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Novel Sulfonated Extended Arm Calixarenes

A thesis presented for the Degree of
Doctor of Philosophy

By

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November, 2001

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Dedicated to my Grandmother Douch Fatima

However laborious and difficult this task may be, whatever impediments and obstacles may lie in the way of its accomplishment, this transmutation does not go counter to nature...

Paracelsus

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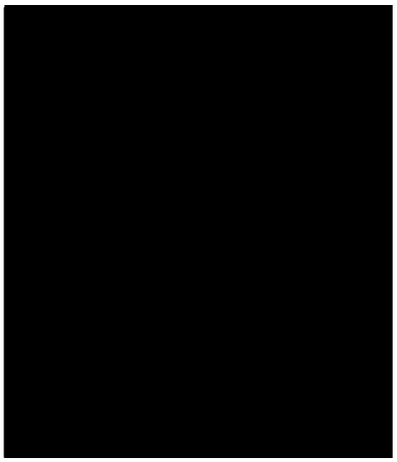
Statement

This thesis contains the results of work carried out by the author in the School of Chemistry at Monash University during the period of April 1998 to April 2001.
The work presented herein contains no materials which the author has submitted or accepted for the award of other degree or diploma at any university and, to the best of the author's knowledge and belief, contains no material previously published or written by another person, except where due reference is made in the text.



Mohamed Makha
November 2001

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Abstract

This research generally describes the application of some calixarenes to molecular recognition and self-assembly. Novel sulfonated *p*-benzylcalix[n]arenes, sulfonated *p*-phenylcalix[n]arenes and sulfonated *p*-cumylcalix[n]arenes have been synthesised and aspects of their host–guest inclusion chemistry explored, notably their interactions with the carotenoid *trans*-β-carotene and with fullerene C_{60} in water. The synthesis of molecular and ionic capsules based on sulfonated calix[5]arene resulted in the encapsulation of two sulfuric acid molecules. The research also resulted in the synthesis and structural authentication of the novel *p*-benzylcalix[4]arene which forms a 1:1 complex with C_{60} fullerene in the solid state. Additional research established the synthesis of novel tubular structures consisting of linked calixarenes, which are potential divergent receptors for supramolecular chemistry.

GENERAL INTRODUCTION

1.1 Overview

The emphasis in this thesis is the supramolecular chemistry of calixarenes in general and host-guest inclusion chemistry of a new class of water-soluble calixarenes, notably sulfonated *p*-phenyl- and *p*-benzylcalix[*n*]arenes. The project also concerns the syntheses of divergent receptors molecules based around fused calixarenes, the so called 'calix-tubes'. The host-guest inclusion chemistry encompasses a range of molecules including C_{60} fullerene, biologically active *trans* β-carotene and alkali metal cations.

1.2 Supramolecular Chemistry

In order to discuss the supramolecular chemistry of the calixarenes as host molecules, there is a need to summarize the concepts and terminology of this growing field of research in order to understand the goals and the challenges of the current work.

For over a century, molecular chemistry was the predominant endeavour in chemical sciences, consisting of covalent chemistry conducted *via* chemical transformations associated with the making and/or the breaking of covalent bonds. The development of synthetic methodologies based on covalent chemistry and the increasing interest in understanding biological processes has helped in the emergence of supramolecular chemistry. This newly established field of science has the potential to give a deeper insight into the realms of biology and into the complexity of amorphous matter, the challenge of the new millenium. Jean-Marie Lehn, one of the leading proponents in the area, defines supramolecular chemistry as:

"Beyond molecular chemistry based on the covalent bond there lies the field of supramolecular chemistry, whose goal it is to gain control over the intermolecular bond"- Jean-Marie Lehn.[1]

Supramolecular chemistry is often described colloquially as chemistry "beyond the molecule"[1] and is concerned with the non-covalent intermolecular forces between discrete molecular components that form assemblies of molecules - "supermolecules".

A supermolecule is defined as the molecular and the structural assemblies resulting from the association and the interaction between the discrete molecular components forming one or more molecular entities.[1] The spontaneous formation of molecules of this

type is a result of a cumulative interplay of relatively weak forces that hold the components together. The result of such association is often a well-ordered system, discrete in structure and dynamic in nature, because of the weak interactions contributing in forming them. Supramolecular assemblies are defined as multi-component assemblies of molecules, behaving as single entities with novel chemical and physical properties and complex structural architectures. These assemblies consist of polymolecular entities that result from the spontaneous association of a large undefined number of components into a specific phase having more or less well-defined microscopic organisation and macroscopic characteristics depending on its nature (such as films, layers, vesicles, micelles, mesomorphic phases, solid state structures, etc.).[1,2]

Supramolecular chemistry is an interdisciplinary field of science, cutting across boundaries which often exist between chemical, physical and biological disciplines and regrouping in a conjoint effort to better understand the aspects of large molecular structures. Figure 1.1 defines and summarises the general concepts behind this growing discipline of science and also the prospects of some utilitarian uses that may emerge from it.[1]

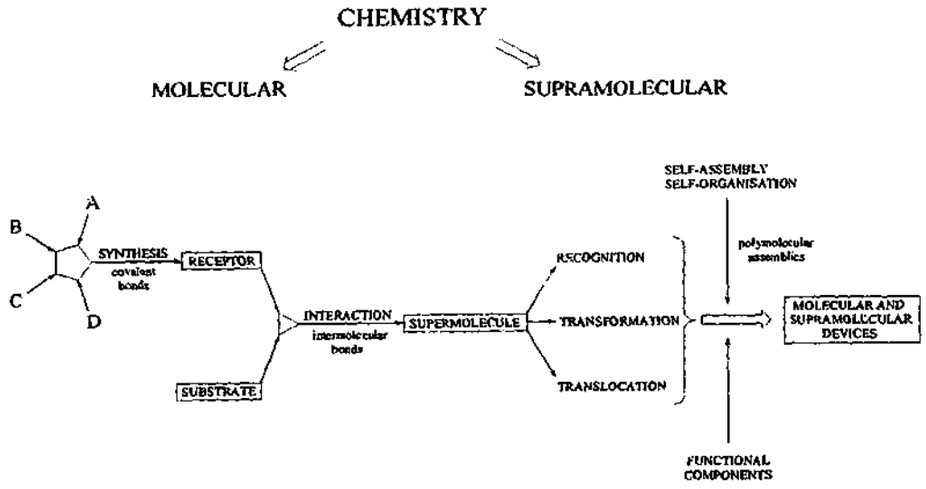


Figure 1.1. A schematic overview of supramolecular chemistry illustrating its aspects, relationship with molecular chemistry and its position in chemistry as a whole.[1]

Intermolecular (supramolecular) interactions are the foundations for highly specific biological processes, such as substrate binding by enzymes or receptors, formation of protein complexes, intercalation complexes of nucleic acids, the decoding of the genetic code, neurotransmission and cellular recognition (immunology).[3] Interest in

biological systems has led supramolecular chemistry to borrow the terminology used in biology such as "receptor/substrate", "molecular recognition" and "binding of substrate".[4]

Central to the description and definition of supramolecular chemistry and of fundamental importance to the present study, apart from the formation of the supermolecule, is the supramolecular terminology used throughout this thesis. The formation of the supermolecule is a result of the interaction between substrate(s) denoted (σ) and a receptor denoted (ρ) or host (h) and guest (g). This process is governed by the principles of molecular recognition, which is synonymous with the term "inclusion phenomena" or "host-guest" chemistry. The terms "guest" (substrate) or "host" (receptor) will be used without discrimination, noting that the nature of the forces involved between host and guest, or receptor and substrate, remain consistent regardless of the terminology used. Furthermore, symbols have been introduced to describe the mode of interaction between the host and the guest. The inclusion of σ into ρ is denoted with ($\sigma \subset \rho$) and partial penetration of ρ by σ is denoted by ($\sigma \cap \rho$), while complete encapsulation of σ by ρ is expressed as σ@ρ.[1,5]

The rapid expansion of supramolecular chemistry over the last decade has resulted in an enormous diversity of chemical research and a complete overview of the subject is beyond the scope of this thesis. Accordingly, the introduction is restricted to the supramolecular chemistry aspects, and the inclusion properties of calixarenes and sulfonated calixarenes. Special emphasis is given to fullerene C_{60} and *trans*-β-carotene inclusion complexes in aqueous media. A brief introduction to host-guest chemistry and molecular recognition is appropriate in highlighting the concepts behind host-guest complex formation and outlining the factors involved which are directly applicable to the present study.

1.3 Host-Guest Chemistry and Molecular Recognition

Molecular recognition is of fundamental importance to biology and chemistry. It provides a means for molecular "communication" and "sociology",[1] and is therefore central to the action and activity of biological systems essential for "life" processes (enzyme and antibody action, membranes and channels, carrier and receptor systems, etc.). While such systems are sometimes inaccessible and inherently complicated, the principles of molecular recognition are evident in relatively smaller synthetic systems (*e.g.* alkali metal binding by crown ethers and cryptands[13]). Also, the noncovalent binding

interactions associated with metal ion coordination within inclusion compounds has attracted much attention in the formation of both molecular and ionic aggregates. The following introduction is concerned only with the general concepts behind molecular recognition and host-guest chemistry on synthetic host-guest systems. It will discuss briefly the factors determining the selectivity (recognition) of a host towards guest molecules, as modelled in Figure1.2.

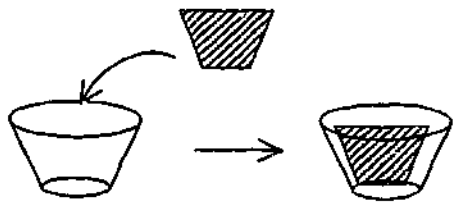


Figure 1.2. Schematic representation of the inclusion phenomenon.

Selective binding was a notion first established by Emil Fisher in 1894 and represented by the steric fit concept of "lock and key", requiring geometrical and interactional complementarity between receptor and substrate - the basis of molecular recognition.[6] More recently Jean-Marie Lehn describes the complementarity leading to molecular recognition as "programmed supramolecular systems" where the structural and interactional features of the components are the information contents embodied within their structures, that evaluate the molecular complementarity.[1] The large difference in free energies of binding between a substrate σ and other competing substrates results in a selective recognition by a receptor ρ and the high affinity between ρ and σ achieves the formation of the supermolecule. Molecular recognition is not merely binding but selective binding – "*binding with a purpose*".[1]

The host-guest interactions may be influenced by other interactions, involving other molecules such as solvent molecules. This kind of foreign force in respect to ρ and σ interactions may contribute constructively or destructively on the mode of binding. The cooperativity (allosteric effects) of the host (in the form of intramolecular or host-host intermolecular interactions) may increase the binding ability of a host by maintaining the desired conformation or directionality necessary for guest inclusion.[7] Such considerations are important in the simultaneous binding of different guests by co-receptor hosts, where the binding of one guest may influence the subsequent binding properties of the host.[8] Alternatively, associations with neighbouring molecules (including solvent) may

effectively compete for host availability thus lowering the overall binding affinity for a particular substrate (guest).

Host-guest formation involves molecular recognition, requiring a geometrical complementarity between the host and the guest. Generally speaking, the host or receptor is a large molecule or aggregate of molecules such as a synthetic macrocyclic compound possessing a central hole or cavity, with convergent binding sites.[9] The guest may be a monoatomic ion, a simple organic molecule or a more complex species such as a hormone. These complexities can be reduced to a framework for describing the factors contributing in the formation of host-guest complexes, and these are summarized below.[1,10]

- *Steric complementarity*; the complementarity between a concave and a convex domain in the correct location on the host ρ and guest σ.
- *Interactional complementarity*; mutual attraction requiring electronic and electrostatic complementarity in the binding sites of a receptor and substrate; such forces involve electrostatic negative/positive, charge/dipole, dipole/dipole, hydrogen bonding, van der Waals interactions, etc.
- *Large contact areas* between host and guest leading to maximising their interactions and enhancing their binding.
- *Multiple interaction sites*; in view of the weak nature of the interactions involved in the binding between the host and guest, cooperative interactions are desirable for stronger binding.
- *Strong overall binding*; efficient recognition requires strong and selective binding.
- *Medium effects*; the receptor and substrate interactions can be influenced by the medium effects of solvent-receptor, solvent-substrate and solvent-solvent interactions and the two should match their hydrophobic or hydrophilic domains in order to overcome the effects of neighbouring molecules, favouring the formation of the host-guest complex.

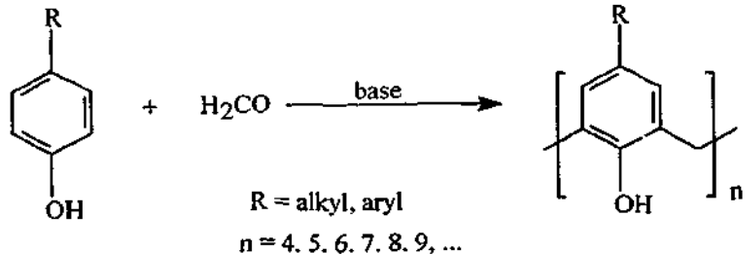
1.4 Calixarene host molecules

The chemistry of cyclodextrins[11,12] and crown ethers[13] has been the focus of interest in host-guest chemistry for several decades. In the late 1970's, Gutsche and coworkers reported the synthesis and properties of a new class of macrocycles called

calixarenes, since their shape is reminiscent to a calix crater (Greek *calix*, chalice; *arene*, indicating the incorporation of aromatic rings).[16] Calixarenes are obtained from the base or acid catalyzed condensation of *p*-alkylphenols and formaldehyde.[14,16-22] The closely related cyclic compounds, resorcarenes[22,25] derived form resorcinol and aldehyde condensation are not discussed here. The history of calixarenes started in the mid-1940s with the work by Zinke and coworkers.[15] Zinke postulated that the product obtained from the base-induced reactions of *p*-alkylphenols with formaldehyde had a cyclotetrameric structure. This belief remained until Gutsche's publication in 1979, when he established the identity of the components of the reaction mixture as consisting of cyclic tetramers, hexamers and octamers.[16] Subsequently, for the last two decades, calixarenes have been extensively investigated and have become the third major supramolecular host compound used in molecular recognition.[22-29] Calixarenes are affordable and accessibile and they have interesting structures, with a more versatile range of cavity sizes than crown ethers and cyclodextrins. They possess well-defined cavities amenable to further structural elaboration. These features have attracted the scientific community with its promise of a wealth of inclusion and molecular recognition phenomena.

1.4.1 Calixarenes synthesis

Calixarenes (or 1_n-metacyclophanes) are obtained from the condensation reaction of formaldehyde and *para*-substituted phenols, under basic conditions, yielding a mixture of macrocyclic rings, Scheme1.1. Without *para*-substituent on the phenol, this condensation reaction produces a polymer, 'Bakelite', instead of calixarenes.



Scheme 1.1

Nevertheless, not all *p*-substituted phenols are suitable for this condensation.[25] Electron donating substituents at the *para* position with respect to the phenolic hydroxy are often required for the reaction to proceed, such as the alkyl and aromatic groups listed

in Table 1.1. Beside the commonly used "one pot" synthesis procedure, calixarenes can also be obtained by indirect methods. Notable are a stepwise synthesis to form the monomeric chain prior to cyclisation,[29-31] and a fragment condensation fusing two or more monomeric fragments together (*e.g.* Scheme 1.2 below).[32-34]

Table 1.1 Yield[%][ref] of some *p*-substituted calix[*n*]arenes using the "one pot" synthesis.[25]

R	*n* = 4	5	6	7	8
Me				22[38]	
Et				24[38]	
i-Pr	10[19]		26[19]		? [19]
t-Bu	49[36]	10-15[50]	83-88[37]	6[40,51]	62-65[35]
t-Pentyl [a]	6-7[41]		30[41]		37-41[41]
t-Octyl [b]	31[42]				30[43]
Adamantyl				71[44]	
n-alkyl					
Benzyl		33[45]	16[45]	5-10[56]	12[45]
Phenyl			10[46]	41[46]	7-14[46]

[a] *t*-Pentyl = 1,1-dimethylpropyl (-$C(CH_3)_2$-CH_2-CH_3)
[b] *t*-Octyl = 1,1,3,3-tetramethylbutyl (-$C(CH_3)_2$-CH_2-$C(CH_3)_3$)

The nomenclature of calixarenes is rather simple, and originally consisted of the term "calixarene" to describe the cyclic array of the phenolic units, with the *para* substituent of the phenol added as a prefix. Now, the number, n (4 to 20), in square brackets denoting the number of the aryl residues in the cyclic array, is inserted in the name calix[-]arene, whereas the phenolic hydroxyls are ignored and implicitly included in the nomenclature. For example, a calixarene made up of four phenolic units bearing R groups, joined by methylene bridges in a cyclic array is named *p*-R-calix[4]arene, Figure 1.3.

