a result of templation as outlined in Figure 84. However, we know from Carey's work[92] that in the case of aryl aldehydes there is no change in stereoiosomer distribution when condensation is carried out in the presence of metal salts under 6N HCl conditions. Thus, metal templation is not occurring, instead we believe that the metal cation acts as a Lewis acid in that it coordinates with the aldehyde oxygen activating it for electrophilic substitution (Figure 85).

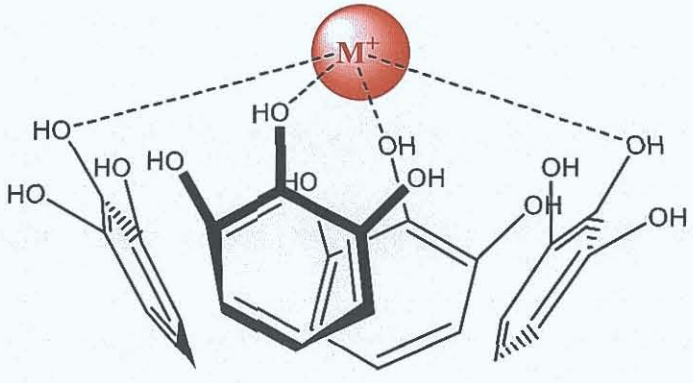


Figure 84: *The metal templation effect on the synthesis of pyrogallol[4]arenes*

We believe this is how all of the metal cations tested in this work are acting under these new conditions.

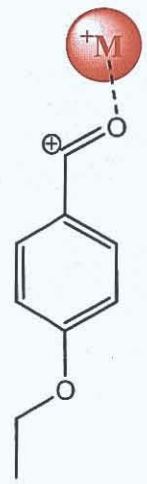


Figure 85: *Metal ion activation of the aldehyde*

The metal ion can interact with the carbonyl oxygen on the aldehyde activating the carbonyl carbon for electrophilic substitution. Furthermore, we found the following reactivity series of $Mg^{+2}>Zn^{+2}>Ni^{+2}>Ca^{+2}$ with metal cations tested.

Interestingly, Mg^{+2} is the hardest of these cations and therefore should behave as the strongest Lewis acid in the series giving the highest yields.

V. Experimental

A. General procedure for the microwave-assisted synthesis of 4-bromophenylpyrogallol[4]arene

0.65mmol (0.08g) of pyrogallol and 0.65mmol (0.12g) 4-bromobenzaldehyde were crushed with a mortar and pestle to ensure an even powder. 3 drops (just enough to make a paste) of the appropriate concentration of acid were added and the reaction mixture was microwaved on full power for five minutes.

In both reactions 29-A and 29-B, red solids formed while in reaction 29-C, only a thick red liquid formed.

Each reaction mixture was centrifuged and washed with 4:1 ethanol:water to yield the desired tetramer. Yields are shown in Table 17 (Page 118).

^{1}H NMR (DMSO-d6): δ[ppm] 7.89 (s, 4H, O**H**), 7.67 (s, 4H, O**H**), 7.59 (s, 4H, O**H**), 7.01 (d, J=8.0Hz, 8H, Ar-**H**), 6.45 (d, J=8.0Hz, 8H, Ar-**H**), 5.78 (s, 2H, Ar-**H**), 5.54 (s, 4H, C**H**), 4.93 (s, 2H, Ar-**H**).

The microwave oven used in all microwave-assisted reactions was a Tesco brand 17L Microwave oven. Model: MCM01 Output: 700W 2450MHz.

B. Microwave-assisted synthesis of protected tetramer

The general procedure for the microwave-assisted synthesis was followed using 0.12g (1mmol) of pyrogallol, 0.14mls (1mmol) of 4-acetoxybenzaldehyde and 3 drops of the appropriate concentration of hydrochloric acid to produce the tetra-4-hydroxyphenylpyrogallol[4]arene product. Yields shown in Table 18 (Page 119).

^{1}H NMR (DMSO-d6): δ[ppm] 8.71 (s, 4H, O**H**), 7.79 (s, 2H, O**H**), 7.71 (s, 2H, O**H**), 7.52 (s, 4H, O**H**), 7.36 (s, 4H, O**H**), 6.40 (d, J=8.4Hz, 8H, Ar-**H**), 6.32 (d, J=8.8Hz, 8H, Ar-**H**), 5.93 (s, 2H, Ar-**H**), 5.57 (s, 4H, Ar-C**H**-Ar), 5.53 (s, 2H, Ar-**H**)

C. Preparation of tetra-4-bromophenyl pyrogallol[4]arene using Lewis acid catalysis

2.8 mmol (0.35 g) of pyrogallol, and 2.8 mmol (0.52 g) of 4-bromobenzaldehyde, were placed into 5 ml of dry dichloromethane in an ice bath with salt. 5.6 mmol (0.8 ml) boron trifluoride diethyl etherate was added. The reaction mixture was stirred at room temperature for 4 hours. Addition of water (6 ml) resulted in formation of an insoluble precipitate, which was collected by filtration. The collected powder was washed exhaustively with water, then dicloromethane. 0.73 mmol (0.85 g, 104% yield) of crude product was obtained.

H^1 NMR analysis showed that trace amounts of tetra-4-bromophenylpyrogallol[4]arene were present, but the product was highly impure.

D. Reaction of decanal with pyrogallol in presence of boron trifluoride diethyl etherate

Reaction was carried out as in 3 above using 2.8 mmol (0.44 g, 0.83 ml) of decanal. Addition of water (6 ml) was followed by extraction with water (6 ml) and brine (6 ml). The organic layer was dried over magnesium sulphate and concentrated under vacuum to obtain a deep red substance.

H^1 NMR analysis showed that macrocycle was not obtained.

Product from above was refluxed in HCl/ethanol (1:3) 78°C - 80°C overnight. The resulting (insoluble) product was collected by filtration. The collected powder was exhaustively washed with a 80:20 mixture of ethanol:water. 0.09 g of product was collected.

H^1 NMR analysis showed that macrocycle was not obtained

E. General procedure for the acid-free thermal synthesis of tetra-4-ethoxyphenylpyrogallol[4]arene

0.12g (1mmol) of pyrogallol and 0.1mls (1mmol) of 4-ethoxybenzaldehyde were mixed in 1.5mls of ethanol. To this solution, 0.14g (1mmol) of $NiCl_2$ was added and the reaction was stirred at 80°C for 18 hours. The resulting pink reaction mixture was centrifuged and washed with 4:1 ethanol:water. After drying, 0.06g (0.06mmol) of the tetramer was formed (24% yield).

^{1}H NMR (DMSO-d6): δ[ppm] 7.85 (s, 2H, O**H**), 7.71 (s, 2H, O**H**), 7.57 (s, 4H, O**H**), 7 42 (s, 4H, O**H**), 6.50 (d, J=8.8Hz, 8H, Ar-**H**), 6.44 (d, J=8.8Hz, 8H, Ar-**H**), 5.94 (s, 2H, Ar-**H**), 5.58 (s, 4H, Ar-C**H**-Ar), 5.30 (s, 2H, Ar-**H**), 3.81 (q, J=7.2Hz, 8H, O-C**H**$_2$-CH$_3$), 1.29 (t, J=7.2Hz, 12H, O-CH$_2$-C**H**$_3$)

F. Acid-free thermal synthesis of tetra-4-ethoxyphenyl pyrogallol[4]arene using $CaCl_2$

The general procedure for the acid-free thermal synthesis of tetra-4-ethoxyphenylpyrogallol[4]arene was followed using 0.10g (1mmol) $CaCl_2$ to produce 0.04g (0.04mmol) of product (16% Yield).

G. Acid-free thermal synthesis of tetra-4-ethoxyphenyl pyrogallol[4]arene using $MgCl_2$

The general procedure for the acid-free thermal synthesis of tetra-4-ethoxyphenylpyrogallol[4]arene was followed using 0.11g (1mmol) $MgCl_2$ to produce 0.11g (0.11mmol) of product (44% Yield).

H. Acid-free thermal synthesis of tetra-4-ethoxyphenyl pyrogallol[4]arene using $ZnCl_2$

The general procedure for the acid-free thermal synthesis of tetra-4-ethoxyphenylpyrogallol[4]arene was followed using 0.13g (1mmol) $ZnCl_2$ to produce 0.07g (0.07mmol) of product (28% Yield).

I. Acid-free thermal synthesis of tetra-4-ethoxyphenyl pyrogallol[4]arene using KCl

The general procedure for the acid-free thermal synthesis of tetra-4-ethoxyphenylpyrogallol[4]arene was followed using 0.07g (1mmol) KCl. No product was formed.

Magnesium Sulphate reaction

J. Acid-free thermal synthesis of tetra-4-ethoxyphenylpyrogallol[4]arene using magnesium sulphate

The general procedure for the acid-free thermal synthesis of tetra-4-ethoxyphenylpyrogallol[4]arene was followed using 0.12g (1mmol) $MgSO_4$ to produce 0.11g (0.11mmol) of product (44% Yield).

K. Acid-free thermal synthesis of tetra-4-bromophenyl pyrogallol[4]arene

The general procedure for the acid-free thermal synthesis of pyrogallol[4]arene was followed using 0.12g (1mmol) pyrogallol, 1.5mls ethanol, 0.11g (1mmol) $MgCl_2$ and 0.19g (1mmol) 4-bromobenzaldehyde to produce 0.04g (0.03mmol) of product (12% Yield).

^{1}H NMR (DMSO-d6): δ[ppm] 8.03 (s, 2H, O**H**), 7.85 (s, 2H, O**H**), 7.78 (s, 4H, O**H**), 7.71 (s, 4H, O**H**), 7.11 (d, J=8.4Hz, 8H, Ar-**H**), 6.54 (d, J=8.4Hz, 8H, Ar-**H**), 5.88 (s, 2H, Ar-H), 5.62 (s, 4H, Ar-C**H**-Ar), 5.02 (s, 2H, Ar-**H**)

L. Acid-free thermal synthesis of tetra-3,4-difluoro phenylpyrogallol[4]arene

The general procedure for the acid-free thermal synthesis of pyrogallol[4]arene was followed using 0.12g (1mmol) pyrogallol, 1.5mls ethanol, 0.11g (1mmol) $MgCl_2$ and 0.11mls (1mmol) 3,4-difluorobenzaldehyde. The desired product was not formed.

M. Acid-free thermal synthesis of tetraphenyl pyrogallol[4]arene

The general procedure for the acid-free thermal synthesis of pyrogallol[4]arene was followed using 0.12g (1mmol) pyrogallol, 1.5mls ethanol, 0.11g (1mmol) $MgCl_2$ and 0.10mls (1mmol) benzaldehyde to produce 0.07g (0.08mmol) of product (32% Yield).

^{1}H NMR (DMSO-d6): δ[ppm] 7.91 (m, 8H, OH), 7.71 (m, 4H, OH), 6.85-6.77 (broad m, 20H, Ar-H), 6.00 (s, 2H, Ar-H), 5.77 (s, 4H, Ar-CH-Ar), 5.66 (s, 2H, Ar-H)

N. Acid-free thermal synthesis of tetradecyl pyrogallol[4]arene

The general procedure for the acid-free thermal synthesis of pyrogallol[4]arene was followed using 0.12g (1mmol) pyrogallol, 1.5mls ethanol, 0.11g (1mmol) $MgCl_2$ and 0.19mls (1mmol) n-decanal. The product was collected in trace yields and the ^{1}H NMR suggested a mixture of isomers.

O. Acid-free thermal synthesis of tetra-4-ethoxyphenyl resorcin[4]arene

The general procedure for the acid-free thermal synthesis of tetra-4-ethoxyphenylpyrogallol[4]arene was followed using 0.11g (1mmol) resorcinol, 1.5mls ethanol, 0.10g (1mmol) $MgCl_2$ and 0.1mls (1mmol) 4-ethoxybenzaldehyde to produce 0.04g (0.04mmol) of product (16% Yield).

^{1}H NMR (DMSO-d6): δ[ppm] 8.53 (broad s, 8H, O**H**), 6.59 (broad s, 8H, Ar-**H**), 6.53 (broad s, 8H, Ar-**H**), 6.12, (broad s, 4H, Ar-**H** ortho to OH), 6.29 (broad s, 2H, Ar-**H** meta to OH), 6.23 (broad s, 2H, Ar-**H** meta to OH), 5.57 (broad s, 4H, Ar-C**H**-Ar), 3.93 (broad s, 8H, O-C**H**$_2$-CH$_3$), 1.33 (broad s, 12H, O-CH$_2$-C**H**$_3$)

P. Acid-free thermal synthesis of tetra-4-bromophenyl resorcin[4]arene

The general procedure for the acid-free thermal synthesis of pyrogallol[4]arene was followed using 0.11g (1mmol) resorcinol, 1.5mls ethanol, 0.10g (1mmol) $MgCl_2$ and

0.19g (1mmol) 4-bromobenzaldehyde to produce 0.002g (0.002mmol) of product (1% Yield).

^{1}H NMR (DMSO-d6): δ[ppm] 8.75 (s, 8H, O**H**), 7.18 (d, J=8.4Hz, 8H, Ar-**H**), 6.55 (d, J=8.4Hz, 8H, Ar-**H**), 6.35 (s, 2H, Ar-**H** meta to OH), 6.22 (s, 2H, Ar-**H** ortho to OH), 6.13 (s, 2H, Ar-**H** ortho to OH), 5.67 (s, 2H, Ar-**H** meta to OH), 5.59 (s, 4H, Ar-C**H**-Ar)

Q. Acid-free thermal synthesis of tetraphenyl resorcin[4]arene

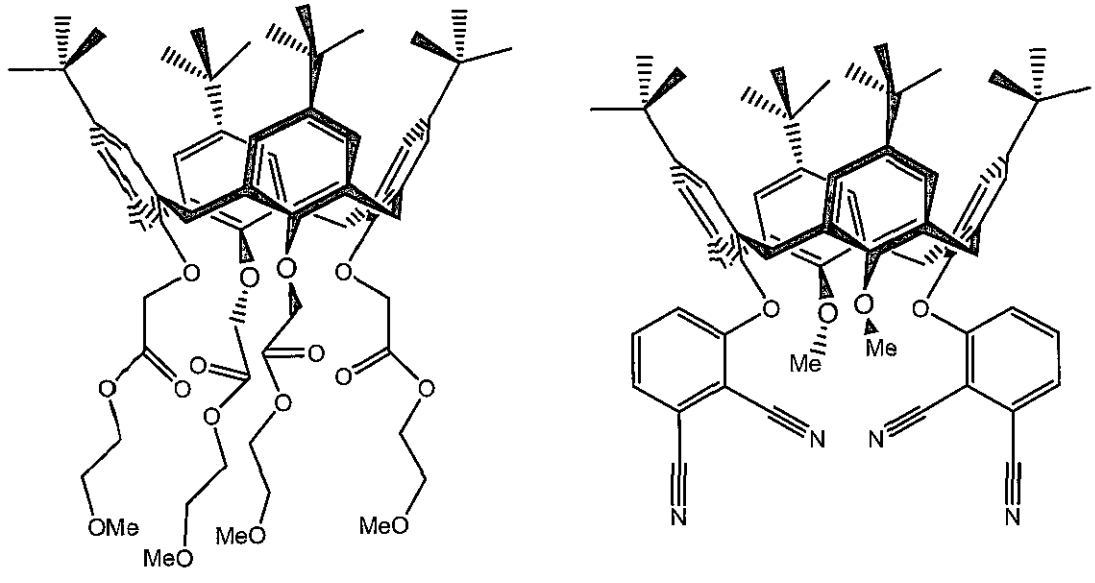
The general procedure for the acid-free thermal synthesis of pyrogallol[4]arene was followed using 0.11g (1mmol) resorcinol, 1.5mls ethanol, 0.10g (1mmol) $MgCl_2$ and 0.1mls (1mmol) benzaldehyde to produce a mixture of products. Separation proved unsuccessful.

