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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

at Massey University

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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 *hom O-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.

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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 Gutsche¹ 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}]octacos-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 Gutsche¹ and is derived from the word *calix*, the Greek for “vase” that relates to the distinct shape of the cyclic tetramer (**Figure 1.1**).

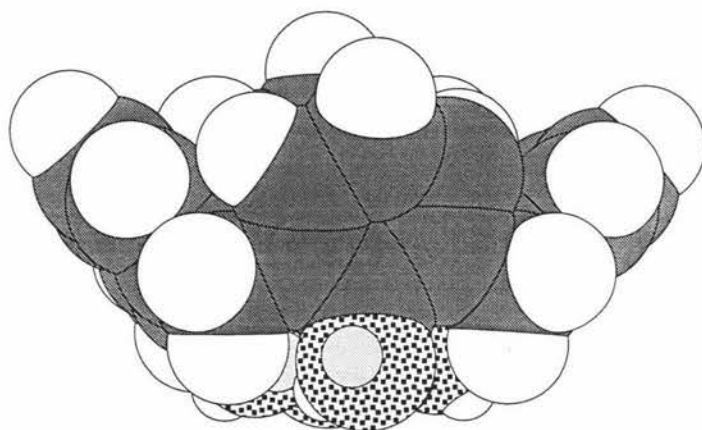


Figure 1.1. Chem3D™ representation of a space filling model of calix[4]arene.

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

† For a more extensive treatment, see Chapter 1 of the book by C. D. Gutsche¹ 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**.

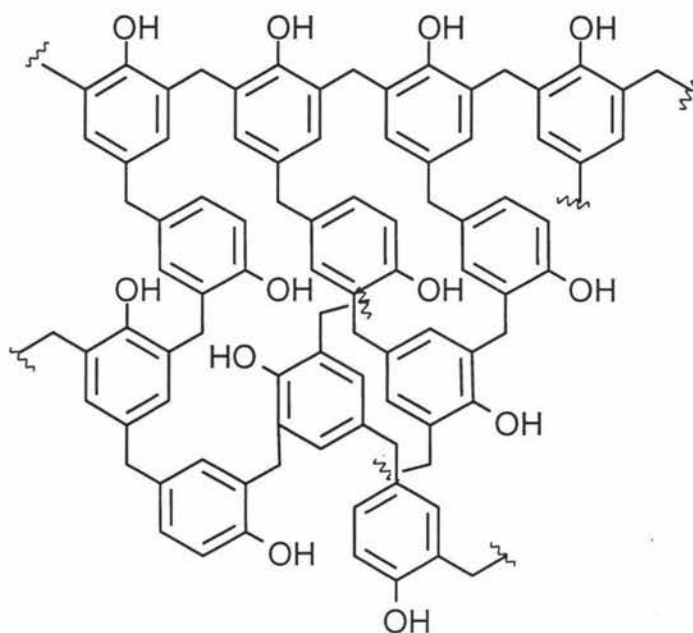


Figure 1.2. The disordered structure of a phenol-formaldehyde polymer as proposed by Zinke.

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.

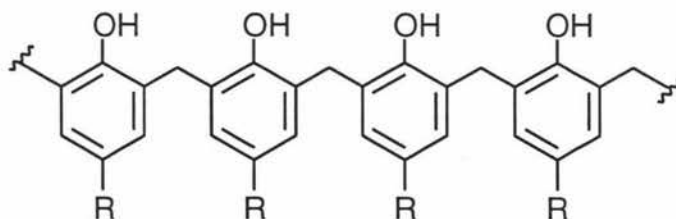


Figure 1.3. A polymer formed from the condensation of a *p*-alkylphenols and formaldehyde.

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 $>300^{\circ}\text{C}$ 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**).