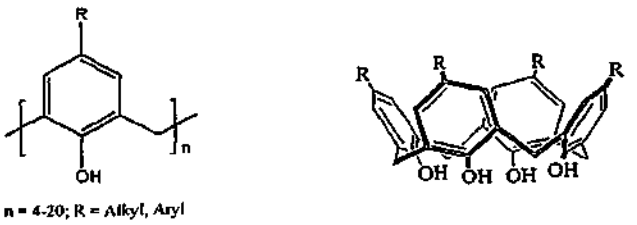
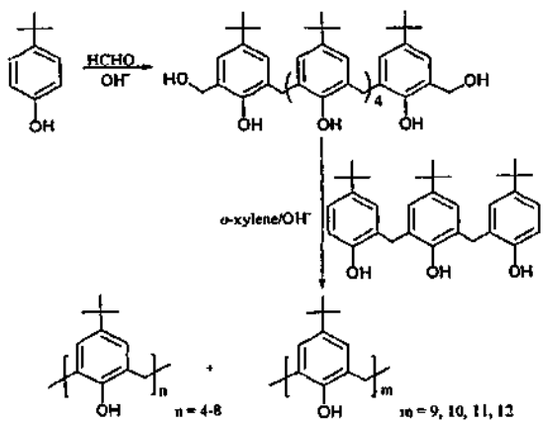


Figure 1.3 Shows the general representation of *p*-R-calixarenes (left) and the bowl shaped structure of *p*-R-calix[4]arene (right).

To avoid unnecessary repetition throughout this thesis, a particular calixarene will be represented by a bold number (*i.e.* **4-8**) which specifies the number of repeat units in

its ring structure and a superscript which specifies the *p*-substituent (*i.e.* ^{t}Bu for *tert*-butyl, CH_2Ph for benzyl, Ph for phenyl, SO_3H for sulfonato groups, *etc.*). Thus, *p*-phenylcalix[4]arene is represented as $\mathbf{4}^{Ph}$, *p-tert*-butylcalix[4]arene is represented as $\mathbf{4}^{tBu}$ and *p*-sulfonato-phenylcalix[4]arene is represented as $\mathbf{4}^{SO_3H}$. Following the same approach, this nomenclature is extended to sulfonated *p*-phenylcalix[n]arene and sulfonated *p*-benzylcalix[n]arene and are represented as $\mathbf{n}^{PhSO_3H}$ and as $\mathbf{n}^{CH_2PhSO_3H}$ respectively. Also, calixarene ether derivatives, made by alkylating the phenolic –OH groups about the lower rim of the calixarene, are generally named as (alkyloxy)-*p*-^{t}Bu-calix[n]arene, and will be represented as alkyl$\mathbf{n}^{tBu}$ (*i.e.* the tetra-ethyloxy-*p*-sulfonato-calix[4]arene bearing ethyl groups at the lower is represented with $Et\mathbf{4}^{SO_3H}$).

It is noteworthy that *p-tert*-butylcalix[n]arenes are the easiest class of calixarenes to make. This is largely due to the efforts of Gutsche *et al.*, who devised simple and reproducible synthetic procedures. Their base catalysed "one pot" synthesis affords the major *p-tert*-calix[n]arenes (n = 4, 6, 8) in good yields[35,36,37] and two minor calixarenes (n = 5, 7) in moderate yields.[50,51] Larger calixarenes from the base induced reactions can be separated from the reaction mixture, affording calix[n]arenes, n = 9-16, but the yields for each are generally well below 1%.[22] Moreover, the synthesis of large calixarenes (*p-tert*-calix[n]arenes, n = 9, 10, 11, 12) can be achieved in less than 1.5% yield, by a procedure involving fragment condensation of a linear hexamer, "precursor" to the *p-tert*-butylcalix[6]arene with a linear trimer, as outlined in Scheme 1.2.[55]



Scheme 1.2

More recently it has been established that a major source of these large calixarenes is the acid catalysed reaction, yielding calixarenes as large as n = 20.[23] Alternatively, calixarenes can be prepared by controlled stepwise syntheses[29,31,52] or fragment condensations,[32-34] yielding calixarenes with different *para*-substituted phenolic units.

The product of the base catalysed condensation reaction and the distribution of calixarenes in the reaction mixture is influenced by the reaction conditions and reagents. Most important is the catalytic amount of base used (conveniently described by the molar ratio of the base to the phenol) along with its type and the temperature during the reaction.[14,21,22] Base-promoted condensation of *p*-substituted phenols and formaldehyde result in a mixture of linear and cyclic oligomers.[20,21] From *p*-^{t}Bu-phenol and formaldehyde mainly the tetrameric, hexameric and octameric cyclic products are isolated. Investigations by Gutsche *et al.* involving variations in the molar equivalents of base used, ratio of reactants and reaction temperature, resulted in multi-scale, reproducible procedures for the synthesis of **4**^{tBu} [35], **6**^{tBu} [36] and **8**^{tBu}.[37] This work established also the optimum base equivalents for the production of calix[4, 6 and 8]arenes. Generally, a molar equivalent of 0.02 - 0.03 mole (usually added as a NaOH or KOH solution) is needed to produce calix[4 and 8]arenes.[35,36] The thermodynamically favoured tetramer is obtained at high temperatures,[18,24,36] while the octamer is favoured under milder conditions (xylene reflux, 160°C).[35] Greater equivalents of base, 0.3 - 0.4 molar equivalents per *p*-substituted phenol, favours the formation of calix[6]arene, as illustrated in Figure 1.4.[18,37] It is noteworthy that these results are derived from the study of *p*-^{t}Bu-phenol and formaldehyde condensation and are used only as guidelines for the condensation of other *p*-substituted phenols.

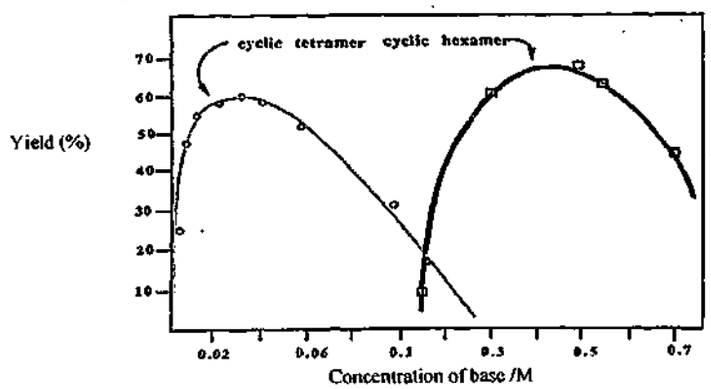


Figure 1.4 The calixarene yield (%) as a function of the molar ratio of the base used in the condensation reaction.[21]

The base-catalysed synthesis of calixarenes generally produces the calix[5,7]arenes in low yields.[19,46-50,56] *p*-^{t}Bu-calix[5]arene can be prepared with an overall isolated yield of 15-16%.[49,50] The reported syntheses specify careful temperature control to maximise the yield, using the base equivalent value found in the region of the intersection of the two curves shown in Figure 1.4.

In the method described by Gutsche *et al.*, a tetralin mixture of *p*-^{t}Bu-phenol, paraformaldehyde and base (KOH, 0.277 equivalents per phenolic unit) is preheated to a temperature of 80-85 °C for 1.5 hrs, followed by a quick ramp in temperature to 180-185 °C. The reaction is held at this temperature for 10 minutes, then immediately lowered to 160-165 °C for 3 hours.[50] Higher yields for the production of *p*-^{t}Bu-calix[5]arene (up to 22%) have been reported by Shinkai *et al.* where the preparation involves preheating the reaction mixture (base used: ^{t}BuOK, 0.26 equivalents per phenolic unit) at 55 °C for 2 hrs, then increasing the temperature to 150 °C, where it is held for 3 hrs and resulting in an isolated yield of 16.1%.[49] The synthesis of the *p*-benzylcalix[5]arene has been achieved with the relatively higher yield of 33%.[45] In this case, a tetralin mixture (base used KOH, 0.185 equiv. per phenolic group) is held at 190-200°C for four hours.[45] In a more recent publication, using similar reaction conditions with half the amount of base required for the synthesis of *p*-benzylcalix[5]arene (base used KOH, 0.092 equiv. per phenolic group), *p*-benzylcalix[7]arene has been isolated in 15-20%.[56]

Reasonable quantities of the odd-numbered *p*-^{t}Bu-calix[7]arene have been prepared by Gutsche[50] and others,[40] with the yield optimised to 16.8% yield.[51] Acid-catalysed condensation affords the heptamer in yields up to 25%.[23] Stepwise synthesis of the pentamer has been described,[52] along with fragment condensation,[53,54] yielding calix[5]arenes with different *para*-substituted phenolic units.

The synthesis of higher order calix[n]arenes have been reported for *p*-^{t}Bu-calix[n]arenes, n = 9 – 12[55] and n = 12 – 20.[22,23] The former group were isolated in 1-1.5% yields from treating the *p*-^{t}Bu-calix[6]arene "precursor" with a linear trimer. The latter groups were made by an acid-catalysed process, where the linear oligomers may undergo different mechanistic pathways before cyclisation, affording yields of 8.6%, 5.2%, 3.7%, 1.3%, 1.5%, 0.3% and 0.2% for **9**^{tBu}, **10**^{tBu}, **11**^{tBu}, **13**^{tBu}, **15**^{tBu}, **16**^{tBu} and **20**^{tBu} respectively.[23] The proposed mechanism includes: (i) hydroxymethylation at one terminus followed by carbocation formation and intramolecular attack at the other terminus to form a cyclic oligomer, without loss of an aryl residue; (ii) hydromethylation

at one terminus followed by carbocation formation and intramolecular *ipso* attack to form cyclic oligomers with loss of one or more aryl residues; or (iii) external attack by an electrophile to form other linear oligomers.[23] Mixtures of small amounts of larger calixarenes were first detected in the base-induced condensation of *p*-^{t}Bu-phenol and formaldehyde and are generally isolated in 1-3% yield from the residue of the preparation of calix[5]arene.[50] Within the same range of yields, larger calixarenes are obtainable from the base-induced procedure.[55]

1.4.2 Conformational behaviour of calixarenes

One of the most interesting feature of the calixarenes is their structural flexibility/mobility and their consequent ability to assume a variety of shapes *via* conformational interconversion. This mobility in solution increases with increasing ring size, or by incorporating less bulkier substituents at the *para*-position of the phenolic units. Solvent also has an influence on the rate of interconversion, which in general involves rotation about the methylene bridging groups whereby the hydroxy (lower rim) or the *para*-substituents (upper rim) swing through the annulus, as shown in Figure 1.5(a).[21,27,18] Restricted motion of the aryl units through the annulus results in a set of conformations for each calixarene. These conformational isomers are determined by hydrogen bonding between hydroxy groups, bulkiness of the *para*-substituents and the amount of the steric strain at the methylene bridges. The optimisation of the balance between all these contributing elements determines the stability of the conformations. Special interest in these conformations has lead to further definitions and descriptions for each isomer. For instance, the cone conformation is quantified by the pitch angle, θ, which is defined by the plane of the aryl residue and the plane formed by the bridging methylene groups, Figure 1.5(b).[21,57]

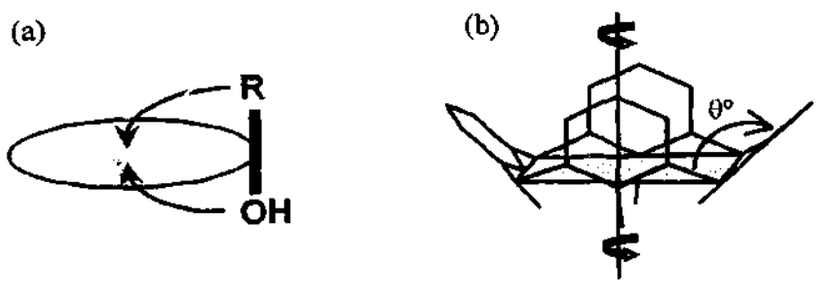


Figure 1.5. (a) The 'swinging' mechanism pathway of aryl groups through the calixarene annulus; (b) the pitch angle defining the relative position of the aryl groups (in this case calix[4]arene).

For the smaller ring *p*-^{t}Bu-calix[n]arenes (n = 4, 5) the interconversion can be restricted to only involve the lower rim annulus pathway due to the bulkiness of the substituents at *para* position. *p*-^{t}Bu-calix[4]arene has principally four possible conformations designated as cone, partial-cone (paco), 1,2-alternate (1,2-alt) and 1,3-alternate (1,3-alt), Figure 1.6.[18,58]

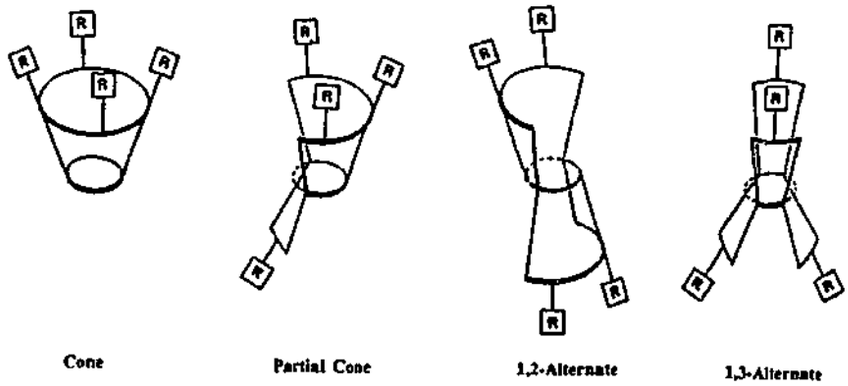


Figure1.6 Conformational isomers of calix[4]arenes.

The cone conformation is preferred both in solution and the solid state. In solution and at room temperature, the cone conformation is translated in the ^{1}H NMR experiment by a pair of doublets as an AB spin system for the geminal protons of the bridging methylene, with ^2J coupling values between 12 and 14 Hz, with one environment for the hydroxy, aryl and *para*-substituents of the phenolic units.[18,58,61,62] The ^{13}C NMR spectra identify this conformation by a single peak for the carbon of the methylene groups.[59]

It is noteworthy that the most favoured or preponderant conformation is a result of the strength of the hydrogen bonding at the lower rim and the optimisation of the steric strain between the bridging methylene, *para*-substituents and the solvent molecules.[18,63] Polar solvents interfere with the hydrogen bonding network of the calixarenes, by interacting with the lower rim hydroxy groups, thus lowering the coalescence temperature and the interconversion energy.[18,63] The disruption of the otherwise optimised hydrogen bonding, by polar solvents, can influence the outcome of lower rim derivatisation reactions. Then there is the affect of temperature on the calixarene adopting the stable optimised hydrogen bonded conformation. The dynamic behaviour of the calixarenes can be discussed in terms of the number of available conformations or in terms of the activation energy ($\Delta G^{\ddagger}$)[18] of the conformational interconversion, calculated by an

empirical formula involving the coalescence temperature *Tc* as its variable[21,76] (Table 1.2). The coalescence temperature is defined as the temperature at which the rate of interconversion on the NMR time scale is slow, rendering the equatorial and axial protons of the bridging methylene inequivalent (Figure 1.7).

Figure 1.7 The interconversion mechanism showing the equatorial and axial protons of the methylene bridges; above *Tc* temperature (see Table 1.2) H_a and H_b are equivalent giving rise to a singlet in the ^1H NMR, and below *Tc* the inequivalence of these protons gives rise to an AB system.[21]

The evaluation of the coalescence temperature is performed by a temperature-dependent NMR experiment, either by lowering or increasing the temperature, depending on the conformational state of the calixarene and following the changes in the chemical shift of the bridging methylene protons. The cone conformation of 4^{tBu} at ambient temperature exhibits a pair of doublets for the methylene protons. An increase in temperature is followed by a gradual broadening of these methylene doublets and, above *Tc*, each doublet is collapsed to a singlet, indicative of rapid interconversion of the calixarene between two equal conformations. This interconversion 'flipping' motion renders the equatorial and axial protons of the methylene group equivalent on the NMR time scale.[18,63] The coalescence temperature (*Tc*) and the activation energy ($\Delta G^{\neq}$) are regarded as a gauge of conformation stability. *p*-^{t}Bu-calix[4]arene has a *Tc* of 325 K corresponding to an activation energy of 14.9 kcal mol^{-1}, and therefore the cone conformation is stable. This finding encourages the prospect of chemically modifying the O-rim whilst retaining the cone conformation. Table 1.2 gives the interconversion activation energies and coalescence temperatures for some selected calixarenes.

Table 1.2. Coalescence temperatures (T_c) and thermodynamic free energies of activation ($\Delta G^{\ddagger}$) for conformational interconversion of some selected *p*-R-calix[n]arenes ($\mathbf{n}^{R}$) in chloroform and pyridine.[25]

$\mathbf{n}^{R}$	$CDCl_3$		[D5]Pyridine	
	$\Delta G^{\ddagger}$ (kcal mol^{-1})	T_C (K)	$\Delta G^{\ddagger}$ (kcal mol^{-1})	T_C (K)
4^{H}	14.9	309	11.8	251
4^{tBu}	15.7	325	13.7	298
4^{C6H5}	15.3	317	12.8	271
$4^{t\text{-octyl}}$	14.6	303	12.4	260
5^{tBu}	13.2	271		
6^{tBu}	13.3	284	9.0	219
7^{tBu}	13.4	288		
8^{tBu}	15.7	326	<9	<183
$8^{t\text{-octyl}}$	15.2	316	<9	<183
9^{tBu}	13.5	290		

Calix[5]renes can also adopt the cone conformation.[65-67] Atwood *et al.*[67] and others have established that the cone structure adopted in the solid state has a distorted structure approximating C_5-symmetry, with different pitch angles for the aryl groups making up the ring,[66] Figure 1.8. In solution, however, the ^{1}H NMR spectrum divulges that calix[5]arene is freely interconverting between intermediate conformations at ambient temperature. The weakening of the hydrogen-bonding, due to the hydroxyls being further apart relative to the calix[4]arene situation, makes the cone conformation less stable at room temperature. This conformational flexibility of calix[5]arene is supported by temperature-dependent ^{1}H NMR analysis, that gives a *Tc* value of 273 K (*c.f.* calix[4]arene *Tc* = 325 K). Comparison of the $\Delta G^{\ddagger}$ values relative to calix[4]arene shows that calix[5]arene requires less energy to interconvert, $\Delta G^{\ddagger}$ = 13.2 kcal mol^{-1} (*c.f.* $\Delta G^{\ddagger}$ = 15.7 kcal mol^{-1} for the tetramer) and this influences subsequent formation of the lower rim *O*-derivatives.

