Synthetic Routes to *Bis*-Calix[*n*]arenes

A thesis presented in partial fulfilment of the requirements for the degree of

Masterate of Science in Chemistry

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In memory of Faye Kerr

ABSTRACT

The literature procedures for the targeted syntheses of *p-tert*-butylcalix[4]arene, *p-tert*-butylcalix[5]arene, *p-tert*-butylcalix[6]arene, *p-tert*-butylcalix[7]arene, and *p-tert*-butylcalix[8]arene have been repeated successfully. In the case of *p-tert*-butylcalix[4]arene, alterations led to a less capricious procedure, synthesis of the pure product directly and in higher yield. The residual xylene and toluene solutions from the targeted *p-tert*-butylcalix[8]arene preparation were utilised to obtain workable quantities of the rare calix[5]- and calix[7]arenes, a protocol that is far simpler and less time-consuming than the low-yielding targeted synthesis of these compounds.
Dealkylation of *p-tert*-butylcalix[*n*]arenes is best accomplished at 30°C in 0.16-0.05 $molL^{-1}$ toluene solution. The insolubility of calix[8]arene in all common organic solvents is expected to limit its synthetic use.

Two new protocols have been devised for the highly selective mono-*O*-alkylation of calixarenes 4 through 8. This work represents the realisation of the first selective functionalisation methods that are applicable to the calixarene *family*, and also the first selective functionalisation of a calix[7]arene. These findings will lead to more efficient synthesis of multiple calixarenes (*cf.* **Chapter 3**) and may allow for a better understanding of the reasons for selectivity in calixarene-*O*-alkylations.

We have been able to synthesise a variety of *bis*-calixarenes by two different routes. Glaser-Hay coupling allowed the synthesis of symmetrical diyne bridged *bis*-calix[4, 6 and 8]arenes in high yield.
Extension of the first *general* mono-*O*-alkylation procedure for calixarenes has made it possible to synthesise homo-*bis*-calixarenes in good yield in *one step* from the parent calixarenes.
The unexpected formation of monobromoxylyl calixarenes allows the prospect of the synthesis of *hetero-bis*-calixarenes under more forcing conditions. Most importantly this allows us to further explore the chemistry of *bis*-calixarenes by making them readily available (in large quantities) for more elaborate syntheses.

ACKNOWLEDGEMENTS

I would foremost like to thank my supervisor Dr. Mick Sherburn for his patience and help over the last two years. Without his help I may never have finished (or started).

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To my Grandparents both, I hope that this is what you would have liked though you cannot all be here. For your patience and humour thank you to Charlotte for being a good friend and cohort.

To all those people who I have not mentioned here, but have made my life easier over this time, thank you (this is for my flatmates both past and present, and the rest of those interesting people who are "out there").

Last, but not least I would like to thank my parents for giving me the opportunity to be here and for your support (albeit long distance).

ABBREVIATIONS

Bn	benzyl
Bz	benzoyl
DMF	dimethylformamide
FAB	fast atom bombardment
HRMS	high resolution mass spectroscopy
Hz	Hertz
i.r.	infra red spectroscopy
n.m.r.	nuclear magnetic resonance
ppm	parts per million
py	pyridine
THF	tetrahydrofuran
t.l.c.	thin layer chromatography
w.r.t.	with respect to

NOMENCLATURE

In the main body of text trivial names have been used to refer to the various calixarenes. In the experimental section the systematic naming as introduced by Gutsche[1] has been followed. Shown below is the *Chemical Abstracts* nomenclature for calixarenes.

calix[4]arene Pentacyclo[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.
CAS [281-54-9]

calix[5]arene Hexacyclo[25.3.1.1^{3,7}.1^{9,13}.1^{15,19}.1^{21,25}]pentatriaconta-1(31),3,5,≈7(35),9,11,13(34),15,17,19(33),21,23,25(32)27,29-pentadecaene.
CAS [82040-64-0]

calix[6]arene Heptacyclo[31.3.1.1^{3,7}.1^{9,13}.1^{15,19}.1^{21,25}.1^{27,31}]dotetraconta-1≈(37),3,5,7(42),9,11,13(41),15,17,19(40),21,23,25(39),27,29,31(38),33,35-octadecaene.
CAS [96627-08-6]

calix[7]arene Octacyclo[37.3.1.1^{3,7}.1^{9,13}.1^{15,19}.1^{21,25}.1^{27,31}.1^{33,37}]nonatetraco≈nta-1(43),3,5,7(49),9,11,13(48),15,17,19(47),21,23,25(46),27,29,3(45),33,35,37(44)39,≈41-heneicosaene.
CAS [96356-47-7]

calix[8]arene Hexacyclo[43.3.1.1^{3,7}.1^{9,13}.1^{15,19}.1^{21,25}.1^{27,31}.1^{33,37}.1^{39,43}]hexa≈pentaconta-1(49),3,5,7(56),9,11,13(55),15,17,19(54),21,23,25(53),27,29,31(52),33,35,≈37(51),39,41,43(50),45,47-tetracosaene.
CAS [82040-66-2]

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Chapter 1

STARTING MATERIALS

1.1 INTRODUCTION

Calix[n]arenes are a group of 1_n-metacyclophanes consisting of n phenol subunits linked by CH_2 groups. The term calixarene was introduced by Gutsche[1] and is derived from the word *calix*, the Greek for "vase" that relates to the distinct shape of the cyclic tetramer (**Figure 1.1**).

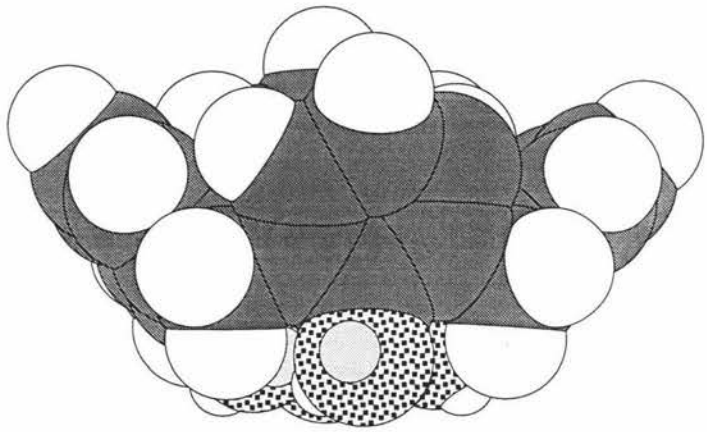

Figure 1.1. Chem3D™ representation of a space filling model of calix[4]arene.

1.2 HISTORY†

Unknowingly, calixarenes were probably first synthesised in the mid to late 1800's. The early experiments of Aldolf Bayer in the 1870s involved condensing phenol and formaldehyde in the presence of a strong mineral acid. The products that he isolated were intractable mixtures and impossible to characterise. Almost 20 years later a similar condensation reaction, this time base catalysed, was studied by Lederer and Manasse. Under relatively mild reaction conditions they were able to isolate and characterise *o*-hydroxymethylphenol and *p*-hydroxymethylphenol. Under more forcing conditions they isolated a material that could not be characterised.

By the 1940s, many people were working in the area of phenol-formaldehyde chemistry. One of the most notable was Leo Baekeland who made a significant

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† For a more extensive treatment, see Chapter 1 of the book by C. D. Gutsche[1] and references cited therein.

contribution to this field by producing the phenol-formaldehyde condensate, Bakelite, the first synthetic plastic. At the time, little was known about the polymer forming (or curing) process. Some 20 years following the patenting of Bakelite, Zinke began studying the "curing" process. The most common polymers were phenol-based and had a structure proposed as shown in **Figure 1.2**.

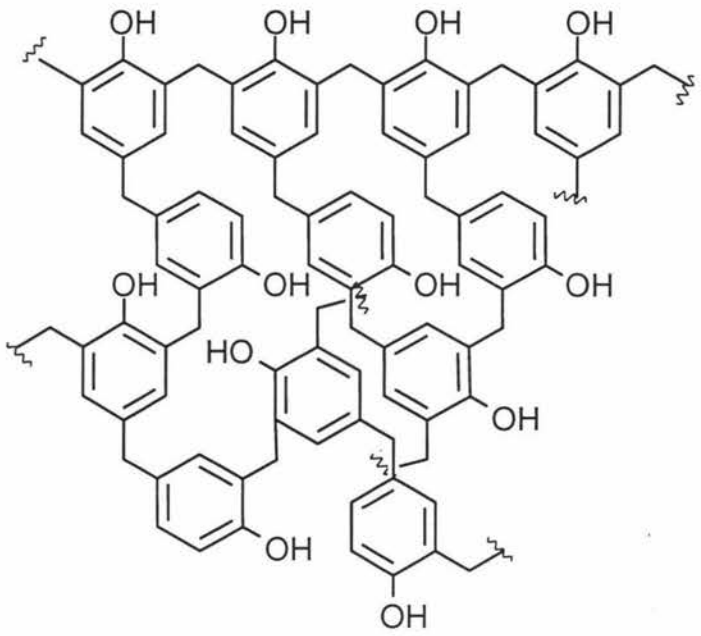


Figure 1.2. The disordered structure of a phenol-formaldehyde polymer as proposed by Zinke.

Zinke sought to simplify the problem of the polymer expanding *via* connection to three neighbouring phenols (**Figure 1.2**) by blocking the *para*-position of the phenol. The idea behind this strategy was that condensation could only occur at the two free *ortho*-positions, thus linear oligomers (**Figure 1.3**) should be formed.

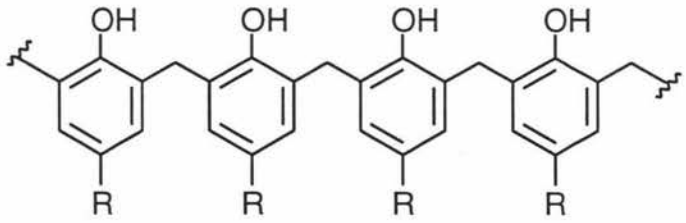


Figure 1.3. A polymer formed from the condensation of a *p*-alkylphenols and formaldehyde.

In the specific case of *p-tert*-butylphenol, Zinke found that upon heating in the presence of a base (such as NaOH), a crystalline material was isolated melting at >300°C with an

empirical formula of $C_{11}H_{14}O$ could be isolated. Several years later he proposed the cyclic structure depicted below (**Figure 1.4**).

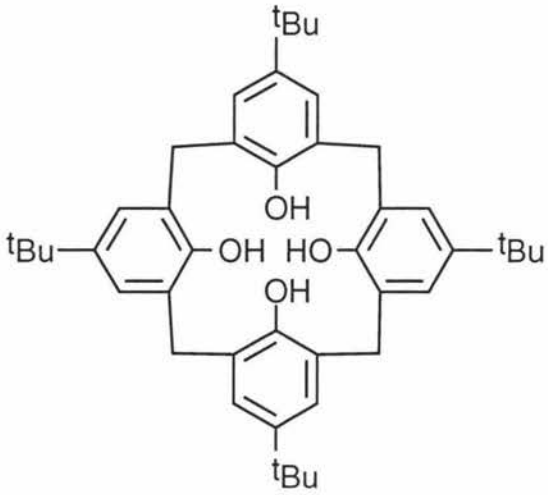


Figure 1.4. The cyclic structure of a condensate from the work of Zinke.

Chemists working for the Petrolite company in the 1950s were utilising phenol-formaldehyde resins as oil demulsifiers. The resins, sold in a mixture of aromatic hydrocarbons, had a drawback in that they precipitated from solution upon application. In an effort to solve the problem, these workers discovered that cyclic products (like those proposed by Zinke) made up the precipitate. Over 25 years the Petrolite workers filed a number of patents and by 1977 the Petrolite Procedure for the preparation of calixarenes had been born. The structure of the cyclic tetramer (**Figure 1.4**) was proven unequivocally by the first single crystal x-ray analysis in 1979.[2] The past 20 years have seen an almost exponential growth in the number of papers published on calixarenes.[3]

1.3 THE SIMPLE CALIXARENE SKELETON

1.3.1 Introduction

To date there has been more work published on the chemistry of *p-tert*-butylcalix[4]arene than any other calixarene. Recently, *p-tert*-butylcalix[6]arene and *p-tert*-butylcalix[8]arene have been the subject of increasing synthetic interest. This is thought to be due primarily to the availability of these three starting materials, since good published targeted[#] procedures (operationally simple, 50-90% yields) are

[#] A "targeted" procedure is the term used to describe a calixarene preparation which is tailored toward a cyclic oligomer.

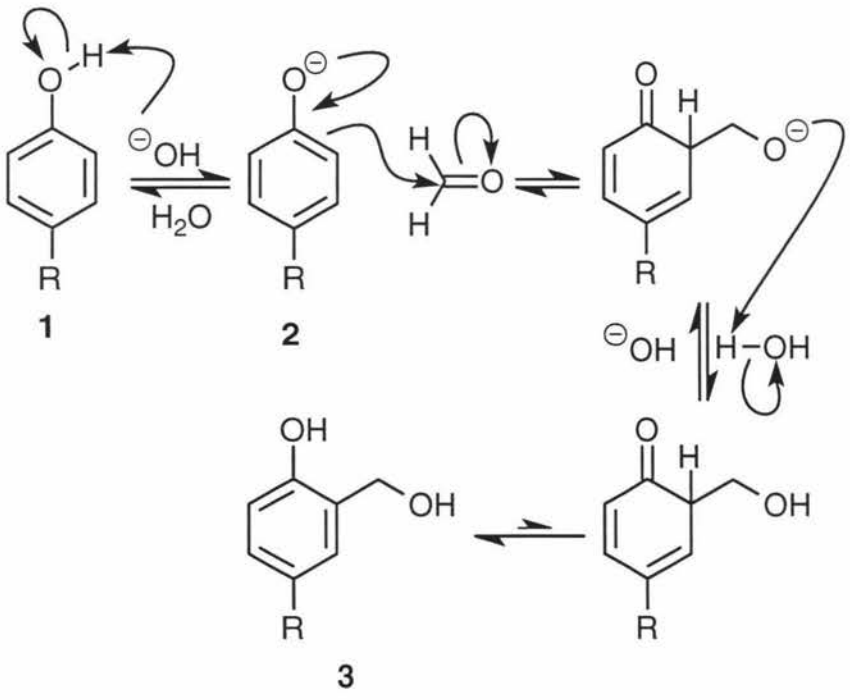
available.[4-6] We have been able to repeat these procedures, modify and improve one of them, and also isolate useful quantities of the less common odd numbered calixarenes (*p-tert*-butylcalix[5]arene and *p-tert*-butylcalix[7]arene) by working with the residues from the published procedures for the hexamer and octamer (see **Section 1.6**).

Some work has been carried out on the *targeted synthesis* of the odd numbered calixarenes, *p-tert*-butylcalix[5]arene and *p-tert*-butylcalix[7]arene, however, in our hands, these procedures were found to be very laborious and low yielding (10-16%[7,8] and 17% yield,[9] respectively). The paucity of synthetic work on calix[5]- and calix[7]arenes is undoubtedly a reflection of their unavailability in large quantities by a manageable procedure.

Multistep synthetic routes to calixarenes have also been devised. Thus, Böhmer has carried out *fragment condensation* reactions (*cf.* **Section 3.2.1**) on polyphenolic compounds.[3] The key condensation step generally involves the use of a Lewis acid and a *bis*(bromomethyl)polyphenol.[10]

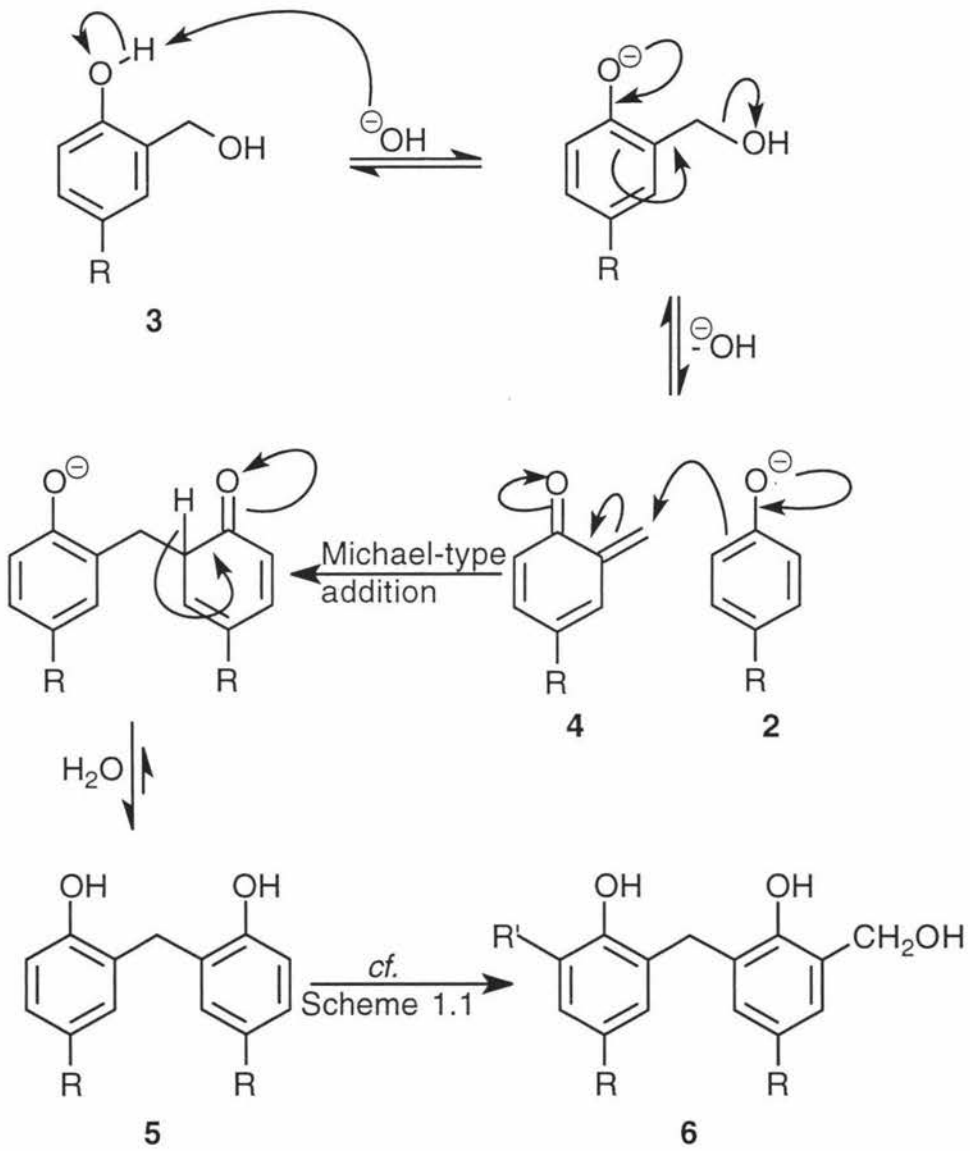
1.3.2 Mechanism of *p*-Alkylcalix[*n*]arene Formation

Synthesis of the *p*-alkylcalixarenes is always carried out by base-catalysed condensation of an appropriate *p*-alkylphenol with formaldehyde. In the first part of the process, linear oligomers are formed. The proposed mechanism (**Scheme 1.1**) involves the hydroxymethylation of the phenol by formaldehyde to give benzyl alcohol **3**.



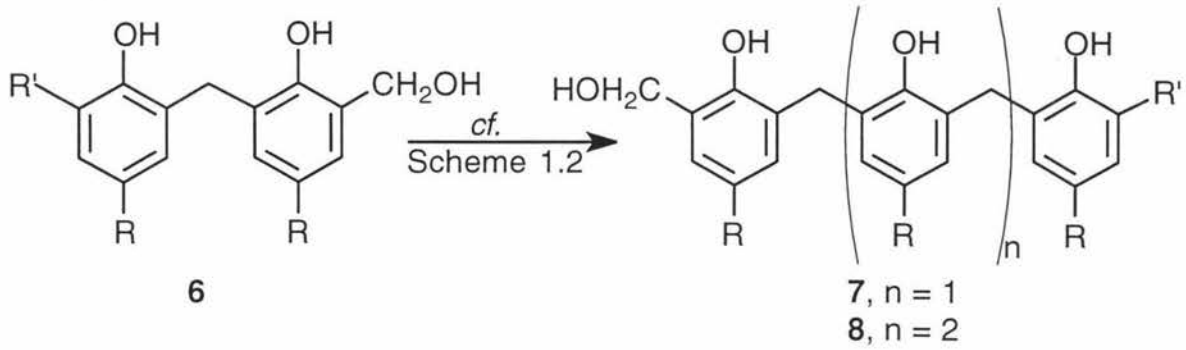
Scheme 1.1. Formation of the *p*-alkyl-*o*-(hydroxymethyl)phenol precursor.

Benzyl alcohol **3** is the acidic precursor for oligomerisation. Oligomerisation involves the condensation of **3** with the salt of the starting phenol **1** (**Scheme 1.2**). This is thought to occur *via* dehydration of benzyl alcohol **3** brought about by a catalytic quantity of hydroxide to provide trienone **4**, which suffers Michael addition with **2**.
The conversion of **5** → **6** involves repeating the same steps as previously shown for **1** → **3** (**Scheme 1.1**).



Scheme 1.2. Proposed mechanism for the dimerisation of two phenolic residues (R' = H or CH_2OH).

By condensation of a phenoxide with a Michael acceptor derived from **6**, longer linear oligomers can be formed by the same process (**Scheme 1.3**). The cyclisation of these small acyclic units results in the formation of *p*-alkylcalix[*n*]arenes. Thus, dimers of **6** will give calix[4]arenes and linear trimers, and tetramers give rise to cyclic hexamers and octamers, respectively.



Scheme 1.3. The formation of linear oligomeric calixarene precursors (R' = H or CH_2OH).

Formation of calix[5]arenes and calix[7]arenes results from the coupling of two different linear units prior to cyclisation (such as a trimer and dimer condensing to form a cyclic pentamer). Hydrogen bonding between the phenolic groups of the linear oligomers can also hold the precursors in a arrangement that assists cyclisation.
Thus, Gutsche has proposed,[11] (based on i.r. evidence) that calix[4]arenes form by one of two pathways, in which either an *intra*molecular or *inter*molecular hydrogen bonded "coil" is formed. Gutsche termed these two arrangements "*psuedo*calixarenes" and "*hemi*calixarenes", respectively (**Figure 1.5**).

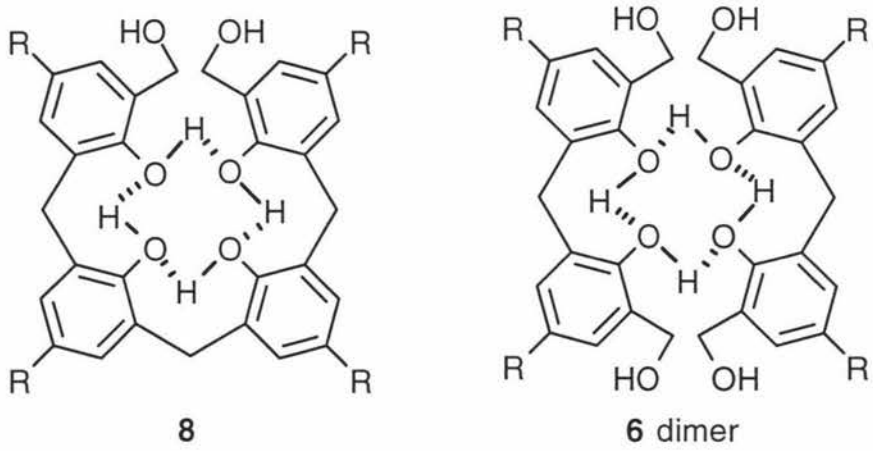
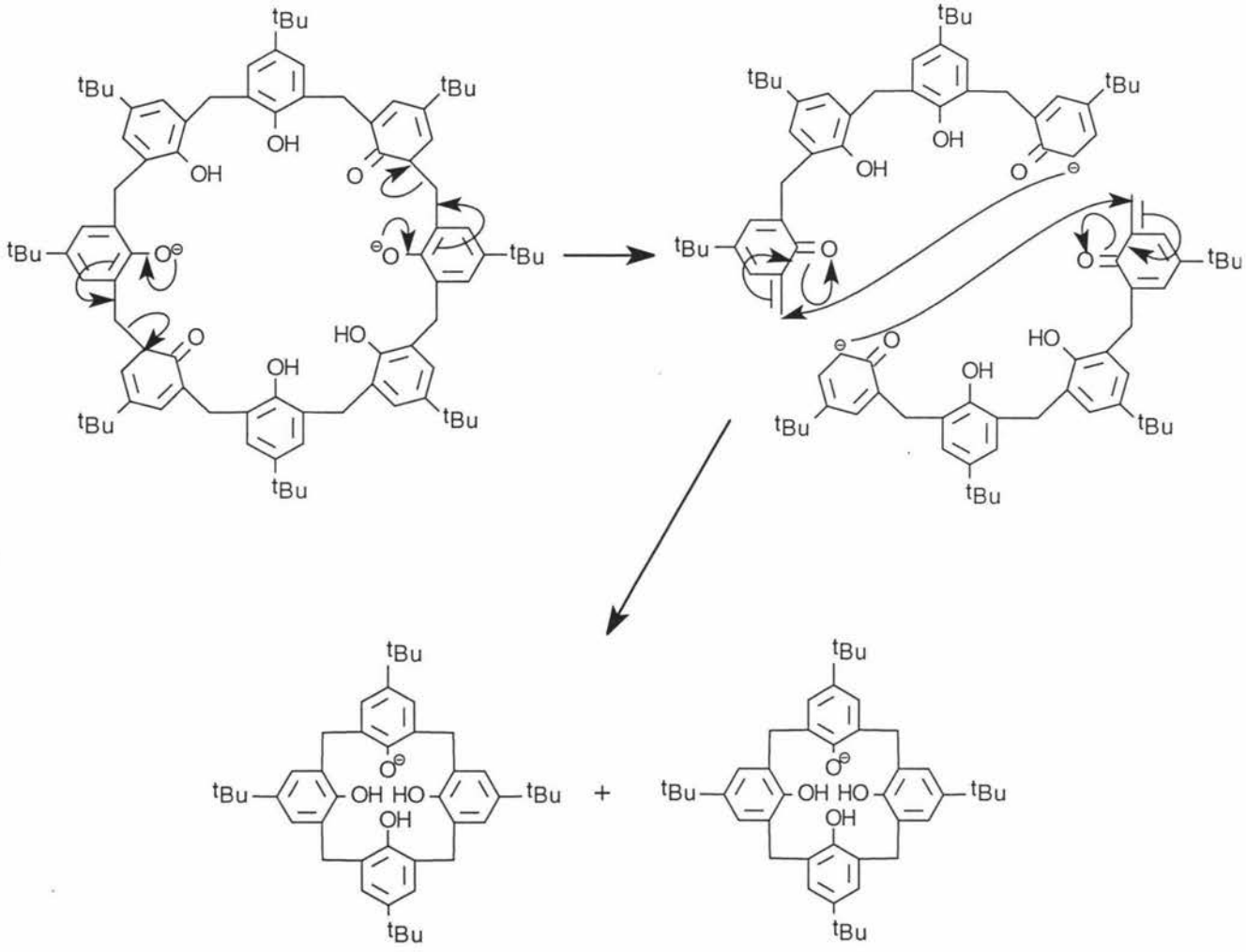


Figure 1.5. Precursors to *p-tert*-butylcalix[4]arene, the "*psuedo*calix[4]arene" conformation (**8**) and the "*hemi*calix[4]arene" arrangement (**6** dimer).

In both cases the elimination of formaldehyde and water molecules are necessary to complete the cyclisation. The *hemi*calixarene (**6** dimer) is presumably a precursor to the *psuedo*calixarene **8**, where a methylene bridge has been formed at the expense of two hydroxymethylene groups. Similar coupling and cyclisation events with dimeric, trimeric and tetrameric linear oligomers would afford calix[5, 6, 7, and 8]arenes.

The intriguing phenomenon of "molecular mitosis" has also been observed during calixarene formation.[12] This ring contraction is a base-catalysed pyrolysis of a larger calixarene to a more thermodynamically favoured, smaller macrocycle. A mechanism to explain the ring contraction is provided in **Scheme 1.4**. The yields of *p-tert*-butylcalix[4]arene from *p-tert*-butylcalix[8]arene (or *p-tert*-butylcalix[6]arene) can as high as 75%.



Scheme 1.4. The mechanism of the base catalysed "molecular mitosis" of *p-tert*-butylcalix[8]arene into two *p-tert*-butylcalix[4]arenes molecules.

One of the byproducts of calixarene preparations involves the formation of an ether linkage in place of an aromatic residue. These products are termed *dihomooxa*calix[*n*]arenes and the structure of *p-tert*-butyldihomooxacalix[4]arene is depicted in **Figure 1.6**.

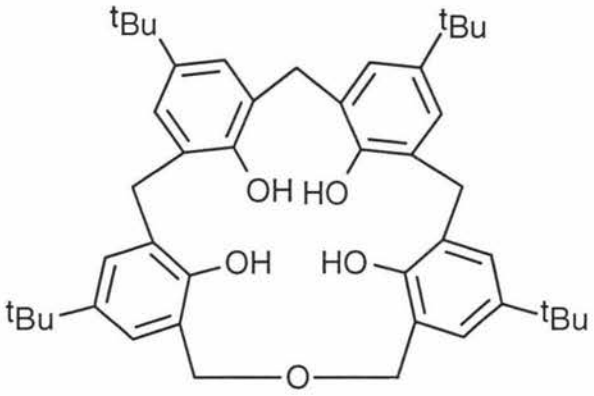


Figure 1.6. The structure of *p-tert*-butyldihomooxacalix[4]arene.

Formation of the homooxacalixarenes occurs during the pyrolysis of the *bis*(hydroxymethyl)tetramer (**Figure 1.7**) in the presence of a base.[13]

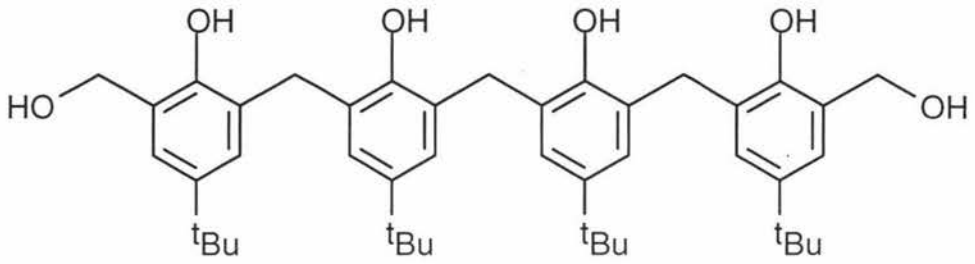


Figure 1.7. The *bis*(hydroxymethyl)tetramer precursor to *p-tert*-butyldihomooxacalix[4]arene.

The ether linkage is formed when water (but not formaldehyde) is eliminated in the pyrolysis. During targeted syntheses of *p-tert*-butylcalix[4]arene and *p-tert*-butylcalix[8]arene, a small quantity of *p-tert*-butyldihomooxacalix[4]arene is formed and this byproduct can be observed by t.l.c.[6] We have been able to isolate pure samples of dihomooxacalix[4]arene from the residues obtained in the preparation of *p-tert*-butylcalix[8]arene (see **Section 1.6**).

A recent paper[14] provided new information on the mechanism of formation of *p-tert*-butylcalix[4]arene and *p-tert*-butylcalix[8]arene. The authors found that in the synthesis of *p-tert*-butylcalix[4]arene, linear oligomers were observed in the initial pyrolysis stage before any calixarenes were formed. In the second pyrolysis stage, calixarenes formed and upon continued heating more *p-tert*-butylcalix[4]arene formed whilst quantities of other calixarenes diminished. For example, the amount of *p-tert*-butylcalix[6]arene (a maximum of 18.8%) gradually drops to a constant value of *ca.* 9%. Similarly, *p-tert*-butylcalix[8]arene is formed (a maximum of *ca.* 13%) and slowly disappears (to a constant 3.5%); a result that was put forward as further evidence for the "molecular mitosis" phenomenon.

During the synthesis of *p-tert*-butylcalix[8]arene, *p-tert*-butyldihomooxacalix[4]arene was formed initially in yields of 36%, decreasing to 2.5%. The authors conclude that dihomooxacalix[4]arene must be undergoing a ring *expansion* to form the cyclic octamer as the quantity of *p-tert*-butylcalix[4]arene does not increase significantly (from *ca.* 5%). There were no linear octamers observed in this experiment, only linear tetramers, pentamers and hexamers. Therefore, the formation of *p-tert*-butylcalix[8]arene proceeds *via* the *hemi*calixarene route where two linear tetramers come together.