Chapter 6

Ion Selectivity of Calix[4]arenes

I. Introduction

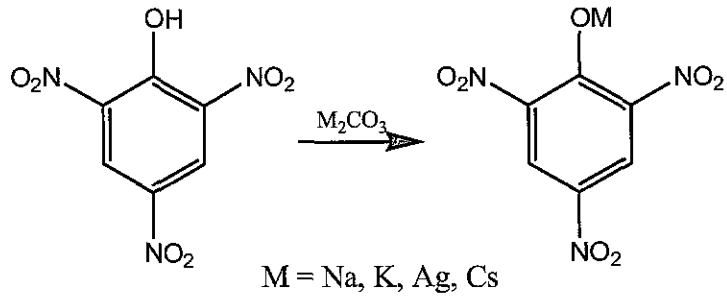
Two calixarenes (Figure 86) were previously tested for ion selectivity by ion selective electrode (ISE) based potentiometry and were found to be selective for sodium (**180**) and silver (**181**) respectively[101].



180 **181**

Figure 86: *Calixarenes **180** and **181** (5,11,17,23-tetra-p-tert-butyl-26,28-dimethoxy-25,27-(3-phthalonitrile)calix[4]arene)*

We decided to test these compounds for selectivity by electrospray ionisation mass spectral (EI-MS) techniques so that we could validate the reliability of the mass spectral screening method compared to potentiometry. To achieve this goal each compound was screened against a variety of individual metal salts and then screened with a mixture of these metal salts using ESI-MS. Picrate extraction studies were also performed using the picrate salts of the same series of cations used in the ESI-MS studies [102]. The picrate salts were synthesised from picric acid as shown in Scheme 42[103].



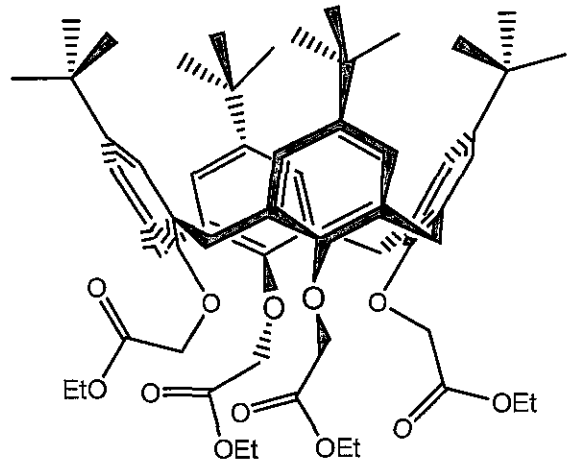
182 **183**

Scheme 42: *Picrate Salt Synthesis*

II. Results and Discussion

The first calix[4]arene screened was **180** (Figure 86). When analysed by mass spectrometry it was found to show sole affinity for sodium with an $[M+Na]^+$ peak at 1135*m/z*. The ion source required considerable cleaning after running this tetraester compound before all traces of the calixarene had been removed.

This sodium ion selectivity is similar to results found for the well-documented tetraester calix[4]arene **184** (Figure 87), which is selective for the hard sodium ion[101, 104]. The selectivity of this compound for the sodium ion is due to the preorganised nature of the four polar carbonyl oxygen atoms[105]. These atoms are hard donor oxygen atoms, which can coordinate affectively with the hard sodium ion. Further studies by Cadogan *et al.*[105] have concluded that selectivity for the sodium ion is reduced in the absence of the carbonyl oxygen atoms. Therefore the phenolic oxygen atoms do not play a large role in the binding of sodium ions.



184

Figure 87: *Tetraester calix[4]arene (Calixarene 184)*

However, the bisphthalonitrile calixarene **181** (Figure 86) showed significant selectivity for silver ions following ISE studies. Ag^{+} was the only ion to show a significantly higher response in the presence of **181** compared to the 'blank' ISE.

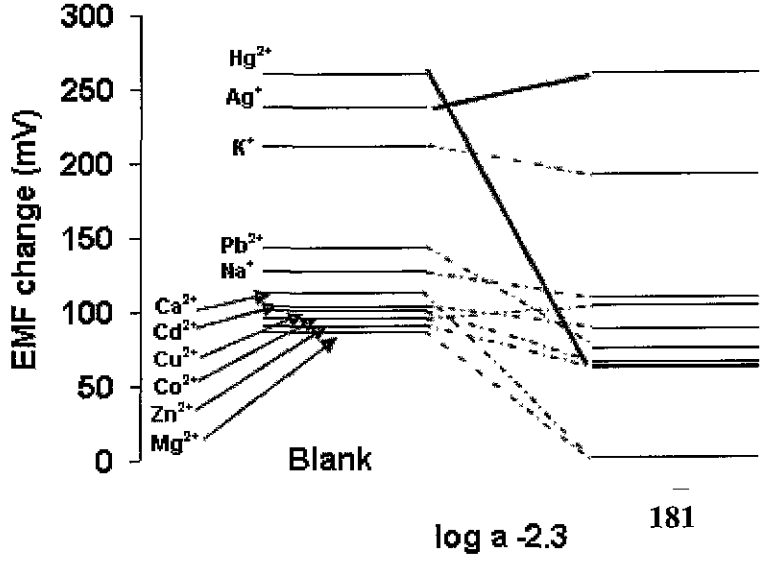


Figure 88: *The response of a 'blank' ISE compared to an ISE with* ***181****. A log a = -2.3 solution of the specified cation in water was tested in each case*

Picrate extraction studies were carried out on compound **181** and the % extraction values of various ions were calculated using the following equation:

$$\%E = 100\left(\frac{A_0 - A_e}{A_0}\right)$$

where A_0 is the absorbance of the picrate salt solution and A_e is the absorbance of the picrate salt solution after extraction.

Both the ISE and picrate extraction methods revealed compound **181** to be selective for Ag^+, although the ISE method showed K^+ to be the main interferant. The picrate extraction method revealed Cs^+ to be the main co-extractant (equivalent to interferant in sensor terms). This slight difference is probably due to the difference in techniques i e. liquid-liquid extraction compared to a partially solid-based method.

	% Extraction			
	Na Picrate	K Picrate	Ag Picrate	Cs Picrate
Calixarene 181	0	0	10.9	0.9
Calixarene 185	0	0	12.4	1.3
Calixarene 186	0.5	0	12.9	0.8

Table 21: *% Extraction values for metal picrates with calixarenes **181, 185 and 186***

Mass spectral studies were then carried out on **181** to determine if the same selectivity to silver would be observed under ESI-MS conditions. When a sample of **181,** co-dissolved in the presence of a mixture of sodium, potassium, caesium and silver salts, was analysed by ESI-MS a single peak was observed in the MS at 1036*m/z* corresponding to $[M+Ag]^+$ (Figure 89). These results corroborate what was found by both ISE methods and picrate extraction techniques, demonstrating the reliability of the ESI-MS method as a screening tool for ionophores.

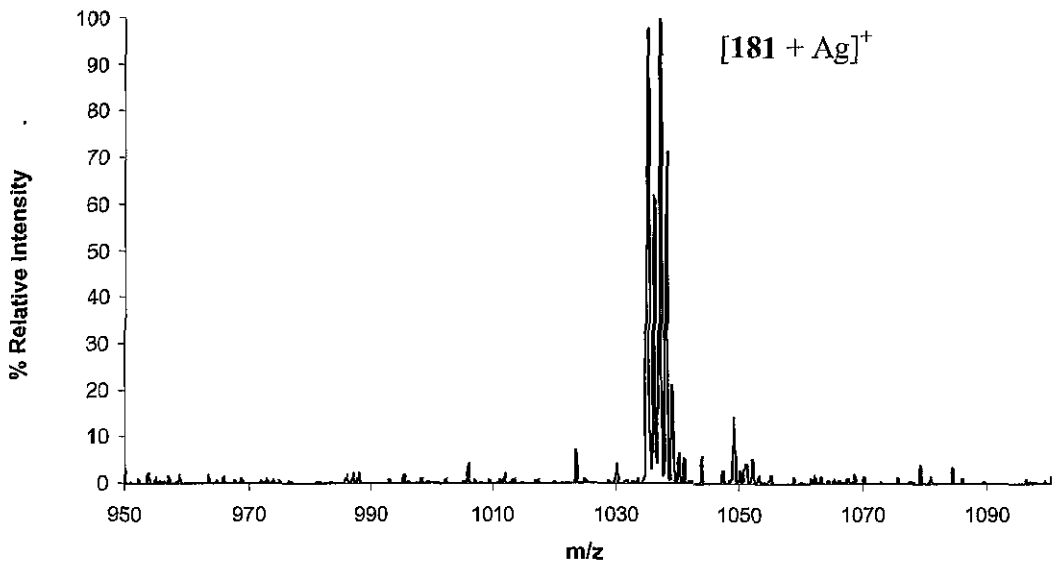
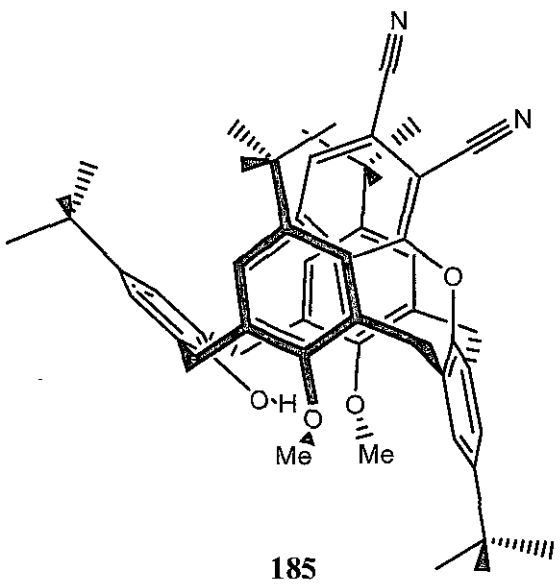


Figure 89: *Mass spec of 5,11,17,23-tetra-p-tert-butyl-26,28-dimethoxy-25,27-(3-phthalonitrile)calix[4]arene (**181**) in the presence of Na^+, K^+,Cs^+ and Ag^+*

The silver selectivity found for **181** is not surprising considering the well-documented attraction between nitrogen and silver atoms. The nitrile groups are soft and so prefer to complex soft metals. Khlobystov *et al.*[106] have reported on the interaction between Ag(I) and N-donor pyridyl ligands being comparable to that of a strong hydrogen bond. Williams *et al.*[107] reported the difference between the silver selectivity of 18-crown-6 and diaza-18-crown-6. The crown ether shows only 2% silver binding in the presence of lithium, sodium, potassium and rubidium ions whereas, when two of the oxygen atoms are replaced by nitrogen atoms, the diaza-18-crown-6 shows 99% silver selectivity. This increase in selectivity for silver ions comes at the expense of potassium binding ability. The inclusion of soft donor atoms such as nitrogen into the crown ether ring increases selectivity for softer ions such as silver[95].

However, we were very curious at this point in time as to whether two phthalonitrile groups were required for selective silver cation coordination, as is the case in **181**, or would a calix[4]arene bearing a single phthalonitrile also demonstrate selective silver binding?

To answer this question we decided to screen a second calix[4]arene, **185**, (prepared recently in our group[107a]) which contains a single phthalonitrile in the upper rim using both ESI-MS and picrate extraction methods. Calixarene **185** was ionised in the presence of a mixture of sodium, potassium, silver and caesium salts. The obtained mass spectrum, shown in figure 91, shows two peaks: the first at 911*m/z* [**185**+Ag]$^+$ and the second at 935*m/z* [**185**+Cs]$^+$, a definite preference being shown for complexation of **185** with silver. These results were also in accordance with the picrate extraction studies of **185**, which gave a 12.4% extraction for Ag^+, and 1.3% for Cs^+ (Table 21).



185

Figure 90: *5,11,17,23-tetra-p-tert-butyl-27-hydroxy-26,28-dimethoxy-25-(3-phthalonitrile)calix[4]arene (**185**)*

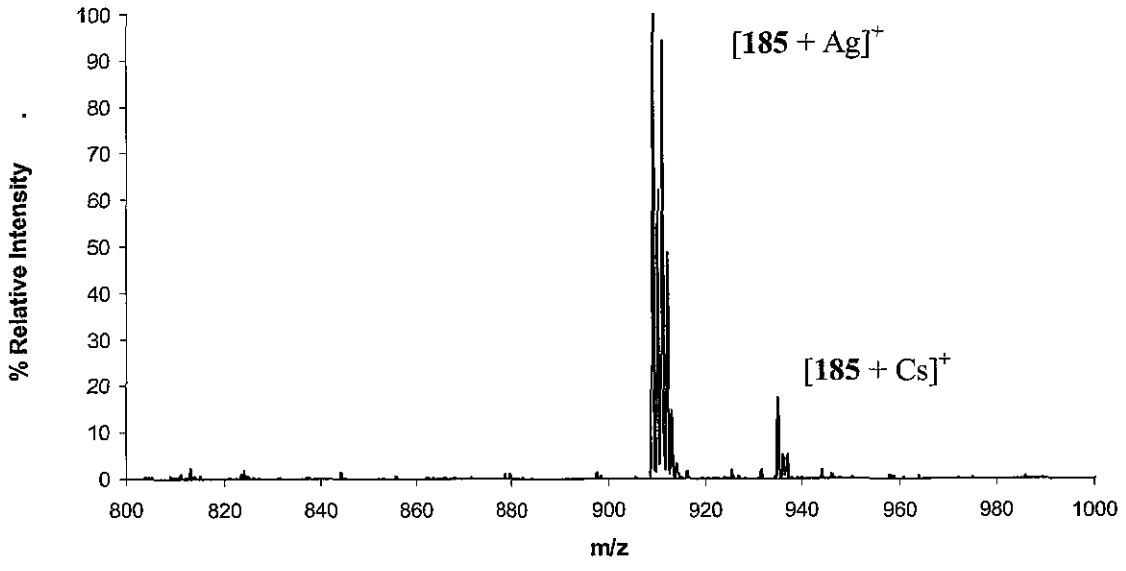


Figure 91: *Mass spec of di methoxy monohydroxy mono 3-phthalonitrile calixarene (185)*

Calixarene **186** (Figure 92), which exists as a conformational mixture of both cone (**186a**) and partial cone (**186b**) (as determined by both x-ray crystallography and ^{1}H NMR), was screened by ESI-MS. The results are shown in Figure 93. It is evident that the conformational mixture binds silver (911*m/z* [**186**+Ag]$^{+}$) preferentially over the other cations tested, however **186** seems to have a stronger affinity for caesium cation than **185**. This could be due to the presence of the cone conformation, which is absent in the case of **185**, or perhaps the phthalonitrile being substituted in the 4 position instead of the 3 position as is the case in **185** affects selectivity.