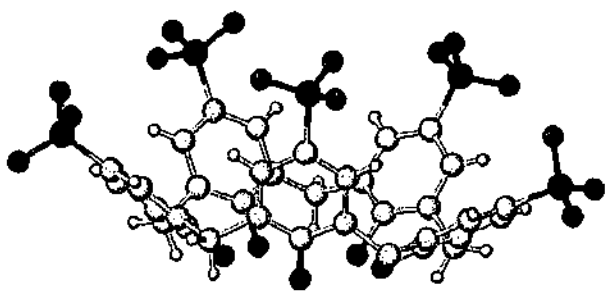


Figure1.8 The crystal structure of 5^{SO_3H} adopting the cone conformation[213]

Calix[6]arenes have a distinctive conformations in the solid state consisting of either a pinched cone conformation where all the hydroxyls are hydrogen-bonded in a cyclic array,[68,71] or in a double partial cone arrangement which has two sets of hydrogen bonded phenolic groups (Fig. 1.9b).[69,73] In solution, the ^{1}H NMR spectrum at ambient temperature shows a singlet resonance for the methylene protons, but below the *Tc*, the calix[6]arene is fixed into a conformation giving rise of three pairs of doublets for the methylene protons and three peaks of equal integration for the hydroxy protons.[70]

Given the larger cavity of the calix[6]arene macrocycle, several conformational isomers are possible, including "cone", "partial-cone", "1,2-alternate", "1,3-alternate", "1,4-alternate", "1,2,3-alternate", "1,2,4-alternate" and "1,3,5-alternate".[21,25] From these possible conformations, the "pinched" cone conformation (1,2,3-alternate or +,+,+,-,-,-) has been observed in the solid state,[72,73] and is the adopted conformation for a wide variety of lower-rim calix[6]arene derivatives,[22,27] Figure 1.9.[73] Solution studies are consistent with a "winged" (or "pinched" cone) conformation where two opposite aryl groups are in an "out" alignment in respect to the other aryls, whereas the remaining four are in an "up" and/or "down" orientation to maximise the hydrogen bonding.[18] The low interconversion energy of the hexamer suggests that "extra-molecular" factors (*eg.* solvent) may play a decisive role in determining the conformation.

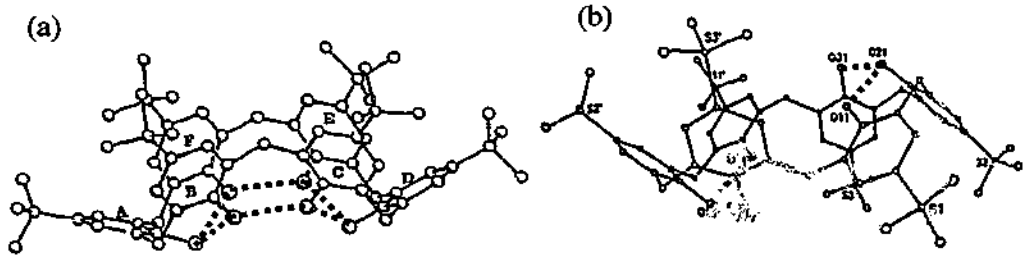


Figure 1.9 Molecular structures of calix[6]arene showing hydrogen bonding networks: (a) *p*-^{t}Bu-calix[6]arene in a 'pinched' cone conformation[71] and (b) *p*-sulfonatocalix[6]arene the double partial cone '1,2,3 alternate' conformation.[73]

Calix[7]arene, with an odd number of phenolic residues in the ring is considered more conformationally mobile and behaves somewhat like higher calixarenes. In the solid state, X-ray determination shows the molecule adopts either a flattened cone,[74] a pinched cone or a C_1 symmetry conformation,[75] Figure 1.10. In solution, the ^{1}H NMR specrum shows a singlet for the methylene resonance, which splits into seven pairs of doublets at lower temperature. The hydroxy resonance splits into seven peaks at low temperature, supporting the C_1 symmetry assignment.

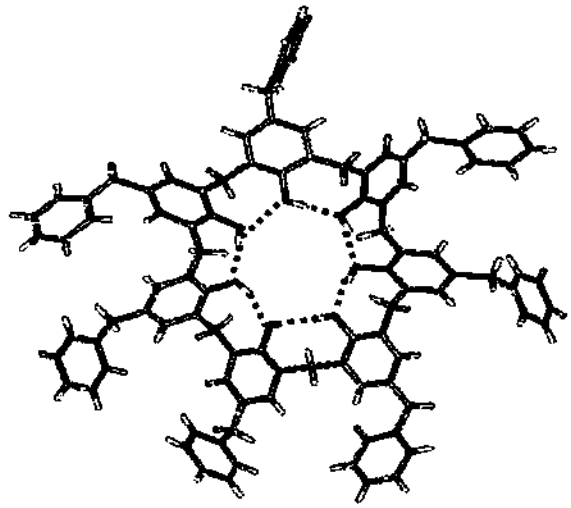


Figure1.10 The crystal structure of *p*-benzylcalix[7] arene showing the C_1 symmetry conformation.[56]

Two conformations of calix[8]arene have been identified: the 'pinched' double cone and the 'pleated loop'.[76] The ^{1}H NMR spectrum is somewhat similar to that of the calix[4]arene - exhibiting a doublet spin system for the methylene protons, indicative of a cone conformation.[18,23,64] Calix[8]arene, with its larger ring, has limitations in accommodating all the hydroxyls in a strong hydrogen bonded network if it adopts a cone conformation. Rather it adopts a 'pinched' double cone conformation which maximizes the H-bonding and this has a conformational mobility comparable to that of calix[4]arene (identical inversion barrier, $\Delta G^{\ddagger}$), Figure 1.11.

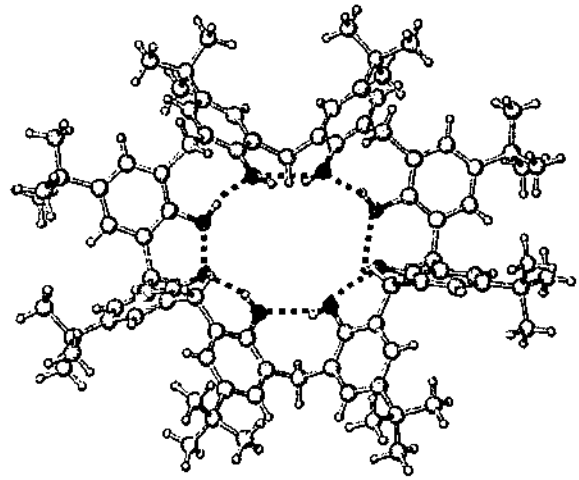


Figure1.11 The Molecular structure of *p*-^{t}Bu-calix[8]arene(taken from Raston *et al.* unpublished results)[213]

The cone and pleated loop furnish the best conformation-stabilising structures in the calixarene family and it is postulated that all of the other parent calixarenes incorporate as many cone like and/or pleated loop like conformational segments as possible.[23]

Larger calix[n]arenes (n = 9 to 20) are more flexible and, unlike the 'major' calixarenes, stable conformations of them are ill defined. Stability can be achieved for larger calixarenes containing aryl residues, which have integers that are a multiple of 4, *e.g.* calix[8, 12, 16 and 20]arenes. This can be ascribed to their ability to incorporate complete cone-like and /or pleated loop-like segments in their cyclic arrays,[23] with higher interconversion energies, Figure 1.12.

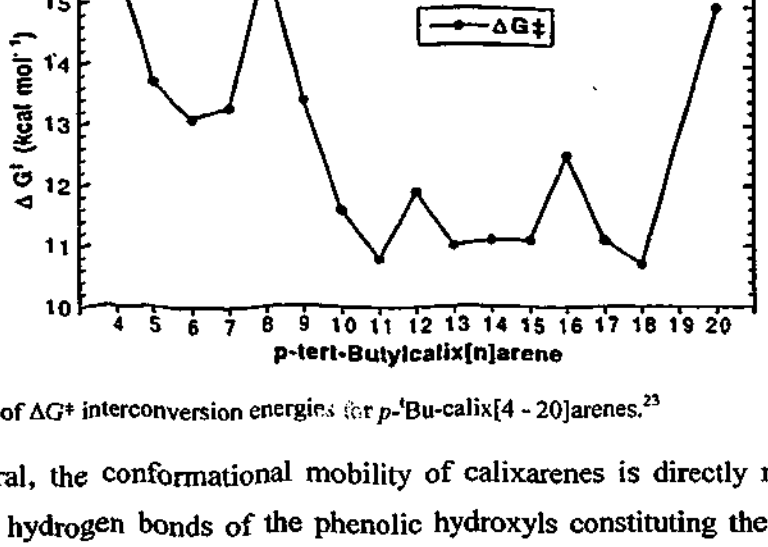


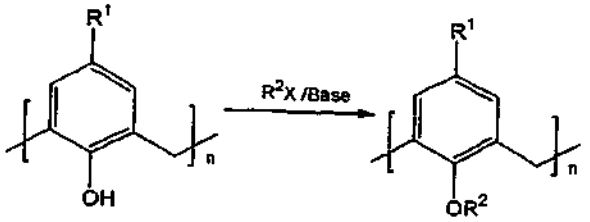
Figure 1.12. Plot of $\Delta G^{\ddagger}$ interconversion energies for *p*-^{t}Bu-calix[4 - 20]arenes.[23]

In general, the conformational mobility of calixarenes is directly related to the intramolecular hydrogen bonds of the phenolic hydroxyls constituting the cyclic array. This hydrogen bond interplay is reflected in both low OH stretching frequencies in the IR spectrum and downfield υOH positions in the ^{1}H NMR spectra.[77]

1.4.3 Functionalisation and conformational effect on derivatized calixarenes

Calixarenes can undergo multiple transformations both at the lower and upper rims.[21,25] The phenolic hydroxy group at the lower rim of the calixarene represent an excellent reactive site for the introduction of new groups, which modify the structure and the properties of these molecules and yield molecules with novel structures, and physical and chemical properties.[21,22,78] This functionalisation can be carried out principally in two ways. (i) The phenolic hydroxy groups of the calixarenes can be completely

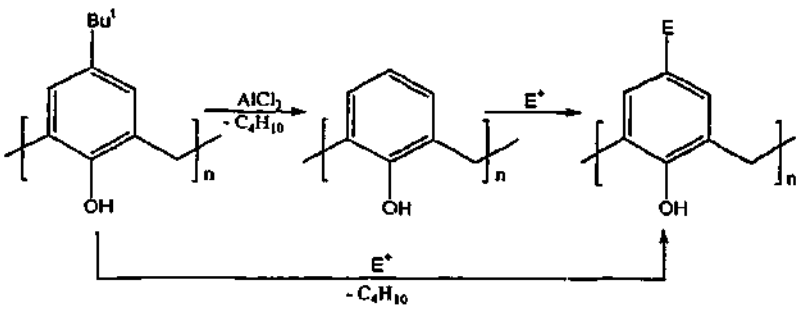
functionalised by using a variety of alkylating or acylating agents with various reaction conditions.[21,25] Scheme 1.3 shows some common lower rim transformations of *p*-R^1-calix[n]arenes.



n = 4-8; R^1 = H, Alkyl; R^2 = Alkyl, allyl, benzyl, $CH_2CO_2R^3$ $CH_2CH_2R^3$, $CH_2CONR^3_2$, CH_2CO_2H, $CH_2CONHOH$, COR, etc.

Scheme 1.3

(ii) ^{t}Bu groups at the *para* position of the calixarene can be removed by a transalkylation using $AlCl_3$ and an acceptor solvent such as toluene, Scheme 1.4.[21,79,80,81]



Scheme 1.4

Access to calix[n]arenes unsubstituted at the *para*-position allows the introduction of a variety of functional groups at the upper rim by addition of electrophiles. *Ipso* substitution of ^{t}Bu groups is another possible route to obtain upper-rim functionalised calixarenes (Scheme 1.4).

Complete functionalisation, such as alkylation or acylation at the lower rim is general for all ring sizes, proceeding by deprotonation of the hydroxyls and subsequent nucleophilic attack, leads to a tetra, penta, hexa, hepta or octa derivatized calix[n]arenes. This addition has allowed the introduction of a wide variety of functional groups at the lower rim. In most cases they are produced generally as mixture of isomers, providing a range of compounds but presenting difficulties in expanding their chemistry. Figure 1.13 shows general manipulations and synthetic strategies of the calixarene frame work.[25]

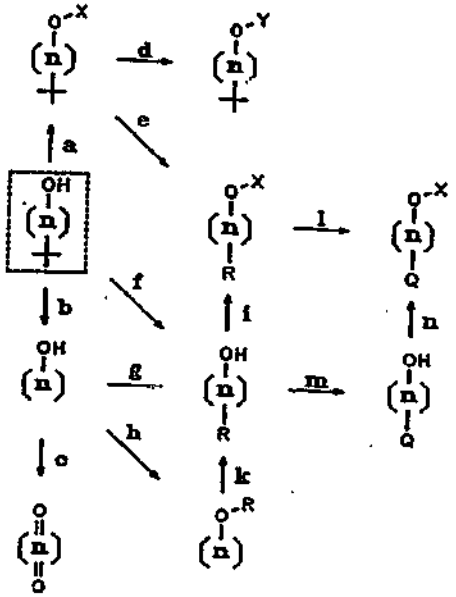


Figure 1.13. Summary of various synthetic strategies and methods for calixarene chemical modification: (a,h,i,n) formation of ethers and esters; (b) *trans*-butylation; (c)oxidation to quinones; (d) hydrolysis of ester groups, reduction of ester, amide, or nitrile groups; (e) *ipso*-nitration; (f) sulfonation; (g) electrophilic substitutions (halogenation, sulfonation, chlorosulfonation, formylation, acylation, coupling with diazonium salts, chloromethylation, aminomethylation); (k) Claisen rearrangement, Fries rearrangement, (l) reduction of nitro groups, aryl-aryl coupling, haloform oxidation, transformation of allyl groups; (m) nucleophilic substitution of quaternary ammonium groups.[25]

The conformational possibilities of calix[4]arene following complete alkylation lead to mixture of conformational isomers (cone, partial cone, 1,2-alternate and 1,3-alternate) as a result of breaking the hydrogen–bonding network responsible in maintaining the cone structure of the original framework. During lower rim alkylation, the hydrogen-bonding network is broken and the alkylated derivatives can take one conformation or a mixture of all possible conformations as illustrated in Figure 1.14.[82-84]

There can be some control of the stereochemistry achieved in the alkylation of calix[4]arene. Foe example, the use of NaH as a base in DMF or THF/DMF gives products in the fixed cone conformation.[85] It is believed that the reaction proceeds by the formation of the proximal 1,2-dialkylated intermediates with a sodium cation acting as template.[86] The use of caesium carbonate in acetonitrile gives compounds in the 1,3-alternate conformation, whereas the partial cone conformation is obtained by the use of potassium *tert*-butoxide in benzene.

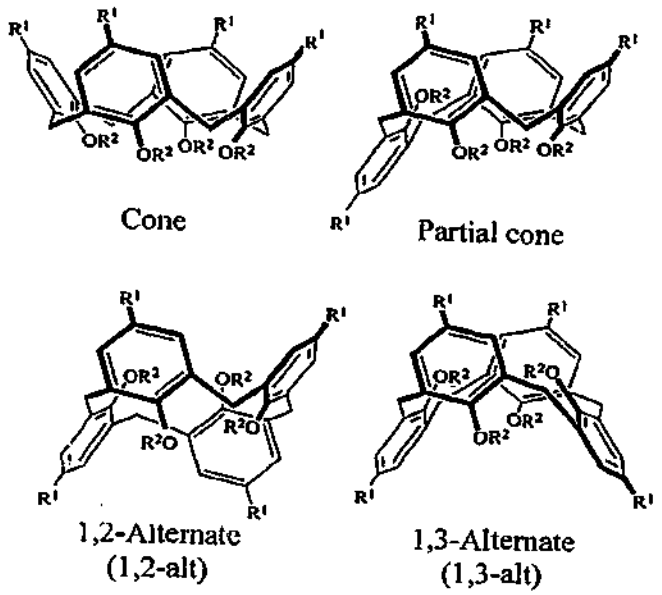


Figure 1.14. Possible conformers of the lower rim functionalised *p*-R^1-calix[4]arenes.[199]

It is noteworthy that the solvent polarity has an effect on conformer distribution.[87,89,90] This effect is more pronounced for cone ⇔ partial-cone interchange and is considered to be due to the difference in dipole moments between the different conformations.[89,90] The cone (μ = 0.835 D) is favoured in polar solvents over the partial cone (μ = 0.538 D).[90] Similarly, the conformer distribution is affected by the presence of metal ions.[83,89,90] Addition of $LiClO_4$ to a $CHCl_3$-CD_3CN (1:1 v/v) solution of *p*-^{t}Bu-calix[4]arene clearly forms of a lithium calixarene complex [Li ⊂ (*p*-^{t}Bu-calix[4]arene)]$^+$ as shown in the ^{1}H NMR spectra by an increase in the percentage of the cone conformation.[90] No such distribution change was observed on addition of $KClO_4$ instead.