In both experiments a trace of the *bis*(hydroxymethyl)hexamer was observed. This could support the notion that *p-tert*-butylcalix[6]arene is cyclised by a *psuedo*calixarene route, although further evidence is necessary before a definite conclusion can be made. Pyrolysis of *p-tert*-butyldihomooxacalix[4]arene produces *p-tert*-butylcalix[4]arene by elimination of formaldehyde.[1]

1.3.3 Factors in Calix[*n*]arene Formation

The main contributing factors that influence the outcome of phenol-formaldehyde condensation reactions are the time and severity of the heating period, the nature and quantity of the base and the nature of the starting phenol.[15]

1.3.3.1 Base

Synthesis of the cyclic hexamer is best performed with more base (34 mol% w.r.t. phenol) than for the cyclic octamer (3 mol% w.r.t. phenol). The targeted synthesis of the cyclic tetramer requires almost identical base quantity and type to the cyclic octamer, but the heating is more intense. The nature of the alkali metal hydroxide also affects the outcome, presumably due to (*cf.* crown ether chemistry[16]) template effects with the alkali metal cation. When using *p-tert*-butylphenol, LiOH furnishes only low yields of cyclic octamer (*ca.* 25%[15] yield) along with trace amounts of the other cyclic oligomers. The use of NaOH is most effective for the synthesis of the cyclic octamer (62-65% yield), but KOH is best for the cyclic hexamer (83-88% yield). The use of larger alkali metal cations (RbOH or CsOH) tends to favour the formation of the cyclic octamer and hexamer, but yields are not as high as those obtained with KOH.[12]

1.3.3.2 Starting Phenol

Calixarene formation has been trialed with many different *p*-alkyl and *p*-aryl phenols.[3] The most commonly used starting material is *p-tert*-butylphenol due mainly to its low cost (see **Table 1.1**) and availability.

p-Substituent, R	Cost (US cents/g)
Methyl	2.3
Ethyl	5.2
i-Propyl	10.3
t-Butyl	0.9
t-Pentyl	9.5
t-Octyl	2.5
Phenyl	5.0
Benzyl	206.4
Adamantyl	3155

Table 1.1. Relative costs of starting phenols for calixarene formation (based on price/g for the largest unit from 1996-7 Aldrich catalogue).

The *p*-substituent of the starting phenol has a dramatic effect on product distribution, with the steric requirements of the group leading to the formation of different size macrocycles. For example, *p*-phenylcalix[4]arene is not detected in a one-step Petrolite-type procedure from *p*-phenylphenol, instead the cyclic hexamer (10%), heptamer (trace), octamer (14%) and dihomooxacalixarene (trace) were produced. The yield of *p*-phenylcalix[7]arene from *p*-phenylphenol has since been improved to 41%[3] by modifying the reaction conditions.

As mentioned previously, the "rarest" in the series are the odd-numbered members, *p*-alkylcalix[5]arene and *p*-alkylcalix[7]arene. The *p-tert*-butyl derivatives have been isolated in yields of only 10-16% from targeted procedures. Of the other *p*-alkylcalix[7]arenes that have been synthesised, the most notable is *p*-adamantylcalix[7]arene which has been prepared by a targeted synthesis in 71% isolated yield.[3]

1.3.3.3 Temperature (Solvent)

As already mentioned, in basic media each of the calixarenes has a different thermal stability. For example, the synthesis of *p-tert*-butylcalix[4]arene is carried out at high temperature (*ca.* 260°C), but for the larger *p-tert*-butylcalix[6]- and *p-tert*-butylcalix[8]arenes the temperature is lower (*ca.* 140°C). In a study on the mechanism *p-tert*-butylcalix[4]arene formation it was found that a significant amount of *p-tert*-butylcalix[8]arene is formed before any calix[4]arene can be detected.[12] This would tend to indicate that the formation of *p-tert*-butylcalix[4]arene proceeds *via* a molecular mitosis mechanism (*vide supra*).

1.4 CALIX[*n*]ARENES

Since the condensation of phenol with formaldehyde leads to polymers and not cyclic structures, the direct synthesis of *p*-H calixarenes is impossible. Synthesis of upper rim‡ functionalised calixarenes must therefore be carried out *via* removal of the *p*-alkyl substituent, after formation of the macrocycle.

The great utility of *p-tert*-butylphenol is that the alkyl group can be easily removed from the upper rim. In the presence of $AlCl_3$[17] the *tert*-butyl groups are transferred to another aromatic molecule using a Friedel-Crafts transalkylation process. Initially,[18] this procedure was carried out in toluene, but it was later found that when a more electron rich aromatic compound (phenol) was present, the rate of reaction was enhanced. *p-tert*-Butylcalixarene dealkylations (or more accurately transalkylations) have now been reported for all *p-tert*-butylcalixarenes (n = 4 through 8).[17,19]

As the *p*-unsubstituted calixarenes have a free position *para*- to the hydroxyl group, they undergo electrophilic aromatic substitution reactions. A number of methods have been trialed and a very wide variety of functional groups have been installed (the most synthetically useful include chloromethylation, sulphonation, halogenation, alkylation and acylation[3]). Favourable properties of the *p*-functionalised calixarenes include enhanced solubility, polarity and binding characteristics.

1.5 SPECTROSCOPIC PROPERTIES OF CALIXARENES

Calixarenes have some interesting spectroscopic characteristics due to unusual hydrogen bonding and conformational flexibility. The calixarene lower rim participates in strong hydrogen bonding and the effects of this phenomenon are observed in i.r. and n.m.r. spectra.

From ^{1}H n.m.r. data (**Table 1.2**) it is apparent that, as might be expected from a series of oligomeric compounds, all of the calixarenes have similar spectral characteristics. At r.t. both *p-tert*-butylcalix[4]arene and *p-tert*-butylcalix[8]arene display a pair of broad doublets (J = 13.3 Hz). These doublets arise from the methylene protons existing in two magnetically different environments (**Figure 1.8**). The pair of doublets observed for *p-tert*-butylcalix[4]arene and *p-tert*-butylcalix[8]arene at room temperature are indicative of a cone (calix[4]arene) or cone like (calix[8]arene) structure. Interconversion between conformers is slow relative to the n.m.r. timescale for *p-tert*-butylcalix[4]- and *p-tert*-butylcalix[8]arenes. For the cyclic pentamer, hexamer and

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‡ The term *upper rim* refers to the all carbon mouth of the calixarene cavity. The *lower rim* is that which contains the phenolic hydroxy groups (and is significantly narrower than the upper rim).

heptamer, broad singlets are observed for the methylene bridge protons, which indicates that the rate of interconversion of conformational isomers (**Figure 1.8**) is occurring within the n.m.r. timescale.

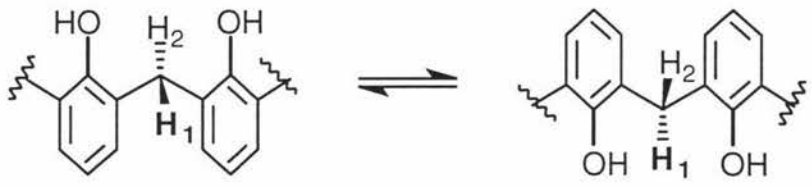


Figure 1.8. The conformational interconversion of a calixarene segment showing the different environments of the methylene protons.

Variable temperature n.m.r. studies[1] have shown that the conformational interconversion process can be slowed at low temperatures and speed up at higher temperatures. As the temperature is lowered, broad singlets separate out to the expected pairs of doublets, and the regular pair of doublets observed for the tetramer and octamer at r.t. collapses to a broad singlet at 89°C and 84°C, respectively as the conformational interconversion becomes rapid (*cf.* the n.m.r. timescale).[20]

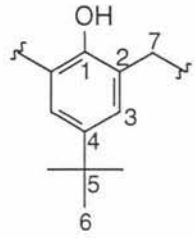
Assignment	$n = 4$	5	6	7	8
Ar-O*H*	10.35 (s)	8.68 (s)	10.54 (s)	10.35 (s)	9.65 (s)
Ar-*H*	7.06 (s)	7.22 (s)	7.16 (s)	7.22 (s)	7.20 (s)
Ar-CH_2-Ar	4.26 (d, J=13.3 Hz)	3.80 (br s)	3.90 (br s)	3.93 (br s)	4.38 (d, J=13.3 Hz)
	3.50 (d, J=13.3 Hz)				3.52 (d, J=13.3 Hz)
C(CH_3)3	1.22 (s)	1.27 (s)	1.27 (s)	1.30 (s)	1.27 (s)

Table 1.2. ^{1}H shifts (δ/ppm in $CDCl_3$ at 25°C, 270 MHz) of the *p-tert*-butyl[*n*]calixarenes.

Perhaps the most distinctive difference between the oligomeric calixarenes is the shift of the Ar-O*H* signals in the n.m.r. spectra. Shinkai[21] has proposed that the hydrogen bond strength between the phenolic groups can estimated by using i.r. and n.m.r. methods. In the n.m.r. spectra the increase in hydrogen bond strength is observed as a down-field shift of the phenolic OH signal. In the corresponding i.r. spectra the ν_{OH} occurs at a lower wavenumber with increasing hydrogen bond strength. Hence, after analysis of the data from **Table 1.2**, the hydrogen bond strengths in decreasing order are hexamer > heptamer ≈ tetramer > octamer > pentamer.

More simple to interpret are the ^{13}C n.m.r. spectra (**Table 1.3**), which are very similar for all members of the family (usually <1 ppm difference in chemical shift of each calixarene).

Assignment	n =4[a]	5[a]	6[b]	7[a]	8[a]
C1	146.5	147.4	147.0	147.1	146.5
C4	144.2	143.8	144.3	144.2	144.6
C2	127.6	126.1	126.8	127.3	128.6
C3	125.8	125.5	125.9	126.0	125.4
C5	34.1	34.0	33.9	34.1	34.1
C7	32.7	31.6	32.7	33.0	32.4
C6	31.5	31.5	31.2	31.6	31.5



[a] in $CDCl_3$; [b] in CD_2Cl_2

Table 1.3. ^{13}C shifts in ppm at 25°C and 69 MHz for the basic *p-tert*-butyl[*n*]calixarenes.

Some i.r. studies have been performed on the simple *p-tert*-butylcalixarenes.[1] The i.r. spectra of calixarenes are complex, making assignment of particular absorbances to bending or stretching modes difficult. Some interesting correlations do exist and the signals below 850 cm^{-1} have been used characterise each of the calixarenes[1] (**Table 1.4**). It is interesting to note that the order of hydrogen bonding, based on O-H

stretching frequency (hexamer> heptamer> tetramer> octamer> pentamer) follows closely to that observed in the ^{1}H n.m.r. spectrum (*vide supra*), even though the i.r. spectra are recorded in the solid state and the n.m.r. spectra in solution.

$n = 4$	5	6	7	8
3179	3298	3132	3178	3222
1516	1516	1486	1485	1486
	1361	1362	1362	1361
1242	1291		1292	
1200	1205	1202	1204	1204
915	885	872	873	875
834				
792	799	810		783
	667	747		600
		722		

Table 1.4. The infra red absorbances (in cm^{-1}) for the *p-tert*-butylcalix[*n*]arenes (KBr disc).

Probably the most obvious technique for distinction between the oligomeric calixarenes is mass spectrometry. Calixarenes and derivatives are often analysed by fast atom bombardment (FAB) or electrospray techniques, though interpretation of the mass spectrum is often difficult.

We have found that one of the most useful techniques in the analysis of the *p-tert*-butylcalix[*n*]arenes is t.l.c. on silica gel. This allows a qualitative analysis of the progress of calixarene forming reactions and assists greatly in the workup and purification procedures to isolate the odd numbered calixarenes.

In **Figure 1.9** a thin layer chromatogram of each calixarene in the two most useful solvent systems is depicted.

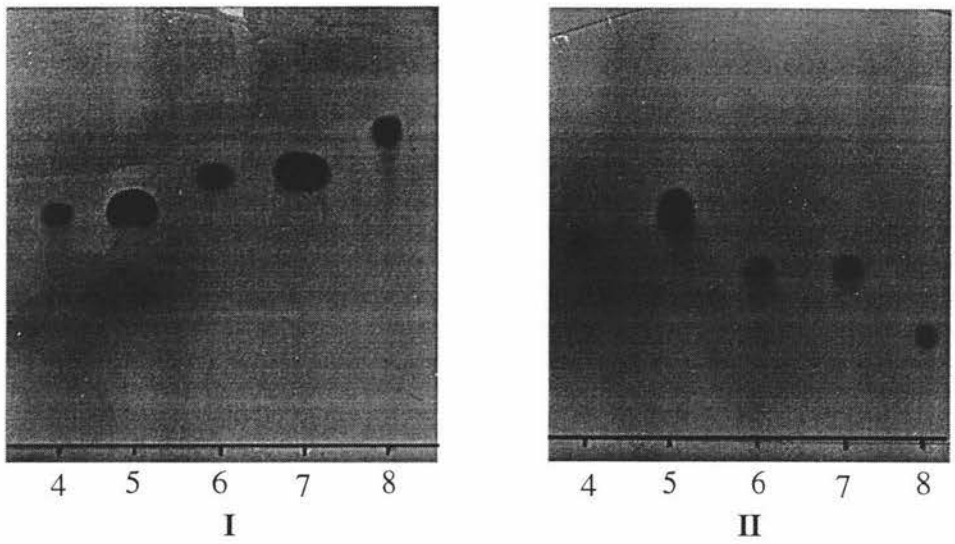


Figure 1.9. Two t.l.c. plates with samples of *p-tert*-butylcalix[*n*]arenes eluted in; I 1:1 hexane:CH_2Cl_2, and II 10:1 hexane:acetone.

This is reproduced here since R_f values reported in the literature[6,8] were not repeatable in our hands, and the order of calixarene polarities on t.l.c. plates in the same solvent is not consistent in the literature.[5,6] It is intriguing to note that the order of elution is reversed between these two solvent systems. This change in polarities may be a manifestation of inter/intramolecular hydrogen bonding switching in different solvents.

1.6 DISCUSSION

1.6.1 SYNTHESIS OF THE *p-tert*-BUTYLCALIX[*n*]ARENES

Although the literature procedures for the targeted synthesis of the even numbered calixarenes are reliable, care must be taken. In the preparation of *p-tert*-butylcalix[4]arene, two factors need to be insured:the first is in the formation of the precursor (pre-reflux condensate) where the mixture *must* become golden and of a taffy-like consistency in order to obtain good yields of cyclic products. The other factor is the duration of pyrolysis to which the precursor material is subjected. By refluxing for the prescribed 1.5-2 hours, in our hands, yields of undesired calixarenes were higher than those obtained when the mixture was refluxed for a longer period (*ca.* 3 hours). Presumably, this prolonged heating allows for the linear oligomers and larger calixarenes (dihomooxacalix[4]arene and the cyclic octamer) to be thermally "reduced" to cyclic tetramers. On one occasion, during the preparation of *p-tert*-butylcalix[4]arene, the precursor was not heated strongly enough (*ca.* 170°C rather than 200°C) and the isolated product was a 50:50 mixture of *p-tert*-butylcalix[8]arene and *p-tert*-butylcalix[4]arene.

Purification of *p-tert*-butylcalix[4]arene was initially carried out by recrystallisation from toluene as described in the literature preparation.[4] While this method *is* effective for purifying *p-tert*-butylcalix[4]arene, it affords a *p-tert*-butylcalix[4]arene:toluene (1:1) adduct, which must be heated strongly under high vacuum to provide pure, uncomplexed *p-tert*-butylcalix[4]arene. In one run, ethyl acetate was added to the diphenyl ether post-pyrolysis mixture *before* the solution had cooled to room temperature. Surprisingly, it was found that copious amounts of a highly crystalline product were formed upon cooling to room temperature overnight. After analysis (by comparison with an authentic sample) the material was characterised as pure *p-tert*-butylcalix[4]arene, not complexed to the ethyl acetate or any other compounds. This not only provides uncomplexed *p-tert*-butylcalix[4]arene *directly* but also improves the yield to 71% (from 61% for the *Organic Synthesis* procedure[4]).

Synthesis of *p-tert*-butylcalix[6]arene and *p-tert*-butylcalix[8]arene did proceed as stated in the *Organic Synthesis* papers.[5,6] In the preparation of *p-tert*-butylcalix[8]arene, the condensation occurred readily but the workup procedure required a final wash with water. The water binds remarkably tightly with the calixarene and thus required very long periods of drying (36-54 hours) *in vacuo* (0.1 mmHg) with heating (100-150°C) to obtain a pure, dry product.

In the synthesis of *p-tert*-butylcalix[5]arene, two literature procedures were trialed[7,8] but neither gave high yields (similar yields were obtained from both procedures). After testing various solvents to recrystallise *p-tert*-butylcalix[5]arene it was found that acetone was most effective. Shinkai has reported[7] that *p-tert*-butylcalix[5]arene can be recrystallised from ethanol but we have not, at any stage, found the cyclic pentamer to be even sparingly soluble in ethanol. In the recrystallisation process a large quantity of other material is removed (this other material is mainly cyclic hexamer and octamer). In a procedure reported by Gutsche[8], an elaborate series of heating and cooling stages is required. This is (practically) difficult to perform and yields of the desired cyclic pentamer are low (10-15%). Similar problems were encountered in the synthesis of *p-tert*-butylcalix[7]arene where the literature procedure[9] gave yields similar to those reported (*ca.* 17%) but was again practically difficult (especially on a large scale).

In the targeted synthesis of *p-tert*-butylcalix[8]arene, only *ca.* 60% of the starting material is converted to the cyclic octamer. In an effort to utilise the remaining material, the filtrate (both that of the reaction and the toluene washing of the product) was examined by t.l.c. This showed that a substantial quantity of the odd numbered calixarenes was present. Thus, the separation of *p-tert*-butylcalix[5]arene and *p-tert*-butylcalix[7]arene from this mixture was investigated. At this point the different solublities of the calixarenes (*cf.* **Chapter 2**) becomes useful. Both of the odd numbered calixarenes have very good solubility in most common organic solvents, whereas the even numbered calixarenes have poorer solublities. Thus, successive

recrystallisations from chloroform and acetone and a filtration column through silica gel gave workable quantities of the rarer calixarenes.

In one of several runs of the *p-tert*-butylcalix[8]arene targeted synthesis, the flask was not fitted with a Dean-Stark trap until the reaction had been running for *ca.* 1.5 hours. After fitting the trap, leaving the reaction for a further 2.5 hours then carrying out the standard workup, much less cyclic octamer was isolated (*ca.* 45%) and the filtrates contained more *p-tert*-butylcalix[5]arene and *p-tert*-butylcalix[7]arenes. This would suggest that the presence of water has in some way affected the outcome of the cyclisation process, and it may be possible to further improve the yield of calix[5]- and calix[7]arenes in this way.

We find that it is more effective to carry out one reaction and isolate workable quantities of *p-tert*-butylcalix[5]arene, *p-tert*-butylcalix[7]arene and *p-tert*-butylcalix[8]arene than to carry out three separate (and somewhat laborious) reactions.

1.6.2 SYNTHESIS OF THE CALIX[*n*]ARENES

The synthesis of the simple *p*-H calixarenes was carried out by the application of $AlCl_3$-catalysed dealkylation of the corresponding *p-tert*-butylcalixarenes. This reaction proceeded smoothly for all calixarenes, however, the reaction was generally slower than expected. Gutsche has stated[17] that the reaction takes *ca.* 1 hour at r.t., whereas the reaction in our hands requires *ca.* 2 hours at 30°C to give complete conversion . As expected for this intermolecular reaction the rate is very dependant upon the dilution. If the concentration is too high then byproducts form and complex mixtures result; alternatively if the dilution is too high then the reaction is prohibitively slow.

The *p*-H calixarenes are generally much less soluble than their *p*-alkylated analogues in organic solvents. We found that calix[8]arene is insoluble in all solvents tested except sparingly in pyridine. The synthetic use of this compound is expected to be greatly limited due to its insolubility.

1.7 CONCLUSION

The literature procedures for the targeted syntheses of *p-tert*-butylcalix[4]arene, *p-tert*-butylcalix[5]arene, *p-tert*-butylcalix[6]arene, *p-tert*-butylcalix[7]arene, and *p-tert*-butylcalix[8]arene have been repeated successfully. In the case of *p-tert*-butylcalix[4]arene, alterations led to a less capricious procedure, synthesis of the pure product directly and in higher yield. The residual xylene and toluene solutions from the targeted *p-tert*-butylcalix[8]arene preparation were utilised to obtain workable

quantities of the rare calix[5]- and calix[7]arenes, a protocol that is far simpler and less time-consuming than the low-yielding targeted synthesis of these compounds.
Dealkylation of *p-tert*-butylcalix[*n*]arenes is best accomplished at 30°C in 0.16-0.05 $molL^{-1}$ toluene solution. The insolubility of calix[8]arene in all common organic solvents is expected to limit its synthetic use.

Chapter 2

MONOFUNCTIONALISATION

2.1 INTRODUCTION

The aim of the project was to develop a general, high yielding syntheses of *bis*-calixarenes from "unprotected" calixarenes. In order to achieve this goal, it was necessary to develop a highly selective monofunctionalisation protocol for calixarenes. To date no *general* monofunctionalisation reaction of calixarenes has been reported, with most procedures being employed for only one calixarene.[22,23] The ideal procedure would be applicable to any size of macrocycle, tetramer or larger, and be operationally simple and high yielding for all alkylating agents (RX).

The first, and perhaps most restricting problem, relates to the different solublities of the various calixarenes in common organic solvents. Toward this end, the solublities of the each of the *p-tert*-butylcalix[*n*]arenes were determined (**Table 2.1**).

	Solvent at r.t.					Solvent at reflux				
Solvent	$n = 4$	**5**	**6**	**7**	**8**	**4**	**5**	**6**	**7**	**8**
MeOH	-	-	-	-	-	-	-	-	+	-
DMF	-	++	-	-	-	+	++	++	++	++
MeCN	-	-	-	-	-	+	++	+	-	-
t-BuOH	-	-	-	-	-	-	++	-	++	-
Me_2CO	-	-	-	-	-	+	++	+	++	+
THF	-	++	-	++	-	+	++	+	++	+
EtOAc	-	++	-	++	-	-	++	+	++	-
$CHCl_3$	+	++	+	++	+	+	++	+	++	++
CH_2Cl_2	-	++	++	++	+	-	++	++	++	+
PhH	+	++	-	++	-	++	++	+	++	+
PhMe	-	++	+	++	-	++	++	++	++	+
n-Hex	-	-	-	-	-	-	++	-	++	+

Table 2.1. The solublities of the *p-tert*-butylcalix[*n*]arenes. ++ = soluble, + = sparingly soluble, - = insoluble.

Clearly, *p-tert*-butylcalix[8]arene and *p-tert*-butylcalix[4]arene are the least soluble of all the calixarenes and they have, at best, poor solubility in most common organic solvents. Conversely, *p-tert*-butylcalix[7]arene and *p-tert*-butylcalix[5]arene are quite soluble in

most common solvents (the heptamer is even sparingly soluble in hot methanol). The reasons for these solubility differences are not known, but the different hydrogen bonding arrangements may play a role. It is also clear from **Table 2.1** that DMF, acetone, THF, chloroform, benzene and toluene are the solvents of choice if a general procedure is to be developed.

2.2 THE *O*-ALKYLATION PATTERNS OF CALIXARENES

O-Alkylations of calixarenes do not proceed in a statistical manner. There is a degree of selectivity in any calixarene *O*-alkylation, and certain products are favoured under particular conditions.

Calix[4]arene is a case in point, and the two possible routes to the tetraalkylated calix[4]arene are shown in **Figure 2.1**. In this progressive alkylation, only one mono-, tri-, and tetraalkyl product is possible. However, functionalisation of the monoalkyl calixarene can give rise to two discrete dialkylated products, one in which alkylation occurs at an *adjacent* or *proximate* phenol (pathway **A**) and the other at the *alternate* or *distal* phenol.[24]

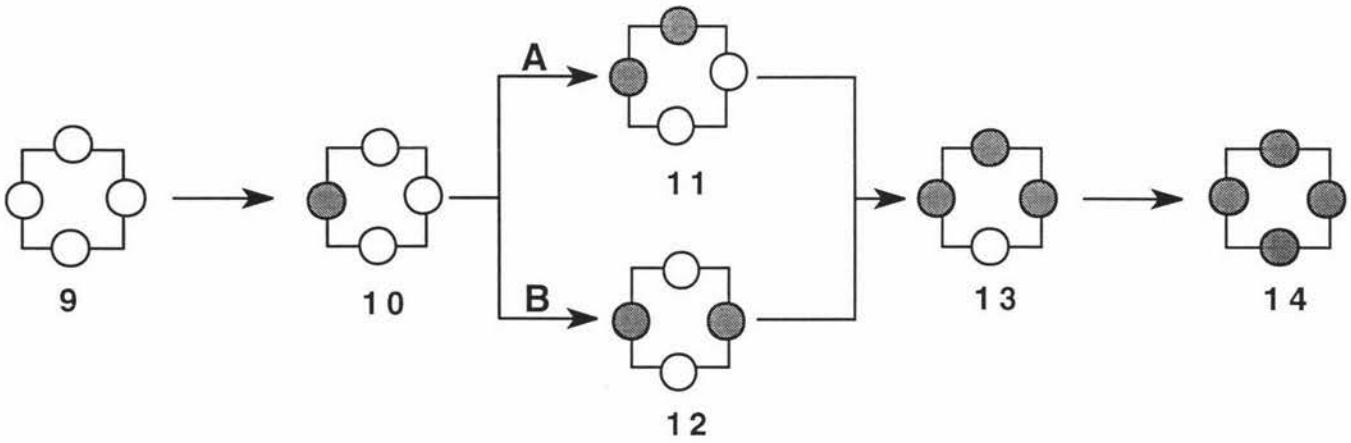


Figure 2.1. The pattern of progressive alkylation of a calix[4]arene, **9**. ○ are free phenolic positions, OH and ● are alkylated positions, OR.

Dialkylation along pathway **A** is rare, and reported syntheses of 1,2-dialkylated products (**11**) require the use of a strong base such as NaH or KH.[25] This mode of alkylation is carried out using stoichiometric quantities of the alkylating agent and an excess of the base. The steric interaction of closely neighbouring functional groups would disfavour the formation of 1,2-substituted products and only groups that have minimal steric requirements can be installed in these positions (the largest being benzyl).[25]

In contrast, pathway **B** is common. Again, on the basis of steric effects, 1,3-products should be favoured over 1,2-products and this regioselectivity should be enhanced as the size of the alkyl group is increased. Reactions that progress along this pathway are usually carried out with a milder base (such as K_2CO_3) and to gain good control over this mode of dialkylation, stoichiometric quantities of both base and alkylating agent are required.

The preference for *alternate* alkylation with mild bases is not limited to *p-tert*-butylcalix[4]arene.[26,27] For *p-tert*-butylcalix[8]arene, substitution occurs preferentially in the 1,3,5,7- positions.[28,29] Similarly, *p-tert*-butylcalix[6]arene undergoes 1,3,5-substitution before forming further alkylated products.[28]

To complicate matters, the outcome of substitution reactions for *p*-alkyl and *p*-H calixarenes can be very different.[3] For example, under the same reaction conditions (K_2CO_3, acetone and MeOTs), *p-tert*-butylcalix[6]arene produced 1,3,5-trimethoxy-*p-tert*-butylcalix[6]arene, whereas calix[6]arene was transformed into 1,2,3-trimethoxycalix[6]arene.[30] The authors proposed that this outcome was due to reduced steric interactions rather than altered electronic characteristics.

As yet, there have been no systematic studies on the alkylation of calix[5]arenes and calix[7]arenes. There have been several functionalisations of *p-tert*-butylcalix[5]arene using the mild base K_2CO_3 to give 1,3-dialkylated products,[31] however, there are no reported selective functionalisations of *p-tert*-butylcalix[7]arene and only complete *O*-alkylations have been performed.[32]

As alluded to above, a property of calixarenes that impacts upon their reactivity is their conformational mobility. As the macrocyclic ring is increased in size, the number of degrees of freedom increase accordingly. The calix[4]arenes have only four discrete low energy conformations, but calix[8]arenes have many more.[1] Although it has not been treated here, the reader should be aware that it is possible to synthesise calixarenes in specific conformations by selective functionalisation with sterically encumbering groups (for a review, see[33]).

2.2.1 Acidity of Calixarenes

The preferred conformation of the calixarenes is such that the -OH groups are held in a pattern which maintains a hydrogen bonding arrangement. For the smaller calix[4]- and calix[5]arenes, a cone conformer can be adopted (all the phenolic residues are aligned in the same direction). As the macrocycle becomes larger, the ability to maintain a true cone conformation becomes more difficult due to the increased conformational mobility (or degrees of freedom). In the larger calixarenes, the hydrogen bonding still occurs but not necessarily along only one rim. The hydrogen bonding can pass through the "annulus" and continue on an alternate face of the calixarene (illustrated in **Figure 2.2**).

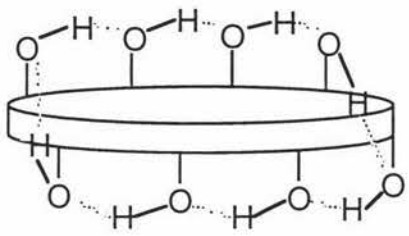


Figure 2.2. "Through-the annulus" type hydrogen bonding in calix[8]arene.

This hydrogen bonding can help to explain selective substitution reactions and indicates why calixarenes do not react in the same manner as simple phenols.

As described above, the predominant pattern of alkylation is such that every second hydroxyl group is functionalised. To explain the formation of 1,3-substituted products from calix[4]arenes, two possible mechanisms must be considered (**Figure 2.3**). The first (pathway **C**) involves two consecutive acid-base steps to form dianion **16** then two consecutive alkylation steps provide product **12**. The second possible mechanism (pathway **D**) involves the alkylation of monoanion (**15**) to give monofunctionalised calix[4]arene (**10**), then formation of a second monoanion followed by a second alkylation.

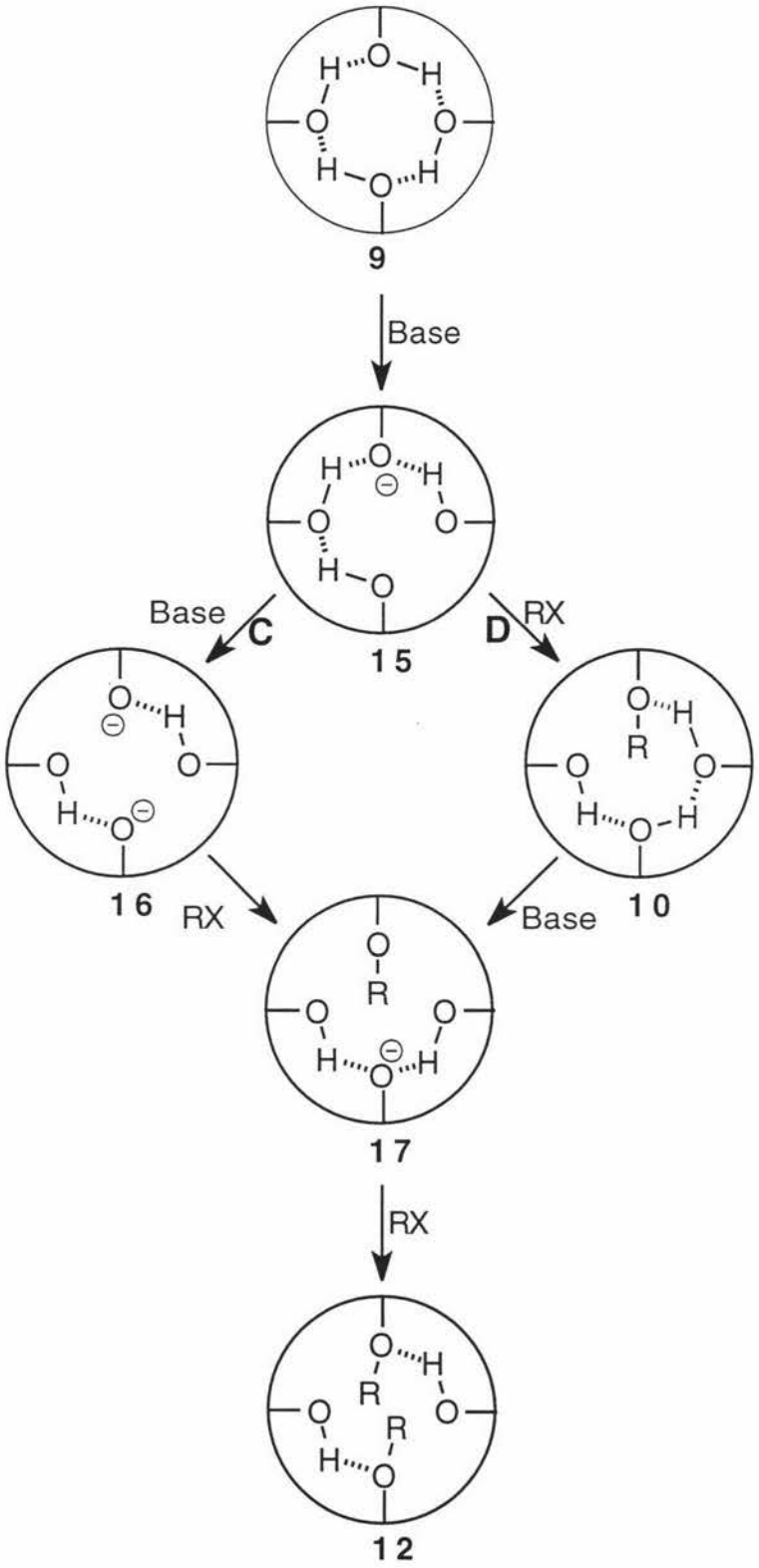


Figure 2.3. A representation of two possible routes to 1,3-diethers of *p-tert*-butylcalix[4]arene *via* pathway **C**, and pathway **D**.