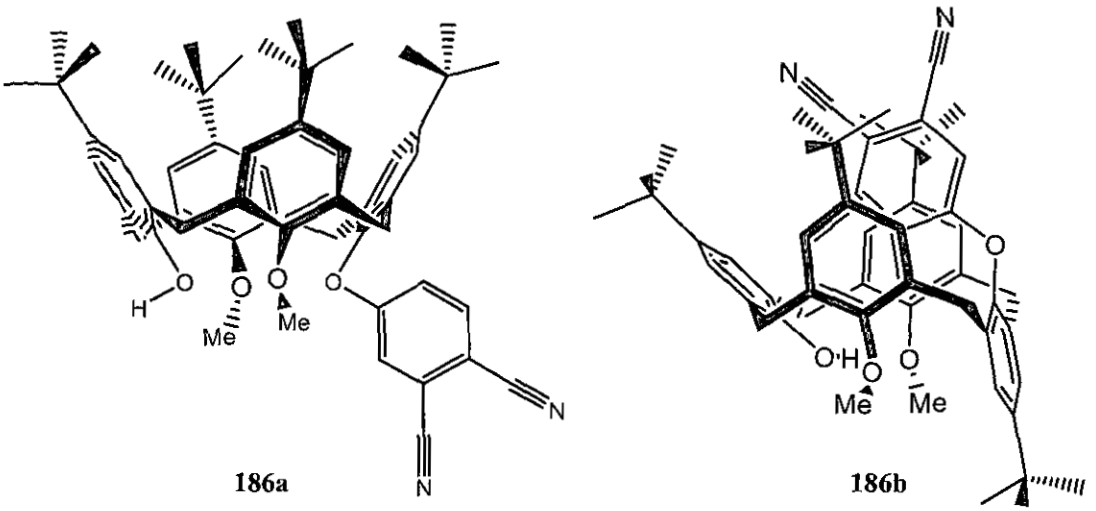


Figure 92: *5,11,17,23-tetra-p-tert-butyl-27-hydroxy-26,28-dimethoxy-25-(4-phthalonitrile)calix[4]arene in the cone (**186a**) and partial cone (**186b**) conformations*

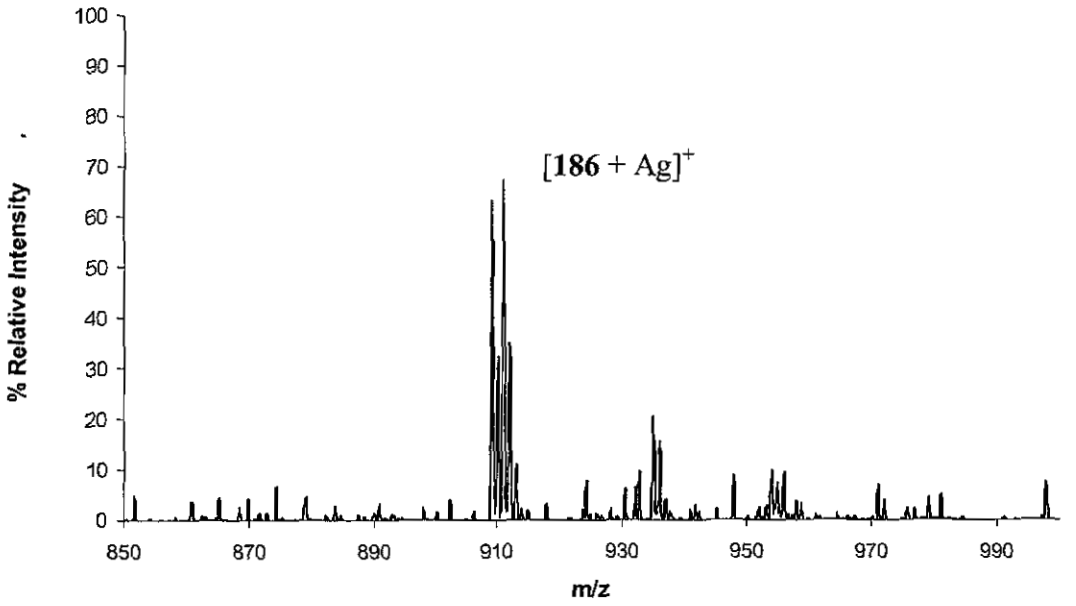


Figure 93: *Mass Spec of di methoxy 4-phthalonitrile calixarene (**186**)*

We decided to have calixarene **185** screened using ISE methods and the results are shown in Figure 94. (Note: there was not enough of sample **186** for ISE studies.)

The ISE results for **185**, also shows the highest affinities for silver ions although it should be noted that all cations showed a net increased potential change compared to the blank membrane in the presence of **185**. These results again corroborate what was

found by both ESI-MS screening and picrate extractions for **185**. However, what is evident from these results is that we have achieved silver selectivity using a single phthalonitrile substituent, albeit a 'sophisticated' phthalonitrile (**185**). Is it possible that simpler, commercially available phthalonitriles could in fact be applied as silver ionophores or extractants?

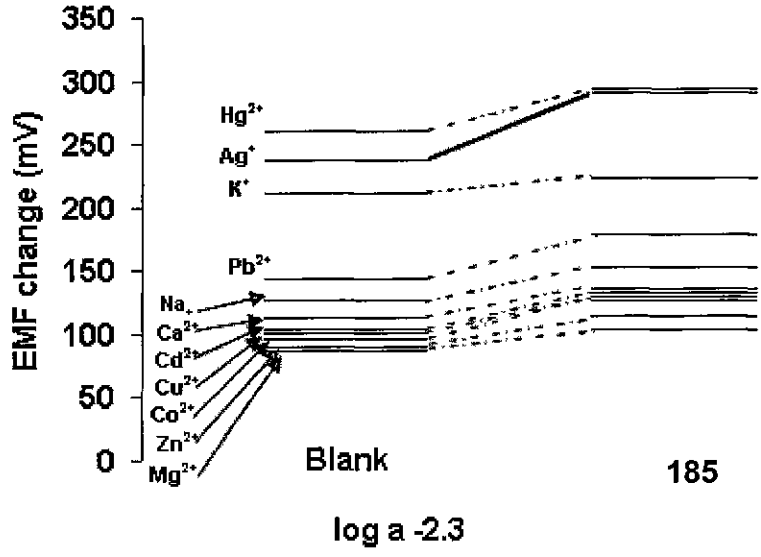


Figure 94: *The response of a 'blank' ISE compared to an ISE with **185** A log a = -2.3 solution of the specified cation in water was tested in each case*

Host	181	185
Hg^{2+}	-5.09±0.05	-1.10±0.02
Ag^{+}	0	0
Pb^{2+}	-4.50±0.02	-3.02±0.06
Cu^{2+}	-4.90±0.02	-3.91±0.04
Co^{2+}	-4.57±0.03	-3.83±0.07
Cd^{2+}	-4.96±0.04	-3.86±0.04
Zn^{2+}	-5.09±0.04	-4.12±0.02
H^{+}	-3.86±0.05	N/A
Mg^{2+}	-6.66±0.10	-4.32±0.09
Ca^{2+}	-6.11±0.10	-3.75±0.04
Li^{+}	-4.00±0.01	N/A
K^{+}	-1.78±0.03	-1.18±0.08
Na^{+}	-3.38±0.03	-2.58±0.06

Table 22: *The selectivity coefficients, log $K^{pot}_{I,J}$, for **181** and **185**, as calculated by the SSM method*[*]

We decided to analyse a number of simpler phthalonitriles, which are outlined in Figure 95.

[*] I is the primary ion Ag^{+} and J is the interferant specified. The Separate Solutions Method (SSM) was used where log a_I=log a_J=-2.3 Reproducibility based on three ISEs

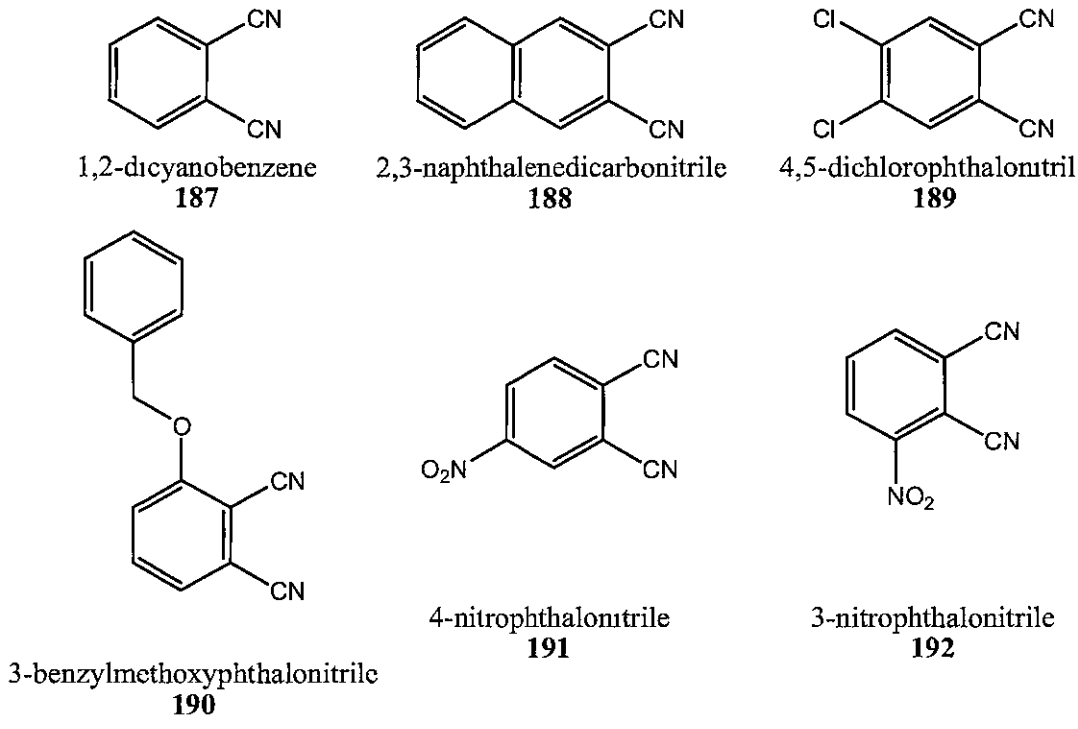


Figure 95: *Phthalonitriles that were tested for cation selectivity by UV picrate extraction analysis*

The 6 phthalonitriles represented in Figure 95 were tested for cation selectivity using UV picrate extraction techniques. Five of the phthalonitrile compounds (**187** – **191**) showed a greater affinity for silver than the phthalonitrile-containing calixarenes and they also showed an increased affinity for caesium. Again, there was only marginal affinity shown for potassium but in all five cases, the % extraction of sodium was greater for the phthalonitriles compared to the pthalonitrile-containing calixarenes. The sixth phthalonitrile (**192**) showed an equal affinity for all four ions (sodium, potassium, silver and caesium) with little selectivity.

	% Extraction			
	Na Picrate	K Picrate	Ag Picrate	Cs Picrate
Phthalonitrile 187	1.4	0	13.6	1.0
Phthalonitrile 188	0.7	0	13.8	1.4
Phthalonitrile 189	1.4	0.5	13.9	1.4
Phthalonitrile 190	1.5	0.6	13.5	1.8
Phthalonitrile 191	1.5	0.7	14.2	2.7
Phthalonitrile 192	6.7	6.3	7.6	6.1

Table 23: *% Extraction values for metal picrates with phthalonitriles **187-192**.*

The increased affinity of the 3-nitrophthalonitrile for sodium, potassium and caesium compared to the other phthalonitriles, could be due to the electron withdrawing nature of the nitro group. However, **191** does not show increased affinity for these three metal ions, therefore the increased affinity observed for **192** results from the spatial orientation of the nitro group relative to the nitrile.

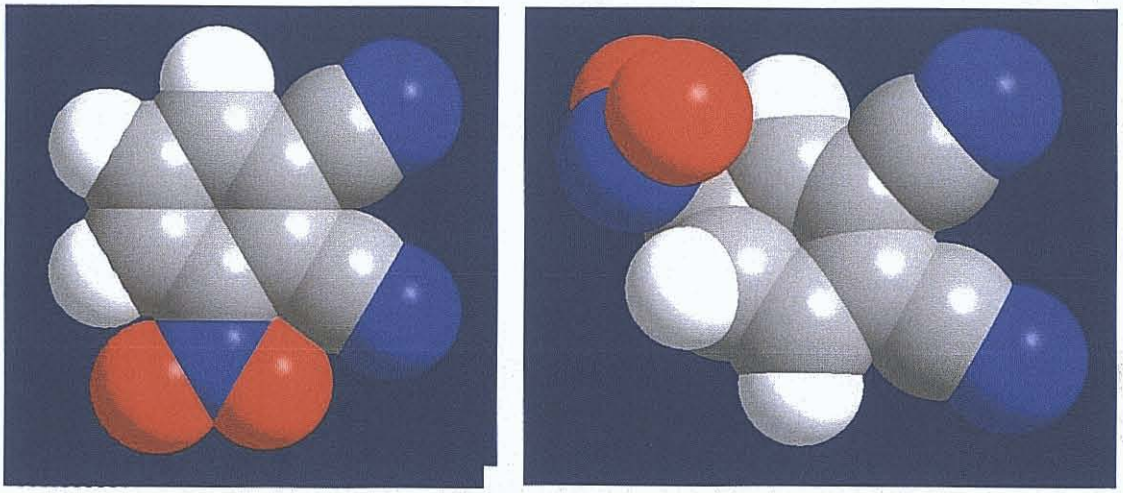


Figure 96: *Space filled models of 3-nitrophthalonitrile (**192**) and 4-nitrophthalonitrile (**191**)*

As can be seen from the models in Figure 96, the oxygen of the nitro group in **192** and the nitrogen of the ortho nitrile group are capable of chelating metal cations, resulting in a loss of selectivity.

One of the phthalonitriles in the above series, **190,** was screened by ISE methods. The compound showed an increase in response with the addition of Ag^+, however many of other cations also caused an increase in response compared to the 'blank' ISE.

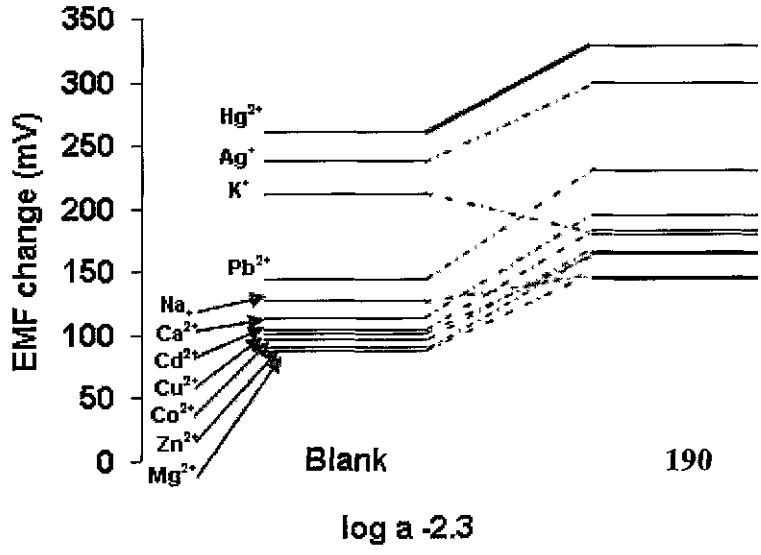


Figure 97: *The response of a 'blank' ISE compared to an ISE with **190** A log a = -2.3 solution of the specified cation in water was tested in each case*

Host	190
Hg^{2+}	-0.67±0.24
Ag^+	0
Pb^{2+}	-2.33±0.15
Cu^{2+}	-2 92±0.07
Co^{2+}	-3.44±0.2
Cd^{2+}	-3.2±0.15
Zn^{2+}	-3.42±0.12
Mg^{2+}	-3.75±0.12
Ca^{2+}	-3.18±0.18
K^+	-2.01±0.04
Na^+	-2.63±0.02

Table 24: The selectivity coefficients, log $K_{I,J}^{pot}$, for **190** as calculated by the SSM method

We believe based on these results that some form of preorganisation or preformed cavity incorporating the phthalonitrile is required for successful ISE performance of the phthalonitrile unit.

III. *Conclusion*

We have now developed ESI-MS methods for the screening of ionophore selectivity. We validated these methods by comparing them to picrate extraction methods and ISE. The significance of this work is that we can now apply this fast screening methodology to new pyrogallolarene ionophores described in the next chapter.