Lower rim alkylation such as *O*-ethylation predominantly yields the partial-cone conformation,[61] the yield increasing with longer reaction times.[86] Interconversion, however, requires heating to > 100°C.[92] This puts the ethyl ether derivative at the threshold of interconversion since propyl, acyl or sterically bulkier derivatives do not undergo interconversion, even at high temperatures.[61,86,93] This inability to interconvert provides a mechanism for controlling the conformational distribution of the product.[83] Generally, it has been found that small cations ($Na^+$and Li^+), which have been shown to form complexes with calix[4]arenes,[21,28] yield predominately cone-conformations.[28,90,93,94] This is considered to be due to the stabilisation of the cone conformation by template action, Figure 1.18.[28] Alternatively, bulkier cations (Cs^+ and Ba^{2+}) have generally promoted partial-cone products.[25,83,90] Gutsche *et al.* have proposed

that competition between the rate of conformational interconversion and the rate of derivatisation and/or 1,3-alternate conformations, is responsible for the product ratio.[93] Therefore, factors influencing such equilibria include reactivity of the alkylating agent, strength of base used, bulk of *para*-substituent of the calixarene, temperature and nature of the solvent. All these factors influence the distribution of the conformations,[93,95] When DMF is used as the solvent and Cs_2CO_3 as the base, the 1,3-alternate conformation can be selectively obtained in 100% efficiency (75% isolated yield).[84] Although there have been several attempts to rationalise all of the available data,[21,28,86,93] Böhmer has suggested that "a general concept for the synthesis of a particular *O*-acyl or *O*-alkyl derivative in a certain conformation is not in sight at present because of the many factors involved and may perhaps never be achieved".[25]

Selective synthesis of the tetra-alkylated products in the 1,2 alternate conformation cannot be achieved by standard methods, but can by indirect procedures.[84,83] The mechanism for formation of a particular conformational isomer is complex and not well understood, due to varying factors influencing the conformational outcome.[85,97] It is believed that the cone conformation product is favoured over the others due to its faster alkylation rate (substrate, solvent, cation, alkylating agent) and/or its slower ring inversion rate (templating cation, solvent, *etc.*). The variation in most factors influencing the conformational outcome of the functionalisation reactions, has led to well established procedures for the preparation of a particular conformer, *e.g.* the esterification products of *p*-R-calix[4]arene are shown in Figure 1.15.[20]

Aside from X-ray crystallography, ^{1}H NMR spectroscopy is informative in establishing the conformations of calix[4]arenes. Each conformer displays a distinctive pattern in the methylene protons resonances: one pair of doublets for the cone conformation, two pairs of doublets or one pair of doublets and one singlet for the partial cone, one singlet and two doublets for the 1,2-alternate, and one singlet for the 1,3-alternate.[84] The larger ring size and the weakened hydrogen bonding in calix[5]arene enables it to take on several conformations, especially if the introduced group is small enough to move through the annulus.

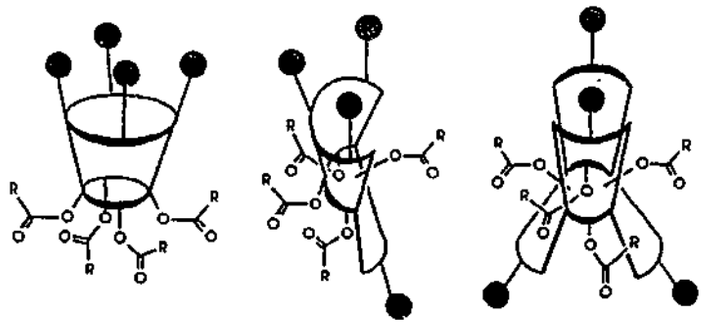
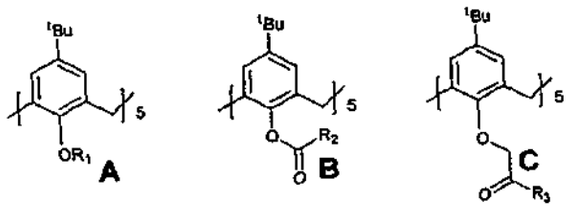


Figure 1.15 Conformers of the ester of calix[4]arene (derivatives in the 1,2-alternate conformation are rarely observed).[25]

Ether derivatives of type **A**, show a high mobility of the methyl ether of methyl-calix[5]arene ($Me5^{Me}$), with an expected $\Delta G^{\neq}$ of interconversion of 9.3 kcal mol^{-1}.[77] It has been reported that interconversion is possible with bulkier groups such as *n*-butyl, with a $\Delta G^{\neq}$ = 15.3 kcal mol^{-1}.[77,98] Unlike calix[4]arene derivatives, functionalised calix[5]arene assumes a variety of conformations, depending on the degree and the nature of substitution. Therefore, sufficient bulkiness of the *para* substituents (*e.g.* ^{t}Bu groups) is necessary to prevent *para* alkyl movement through the annulus, leaving only the rotation of the aryl moieties *via* the lower rim through the annulus pathway to be controlled. The pentaethylether **2** is somewhat more conformationally constrained than the pentamethylether **1**, but nevertheless it remains highly mobile. The penta-*n*-propylether **3**, the penta-*iso*-propylether **4** and the pentaallylether **5** are all conformationally mobile at ambient temperature. The penta-*n*-butylether **6**, with $\Delta G^{\neq}$ = 15.3 kcal mol^{-1}, has approximately the same conformational mobility as the tetramer *p*-^{t}Bu-calix[4]arene.[99] Benzyl groups, however, prove to be large enough to prevent the rotation of the aryl moieties through the annulus. Thus, the pentabenzylether **7** appears to be conformationally fixed on the ^{1}H NMR time scale, whereas the introduction of the same groups (benzyl) at the lower rim of calix[5]arene produces a 1,2-alternate conformation both in solution and in the solid state.[102] Similarly, aliphatic groups such as *n*-octyl have been reported to be large enough to immobilise the ring and lock it in the cone conformation.[100,101]

A systematic study conducted by Gutsche *et al.*[77] using a variable temperature ^{1}H NMR spectroscopy, over a wide range of calix[5]arene derivatives bearing different groups at the lower rim, was inconclusive in determining the threshold size required to

lock the ring into the cone conformation. The conformational behaviour of the ester derivatives of calix[5]arene of type **B**, were studied in a similar fashion to those described above. The ambient temperature ^{1}H NMR spectrum of the pentaacetate **8** shows a broad semi-resolved set of resonances arising from the bridging methylene groups, which coalesce to a singlet at higher temperature. The VT-NMR produces a coalescence temperature *Tc* of 318 K, corresponding to a $\Delta G^{\neq}$ = 15.3 kcal mol^{-1}. The estimated activation energy for **8** is greater than the $\Delta G^{\neq}$ for the parent compound (*c.f.* 13.2 kcal mol^{-1} for $\mathbf{5}^{t\mathrm{Bu}}$), showing that **8** is slightly less conformationally mobile than *p*-^{t}Bu-calix[5]arene. The results for the penta-*n*-propanoate **9**, penta-*n*-butanoate **10**, penta-*iso*-butanoate **11**, pentapivaloate **12** and pentabenzoate **13** indicate that conformational mobility diminishes on increasing the size of the OR groups, although the isobutanoate is regarded as the limiting group for interconversion; complete immobilisation can be achieved with benzoate or tosylate groups, Chart 1.1.[77]



	R_1
1	CH_3
2	C_2H_5
3	*n*-C_3H_7
4	*i*-C_3H_7
5	$CH_2CH{=}CH_2$
6	*n*-C_4H_9
7	$CH_2C_6H_5$

	R_2
8	CH_3
9	C_2H_5
10	*n*-C_3H_7
11	*i*-C_3H_7
12	$C(CH_3)_3$
13	C_6H_5

	R_3
14	OMe
15	OEt
16	O^{i}Pr
17	OBu^t

Chart 1.1

Ether esters of type **C** appear to have stable cone conformations at ambient temperature, as supported by the ^{1}H NMR spectroscopy, which shows a singlet for the ^{t}Bu groups and one pair of doublets for the $ArCH_2Ar$ methylene groups.[167] Exhaustive alkylation of the parent ^{t}Bu-calix[5]arene with an excess of the appropriate electrophile ($BrCH_2CO_2R_3$, R_3 = Me, Et, ^{i}Pr or ^{t}Bu) and K_2CO_3 in acetonitrile at reflux affords compounds **14**, **15** or **17**, respectively. The ethyl ester **15** of type **C** has been structurally authenticated in the solid state as having the cone conformation, which is consistent with ^{1}H NMR results.[102] While the penta-ethoxycarbonylmethyl $\mathbf{5}^{t\mathrm{Bu}}$ retains a distorted cone

conformation,[103] penta-*i*-propylcarbonylmethyl 5^{tBu} **16** adopts a 1,2-alternate conformation both in solution and in the solid state.[102,104] Carrying out similar alkylation, the penta-^{t}Bu-carbonylmethyl5^{H} analogous to **17** was found to adopt a partial cone conformation in solution.[102]

Removing intramolecular hydrogen bonding in the process of O-rim functionalisation results in the formation of variety of conformational isomers. Applying the methodology used previously for calix[4]arene, and molecular mechanics, enabled Gutsche *et al.* to propose a schematic representation for the major conformations of calix[5]arene derivatives, as illustrated in Figure1.16.[22,77]

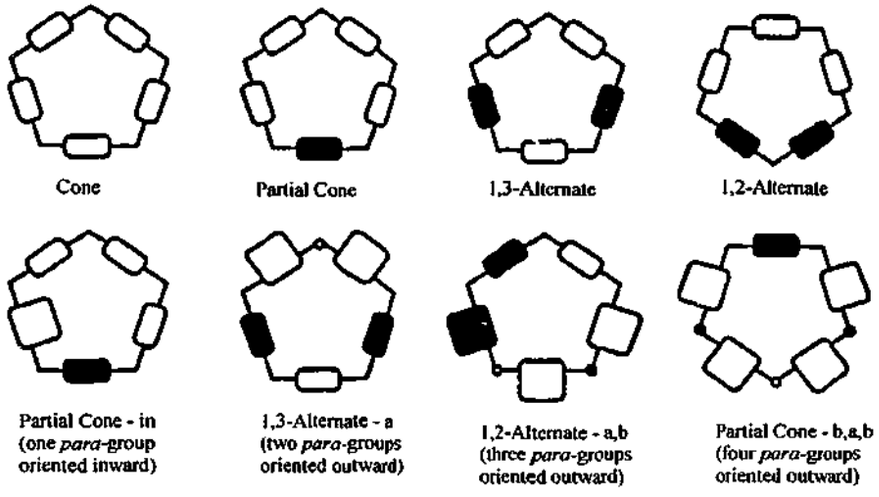
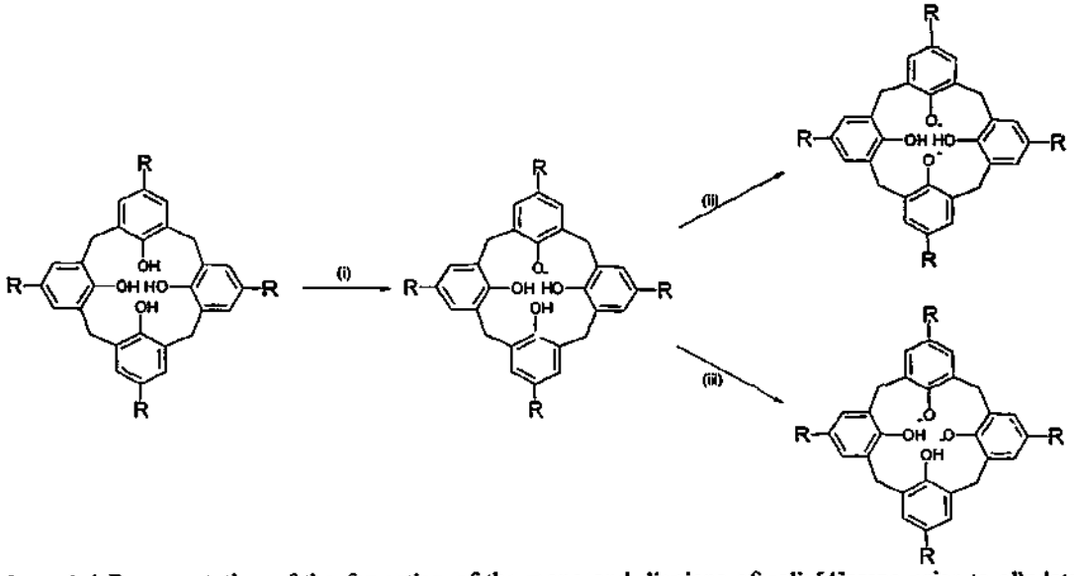


Figure 1.16. The conformations of lower rim functionalised calix[5]arene, with the phenolic units shown as rectangle or squares depending on their orientations, up/down or out/in.[22,77]

The direct selective alkylation of calixarenes at the lower rim exploits the difference in acidity of the phenolic hydroxy groups. It is difficult to obtain accurate p*Ka* data for calixarenes, especially in aprotic media (alkylation medium). Nonetheless, some data available on calix[4]arene[105] and sulfonated calix[4]arene[106,107] has led to the conclusion that the first hydroxy group is more acidic than the others. The mono-conjugate anion resulting from removal of the first proton can be stabilised by two intramolecular hydrogen bonds, and the second dissociation occurs generally at the distal position. The use of 1.2 equivalents of weaker bases such as CsF in DMF, or K_2CO_3 in acetonitrile with an excess of alkylating agent, results in a good yield of mono-alkylated calix[4]arenes.[108] The di-alkylated calix[4]arene in the 1,3-distal position can be easily obtained by the use of a weak base in acetone or acetonitrile,[109-111] thereby opening the

way for the synthesis of calix-crown derivatives specifically tailored for selective metal cation binding.[112-114] The 1,2 proximal dialkylated calix[4]arene can be obtained by using NaH and 2.2 equivalents of the alkylating agent in DMF.[115,116] The di-anion formation in the presence of strong base such as NaH favours the alkylation in the 1,2 proximal position. This method selectively produces the 1,2 isomer, noting that under these conditions the 1,3 isomer can be produced but reacts quickly to form fully alkylated products.[117] The production of the tri-alkoxy-calix[4]arenes can be obtained by using the mixed base BaO-$Ba(OH)_2$.[87] Scheme 1.4 summarises the effect of the base in the formation of the anionic species prior to the alkylation reaction.[199]



Scheme1.4 Representation of the formation of the mono and dianions of calix[4]arene prior to alkylated products: (i) 1.2 equiv. of K_2CO_3 in MeCN or CsF in DMF, (ii) K_2CO_3 in MeCN, (iii) NaH in DMF.[199]

An adaptation of the synthetic methodologies used in the selective functionalisation of calix[4]arene can to some extent produce the partially alkylated derivatives of calix[5]arene. Unlike the partial alkylation of calix[4]arene, the regioselective derivatisation of calix[5]arene has yet to been established. However, variation in the strength and stoicheiometry of the base used, along with the limiting amounts of the alkylating agents, increases the probability of obtaining a particular derivative, while noting that mixtures of all possible outcomes are inevitable.[77,119,120] Thus, the use of weak bases such as $KHCO_3$, NMe_3, CsF, $BaO/Ba(OH)_2$ with one equivalent of alkylating agent affords the mono-alkylated calix[5]arene in good yield.[77,119] Selective formation of the 1,3-di-O-alkyl and subsequent 1,3,4-trialkyl) derivatives over the 1,2-di-O-alkylation (and subsequent 1,2,3-trialkylation) is possible

using CsF. However, [illegible]ether is obtained in preference with low equivalents (1 or 2) of K_2CO_3 instead of CsF.[119] Figure 1.17 shows the effect of the base strength on product selectivity of the calix[5]arene derivatisation.