The probability of either pathway **C** or **D** occurring will be dependant upon the relative stability of the anions in each case. The formation of a 1,3-dianion is expected to be

less favoured than a monoanion due to the proximity of the anionic charge. Moreover, the dianion (**16**) is significantly less stabilised than the monoanion (**15** and **17**) due to hydrogen bonding to adjacent -OH groups. Another possible stabilisation effect of the hydrogen bonding could be a charge *delocalisation.* Thus, a dynamic equilibrium can be set up through a series of intramolecular acid-base reactions. On these grounds, monoanion **15** can exist with the charge distributed over all four oxygen atoms, in addition to each of the aromatic rings associated with those oxygens (**Figure 2.4**). A similar arrangement could be set up for the dianion (**16**), where the two changes might follow each other around the lower rim.

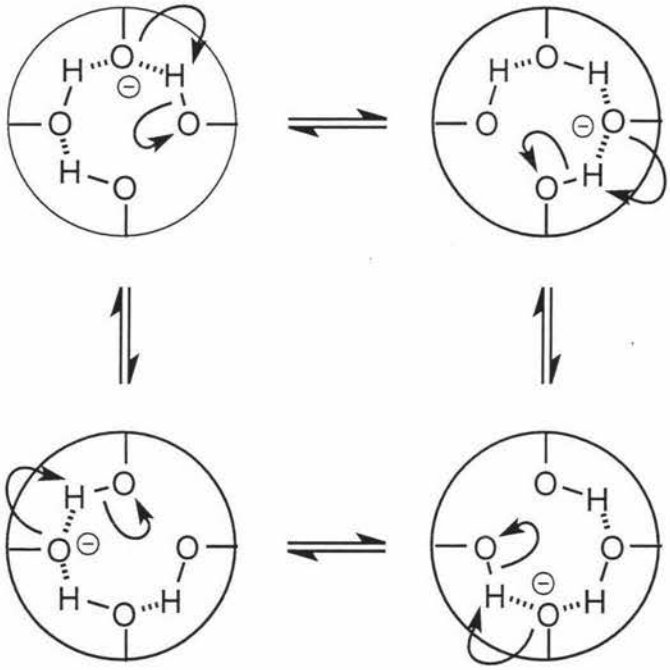


Figure 2.4. The delocalisation of charge on a *p-tert*-butylcalix[4]arene monoanion over each oxygen.

The overall result of these effects is to increase the stability of calixarene phenoxides. This stabilisation is reflected in the pK_a values for the *p-tert*-butylcalix[*n*]arenes. Shinkai[21] has attempted to measure the pK_a of *p-tert*-butylcalix[4, 6, and 8]arenes and mono-, 1,3-di-, and tri-methyl-*p-tert*-butylcalix[4]arenes using *p*-nitrophenolate (NP^-), 2,4-dinitrophenolate (DNP^-), and picrate (P^-) salts in spectrophotometric titrations in THF. With NP^- and DNP^-, no pK_a values for the "free" calixarenes could be measured due to the simultaneous loss of 2-4 protons. For P^-, the pK_{app} (apparent pK_a) values followed the order hexamer (3.62) >octamer (4.05) > tetramer (4.11). This is unexpected as n.m.r. and i.r. evidence point to the tetramer containing stronger hydrogen bonds than the octamer (*vide supra*). In a similar titration of monomethoxy-*p-tert*-butylcalix[4]arene, the measured pK_{app} = 3.98 (*cf.* **10→17** in **Figure 2.3**) which

compares favourably with *p-tert*-butylcalix[4]arene (pK_{app} = 4.11). When the same compound was titrated with the NP^- and DNP^- salts, however, the values obtained were not in agreement, with pK_{app} = 6.95, 7.10 and 3.98 for NP^-, DNP^- and P^-, respectively. The authenticity of these values must, therefore, be questioned.

In a later study with more acidic calixarenes, Shinkai reported values of pK_{a1} 1.5-3 and pK_{a2} *ca.* 10 (dissociation of the first and second protons, respectively) in water.[34] Although this study was carried out on *p*-nitro and *p*-sulphonato calixarenes, similar *differences* in pK_a values for each proton dissociated are expected for the *p*-alkyl calixarenes. These values are thought to be a better indication of the *relative* acidity of each phenolic residue since the results appear to be repeatable and self-consistent.

Regardless of the problems associated with these studies, it would appear that the first phenolic proton of a calixarene is *ca.* 10^{4-5} times more acidic than that of the corresponding phenol, hence the unusual behaviour of calixarene substitution reactions. Moreover, it can be concluded that there *is* a significant difference between the pK_a values for the removal of the first and second protons (*cf.* **9**→**15** and **15**→**16** in **Figure 2.3**) but these results do *not* provide clear evidence of a difference between the pK_as of the parent calixarene and the mono-*O*-alkylated derivative (i.e. **9**→**15** versus **10**→**17**).

In the formation of 1,2-dialkylated products a pathway can be envisioned in which the monoether **10** is formed in a similar manner to a 1,3-dialkylation. With an excess of NaH, the remaining free phenols are deprotonated and can give the 1,3-dianion **17a**. The repulsion of like charges causes the anions in **17a** to maintain as great a separation as possible to reduce electronic interactions. This requires that the anions be adjacent to the monoether and, if only 1.0 equiv. of the alkylating agent is added then the position most suitable for alkylation will be at the 2-position, hence formation of 1,2-dialkylated products (**11**).

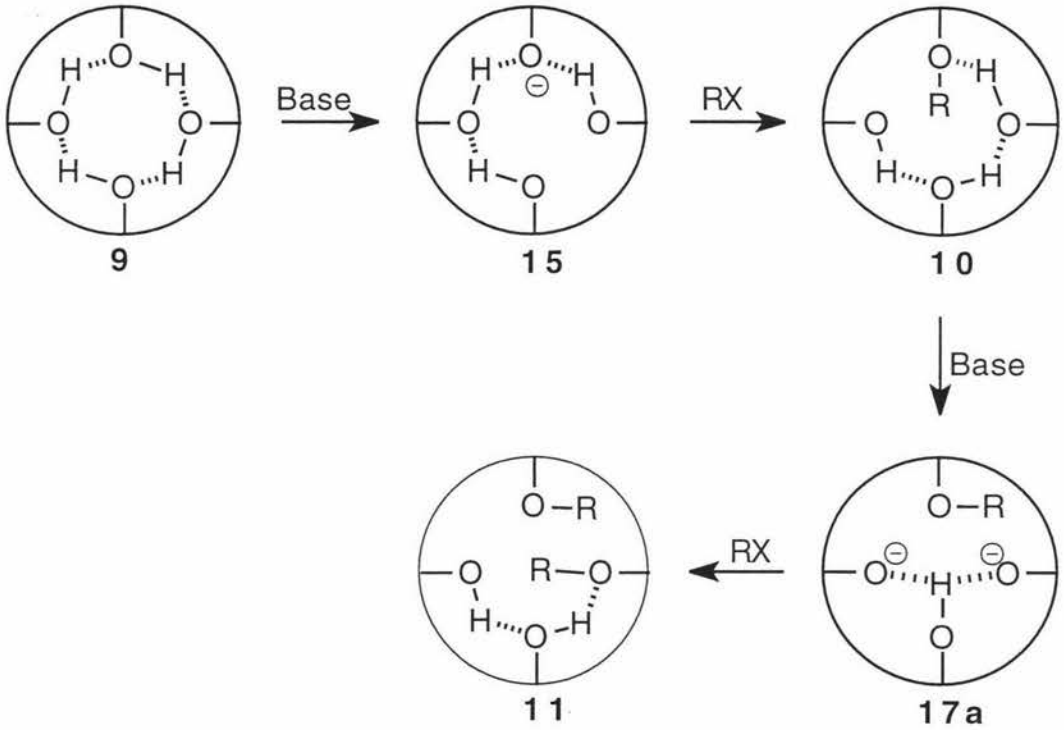


Figure 2.5. A representation of a possible route to 1,2-diethers of *p-tert*-butylcalix[4]arene.

During the preparation of this review, three main strategies were uncovered for the preparation of monofunctionalised calixarenes and these are summarised below.

2.2.2 Indirect Protection-Deprotection (I.P.D.)

This is the most laborious route to monofunctionalised calixarenes. The I.P.D. method is where a calixarene is protected such that one phenolic residue is left unsubstituted, (**9**→**13**). The free position can then be alkylated (**13**→**18**) and subsequently the other positions deprotected (**Figure 2.6**).

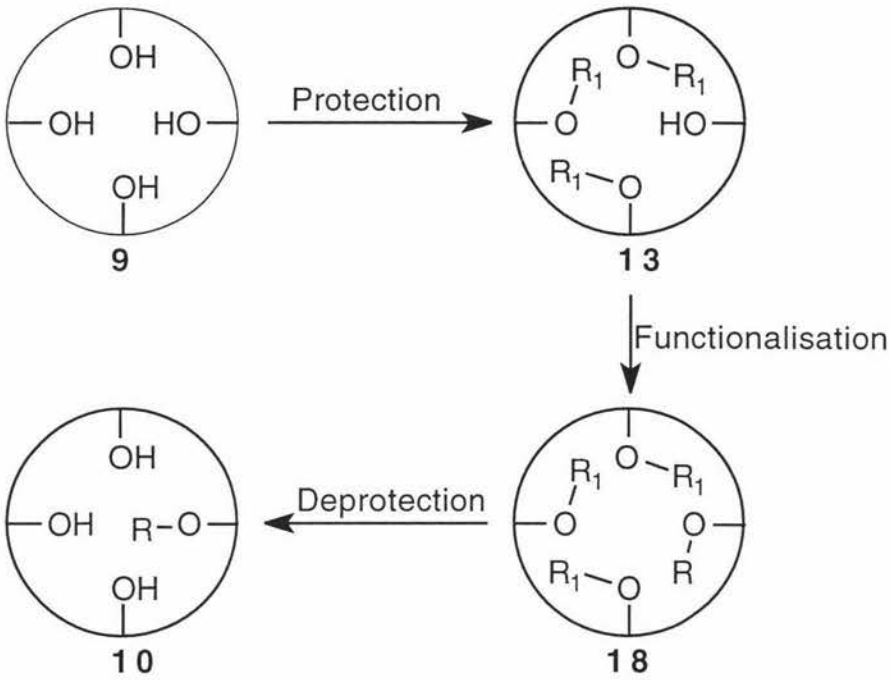
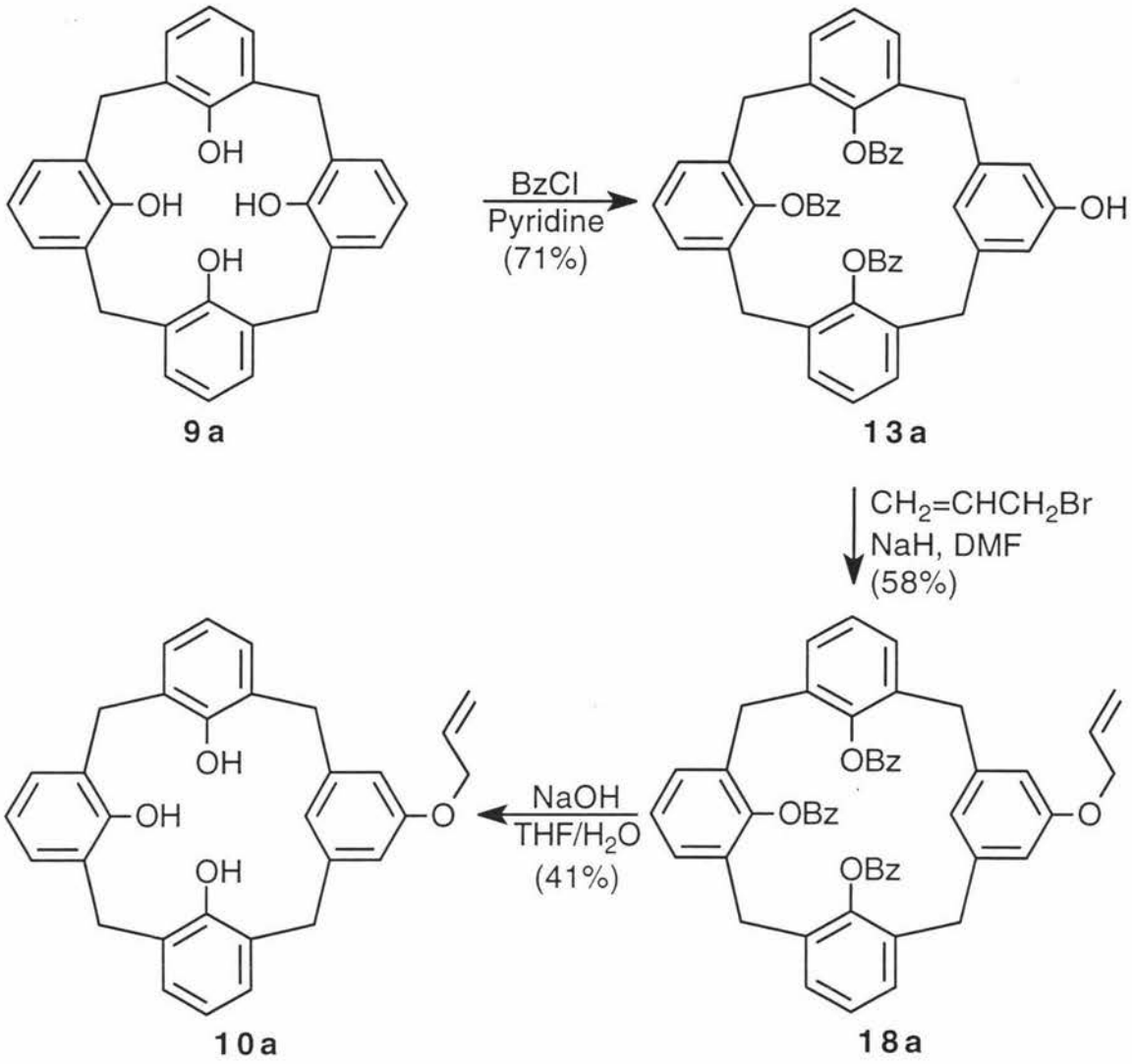


Figure 2.6. A schematic representation of the I.P.D. route to monofunctionalised calix[4]arenes.

The I.P.D. method is not widely used as there are more efficient routes to monoalkylated calixarenes. This is historically important as it was used by Gutsche and coworkers[17] to synthesise the first monofunctionalised calix[4]arene.

As summarised in **Scheme 2.1**, the transformation of calix[4]arene **9a** into the tribenzoyl ester **13a,** is carried out by reaction with benzoyl chloride in pyridine. The triester appears to be formed exclusively, presumably due to the steric requirements of the benzoyl group. Further reaction with NaH and allyl bromide affords tetrafunctionalised **18a**. Deprotection of **18a** provides 41% of the monoallyloxycalix[4]arene, **10a**.



Scheme 2.1. The first monofunctionalised calix[4]arene synthesised by Gutsche.[17]

Since this seminal work more efficient strategies have been realised which are described below. There are still some compounds, however, that require this type of synthesis.[35,36] The I.P.D. approach has been employed only with the cyclic tetramer.

2.2.3 Indirect Monofunctionalisation (I.M.)

This is a more efficient method than I.P.D., although it relies upon some of the ideas from that procedure. In an I.M. synthesis, the desired calixarene is partially or completely *O*-functionalised and then selectively deprotected to leave a monofunctionalised product (**Figure 2.7**).

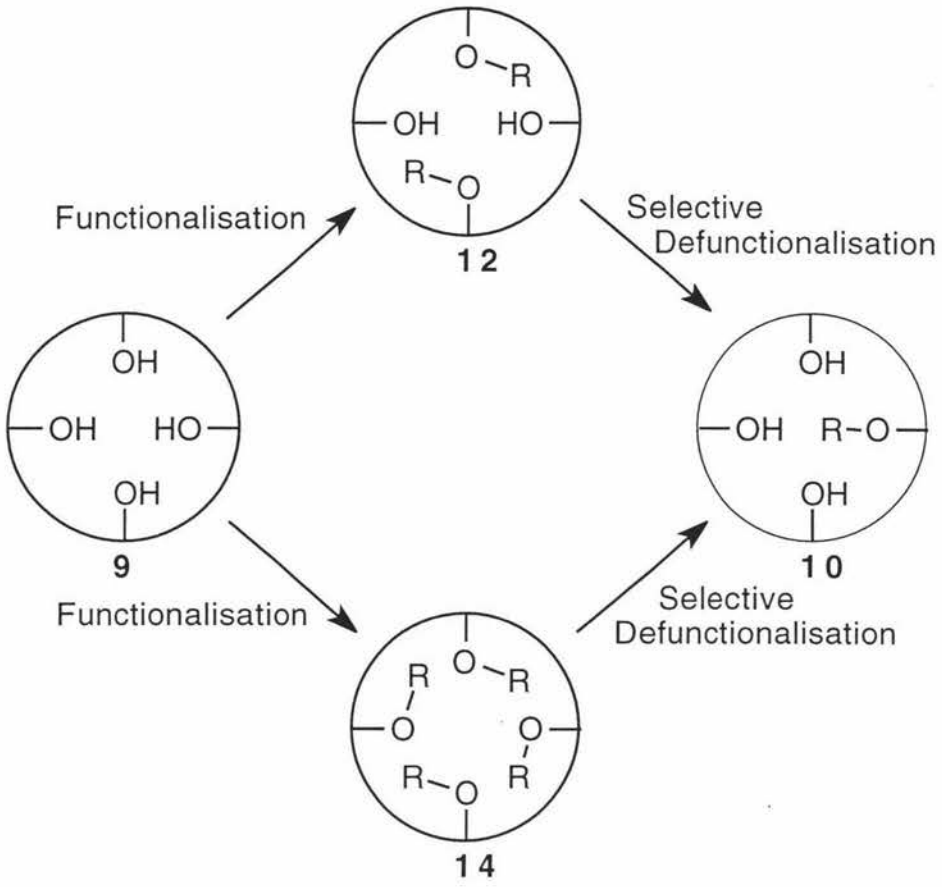
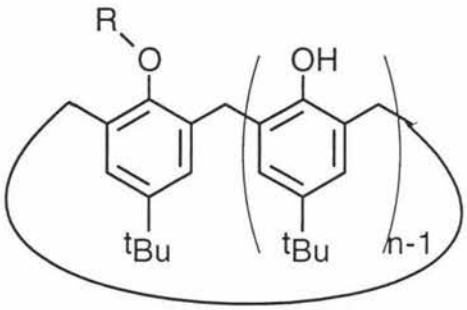


Figure 2.7. The routes to monofunctionalised calix[4]arenes *via* the I.M. pathway.

The exhaustive functionalisation of calixarenes is generally easy to accomplish, as is the 1,3-difunctionalisation of calix[4]arenes (*vide supra*). Alkyl or acyl groups may be used and selective reagents for ester or ether cleavage yield a range of monofunctionalised calix[4]arenes (**Table 2.2**). This two step method can now be carried out in one pot.[37]



Precursor	Solvent	Reagent	R	Yield[a]	Ref.
1,3-diester	$CHCl_3$/MeCN[b]	methylimidazole	3,5-$(NO_2)_2C_6H_3CO$	34	38
1,3-diester	$CHCl_3$/MeCN[b]	methylimidazole	3,5-$(NO_2)_2C_6H_3CO$	48	38
1,3-diether	$CHCl_3$[b]	$(CH_3)_3SiI$	Bn	68	37
1,3-diether	$CHCl_3$[c]	$(CH_3)_3SiI$	Et	80	37
1,2,3,4-tetraether	$CHCl_3$[c]	$(CH_3)_3SiI$	*i*-Pr	90	37
1,2,3,4-tetraether	$CHCl_3$[b]	$(CH_3)_3SiI$	Bn	60	37
1,2,3,4-tetraether	$CHCl_3$[c]	$(CH_3)_3SiI$	Me	85	37
1,2,3,4-tetraether	$CHCl_3$[c]	$(CH_3)_3SiI$	Et	65	37

[a] % from free calixarene. [b] r.t. [c] reflux.

Table 2.2. A selection of monosubstituted calix[4]arene derivatives that have been synthesised *via* the indirect monofunctionalisation route.

Of the two reagents listed in **Table 2.2**, it is clear that the use of $(CH_3)_3SiI$ (TMSI) is the more efficient, although it has only been applied to calix[4]arenes thus far. It may be possible to synthesise monofunctionalised calix[6]arenes in this way, since higher alkylated analogues (1,4-, 1,2,3-, 1,2,4- and 1,2,3,4- methylcalix[6]arenes) have already been prepared by treating permethylated calix[6]arene with $TiCl_4$ or TMSBr.[26] Likewise, there has been a report of the use of $TiBr_4$ for formation of 1,2-diethers of calix[4]arene.[39]

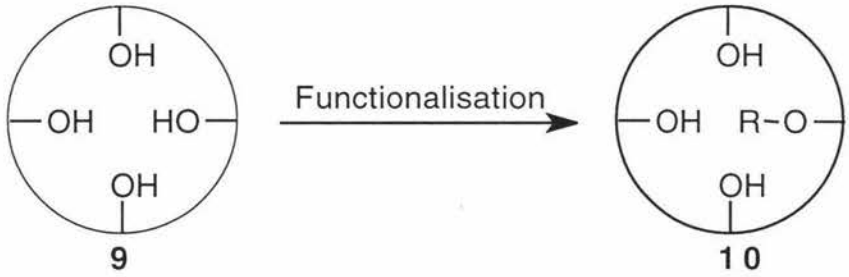
The use of strong Lewis acids for the cleavage of calixarene ethers is convenient only if the substrate is stable enough to withstand these somewhat harsh conditions. As alluded to previously, the advantage with this procedure is that the starting materials are readily available in almost quantitative yields from the free calixarene. For example, the 1,3-diethers of calix[4]arenes can be obtained in yields >80%.[3] Methods allowing the selective deprotection of a 1,3-diether or 1,3-diester can be far higher yielding than even direct monofunctionalisation (*vide infra*).

Imidazoles are reagents of choice in the selective cleavage of polyesters to give monoester products. An interesting observation from this work is that differently substituted imidazoles give vastly different rates of ester cleavage. For example, the use of 4-methylimidazole gives rates up to 2000 times faster than other imidazole

derivatives. The slowest reaction was observed when using 1-methylimidazole (a result of the increased nucleophilicity of 4-methylimidazole over other imidazoles).

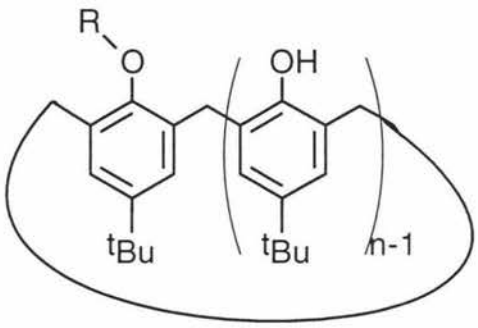
2.2.4 Direct Monofunctionalisation (D.M.)

This is the most efficient way to synthesise monofunctionalised calixarenes. It requires conditions that are chemoselective enough to substitute at only one phenolic residue. This route relies upon a difference in pK_a of each calixarene phenol group and the tailoring of the base to suit these acidities. The D.M. method is depicted below in **Figure 2.8**.



9 **10**

Figure 2.8. The most efficient route to monofunctionalised calixarenes is by D.M.



n	Base	Solvent	R	Yield (%)	Ref.
4	K_2CO_3	MeCN[a]	Me	67	40
4	K_2CO_3	MeCN[a]	Et	44	40
4	K_2CO_3	MeCN[a]	$CH_2CH{=}CH_2$	47	40
4	K_2CO_3	MeCN[a]	CH_2COOEt	61	40
6	K_2CO_3	DMF[b]	Pic[c]	5	41
6	K_2CO_3	Me_2CO[d]	Me	82	42
6	K_2CO_3	Me_2CO[a]	Bn	78	12
5	$KHCO_3$	DMF[b]	Pic[c]	66	43
5	$KHCO_3$	Me_2CO[a]	Me	44	44
5	$KHCO_3$	MeCN[a]	Et	87	44
5	$KHCO_3$	Me_2CO[a]	*n*-Pr	61	44
5	$KHCO_3$	MeCN[a]	Bn	68	44
4	$NaHCO_3$	MeCN[a]	btz[e]	71	45
4	CsF	DMF[f]	Et	65	40
4	CsF	DMF[f]	CH_2COOEt	75	40
8	CsF	THF/DMF (10:1)[a]	4-$CH_3C_6H_4CH_2$	50	27
4	$Ba(OH)_2$/BaO	DMF[g]	*i*-Pr	67	46
6	$KOSiMe_3$	DMF[g]	$CH_2C{\equiv}CH$	61	47
4	NaH	PhMe[h]	Pic[c]	59	48
6	NaH	THF/DMF (10:1)[i]	4-$CH_3OC_6H_4CH_2$	22	49
6	KH	THF[j]	Me	85	42
4	1-Butylimidazole	MeCN[f]	3,5-$(NO_2)_2C_6H_3CO$	83	38

[a] reflux. [b] 60°C. [c] 2-pyridylmethyl. [d] 70°C in autoclave. [e] 2,2'-bithiazolyl. [f] 40°C. [g] r.t. [h] 70°C. [i] r.t. then reflux. [j] under sonication.

Table 2.3. Some monosubstituted *p-tert*-butylcalix[*n*]arene derivatives synthesised by the direct monofunctionalisation path.

It should be noted that there are no previous monofunctionalisations of *p-tert*-butylcalix[7]arene. It is also clear from inspection of **Table 2.3** that there is no single

set of reaction conditions that have been used for the selective monofunctionalisation of all *p-tert*-butylcalix[4, 5, 6, and 8]arenes.

As discussed previously, for calixarenes, the selectivity of functionalisations that occur at the lower rim appear to be governed by the effect of the base and solvent on hydrogen bonding. Using CsF in DMF gives moderate yields of monoalkylated products, yet the mechanism of this reaction is not well understood. Reinhoudt and coworkers have suggested that a phenolic proton forms a strong hydrogen bond with the fluoride ion, thereby destablising the phenoxy group (and not generating the phenoxide anion). Use of CsF has also been reported as a method to obtain higher alkylated calix[*n*]arenes.[27]

The use of $Ba(OH)_2$/BaO has been reported as a good method for the selective trialkylation of *p-tert*-butylcalix[4]arene.[50] The monoalkylated product was obtained from a reaction that was allowed to proceed at r.t. for 21 hours rather than 30°C for 1 hour. Both reactions were carried out in DMF but the ratio of *p-tert*-butylcalix[4]arene:$Ba(OH)_2$:BaO was 1.0: 1.1: 1.1 for the monoalkylation and 1.0: 3.0: 5.8 for trialkylation. Shinkai has suggested[46] that the selectivity was achieved by complexation of the phenoxide ion to Ba^{2+} causing its nucleophilicity to be reduced. There have been no reports of the $Ba(OH)_2$/BaO system being used for the larger macrocycles although this is likely to be studied in future.

Use of NaH or KH in toluene or THF affords monoalkylated products in varying yields. These bases suffer from poor selectivity presumably due to their high basicity. Good yields of monofunctionalised calixarenes have been obtained, however, by restricting the quantity of base and preforming the phenoxide salt. These conditions are most commonly used for complete *O*-alkylation. A similar level of selectivity is observed when using $KOSiMe_3$.

The use of imidazole and its derivatives for the esterification of calixarenes is interesting as they can also be used for deprotection of this functional group (see **2.2.3**). In the paper referenced in the table, the authors report a yield of 83% of a calix[4]arene ester by using 1-butylimidazole as a base.

The most commonly used procedure for mono-*O*-alkylation employs K_2CO_3 as base and a polar aprotic solvent. These reactions are carried out by using *ca.* 0.6 mol equiv. of K_2CO_3 which presumably reacts initially as CO_3^{2-} and then HCO_3^-. The pK_a of HCO_3^- (conjugate base CO_3^{2-}) is 10.3, with that of H_2CO_3 (conjugate base HCO_3^-) is 6.4. Since the pK_a of *p-tert*-butylcalix[4]arene is *ca.* 4 and the pK_a of a monoalkylated calix[*n*]arene is unknown (*vide supra*), it is not known if bicarbonate is a strong enough base to effect 1,3-dialkylation. The reader is reminded that K_2CO_3 effects 1,3-dialkylation.

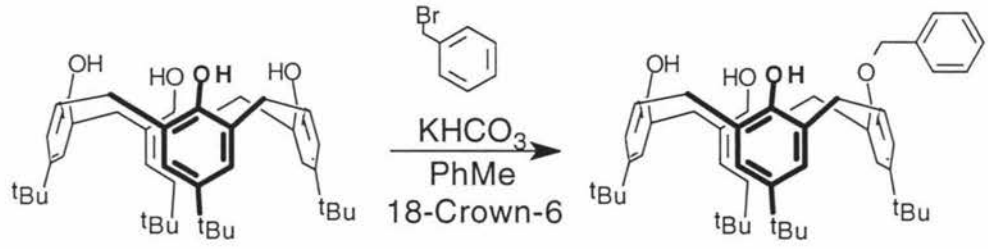
Bicarbonate would appear to be more suitable as a base for monofunctionalisation as its conjugate acid has a pK_a which matches closely to that of a calixarene. Interestingly, it

has been stated that $KHCO_3$ is not a weak enough base to effect selective alkylation of calix[*n*]arenes.[40] During the course of this project, $NaHCO_3$ and $KHCO_3$ were reported to give good selectivity and yields in the monoalkylation of *p-tert*-butylcalix[4]arene[45] and *p-tert*-butylcalix[5]arene.[43,44]

2.3 DISCUSSION

In an attempt to improve the selectivity of calixarene mono-O-alkylation reactions, the use of a non-polar solvent (toluene), the alkylating agent (benzyl bromide), a mild base ($KHCO_3$) and a catalytic amount of 18-crown-6 were tried. Similar conditions have been utilised previously for the displacement of mesylates with CsOAc.[51]

Initially, a mixture of *p-tert*-butylcalix[6]arene (or *p-tert*-butylcalix[4]arene), $KHCO_3$ (1.0 equiv), 18-crown-6 (0.1 equiv) and an alkylating agent (benzyl bromide, 1.0 equiv) in anhydrous toluene (0.1 molL^{-1} in calixarene) was heated to 90°C overnight (**Scheme 2.2**). A t.l.c. and ^{1}H n.m.r. analysis indicated a relatively clean reaction: the starting material and monosubstituted product were by far the major products, with only minor quantities of higher alkylated calixarenes present. Only 40-50% conversion of the starting material was observed, yet the yield of monoalkylated product based on recovered starting material was high (80-90%). Longer reaction times did not lead to higher conversions. This new procedure for calixarene alkylations did appear promising, however, so further work was carried out in order to optimise the procedure.



Scheme 2.2. Monofunctionalisation of *p-tert*-butylcalix[4]arene with benzyl bromide in toluene.

Since calixarenes contain several phenolic residues that are capable of coordinating to a metal cation,[1] it was necessary to investigate whether the calixarene was capable of catalysing its own alkylation. On repeating the experiment without 18-crown-6, however, no reaction was observed. Even prolonged refluxing of the toluene dispersions/solutions for several days led only to the recovery of unchanged starting material. Only upon addition of a catalytic quantity of 18-crown-6 did the reaction take

place. These experiments demonstrate that the calixarene clearly does not act as a salt solublising agent and that the successful alkylation reaction must involve the 18-crown-6. In further experiments, little change was observed when the amount of 18-crown-6 was altered between 0.1 to 0.2 mol%.

In order to drive the reaction to completion, the concentration of the solution of starting material was doubled to 0.2 molL^{-1}. Interestingly, this change resulted in the formation of a more complex product mixture: presumably di-, tri-, etc. functionalised products were being produced. A decrease in the substrate concentration (to 0.05 molL^{-1}) led to a reduced reaction rate but with a similar high selectivity to the original procedure. No further modification was made to the concentration of the reaction mixture at this point since it appeared that a value close to optimum was being employed.

Variations in temperature were found to make a substantial difference to the outcome of the reaction. The initial reaction conditions entailed heating to 90°C overnight. Assuming that the selectivity would improve further on carrying out the reaction at lower temperatures, a reaction was initiated at r.t. (*ca.* 18°C). After overnight stirring, however, no change from starting material could be detected by t.l.c. Increasing the temperature to 30°C led to a very sluggish reaction, with only ca. 5% conversion after 3-4 days. A reaction carried out with *p-tert*-butylcalix[4]arene heated to 60°C with benzyl bromide gave the most impressive selectivity with no byproducts detectable on t.l.c. and n.m.r. This reaction took four days to reach a ca. 60% conversion.