But perhaps what is of great significance in this work is that we have demonstrated the possible usage of phthalonitriles as selective silver extractants. To date, there has never been a report on the application of phthalonitriles as silver extractants, most silver selective extractants reported are quite sophisticated and are prepared from multiple step synthesis, making them rather expensive to prepare.

IV. Experimental

A. Mass Spectrometry Ion Screening

Each macrocycle solution was made up to a concentration of $5x10^{-5}$M in methanol. Solutions of ion salts were made up to a concentration of $5x10^{-3}$M in water. Each macrocycle was tested initially without addition of metal salt solutions. After initial analyses to ensure that the macrocycles ionised, 250µl of each of the salts were added to 0.5mls of the macrocycle solutions and the resulting mass spectra were compared to the initial spectra.

Mass spectra were analysed on an Esquire-Bruker/Hewlett Packard LC/MS 1100 series, equipped with an electrospray ion source. Direct infusion analyses were performed at an injection flow of 300µl/min.

B. Sodium Picrate Salt Synthesis[103]

40mls of water were heated to 60°C and picric acid (**182**) was added to make a saturated solution. Sodium carbonate was added slowly to the hot solution with stirring until evolution of CO_2 ceased. The solution was allowed to cool to 0°C slowly and the yellow precipitate was washed with 30mls cold water, filtered (gravity filtration) and allowed to air-dry.

Yield: 0.03g sodium picrate.

C. Potassium Picrate Salt Synthesis

The procedure was followed as for sodium picrate salt synthesis with the addition of potassium carbonate instead of sodium carbonate.

Yield: 0.516g potassium picrate

D. Silver Picrate Salt Synthesis

The procedure was followed as for sodium picrate salt synthesis with the addition of silver carbonate instead of sodium carbonate.

Yield: 0.02g silver picrate

E. Caesium Picrate Salt Synthesis

The procedure was followed as for sodium picrate salt synthesis with the addition of caesium carbonate instead of sodium carbonate.

Yield: 1.36g caesium picrate

All picrate salts were analysed by ^{1}H NMR, which showed an absence of the Picric acid OH peak at 5ppm.

F. Picrate Extraction Studies[102]

7 x 10^{-5} M solutions of each of the four picrate salts were made up in water. The solutions of the receptors were made up to a concentration of 1.75 x 10^{-5} M in chloroform except for the pyrogallolarenes and phthalonitrile **192** which were dissolved in 5mls of DMSO and then made up to 100mls in chloroform. 6mls of each picrate solution were mixed with 6mls of each receptor solution and shaken on an automatic shaker at 500 osc/min for 10 minutes. For each solution made up with DMSO, the blank was changed from 100% water to 5% DMSO in water.

The UV absorption spectrum for each picrate salt (A_0) was measured at 356nm and this was compared to the aqueous layer of each mixture after shaking (A_e). The percentage extraction of alkali metal picrate into the organic layer was calculated and the results are shown in Tables 21 and 23 (pages 140 and 148 respectively).

Chapter 7

Ion Selectivity of Pyrogallol[4]arenes

I. Introduction

The synthesis of a pyrogallol[4]arene compound possessing four crown ethers (tetra-3,4-(15-crown-5)phenylpyrogallol[4]arene (**193**)) is of significant interest due to the potential of an extended ion-binding system. This novel compound as illustrated in Figure 98, should result in ionophoric ability with potential for selective binding of large ions.

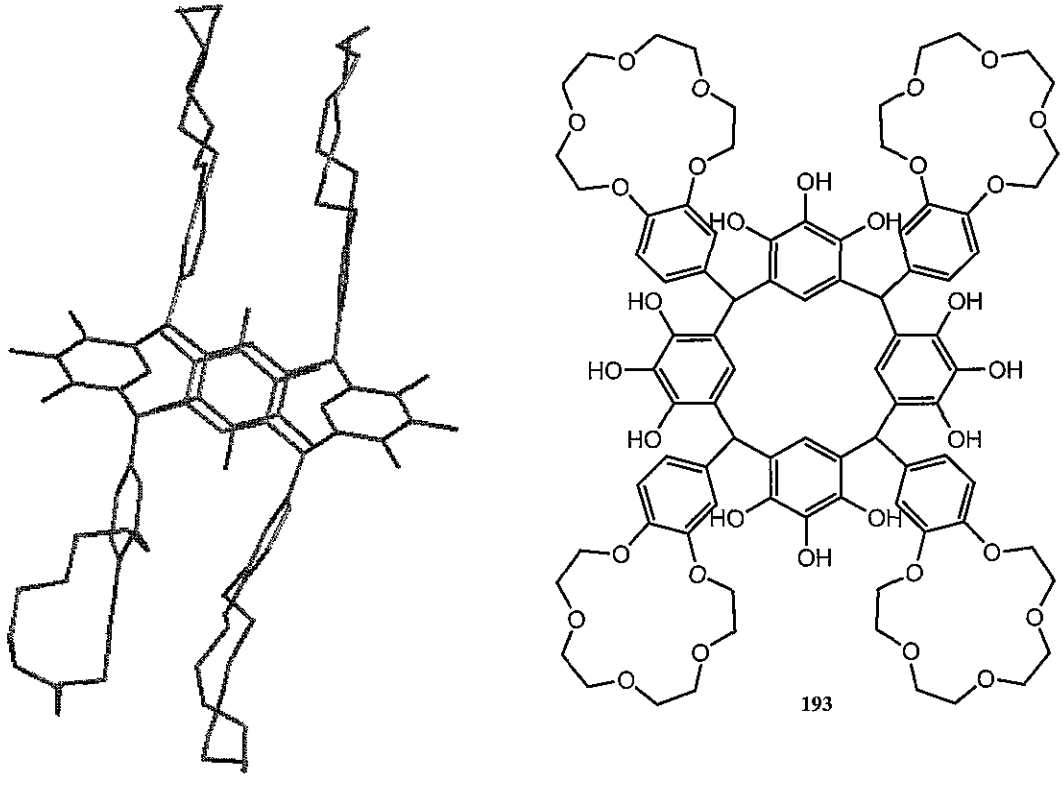
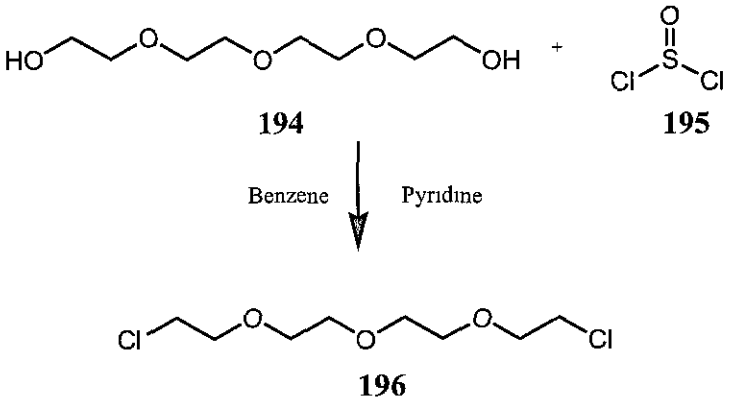


Figure 98: *Two representations of tetra-3,4-(15-crown-5)phenylpyrogallol[4]arene (193)*

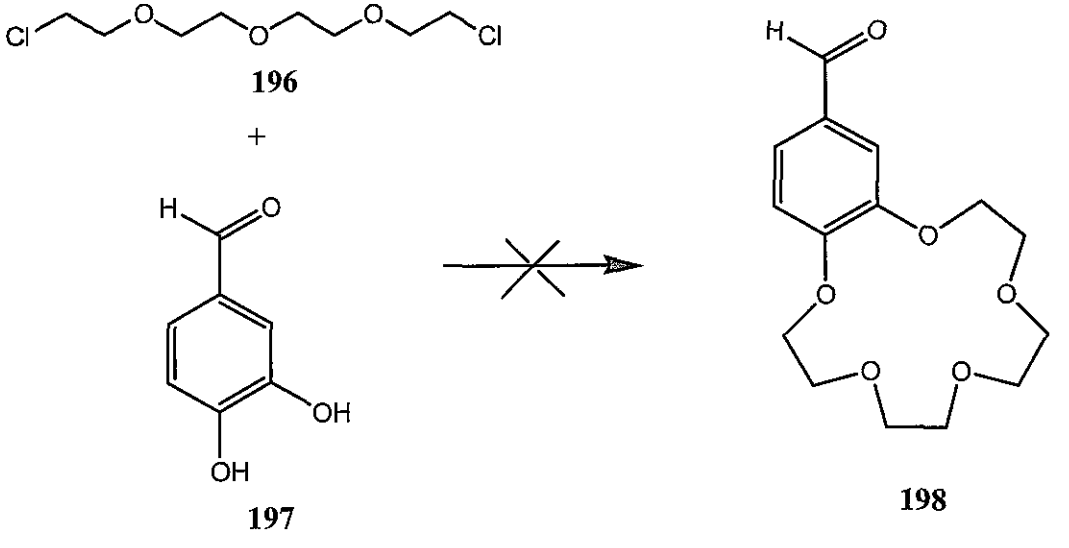
II. Discussion

We decided to use a procedure first described by Pedersen[108] to prepare the crown aryl aldehyde required for the preparation of **193**. The procedure involved the synthesis of 1,11-dichloro-3,6,9-trioxaundecane (**196**) as shown in Scheme 43. Tetraethylene glycol (**194**) was chlorinated using thionyl chloride (**195**) under reflux. The presence of the product was confirmed by infra-red spectroscopy.



Scheme 43: *Chlorination of tetraethylene glycol*

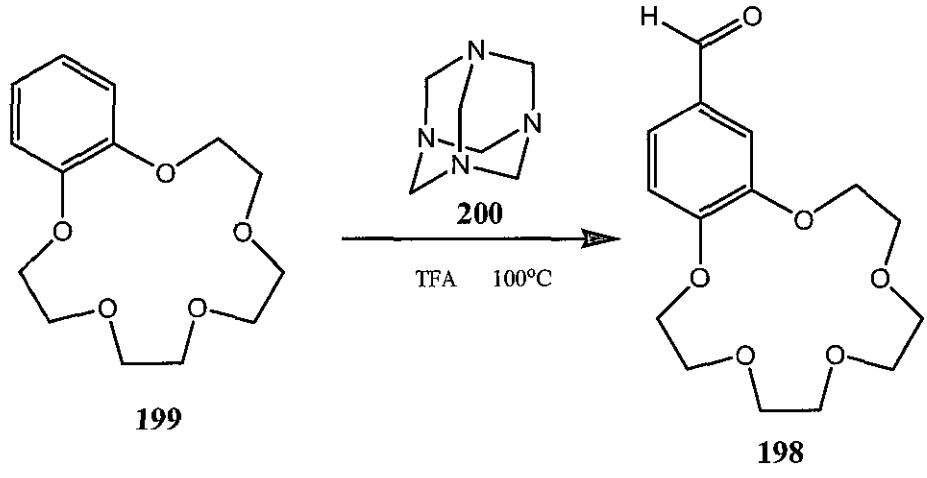
This starting material was then used in the attempted synthesis of 4'-formylbenzo-15-crown-5 (**198**) as shown in Scheme 44. Pedersen[108] produced benzo-15-crown-5 from catechol in 62% yield using this method. However, using 3,4-dihydroxybenzaldehyde (**197**), we found that a complex mixture of products was formed. Numerous attempts were made using column chromatography to purify the mixture however our target compound could not be separated.



Scheme 44: *Attempted synthesis of 4'-formylbenzo-15-crown-5 (198)*

An alternative approach was chosen using the procedure developed by Kryatova et al[109]. This method involved reflux of benzo-15-crown-5 (**199**) and hexamethylene tetramine (**200**) with trifluoroacetic acid (TFA) under nitrogen for 24 hours. The work-up of the reaction mixture was long and tedious. Extraction into chloroform

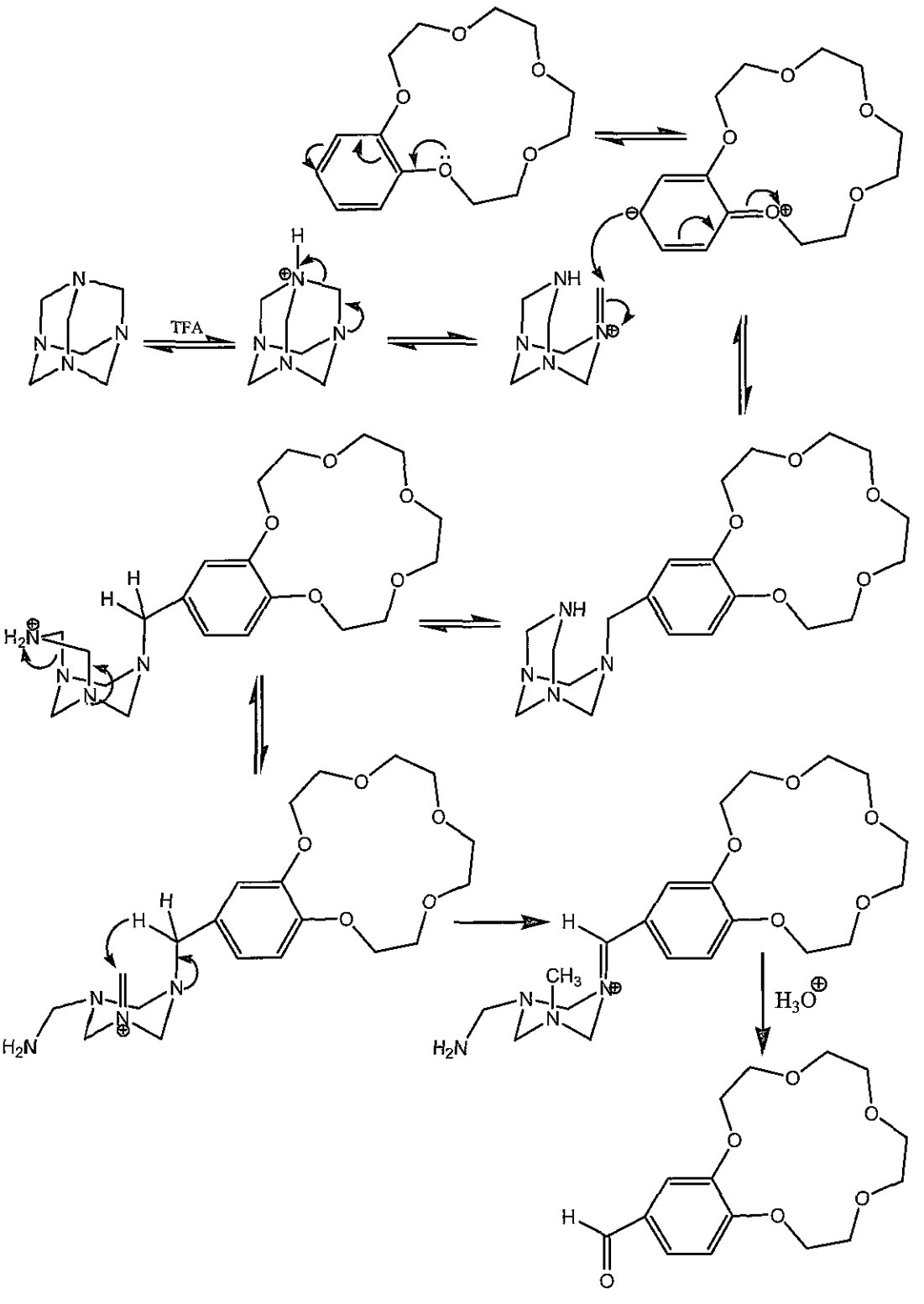
resulted in a red solution, which was dried with magnesium sulphate, filtered, and the volume was reduced by rotary evaporation. The dark red residue was purified on a silica column using a mobile phase of 80:20 chloroform:methanol. The product emerged first from the column and was evaporated under reduced pressure to yield a yellow oil. After recrystallisation in hexane, the desired product (**198**) was synthesised in low yields (Scheme 45).