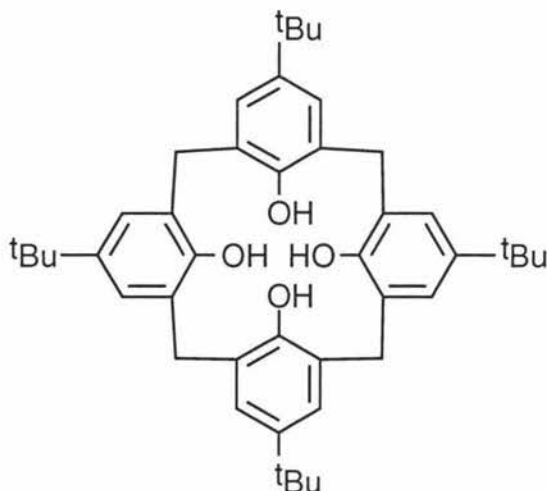


Figure 1.4. The cyclic structure of a condensate from the work of Zinke.

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.

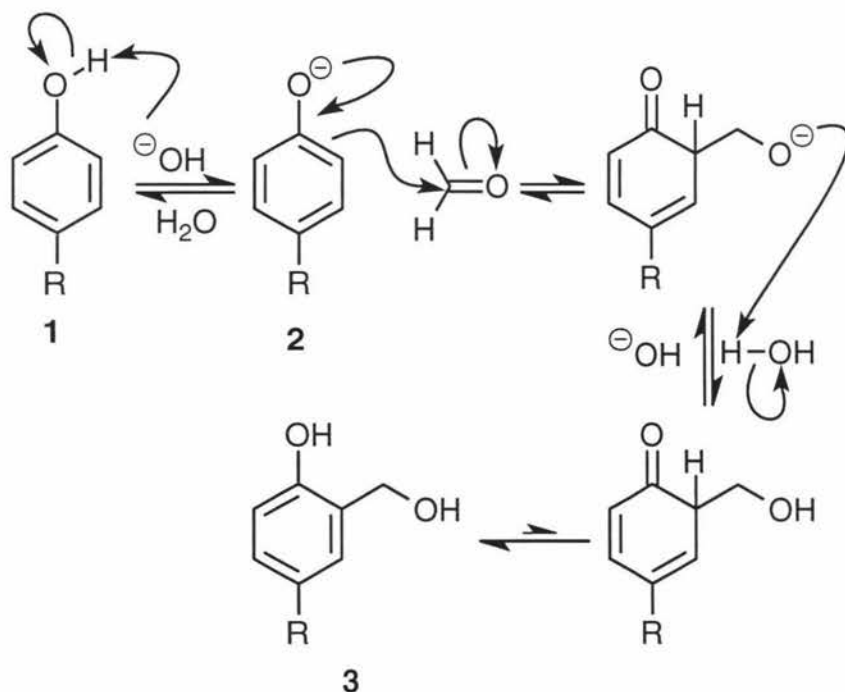
available.⁴⁻⁶ We have been able to repeat these procedures, modify and improve one of them, and also isolate useful quantities of the less common odd numbered calixarenes (*p*-*tert*-butylcalix[5]arene and *p*-*tert*-butylcalix[7]arene) by working with the residues from the published procedures for the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