The last variables to investigate were the relative proportions of base, starting material and alkylating agent. A 0.1 molL^{-1} solution of the starting material in toluene at 90°C was maintained and the relative quantities of base and alkylating agent were successively altered. With a slight excess of alkylating agent (1.3 equiv. w.r.t. starting material) and a stoichiometric amount of base (in practice 1.05 equiv.), a mixture of monofunctionalised calixarene (65%) and starting material was obtained. Reversing this ratio of reagents (1.05 equiv. alkylating agent, 1.3 equiv. base) gave a poorer yield (40%) of the monofunctionalised product with traces of higher alkylated calixarene byproducts. Many further experiments were carried out with *p-tert*-butylcalix[4]- and *p-tert*-butylcalix[6]arenes in order to improve the selectivity and increase conversion but it is thought that the optimum conditions for these substrates have been found. These conditions were applied to *p-tert*-butylcalix[5]-arenes and *p-tert*-butylcalix[7]arenes with the monobenzylated products being obtained in satisfactory yields (**Figure 2.9**)

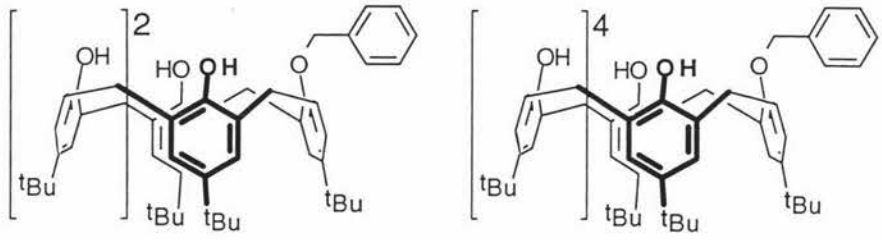


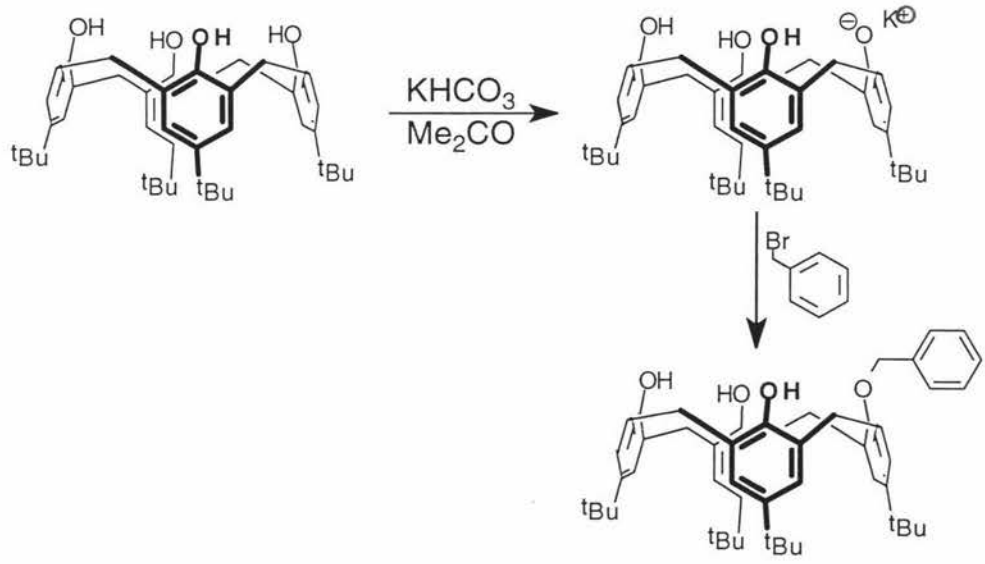
Figure 2.9. Monobenzylated *p-tert*-butylcalix[5]arene and *p-tert*-butylcalix[7]arene

Interestingly, it was found that the stronger base K_2CO_3 does not react under these conditions. Thus, a mixture of *p-tert*-butylcalix[6]arene, K_2CO_3, benzyl bromide and 18-crown-6 in toluene under the standard conditions was found to undergo no change even upon prolonged heating. Only after addition of $KHCO_3$ to this mixture did reaction take place.

Throughout these experiments *p-tert*-butylcalix[8]arene displayed its frustratingly poor solubility and underwent no reaction, even with large excesses of reagents. The solvent was changed to benzene but still with no success. Thus, in order to obtain monosubstituted calix[8]arenes, and to pursue higher yielding protocols for the other calixarenes, it was decided that a reinvestigation of the more traditional methods should be carried out.

Reinhoudt and collaborators[42] have reported a high yielding method for converting *p-tert*-butylcalix[6]arene to monobenzyl calix[6]arene by refluxing the starting calixarene with K_2CO_3 for two hours before the addition of the alkylating agent. Following this procedure led to an improved conversion to monofunctionalised products. To investigate this procedure further, a slurry of *p-tert*-butylcalix[6]arene was refluxed in acetone (0.1 $molL^{-1}$) with $KHCO_3$ (1.5 equiv.) for 20 hours. Surprisingly, an almost clear solution was formed (presumably the monopotassium salt of the calixarene is more soluble in acetone than the parent calixarene) and, after addition of the alkylating agent (1.05 equiv.), a thick white precipitate (presumably potassium bromide) began to form. Following the reaction closely by t.l.c. it was possible to watch the formation of the calixarene products. Within 10 minutes a substantial quantity of the monoalkylated product had formed. The optimum time for reaction was 30 minutes, with significant quantities of byproducts being produced after this time. With a reaction time of 1.5 hours, a substantial quantity of the 1,3-dialkylated and even higher alkylation products was formed. Trials with the other macrocycles led to similarly high selectivities for this protocol. Further modification of the conditions over a series of runs led to the optimum procedure: the calixarene is refluxed in anhydrous acetone (0.1 $molL^{-1}$) with $KHCO_3$ (1.5 equiv.) for at least 16 hours after which an essentially homogeneous

solution is obtained. An excess of the alkylating agent (2.0 equiv.) is then added and the mixture refluxed for a further 30 minutes. This affords monoalkylated calixarenes in yields of up to 80%, based on recovered starting material (in most cases easily removable by reprecipitation from hydrocarbon solvents).



Scheme 2.3. The formation of monobenzyl *p-tert*-butylcalix[4]arene by preformation of a calixarene anion.

This development was important since the poor solubility of calixarene starting materials in chromatography solvents (except the pentamer and heptamer) was problematic, often causing streaking, mixed fractions and difficult separations (even with large R_f differences).

This protocol allows the synthesis of monobenzylated derivatives of all *p-tert*-butylcalix[*n*]arenes in good yield, however, when the alkylating agent was changed to propargyl bromide, monopropargylated *p-tert*-butylcalix[4]arene was produced cleanly and in high yield (based on recovered starting material) but the conversion rate was very poor. The reasons for this are not known, but this may be a reflection of the lower electrophilicity of propargyl bromide (*cf.* benzyl bromide).

2.4 CONCLUSION

Two new protocols have been devised for the highly selective mono-*O*-alkylation of calixarenes 4 through 8. This work represents the realisation of the first selective functionalisation methods that are applicable to the calixarene *family*, and also the first selective functionalisation of a calix[7]arene. These findings will lead to more efficient

synthesis of multiple calixarenes (*cf.* **Chapter 3**) and may allow for a better understanding of the reasons for selectivity in calixarene-*O*-alkylations.

Chapter 3

BIS-CALIXARENES

3.1 INTRODUCTION

The areas of molecular recognition and supramolecular chemistry are of great importance to contemporary physical and biological science.[52-54] Calixarenes have been used in imaginative ways for a variety of applications with recent reports on their use as sensors[55] and in the purification of fullerenes.[56] It is clear that these compounds hold much promise for the future and the utilisation of these bowl-shaped molecules relies upon their conversion, in a practical manner, into functional molecular architecture.

It has been demonstrated that anions,[57] cations[58] and small neutral molecules[59] can be recognised and bound strongly by calixarenes (and calixarene derivatives). Based on this property, calixarene derivatives have been put forward as enzyme mimics[11]. In breathtaking work with the related *bis-resorcinarene* molecules,[60] Cram has been able to achieve full encapsulation of small guest molecules, an arrangement which confers exceptional stability on otherwise unstable guests.[61] This result has led Cram to describe the interior of a fully-encapsulating molecule as "a new phase of matter".[61]

While there has been a considerable amount of synthetic work relating to the selectivity of various types of reactions on the more readily available members of the calixarene series (*vide supra*), the design and construction of calixarene-based materials is very much in its infancy. The goal of this final phase of the project was to develop a *general* one-step synthesis of *bis*-calixarenes from "unprotected" calixarenes - compounds that may have wide-reaching applications from drug delivery to waste management. With an efficient monoalkylation protocol in hand (**Chapter 2**), it was possible to work towards this goal. In order to contextualise this novel approach, a summary of existing work towards polycalixarenes is presented here (for reviews, see[3,62]).

3.2 STRATEGIES TOWARDS *BIS*-CALIXARENES

When synthesising *bis*-calixarenes, there are three broad classes of products: "upper rim-upper rim", "lower rim-lower rim" and "upper rim-lower rim" linked macrocycles.

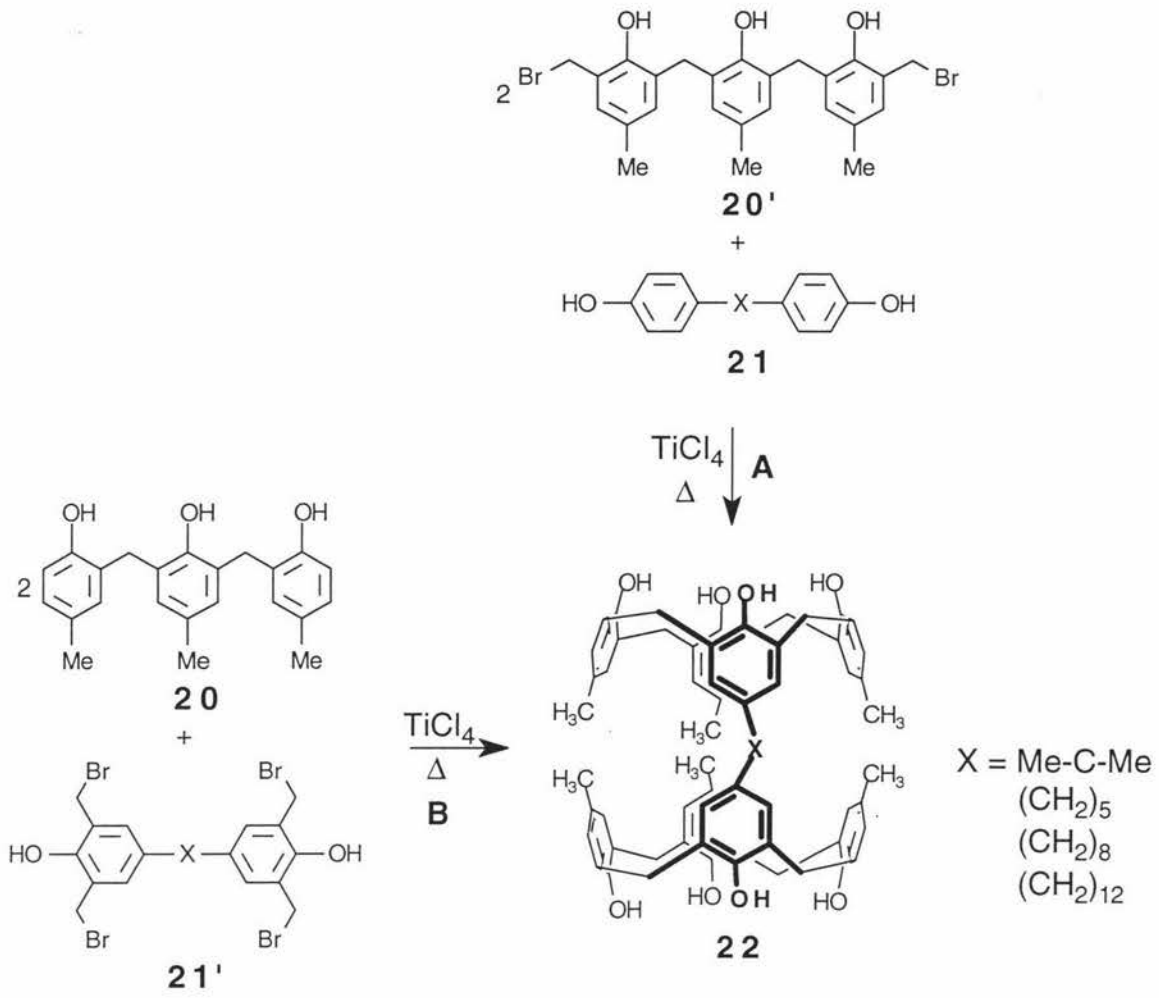
The "upper rim-upper rim" linked calixarenes are joined directly through the phenolic *para* position. This attachment is to the carbon skeleton of the macrocycle and usually involves electrophilic aromatic substitution reactions. In the "lower rim-lower rim" linked calixarenes, connection is generally *via* *O*-alkylation or *O*-acylation to give O-O

coupled products. Combinations of these two lead to "upper rim-lower rim" attached polycalixarenes.

There are three main strategies for the synthesis of covalently linked *bis*-calixarenes, outlined hereafter (**Section 3.2.4**, "Supramolecular Assemblies", contains special examples of non-covalently-linked calixarene-based structures). After the first report of a *bis*-calixarene in 1989,[63] the literature in this area has expanded at an astounding rate.[64] There follows a synopsis of the literature in this field to December 1996.

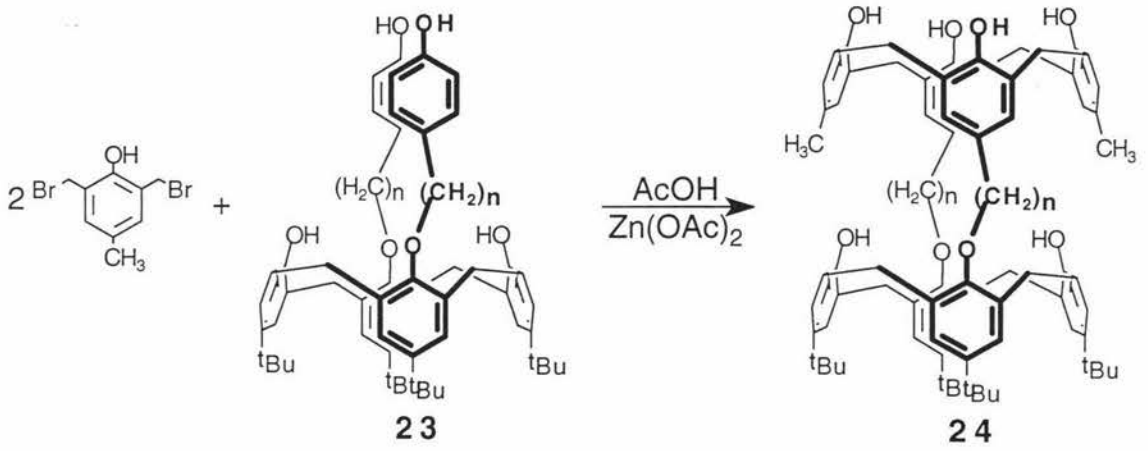
3.2.1 Fragment Condensation

This is the first method by which *bis*-calixarenes were synthesised. This approach differs from the three other strategies in that the *bis*-calixarene is not constructed from calixarene starting materials. Thus, a *fragment condensation* (*c.f.* **Chapter 1**) of polyphenolic precursors with a *para*-linked diphenol is carried out. This approach, developed by Böhmer and coworkers,[63] often leads to low yields of the desired product. An example of this approach is depicted in **Scheme 3.1**, in which singularly-bridged *bis*-calix[4]arene **22** was synthesised by route **A** in *ca.* 10% yield and by route **B** in "very low" yield.



Scheme 3.1. The condensation of polyphenols **20** and **21** to give *bis*-calixarene **22**.

These reactions proceed by condensations between the *bis*(bromomethyl) phenols **20'** and **21'** and the *ortho*-unsubstituted phenols **21** and **20** respectively. A strong Lewis acid ($TiCl_4$) was required to effect these transformations, which occur by four consecutive electrophilic aromatic substitution reactions. In the same paper, syntheses of doubly-bridged and quadruply-bridged *bis*-calix[4]arenes were also described. More recently, Böhmer reported[65] a related reaction which results in the formation of upper rim-lower rim linked *bis*-calix[4]arenes (**24**). In this case the milder Lewis acid zinc acetate was used to effect condensation between a 1,3-disubstituted *p-tert*-butylcalix[4]arene (**23**) and *bis*(bromomethyl)-*p*-cresol to give **24** in *ca.* 4% yield (**Scheme 3.2**).



Scheme 3.2. A *fragment condensation* route *via* mild Lewis acid catalysis to form *bis*-calixarenes **24a** (n = 3) and **24b** (n = 4).

While the fragment condensation approach has provided a range of *bis*-calix[4]arenes, yields tend to be low and extension to other sizes of macrocycle may not be possible.[3]

3.2.2 Two Component Coupling

The two component coupling approach was first introduced by Cram[66] in 1988 for the construction of the resorcinarene-based *carcerand*. There has been much work in this area by Cram and coworkers (for a review, see[67]) but little was carried out with phenol-based calixarenes until the 1990s. The general principle is depicted in **Figure 3.1**. Appropriately functionalised calixarene precursors (with reactive groups X and Y) come together in an intermolecular reaction to form the covalently-linked *bis*-calixarene **C**. The number of pendant functional groups (*protethers*) attached to the calixarene starting materials will dictate the number of bridges (*tethers*) in the *bis*-calixarene product.

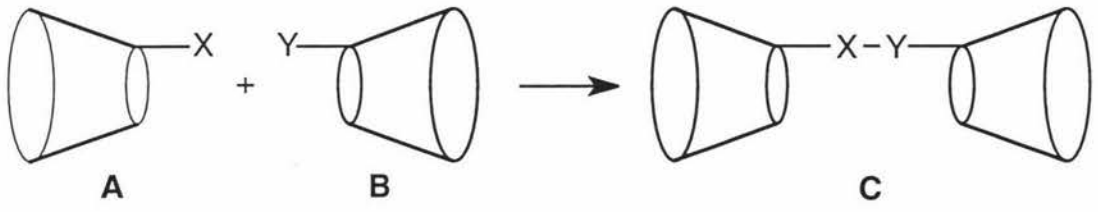
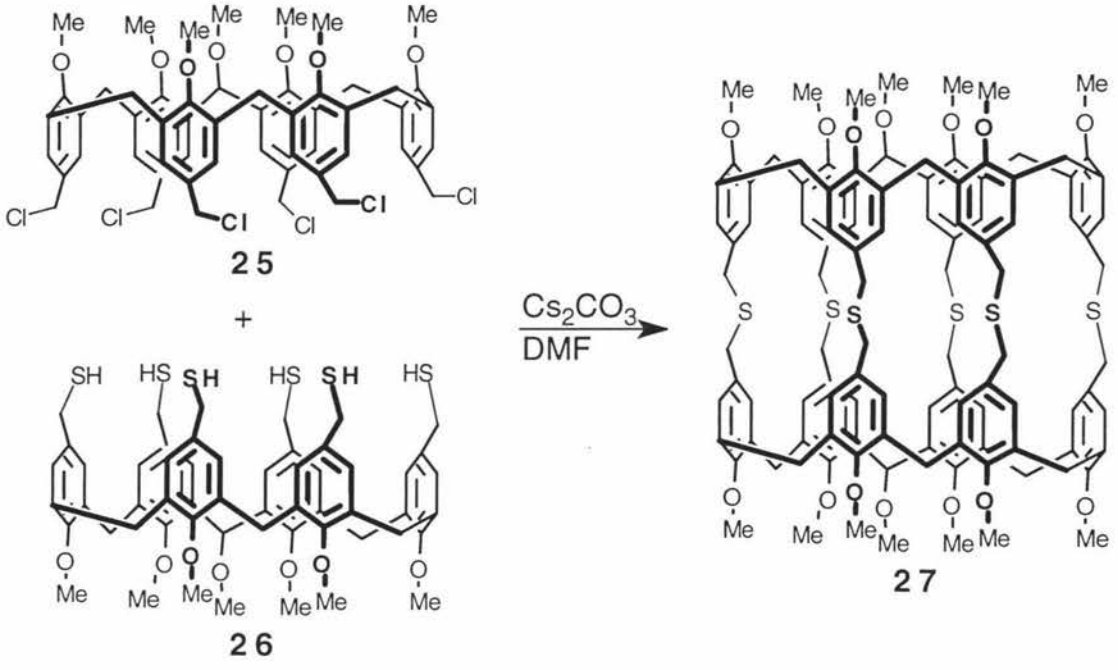


Figure 3.1. A "lower rim-lower rim" coupling schematic for obtaining *bis*-calixarenes by the Two Component Coupling method.

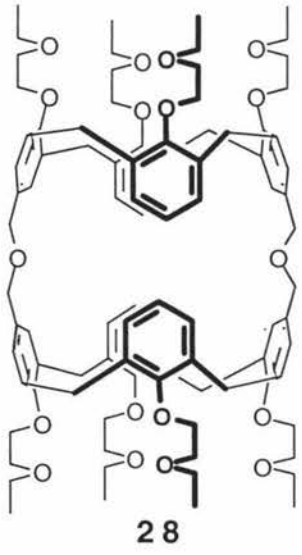
One of the first examples of two component coupling with calixarenes was carried out by the Shinkai group,[68] in which two calix[6]arene units were coupled at the upper rim to form a highly symmetrical product (**27**). This route involved the preparation of two upper rim hexafunctionalised calix[6]arene derivatives, one with chloromethyl groups

(**25**), the other with thiolmethyl groups (**26**). Then, in DMF with Cs_2CO_3 as base, a series of one intermolecular, followed by five intramolecular nucleophilic substitution reactions take place to provide *ca.* 11% yield of the hexabridged *bis*-calix[6]arene (**Scheme 3.3**). During the cyclisation process some DMF molecules become included within the *bis*-calixarene molecule (*ca.* 10 mol%).

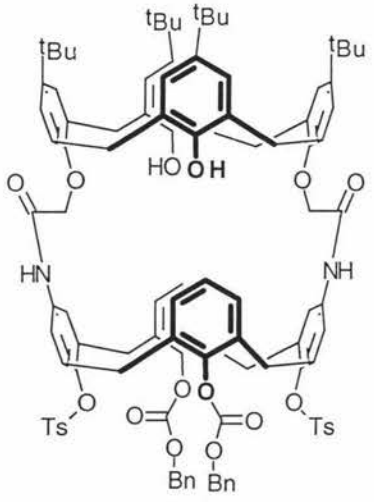


Scheme 3.3. One of the few two component coupling reactions.

Pochini *et al.*[69] prepared upper rim-upper rim coupled, doubly bridged *bis*-calix[4]arene (**28**) in 25% yield from 1,3-diformyl-tetra-*O*-ethoxyethyl calix[4]arene. The synthetic sequence involved sodium borohydride reduction of the 1,3-diformyl-tetra-*O*-ethoxyethyl calix[4]arene dialdehyde and dimerisation of the resulting diol with tosyl chloride and sodium hydride.



Beer *et al.*[70] prepared an unsymmetrical, doubly bridged *bis*-calix[4]arene (**29**) by amide formation between the calix[4]arene upper rim amine and the lower rim functionalised acid chloride (60% yield). The Pochini group recently reported a synthesis of the intriguing quadruply bridged *hetero-bis*-calixarene (**30**) in 30% yield by the reaction between an upper rim tetrachloromethylated calix[4]arene and the *p-tert*-butyl calix[8]arene.[71]



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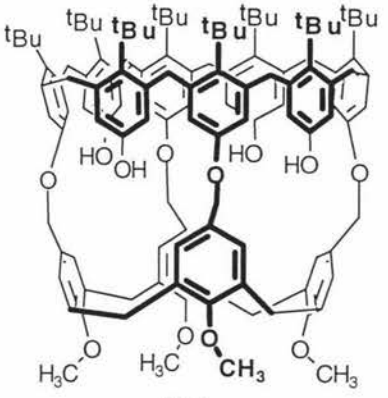
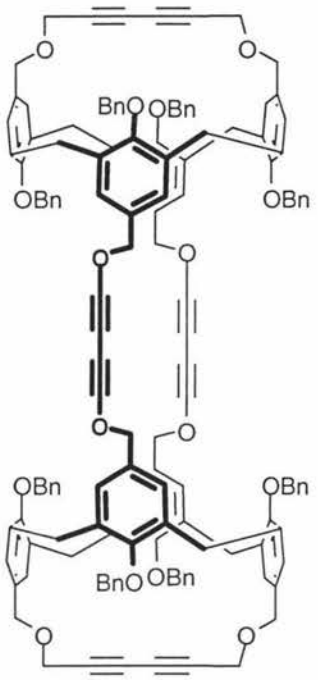


30

The use of one-step coupling reactions is desirable but the yields (as shown above) are often not as high as those obtained by more indirect approaches. The next two examples demonstrate that transition metal catalysis allows the coupling (in sometimes high yield) of calixarenes containing terminal alkynyl or alkenyl functionality to form symmetrical *bis*-calixarenes in one step.

In work by Gutsche, a Glaser-Hay coupling of tetrapropargyl calix[4]arene with copper(II) acetate hydrate in pyridine provided the symmetrical *tetrakis*(diyne) doubly bridged *bis*-calix[4]arene **31** in 7% yield.[72]



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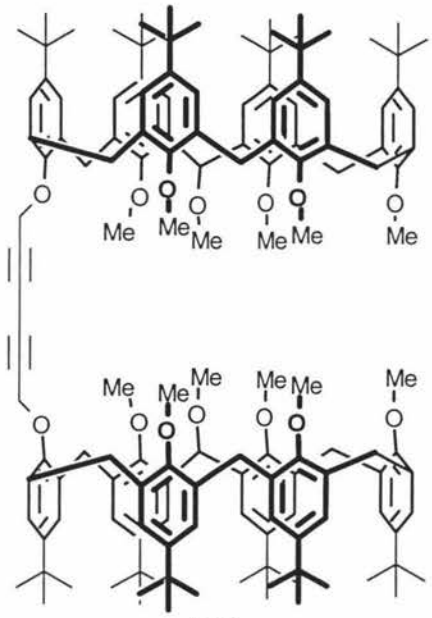
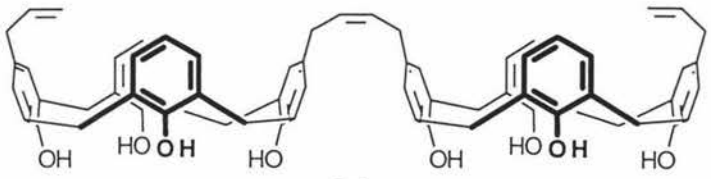


32

The Glaser-Hay coupling is an operationally simple procedure that often affords high yields of symmetrical diyne products. Applying this technique to monopropargyl-penta-*O*-methyl calix[6]arene, Gutsche reported that an almost quantitative yield of singularly-bridged calix[6]arene **32** could be obtained.[47]

In an attempt to carry out a ring-closing metathesis on 1,3-di-*O*-but-3-enyl-calix[4]arene, McKervey *et al* .[73] observed the exclusive formation (53% isolated yield) of the 1,3-doubly-bridged, symmetrical *bis*-calix[4]arene (**34**). A further experiment with 1,3-di-*p*-allyl-calix[4]arene gave a mixture of singularly-bridged *bis*-calix[4]arene (**33**, 25%), doubly bridged *bis*-calix[4]arene (**35**, 5.5%) and a *tris*-calix[4]arene (**36**, 20%)



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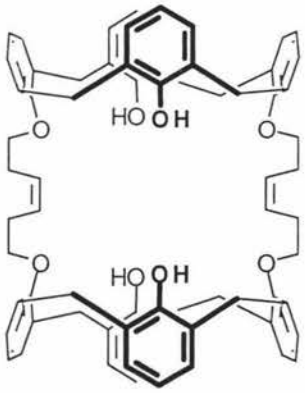

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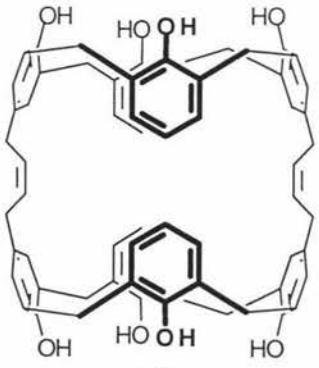

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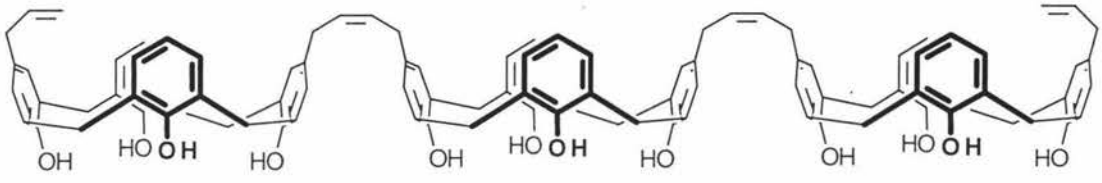
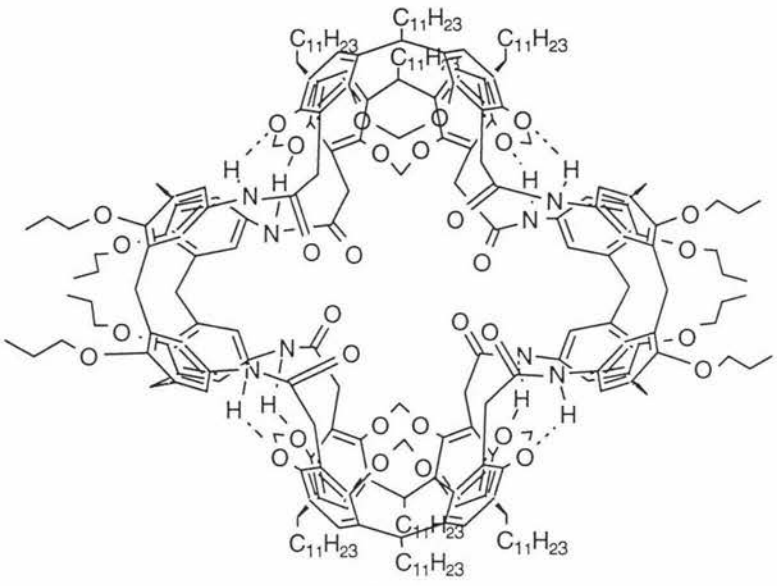


36

In a study directed towards the synthesis of receptor molecules with interesting complexation properties, Reinhoudt has prepared a series of impressive resorcinarene-calix[4]arene tetramers. The first reports, which appeared in 1994[74] described the synthesis of *holand*‡ **37** (albeit in low yield) based on a series of three consecutive two component coupling reactions.

‡ A holand is defined as a molecule which contains a permanent hole (or cavity).



37

The full paper[75] subsequently described the formation of *bis*-, *tris*-, and *tetrakis*-resorcinarene-calix[4]arene molecules, along with the introduction of the terms *endo* and *exo* to describe the stereochemical outcome of the *bis*- and *tris*-calixarene forming reactions (*endo* indicates that the cavities of the two calixarenes are facing towards each other in the coupling product and *exo* indicates that they point away from each other). A later paper[76] reported the complexing abilities of the various products. Holand **37** has no known complexing ability but the *bis*- and *tris*- calix[4]arene precursors in the synthesis of **37** have been shown to complex steroids in a selective manner.

3.2.3 Three Component Coupling

In a three component coupling, two calixarene molecules combine with one molecule of a bifunctional reagent to give a *bis*-calixarene (**Figure 3.2**).

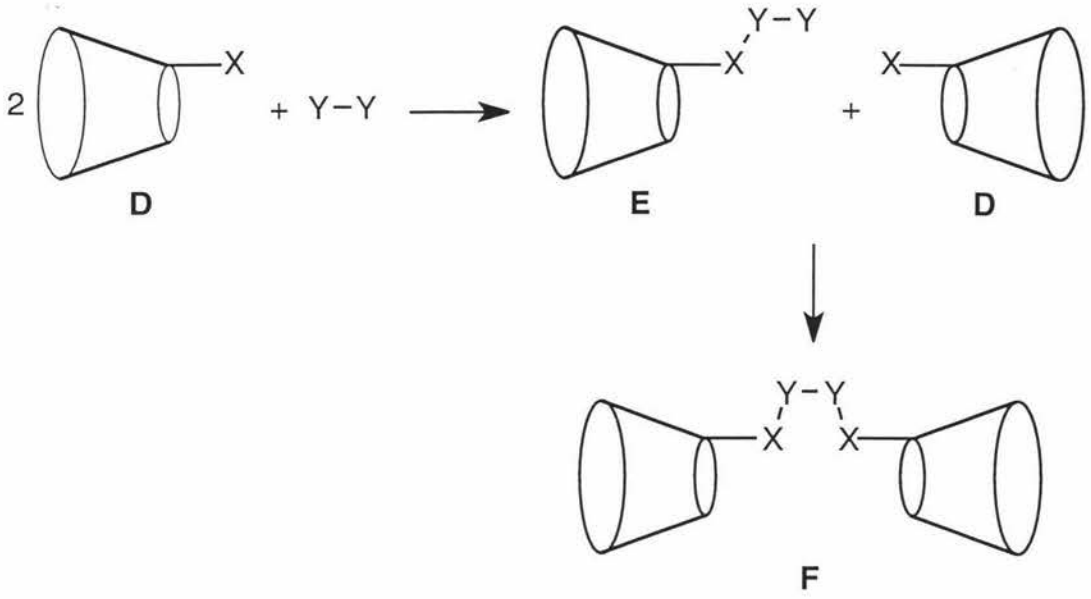
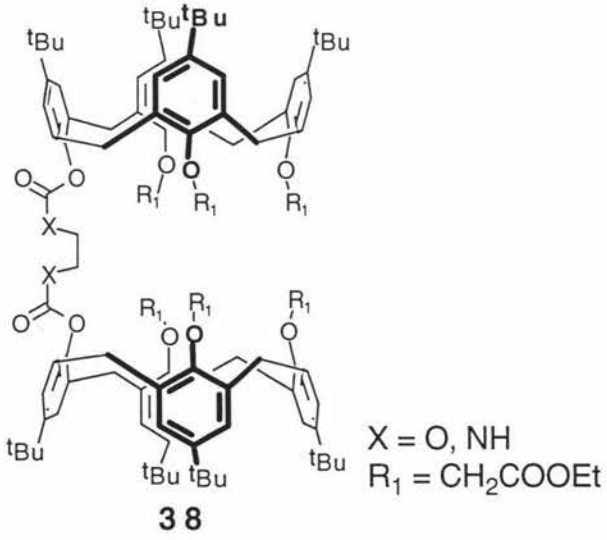


Figure 3.2. A lower rim-lower rim coupling schematic of a Three Component Coupling utilising bifunctional reagent Y-Y.