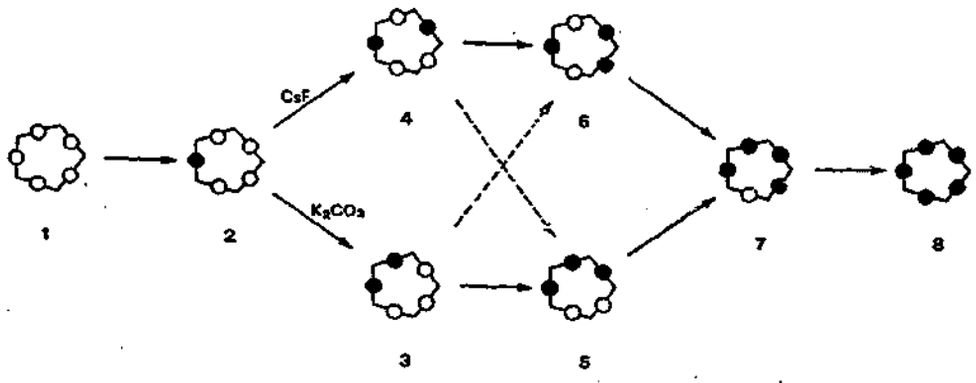


Figure 1.17 Schematic representation of the possible reaction pathways for the formation of *p*-^{t}Bu-calix[5]arene lower rim derivatives, depending on the type of base applied. Filled and empty spheres represent the alkylated and unalkylated aryls in the ring, respectively.[119]

1.5 Inclusion and binding properties of calixarenes

The inclusion and binding inclinations of calixarenes relate to their principal structural feature, namely the ability to form a cavity from the phenolic groups, which can also be used for metal complexation. This cavity has enabled calixarenes to form host-guest complexes in the solid state[19,25] with solvent molecules, fullerene C_{60} and cations (often as metal templates). It is noted that the formation of a metal template is considered primarily responsible for directing the synthesis of calixarenes.[121] In smaller calixarenes the metal template is thought to be responsible for the conformation selectivity, when the appropriate bulky groups are introduced at the lower rim and appropriate base (source of metal cations) are used, Figure 1.18.[28]

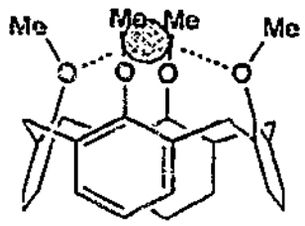


Figure 1.18. The template action of Na^+ and Li^+.[28]

The versatility in shaping calixarenes and constructing new derivatives, by careful choice of upper and lower rim functional groups, render them as a highly tuneable class of macrocyclic compounds. They are capable of forming a wide range of inclusion and binding modes. The interactions between calixarene derivatives and metal ions are largely dependant on the functional-group moieties (carbonyl, amide, carboxylic acid, *etc.*) introduced into the macrocycle. The calixarene acts as a backbone, maintain groups in close proximity to one another, allowing a cooperative convergent action on the metal. Such elaboration of the macrocyclic backbone has led to the targeted construction of specific host molecules, with steric and electrostatic requirements favouring host-guest interactions. The conformational abundance of calixarenes, manifested in a number of different isomers, makes them versatile inclusion hosts, capable of a variety of molecular recognitions.[19,21,25,27]

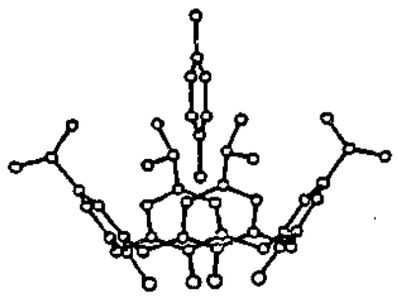


Figure 1.19 Solid state structure of the inclusion of *p*-xylene in *p*-propylcalix[4]arene (taken from Perrin *et al.*) [*p*-xylene ⊂ *p*-propylcalix[4]arene].[60]

It is beyond the scope of this thesis to give a complete review on the metal complexes of calixarenes and their associated inclusion phenomena. However, a brief account of their chemistry relevant to this thesis is included. Special emphasis is given to alkali metal complexes involving calixarene derivatives, some examples of neutral and charged organic molecules binding, noting also that calixarenes can bind transition metals[122-131] and lanthanides,[122,132-136] and can form complexes with a wide range of main group species. The presence of ligating phenolic sites results in the formation of metal-oxygen bonded compounds with a range of cations, *e.g.* Li, Na and Ca,[137-141]; W, Mo, Cr, Zr, Ti and Zn,[142-1451]; P, As and Al.[152-155]

Unmodified calixarenes such as *p*-^{t}Bu-calix[4]arene adopt a cone conformation due to the stabilisation of the intermolecular hydrogen bonding interactions among OH groups. Thus, adopting a C_{4v} symmetry enables the inclusion of a variety of solvent

molecules in the solid state (toluene, acetonitrile, *etc.*).[156-158] They can selectively transport Cs^+ in preference to Rb^+, K^+ or Na^+ (greatest selectivity by calix[4]arene, largest flux for calix[6 and 8]arene, across an organic phase, from one aqueous phase to another.[159] In each case, alkali cation transport was coupled with the reverse flux of protons. The crystal structure of a Cs^+-calixarene complex shows the metal ion is bound within the cup formed by the ligand and, surprisingly, is found closer to the aromatic carbon atoms than to the phenolic oxygens, Figure 1.20.[160]

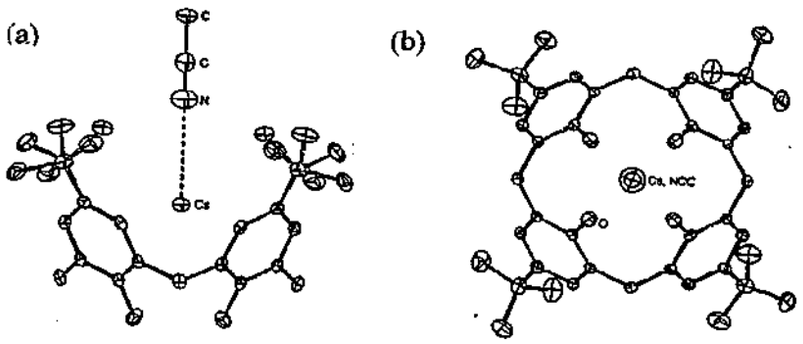


Figure 1.20. Top and side view of the crystal structure of [$Cs^+ \subset$ *p*-^{t}Bu-calix[4]arene (NCMe)] showing the interaction with an acetonitrile solvent molecule.[160]

Thus, the aryl residues in calixarenes appear to have importance in the binding and control of metal selection, by cation-π interactions.[161] Similarly, the modified calix[4]arene, reported by Shinkai *et al.* shows similar behaviour, including a Ag^+ cation in the π-basic aryl cavity with no observed interactions with the phenolic oxygens at the lower rim. The flattening of two distal aryl groups and the other two standing upright with overall molecular C_2 symmetry shows the cavity of the cone conformer of *O*-alkylated calixarene can preorganise to bind a metal cation.[27]

Lower rim functionalisation of calixarenes allows the introduction of electron "donating" groups for classical metal cation binding. Indeed, studies of the complexation properties of alkali metals by calixarenes have mostly involved the ether (ester), ketone, amide and carboxylic acid lower rim derivatives.[27,122,162,163] In general, trends observed in extraction constants from aqueous to organic phases for a number of calix[n]arene esters suggest that size is an important factor in complex formation and thereby selectivity.[122,164,165]

Aspects of the ionophoric properties of calixarenes esters and ketones toward alkali metal cations have been probed experimentally,[163] using the Pederson method to

assess their ion-transport ability from aqueous solution into non polar organic solvents.[166] The smallest calixarenes, calix[4]arene esters and ketones, clearly show a preference for the Na^+ cations (selectivity for Na^+ over K^+ ($S_{Na+/K+}$) 400 for the ethyl ester of the cyclic tetramer),[163] while the calix[5]arene esters show the largest extraction for all alkali metals with a preference for the larger cations K^+, Rb^+ and Cs^+.[167] Figure 1.21 shows the percentage extraction values (E%) for the ethyl ester **15** and *tert*-butyl ester **17** of the pentamer.

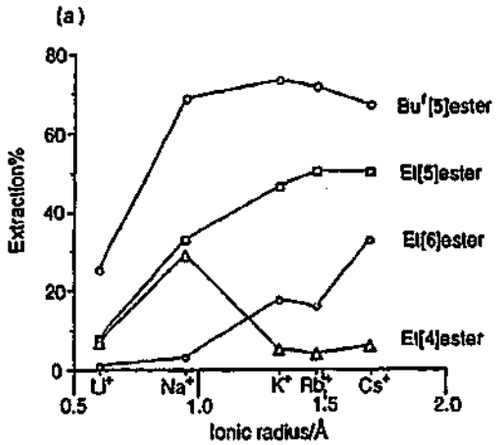


Figure 1.21. Percentage extractions (E%) for the alkali metals by ethyl ester calix[n = 4,5,6]arene derivatives (taken from Arnaud-Neu *et al.*).[167] The larger hexamer ketones and esters show less affinity for Na^+ and K^+ and less preference for Rb^+ and Cs^+. The octamer analogues shows the least affinity, with a low level of phase transfer for all alkali metal cations and poor discrimination.[163] The "fine tuning" of the selectivities is possible by variation of the alkoxy group.[168] The methyl and *n*-butyl ester show lower extraction and higher selectivity values $S_{Na/K}$ relative to the ethyl ester, while the *tert*-butyl ester diminishes in selectivity.[163,169]

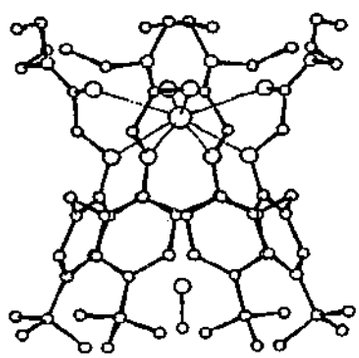
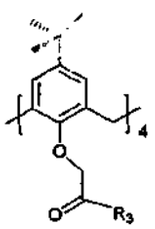


Figure 1.21. Molecular structure of **20** encapsulating a potassium cation and a methanol molecule.[172]

The conformation of the calixarene esters is also important in binding metal ions, particularly for the tetramer.[170] The cone conformation of the tetraethyl ester of calix[4]arene **19** is found to be selective towards Na^+, while the partial-cone and 1,2-alternate show K^+ selectivity. The highest levels of extraction for the relatively larger alkali metals Cs^+ and K^+ are found for the 1,3-alternate conformation, with extraction percentage values, E% 98.9 and 100%, respectively.[170] The amide derivatives show a stronger affinity towards the alkali metals than their corresponding esters (and ketones),[171] although the observed selectivity is relatively poor compared to the ester derivatives.[122] It is noteworthy that although the selectivity between Na^+ and K^+ is poor, the amides have an exceptionally high selectivity for Na^+ and K^+ with respect to Rb^+.[122] The molecular structure of **20**.KSCN complex shows the complete encapsulation of the cation within a symmetrical cavity defined by the four inward pointing amide groups and the eight ethereal oxygen atoms, while the hydrophobic calixarene cavity contains a methanol molecule, Figure 1.22.[172] This highlights the major form of interaction of ester/amide calixarene derivatives towards cations in general, utilising the high electron donation capabilities of oxygen containing functional groups in a cooperative and cumulative fashion, aided by the proximity of the binding units due to the inherent macrocyclic nature of the calixarene. The introduction of aminoacid moieties at the lower rim of calix[4]arene enhances the metal binding of these amide derivatives towards alkali metal cations. The ^1H NMR studies show that the complexation of Na^+ ions by **21** induces a change in the orientation of the amide groups from a network-like pattern with circular N-H···O=C hydrogen bonds, to a pattern in which the carbonyl groups shroud the Na^+ cation guest,[173] Chart 1.2.

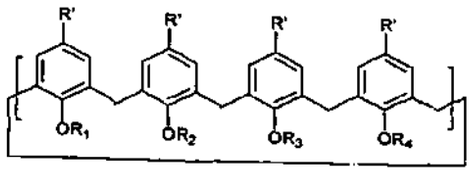


	R_3
18	OMe
19	OEt
20	NEt
21	$CH_2CONHC(H)CH_2(CH_3)_2CO_2Bn$

Chart 1.2

The stability constants for the complexation of alkali metals by calixarene carboxylic acid derivatives **22** and **23** show stronger binding than the corresponding nonionisable esters, ketones and amides,[174,175] highlighting the relative strength of opposite-charge electrostatic attraction (*c.f.* dipole-charge interactions). Such carboxylic

calixarenes can form a number of protonated complexes in addition to the 1:1 complex formed with alkali metal cations, with complexes corresponding to the mono-, di-, and triprotonated forms possible,[122,176,177] Chart 1.3.



22	23
R' = Bu^t	R' = Bu^t
$R_1 = R_3 = CH_2CO_2H$	$R_1 = CH_2CO_2H$
$R_2 = R_4 = OH$	$R_3 = CH_2CO_2Et$
	$R_2 = R_4 = OH$

Chart 1.3

The tendency of solvent molecules to occupy the calixarene cavity has not only been observed in the solid state but can be seen in solution NMR studies of inclusion processes, with solvent molecules in direct competition with complex formation.[178] The smaller, less flexible hydrophobic cavities of the calix[4]arenes and calix[5]arenes are well suited for neutral organic molecule (solvent) inclusion, given the favourable steric complementarity, while the larger calixarenes are less effective as hosts due to their inherent conformational flexibility. A noteworthy exception is the inclusion of fullerenes by *p*-^{t}Bu-calix[8]arene.[179,180]

1.6 Bridged calixarenes

The introduction to bridged calixarenes will be restricted to calixarenes linked *via* the lower rim, following the synthesis of the basic ring structure. The overview will focus on the class of compounds where all the hydroxyls are involved in the linkage, leading to a pair or more of calixarene units intermolecularly joined, the so called 'calixtubes'. Some intramolecular bridges involving mainly calix[5]arene will also be introduced along with a brief overview on the formation and chemistry of the calixcrowns.

1.6.1 Intramolecular bridged calixarenes: Calixcrowns

The selective alkylation of calixarenes has helped tremendously in the development of calixcrown chemistry, producing a variety of calix[n]crowns and double crowns. The naming of calix[n]crowns stemmed originally derived from the introduction of a polyethylene glycol functionality at the lower rim of the calixarene. The distal 1,3-bridged calix[4]arene involving a polyethylene glycol link was the first calixcrown to be synthesised,[181,182] explicitly bringing together crown ether and calixarene chemistry. Figure 1.22 shows their general structure. This terminology has expanded to encompass calixarenes intramolecularly bridged by various spacers, such as calixsalophen crown,[183] calixbinaphthyl crown ether,[184] calixazacrowns,[185,186] and the anisylmethylene compounds.[187] The chemistry of calix[5]crowns has not been fully explored. There are reports on the 1,3-bridged *p*-^{t}Bu-calix[5]crown by tetra-, penta- and hexa-ethyleneglycol chains.[191,192] This aside, there are few synthetic procedures for the preparation of 1,2-proximal bridged species, with the exception of hexaethylene glycol calix[5]crown, which is obtained in 20% yield.[192]

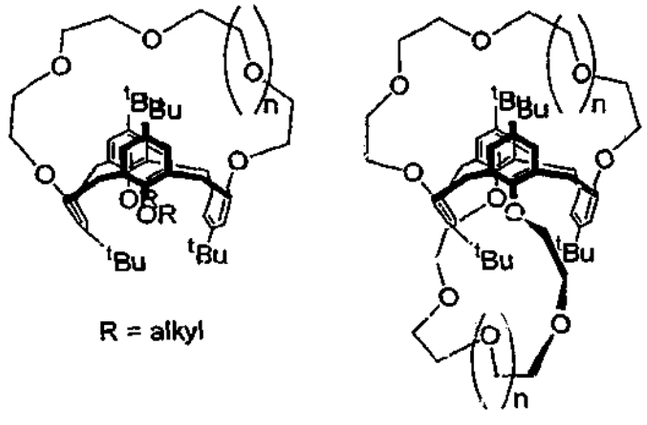


Figure 1.22 Structural representation of the mono- and the di- oligoethylene glycol-*p*-^{t}Bu-calix[4]crown.

1.6.2 Intermolecular bridged calixarenes: "Calixtubes"

The availability of calixarene macrocycles,[21] and the synthetic protocol for the elaboration of their original framework at the lower rim, has contributed in the development of calixcrowns (discussed above) and a new class of macrocycle-fused calixarenes.[22,193,194] The introduction of these novel macrocycles has caused the conformational rigidification of calixarenes and resulted in selective hosts for alkali metal recognition.[195-198] The progress in the selective functionalisation methodologies at the lower rim of calix[4]arene has helped tremendously in preparing the fixed cone

derivatives, as building blocks for fused calixarenes.[199-202] There are many examples in the literature of calixarene units joined at their lower rim with a variety of [22,203] Bis-calixarenes that are singly or doubly bridged *via* ether or other linkage [most] common type of linked calixarene.[204-208] On the other hand, less interest was given to the multi-linkage of a pair of calixarenes *via* the lower rim forming barrel type structures,[209] and particularly the class of receptors with oligoethyl ether bridges, illustrated in Figure 1.23.

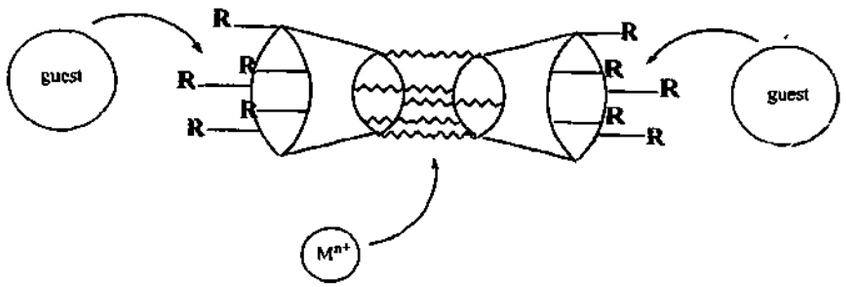


Figure 1.23 Schematic representation of fused calixarene showing the complexation sites, R = alkyl or aryl.