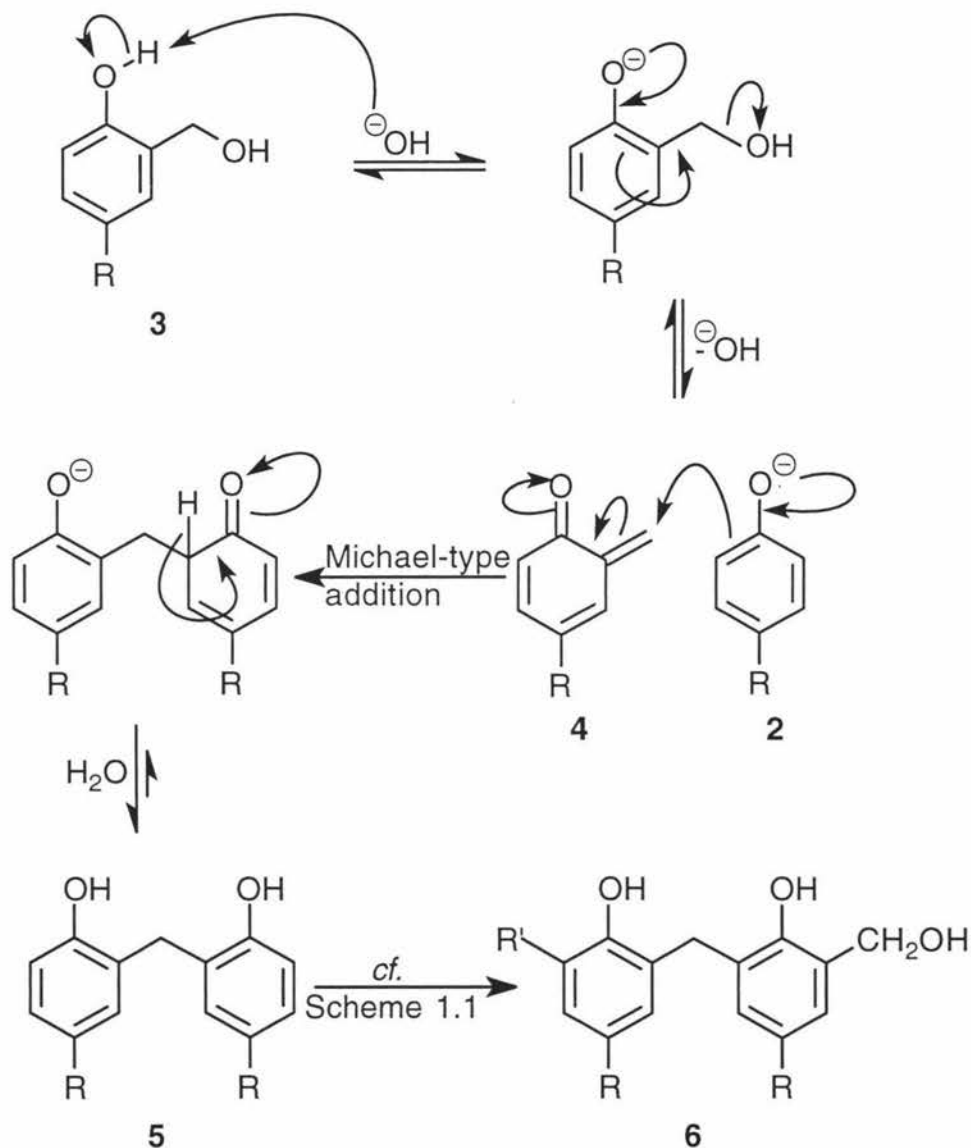
Synthesis of the *p*-alkylcalixarenes is always carried out by base-catalysed condensation of an appropriate *p*-alkylphenol with formaldehyde. In the first part of the process, linear oligomers are formed. The proposed mechanism (**Scheme 1.1**) involves the hydroxymethylation of the phenol by formaldehyde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



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

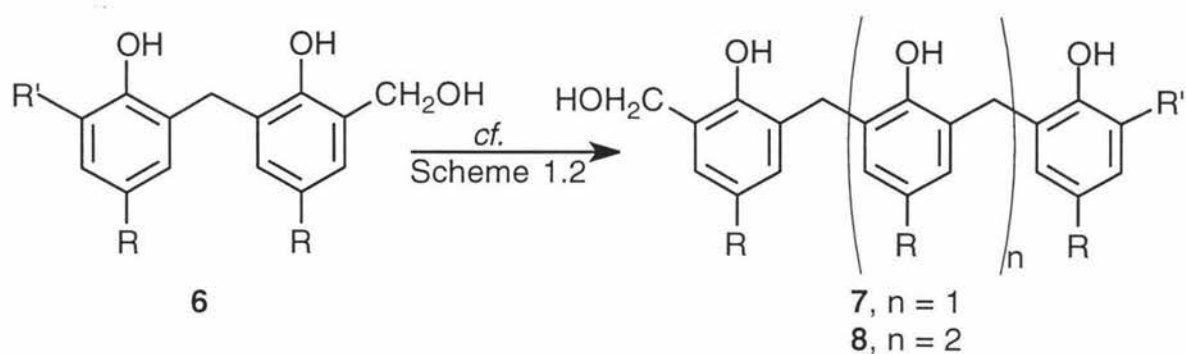
Benzyl alcohol **3** is the acidic precursor for oligomerisation. Oligomerisation involves the condensation of **3** with the salt of the starting phenol **1** (Scheme 1.2). This is thought to occur *via* dehydration of benzyl alcohol **3** brought about by a catalytic quantity of hydroxide to provide 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 ($\text{R}' = \text{H}$ 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 ($\text{R}' = \text{H}$ 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 *intramolecular* or *intermolecular* hydrogen bonded “coil” is formed. Gutsche termed these two arrangements “*psuedocalixarenes*” and “*hemicalixarenes*”, respectively (**Figure 1.5**).