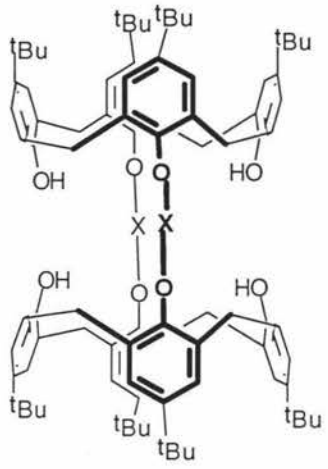
The great advantage of this route to *bis*-calixarenes is that there is an extensive range of readily available bifunctional reagents that can be utilised. *Moreover, the procedure can be used to form bis-calixarenes in a single step from the parent calixarene.* In general, this method will lead to a symmetrical *bis*-calixarene with either an upper rim-upper rim, or lower rim-lower rim linkage unless the rates of bond formation between the bifunctional reagent and calixarenes are sufficiently different for the intermediate (**E**) to be isolated.



38

The first example of this type was reported in 1990 by McKervey and Böhmer[77] in which a calix[4]arene, functionalised at the lower rim as a mono acid chloride, was allowed to react with either 1,2-diaminoethane or ethylene glycol to form symmetrical *bis*-calix[4]arenes (**38**) with diamide or diester bridges in *ca.* 40% yield.

Not long after, McKervey, Böhmer and Reinhoudt[78] reported related examples of lower rim, doubly-bridged, ester-linked *bis*-calix[4]arenes and *tris*-calix[4]arenes (X = 4,4'-biphenyldisulphonyl in **39** and **40**, R = ^{t}Bu) in *ca.* 15-35% yield in one step from *p-tert*-butylcalix[4]arene. Beer[79] reported a similar study using a *bis*-(chlorocarbonyl) metallocene to form lower rim, singularly and doubly-bridged, ester-linked *bis*-calix[4]arenes (X = 1,1'-*bis*(carbonyloxy) ferrocene, ruthenocene, cobaltocenium in **39** in *ca.* 12-64% yield, again in one step from *p-tert*-butylcalix[4]arene. Interestingly, under the same reaction conditions, the parent calix[4]arene reacted with *bis*-(chlorocarbonyl) ferrocene to afford a 34% yield of the *tris*-calix[4]arene (**40**, R = H).



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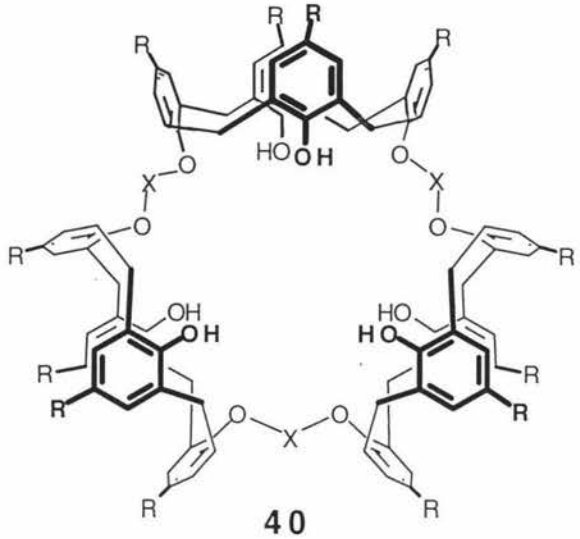
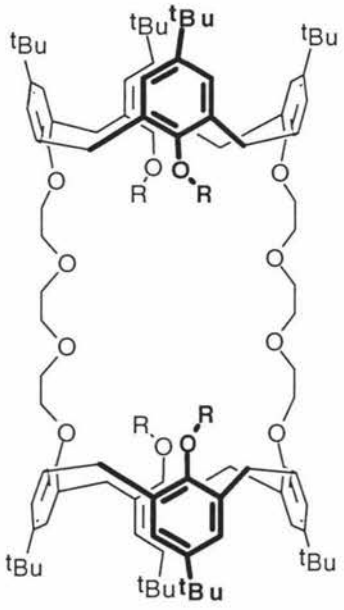


40

Polyether chains have been used as tethers between calix[4]arenes with a view to cation binding.[62] Alkylating protected *p-tert*-butylcalix[4]arenes with polyglycolic ditosylates, the "calixcrown" *bis*-calixarenes **41** and **42** could be formed.



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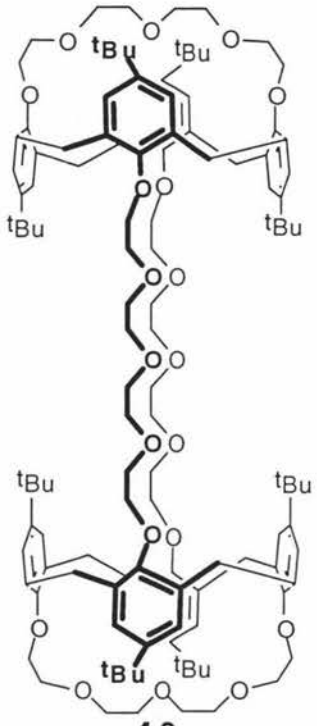
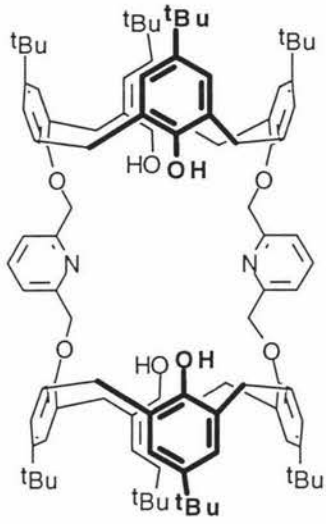


42

Thus when *p-tert*-butylcalix[4]arene (or its 1,3-dimethoxy ether) was treated with K_2CO_3 and triethylene glycol ditosylate (2 equiv.) **41** was formed. On stirring *p-tert*-butylcalix[4]arene with an excess of both K_2CO_3 and ditosylate, the capped *bis*-calixarene (**42**) was formed.

More recently, Lüning[80] and Zhong[81] have reported similar approaches to 1,3-doubly bridged *bis*-calix[4]arenes. Thus, Lüning heated a mixture of *p-tert*-butylcalix[4]arene (1.0 equiv), 2,6-*bis*(bromomethyl)pyridine (1.0 equiv), K_2CO_3 (2.0 equiv) and 18-crown-6 (0.025 equiv) in acetonitrile to afford symmetrical *bis*-calix[4]arene (**43**) in a respectable 52% yield. Zhong heated a mixture of *p-tert*-butylcalix[4]arene (1.0 equiv), 2,6-*bis*(bromomethyl)-4-methylanisole (1.0 equiv), K_2CO_3 (2.5 equiv) and KI (quantity not reported) in benzene for 3 days to afford symmetrical *bis*-calix[4]arene (**44**) in a similar 51% yield.



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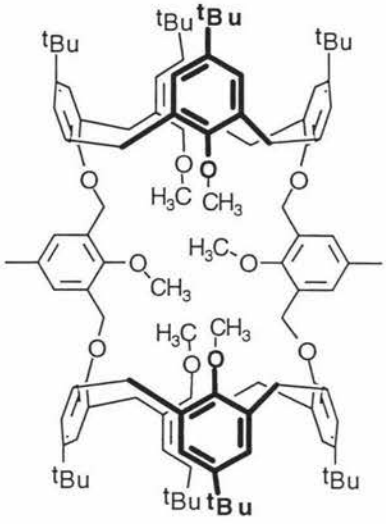
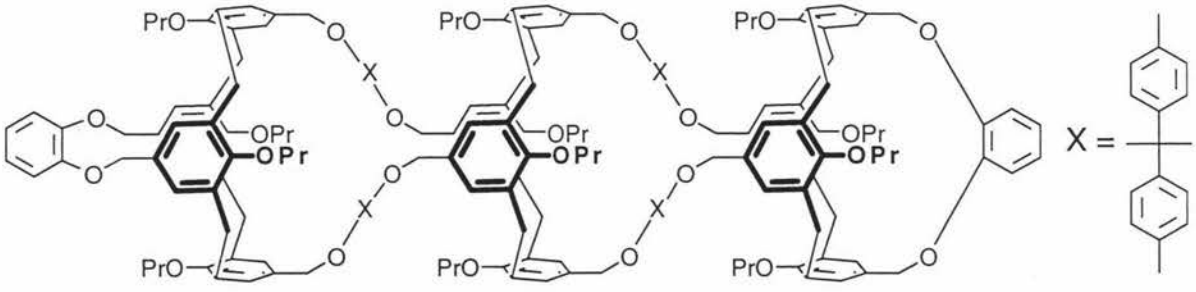


44

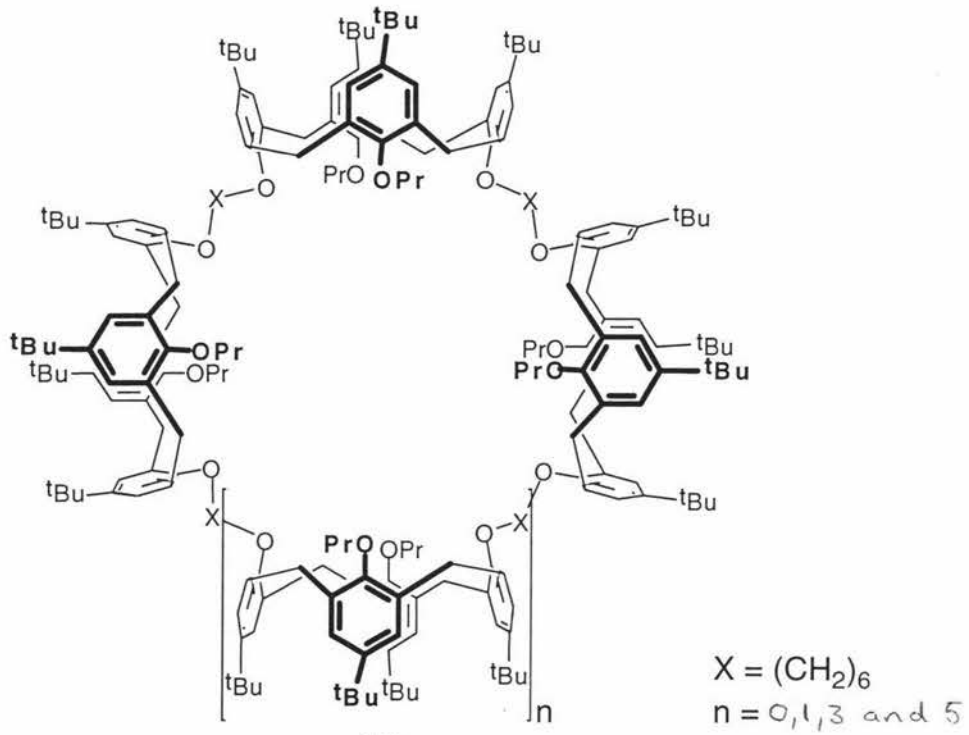
Calix[4]arene dimers and trimers have also been prepared by the three component coupling method in which the calix[4]arene is fixed in a 1,3-alternate conformation.[82] Shinkai describes such compounds as 'synthetic nanotubes' due to the π-basic hole within these molecules which may allow for metal tunnelling. Thus, reaction of 1,3-alternate tetra-*O*-propyl-tetra-*p*-chloromethyl-calix[4]arene with catechol and K_2CO_3/NaI in refluxing acetone, followed by treatment with bisphenol A gave trimer **45** in 17% yield. A similar procedure provided a dimeric analogue in 10% yield.



45

More recently, Shinkai has reported approaches to calix[4]arene dendrimers by consecutive alkylation reactions with dibromoalkanes and selectively functionalised calix[4]arenes.[83] Using tri- and di-protected *p-tert*-butyl-calix[4]arenes and *p*-H-calix[4]arenes, the corresponding *bis*- (>33%), *tris*- (>30%), and *pentakis*- (38% and 7%) calix[4]arenes were obtained. The yields for these alkylation reactions are often compromised by competing HBr elimination of the dibromoalkanes.

The largest of all calixarene assemblies prepared thus far were reported by Shinkai in 1996.[84] These impressive compounds (**46**, termed "macrocycle of macrocyles") containing between four and eight calix[4]arene subunits connected at the lower rim, were constructed in sequence of three component coupling reactions.



46

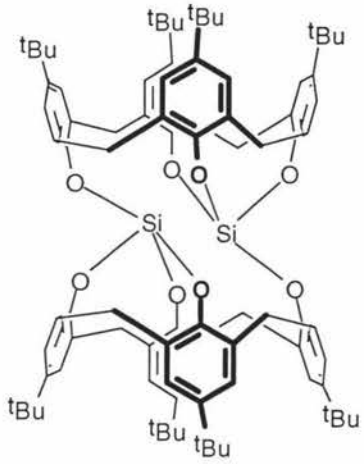
This work employed selectively protected (lower rim 1,3-disubstituted and 1,2,3-trisubstituted) calix[4]arenes and some remarkably high yields were reported (*e.g.* 32% for the tetramer). Coupling of these selectively protected calix[4]arene starting materials led to linear oligomers which could be cyclised under high dilution conditions to form macrocycles (**46**).

As noted earlier, this route is the most effective for generating oligocalixarenes, since prior synthetic manipulation of the calixarene skeleton is not necessary. If the functionalisation protocols are selective enough, relatively large quantities of oligocalixarenes might be accessible for use in studies on complexation, catalysis, and molecular recognition. To summarise the previous work in this area, it appears that all examples published relating to the three component coupling approach have been carried out on calix[4]arene. Moreover, the majority of these existing methods have been used to prepare 1,3-doubly-bridged *bis*-calix[4]arenes: these procedures take advantage of the facile 1,3-dietherification and esterification of calix[4]arenes with mild bases (*cf.* **Chapter 2**).

3.2.4 Supramolecular Assemblies

The design and construction of multiple calixarene-based structures in which the individual units are connected by noncovalent interactions (*i.e.* metal-oxygen bonds, hydrogen bonds) is a relatively new area.

The strong silicon-oxygen bond has been employed by Hosseini *et al.* in a series of papers[85-87] to form *bis*-calix[4]arenes and a *tris*-calix[4]arene. For example, adding $SiCl_4$ to a solution of *p-tert*-butylcalix[4]arene and sodium hydride, *bis*-calix[4]arene **47** was obtained in 52% yield.[86]



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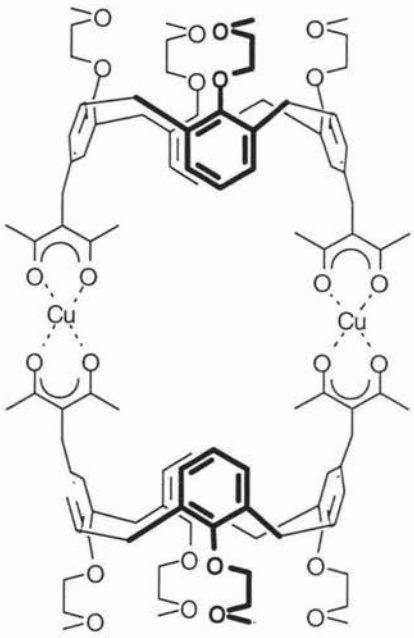
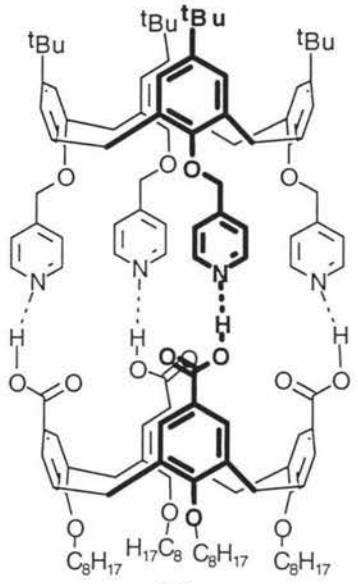


48

The analogous titanium compound was also prepared, this time from a direct reaction between of *p-tert*-butylcalix[4]arene with titanium tetrachloride.[87]

Cu(II)-chelate bridges were used by Shinkai to form a novel symmetrical *bis*-calix[4]arene structure that recognised diamine substrates.[88] Thus, the 1,3-di-*p*-diacetylacetone-derived calixarene, upon the addition of $[Cu(NH_3)_4]^{2+}$ in chloroform-water, provided doubly-bridged complex **48** in 50% yield.

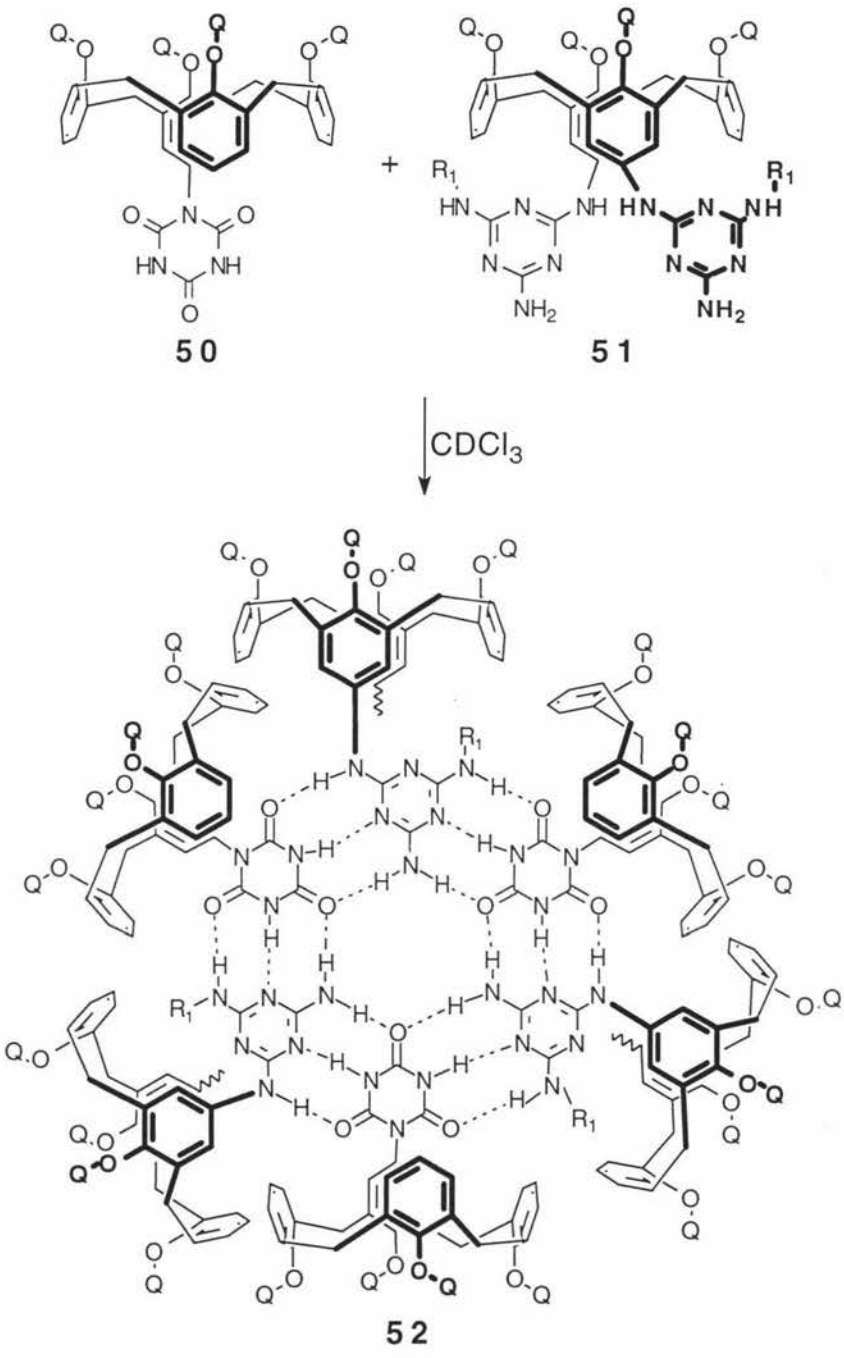
Intramolecular hydrogen bonds govern the conformational preferences of calixarenes (*vide supra*). Strong mass spectrometric evidence for intermolecular hydrogen bonds between *p-tert*-butylcalix[*n*]arenes (n=4 to 8) was recently reported by Shinkai.[89] These results may explain a number of physical properties of the calixarenes such as variable solubility in organic media and gel formation, but as yet there is no evidence for regular arrangements of calixarenes in the solution phase. Several groups have successfully prepared calix[4]arene derivatives containing functionality that can hydrogen bond in a regular arrangement, and these huge structures may find application in a range of areas. Once again, the Shinkai group was the first to publish an example of a hydrogen-bonded *bis*-calixarene dimer.[90] The interaction between an upper rim, *p*-carboxylic acid-derived calix[4]arene and a complimentary upper rim, *p*-pyridine-substituted calix[4]arene gave hydrogen bonded adduct **49**, detectable by ^1H nmr.



49

Reinhoudt's group subsequently produced a hydrogen-bonded *bis*-calix[4]arene with the same linking functionalities except that the pyridyl units are bound to the lower rim.[91] Related examples reported by the Rebek[92] and Böhmer[93] groups used urea-based functional groups to construct symmetrical dimeric *bis*-calix[4]arenes, the former exhibiting reversible encapsulation properties.

Reinhoudt's group has also reported trimeric and hexameric hydrogen-bonded complexes between upper rim 1,3-dimelamine substituted calix[4]arene (**51**) and upper rim (**50**) or lower rim isocyanuric acid-substituted calix[4]arene to give the "double rosette structure" of *hexakis*-calix[4]arene, **52**.[94]



Scheme 3.4. The formation of the hydrogen bonded hexamer **52**. Only the top layer has been shown for clarity.

Hence, from all of the examples shown above it is clear to see that the vast majority of work has been carried out on calix[4]arenes. Very little work has been carried out on the other cyclic oligomers thus leaving many unexplored possibilities.

To date, most methods have provided considerably less than 40% of *bis*-calixarene from the parent calixarene. Moreover, most have employed a number of steps to obtain the desired products. In many cases the outcome of the reactions of unprotected calixarenes

has led to unexpected products (i.e. the formation of trimers) and as such, many protocols have utilised protected calixarene starting materials.

3.3 DISCUSSION

An important consideration in designing a synthesis of *bis*-calixarenes is to obtain the desired product cleanly and in high yield. It was deemed to be very important to devise the shortest synthetic route possible to *bis*-calixarenes, hence protection and deprotection steps should be kept to a minimum. In this model study, it was decided to approach the synthesis of singularly-bridged *bis*-calixarenes by:

i) taking advantage of our previously developed selective monoalkylation protocol to obtain lower rim monofunctionalised calixarenes (the schematically-represented starting materials in **Figure 3.3**)

ii) using a "two component coupling" strategy (**Section 3.2.2**, **Figure 3.1**) to obtain a range of different tethers (bridges).

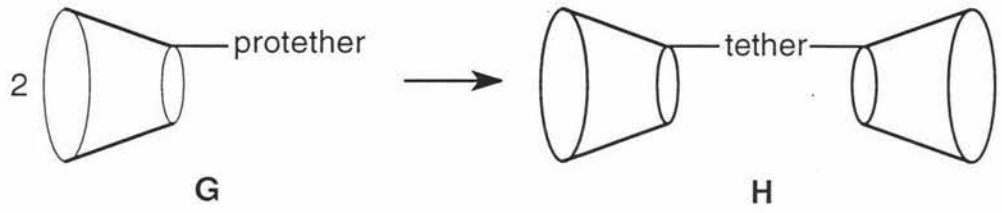


Figure 3.3. The schematic coupling of lower rim monofunctionalised calixarenes (G has a protether functionality) to give a *bis*-calixarene (H).

Some typical *protethers* are alkynes, alkenes, aryl halides, and alkyl halides. Besides the obvious advantage of improving synthetic efficiency, other desirable attributes of this approach are apparent, for example, the protethers would allow the construction of a wide range of different tethers with various properties, and the coupling step would allow both *homo*- and *hetero-bis*-calixarenes to be prepared.

3.3.1 Synthesis of Diyne Bridged *Bis*-Calixarenes

One of the long term goals of this project is to use the terminal acetylenic functionality for palladium catalysed coupling reactions with aryl- and vinyl halides to form enediyne bridged *bis*-calixarenes. This novel bridge would allow a thermally induced cycloaromatisation that would bring the two calixarenes into closer proximity. This type of process might have application in waste management by irreversibly binding cations, anions or neutral molecules (**Figure 3.4**).

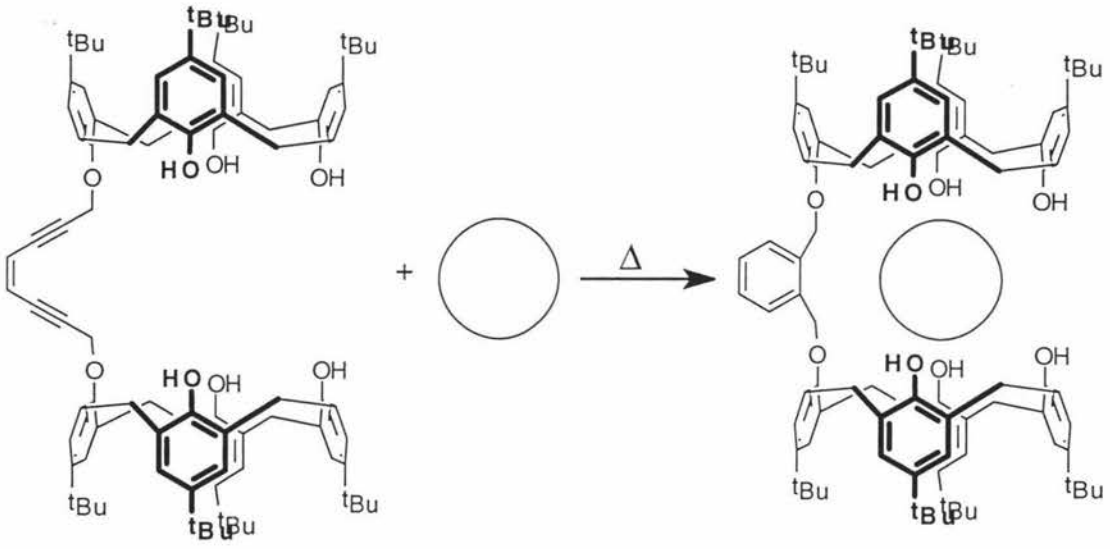


Figure 3.4. The cycloaromatisation of a *bis*-calixarene bridged enediyne encapsulating a guest species (represented by an unshaded circle).

Many problems were encountered with the palladium catalysed coupling reactions. The first of these were performed on monopropargylated calix[6]arene in which the remaining phenolic residues were not protected. This led to intractable mixtures of unidentified products. It was thought that the presence of the free phenolic residues might be allowing undesired redox reactions to occur. Hence, the most obvious approach was to use a monofunctionalised calixarene with the remaining phenolic groups protected (**Figure 3.5**).

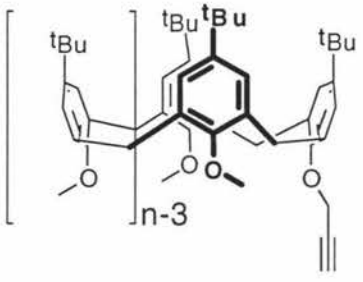
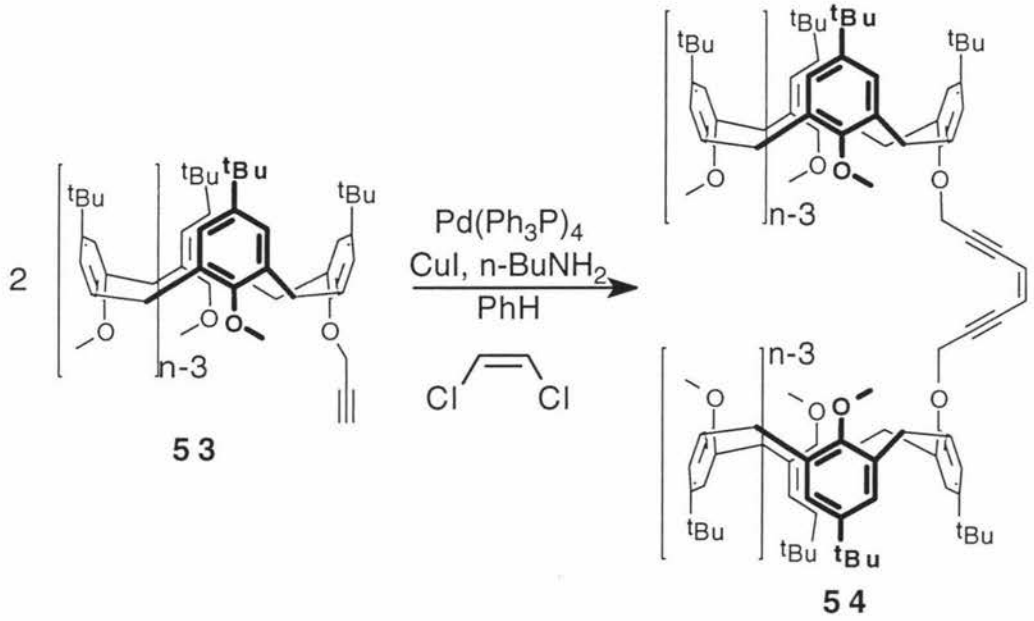


Figure 3.5. The general structure of the methylated propargyloxycalix[*n*]arenes.

After protection of the free phenolic residues as methyl ethers, the palladium catalysed couplings with *cis*-1,2-dichloroethylene were revisited. This time the results were far more encouraging. In a reaction of a protected monopropargylated *p-tert*-butylcalix[6]arene **34** with *cis*-1,2-dichloroethylene in the presence of copper(I) iodide

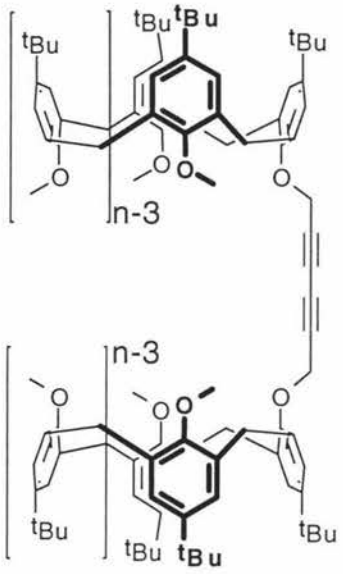
and palladium(0) a trace quantity (<1%) of the desired enediyne **35**† was observed in the ^{1}H n.m.r. spectrum (**Scheme 3.5**).



Scheme 3.5. The formation of an enediyne bridged *bis*-calix[6]arene **54** (n = 6).