The incorporation of an oligoethyl ether cage-like into the middle of these calix receptors, and its design for metal recognition, is regarded as a biomimetic model for cation transport through the cell membrane.[210] The embodied aryl residues in these tubular receptors are also of importance in the control of metal selectivity, behaving as filtering gates by way of cation-π interactions.[211] Beer *et al.* have reported the synthesis of quadruply-linked bis ^{t}Bu-calix[4]arenes (calix[4]tube) by ethylene spanning, which shows a remarkable affinity for potassium ions.[210]

Calix[4]arene is regarded as a useful molecular substructure on which to assemble collections of covalently bound functional groups. The majority of *O*-alkylated calix[4]arenes reside in the cone conformation, conferring a considerable degree of preorganisation, and they are potential building block for larger, more elaborate assemblies. Macrocyclic assemblies in which two or three calixarenes units are connected *via* bridges between their respective hydroxy have been reported.[203] Applying similar methodologies, unsymmetrical fused calixarenes consisting of linked calixarenes of two different ring sizes has also been reported, notably linking *p*-^{t}Bu-calix[8]arene and calix[4]arene in a head to tail arrangement.[212]

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SULFONATED CALIXARENES

2.1 Introduction

The chemistry of cyclodextrins and cyclophanes has occupied a central interest in host-guest chemistry, and many derived host molecules have been exploited in the mimicking of the *in vivo* action of enzymes.[1-3] In the last two decades, water soluble calixarenes have become an increasingly important class of compounds in the field of supramolecular chemistry because they allow the study of the interactions involved in host-guest chemistry in water. These studies give a deeper understanding of the types of forces involved, as this is important for the design of receptors mimicking biological systems.[4]

A characteristic feature of conventional calixarene molecules is that they are sparingly soluble in water and they exhibit meagre inclusion performance in organic solvents. These macrocycles have been functionalised with polar groups, making them water soluble and thus more closely related to cyclodextrins. The host-guest chemistry of cyclodextrins has been studied in aqueous systems and a variety of soluble host-guest type complexes are possible.[1,5] Similarly, in aqueous systems the hydrophobic forces of water soluble calixarenes is expected to encourage the host-guest complexation[6] and indeed several examples have already been reported[7-20] (discussed in sections 2.2.3 and 2.2.4).

Calixarenes can be made water soluble by introducing sulfonate groups at the upper rim of the calixarene,[21,22] introducing carboxylates at the bottom rim of the calixarene[23] or forming alkyl ammonium salt derivatives,[24,25] Figure 2.1.

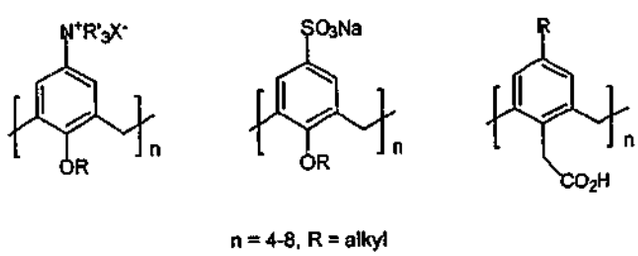
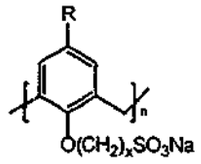


Figure 2.1 Water soluble calixarenes

The rapid expansion of the chemistry of *p*-sulfonato-calix[n]arenes (n = 4-8) is due their good solubility in water (> 0.1 mol cm^{-3}).[4,22] In contrast, the host-guest chemistry of carboxylic acids of calixarenes has not been studied extensively because of their limited solubility in water, especially in the presence of salts.[23,2] Therefore, in order to enhance their water solubility, novel calixarenes have been synthesised bearing double polar groups, sulfonates and carboxylic acids.[27,28] The calix[4]arene derivative of these doubly polar water soluble calixarenes fixed in the cone conformation have been shown to specifically recognise alkyl and aromatic ammonium cations.[29] There are also reports of water soluble calixarenes having anionic sulfonate groups on the 'lower rim' of the calixarene cavity, which have been shown to have a weak but selective binding process,[24] Figure 2.2. The calix[8]arene type compound where R = H, n = 8 and x = 3 was reported to encapsulate fullerene (C_{60}) in water.[30]



R = H, Alkyl; n = 4 - 8; x = 1 - 3

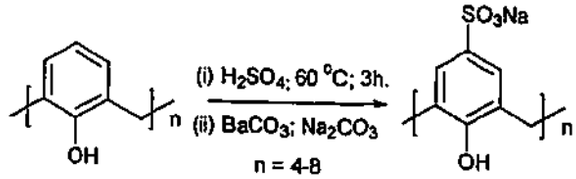
Figure 2.2 Water soluble calixarene bearing sulfonate groups at the lower rim.

2.2 Sulfonated calixarenes

2.2.1 Synthesis

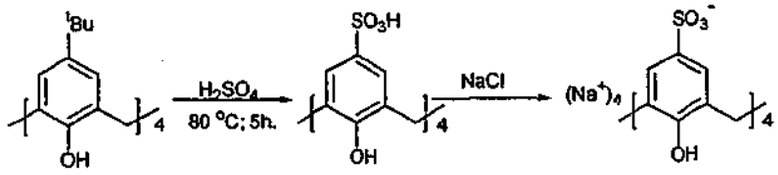
In 1984, Shinkai *et al.*[22] reported the synthesis of the first sulfonated calixarene, followed by an improved procedure in 1986 for the hexa-sulfonato-calix[6]arene.[21] The preparation consists of treating calix[6]arene with an excess of concentrated sulfuric acid at 80°C for 3 hours. The reaction mixture is allowed to cool to room temperature and the resulting precipitate is collected by filtration and then dissolved in water. The aqueous solution is neutralised with $BaCO_3$, precipitating $BaSO_4$, which is removed by filtration then Na_2CO_3 is then added to the filtrate for countercation exchange. When the pH is 8-9, the solution is treated with activated charcoal followed by filtration and concentration *in vacuo* to afford the crude product. Upon addition of ethanol, the hexasodium salt of calix[6]arene hexasulfonate is obtained as a white precipitate. This method is general to all calix[n]arenes to afford the readily isolated sodium salts of the sulfonated analogues

(Scheme 2.1). In contrast, the corresponding sulfonic acids are very difficult to isolate from neat sulfuric acid.



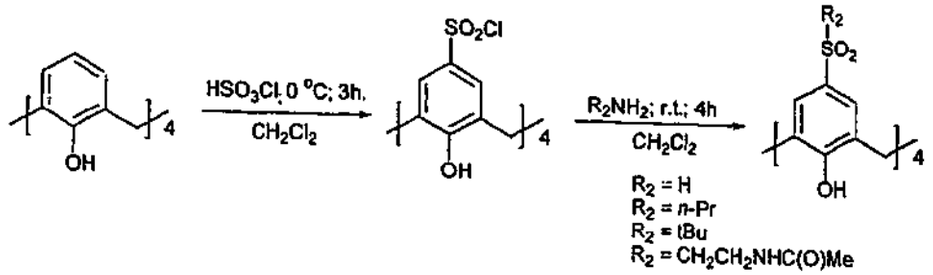
Scheme 2.1

A closely related procedure developed by Atwood *et al.*[31] consists of reacting directly *p*-^{t}Bu-calix[4]arene with an excess of neat sulfuric acid at 80°C, followed by pouring the reaction mixture into a large volume of concentrated brine solution. The resulting crude precipitate is dissolved in water and treated with activated charcoal, and after filtration and concentration of the solution, the sodium tetrasulfonate of calix[4]arene is then obtained as a colourless crystalline solid. The penta sulfonate salt can be obtained by adjusting the pH to 9 with sodium bicarbonate after the charcoal treatment stage (Scheme 2.2). The latter procedure has also been used when starting with calix[4]arene instead of *p*-^{t}Bu-calix[4]arene.[10]



Scheme 2.2

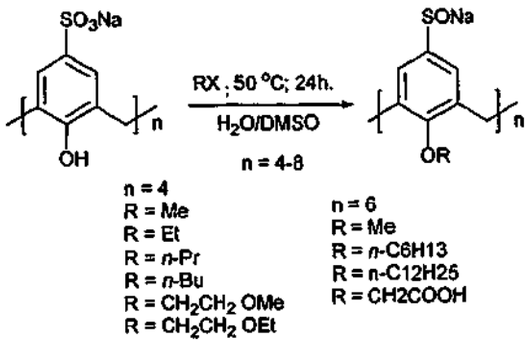
A closely related compound is the chlorosulfonated calix[4]arene, which can be produced by chlorosulfonation with chlorosulfonic acid. The preparation consists of adding dropwise chlorosulfonic acid to a chloroform solution of calix[n]arenes at 0°C and then stirring the mixture at room temperature for 5 hours under inert atmosphere.[32] The chlorosulfonation reaction also allows access to the bis (chlorosulfonyl)calix[4]arene derivatives when amide functionality is introduced at the lower rim.[32] The tetrakis-(chlorosulfonyl)-calix[4]arene can be further elaborated to the corresponding sulfamides,[32] Scheme 2.3.



Scheme 2.3

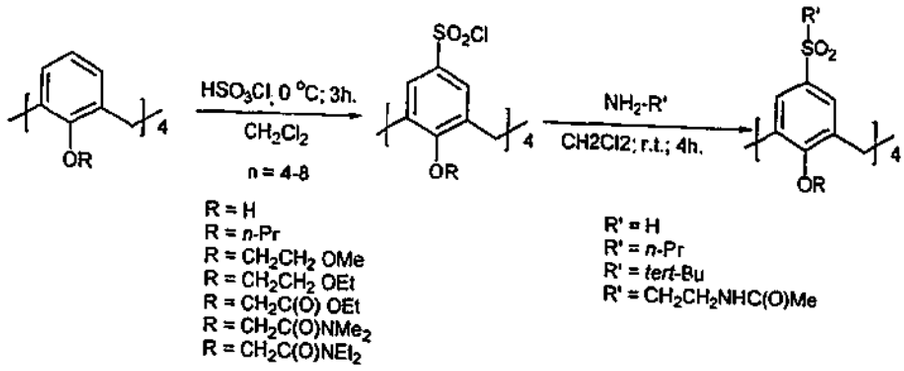
2.2.2 Derivatives of sulfonated calixarenes

At the lower rim of calixarenes a diverse range of groups can be introduced to form novel receptors, particularly alkyl chains of various length,[21] carboxylic acids, ester or amide groups.[27] The general approach for their preparation consists of first functionalising the lower rim with an appropriate groups, followed by sulfonation.[27] Shinkai *et al.* have reported an alternative procedure starting directly with sulfonated calixarenes.[21] The reaction is carried out in two miscible solvents, water and dimethyl sulfoxide in order to solubilize the reagents used. The procedure consists of mixing sulfonated calixarene and sodium hydroxide in water with the alkyl halide in dimethyl sulfoxide, and the reaction mixture is heated at 60°C for 24 hours. Upon cooling to room temperature, the crude product is precipitated using methanol and dissolved in water. Filtration to remove any insoluble material, followed by dilution of the filtrate with ethanol affords the sulfonated derivatives, Scheme 2.4.



Scheme 2.4

Sulfonated calixarenes can be functionalised either at the lower rim hydroxy or at the upper rim sulfonato groups *via* the chlorosulfonyl intermediates. These synthetic manipulations yields novel receptors for anion and organic molecule binding.[32] Scheme 2.5 shows some possible derivatives made from the chlorosulfonyl functionality.



Scheme 2.5

2.2.3 Inclusion and binding properties of sulfonated calixarenes

Due to the extensive literature in the inclusion chemistry of sulfonated calixarenes, this introductory review will be restricted to specific examples directly related to the project undertaken. The introduction of the polar sulfonate group into the aromatic ring of calixarenes has not only rendered them water soluble but also has enabled the exploitation of their hydrophobic cavity.

The amphiphilic character of sulfonated calixarenes constrains them to interact with molecules and ions in a specific fashion. In aqueous medium, they behave as surfactants, where the hydrophobic pockets hide themselves from the water molecules whilst exposing the anionic parts. The hydrophobic effect is the driving force behind the inclusion properties of sulfonated calixarenes, while the anionic sulfonates are generally responsible for metal cation coordination. Sodium *p*-sulfonato-calix[4,5]arenes are the most studied since they usually adopt a cone conformation, whereas larger calixarenes adopt non-cone conformation due to their higher degree of flexibility. In the presence of water alone, the sodium salt of [*p*-sulfonatocalix[4]arene]$^{4+}$ crystallises with a water molecule deeply imbedded within the calixarene cavity. This observation constituted the first X-ray diffraction evidence for aromatic π hydrogen bonding to water.[10] The water in the cavity can be displaced by an appropriately sized hydrophobic part of an organic molecule. The inclusion of neutral, anionic and cationic species has already been established by a number of solid state structures, e.g. acetone,[8] methyl sulfate,[9] pyridinium,[11,12] morpholinium,[12] and NMe_4^+.[13,14]

The inclusion chemistry of *p*-sulfonato-calix[4,5]arene shows a pH dependency [33] and therefore determining its acidity constants is important. The good solubility in water of these sulfonated calixarenes has allowed accurate measurements of the acidity

constants of the phenolic hydroxy groups. *p*-Sulfonato-calix[4]arene show the first dissociation occurs at *ca.* pH 4.0 with three of the remaining groups following suit successively in basic media (pH > 11). It is noteworthy that many of the studies involving *p*-sulfonatocalix[4]arene have been carried out using the pentaanion existing at neutral pH.[9] The pK_a values determination for the phenolic moieties of *p*-sulfonato-calix[5]arene shows that the molecule possesses three ionisable phenolic protons (pK_a values 10.96, 7.63 and 4.31) and that it exists as a heptaanion at neutral pH.[7] At neutral pH the *p*-sulfonato-calix[6]arene exists as an octaanion since the first phenolic hydroxy groups are rather acidic (p*Ka* values 3.44 and 4.76).[34] The pK_a values of 7.5 and 9.0 have been found for the first two phenolic hydroxyl dissociation in *p*-sulfonato-calix[8]arene.[34]

Structural studies have also been carried out on complexes of *p*-sulfonato-calix[5]arene with hydrated rare-earth metal salts such as La(III), Eu(III), Gd(III), Tb(III) and Yb(III) and pyridine or pyridine N-oxide.[7] In the structure of $Na_2[La(H_2O)_9][p$-sulfonatocalix[5]arene$].ONC_5H_5.10H_2O$, the La(III) centre is not coordinated to the macrocycle and exists as the simple hydrated $La(H_2O)_9^{3+}$ counterion. The calixarene serves as a second sphere ligand to the $La(H_2O)_9^{3+}$ ion with a large number of hydrogen bonded contacts formed between the lanthanum aqua ligands and the calixarene sulfonato oxygen atoms. A pyridine *N*-oxide molecule is situated in the calixarene cavity and interacts with sodium ions and water molecules in the lattice, but is not coordinated to the La^{3+} centre.

2.2.4 Clay like and capsule structures of sulfonated calixarenes

p-Sulfonatocalix[4]arene is shaped like a truncated cone with hydrophilic upper and lower rims separated by a hydrophobic mid-region. Usually the solid state packing arrangements of structures involving this molecule are overwhelmingly dominated by these strongly structure-directing topological and electronic characteristics. Water-solubility is an important property of the compound and crystals grown in aqueous media tend to produce structures in which the hydrophobic aromatic regions associate with one another, leaving the hydrophilic ends exposed. This arrangement results in a high degree of solvation at the upper and lower rims of the molecules. Indeed, early work by Atwood *et al.* [8,9] showed that the preferred packing motif consists of an up-down arrangement to form bi-layers as shown in Figure 2.3. These bi-layers are reminiscent of clays with broad hydrophilic and hydrophobic regions. The hydrophilic layer consists of sodium

cations and a vast array of hydrogen bonded water molecules and sulfonate head groups of the calixarenes.

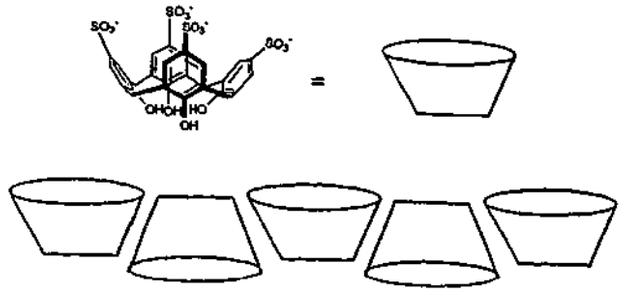


Figure 2.3 Diagrammatic representation of the bi-layer structure often adopted by *p*-sulfonato-calix[4]arene in the solid state.