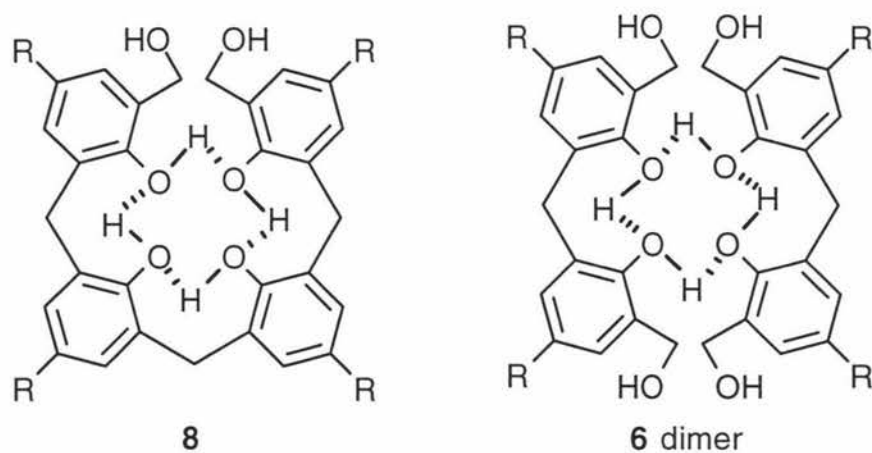
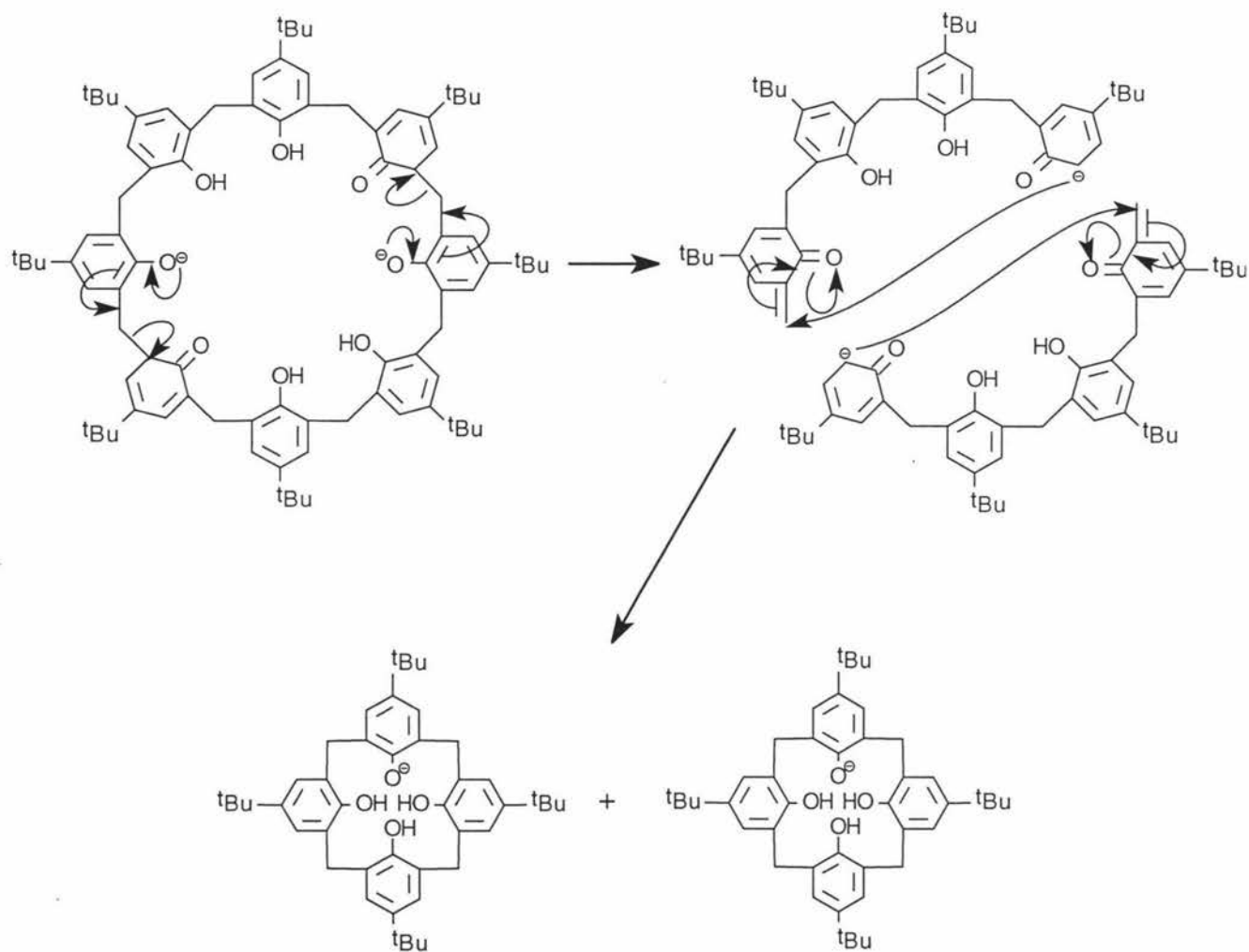