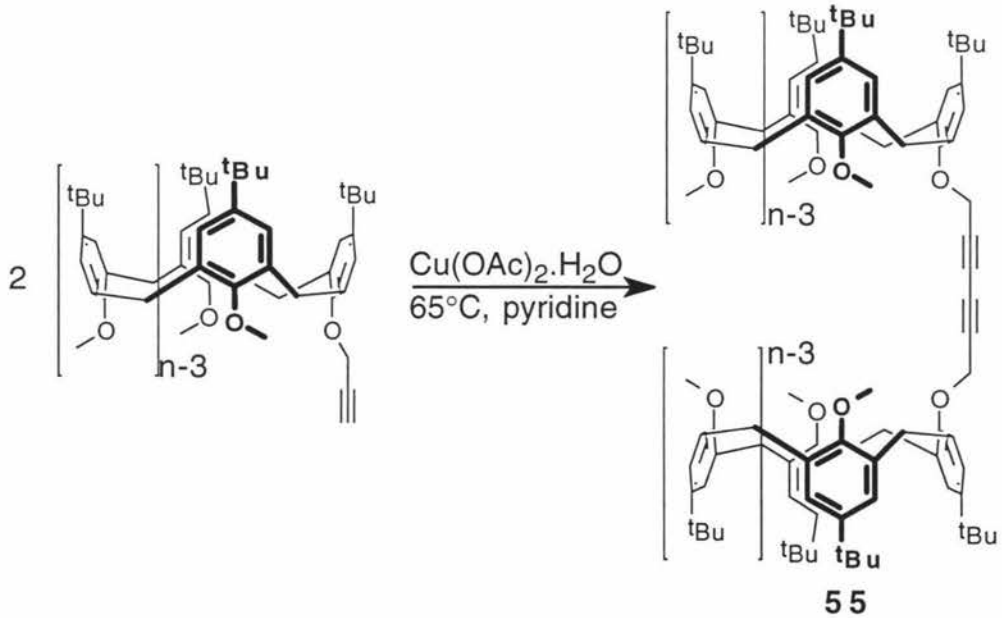
In spite of the low yield, all of the starting material had been consumed in the course of the reaction. The ^{1}H n.m.r. spectrum showed an upfield shift for the signal corresponding to the propargylic CH_2 and disappearance of the terminal propargylic C-H signal. Mass spectral data showed clearly that the major product from the reaction was the symmetrical diyne bridged *bis*-calixarene **55**. Despite many attempts to avoid the formation of the diyne, including conducting the reaction in a Schlenck tube under strictly anaerobic conditions, this undesirable side reaction was unavoidable.

† Unfortunately, due to the small quantity and similarity in R_f with the byproducts, it was not possible to isolate and fully characterise this compound.



55

In view of time constraints, it was decided to take advantage of this simple method for synthesising symmetrical *bis*-calix[4, 6 and 8]arenes. When a large excess of $Cu(OAc)_2.H_2O$ (30 equiv.) in a highly concentrated solution of pyridine was stirred with the starting propargylated calixarene an almost quantitative yield of the desired diyne (**55**) was obtained.



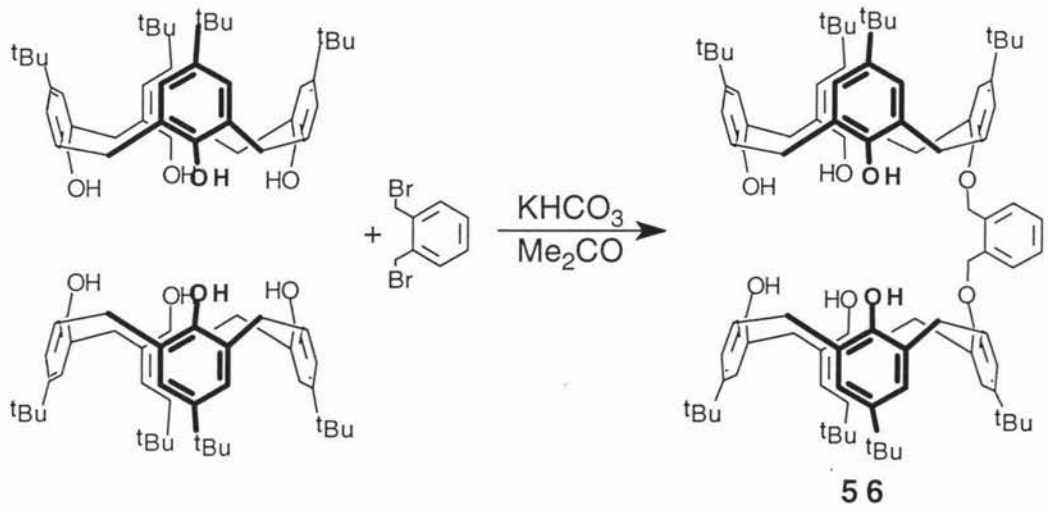
55

Scheme 3.6. The successful Glaser-Hay coupling of calix[6]arene derivative **55**.

During the course of this work, Gutsche has described the synthesis of diyne bridged *bis*-calixarenes.[47]

3.3.2 The One-Step Synthesis of α,α'-Xylene Bridged *Bis*-Calixarenes

The ultimate test for the previously developed monoalkylation reactions was in an investigation into the use of a bifunctional alkylating agent in a "three component coupling" approach (**Section 3.2.3**) to form lower rim-lower rim bridged *bis*-calixarenes from the parent calixarenes (**Scheme 3.7**).



Scheme 3.7. The synthesis of *bis*-calix[4]arene **56** from *p-tert*-butylcalix[4]arene and α,α'-dibromo-*o*-xylene.

The monofunctionalisation procedures that are discussed in the previous chapter were designed to be applicable for the one-step synthesis of *bis*-calixarenes. Thus, extensive measures were undertaken to optimise both conversion and selectivity for monoalkylated products. A natural extension of this project was to use α,α'-dibromo-*o*-xylene in place of benzyl bromide because it is an activated alkylating agent that can be disubstituted with two calixarene moieties.

We expected to observe similar reactivity towards the *bis*-electrophile with all calixarenes. Interestingly this was not the case and the reactivity of each calixarene towards dibromo xylene varied considerably. The distribution of products appeared to relate to the steric bulk of each calixarene (with the exception of the cyclic pentamer) as can be seen by the yields of these reactions. The tetramer, pentamer and hexamer gave 55%, 69% and 64% respectively, of the xylene bridged *bis*-calixarene . The high yield of *bis*-calix[5]arene from the standard reaction conditions is possibly related to the macrocycle having the weakest hydrogen bonding around the lower rim (*cf.* **Chapter 1**).

Under the standard conditions the two largest macrocycles produced the monoalkylated calixarene products exclusively. This reduction in the rate of alkylation may be due to steric effects. The larger members may be able to accommodate the bromobenzyl moiety inside the cavity, thus shielding approach by another calixarene.

3.4 CONCLUSION

We have been able to synthesise a variety of *bis*-calixarenes by two different routes. Glaser-Hay coupling allowed the synthesis of symmetrical diyne bridged *bis*-calix[4, 6 and 8]arenes in high yield.

Extension of the first *general* mono-*O*-alkylation procedure for calixarenes has made it possible to synthesise homo-*bis*-calixarenes in good yield in *one step* from the parent calixarenes.

The unexpected formation of monobromoxylyl calixarenes allows the prospect of the synthesis of *hetero-bis*-calixarenes under more forcing conditions. Most importantly this allows us to further explore the chemistry of *bis*-calixarenes by making them readily available (in large quantities) for more elaborate syntheses.

Chapter 4

EXPERIMENTAL WORK

4.1 GENERAL DETAILS

^{1}H nuclear magnetic resonance spectra were obtained using a JEOL GX270 spectrometer at 270 MHz and ambient temperature. Data is expressed in parts per million downfield shift from tetramethylsilane (internal standard), and reported as position (δ), multiplicity (s = singlet, d = doublet, t = triplet), coupling constant (J in Hz), relative intensity and assignment.

^{13}C nuclear magnetic resonance spectra were recorded on a JEOL GX270 spectrometer at 68 MHz at ambient temperature with complete proton decoupling. Data is expressed in parts per million downfield shift from tetramethylsilane (internal standard) and reported as position (δ) and assignment. In cases where large numbers of signals were observed within 2 parts per million a range has been reported.

Both high and low resolution spectra were obtained using a VG-70S double focusing Magnetic sector mass spectrometer. Spectra were calibrated against CsI standard in a matrix of *p*-nitrobenzyl alcohol or CH_2Cl_2. The ionisation method was fast atom bombardment run in the positive mode (FAB^+) at 20 keV.

Infra-red data were collected using a BIO-RAD FTS-7 or Perkin-Elmer PARAGON 1000 FT-IR spectrometer. Samples were prepared as KBr discs and the data reported in wavenumbers (cm^{-1}).

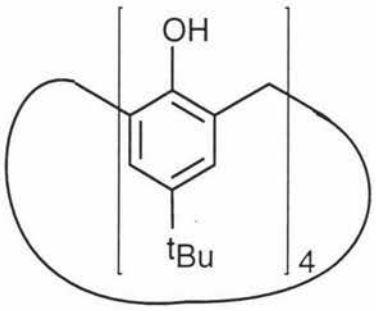
Thin layer chromatography (t.l.c.) was carried out on 0.2 mm silca gel coated aluminium plates (Merck Kieselgel 60 F_{254}). Visualisation was by use of u.v. light (254 nm) and staining with aqueous $KMnO_4$ solution or anisaldehyde in ethanolic sulphuric acid.

Flash chromatography was performed according to the method of Still *et al.*[95] using Merck Kieselgel 60 (230-400 mesh) with the solvent mixture indicated. Gradient elutions were monitored closely by t.l.c. before increasing solvent polarity.

Solvents and reagents were dried (where necessary) according to the methods of Perrin and Amarego.[96] *p-tert*-Butylphenol was purchased from Merck-Schuchardt and used without further purification. Paraformaldehyde was supplied by Pauling Industries Ltd. and 37% aqueous formadehyde supplied by Ajax Chemicals Ltd. Acetone and acetonitrile were A.C.S. reagent grade and used as supplied by Riedel-de Haen or BDH Laboratory Supplies.

Analytical samples were dried at ~100°C and 0.1 Torr for 36 hours. Melting points were not obtained as almost all of the compounds synthesised melted above 250°C.

4.2 CHAPTER 1 EXPERIMENTS⊗



5,11,17,23-Tetra-*tert*-butyl-25,26,27,28-tetrahydroxycalix[4]arene.

This is a modified procedure of that reported by Gutsche.[4] In a 3L, three-necked round bottom flask equipped with a mechanical stirrer, a mixture of 37% aqueous formaldehyde (62 mL, 0.83 mol), *p-tert*-butylphenol (100 g, 0.67 mol) and sodium hydroxide (1.2 g, 0.030 mol) was heated at 110-120°C for *ca.* 2 h† Throughout this time into the flask was blown N_2 (*ca.* 200 bubbles/min) to help the removal of water and excess formalin. Warm diphenyl ether‡ (900 mL) was added, with stirring, to dissolve the residue. A condenser was fitted to the flask and the solution heated under a strong flow of N_2 before attaining reflux.# The N_2 flow was reduced and the mixture left to reflux for 2.5-3 h Upon cooling (at *ca.* 65°C) the mixture was poured into ethyl acetate (2 L) and stirred vigorously for 20 min, then left to stand for 16 h at room temperature. The crystalline solid was filtered off and washed with

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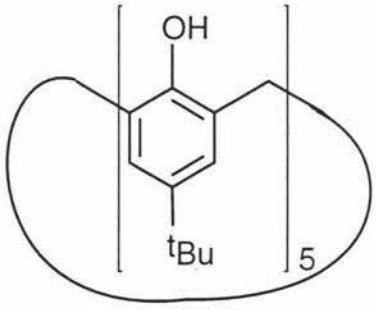
⊗ The synthesis of the starting materials is outlined here as the literature procedures have reported incomplete data.

† The mixture should become clear then go to a thick, golden taffy like consistency.

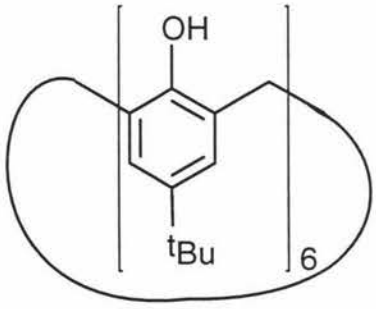
‡ The diphenyl ether has been recycled from previous preparations by high vacuum distillation.

An increased N_2 flow is used to remove the last traces of water.

ethyl acetate (2x100 mL), acetic acid (200 mL) then water (3x100 mL) and dried *in vacuo* (at 100°C) to give an off-white, highly crystalline solid (77 g, 71%): ^{1}H NMR (270 MHz, $CDCl_3$) δ 10.35 (s, 4H, -O*H*), 7.06 (s, 8H, Ar-*H*), 4.26 (d, *J*=13.3 Hz, 4H, Ar-CH_2-Ar), 3.50 (d, *J*=13.3 Hz, 4H, Ar-CH_2-Ar), 1.22 (s, 36H, -C (CH_3)$_3$); ^{13}C NMR (68 MHz, $CDCl_3$) δ 146.5 (s, ^{Ar}C-OH), 144.2 (s, ^{Ar}C-^{t}Bu), 127.6 (s, ^{Ar}C-CH_2Ar), 125.8 (s, ^{Ar}C-H), 34.1 (s, -*C* (CH_3)$_3$), 32.7 (s, Ar-*C*H_2-Ar), 31.5 (s, -C (CH_3)$_3$); IR (KBr disc) 3179, 1516, 1242, 1200, 915, 834, 792 cm^{-1}; HRMS (FAB$^+$) *m/z* calc'd for $C_{44}H_{56}O_4$: 648.4179, found 648.4107.

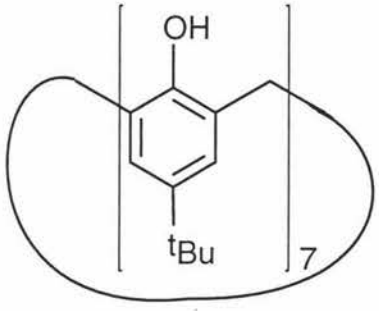


5,11,17,23,29-Penta-*tert*-butyl-31,32,33,34,35-pentahydroxy calix[5]arene. Prepared from 112.5 g of *p-tert*-butylphenol as described by Gutsche.[8] *p-tert*-Butylcalix[5]arene was obtained as a white crystalline solid (13.3 g, 11%; lit.[8] 10-15%): ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.68 (s, 5H, -O*H*), 7.22 (s, 10H, Ar-*H*), 3.80 (br s, 10H, Ar-CH_2-Ar), 1.27 (s, 45H, C(CH_3)$_3$); ^{13}C NMR (68 MHz, $CDCl_3$) δ 147.4 (s, ^{Ar}C-OH), 143.8 (s, ^{Ar}C-^{t}Bu), 126.1 (s, ^{Ar}C-CH_2Ar), 125.5 (s, ^{Ar}C-H), 34.0 (s, -*C* (CH_3)$_3$), 31.6 (s, Ar-*C*H_2-Ar), 31.5 (s, -C (CH_3)$_3$); IR (KBr disc) 3298, 1516, 1361, 1291, 1205, 885, 799, 667 cm^{-1}; HRMS (FAB$^+$) *m/z* calc'd for $C_{55}H_{70}O_5$: 810.5223, found 810.5183.

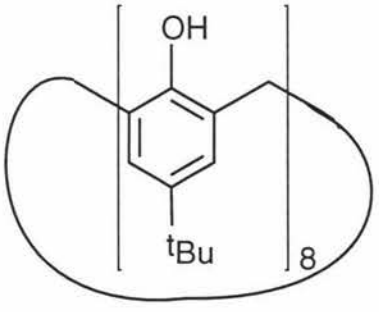


5,11,17,23,29,35-Hexa-*tert*-butyl-37,38,39,40,41,42-hexahydroxy

calix[6]arene. Prepared from 100 g of *p-tert*-butylphenol as reported by Gutsche.[5] *p-tert*-Butylcalix[6]arene was obtained as a white powder (90.5 g, 84%, lit.[5] 83-88%): ^{1}H NMR (270 MHz, $CDCl_3$) δ 10.54 (s, 6H, -O*H*), 7.16 (s, 12H, Ar-*H*), 3.90 (br s, 12H, Ar-CH_2-Ar), 1.27 (s, 54H, C(CH_3)$_3$); ^{13}C NMR (68 MHz, $CDCl_3$) δ 147.1 (s, ^{Ar}*C*-OH), 144.1 (s, ^{Ar}*C*-^{t}Bu), 126.8 (s, ^{Ar}*C*-CH_2Ar), 126.1 (s, ^{Ar}*C*-H), 34.1 (s, -*C* (CH_3)$_3$), 33.1 (s, Ar-*C*H_2-Ar), 31.6 (s, -C (*C*H_3)$_3$); IR (KBr disc) 3132, 1486, 1362, 1202, 872, 810, 747, 722 cm^{-1}; HRMS (FAB$^+$) *m/z* calc'd for $C_{66}H_{84}O_6$: 972.6268, found 972.6358.

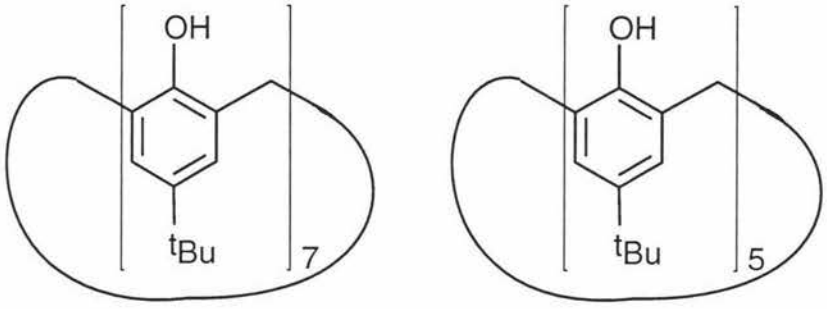


5,11,17,23,29,35,41-Hepta-*tert*-butyl-43,44,45,46,47,48,49-hepta hydroxycalix[7]arene. Prepared on the same scale as Vocanson.[9] *p-tert*-Butylcalix[7]arene was obtained as a white powder (765 mg, 6%, lit.[9] 16.8%): ^{1}H NMR (270 MHz, $CDCl_3$) δ 10.35 (s, 7H, -O*H*), 7.22 (s, 14H, Ar-*H*), 3.93 (br s, 14H, Ar-CH_2-Ar), 1.30 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (68 MHz, $CDCl_3$) δ 147.1 (s, ^{Ar}*C*-OH), 144.2 (s, ^{Ar}*C*-^{t}Bu), 127.3 (s, ^{Ar}*C*-CH_2Ar), 126.0 (s, ^{Ar}*C*-H), 34.1 (s, -*C* (CH_3)$_3$), 33.0 (s, Ar-*C*H_2-Ar), 31.6 (s, -C (*C*H_3)$_3$); IR (KBr disc) 3178, 1485, 1362, 1292, 1204, 873 cm^{-1}; HRMS (FAB$^+$) *m/z* calc'd for $C_{77}H_{98}O_7$: 1134.7313, found 1134.7282.



5,11,17,23,29,35,41,47-Octa-*tert*-butyl-49,50,51,52,53,54,55,56-octahydroxycalix[8]arene. Prepared on the same scale as Gutsche.[6] *p-tert*-

butylcalix[8]arene was obtained as a white powder (65.7 g, 61%, lit.[6] 62-65%): ^{1}H NMR (270 MHz, $CDCl_3$) δ 9.65 (s, 1H, -O*H*), 7.20 (s, 2H, Ar-*H*), 4.38 (d, *J*=13.3 Hz, 1H, Ar-CH_2-Ar), 3.52 (d, *J*=13.3 Hz, 1H, Ar-CH_2-Ar), 1.27 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (68 MHz, $CDCl_3$) δ 146.5 (s, ^{Ar}*C*-OH), 144.6 (s, ^{Ar}*C*-^{t}Bu), 128.6 (s, ^{Ar}*C*-CH_2Ar), 125.4 (s, ^{Ar}*C*-H), 34.1 (s, -*C* (CH_3)$_3$), 32.4 (s, Ar-*C*H_2-Ar), 31.5 (s, -C (*C*H_3)$_3$); IR (KBr disc) 3222, 1486, 1361, 1204, 875, 783, 600 cm^{-1}; HRMS (FAB$^+$) *m/z* calc'd for $C_{88}H_{112}O_8$: 1296.8357, found 1296.8264.

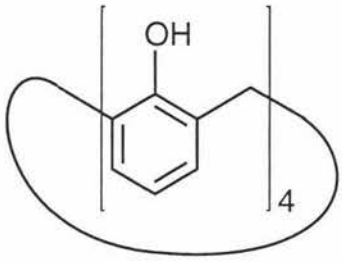


Alternative preparation of **5,11,17,23,29,35,41-Hepta-*tert*-butyl-43,44,45,46,47,48,49-heptahydroxycalix[7]arene** and **5,11,17,23,29-penta-*tert*-butyl-31,32,33,34,35-pentahydroxy calix[5]arene.**

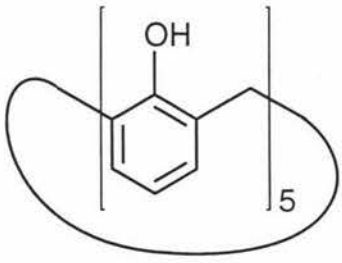
Combination of xylene residues and toluene washings from the preparation of *p-tert*-butylcalix[8]arene (see above[6]) and removal of the solvents *in vacuo* gave a brown gummy solid (*ca.* 50 g). This was stirred with $CHCl_3$ (150 mL) until homogenous, then 2N HCl (100 mL) was added and the biphasic mixture stirred vigorously for 10 minutes.* The organic phase was separated and left to stand at 20°C for 2 days and the precipitated *p-tert*-butylcalix[6]arene (*ca.* 1.0 g) was isolated by filtration. The filtrate was dried ($MgSO_4$), the solvent removed *in vacuo* and the residue was taken up in acetone (100 mL). Standing at 20°C for 15 minutes caused the crystallisation of more *p-tert*-butylcalix[6]arene (*ca.* 2.2g). Into the filtrate was placed several seed crystals of *p-tert*-butylcalix[5]arene and the solution was left at -15°C for 3 hours to yield pure *p-tert*-butylcalix[5]arene (1.1g). Evaporation of *ca.* 10 mL of acetone and further cooling provided more pure *p-tert*-butylcalix[5]arene (after three repetitions a total of 3.5 g was isolated). The solvent was removed *in vacuo* to afford a brown foam (*ca.* 26 g) which was dissolved in acetone (25 mL) then left overnight at -15°C. Filtration gave a mixture of *p-tert*-butylcalix[8]arene and *p-tert*-dihomooxacalix[4]arene (*ca.* 4

* Some white solid may precipitate out of the solution. Filtration yields a small quantity of mainly *p-tert*-butylcalix[6]arene.

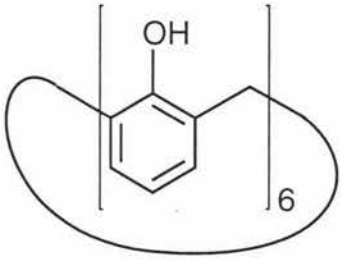
g), and evaporation of the filtrate gave a brown foam (*ca.* 22 g). This was adsorbed onto SiO_2 (50 g), placed on a column of SiO_2 (50 g), then eluted with 3:1 hexane:$CHCl_3$ to give ~95% pure *p-tert*-butylcalix[7]arene (R_f = 0.27, *ca.* 11 g). Further purification was achieved by low temperature crystallisation from acetone.



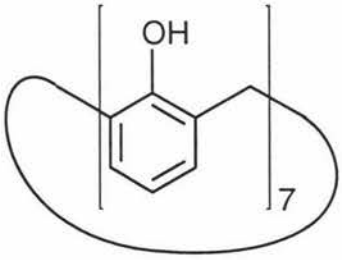
25,26,27,28-Tetrahydroxycalix[4]arene. This is a modified procedure of that reported by Gutsche.[17] A mixture of 5,11,17,23-tetra-*tert*-butyl-25,26,27,28-tetrahydroxycalix[4]arene (13.3 g, 20.5 mmol), aluminium trichloride (14.0 g, 105 mmol) and phenol (9.02 g, 95.8 mmol) in dry toluene (125 mL) was stirred at 30°C for 2 hours under argon. The reaction was quenched by addition of 0.2N HCl (250 mL) then extracted with toluene (3 x 15 mL). The combined organic extracts were washed with sat. brine (1 x 60 mL) and the solvent was removed *in vacuo* to give an off-white gummy solid (*ca.* 8 g). After trituration with methanol the solid was filtered off and washed with cold methanol (20 mL) then dried to give 25,26,27,28-tetrahydroxycalix[4]arene as a white powder (7.01 g, 80%). This can be further purified by recrystallisation from MeOH-$CHCl_3$: ^{1}H NMR (270 MHz, $CDCl_3$) δ 10.23 (br s, 4H, Ar-O*H*), 7.09 (d, *J*=7.5 Hz, 8H, *m*-Ar-*H*), 6.77 (t, *J*=7.5 Hz, 4H, *p*-Ar-*H*), 4.28 (br s, 4H, Ar-CH_2-Ar), 3.59 (br s, 4H, Ar-CH_2-Ar); IR (KBr disc) 3149, 1615, 1593, 1470, 1455, 1258, 833, 757 cm^{-1}; HRMS (FAB$^+$) *m/z* calc'd for $C_{28}H_{24}O_4$: 424.1675, found 424.1636.



31,32,33,34,35-Pentahydroxycalix[5]arene.[32] Prepared by the same method as that for 25,26,27,28-tetrahydroxycalix[4]arene above, but using 5,11,17,23,29-penta-*tert*-butyl-31,32,33,34,35-pentahydroxy calix[5]arene (406 mg, 0.500 mmol), aluminium trichloride (433 mg, 3.25 mmol) and phenol (282 mg, 3.00 mmol) in dry toluene (3 mL). 31,32,33,34,35-Pentahydroxycalix[5]arene was obtained as a white powder (132 mg, 50%): ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.95 (s, 5H, Ar-O*H*), 7.22 (d, *J*=7.5 Hz, 10H, *m*-Ar-*H*), 6.77 (t, *J*=7.5 Hz, 5H, *p*-Ar-*H*), 3.88 (br s, 10H, Ar-CH_2-Ar); IR (KBr disc) 3301, 1468, 1448, 1242, 1242, 1210, 1086, 907, 752 cm^{-1}; HRMS (FAB$^+$) *m/z* calc'd for $C_{35}H_{30}O_5$: 530.2093, found 530.2130.

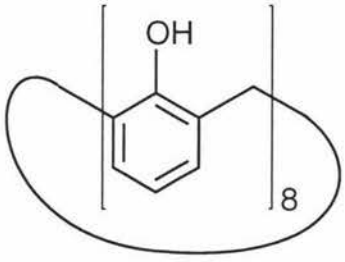


37,38,39,40,41,42-Hexahydroxycalix[6]arene.[17] Prepared by the same method as that for 25,26,27,28-tetrahydroxycalix[4]arene, but using 5,11,17,23,29,35-hexa-*tert*-butyl-37,38,39,40,41,42-hexahydroxycalix[6]arene (19.5 g, 20.0 mmol), aluminium trichloride (21.7 g, 162 mmol) and phenol (11.4 g, 121 mmol) in dry toluene (230 mL). 37,38,39,40,41,42-Hexahydroxycalix[6]arene was obtained as a white powder (9.71 g, 76%): ^{1}H NMR (270 MHz, $CDCl_3$) δ 10.44 (s, 6H, Ar-O*H*), 7.19 (d, *J*=7.3 Hz, 12H, *m*-Ar-*H*), 6.87 (t, *J*=7.3 Hz, 6H, *p*-Ar-*H*), 3.94 (br s, 12H, Ar-CH_2-Ar); IR (KBr disc) 3137, 1609, 1589, 1464, 1396, 1260, 1244, 1081, 752 cm^{-1}; HRMS (FAB$^+$) *m/z* calc'd for $C_{42}H_{36}O_6$: 636.2512, found 636.2475.



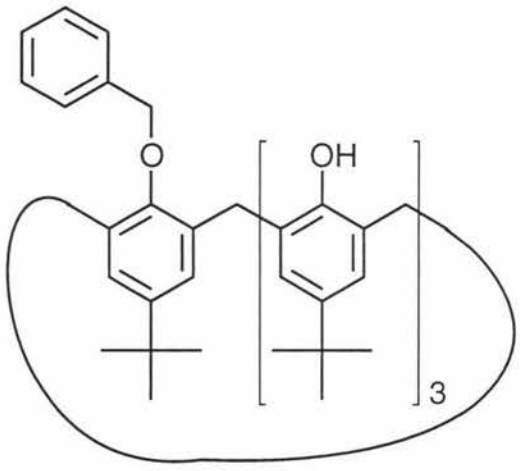
43,44,45,46,47,48,49-Heptahydroxycalix[7]arene.[32] Prepared by the

same method as that for 25,26,27,28-tetrahydroxycalix[4]arene, but using 5,11,17, 23,29,35,41-hepta-*tert*-butyl-43,44,45,46,47,48,49-heptahydroxycalix[7]arene (568 mg, 0.500 mmol), aluminium trichloride (606 mg, 4.51 mmol) and phenol (395 mg, 4.2 mmol) in dry toluene (3 mL). 43,44,45,46,47,48,49-Heptahydroxycalix[7]arene was obtained as a white powder (158 mg, 43%): ^{1}H NMR (270 MHz, $CDCl_3$) δ 10.42 (br s, 7H, Ar-O*H*), 7.22 (d, *J*=7.3 Hz, 14H, *m*-Ar-*H*), 6.88 (t, *J*=7.3 Hz, 7H, *p*-Ar-*H*), 3.96 (br s, 14H, Ar-CH_2-Ar); IR (KBr disc) 3170, 1467, 1259, 1211, 1093, 905, 754 cm^{-1}; HRMS (FAB$^+$) *m/z* calc'd for $C_{49}H_{42}O_7$: 742.2931, found 742.2856.



49,50,51,52,53,54,55,56-Octahydroxycalix[8]arene.[17] A mixture of 5,11,17,23,29,35,41,47-octa-*tert*-butyl-49,50,51,52,53,54,55,56-octahydroxycalix[8]arene (25.6 g, 19.7 mmol), aluminium trichloride (32.1 g, 240 mmol) and phenol (15.1 g, 160 mmol) was stirred in dry toluene (390 mL) under argon at 30°C for 2 hours. The reaction was quenched by the addition of ice water (250 mL) then the solid was collected by suction filtration. This was washed with acetone-10% HCl (1:1 v/v) to remove any remaining orange colour, then successively with methanol (100 mL), chloroform (100 mL), acetone (100 mL), and ether (100 mL). The solid was then dried at 100 °C under high vacuum for 10 hours to give an off white powder (15.8 g, 94%): ^{1}H NMR (270 MHz, pyridine-d_6) δ 10.23 (s, 4H, Ar-O*H*), 7.09 (d, *J*=7.5 Hz, 8H, *m*-Ar-*H*), 6.77 (t, *J*=7.5 Hz, 4H, *p*-Ar-*H*), 4.28 (br s, 4H, Ar-CH_2-Ar), 3.59 (br s, 4H, Ar-CH_2-Ar); IR (KBr disc) 3227, 1607, 1593, 1469, 1390, 1258, 1244, 1210, 787, 748 cm^{-1}; HRMS (FAB$^+$) *m/z* calc'd for $C_{56}H_{48}O_8$: 830.3243 (M$^+$-H_2O), found 830.3271.

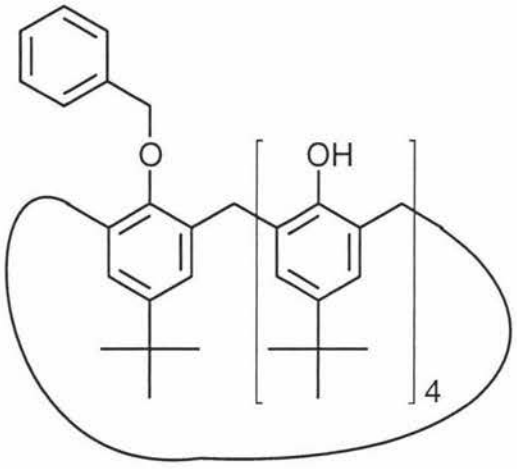
4.2 CHAPTER 2 EXPERIMENTS[Ω]



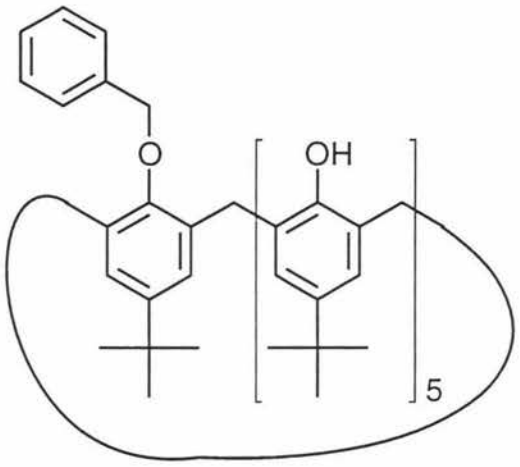
5,11,17,23-Tetra-*tert*-butyl-25-(benzyloxy)-26,27,28-trihydroxy calix[4]arene. A slurry of 5,11,17,23-tetra-*tert*-butyl-25,26,27,28-tetrahydroxy calix[4]arene (649 mg, 1.00 mmol) and potassium bicarbonate (150 mg, 1.50 mmol) in acetone (10 mL) was refluxed for 16 h under Ar. To the resulting homogenous solution was then added benzyl bromide (237 μL, 2.00 mmol) and reflux was continued for a further 30 min. The mixture was cooled to r.t. and the solvent removed *in vacuo*. Hexane (15 mL) was added to the residue and the resulting precipitate was filtered. The filtrate was dried *in vacuo,* pentane (20 mL) was added to the residue and the resulting precipitate was filtered.[¶] The solvent was removed from the filtrate to give pure 5,11,17,23-tetra-*tert*-butyl-25-(benzyloxy)-26,27,28-trihydroxycalix[4]arene as a white solid (189 mg, 74%): ^{1}H NMR (270 MHz, $CDCl_3$) δ 10.01 (s, 1H, ArO*H*), 9.40 (s, 2H, ArO*H*), 7.78 (d, *J*=7.8 Hz, 2H, Ar*H*), 7.45 (t, *J*=7.5 Hz, 2H, Ar*H*), 7.36 (t, *J*=7.5 Hz, 1H, Ar*H*), 7.12 (s, 4H, Ar*H*), 7.13 (s, 4H, Ar*H*), 7.11 (s, 2H, Ar*H*), 7.09 (s, 2H, Ar*H*), 5.18 (s, 2H, ArO-CH_2-Ar), 4.35 (d, *J*=13.1 Hz, 2H, ArCH_2Ar), 4.23 (d, *J*=14.6 Hz, 2H, ArCH_2Ar), 3.41 (d, *J*=13.1 Hz, 4H, ArCH_2Ar), 1.21 (br s, 36H, C(CH_3)$_3$); ^{13}C NMR (68 MHz, $CDCl_3$) δ 154.1, 153.6, 151.5, 146.2, 145.5, 133.8-133.0, 127.1, 126.8, 126.5, 125.8-124.8 (^{Ar}C), 75.5 (ArO-CH_2-Ar), 34.2, 31.8-31.0; IR (KBr disc) 3300, 3046, 2953, 1598, 1492, 1361, 1299, 1263, 1031, 871, 732, 675 cm^{-1}; HRMS (FAB$^+$) *m/z* calc'd for $C_{51}H_{62}O_4$: 738.4648, found 738.4664.