Early work on sulfonated calix[4,5]arenes established the formation of clay-like bi-layer structures which show remarkable inclusion properties encompassing ionic guests and molecules [7-20] including water in the hydrophobic cavity associated with $H_2O\cdots$aromatic-π hydrogen bonding, [10] and incorporating metal ions. It was also shown[15] that varying the alkali metal cation from Na^+ to Cs^+ does not alter the bi-layer structure, but that the degree of hydration decreases accordingly (*i.e.* the following stoichiometries are obtained: Na_5[*p*-sulfonatocalix[4]arene].$12H_2O$, K_5[*p*-sulfonatocalix[4]arene].$8H_2O$, Rb_5[*p*-sulfonatocalix[4]arene].$5H_2O$, Cs_5[*p*-sulfonatocalix[4]arene].$4H_2O$). Substitution of the alkali metal cation with organic cationic species such as in the structures of [adeninium]$_4$[*p*-sulfonatocalix[4]arene].$14H_2O$[16] and [NMe_4]$_5$[*p*-sulfonatocalix[4]arene].$4H_2O$ [14] still results in the formation of the bi-layer structure.

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PREPARATION AND SUPRAMOLECULAR CHEMISTRY OF CALIX[n]ARENES

3.1 Introduction

The results presented in this discussion include the synthesis of calixarene supramolecular building blocks (tectons), with particular emphasis on *p*-phenylphenol and *p*-benzylphenol using the traditional approach "one pot synthesis" and a "green" approach using a melt and a ball mill "UHIG" as solvent free methods. These approaches resulted in the synthesis of novel *p*-phenylcalix[5]arene, *p*-benzylcalix[4]arene and improved yields and preparation of a diverse number of calixarenes. Discussion includes conformational analysis of these calixarenes, and the structural authentication of *p*-^{t}Bu-calix[10]arene and the novel *p*-benzylcalix[4]arene, complexed with both water and fullerene C_{60}.

The *p*-phenylcalix[n]arene (n = 4,5,6,8) and *p*-benzylcalix[n]arene (n = 4,5,6,7,8) families were sulfonated producing two new classes of water soluble calix[n]arenes. *p*-Phenylcalix[5,6]arene sulfonates and their analogues *p*-benzylcalix[5,6]arenes show inclusion properties towards rod shaped carotenoids (*trans*-ß-carotene) and globular molecules such as fullerenes, and resulted in their aqueous solubilisation. The non-covalent host-guest complexes are of current scientific and technological interest for their chemical, physical and biological properties. The inclusion complexes (water soluble C_{60}) of these sulfonated calix[5, 6]arenes and fullerene C_{60} allows for the study of C_{60} molecules in water. Fullerene C_{60} in the supermolecule has been found to exhibit essentially the same electronic spectra as those of the free C_{60}. Biologically active molecules such as *trans*-ß-carotene and asthaxathin also form supramolecular complexes with *p*-phenyl- and *p*-benzyl-calix[5,6]sulfonates in water. Such non-covalent association demonstrates the water solubility of these lipophilic molecules with the retention of their original electronic spectra, emphasising their stability within the supermolecule. The aggregation behaviour of these novel sulfonated calixarenes and their complexes in water, using UV-Vis studies and particle sizing measurements is also presented.

3.2 Calixarene host molecules

Calixarene macrocycles are regarded as the third major class of inclusion compounds in supramolecular chemistry, following crown ethers[1] and cyclodextrins.[2,3,4] Their ready availability and electronic rich hydrophobic cavity for host-guest inclusion make them ideal hosts for supramolecular chemistry. The amenable transformation both at the lower and upper rim to build up novel hosts bearing different functionalities has expanded their chemistry and versatility as hosts, with seemingly unlimited possibilities.[5]

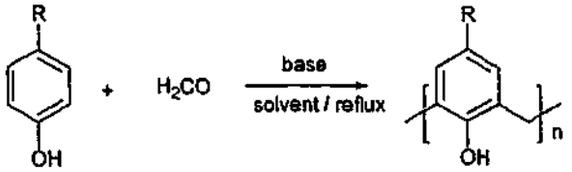
Unmodified calixarenes are known to have inclusion and binding properties towards globular guest molecules such as fullerenes. Such inclusion host-guest complex formation demands a large cavity for the host to meet the steric requirements of the guest molecule.[6,7,8] The macrocycle must also be capable of adopting an appropriate conformation suitable for inclusion or interaction. Taking into account these considerations, Atwood *et al.* have discovered that *p*-^{t}Bu-calix[8]arene can selectively bind electron deficient C_{60} from toluene solutions of carbon soot by way of an inclusion complex. The isolated calixarene/C_{60} complex is later treated to dissociate the supermolecule and recovery of pure C_{60}. Thus this novel supramolecular approach becomes a useful technique to obtain C_{60} inexpensively in large quantity and with high purity.[6]

The aptitude and effectiveness of the macrocycle in complexing a guest molecule depends on the nature and balance of attractive and repulsive forces or interactions between the host and guest. The nature of such observed interactions are π····π, van der Waals interactions, and charge transfer (CT).[6,7,8,9] Hence, calixarenes containing aryl-moities such as *p*-benzylcalixarenes,[10] *p*-cumylcalixarenes[11] and *p*-phenylcalixarenes having relatively electron rich *para*-groups to meet the inclusion requirements, were of interest. Their water soluble sulfonated derivatives, bearing sulfonate groups as electron rich groups for a cumulative interaction with electron deficient C_{60} and *trans*-β-carotene guest molecules were also investigated, with the gaol of achieving solubilisation in water. Thus far, inclusion complexes of C_{60} had been obtained in aqueous system only with cyclodextrins[12-13] and with water soluble calixarenes bearing sulfonates at the lower rim[14] (discussed in Section 2.1). There are also examples of inclusion of *trans*-β-carotene by cyclodextrins in aqueous medium[15-18] but at the time that the present study was undertaken, there are no reports concerning the inclusion complex formation of carotenoids using calixarenes.

The modification of the original framework of calixarenes, by attaching other functional groups for specific binding, or to enhance their binding ability, is regarded as a major endeavour in supramolecular chemistry.[8] Particular interest is given to the introduction of ionic sulfonato groups at the upper rim, achieving water solubility and enabling the study of their interactions with other molecules in aqueous medium, and indeed the work involving *p*-sulfonato-calix[4,5]arenes has given remarkable results in the inclusion of organic molecules,[20-24] forming a variety of metal complexes[25-28] and a multitude of supramolecular architectures, notably ionic capsules,[29-33] helical and spherical structures,[34] and more.[35,36]

3.2.1 Building blocks syntheses

The one-pot synthesis of calixarenes devised by Gutsche *et al.* provides general guidelines and allows the optimised synthesis of *p*-^{t}Bu-calix[4]arene, *p*-^{t}Bu-calix[6]arene and *p*-^{t}Bu-calix[8]arene, in multigram quantities. Scheme 3.1 shows the general procedure for the synthesis of *p*-R-calix[n]arenes.



R = ^{t}Bu, Benzyl, Cumyl, Phenyl $n = 4 - 10$

Scheme 3.1

A high number of molar base equivalents per molar equivalent of the phenolic monomer (0.4) yields predominantly *p*-^{t}Bu-calix[6]arene, whereas low equivalents (0.03) favour *p*-^{t}Bu-calix[4 and 8]arenes.[37,38] *p*-^{t}Bu-calix[4]arene being the thermodynamically favoured product can be discriminately targeted by temperature control (requiring high temperature).[37,38] The syntheses of *p*-^{t}Bu-calix[5]arene, however, have always resulted in a mixture of calixarenes[39,40] and the reactions are generally low yielding. Gutsche *et al.* achieved the preparation of *p*-^{t}Bu-calix[5]arene in 12% yield, when using 0.27 equivalent of KOH (per mole of phenolic monomer), with careful temperature control.[40] In contrast *p*-benzylcalix[5]arene can be isolated in 33% yield in a similar fashion, using 0.185 equivalents of base (KOH) with tetralin as the solvent. Fundamentally, the strategy attempted in preparing *p*-^{t}Bu-calix[5]arene consists of using base equivalents for which calix[6 and 8]arene synthesis is minimal, generally between 0.15 and 0.30, near the point of intersection of the curves in Figure 1.4.[37]

The attempted synthesis of *p*-^{t}Bu-calix[5]arene *via* the methodology described above consisted of heating a mixture of *tert*-butylphenol (11.25 g, 74.8 mmol) and paraformaldehyde (7.5 g, 250 mmol), suspended in tetralin at 80-85°C. Following the addition of potassium hydroxide (1.35 g, 20.7 mmol), the temperature was increased rapidly to 205-210°C and the reaction mixture held in this temperature range for 3 hours. Following similar work up to that described earlier, *p*-^{t}Bu-calix[5]arene was isolated in 15% yield and, unexpectedly, further work up of the filtrate by successive precipitations with acetone yielded *p*-^{t}Bu-calix[10]arene in greater than 5% yield as the only large calixarene present.

The one-pot procedures form the basis for the synthesis of other calixarenes derived from various *p*-alkylphenols, with slight variation in the reaction conditions. The base induced condensation reaction of *p*-benzyl phenol and formaldehyde proceeds smoothly and quickly relative to the similar condensation of the *p*-^{t}Bu-phenol analogue.[41] Oligomerization of *p*-benzylphenol is firstly carried out at 120°C using aqueous formaldehyde, in the absence of an organic solvent with a catalytic amount of sodium hydroxide, affording a clear beige glass containing *p*-benzylcalix[8]arene as the sole calixarene formed, by the consumption of all the starting phenol. Other products presumably are linear oligomers, noting that corresponding oligomers are formed in the condensation of *p*-^{t}Bu-phenol. Upon addition of diphenyl ether to this material and ramping the temperature quickly to 260°C over half an hour, followed by the reflux of the reaction mixture at this temperature for 3 hours gave *p*-benzylcalix[4]arene in 60% isolated yield.

It is noteworthy that the synthesis of *p*-benzylcalix[4]arene is affected dramatically when either the ramping period or the reflux temperature is altered. For instance, when the ramping is over one hour, instead of half an hour, and the reflux temperature is 220°C instead of 260°C, and even over an extended period of reflux (10 hours), the conversion to *p*-benzylcalix[4]arene accounts for only 16% of the starting material. The organic solvent-free condensation to give the *p*-benzylcalix[8]arene also depends on the reaction conditions, particularly, the molar ratio of the base to *p*-benzylphenol and the amount of formaldehyde used. Interestingly, this reaction always gives some *p*-benzylcalix[8]arene byproduct in varying amounts, but it is easily separated, precipitating from the reaction mixture upon addition of acetonitrile. The

mother liquor contains a mixture of *p*-benzylcalix[4,5,6,7]arenes which can be recycled and if desired, they can be separated, Table 3.1.

Table 3.1 Product distributions of the solvent free base induced condensation of *p*-benzylphenol (10 g) and formaldehyde (15 ml) using different molar ratios of base to *p*-benzylphenol at 110°C.

Base molar ratio	*p*-BenzylCalix[n]arene distributions
0.045 NaOH	n = 8, 30%[a]
0.045 KOH	n = 8, 30%[a]
0.26 NaOH	n = 8 > 6 > 4 > 7
0.26 KOH	n = 8 > 7 > 4
0.34 NaOH	n = 8 > 5 > 4
0.34 KOH	n = 6 > 5 > 8

[a] Isolated yield, no other calixarenes present.

Following the solvent free methodology, similar attempts were studied on the synthesis of *p*-^{t}Bu-calix[n]arenes, but unfortunately only the kinetically favoured *p*-^{t}Bu-calix[8]arene was isolated as the sole calixarene product, in modest yield. Although the solvent free approach for the synthesis of *p*-benzylcalix[5,6,7]arenes was successful with the production of these calixarenes in moderate yield, the thermal synthesis is considered to be the major source for their production. The one-pot thermal synthesis was carried out in a similar fashion to that reported by Vicens *et al.*[10] by suspending *p*-benzylphenol and paraformaldehyde in tetralin and raising the temperature of the mixture to 80-85°C, at which point the condensation reaction was initiated by addition of a 14 *M* solution of base (KOH, 0.185 equivalents per phenolic monomer). The temperature was then immediately ramped to 200°C and the reaction mixture kept at this temperature under nitrogen for 4 hours. Evaporation of tetralin followed by work up of the reaction product yielded a mixture of *p*-benzylcalix[5,6,7,8]arenes. Successive precipitations using acetone resulted first in the isolation of *p*-benzylcalix[8]arene in 10% yield, followed by *p*-benzylcalix[5]arene in 23% yield and finally a mixture of *p*-benzylcalix[6,7]arenes in *ca.* 37% yield. Further treatment of the latter mixture with acetone, afforded *p*-benzylcalix[7]arene in 20% yield and *p*-benzylcalix[6]arene in 15% yield. Variation of the catalytic amount of base used resulted in the formation of mixtures of *p*-benzylcalix[5,6,7,8]arenes in different isolated yields with all reactions conducted in tetralin. In summary, the outcome of this condensation is sensitive to the type, amount

and concentration of base used, rate of heating and the temperature of the reaction. Neverth less, maximum pentamer and heptamer yields can be achieved with high temperatures (195 – 205°C), 0.185 molar equivalents of KOH and a quick ramping time (< 10 min), while the optimal production of the hexamer and the octamer is obtained at higher molar ratio with 0.5 KOH equivalents, Figure 3.1.

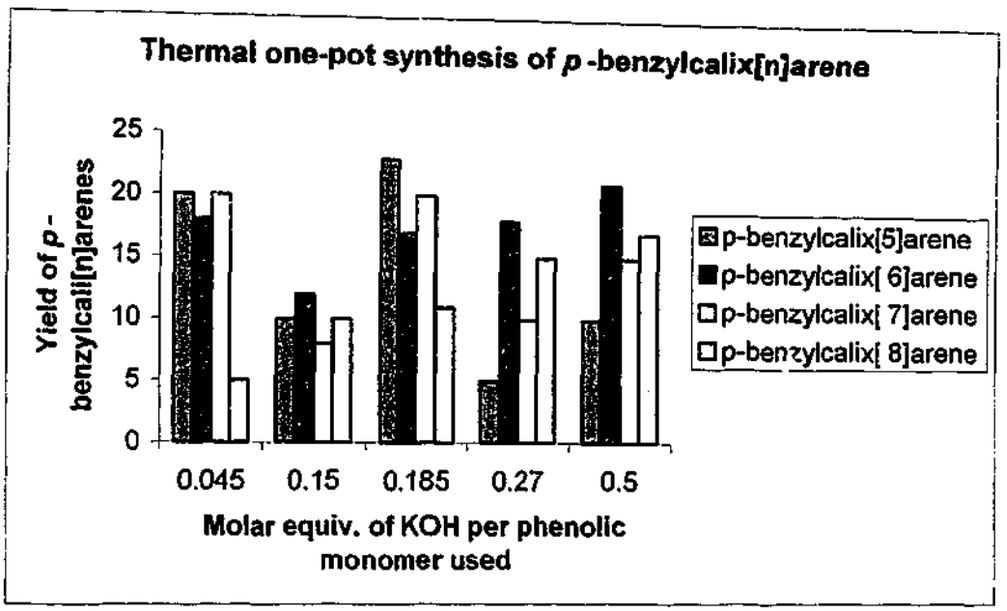


Figure 3.1 *p*-Benzylcalix[n]arene isolated yields obtained *via* the one-pot procedure as a function of base molar ratio used.

Closely related *p*-cumylcalix[4,6]arenes have also been synthesised following the general one-pot procedure, by an adaptation of *p*-benzylcalix[n]arene synthesis, yielding *p*-cumylcalix[4]arene and *p*-cumylcalix[6]arene in 10% and 12% yields respectively. However, no *p*-cumylcalix[5]arene nor *p*-cumylcalix[8]arene was found to be present in the product mixtures. Investigation of this condensation by variations in the reaction conditions, base equivalents and temperature, was not pursued.

Constructing calixarenes with larger/deeper cavities is of interest in confining large molecules and as an entry to new supramolecular arrays. In this context *p*-phenylcalix[n]arenes, n = 4, 5, essentially have rigid hydrophobic cavities capable of binding large molecules. However, they are not readily available. In the search for deep-cavity calixarenes, various researchers have introduced groups other than Bu^t at the *para*-position of calix[4]arene such as benzoyl[42] and piperidinomethyl moieties.[43] Some procedures for the preparation of *p*-phenylcalix[n]arenes have been reported, the synthesis of *p*-phenylcalix[6 and 8]arenes using one pot synthesis involving the

condensation of *p*-phenylphenol and formaldehyde, with 10 and 7% isolated yields respectively.[42] There is no detailed report on the synthesis of *p*-phenylcalix[4 and 5]arenes using this approach.[42]

It is well known that base catalysed condensation reactions of *p*-substituted phenols with formaldehyde depends on temperature (and temperature gradient), the type of base and the molar ratio of phenol to base.[44] In the present study the ratio of phenol to potassium or sodium hydroxide was systematically varied, with all reactions conducted in tetralin. A higher molar ratio of base (KOH, *ca.* 0.45) was required to achieve the optimal production of *p*-phenylcalix[4]arene, whereas formation of *p*-phenylcalix[5]arene was optimized at a molar ratio of base *ca.* 0.045. Results of the optimisation experiments are summarised in Table 3.2.

Table3.2 Molar ratio of base to phenol, and the resulting isolated yields of *p*-phenylcalix[n]arenes.