199 **198**

Scheme 45: *Synthesis of 4'-formylbenzo-15-crown-5 (198)*

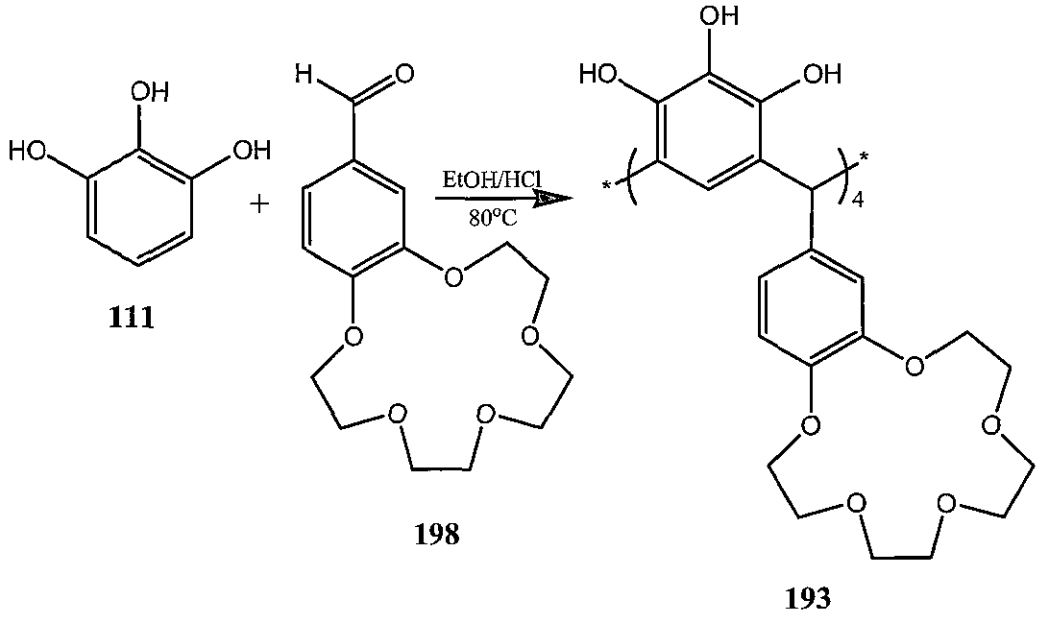
Phenols are converted to phenol aldehydes via the Duff reaction with the use of hexamethylene tetramine. The Duff reaction is generally a high yielding reaction due to the presence of strongly activating substituents on the aromatic ring such as hydroxy groups and the formyl group goes either *ortho* or *para*. The low yields in this case we believe may be due to the crown ether co-ordinating the ammonium cation intermediates, thereby lowering their reactivity. Steric hindrance of the *meta*-position caused by the presence of the crown ring may also lead to a reduced yield. The mechanism of this reaction is outlined in Scheme 46.



Scheme 46: *Mechanism for the synthesis of 4'-formylbenzo-15-crown-5* ***(198)***

Due to the difficulty in synthesising the aldehyde by this method, a microwave-assisted synthesis using the same reagents was attempted. A small-scale reaction was performed using the same reactants as in the thermal method but a very dilute amount of trifluoroacetic acid was used. The reactants were mixed to a paste and irradiated for 2 minutes at 700W but the product was not obtained. The concentration of the trifluoroacetic acid was increased and the reaction time was increased to 5 minutes for the second attempt. The reaction was carried out under nitrogen but again the product was not obtained.

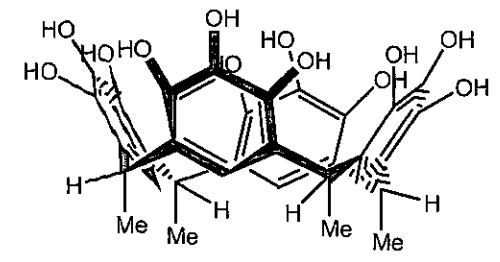
Tetra-3,4-(15-crown-5)phenylpyrogallol[4]arene (**193**) was synthesised following a relatively simple procedure of reflux under acidic conditions and yielded the desired tetramer in adequate yields (Scheme 47).



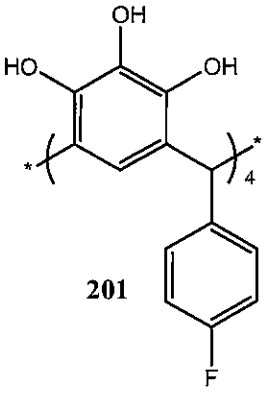
Scheme 47: *Synthesis of tetra-3,4-(15-crown-5)phenylpyrogallol[4]arene (**193**)*

A. Ionophore properties of pyrogallol[4]arenes

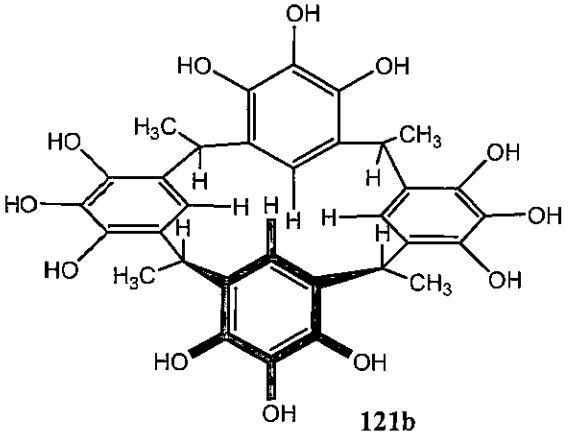
We decided to screen **193** and a selection of other pyrogallol[4]arenes against various metal cations using the ESI-MS methods developed in the previous chapter. The pyrogallol[4]arenes selected are shown in Figure 99. Tetramethylpyrogallol[4]arene (**121**) (in both the cone (**121a**) and chair (**121b**) conformations), tetramethylpyrogallol[4]arene dodecaacid (**142**), tetra-4-fluorophenylpyrogallol[4]arene (**201**) and tetra-3,4-(15-crown-5)phenylpyrogallol[4]arene (**193**) were used. All compounds were initially tested for mass spectral suitability in methanol. The tetramethylpyrogallol[4]arene in the flattened partial cone conformation (**121b**) was sparingly soluble in methanol and was found to be unsuitable for electrospray ionisation mass spectrometry due to its resistance to ionisation.



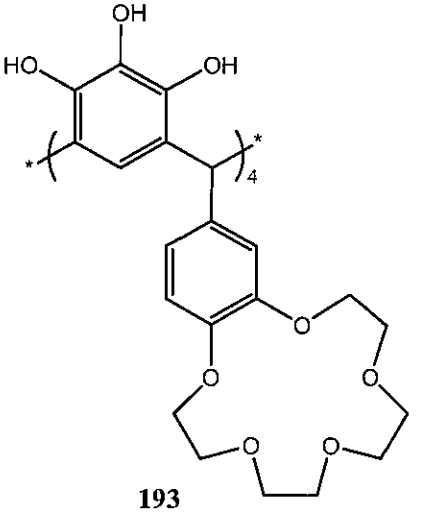
121a



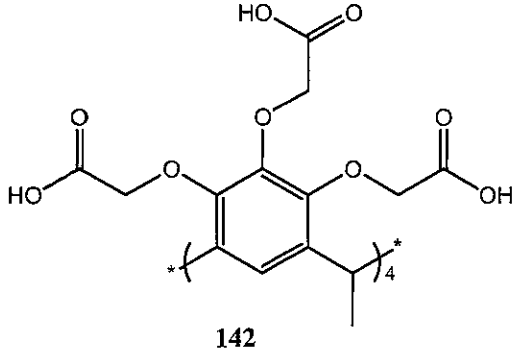
201



121b



193



142

Figure 99: *Pyrogallol[4]arenes tested by electrospray ionisation mass spectrometry*

Tetramethylpyrogallol[4]arene (**121a**) showed a preference for sodium over potassium with peaks appearing at 631*m/z* ($[M+Na]^+$) and 647*m/z* ($[M+K]^+$) when ionised in the absence of metal salt additives. However, when a mixture of salts (LiCl, NaCl and CsCl) was added to **121a**, only the caesium complex was evident (741*m/z*). It appears from initial screening that **121a** has a very high affinity for caesium over lithium, sodium and potassium ions. It should be noted that **121a** also showed strong intensity signals when in the presence of silver nitrate with an $[M+Ag]^+$ peak at 715*m/z*.

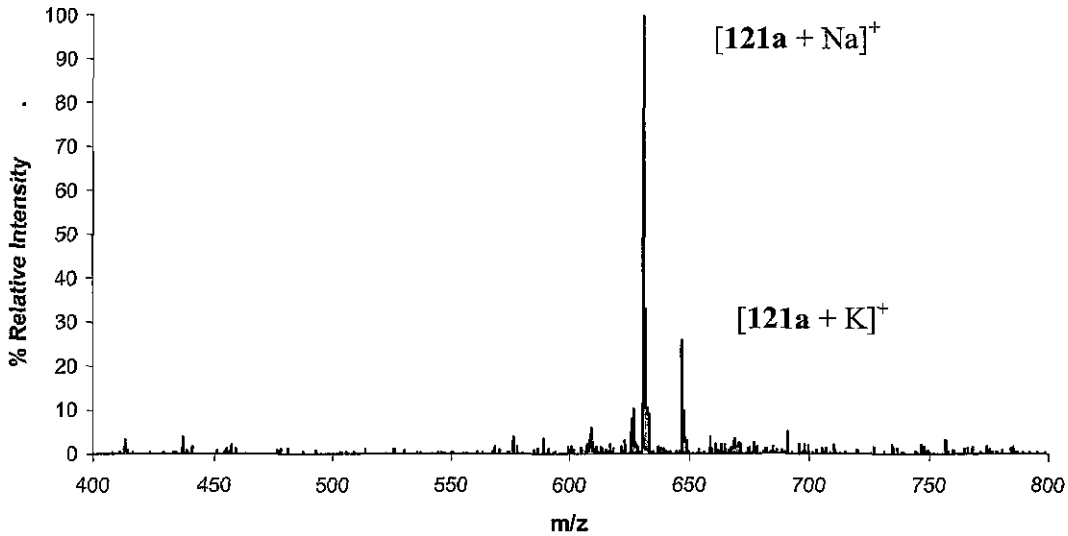


Figure 100: *Mass spectrum tetramethylpyrogallol[4]arene in the cone conformation (**121a**)(no metal salt additives)*

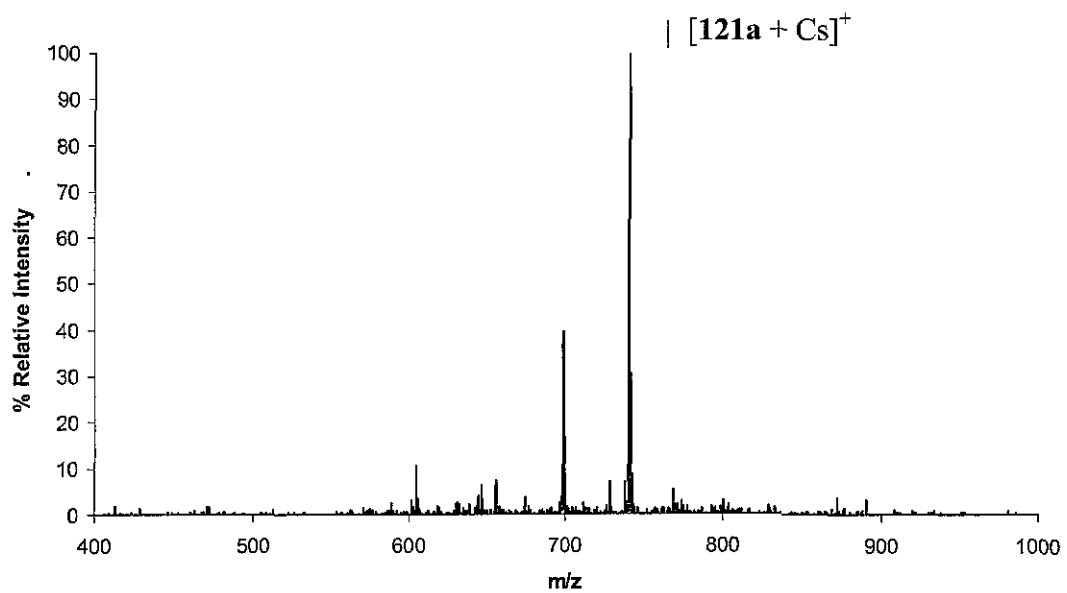


Figure 101: *Mass spectrum of tetramethylpyrogallol[4]arene in the cone conformation (**121a**) in the presence of caesium*

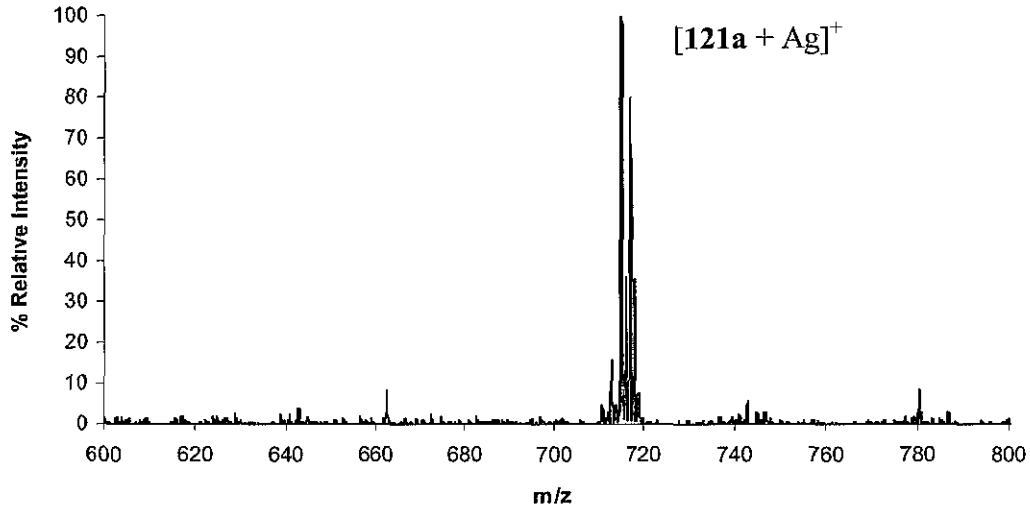


Figure 102: *Mass spectrum of tetramethylpyrogallol[4]arene in the cone conformation (**121a**) with silver nitrate.*

Tetramethylpyrogallol[4]arene dodecaacid (**142**) gave peaks of 1327*m/z* and 1343*m/z* which correspond to $[M+Na]^+$ and $[M+K]^+$ respectively. The $[M+Na]^+$ peak was much more intense than the $[M+K]^+$ peak, which shows a selectivity for Na^+ over K^+. When equal aliquots of LiCl, NaCl, CsCl and $AgNO_3$ solutions were added to **142**, the resulting spectrum was unclear with some evidence of complexation to sodium and potassium and trace evidence of complexation to caesium. This result reveals that the conversion of the upper rim phenoxy groups of **121** into acetate derivatives results in the loss of cation selectivity, which is quite the opposite as to what is observed for the calix[4]arenes. It is possible that the size of the upper rim of **142** is either too large or not properly preorganised to allow for selective binding with the metals used in this study.