Figure 1.5. Precursors to *p*-*tert*-butylcalix[4]arene, the “*psuedocalix*[4]arene” conformation (**8**) and the “*hemicalix*[4]arene” arrangement (**6 dimer**).

In both cases the elimination of formaldehyde and water molecules are necessary to complete the cyclisation. The *hemicalixarene* (**6 dimer**) is presumably a precursor to the *psuedocalixarene* **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 *dihomooxalix*[*n*]arenes and the structure of *p*-*tert*-butyldihomooxalix[4]arene is depicted in **Figure 1.6**.

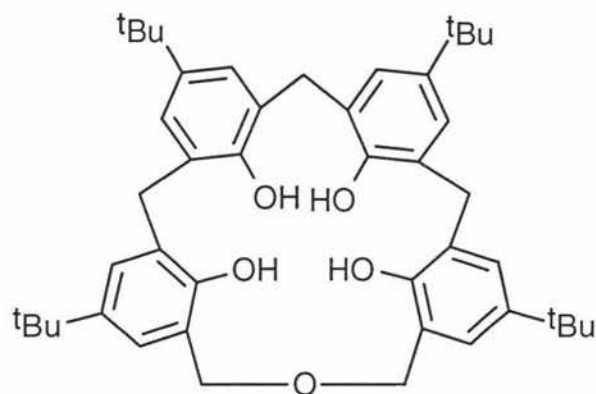


Figure 1.6. The structure of *p*-*tert*-butyldihomooxalix[4]arene.

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

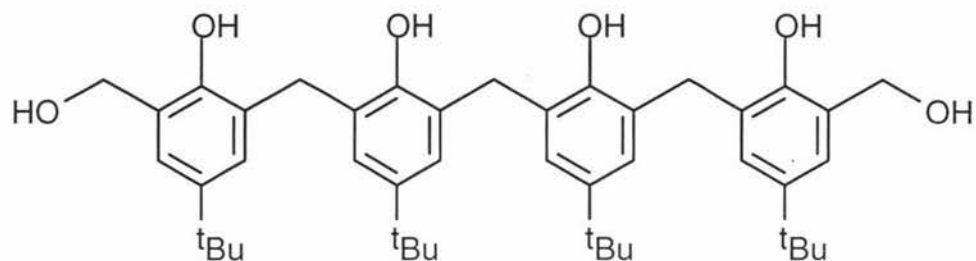


Figure 1.7. The *bis*(hydroxymethyl)tetramer precursor to *p*-*tert*-butyldihomooxalix[4]arene.

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*-butyldihomooxalix[4]arene is formed and this byproduct can be observed by t.l.c.⁶ We have been able to isolate pure samples of dihomooxalix[4]arene from the residues obtained in the preparation of *p*-*tert*-butylcalix[8]arene (see **Section 1.6**).