Ω Yields hereafter are ~~based on~~ recovered starting material

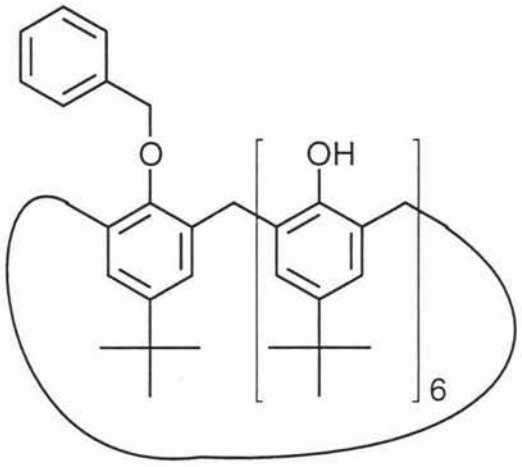
¶ The precipitates from these steps contain starting material, contaminated only with inorganic salts (these can be removed by aqueous washing)



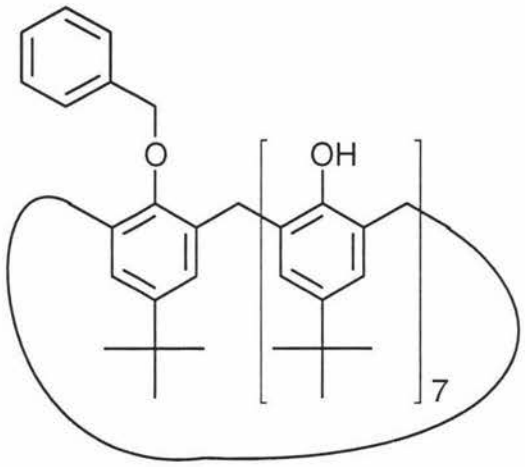
5,11,17,23,29-Penta-*tert*-butyl-31-(benzyloxy)-32,33,34,35-tetra hydroxycalix[5]arene. A slurry of 5,11,17,23,29-penta-*tert*-butyl-31,32,33,34,35-pentahydroxy calix[5]arene (406 mg, 0.500 mmol) and potassium bicarbonate (75.0 mg, 0.750 mmol) in acetone (5 mL) was refluxed for 16 h under Ar. To the resulting homogenous solution was then added benzyl bromide (119 μL, 1.00 mmol) and reflux was continued for a further 30 min. The mixture was cooled to r.t. and the solvent removed *in vacuo* and the residue taken into $CHCl_3$ (50 mL) and adsorbed onto SiO_2 (*ca.* 1.5 g). Pure 5,11,17,23,29-penta-*tert*-butyl-31-(benzyloxy)-32,33,34,35-tetrahydroxycalix[5]arene was obtained by flash chromatography R_f=0.25 (10 g SiO_2, 2:1 hexane:CH_2Cl_2) as a white solid (260 mg, 84%): ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.84 (s, 2H, ArO*H*), 7.78 (m, 1H, Ar*H*), 7.75 (m, 2H, Ar*H*), 7.74 (s, 2H, ArO*H*), 7.56 (m, 2H, Ar*H*), 7.67 (t, *J*=7.4 Hz, 2H, Ar*H*), 7.52 (t, *J*=7.4 Hz, 1H, Ar*H*), 7.25 (s, 4H, Ar*H*), 7.23 (s, 4H, Ar*H*), 7.21 (s, 2H, Ar*H*), 5.22 (s, 2H, ArO-CH_2-Ar), 4.67 (d, *J*=14.1 Hz, 2H, ArCH_2Ar), 4.16 (d, *J*=14.0 Hz, 2H, ArCH_2Ar), 4.13 (d, *J*=14.0 Hz, 1H, ArCH_2Ar), 3.53 (d, *J*=14.0 Hz, 1H, ArCH_2Ar), 3.50 (d, *J*=14.0 Hz, 2H, ArCH_2Ar), 3.49 (d, *J*=14.1 Hz, 2H, ArCH_2Ar), 1.34 (s, 18H, C(CH_3)$_3$), 1.29 (s, 18H, C(CH_3)$_3$), 1.16 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (68 MHz, $CDCl_3$) δ 149.9, 149.0, 147.4, 143.7, 142.6, 136.2, 132.1, 128.7-128.2, 126.7-125.4 (^{Ar}C), 77.7 (ArO-*C*H_2-Ar), 34.2, 33.9, 31.6-31.3; IR (KBr disc) 3300, 3046, 2951, 1602, 1486, 1361, 1292, 1205, 1112, 872, 817, 757 cm^{-1}; HRMS (FAB$^+$) *m/z* calc'd for $C_{62}H_{76}O_5$: 882.5587 (M^+-H_2O), found 882.5596.



5,11,17,23,29,35-Hexa-*tert*-butyl-37-(benzyloxy)-38,39,40,41,42-pentahydroxycalix[6]arene. A slurry of 5,11,17,23,29,35-hexa-*tert*-butyl-37,38,39,40,41,42-hexa hydroxycalix[6]arene (973 mg, 1.00 mmol) and potassium bicarbonate (150 mg, 1.50 mmol) in acetone (10 mL) was refluxed for 16 h under Ar. To the resulting homogenous solution was then added benzyl bromide (237 μL, 1.00 mmol) and reflux was continued for a further 30 min. The mixture was cooled to r.t. and the solvent removed *in vacuo* and the residue triturated with hexane (15 mL), filtered and the filtrate dried *in vacuo*. Several further precipitations gave pure 5,11,17,23,29,35-hexa-*tert*-butyl-37-(benzyloxy)-38,39,40,41,42-pentahydroxy calix[6]arene as a white solid (263 mg, 82%): ^{1}H NMR (270 MHz, $CDCl_3$) δ 10.02 (br s, 2H, ArO*H*), 9.82 (br s, 1H, ArO*H*), 9.12 (br s, 2H, ArO*H*), 7.78 (d, *J*=7.8 Hz, 2H, Ar*H*), 7.45 (t, *J*=7.5 Hz, 2H, Ar*H*), 7.36 (t, *J*=7.5 Hz, 1H, Ar*H*), 7.16 (s, 4H, Ar*H*), 7.13 (s, 4H, Ar*H*), 7.11 (s, 2H, Ar*H*), 7.09 (s, 2H, Ar*H*), 5.21 (s, 2H, ArO-CH_2-Ar), 4.50 (d, *J*=13.4 Hz, 2H, ArCH_2Ar), 4.27 (d, *J*=14.2 Hz, 2H, ArCH_2Ar), 4.01 (d, *J*=13.7 Hz, 2H, ArCH_2Ar), 3.57 (d, *J*=14.2 Hz, 2H, ArCH_2Ar), 3.55 (d, *J*=13.7 Hz, 2H, ArCH_2Ar), 3.39 (d, *J*=13.4 Hz, 2H, ArCH_2Ar), 1.29 (s, 18H, C(CH_3)$_3$), 1.27 (s, 18H, C(CH_3)$_3$), 1.24 (s, 9H, C(CH_3)$_3$), 1.19 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (68 MHz, $CDCl_3$) δ 149.4, 148.1, 146.6, 144.4, 143.5, 142.9, 136.3, 132.5, 129.1, 128.5, 127.4-125.4 (^{Ar}C), 77.9 (ArO-CH_2-Ar), 34.4-34.1, 33.5, 32.8, 31.7-31.4; IR (KBr disc) 3310, 2955, 1602, 1492, 1361, 1291, 1207, 1117, 985, 872, 817, 794 cm^{-1}; HRMS (FAB$^+$) *m/z* calc'd for $C_{73}H_{90}O_6$: 1062.6737, found 1062.6754.

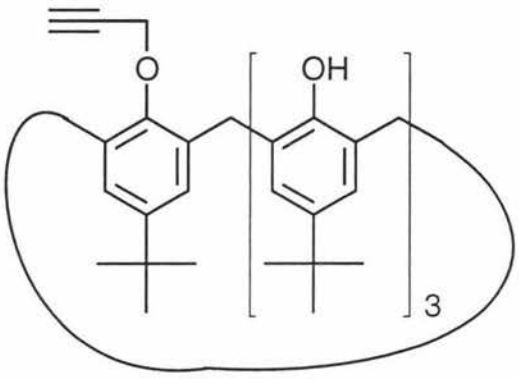


5,11,17,23,29,35,41-Hepta-*tert*-butyl-43-(benzyloxy)-44,45,46,47, 48, 49-hexahydroxycalix[7]arene. A slurry of 5,11,17,23,29,35,41-hepta-*tert*-butyl-43,44,45,46,47,48,49-heptahydroxycalix[7]arene (568 mg, 0.500 mmol) and potassium bicarbonate (75.0 mg, 0.750 mmol) was refluxed in acetone (5 mL) for 16 h under Ar. To the resulting homogenous solution was then added benzyl bromide (119 μL, 1.00 mmol) and reflux was continued for a further 30 min. The mixture was cooled to r.t. and the solvent removed *in vacuo* and the residue taken into $CHCl_3$ (60 mL) and adsorbed onto SiO_2 (*ca.* 2.0 g). Pure 5,11,17,23,29,35,41-hepta-*tert*-butyl-43-(benzyloxy)-44,45, 46,47,48,49-hexa hydroxycalix[7]arene was obtained by flash chromatography R_f=0.25 (10 g SiO_2, 4:1 hexane:CH_2Cl_2) to give a white solid (131 mg, 72%): ^{1}H NMR (270 MHz, $CDCl_3$) δ 10.40 (br s, 2H, ArO*H*), 9.81 (br s, 2H, ArO*H*), 8.83 (br s, 2H, ArO*H*), 7.51 (d, *J*=7.5 Hz, 2H, Ar*H*), 7.48 (t, *J*=7.4 Hz, 2H, Ar*H*), 7.35 (t, *J*=7.4 Hz, 1H, Ar*H*), 7.26-7.15 (br m, 14H, Ar*H*), 4.89 (s, 2H, ArO-CH_2-Ar), 4.48-3.44 (br m, 14H, ArCH_2Ar), 1.33 (s, 18H, C(CH_3)$_3$), 1.32 (s, 18H, C(CH_3)$_3$), 1.31 (s, 18H, C(CH_3)$_3$), 1.29 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (68 MHz, $CDCl_3$) δ 150.6, 148.4, 148.0, 147.6, 147.0, 144.2, 143.8, 143.2, 135.7, 132.6, 129.0-125.4 (^{Ar}*C*), 78.2 (ArO-*C*H_2-Ar), 34.3, 33.0, 32.8, 31.9-31.3; IR (KBr disc) 3242, 2957, 1602, 1485, 1454, 1361, 1205, 1117, 873, 731, 697 cm^{-1}; HRMS (FAB$^+$) *m/z* calc'd for $C_{84}H_{104}O_7$: 1224.7782, found 1224.7839.

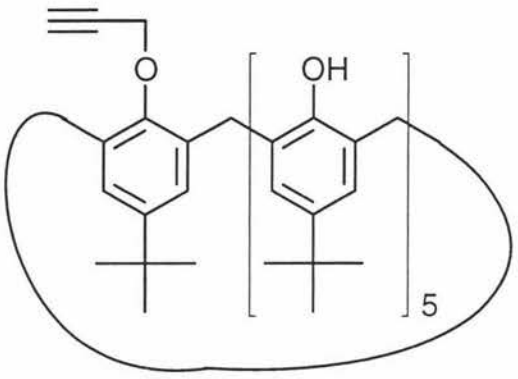


5,11,17,23,29,35,41,47-Octa-*tert*-butyl-49-(benzyloxy)-50,51,52,53, 54,55,56-heptahydroxycalix[8]arene. A slurry of 5,11,17,23,29,35,41,47-octa-*tert*-butyl-49,50,51,52,53,54,55,56-octahydroxycalix[8]arene (1.23 g, 1.00 mmol) and potassium bicarbonate (150 mg, 1.50 mmol) was refluxed in acetone (10 mL) for 16 h under Ar. To the resulting homogenous solution was then added benzyl bromide (237 μL, 2.00 mmol) and reflux was continued for a further 30 min. The mixture was cooled to r.t. and the solvent removed *in vacuo* and the residue taken into $CHCl_3$[§] (60 mL) and adsorbed onto SiO_2 (*ca.* 2.5 g). Pure 5,11,17,23,29,35,41,47-octa-*tert*-butyl-49-(benzyloxy)-50,51,52,53,54,55,56-heptahydroxycalix[8]arene was obtained by flash chromatography R_f=0.05→0.30 (20 g SiO_2, 4:1→2:1 hexane:CH_2Cl_2) to give a white solid (511 mg, 66%): ^{1}H NMR (270 MHz, $CDCl_3$) δ 9.33 (br s, 3H, ArO*H*), 9.18 (br s, 4H, ArO*H*), 7.81 (d, *J*=7.5 Hz, 2H, Ar*H*), 7.67 (t, *J*=7.4 Hz, 2H, Ar*H*), 7.52 (t, *J*=7.4 Hz, 1H, Ar*H*), 7.34-7.11 (m, 16H, Ar*H*), 4.74 (s, 2H, ArO-CH_2-Ar), 4.00-3.79 (br m, 16H, ArCH_2Ar), 1.35 (s, 9H, C(CH_3)$_3$), 1.31 (s, 9H, C(CH_3)$_3$), 1.27 (s, 18H, C(CH_3)$_3$), 1.26 (s, 18H, C(CH_3)$_3$), 1.25 (s, 18H, C(CH_3)$_3$); ^{13}C NMR (68 MHz, $CDCl_3$) δ 150.2, 148.3, 146.9-146.6, 144.4, 143.9, 142.9, 135.6, 133.5, 129.2-125.1 (^{Ar}C), 78.5 (ArO-CH$_2$-Ar), 34.4, 34.0, 32.8, 32.3, 31.5; IR (KBr disc) 3300, 2953, 1601, 1484, 1361, 1291, 1203, 1117, 873, 732 cm^{-1}; HRMS (FAB$^+$) *m/z* calc'd for $C_{95}H_{118}O_8$: 1368.8721 (M$^+$-H_2O), found 1368.8706.

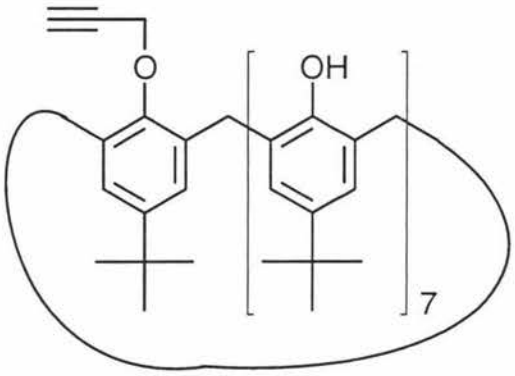
§ A solution may not form here and filtration maybe necessary. The precipitate contains K^+ salts and starting material (*ca.* 57 mg).



5,11,17,23-Tetra-*tert*-butyl-25-(propargyloxy)-26,27,28-trihydroxy calix[4]arene. A slurry of 5,11,17,23-tetra-*tert*-butyl-25,26,27,28-tetrahydroxy calix[4]arene (6.49 g, 10.0 mmol) and potassium bicarbonate (1.50 g, 15.0 mmol) in acetone (100 mL) was refluxed for 16 h under Ar. To the resulting homogenous solution was then added 80 wt% propargyl bromide (2.23 mL, 20.0 mmol) and reflux was continued for a further 30 min. The mixture was cooled to r.t. and the solvent removed *in vacuo* and hexane was added then the resulting precipitate was filtered. The filtrate was evaporated to dryness and pentane added then the precipitate filtered with SiO_2 (4 g). After elution with $CHCl_3$ (60 mL) the product was adsorbed onto SiO_2 (*ca.* 2 g). Pure 5,11,17,23-tetra-*tert*-butyl-25-(propargyloxy)-26,27,28-trihydroxycalix[4]arene was obtained by flash chromatography R_f=0.03→0.35 (20 g SiO_2, 3:1→1:1 hexane:CH_2Cl_2) to give a white powder (253 mg, 69%): ^{1}H NMR (270 MHz, $CDCl_3$) δ 10.16 (s, 1H, Ar-O*H*), 9.30 (s, 2H, Ar-O*H*), 7.14 (s, 2H, Ar-*H*), 7.09 (m, 4H, Ar-*H*), 7.03 (m, 2H, Ar-*H*), 4.97 (d, *J*=2.4 Hz, 2H, ArO-C*H*$_2$CCH), 4.51 (d, *J*=13.1 Hz, 2H, Ar-C*H*$_2$-Ar), 4.32 (d, *J*=13.7 Hz, 2H, Ar-C*H*$_2$-Ar), 3.48 (d, *J*=13.7 Hz, 4H, Ar-C*H*$_2$-Ar), 2.77 (t, *J*=2.4 Hz, 1H, ArO-CH$_2$CC*H*), 1.26 (s, 9H, C(C*H*$_3$)$_3$), 1.25 (s, 18H, C(C*H*$_3$)$_3$), 1.24 (s, 9H, C(C*H*$_3$)$_3$); ^{13}C NMR (68 MHz, $CDCl_3$) δ 149.0-147.6, 143.4, 143.0, 133.5, 128.0-127.6, 126.4, 125.7-125.5 (^{Ar}*C*), 77.9 (ArO-CH$_2$*C*CH), 77.3 (ArO-*C*H$_2$C*C*H), 63.4 (ArO-*C*H$_2$CCH), 34.3-33.9, 33.0, 32.7, 31.5-31.3; IR (KBr disc) 3280, 2959, 2123, 1601, 1484, 1361, 1297, 1204, 1123, 993, 871, 782 cm^{-1}; HRMS (FAB$^+$) *m/z* calc'd for $C_{47}H_{58}O_4$: 686.4335, found 686.4353.



5,11,17,23,29,35-Hexa-*tert*-butyl-37-(propargyloxy)-38,39,40,41,42-pentahydroxycalix[6]arene. A suspension of 5,11,17,23,29,35-hexa-*tert*-butyl-37,38,39,40,41,42-hexahydroxycalix[6]arene (19.5 g, 20.0 mmol) and potassium carbonate (3.04 g, 22.0 mmol) in acetone (1100 mL) was refluxed for 2 h under a drying tube. Into the mixture was then added 80 wt% propargyl bromide in toluene (2.67 mL, 24.0 mmol) and refluxed for another 48 h The reaction was quenched by addition of 0.1%, filtered to remove potassium carbonate and the solvent was removed *in vacuo*. The residue was taken up in CH_2Cl_2 (300 mL) and stirred with 30% aqueous ammonia for 5 min then 10% HCl (200 mL) was added and the aqueous phase extracted with CH_2Cl_2 (3x50 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent removed *in vacuo* to give an off-white solid (19.3 g). Pure 5,11,17,23,29,35-hexa-*tert*-butyl-37-(propargyloxy)-38,39,40,41,42-pentahydroxycalix[6]arene was isolated by flash chromatography R_f=0.05→0.30 (220 g SiO_2, 1:2→3:1 CH_2Cl_2:hexane), as a white powder (9.42g,~~52~~46%).: ^{1}H NMR (270 MHz, $CDCl_3$) δ 9.34 (br s, 2H, Ar-O*H*), 9.55 (br s, 1H, Ar-O*H*), 8.52 (br s, 2H, Ar-O*H*), 7.12 - 7.09 (m, 12H, Ar-*H*), 6.99 (s, 2H, Ar-*H*), 4.84 (d, *J*=2.4 Hz, 2H, ArO-CH_2C), 4.00-3.75 (br m, 12H, Ar-CH_2-Ar), 2.73 (t, *J*=2.4 Hz, 1H, ArO-CH_2CC*H*), 1.28 (s, 18H, C(CH_3)$_3$), 1.26 (s, 18H, C(CH_3)$_3$), 1.22 (s, 9H, C(CH_3)$_3$), 1.13 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (68 MHz, $CDCl_3$) δ 149.4, 149.1, 148.1, 146.7, 144.2, 143.5, 143.0, 132.5, 127.4-125.4 (^{Ar}*C*), 79.6 (ArOCH$_2$*C*CH), 76.9 (ArOCH$_2$C*C*H), 63.0 (ArO*C*H$_2$CCH), 34.2 - 31.3; IR (KBr disc) 3201, 3047, 2960, 2124, 1484, 1392, 1362, 1291, 1203, 1118, 993, 871 cm^{-1}; HRMS (FAB$^+$) *m/z* calc'd for $C_{69}H_{86}O_6$: 1010.6424, found 1010.6411.



5,11,17,23,29,35,41,47-Octa-*tert*-butyl-49-(propargyloxy)-50,51,52, 53,54,55,56-heptahydroxycalix[8]arene. A suspension of 5,11,17,23,29, 35,41,47-octa-*tert*-butyl-49,50,51,52,53,54,55,56-octahydroxycalix[8]arene (26.0 g, 20.0 mmol) and potassium carbonate (3.04 g, 22.0 mmol) in acetone (1100 mL) was refluxed for 2 h under a drying tube. Into the mixture was added 80 wt% propargyl bromide in toluene (2.67 mL, 24.0 mmol) and reflux continued for another 48 h The reaction was quenched by addition of 0.1% water and then filtration to remove potassium carbonate and the solvent removed *in vacuo*. The residue was taken up in CH_2Cl_2 (300 mL) and stirred with 30% aqueous ammonia for 5 min after which 10% HCl (200 mL) was added and the aqueous phase extracted with CH_2Cl_2 (3x50 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent removed *in vacuo* to give an off-white solid (21.4 g). Pure 5,11,17,23,29,35,41,47-octa-*tert*-butyl-49-(propargyloxy)-50,51,52,53,54,55,56-hepta hydroxycalix[8]arene was isolated by flash chromatography R_f=0.07→0.45 (220 g SiO_2, 1:1→3:1 CH_2Cl_2:hexane), to give an off-white solid (9.83 g, 47%): ^{1}H NMR (270 MHz, $CDCl_3$) δ 9.54 (br s, 2H, ArO*H*), 9.43 (br s, 2H, ArO*H*), 9.18 (br s, 1H, ArO*H*), 9.15 (br s, 2H, ArO*H*), 7.21-7.12 (16, Ar*H*), 4.55 (d, *J*=2.5 Hz, 2H, OC*H*2CCH), 4.03-3.91 (16, ArCH_2Ar), 2.92 (t, *J*=2.5 Hz, 1H, OCH_2CCH), 1.31-1.26 (72, $C(CH_3)_3$); ^{13}C NMR (68 MHz, $CDCl_3$) δ 149.6-148.2, 147.1-146.5, 144.6-143.2, 133.7, 128.1-125.2 (^{Ar}C), 78.6 (OCH_2CCH), 63.1 (OCH_2CCH), 63.1 (OCH_2CCH), 34.5, 32.8-31.5; IR (KBr disc) 3280, 2955, 2016, 1484, 1392, 1361, 1291, 1203, 1117, 987, 873 cm^{-1}; HRMS (FAB$^+$) *m/z* calc'd for $C_{91}H_{114}O_8$: 1334.8513, found 1334.8547.

General procedure for preparations of monoalkylated calixarenes in toluene.

A slurry of *p-tert*-butylcalix[*n*]arene (1.00 mmol) in dry toluene (10 mL) was stirred with potassium bicarbonate (130 mg, 1.30 mmol), benzyl bromide (125 mL, 1.05 mmol) and 18-crown-6 (26.4 mg, 0.100 mmol) under Ar at 90°C for 16 h The reaction mixture was then

cooled to r.t. and the solvent removed *in vacuo*. The residue was passed through a plug of SiO_2 (1 g) eluting with CH_2Cl_2. Further purification can be achieved by flash chromatography.

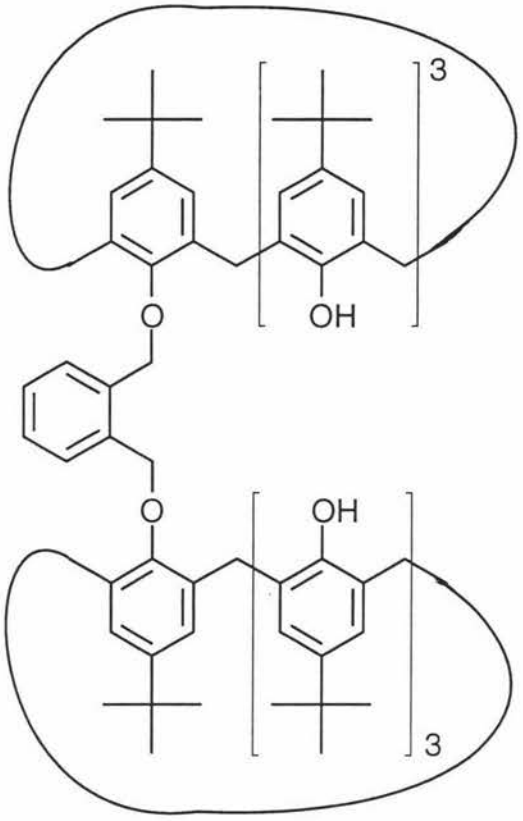
5,11,17,23-Tetra-*tert*-butyl-25-(benzyloxy)-26,27,28-trihydroxy calix[4]arene was prepared according to the general procedure with 5,11,17,23-tetra-*tert*-butyl-25,26,27,28-tetrahydroxycalix[4]arene to give the *title compound* as a white powder (263 mg, 66%)

5,11,17,23,29-Penta-*tert*-butyl-31-(benzyloxy)-32,33,34,35-tetra hydroxycalix[5]arene was prepared according to the general procedure on half the scale, with on half the scale, with (406 mg, 0.500 mmol) of 5,11,17,23,29-penta-*tert*-butyl-31,32,33,34,35-pentahydroxycalix[5]arene to give the *title compound* as a white powder (176 mg, 55%).

5,11,17,23,29,35-Hexa-*tert*-butyl-37-(benzyloxy)-38,39,40,41,42-pentahydroxycalix[6]arene was prepared according to the general procedure with 5,11,17,23,29,35-hexa-*tert*-butyl-37,38,39,40,41,42-hexahydroxycalix[6]arene to give the *title compound* as a white powder (396 mg, 61%)

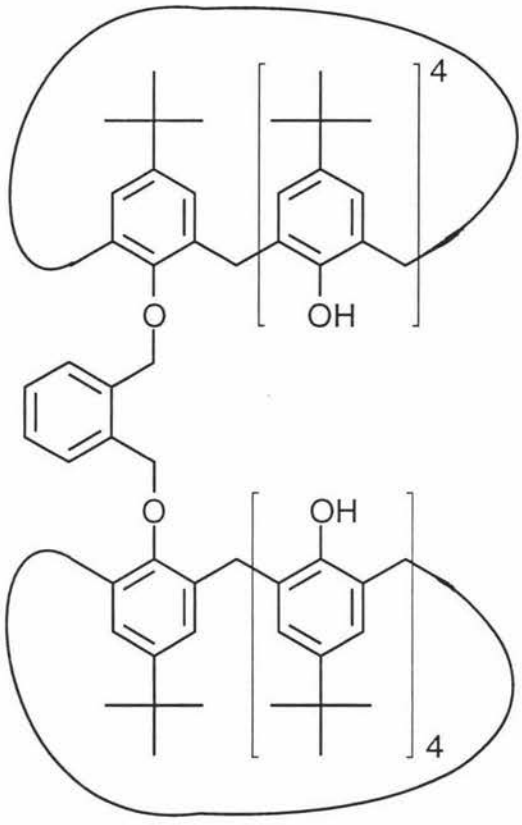
5,11,17,23,29,35,41-Hepta-*tert*-butyl-43-(benzyloxy)-44,45,46,47, 48,49-hexahydroxycalix[7]arene was prepared according to the general procedure on half the scale, with (568 mg, 0.500 mmol) of 5,11,17,23,29,35,41-hepta-*tert*-butyl-43,44,45,46,47,48,49-heptahydroxycalix[7]arene to give the *title compound* as a white powder (141 mg, 45%)

4.3 CHAPTER 3 EXPERIMENTS



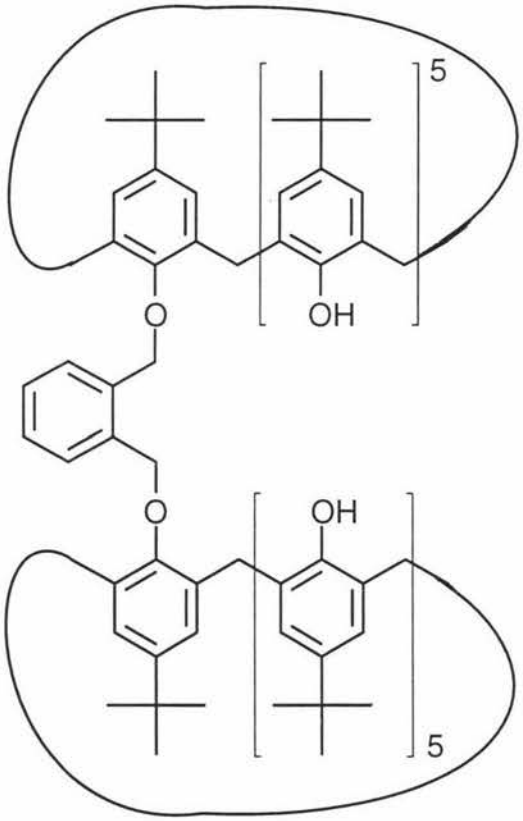
α,α'-Bis{5,11,17,23-tetra-*tert*-butyl-26,27,28-trihydroxy-25-calix[4]aryloxy}-2-xylene. A slurry of 5,11,17,23-tetra-*tert*-butyl-25,26,27,28-tetrahydroxycalix[4]arene (649 mg, 1.00 mmol) and potassium bicarbonate (150 mg, 1.50 mmol) in acetone (10 mL) was refluxed for 16 h under Ar. To the resulting homogenous solution was then added α,α'-dibromo-*o*-xylene (132 mg, 0.500 mmol) and reflux was continued for a further 30 min. The mixture was cooled to r.t. and the solvent removed *in vacuo*. The residue was taken into $CHCl_3$ (60 mL) and adsorbed onto SiO_2 (*ca.* 2 g). Pure α,α'-Bis{5,11,17,23-tetra-*tert*-butyl-26,27,28-trihydroxy-25-calix[4]aryloxy}-2-xylene was obtained by flash chromatography R_f=0.13→0.35 (20 g SiO_2, 3:1→1:1 hexane:CH_2Cl_2) to give a white powder (163 mg, 55%): ^{1}H NMR (270 MHz, $CDCl_3$) δ 10.02 (s, 2H, Ar-O*H*), 9.35 (s, 4H, Ar-O*H*), 7.86 (d, *J*=5.5 Hz, 1H, Ar-*H*), 7.85 (d, *J*=5.5 Hz, 1H, Ar-*H*), 7.60 (d, *J*=5.3 Hz, 1H, Ar-*H*), 7.59 (d, *J*=5.3 Hz, 1H, Ar-*H*), 7.11 (s, 4H, Ar-*H*), 7.05 (s, 8H, Ar-*H*), 6.98 (s, 4H, Ar-*H*), 5.42 (s, 4H, ArO-CH_2-Ar), 4.23 (d, *J*=13.6 Hz, 4H, Ar-CH_2-Ar), 4.22 (d, *J*=13.6 Hz, 4H, Ar-CH_2-Ar), 3.41 (d, *J*=21.1 Hz, 4H, Ar-CH_2-Ar), 3.56 (d, *J*=21.1 Hz, 4H, Ar-CH_2-Ar), 1.24 (s, 18H, C(CH_3)$_3$), 1.23 (s, 36H, C(CH_3)$_3$),

1.22 (s, 18H, $C(CH_3)_3$); ^{13}C NMR (270 MHz, $CDCl_3$) δ 149.5, 148.4, 148.1, 147.5, 143.4, 142.8, 135.0, 133.4, 131.6, 129.8, 128.2-127.2, 126.5, 125.5 (^{Ar}C), 76.5 (ArO-CH_2-Ar), 34.3, 34.0, 33.0, 32.6, 32.0-31.1; IR (KBr disc) 3300, 3049, 2953, 1484, 1392, 1361, 1297, 1204, 1123, 945, 871, 781 cm^{-1}; HRMS (FAB^+) *m/z* calc'd for $C_{96}H_{118}O_8$: 1398.8827, found 1398.8906.