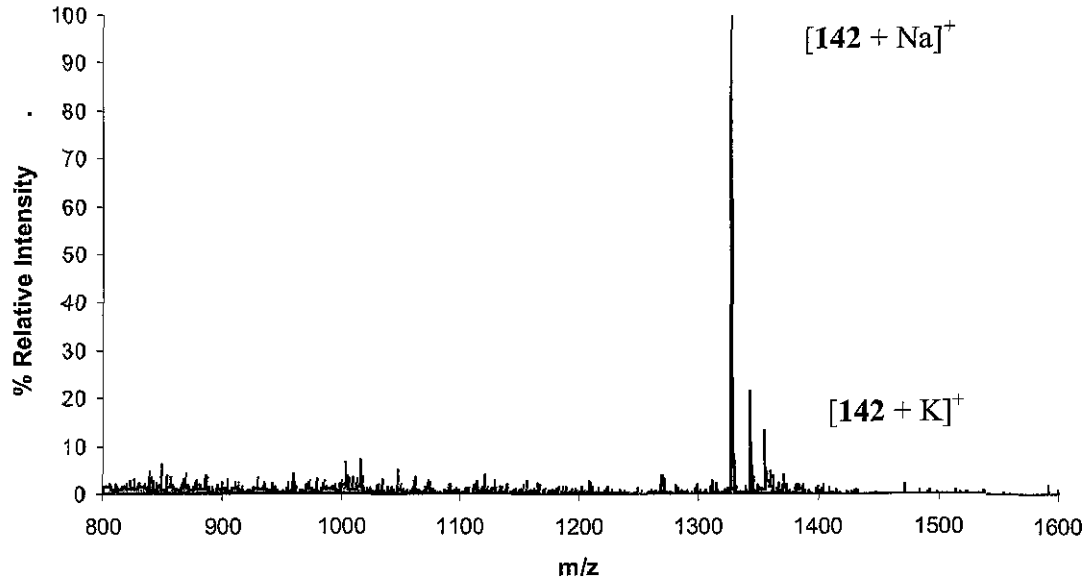


Figure 103: *Mass spectrum of the tetramethylpyrogallol[4]arene dodecaacid (142)*

Tetra-4-fluorophenylpyrogallol[4]arene (**201**) showed a peak at 951*m/z* representing $[M+Na]^+$ which was much more intense than the peak at 967*m/z* ($[M+K]^+$). The spectrum became unresolved upon addition of a mixture of LiCl, NaOAc and CsCl, indicating no selectivity. This result isn't surprising since 174 exists as the rctt isomer, therefore no preformed cavity exists.

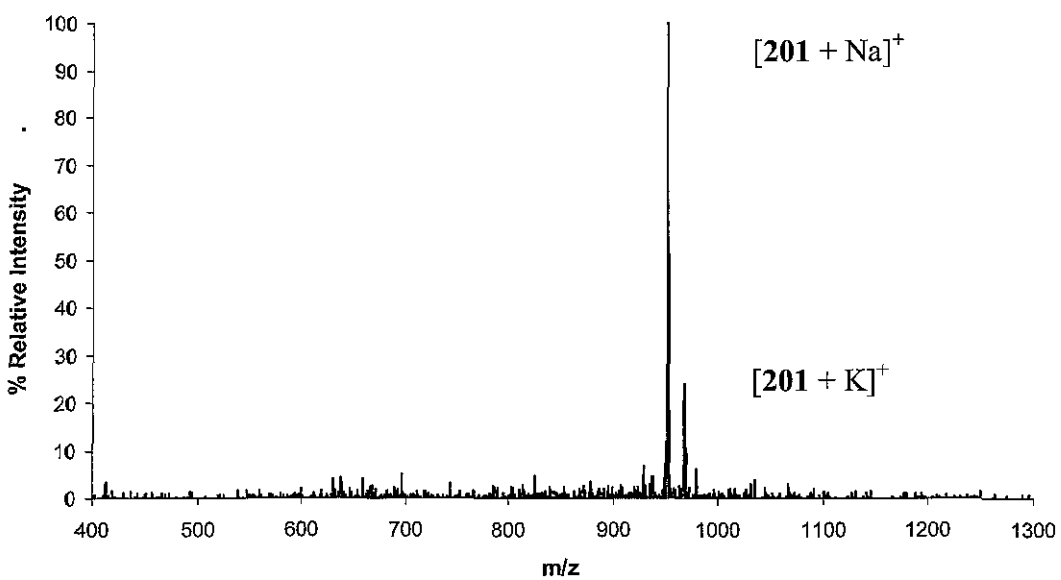


Figure 104: *Mass spectrum of tetra-4-fluorophenylpyrogallol[4]arene (201)*

Unlike all the other pyrogallol[4]arenes that were tested and described above, tetra-3,4-(15-crown-5)phenylpyrogallol[4]arene (**193**) showed selectivity for K^+ over Na^+ with tendency for dimerisation with both K^+ and Na^+. $[M+K]^+$, $[M+Na]^+$, $[M+2K]^{2+}$ and $[M+2Na]^{2+}$ were found at 1656*m/z*, 1639*m/z*, 847*m/z* and 831*m/z* respectively. A peak at 1749*m/z* ($[M+Cs]^+$) appeared in the spectrum of the mixture of **193** with $CsNO_3$. The peak at 941*m/z* shows evidence of a 2:1 ratio of metal ion to tetramer ($[M+2Cs]^{2+}$).

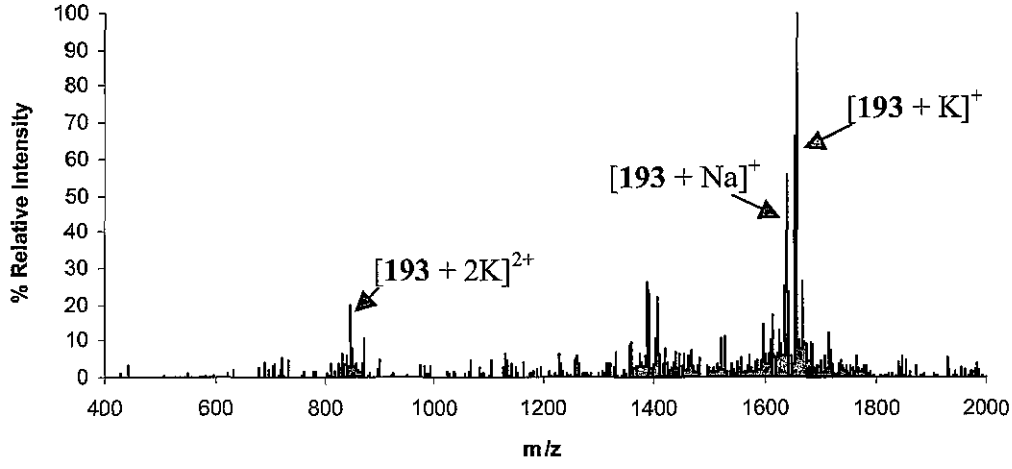


Figure 105: *Mass spectrum of the tetra-3,4-(15-crown-5)phenyl pyrogallol[4]arene (**193**)*

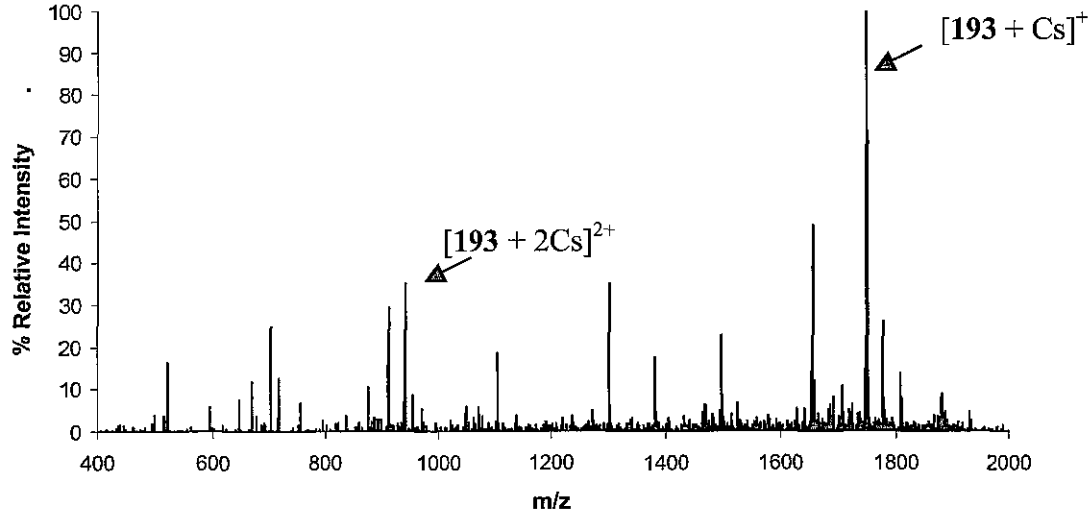


Figure 106: *Mass spectrum of the tetra-3,4-(15-crown-5)phenylpyrogallol[4]arene (**193**) with caesium*

It should be noted that a control study was also carried out using benzo-15-crown-5 (**199**, Figure 108). The results of this investigation are shown in Figure 107, with $[M+K]^+$ peak at 307*m/z* which is more intense than the $[M+Na]^+$ peak at 291*m/z*. A peak at 575m/z shows the presence of a dimer being formed around the potassium ion ($[2M+K]^+$).

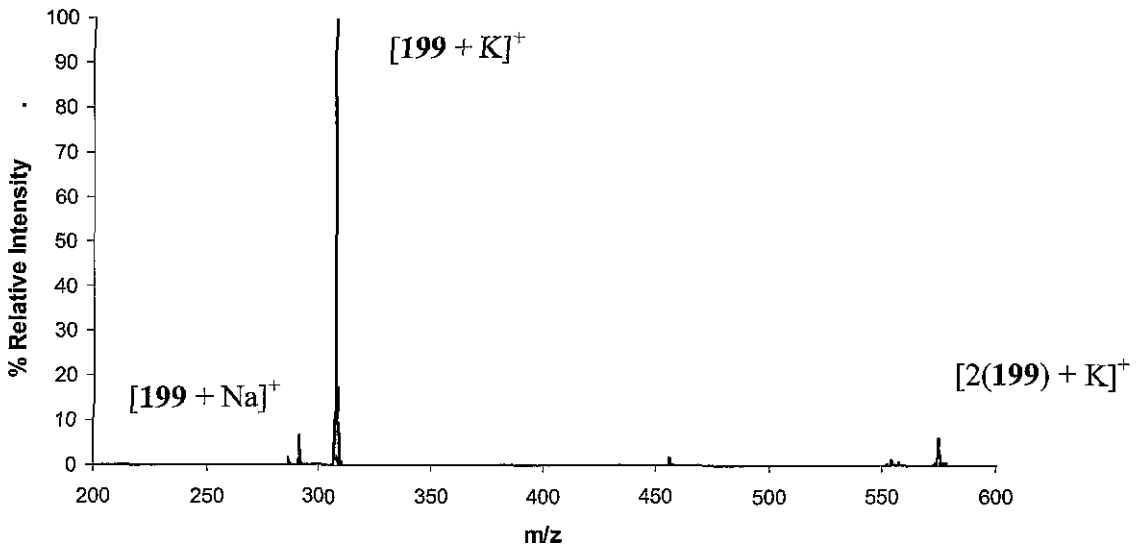
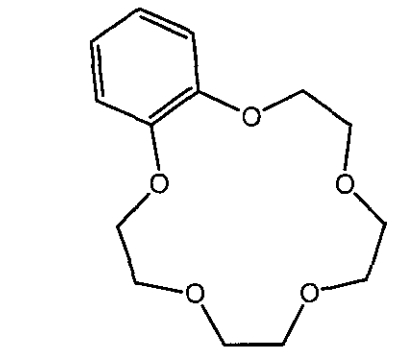
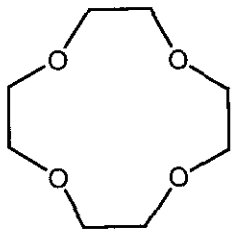


Figure 107: *Mass spectrum of benzo-15-crown-5 (199)*

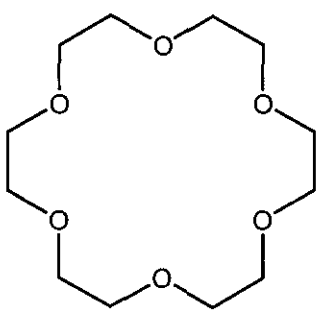
The affinity of a crown ether cavity for metal ions is based on the size of the cavity. Smaller cavity sizes have preference for smaller ions and larger cavities accept larger ions[95]. The cavity size of 15-crown-5 is ideal for the binding of Na^+ while 18-crown-6 shows high affinity for K^+ ions. 21-crown-7 has been shown to selectively bind caesium ions. However, the presence of aromatic substituents can affect the selectivity of the crown ether[107]. 18-crown-6 shows high affinity for K^+, which reduces significantly upon addition of 2 aromatic substituents (dibenzo-18-crown-6). Conversely sodium ion complexation increases with addition of aromatic substituents onto 18-crown-6.



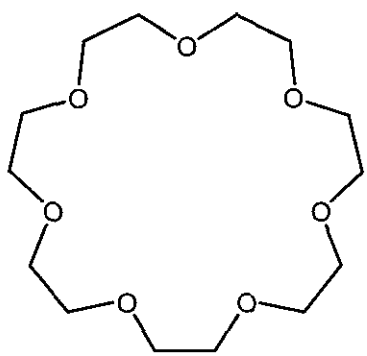
199



202



203



204

Figure 108: *Benzo-15-crown-5 (**199**), 16-crown-4 (**202**), 18-crown-6 (**203**) and 21-crown-7 (**204**)*

Changes in the stability constants for complexation of Na^+ and K^+ with benzo crown ethers can be caused by substituents on the benzene ring[23]. These effects are probably of electronic rather than steric origin. Ungaro *et al.*[110] found that there was a 25-fold difference in the Na^+ formation constants between 4'amino- and 4'nitrobenzo-15-crown-5. This change is thought to be most likely caused by a difference in the basicity of the two aromatic ether oxygen atoms. This is in agreement with the work published by Chan *et al.*[111] stating that the strength of alkali ion interactions with ether is known to depend on the bacisity of the ether oxygen. These substituent effects can be as great as a change in the structure of the ring itself. We believe that the carbon substituent (bridging carbon of the pyrogallolarene ring) located in the 4 position increases the basicity of the aromatic ether oxygens, thereby changing the selectivity from Na^+ to K^+.

The pyrogallolarenes could not be tested using picrate extraction methods since they possess a strong absorption at 356nm, thus making analysis unreliable.

^{1}H NMR titration studies were carried out on **193** to examine the binding with caesium ion. The results are shown in Figure 109. There is a slight upfield shift of one set of the pyrogallol protons of **193** with the addition of 2 equivalents of caesium ion. The shift upfield, we believe is caused by an aniosotropic effect resulting from the 'sandwiching' of the caesium ion between the two crown ether rings of the pyrogallolarene. This effectively brings the two phenyl rings of **193** closer together resulting in the shielding of the two pyrogallol protons.

The NMR results confirm that two caesium ions are bound to every pyrogallol[4]arene when there is sufficient caesium in solution.