A recent paper¹⁴ 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 *hemicalixarene* 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 *psuedocalixarene* 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 chemistry¹⁶) 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.

<i>p</i> -Substituent, R	Cost (US cents/g)
Methyl	2.3
Ethyl	5.2
<i>i</i> -Propyl	10.3
<i>t</i> -Butyl	0.9
<i>t</i> -Pentyl	9.5
<i>t</i> -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 dihomooxalixarene (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 AlCl₃¹⁷ 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 acylation³). 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 ¹H 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

[‡] 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. studies¹ 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

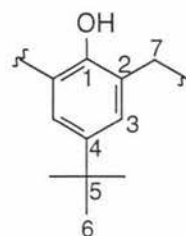
Assignment	$n = 4$	5	6	7	8
Ar-OH	10.35 (s)	8.68 (s)	10.54 (s)	10.35 (s)	9.65 (s)
Ar-H	7.06 (s)	7.22 (s)	7.16 (s)	7.22 (s)	7.20 (s)
Ar-CH ₂ -Ar	4.26 (d, J=13.3 Hz)	3.80 (br s)	3.90 (br s)	3.93 (br s)	4.38 (d, J=13.3 Hz)
	3.50 (d, J=13.3 Hz)				3.52 (d, J=13.3 Hz)
C(CH ₃) ₃	1.22 (s)	1.27 (s)	1.27 (s)	1.30 (s)	1.27 (s)

Table 1.2. ¹H shifts (δ /ppm in CDCl₃ 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-OH signals in the n.m.r. spectra. Shinkai²¹ has proposed that the hydrogen bond strength between the phenolic groups can be 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 \approx tetramer > octamer > pentamer.

More simple to interpret are the ¹³C 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 CDCl₃; ^b in CD₂Cl₂

Table 1.3. ¹³C 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 to characterise each of the calixarenes¹ (**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 ^1H 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.

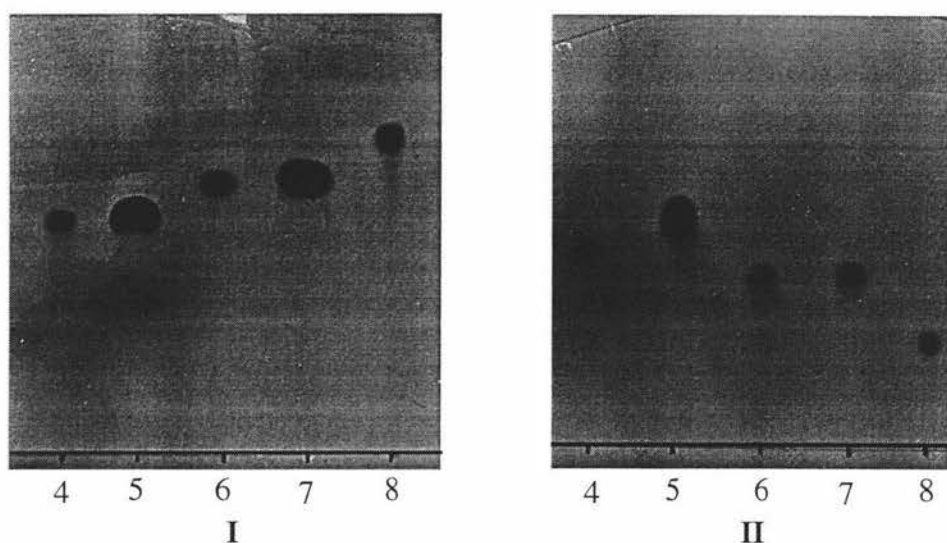


Figure 1.9. Two t.l.c. plates with samples of *p*-*tert*-butylcalix[*n*]arenes eluted in; I 1:1 hexane:CH₂Cl₂, and II 10:1 hexane:acetone.

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 (dihomooxalix[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* procedure⁴).

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 reported⁷ 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 Gutsche⁸, 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 procedure⁹ 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 solubilities 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 solubilities. 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 AlCl₃-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 stated¹⁷ 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.