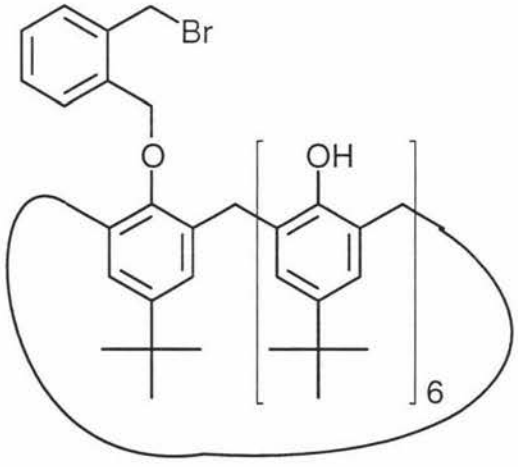
α,α'–Bis{5,11,17,23,29-penta-*tert*-butyl-32,33,34,35-tetrahydroxy-31-calix[5]aryloxy}-2-xylene. A slurry of *p-tert*-butylcalix[5]arene (811 mg, 1.00 mmol) and potassium bicarbonate (150 mg, 1.50 mmol) in acetone (10 mL) was refluxed for 16 h under Ar. To the resulting homogenous solution was then added α,α'-dibromo-*o*-xylene (132 mg, 0.500 mmol) and reflux was continued for a further 30 min. The mixture was cooled to r.t. and the solvent removed *in vacuo* then the residue precipitated with hexane and filtered. The precipitate was taken into $CHCl_3$ (50 mL) and shaken for *ca.* 10 min with 10% HCl (40 mL), the organic phase washed with sat. brine (40 mL) then dried over $MgSO_4$. The solvent was evaporated *in vacuo* to give pure α,α'–bis{5,11,17,23,29-penta-*tert*-butyl-32,33,34,35-tetrahydroxy-31-calix[5]aryloxy}-2-xylene as a white powder (593

mg, 69%): ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.99 (m, 4H, Ar-*H*), 7.85 (br s, 2H, Ar-O*H*), 7.69 (br s, 4H, Ar-O*H*), 7.63 (m, 2H, Ar-*H*), 7.22-7.15 (40, Ar-*H*), 5.59 (s, 4H, ArO-CH_2-Ar), 4.46 (d, *J*=14.2 Hz, 4H, Ar-CH_2-Ar), 4.14 (s, 1H, Ar-CH_2-Ar), 4.06 (d, *J*=14.2 Hz, 4H, Ar-CH_2-Ar), 3.54-3.83 (m, 5H, Ar-CH_2-Ar), 1.32 (s, 36H, $C(CH_3)_3$), 1.27 (s, 36H, $C(CH_3)_3$), 1.08 (s, 18H, $C(CH_3)_3$); ^{13}C NMR (68 MHz, $CDCl_3$) δ 150.5, 149.0, 147.4, 143.6, 142.4, 135.1, 132.0, 129.9, 129.2, 126.8-125.3 (^{Ar}C), 75.3 (ArO-CH_2-Ar), 34.2, 33.9, 31.7-30.9; IR (KBr disc) 3335, 3047, 2953, 1602, 1485, 1361, 1292, 1203, 1115, 985, 944, 909, 872, 789, 732 cm^{-1}; HRMS (FAB$^+$) *m/z* calc'd for $C_{118}H_{146}O_{10}$: 1723.0915, found 1723.0864.



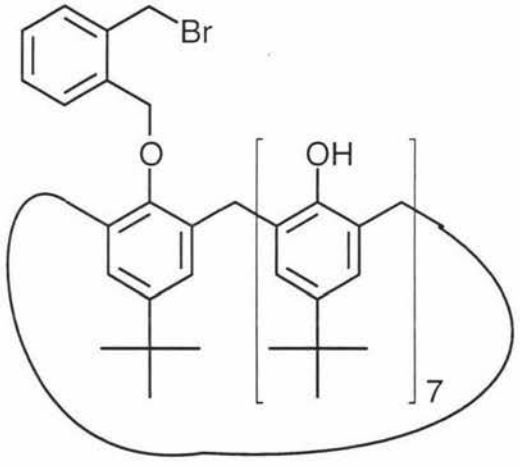
α,α'–Bis{5,11,17,23,29,35-hexa-*tert*-butyl-38,39,40,41-penta hydroxy-37-calix[6]aryloxy}-2-xylene. A slurry of 5,11,17,23,29,35-hexa-*tert*-butyl-37,38,39,40,41,42-hexahydroxycalix[6]arene (973 mg, 1.00 mmol) and potassium bicarbonate (150 mg, 1.50 mmol) in acetone (10 mL) was refluxed for 16 h under Ar. To the resulting homogenous solution was then added α,α'-dibromo-*o*-xylene (132 mg, 0.500 mmol) and reflux was continued for a further 30 min. The mixture was cooled to r.t. and the

solvent removed *in vacuo* then the residue taken into $CHCl_3$ (60 mL). After adsorbing onto SiO_2 (*ca.* 2 g) pure α,α'–bis{5,11,17,23,29,35-hexa-*tert*-butyl-38,39,40,41-pentahydroxy-37-calix[6]aryloxy}-2-xylene was obtained by flash chromatography R_f=0.20→0.60 (20 g SiO_2, 3:1→1:1 hexane:CH_2Cl_2) yielding a white solid (263 mg, 64%): ^{1}H NMR (270 MHz, $CDCl_3$) δ 10.03 (s, 6H, Ar-O*H*), 9.08 (s, 4H, Ar-O*H*), 8.12 (d, *J*=5.7 Hz, 1H, Ar-*H*), 8.11 (d, *J*=5.2 Hz, 1H, Ar-*H*), 7.76 (d, *J*=5.2 Hz, 1H, Ar-*H*), 7.75 (d, *J*=5.7 Hz, 1H, Ar-*H*), 7.16 (d, *J*=2.4 Hz, 4H, Ar-*H*), 7.12 (br s, 8H, Ar-*H*), 7.09 (s, 4H, Ar-*H*), 7.03 (s, 4H, Ar-*H*), 7.01 (d, *J*=2.4 Hz, 4H, Ar-*H*), 5.69 (s, 4H, ArO-CH_2-Ar), 4.42 (d, *J*=13.6 Hz, 4H, Ar-CH_2-Ar), 4.15 (d, *J*=14.0 Hz, 4H, Ar-CH_2-Ar), 4.04 (d, *J*=14.1 Hz, 4H, Ar-CH_2-Ar), 3.42 (d, *J*=14.0 Hz, 8H, Ar-CH_2-Ar), 3.32 (d, *J*=13.6 Hz, 4H, Ar-CH_2-Ar), 1.33 (s, 36H, C(CH_3)$_3$), 1.29 (s, 36H, C(CH_3)$_3$), 1.28 (s, 18H, C(CH_3)$_3$), 1.21 (s, 18H, C(CH_3)$_3$); ^{13}C NMR (68 MHz, $CDCl_3$) δ 150.0, 149.1, 148.0, 147.7, 146.4, 143.3, 142.6, 143.9, 132.3, 129.8, 127.5-125.4 (^{Ar}C), 75.8 (ArO-CH_2-Ar), 34.3, 34.1-33.9, 33.4, 32.9, 32.6, 31.7-31.3; IR (KBr disc) 3335, 2953, 1602, 1484, 1361, 1291, 1204, 1116, 987, 941, 871, 759 cm^{-1}; HRMS (FAB$^+$) *m/z* calc'd for $C_{140}H_{174}O_{12}$: 2180.2060(MCs$^+$), found 2180.2069.



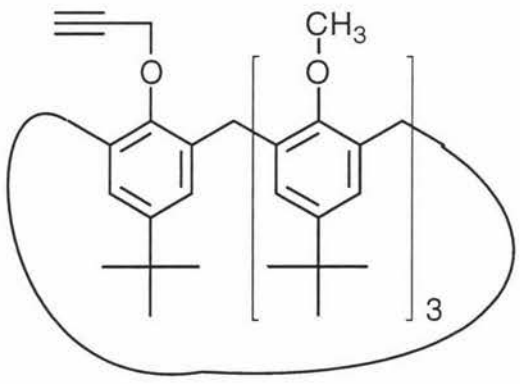
5,11,17,23,29,35,41-Hepta-*tert*-butyl-43-[(2-(α-bromomethyl) benzyloxy]-44,45,46,47,48,49-hexahydroxycalix[7]arene. A slurry of 5,11, 17,23,29,35,41-hepta-*tert*-butyl-43,44,45,46,47,48,49-heptahydroxycalix[7]arene (1135 mg, 1.00 mmol) and potassium bicarbonate (150 mg, 1.50 mmol) in acetone (10 mL) was refluxed for 16 h under Ar. To the resulting homogenous solution was then added α,α'-dibromo-*o*-xylene (132 mg, 0.500 mmol) and reflux was continued for a further 30 min. The mixture was cooled to r.t. and the solvent removed *in vacuo*. The residue was then

taken into $CHCl_3$ (60 mL) and adsorbed onto SiO_2 (*ca.* 2.5 g). Pure 5,11,17,23,29,35,41-hepta-*tert*-butyl-43-[(2-(α-bromomethyl)benzyloxy]-44,45,46,47,48,49-hexahydroxy calix[7]arene was obtained by flash chromatography R_f=0.25 (20 g SiO_2, 3:1 hexane:CH_2Cl_2) to give a white solid (35.6 mg, 86%): ^{1}H NMR (270 MHz, $CDCl_3$) δ 10.26 (br s, 2H, Ar-O*H*), 9.73 (br s, 2H, Ar-O*H*), 8.48 (br s, 2H, Ar-O*H*), 7.77-7.73 (br m, 2H, Ar-*H*), 7.51-7.14 (br m, 16H, Ar-*H*), 5.23 (s, 2H, ArO-CH_2-Ar), 4.65 (s, 2H, ArO-CH_2-Br), 4.36-3.63 (br m, 14H, Ar-CH_2-Ar), 1.31 (s, 18H, C(CH_3)$_3$), 1.29 (s, 18H, C(CH_3)$_3$), 1.28 (s, 18H, C(CH_3)$_3$), 1.23 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (270 MHz, $CDCl_3$) δ 150.6, 148.6, 148.0, 147.3, 147.0, 144.1, 143.9, 143.3, 135.8, 135.0, 132.5, 132.5, 129.7-128.9, 127.8-125.6 (^{Ar}*C*), 73.8 (ArO-*C*H_2-Ar), 34.1, 32.8-32.0, 31.7-30.7; IR (KBr disc) 3298, 3047, 2954, 1484, 1361, 1291, 1204, 1116, 872, 816 cm^{-1}; HRMS (FAB$^+$) *m/z* calc'd for $C_{85}H_{105}BrO_7$: 1316.7044, found 1316.7063.

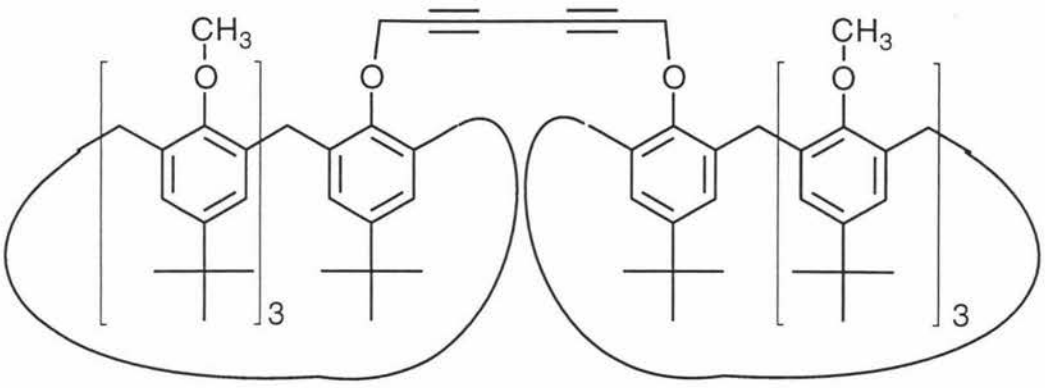


5,11,17,23,29,35,41,47-Octa-*tert*-butyl-49-[2-(α-bromomethyl) benzyloxy]-50,51,52,53,54,55,56-heptahydroxycalix[8]arene. A slurry of 5,11,17,23,29,35,41,47-octa-*tert*-butyl-49,50,51,52,53,54,55,56-octahydroxycalix[8]arene (1297 mg, 1.00 mmol) and potassium bicarbonate (150 mg, 1.50 mmol) in acetone (10 mL) was refluxed for 16 h under Ar. To the resulting homogenous solution was then added α,α'-dibromo-*o*-xylene (132 mg, 0.500 mmol) and reflux was continued for a further 30 min. The mixture was cooled to r.t., the solvent removed *in vacuo* and the residue taken into $CHCl_3$ (60 mL) then adsorbed onto SiO_2 (*ca.* 2.5 g). Pure 5,11,17,23,29,35,41,47-octa-*tert*-butyl-49-[(2-(α-bromomethyl)benzyloxy]-50,51,52,53,54,55,56-heptahydroxy calix[8] arene was obtained by flash chromatography R_f=0.07→0.30 (20 g SiO_2, 3:1→1:1 hexane:CH_2Cl_2) to give a white solid (220 mg, 65%): ^{1}H NMR (270 MHz, $CDCl_3$) δ 9.37

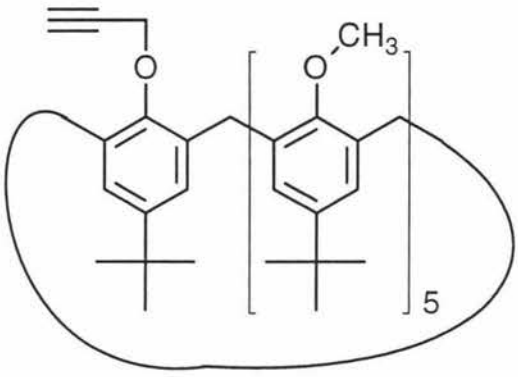
(br s, 1H, Ar-O*H*), 9.32 (br s, 2H, Ar-O*H*), 9.09 (br s, 2H, Ar-O*H*), 8.84 (br s, 2H, Ar-O*H*), 7.77-7.73 (br m, 2H, Ar-*H*), 7.22-7.14 (br m, 16H, Ar-*H*), 4.98 (s, 2H, ArO-CH_2-Ar), 4.46 (s, 2H, ArO-CH_2-Br), 4.03-3.57 (br m, 16H, Ar-CH_2-Ar), 1.33-1.28 (m, 72H, C(CH_3)$_3$); ^{13}C NMR (68 MHz, $CDCl_3$) δ 150.2, 148.9, 148.6-148.3, 147.5, 147.1146.5, 145.3, 144.5, 144.3, 143.0, 135.1, 133.2, 132.0, 132.5, 129.1-128.6, 127.8-125.2 (^{Ar}C), 74.2 (ArO-CH$_2$-Ar), 34.0, 32.7-32.0, 31.7-31.4; IR (KBr disc) 3252, 3051, 2959, 1602, 1485, 1392, 1362, 1292, 1247, 1204, 1117, 943, 874, 816, 783 cm^{-1}; HRMS (FAB$^+$) *m/z* calc'd for $C_{96}H_{119}BrO_8$: 1478.8088, found 1478.8141.



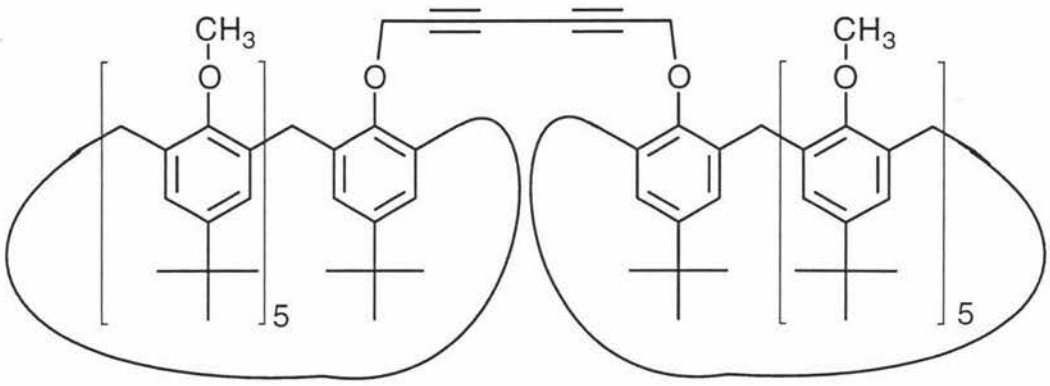
5,11,17,23-tetra-*tert*-butyl-25-(propargyloxy)-26,27,28-trimethoxy calix[4]arene. A slurry of 5,11,17,23-tetra-*tert*-butyl-25-(propargyloxy)-26,27,28-trihydroxycalix[4]arene (155 mg, 0.226 mmol), potassium carbonate (1.09 g, 7.89 mmol) and methyl iodide (421 μL, 6.77 mmol) was stirred in refluxing acetone under Ar for 4 days. After cooling to r.t. the mixture was filtered and the filtrate evapourated to dryness. The residue was taken into $CHCl_3$ (30 mL) and washed with 10% HCl (1x20 mL) then dried over $MgSO_4$ and the solvent removed *in vacuo*. Pure 5,11,17,23-tetra-*tert*-butyl-25-(propargyloxy)-26,27,28-trimethoxycalix[4]arene was obtained by flash chromatography R-=0.40 (4 g SiO_2, 10:1 hexane:ethyl acetate) to give a yellow oil, recrystallised from CH_2Cl_2/methanol to give an off white solid (105 mg, 64%): ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.22 (s, 2H, Ar-*H*), 7.19 (s, 4H, Ar-*H*), 7.15 (s, 2H, Ar-*H*), 4.32 (br s, 2H, ArO-CH_2CCH), 4.15-3.57 (br m, 16H, Ar-CH_2-Ar), 2.33 (br s, 1H, ArO-CH$_2$CC*H*), 1.31-1.26 (m, 36H, C(CH_3)$_3$); ^{13}C NMR (68 MHz, $CDCl_3$) δ 154.9-153.7, 151.8, 146.3, 145.8-144.1, 143.1, 133.2-132.6, 127.4, 125.9-124.7 (^{Ar}C), 79.1 (OCH$_2$*C*CH), 74.1 (OCH$_2$C*C*H), 60.5-60.0 (O*C*H$_3$), 34.0-33.8, 31.8-31.3; IR (KBr disc) 3313, 2961, 2033, 1481, 1463, 1361, 1245, 1207, 1121, 1022, 950, 870, 796 cm^{-1}; HRMS (FAB$^+$) *m/z* calc'd for $C_{50}H_{64}O_4$: 728.4805, found 728.4760.



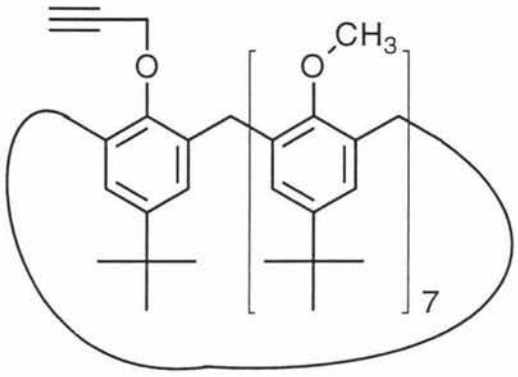
1,6-Bis{5,11,17,23-tetra-*tert*-butyl-26,27,28-trimethoxy-25-calix[4]aryloxy}-2,4-hexadiyne. A mixture of 5,11,17,23-tetra-*tert*-butyl-25-(propargyloxy)-26,27,28-trimethoxycalix[4]arene (41.5 mg, 56.9 μmol) and $Cu(OAc)_2.H_2O$ (148 mg, 739 μmol) was stirred in pyridine at 65°C in air for 3.5 h The mixture was cooled to r.t. and diluted with $CHCl_3$ (30 mL) then washed with water (1x10 mL), 10% HCl (2x10 mL), water (1x10 mL), sat. brine (1x10 mL) and the organic phase dried ($MgSO_4$). The solvent was removed *in vacuo* to give a yellow solid, that was recrystallised from $CHCl_3$/methanol to give pure 1,6-bis{5,11,17,23-tetra-*tert*-butyl-26,27,28-trimethoxy-25-calix[4]aryloxy}-2,4-hexadiyne (35.6 mg, 86%): ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.25 (s, 4H, Ar-*H*), 7.06-6.73 (m, 12H, Ar-*H*), 4.03 (s, 2H, ArO-CH_2CCH), 4.21-3.36 (br m, 16H, Ar-CH_2-Ar), 1.28-1.14 (m, 72H, C(CH_3)$_3$); ^{13}C NMR (68 MHz, $CDCl_3$) δ 155.0, 151.9, 147.5, 145.2-144.5, 143.1, 135.1-134.5, 133.5, 133.0, 127.4-127.1, 125.8-125.1 (^{Ar}C), 73.3 (ArO-CH_2CCH), 71.2 (ArO-CH_2CCH), 60.9 (ArO-CH$_2$CCH), 60.4-60.1 (OCH$_3$), 34.0-33.8, 31.8-31.2; IR (KBr disc) 2961, 2032, 1602, 1481, 1392, 1361, 1244, 1206, 1121, 1022, 949, 870, 797, 733 cm^{-1}; HRMS (FAB$^+$) *m/z* calc'd for $C_{100}H_{126}O_8$: 1454.9453, found 1454.9511.



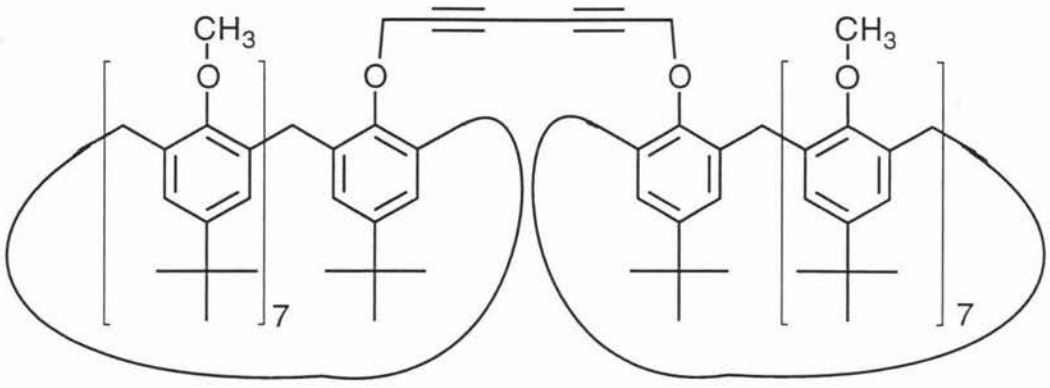
5,11,17,23,29,35-Hexa-*tert*-butyl-37-(propargyloxy)-38,39,40,41, 42-pentamethoxycalix[6]arene. In acetone (100 mL) was stirred 5,11,17,23,29,35-hexa-*tert*-butyl-37-(propargyloxy)-38,39,40,41,42-pentahydroxycalix[6] arene (3.00 g, 2.97 mmol), potassium carbonate (14.4 g, 103 mmol) and methyl iodide (5.54 mL, 88.9 mmol) at reflux for 4 days under a drying tube. The reaction mixture was cooled to r.t. and filtered (the precipitate was washed with $CHCl_3$) and the filtrate evaporated to dryness. The off-white solid was dissolved in $CHCl_3$ (150 mL) and washed with 10% HCl (130 mL) then the organic phase dried over $MgSO_4$. The solvent was removed *in vacuo* and the solid was columned R_f=0.03→0.60 (50 g SiO_2, 3:1 CH_2Cl_2:hexane then EtOAc) yielding pure 5,11,17,23,29,35-hexa-*tert*-butyl-37-(propargyloxy)-38,39,40,41,42-pentamethoxycalix[6] arene (1.83 g, 57%): ^{1}H NMR (270 MHz, $CDCl_3$) δ 6.96 (s, 8H, Ar*H*), 6.94 (s, 4H, Ar*H*), 6.92 (s, 2H, Ar*H*), 6.89 (s, 2H, Ar*H*), 4.28 (d, *J*=2.5 Hz, 2H, OCH_2CCH), 4.09 (br s, 4H, $ArCH_2Ar$), 4.05 (br s, 12H, $ArCH_2Ar$), 3.45-3.39 (21, OCH_3), 2.37 (t, *J*=2.5 Hz, 1H, OCH_2CCH), 1.10 (s, 36H, $C(CH_3)_3$), 1.09 (s, 18H, $C(CH_3)_3$), 1.07 (s, 9H, $C(CH_3)_3$), 1.03 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (68 MHz, $CDCl_3$) δ 154.1-153.5, 145.5, 145.4, 133.7-132.6, 126.7-125.0 (^{Ar}C), 79.6 (OCH_2CCH), 74.9 (OCH_2CCH), 59.9 (OCH_3), 34.1, 31.4; IR (KBr disc) 3306, 3275, 2901, 2014, 1598, 1361, 1289, 1200, 1116, 1013, 873, 756 cm^{-1}; HRMS (FAB^+) *m/z* calc'd for $C_{72}H_{96}O_6$: 1056.7207, found 1056.7228.



1,6-Bis{5,11,17,23,29,35-Hexa-*tert*-butyl-38,39,40,41,42-penta methoxycalix[6]aryloxy}-2,4-hexadiyne. A suspension of 5,11,17,23,29 ,35-hexa-*tert*-butyl-37-(propargyloxy)-38,39,40,41,42-pentamethoxycalix[6]arene (200 mg, 185 μmol) and $Cu(OAc)_2.H_2O$ (480 mg, 2.40 mmol) was stirred in pyridine (2.90 mL) for 3.5 h at 65°C in air. After cooling to r.t. the mixture was diluted with CH_2Cl_2 (50 mL) then washed with water (1x30 mL), 10% HCl (2x30 mL), water (1x30 mL), sat. brine (1x30 mL) and the organic layer dried over $MgSO_4$ and solvent removed *in vacuo.* Recrystallisation from ethyl acetate/methanol gave pure 1,6-bis{5,11,17,23,29,35-hexa-*tert*-butyl-38,39,40,41,42-pentamethoxycalix[6]aryloxy}-2,4-hexadiyne (194 mg, 97%): ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.25 (d, *J*=2.4 Hz, 8H, Ar*H*), 7.13 (s, 4H, Ar*H*), 7.10 (d, *J*=2.4 Hz, 2H, Ar*H*), 7.02 (s, 2H, Ar*H*), 6.95 (d, *J*=2.5 Hz, 2H, Ar*H*), 6.89 (s, 2H, Ar*H*), 6.86 (d, *J*=2.5 Hz, 2H, Ar*H*), 4.28 (d, *J*=2.5 Hz, 2H, OCH_2CCH), 4.44-3.54 (m, $ArCH_2Ar$), 3.21 (s, 12H, OCH_3), 2.98 (s, 12H, OCH_3), 2.78 (s, 6H, OCH_3), 2.55 (s, 8H), 1.10 (s, 36H, $C(CH_3)_3$), 1.09 (s, 18H, $C(CH_3)_3$), 1.07 (s, 9H, $C(CH_3)_3$), 1.03 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (68 MHz, $CDCl_3$) δ 154.1, 154.0, 153.7, 151.5, 146.2, 145.5, 133.8-133.0, 127.1-124.8 (^{Ar}C), 77.2 (OCH_2CCH), 75.5 (OCH_2CCH), 60.8 (OCH_2CCH), 60.0 (OCH_3), 34.3-34.0, 31.6-31.1; IR (KBr disc) 2952, 2015, 1480, 1361, 1291, 1244, 1202, 1117, 1013, 873 cm^{-1}; HRMS (FAB$^+$) *m/z* calc'd for $C_{148}H_{190}O_{12}$: 2159.4257, found 2159.4353.



5,11,17,23,29,35,41,47-Octa-*tert*-butyl-49-(propargyloxy)-50,51,52, 53,54,55,56-heptamethoxycalix[8]arene. In acetone (100 mL) was stirred 5,11,17,23,29,35,41,47-octa-*tert*-butyl-49-(propargyloxy)-50,51,52,53,54,55,56-hepta methoxycalix[8]arene (3.97 g, 2.97 mmol), potassium carbonate (14.4 g, 103 mmol) and methyl iodide (5.54 mL, 88.9 mmol) at reflux for 4 days under a drying tube. The reaction mixture was cooled to r.t. and filtered (the precipitate was washed with $CHCl_3$) and the filtrate evaporated to dryness. The off-white solid was dissolved in $CHCl_3$ (150 mL) and washed with 10% HCl (130 mL) then the organic phase dried over $MgSO_4$. The solvent was removed *in vacuo* and the resulting solid was columned (50 g SiO_2, 3:1 CH_2Cl_2:hexane) yielding pure 5,11,17,23,29,35,41,47-octa-*tert*-butyl-49-(propargyloxy)-50,51,52,53,54, 55,56-hepta methoxycalix[8]arene (1.49 g, 39%): ^{1}H NMR (270 MHz, $CDCl_3$) δ 6.96 (s, 8H, Ar*H*), 6.94 (s, 4H, Ar*H*), 6.92 (s, 2H, Ar*H*), 6.89 (s, 2H, Ar*H*), 4.28 (d, *J*=2.5 Hz, 2H, OCH_2CCH), 4.09 (br s, 4H, $ArCH_2Ar$), 4.05 (br s, 12H, $ArCH_2Ar$), 3.45-3.39 (m, 21H, OCH_3), 2.37 (t, *J*=2.5 Hz, 1H, OCH_2CCH), 1.10 (s, 36H, $C(CH_3)_3$), 1.09 (s, 18H, $C(CH_3)_3$), 1.07 (s, 9H, $C(CH_3)_3$), 1.03 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (68 MHz, $CDCl_3$) δ 154.3, 152.5, 146.4, 145.8, 132.7-132.2, 126.0-125.6 (^{Ar}C), 79.5 (OCH_2CCH), 75.0 (OCH_2CCH), 60.8-60.4 (OCH_3), 34.2, 31.4, 30.5-30.1; IR (KBr disc) 3311, 3266, 2952, 2014, 1538, 1481, 1392, 1286, 1244, 1202, 1112, 1007, 873 cm^{-1}; HRMS (FAB$^+$) *m/z* calc'd for $C_{98}H_{128}O_8$: 1432.9609, found 1432.9607.



1,6-Bis{5,11,17,23,29,35,41,47-Octa-*tert*-butyl-50,51,52,53,54,55, 56-heptamethoxy-49-calix[8]aryloxy}-2,4-hexadiyne. A suspension of 5,11,17,23,29,35,41,47-octa-*tert*-butyl-49-(propargyloxy)-50,51,52,53,54,55,56-hepta methoxycalix[8]arene (265 mg, 185 μmol) and $Cu(OAc)_2.H_2O$ (480 mg, 2.40 mmol) was stirred in pyridine (2.90 mL) for 3.5 h at 65°C in air. After cooling to r.t. the mixture was diluted with CH_2Cl_2 (50 mL) then washed with water (1x30 mL), 10% HCl (2x30 mL), water (1x30 mL), sat. brine (1x30 mL) and the organic layer dried over $MgSO_4$. After the solvent was removed *in vacuo* the solid was recrystallised from $CHCl_3$/methanol gave pure 1,6-bis{5,11,17,23,29,35,41,47-Octa-*tert*-butyl-50,51,52,53,54,55,56-heptamethoxy-49-calix [8]aryloxy}-2,4-hexadiyne (246 mg, 93%): ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.02-6.83 (m, 32H, Ar-*H*), 4.57 (s, 4H, ArO-C*H*$_2$-CC), 4.06 (br s, 16H, Ar-CH_2-Ar), 3.49 (s, 18H, ArO-C*H*$_3$), 3.35 (s, 12H, ArO-C*H*$_3$), 3.34 (s, 12H, ArO-C*H*$_3$), 1.14-0.97 (m, 144H, C(CC*H*$_3$)$_3$); ^{13}C NMR (68 MHz, $CDCl_3$) δ 154.4-154.0, 145.8, 133.3-132.5, 126.3-125.1 (^{Ar}*C*), 75.2 (OCH_2*C*CH), 71.0 (OCH_2C*C*H), 61.0-60.4 (O*C*H$_3$), 34.2, 32.0-31.2; IR (KBr disc) 2953, 2022, 1480, 1361, 1288, 1244, 1203, 1112, 1009, 873, 756 cm^{-1}; HRMS (FAB$^+$) *m/z* calc'd for $C_{194}H_{256}O_{16}$: 2866.9297 (MH$^+$), found 2866.9332.

Chapter 5

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