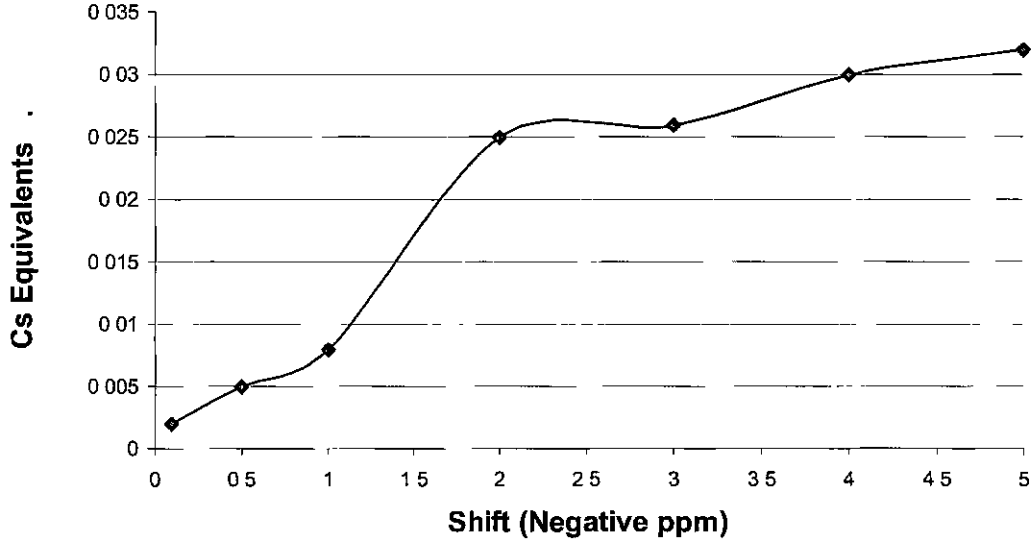


Figure 109: *Change in chemical shift with change in caesium for tetra-3,4-(15-crown-5)phenylpyrogallol[4]arene (193)*

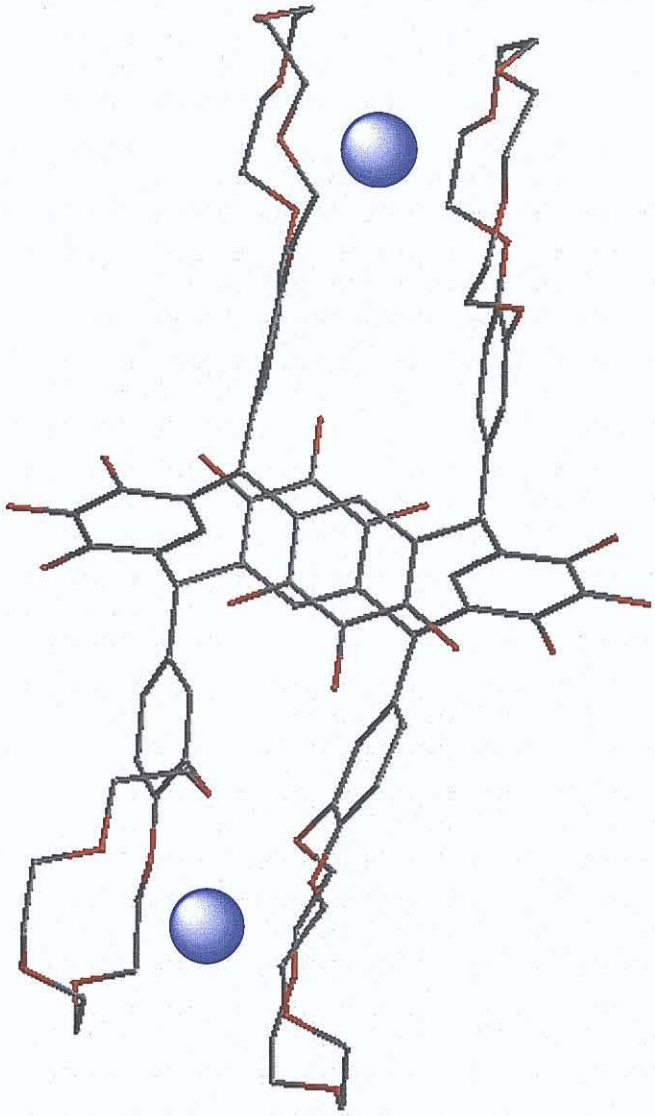


Figure 110: *3-D representation of the crown tetramer (**193**) bound with caesium*

III. Experimental

A. Chlorination of tetraethylene glycol

3.82ml (0.022mol) of tetraethylene glycol (**194**) and 3.45ml (0.049mol) of pyridine were added to 20ml of benzene and heated to reflux (86°C). 3.56ml (0.049mol) Thionyl chloride (**195**) was added drop wise with stirring over one hour to the resulting clear solution. Some white precipitate formed during the addition of thionyl chloride (**195**) and the solution turned yellow. Heating was continued overnight and then the reaction was cooled to room temperature. 0.5ml Concentrated hydrochloric acid diluted in 2ml of water was added drop wise over about 10 minutes and the resulting reaction mixture was separated into two layers. The upper organic layer was taken off, dried with magnesium sulphate and the benzene was evaporated off under reduced pressure yielding a yellow oil (58%). ^{1}H NMR of the product was not conclusive as the ^{1}H NMR spectra for the starting material and the product are very similar. Thin film Infra Red spectra were taken on both the starting material and the product. A broad OH band in the region of 3400-3500υ was present in the spectrum of the tetraethylene glycol (**194**) but was absent in the product spectrum, indicating that the desired product was formed.

B. Attempted synthesis of 4'-formylbenzo-15-crown-5

1.38g (0.01mol) 3,4-dihydroxybenzaldehyde (**197**) was added to 15ml of 1-butanol along with 0.85g (0.02mol) of sodium hydroxide in 1ml of water. This initial reaction mixture was stirred under nitrogen for 5 minutes. After addition of 2.31g (0.01mol) of 1,11-dichloro-3,6,9-trioxaundecane (**196**), the reaction mixture was heated to reflux (110°C) with good agitation overnight. The reaction was acidified with 0.08ml of concentrated hydrochloric acid and it was cooled to 30°C. The solution was filtered and the black solid was washed with methanol. The filtrate and washings were combined and the solvent was reduced in a rotary evaporator. The residue was extracted from chloroform and water, the organic layer was dried with magnesium sulphate and the solvent was evaporated off. The resulting viscous black residue was refluxed in hexane in an attempt to purify it.

^{1}H NMR of the product (in chloroform-d) showed a complex mixture of products.

A thin film Infra Red spectrum, on salt plates, of the starting material, 3,4-dihydroxybenzaldehyde (**197**) showed a strong band in the region of 3400-3500υ indicating the presence of –OH groups while the spectrum of the product showed a thinner band in the same region. This indicates that a mixture of products may be present. (TLC using 75:25 ethyl acetate:hexane showed a single spot for the organic phase of the reaction.)

C. Synthesis of 4'-formylbenzo-15-crown-5

2.9ml Trifluoroacetic acid was added to 1.05g (3.9mmol) of benzo-15-crown-5 (**199**) and 0.57g (4.1mmol) of hexamethylene tetramine (**200**) and the reaction was stirred under nitrogen at 100°C for 24 hours. The mixture turned dark red. After the required reflux time, the reaction mixture was cooled to 5°C and 5g of ice were added. The reaction was stirred for a further hour at room temperature. The product was extracted repeatedly with chloroform; the organic fractions were combined, dried with magnesium sulphate and filtered. The solvent was evaporated under reduced pressure and the oily red residue was purified on a silica column (80:20 chloroform:methanol). The first fraction was collected and the solvent was evaporated off to yield a yellow oil. Further purification from hexane (The oil was heated in hexane to boiling and the solvent was decanted off. Cooling of the solvent yielded the product) produced a white solid in low yields (0.10g, 0.34mmol, 9% yield).

^{1}H NMR (Chloroform-d): δ[ppm] 9.77 (s, 1H, C**H**O), 7.38 (d, J=8Hz, 1H, Ar-**H**), 7.36 (s, 1H, Ar-**H**), 7.68 (d, J=8Hz, 1H, Ar-**H**), 4.12-4.14 (multiplet, 4H, CH_2-C**H**$_2$-O), 3.86-3.89 (multiplet, 4H, CH_2-C**H**$_2$-O), 3.69-3.71 (multiplet, 8H, CH_2-C**H**$_2$-O).

D. Attempted microwave-assisted synthesis of 4'-formylbenzo-15-crown-5

(i) 0.19mmol (0.05g) Benzo-15-crown-5 (**199**) and 0.21mmol (0.03g) of hexamethylenetetramine (**200**) were mixed with dilute trifluoroacetic acid and irradiated at 700W for 2 minutes.

^{1}H NMR analysis showed that 4'-formylbenzo-15-crown-5 (**198**) was not obtained.

(ii) 0.22mmol (0.06g) Benzo-15-crown-5 (**199**) and 0.29mmol (0.04g) of hexamethylenetetramine (**200**) were mixed with concentrated trifluoroacetic acid and irradiated at 700W for 5 minutes.

^{1}H NMR analysis showed that 4'-formylbenzo-15-crown-5 (**198**) was not obtained.

E. Synthesis of tetra-3,4-(15-crown-5)phenylpyrogallol[4]arene

0.3g (1mmol) 4'-Formylbenzo-15-crown-5 (**198**) and 0.13g (1mmol) of pyrogallol (**111**) were stirred at reflux (80°C) in a mixture of 2ml of ethanol and 0.7ml hydrochloric acid for 24 hours. The pink suspension was filtered and washed with 4:1 ethanol:water to yield 0.21g (0.1mmol) of a pink solid (52% yield).

^{1}H NMR (DMSO-d6): δ[ppm] 7.83 (broad s, 4H, O**H**), 7.62 (broad s, 4H, O**H**), 7.39 (broad s, 4H, O**H**), 6.48 (d, J=8.1Hz, 4H, Ar-**H**), 6.19 (s, 4H, Ar-**H**), 6.14 (d, J=8.1Hz, 4H, Ar-**H**), 6.02 (s, 2H, Ar-**H**), 5.58 (s, 4H, Ar-C**H**-Ar), 5.52 (s, 2H, Ar-**H**), 3.89 (multiplet, 4H, CH_2-C**H**$_2$-O), 3.76 (multiplet, 6H, CH_2-C**H**$_2$-O), 3.64 (multiplet, 16H, CH_2-C**H**$_2$-O)

Mass Spec: $C_{84}H_{96}O_{32}$ Expected: *m/z* 1616

Found: *m/z*1639 (M+23), 1656 (M+39)

F. Mass Spectrometry

Each macrocycle solution was made up to a concentration of $5x10^{-5}$M in methanol. Solutions of ion salts were made up to a concentration of $5x10^{-3}$M in water. Each macrocycle was tested initially without addition of metal salt solutions. After initial analyses to ensure that the macrocycles ionised, 250µl of each of the salts were added to 0.5mls of the macrocycle solutions and the resulting mass spectra were compared to the initial spectra.

Mass spectra were analysed on an Esquire-Bruker/Hewlett Packard LC/MS 1100 series, equipped with an electrospray ion source. Direct infusion analyses were performed at an injection flow of 300µl/min.

G. ^{1}H NMR Titration Studies

A solution of $4x10^{-3}$M caesium picrate in DMSO-d6 was made up. 0.4ml of a $6x10^{-4}$M solution of tetra-3,4-(15-crown-5)phenylpyrogallol[4]arene in DMSO-d6 was added to varying volumes of the caesium picrate solution. Each solution was made up to 0.6ml with DMSO-d6. The ratios of pyrogallol[4]arene to caesium picrate ranged from 1:0.1 to 1:5. The ^{1}H NMR spectra of each sample was analysed and showed that the pyrogallol proton shifted upfield with increased picrate.

IV. Thesis Conclusion

After completing many years of research on pyrogallol[4]arenes and revisiting our initial four research proposals, we can conclude the following:

1) The stereochemistry of the reactions can be controlled to a certain extent by the use of metal ions in the reaction mixture.

While the overall yield of the reactions was not increased, the proportion of cone to flattened partial cone isomer of the tetramethylpyrogallol[4]arene could be increased by the addition of certain metal ions into the reaction mixture. The results showed that the smallest metal ion used, Li^+, gave the largest increase in isomer ratios.

Additionally, a simple method was developed to separate the different isomers from the reaction mixture. Interconversion studies were carried out to investigate the possibility of interconversion between the two isomers and to examine the stability of each of the isomers. It was found that no interconversion occurred from either conformation.

2) It is possible to condense pyrogallol with ketones to form the cyclic tetrameric compounds, pyrogallol[4]arenes.

Octamethylpyrogallol[4]arene can be synthesised from pyrogallol and acetone under similar conditions to those used in the pyrogallol/aldehyde condensations. Other tetramers can be synthesised from other ketones such as acetophenone and pentan-3-one. However, the yields of these pyrogallol[4]arenes are low due to the steric hindrance of the ketone group, which is shielded by the larger bulky substituents.

3) Attempts to synthesise the pyrogallol[4]arene tetramer under acid-free conditions have been successful.

We have succeeded in synthesising the pyrogallol[4]arenes under dilute acid conditions using a microwave oven. Furthermore, we have developed a method for

the acid-free synthesis of these tetrameric compounds using a metal salt as a catalyst in the reaction. The smaller harder cations appeared to give the highest yields of product.

4) Mass spectrometric results corresponded to those given by the ion selective electrode methods.

Liquid/liquid extraction methods involving the use of picrate salts also showed comparable results. This implies that the mass spectrometric method is a valid tool for the analysis of ion selectivity. The advantage of this method is that it takes only a few minutes to analyse the ionophore ability of a new macrocycle instead of a few days or a few weeks with existing methods.

Bibliography

[1] Gutsche, C.D.; *Acc. Chem. Res.*, **1983**, *16*, 161

[2] Gutsche, C.D.; Muthukrishnan, R; *J. Org. Chem.*, **1978**, 4905

[3] Zinke, A.; Zigeuner, G.; Hössinger, K.; Hoffmann, G.; *Monatsh. Chem.*, **1948**, *79*, 438

[4] Gutsche, C.D.; *Calixarenes*, Monographs in Supramolecular Chemistry, Stoddart, J.F.; Ed., Royal Society of Chemistry, Cambridge, **1989**

[5] Arnaud-Neu, F.; Schwing Weill, M.J.; *Synthetic Metals*, **1997**, *90*, 157

[6] Perrin, M.; Ehlinger, N.; Viola-Motta, L.; Lecocq, S.; Dumazet, I.; Bouoit-Montesinos, S.; Lamartine, R.; *J. Incl Phenom.*, **2001**, *39*, 273

[7] Gutsche, C.D.; Dhawan, B.; Levine, J.A.; No, K.H.; Bauer, L.J.; *Tetrahedron*, **1983**, *39*, 409

[8] Gutsche, C.D.; Bauer, L.J.; *Tet. Lett.*, **1981**, 4763

[9] Harrowfield, J.M.; Ogden, M.I.; Richmond, W.R.; White, A.H.; *J. Chem. Soc., Chem. Commun.*, **1991**, 1159

[10] Schazmann,B.; *Ph.D. Thesis*, **2006**, Dublin City University

[11] Zinke, A.; Kretz, R.; Leggewie, E.; Hössinger, K.; *Monatsh. Chem.*, **1952**, *83*, 1213

[12] Zinke, A.; Ott, R.; Garrana, F.H.; *Monatsh. Chem.*, **1958**, *89*, 135

[13] Gutsche, C.D.; Dhawan, B.; No, K.H.; Muthukrishnan, R.; *J. Am. Chem. Soc.*, **1981**, *103*, 3782

[14] Patrick, T.B.; Egan, P.A.; *J. Org. Chem.*, **1977**, *42*, 2, 382

[15] Stewart, D.R.; Gutsche, C.D.; *J. Am. Chem. Soc.*, **1999**, *121*, 4136

[16] Ludwig, F.J.; Bailie, A.G.; *Anal. Chem.*, **1986**, *58*, 2069

[17] Gutsche, C.D.; *Calixarenes Revisited.* Monographs in Supramolecular Chemistry, Stoddart, J.F.; Ed., Royal Society of Chemistry, London, **1998**

[18] Metzger, O.; *Angew. Chem., Int. Ed. Engl.*, **1998**, *37*, 2975

[19] Makha, M.; Raston, C.L.; Skelton, B.W.; White, A.H.; *Green Chem.*, **2004**, *6*, 158

[20] Arnaud-Neu, F.; Collins, E.M.; Deasy, M.; Ferguson, G.; Harris, S.J.; Kaitner, B.; Lough, A.J.; McKervey, M.A.; Marques, E.; Ruhl, B.L.; Schwing-Weill, M.J.; Seward, E.M.; *J. Am. Chem. Soc.*, **1989**, *111*, 8681

[21] Barrett, G.; McKervey, M.A.; Malone, J.F.; Walker, A.; Arnaud-Neu, F.; Guerro, L.; Schwing-Weill, M.J.; Gutsche, C.D.; Stewart, D.R.; *J. Chem. Soc. Perkin Trans. 2*, **1993**, 1475

[22] Koshets, I.A.; Kazantseva, Z.I ; Shirshov, Yu. M ; Cherenok, S.A.; Kalchenko, V.I.; *Sensors and Actuators B*, **2005**, *106*, 177

[23] Arnaud-Neu, F.; Barrett, G.; Cremin, S.; Deasy, M.; Ferguson, G.; Harris, S.J.; Lough, A.J.; Guerra, L.; McKervey, M.A.; Schwing-Weill, M.J.; Schwinte, P.; *J. Chem. Soc. Perkin Trans. 2*, **1992**, 1119

[24] Izatt, S.R.; Hawkins, R.T.; Christensen, J.J.; Izatt, R.M.; *J. Am. Chem. Soc.*, **1985**, *107*, 63

[25] Chang, S.K.; Kwon, S.K.; Cho, I.; *Chem. Lett.*, **1987**, 947

[26] Arnaud-Neu, F.; Barrett, G.; Harris, S.J.; Owens, M.; McKervey, M.A.; Schwing-Weill, M.J.; Schwinté, P.; *Inorg. Chem* , **1993**, *32*, 2644

[27] Barakat, N.; Burgard, M.; Asfari,Z.; Vicens, J.; Montavon, G.; Duplâtre, G.; *Polyhedron*, **1998**, *17*, 3649

[28] Arnaud-Neu, F.; Boehmer, V.; Dozol, J.F.; Gruttner, C.; Jakobi, R.A.; Craft, D.; Mauprivez, O.; Rouquette, H.; Schwing-Weill, M.J.; Simon, N.; Vogt, W.; *J. Chem. Soc. Perkin Trans. 2*, **1996**, 1175

[29] Malone, J.F.; Marrs, D.; McKervey, M.A.; O'Hagan, P.; Thomson, N.; Walker, A.; Arnaud-Neu, F.; Mauprivez, O.; Schwing-Weill, M.J.; Dozol, J.F.; Rouquette, H.; Simon, N.; *J. Chem. Soc., Chem. Commun* , **1995**, 2151

[30] Arnaud-Neu, F.; Fanni, S.; Guerra, L.; McGregor, W.; Ziat, K.; Schwing-Weill, M.J.; Barrett, G.; Marrs, D.; Seward, E.M.; McKervey, M.A.; *J. Chem. Soc., Perkin Trans , 2,* **1995**, 113

[31] Arduini, A.; Pochini, A.; Riverberi, S.; Ungaro, R.; Andreetti, C.D.; Ugozzoli, F.; *Tetrahedron*, **1986**, *42*, 2089

[32] Alfieri, C.; Dradi, E.; Pochini, A.; Ungaro, R.; Andreeti, G.D.; *J. Chem. Soc., Chem. Commun.*, **1983**, 1075

[33] Dijkstra, P.J.; Brunink, J.A.; Bugge, K.E.; Reinhoudt, D.N.; Harkema, S.; Ungaro, R.; Ugozzoli, F.; Ghidini, E.; *J. Am. Chem. Soc.*, **1989**, 7567

[34] Ghidini, E.; Ugozzoli, F.; Ungaro, R.; Harkema, S.; El-Fadi, A.A.; Reinhoudt, D.N.; *J. Am. Chem. Soc.*, **1990**, *112*, 6979

[35] Baeyer, A.; *Ber. Dtsch. Chem. Ges.*, **1886**, *19*, 2184

[36] Gale, P.A.; Sessler, J.L.; Král, V.; *J. Chem. Soc. Chem. Commun.*, **1998**, 1

[37] Gale, P.A.; Anzenbacher Jr., P.; Sessler, J.L.; *Coord. Chem. Rev.*, **2001**, *222*, 57

[38] Gale, P.A.; Sessler, J.L.; Král, V.; Lynch, V.; *J. Am. Chem. Soc.*, **1996**, *118*, 5140

[39] Beer, P.D.; Drew, M.G.B.; Gale, P.A.; Leeson, P.B.; Ogden, M.I.; *J. Chem. Soc. Dalton Trans.*, **1994**, 3479

[40] Allen, W.E.; Gale, P.A.; Brown, C.T.; Lynch, V.M.; Sessler, J.L.; *J. Am. Chem. Soc.*, **1996**, *118*, 12471

[41] Golder, A.J.; Milgrom, R.L.; Nolan, K.B.; Povey, D.C.; *J. Chem. Soc. Chem. Commun.*, **1989**, 1751

[42] Floriani, C.; *J. Chem. Soc. Chem. Commun.*, **1996**, 1257

[43] Jackoby, D.; Floriani, C.; Chiesi-Villa, A.; Rizzoli, A.; *J. Chem. Soc. Chem. Commun.*, **1991**, 220

[44] von Maltzan, B.; *Angew. Chem. Int. Ed. Engl.*, 21, **1982**, *10*, 785.

[45] Gale, P.A.; Sessler, J.L.; Allen, W.E.; Tvermoes, N.A.; Lynch,V.; *J. Chem. Soc. Chem. Commun*, **1997**, 665

[46] Sessler, J.L.; Andrievsky, A.; Gale, P.A.; Lynch, V.; *Angew. Chem. Int. Ed. Engl.*, **1996**, *35*, 2782

[47] Anzenbacher Jr., P.; Jursiková, K.; Sessler, J.L.; *J. Am. Chem. Soc.*, **2000**, *122*, 9350

[48] Furusho, Y.; Kawasaki, H.; Nakanishi, S.; Aida, T.; Takata, T.; *Tetrahedron Lett.*, **1998**, *39*, 3537

[49] Baeyer, A.; *Ber. Dtsch. Chem. Ges.*, **1872**, *5*, 25

[50] Michael, A.; *Am. Chem. J.*, **1883**, *5*, 338

[51] Timmerman, P.; Verboom, W.; Reinhoudt, D.N.; *Tetrahedron*, **1996**, *52*, 2663

[52] Niederl, J.B.; Vogel, H.J.; *J. Am Chem. Soc.*, **1940**, *62*, 2512

[53] Erdtman, H.; Högberg, S.; Abrahamsson, S.; Nilsson, B.; *Tetrahedron Lett.*, **1968**, 1697

[54] Cram, D.J.; Karbach, S., Kim, H-E.; Knobler, C.B.; Maverick, E.F.; Ericson, J.L.; Helgeson, R.C.; *J. Am. Chem. Soc.*, **1988**, *110*, 2229

[55] Egberink, R.J.M.; Cobben, P.L.H.M.; Verboom, W.; Harkema, S.; Reinhoudt, D.N.; *J. Inclusion Phenom.*, **1992**, *12*, 151

[56] Pieroni, O.I.; Rodriguez, N.M.; Vuano, B.M.; Cabaleiro, M.C.; *J. Chem. Research*, **1994**, 188

[57] Ma, B.; Zhang, Y.; Coppens, P.; *Cryst. Growth Des.*, *0*, 1 http://harker.chem.buffalo.edu/group/publication/CEC2.pdf *October 2006*

[58] Mäkinen, M.; Jalkanen, J-P.; Vainiotalo, P.; *Tetrahedron*, **2002**, *58*, 8591

[59] Ma, B-Q.; Coppens, P.; *Chem. Commun.*, **2002**, 424

[60] Avram, L.; Cohen, Y.; *Org. Lett.*, **2002**, *4*, 24, 4365

[61] Avram,L.; Cohen, Y.; *Org. Lett.*, **2003**, *5*, 18, 3329

[62] Avram, L.; Cohen, Y.; *J. Am. Chem. Soc.*, **2004**, *126*, 11556

[63] MacGillivray, M.R.; Atwood, J.L.; *Nature*, **1997**, *389*, 469

[64] http://users.adelphia.net/~eswab/Archimedean.html *September 2006*

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

[66] Thoden van Velzen, E.U.; Engbersen, J.F.J.; Reinhoudt, D.N.; *J. Am. Chem. Soc.*, **1994**, *116*, 3597

[67] Weinelt, F.; Schneider, H-J.; *J Org Chem.*, **1991**, 56, 5527

[68] Högberg, A.G.S.; *J. Org. Chem.*, **1980**, *45*, 4498

[69] Högberg, A.G.S.; *J. Am. Chem. Soc.*, **1980**, *102*, 6046

[70] Botta, B.; Iacomacci, P.; DiGiovanni, C.; DelleMonache, G.; Gacs-Baitz, E.; Botta, M.; Tafi, A.; Corelli, F.; Misiti, D.; *J. Org. Chem.*, **1992**, *57*, 3259

[71] Falana, O.M.; Al-Farhan, E ; Keehn, P.M.; Stevenson, R.; *Tetrahedron Lett.*, **1994**, *35*, 65

[72] Roberts, B.A.; Cave, G.W.V.; Raston, C.L.; Scott, J.L.; *Green Chem.*, **2001**, *3*, 280

[73] Rothenberg, G.; Downie, A.P.; Raston, C.L.; Scott, J.L.; *J. Am. Chem Soc.*, **2001**, *123*, 8701

[74] Schneider, H-J.; Güttes, D.; Schneider, U.; *J. Am. Chem. Soc.*, **1988**, *110*, 6449

[75] Mäkinen, M.; Vainiotalo, P.; Nissinen, M.; Rissanen, K.; *J. Am. Soc. Mass Spectrom.*, **2003**, *14*, 143

[76] Saenger, W.; Bertzel, C.; Hingerty, B.; Brown, G.M.; *Angew. Chem. Intl. Ed. Engl.*, **1983**, *22*, 883

[77] Shivanyuk, A.; Rissanen, K.; Kolehmainen, E.; *Chem. Commun* , **2000**, 1107

[78] Koide, Y.; Oka, T.; Imamura, A.; Shosenje, H.; Yamada, K.; *Bull. Chem. Soc. Jpn.*, **1993**, *66*, 2137

[79] Gerkensmeier, T.; Iwanek, W.; Agena, C.; Fröhlich, R.; Kotila, S.; Näther, C.; Mattay, J.; *Eur. J. Org. Chem.*, **1999**, 2257

[80] Atwood, J.L.; Barbour, L.J.; Jerga, A.; *Proc. Natl. Acad. Sci.USA*, **2002**, *99*, 4837

[81] Atwood, J.L.; Barbour, L.J.; Jerga, A.; *Chem Commun.*, **2001**, 2376

[82] Yamanaka, M.; Shivanyuk, A.; Rebek, J.; *J. Am. Chem. Soc.*, **2004**, *126*, 2939

[83] Atwood, J.L.; Barbour, L.J.; Jerga, A.; *J. Supramol. Chem.*, **2001**, *1*, 131

[84] Shivanyuk, A.; Friese, J.C.; Doring, S.; Rebek, J.; *J. Org. Chem.*, **2003**, *68*, 6489

[85] Shivanyuk, A.; Rebek, J.; *Chem. Commun.*, **2001**, 2374

[86] McKinlay, R.M.; Cave, G.W.V.; Atwood, J.L.; *Proc. Natl. Acad. Sci.USA*, **2005**, *102*, 5944

[87] McKinlay, R.M.; Thallapally, P.K.; Atwood, J.L.; *Chem. Commun.*, **2006**, 2956

[88] McKinlay, R.M.; Thallapally, P.K.; Cave, G.W.V.; Atwood, J.L.; *Angew. Chem. Int. Ed.*, **2005**, *44*, 5733

[89] Antesberger, J.; Cave, G.W.V.; Ferrarell, M.C.; Heaven, M.W.; Raston, C.L.; Atwood, J.L.; *Chem. Commun.*, **2005**, 892

[90] Letzel, M.C.; Agena, C.; Mattay, J.; *J Mass Spectrom.*, **2002**, *37*, 63

[91] Iwanek, W.; Urbaniak, M.; Bocheńska, M.; *Tetrahedron*, **2002**, *58*, 2239

[92] Carey, S.J.; *Ph.D. Thesis*, **2006**, Dublin City University

[93] Busch, D.H.; *J. Inclusion Phenom. Mol. Recognit. Chem.*, **1992**, *12*, 389

[94] Chapman, R.G.; Sherman, J.C.; *Tetrahedron*, **1997**, *53*, 15911

[95] Beer, P.D.; Gale, P.A.; Smith, D.K.; *Supramolecular Chemistry*, Oxford University Press, **1999**

[96] O'Malley, S.; *Ph.D. Thesis*, **2006**, Dublin City University

[97] Microwave Synthesis (URL: http://www.organic-chemistry.org/topics/microwave-synthesis.shtm) *January 2007*

[98] Buckley, B.R.; Page, P.C.; Heaney, H.; Sampler, E.P.; Carley, S.; Brocke, C.; Brimble, M.A.; Tetrahedron, **2005**, *61*, 5876

[99] Buckley, B.R.; Boxhall, Y.J.; Page, P.C.B.; Chan, Y.; Elsegood, M.R.J.; Heaney, H.; Holmes, K.E.; McIldowie, M.J.; McKee, V.; McGrath, M.J.; Mocerino, M.; Poulton, A.M.; Sampler, E.P.; Skelton, B.W.; White, A.H.; *Eur. J. Org. Chem.* **2006**, 5117

[100] Buckley, B.R.; Page, P.C.B; Chan, Y.; Heaney, H.; Klaes, M.; McIldowie, M.J.; McKee, V; Mattay, J.; Mocerino, M.; Moreno, E.; Skelton, B.W.; White, A.H. *Eur J. Org. Chem.* **2006**, 5135

[101] Schazmann, B.; O'Malley, S.; Nolan, K.; Diamond, D.; *Supramolecular Chemistry*, **2006**, *18*, 515

[102] Gürol, I.; Ahsen, V.; *J. Porphyrins Phthalocyanines*, **2000**, *4*, 621

[103] http://www.powerlabs.org/chemlabs/potassium_picrate.htm *January 2007*

[104] O'Connor, K.M.; Arrigan, D.W.M.; Svehla, G.; *Electroanalysis*, **1995**, *7*, 205

[105] Cadogan, A.M.; Diamond, D.; Smyth, M.R.; Deasy, M.; McKervey, M.A.; Harris, S.J.; *Analyst*, **1989**, *114*, 1551

[106] Khlobystov, A.N.; Blake, A.J.; Champness, N.R.; Lemenovskii, D.A.; Majouga, A.G.; Zyk, N.V.; Schröder, M.; *Coord. Chem. Rev.*, **2001**, *222*, 155

[107] Williams, S.M.; Brodbelt, J.S.; Huang,V; Lai, H.; Marchand, A.P.; *Analyst*, **2003**, *128*, 1352

[107a] O'Malley, S.; Alahashimy, N.; O'Mahony, J.; Kieran, A.; Pryce, M.; Nolan, K.; *Tetrahedron Lett.*, *48*, **2007**, 681

[108] Pedersen, C.J.; *J. Am. Chem. Soc.*, 89, 26, **1967**, 7017

[109] Kryatova, O.P.; Kolchinski, A.G.; Rybak-Akimova, E.V.; *Tetrahedron*, 59, **2003**, 231

[110] Ungaro,R.; El Haj, B.; Smid, J.; *J. Am. Chem. Soc.*, **1976**, 5198

[111] Chan, L.; Smid, J.; *J. Am. Chem. Soc.*, **1968**, *90*, 4654