Molar ratio Bases	**% yields**			
	n = 4	n = 5	n = 6	n = 8
0.045 NaOH	0	3	10	30
0.045 KOH	3	15	11	18
0.18 NaOH	0	0	0	0
0.18 KOH	0	2	8	0
0.45 NaOH	2	5	10	20
0.45 KOH	10	5	7.4	38
0.75 NaOH	0	0	0	0
0.75 KOH	0	0	0	0

The formation of host-guest inclusion complexes can be maximised effectively by optimising certain requirements imposed by the C_{60} guest molecule. *p*-Phenylcalix[n]arenes are possible hosts because of their extended upper hydrophobic cavity, with curvature complementarity with fullerene C_{60}. However, solubility problems impeded the formation of such inclusion complexes. *p*-Phenylcalix[8]arene was insoluble in most organic solvents and *p*-phenylcalix[5]arene had poor solubility in solvents required by C_{60}. The latter was regarded as the best candidate for host-guest complexation of C_{60} because of the complementarity of the phenol ring with C_{60} where the calixarene is in the cone conformation.[45]

3.2.2 Alternative syntheses

Alternative synthetic routes to calixarenes that can be accomplished in a 'greener' fashion by avoiding the use of organic solvents and minimising the waste associated with traditional procedures were explored. The extensive investigative work in calixarene

synthesis was of great help in devising 'greener' approaches for their formation.[46] While the work intended is not extensive, it gives some insight and raises interest in its continuation. It is well known that the treatment of *p*-^{t}Bu-calix[8]arene under high temperature reflux conditions (diphenyl ether, 256°C) results in the formation of the thermodynamically favoured tetramer *via* the proposed intramolecular mechanism of molecular mitosis.[47] Similarly, during the second step of *p*-^{t}Bu-calix[4]arene synthesis (reflux in diphenyl ether, at 256°C),[48] the initially formed amounts of *p*-^{t}Bu-calix[6,7 and 8]arene are observed to decrease (as a function of time) during tetramer production.[49] However, a recent study using deuterium-labeled *p*-^{t}Bu-calix[8]arene suggests that the pathway for the observed reversion reaction of the octamer involves fragmentation/recombination and molecular mitosis together in a 3:1 ratio (per octamer).[50]

Ultra High Intensity Grinding (UHIG) is a solid-state mechano-catalysis technique converting mechanical energy into chemical energy.[51-54] The mechanism for action is considered to be the high (localised) temperatures obtained during high energy ball-ball and ball-vial collisions during milling.[55,56] Considering the strict temperature control and high temperature required for odd-numbered calixarene synthesis and other tetrameric calixarenes inaccessible by the thermal procedures (4^{phenyl}, 4^{benzyl}),[42,57,58] UHIG was tested as a possible procedure to synthesise these calixarenes in a solid state, Figure 3.2. As mentioned earlier, the use of solvent free reactions to produce calixarenes in moderate yield and in particularly the octamers of *p*-^{t}Bu-, *p*-benzyl- and *p*-phenyl- systems as the sole calixarenes produced has been established. These accessible octamers have been subjected to ball milling in the presence of paraformaldehyde, NaOH and molecular sieves, and traces of the tetramers and other unidentifiable products were detected using mass spectrometry analysis of the crude product mixture. Longer milling times of up to 16 hours showed a marked increase as expected in the convergence of octamer to tetramers for *p*-benzyl- and *p*-phenyl- systems. Tetramers of calixarenes are known to be the thermodynamically favoured products and require high temperatures, and UHIG with local high temperatures (>257°C), arising from mechanical compression and shearing mechanisms[55,56] supply sufficient thermal energy for reaction to proceed. It is significant that similar experiments have been attempted in the conversion of *p*-benzylcalix[6,8]arenes into *p*-benzylcalix[5,7]arenes in 15% and 7%, respectively, and it believed that the UHIG process involves a pathway similar to calixarene synthesis itself

and that the necessary solution synthetic requirements may be duplicated in the solid state by appropriate adjustment of UHIG conditions.[46]

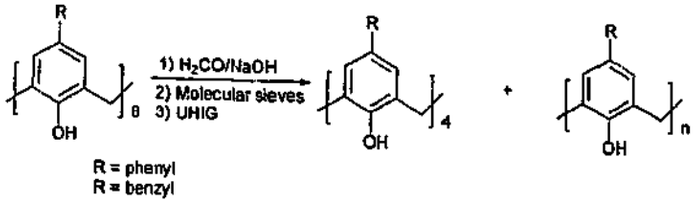


Figure 3.2 The UHIG synthesis of *p*-benzyl- and *p*-phenyl-calix[4]arene starting from the corresponding octamer.

3.2.3 Conformational analysis

Calixarenes have a large degree of rotational freedom by adopting a variety of conformations both in solution and in the solid state. In solution, calixarenes are observed to be dynamic, with their motion dependent on ring-oligomer number and temperature. This conformational mobility is of importance in the host-guest complexation properties of calixarenes and in subsequent shaping the molecular baskets. Such flexibility can be regarded as advantageous, since the host can rearrange to an appropriate structure to meet the guest steric and electrostatic complementarity requirement. Generally, the cone conformation is the desired conformation, which provides a hydrophobic cavity for inclusion of large guest molecules, for example C_{60}. Unfortunately, calixarenes with ring sizes larger than calix[4 or 5]arene have non-cone conformations and require pre-organisation energy to adopt the cone-conformation, and this can impede the complexation process. The non-cone configuration presents difficulties for an organic chemist concerned with immobilising larger calixarenes with their high conformational mobility in the cone conformation. Temperature dependent ^{1}H NMR spectroscopy is important in monitoring the conformational behaviour of calixarenes at different temperatures, thereby subsequently determining the temperature required to carry out modification on the ring. Furthermore variable temperature (VT) NMR experiments in solution at low temperature can give insight into the conformation(s) that can be adopted in the solid state.

Generally, the coalescence points are more difficult to ascertain for the pentamer than the tetramer, because the two resonance envelopes of unequal area coalesce together. Calculations of the coalescence temperatures (T_C), and hence free energy of activation value for conformational interconversion ($\Delta G^{\ddagger}$), following the guidelines

proposed by Gutsche *et al.* have been adopted.[64] For calix[5]arenes there are two resonance envelopes of unequal area which coalesce; if a dip is observed between the methylene envelopes then the system is considered to be just below T_C (spectrum A); if a long smooth transition is seen between the methylene envelopes then the system is regarded to be above T_C (spectrum C). A system is at T_C if a flat gently sloping line is seen between the resonance envelopes or if the transition between the envelopes is not smooth (spectrum B),[64] Figure 3.3. The free energy barrier to conformational interconversion in kcal mol^{-1} was calculated from the empirical formula: $\Delta G^{\ddagger} = 4.58Tc(10.32 + \log Tc/Kc)/1000$, where $Kc = 2.22(\Delta\nu^2 + 6J_{AB}^2)^{1/2}$ is the rate constant (Kc in s^{-1}) for conformational interconversion. The value of $\Delta\nu$ was taken as the average difference in Hertz between the centres of the pairs of the methylene doublets undergoing coalescence. A value of 15 Hz is used for J_{AB}, based for the average value that is observed for the methylene protons in calixarenes.

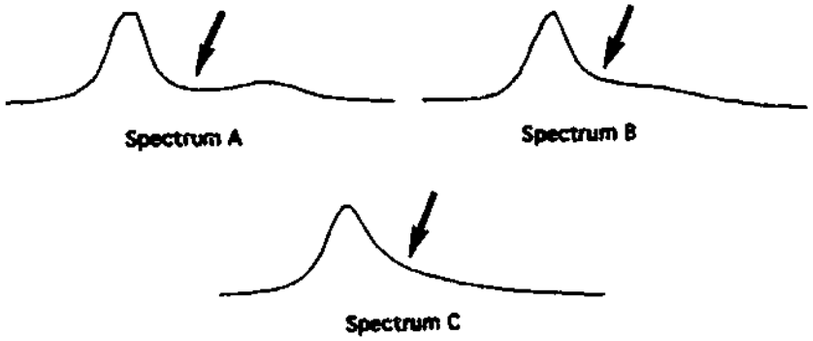


Figure 3.3 Guidelines for the determination of coalescence temperature (*Tc*): Spectrums A, B and C shows the resonances of the $ArCH_2Ar$ methylene protons at different temperatures below *Tc*, at *Tc* and above *Tc* respectively, using variable temperature ^{1}H NMR for a calix[5]arene in $CDCl_3$.[64]

3.2.3.1 VT-^{1}H NMR for *p*-phenylcalix[5,6]arenes

The project involved the preparation of novel calixarene macrocycles and the improvement of the syntheses of existing *p*-alkylcalix[n]arenes, using 'greener' approaches such as solvent free reactions, ball milling and ionic liquids. The work resulted in the preparation of *p*-^{t}Bu-calix[10]arene in unprecedented yield by a simple one-pot procedure, preparation of the novel *p*-benzylcalix[4]arene in good yield and optimisation of the one pot synthesis for *p*-phenylcalix[n]arenes.

In order to correlate between the analytical results and the conformational behaviour of calixarenes, beneficial for understanding the relationship between the description (analysis) and the structural state of these calixarenes (stereochemistry), the

relatively low shift (ppm) for the phenoxy protons is generally found to be indicative of a strong hydrogen bonded network, where the protons are "deshielded" by adjacent oxygens (O-H····O(H)). IR spectra are supportive of the hydroxyl group environments, exhibiting a shift to lower wavenumber values, reflecting the weakened O-H force constant for the ν_{OH} stretching vibration mode. The characteristic chemical shift for the bridging methylene protons is regarded as a common marker in describing the conformational state of calixarenes, noting that the presence of AB spin system of the methylene protons in the ^{1}H NMR spectrum is indicative of the cone conformation (calix[4]arene). Calixarenes with a ring size larger than calix[4]arene give rise to a singlet for the methylene protons which is consistent with fast motion of the phenolic residues through the annulus. This motion is fast on the NMR time scale and cannot discern between the two equatorial and axial protons, behaviour associated with the sharpness of the δ_{OH} peaks. Table 3.3 lists the δ_{OH} and ν_{OH} values observed in the ^{1}H NMR and IR spectra (KBr disc) for all *p*-alkyl/phenylcalix[n]arenes that were prepared.

Table 3.3. Some physical properties of *p*-benzylcalix[n]arenes ($\mathbf{n}^{benzyl}$), *p*-cumylcalix[n]arenes ($\mathbf{n}^{cumyl}$) and *p*-phenylcalix[n]arene ($\mathbf{n}^{phenyl}$).

Calixarene	Value of n	δ_{OH}/ppm in $CDCl_3$	ν_{OH}/cm^{-1} (KBr disk)
$\mathbf{n}^{benzyl}$	4	10.13	
	5	8.81	3229
	6	10.30	3168
	7	1031	3155
	8	9.35	
$\mathbf{n}^{cumyl}$	4	9.52	3240
	6	10.45	3166
$\mathbf{n}^{phenyl}$	4	10.43	3200
	5	9.11	3282
	6	10.57	3173
	8	10.00[a]	3210

The cone conformation is observed for *p*-benzylcalix[4]arene, with a *J*-coupling value (J_{AB}) of 13.1 Hz for the bridging methylene AB-system and δ_{OH} value of 10.1 ppm for the hydroxy group protons. The latter value lies in between those observed for *p*-^{t}Bu-

calix[4]arene/*p*-phenylcalix[4]arene and *p*-cumylcalix[4]arene (Table 3.3). Similarly, the activation energy ($\Delta G^{\ddagger}$) is estimated to lie between those for *p*-^{t}Bu-calix[4]arene/*p*-phenylcalix[4]arene and *p*-cumylcalix[4]arene (15.7 kcal mol^{-1} for 4^{tBu}/15.3 kcal mol^{-1} for 4^{benzyl} < $\Delta G^{\ddagger}$ < 15.98 kcal mol^{-1} for 4^{cumyl}). This energy is relatively large (*c.f.* Table 1.2), suggesting a stable cone conformation, with a slow inversion on the NMR time scale.

Larger macrocycle calix[5]arenes are observed to interconvert freely at ambient temperature and adopt a cone conformation only at lower temperatures (T_C < 20°C). The ^{1}H NMR at ambient temperature, of the *p*-phenylcalix[5]arene shows a lower chemical shift for the hydroxyl indicating a relatively weaker hydrogen bonding network (δ_{OH} value of 9.11 ppm) and absence of an AB spin system for the bridging methylene protons, indicative of the pentamer freely interconverting (singlet at 4.01 ppm). The variable temperature ^{1}H NMR shows that the interconversion of the pentamer is reduced at lower temperatures, giving rise to doublets with an AB spin system for the bridging methylene protons as an indication of the rigidity of its structure, Figure 3.4. The *Tc* temperature was estimated to be 20°C, giving a calculated activation energy for interconversion of 13.4 kcal mol^{-1}.

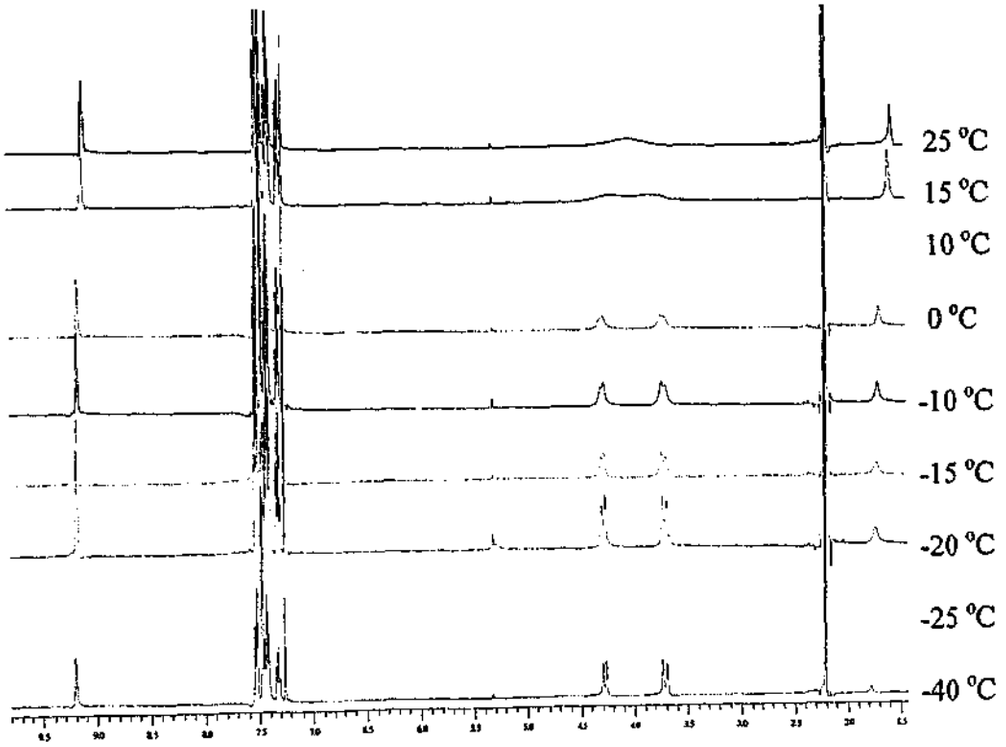


Figure 3.4 Variable temperature NMR study for *p*-phenylcalix[5]arene in $CDCl_3$.

The ^{1}H NMR spectrum of the hexamer of *p*-phenylcalixarene gives a δ_{OH} value of 10.57 ppm (*c.f.* δ_{OH} = 10.42, 10.31 and 10.45 ppm for $\mathbf{6}^{^t\mathrm{Bu}}$, $\mathbf{6}^{\mathrm{benzyl}}$ and $\mathbf{6}^{\mathrm{cumyl}}$ respectively) suggesting a strong hydrogen bonded network. The absence of AB spin system(s) for the bridging methylene protons at ambient temperature suggests that this hexamer is freely interconverting at ambient temperature. However, $\mathbf{6}^{\mathrm{phenyl}}$ has a slower conformational motion at this temperature, when compared to the other calix[6]arenes. This behaviour is manifested by the observed *Tc*, *ca.* 298 K, and a relatively smaller $\Delta G^{\ddagger}$ value, *ca.* 13.7 kcal mol^{-1} (*c.f.* $\Delta G^{\ddagger}$ = 13.3, 13.1 and 13.8 kcal mol^{-1} for $\mathbf{6}^{^t\mathrm{Bu}}$, $\mathbf{6}^{\mathrm{benzyl}}$ and $\mathbf{6}^{\mathrm{cumyl}}$ respectively). The difference in the interconversion activation energies can be attributed to the sterically bulkier phenyl substituent at the *para*-position, which can rotate, forcing the hydroxyls to be closer, possibly forming a double cone arrangement.

At low temperatures *p*-phenylcalix[6]arene behaves in a similar fashion to *p*-^{t}Bu-calixarene. The ^{1}H NMR spectrum for $\mathbf{6}^{\mathrm{phenyl}}$ (-50°C) shows three different phenolic protons integrating for 1:1:1 and three AX systems for the bridging methylene protons, with the overlapping of two doublets; while the aromatic protons have no change in their chemical shift even at -60°C (Figure 3.5). These observations are consistent with a conformation that contains either a C_2 symmertry axis perpendicular to the mean plane of the macrocyclic ring, or a centre of symmetry. The two possible conformations consistent with the spectra, which contain these symmetry elements, are the "pinched-cone" and the 1,2,3 –alternate arrangement.

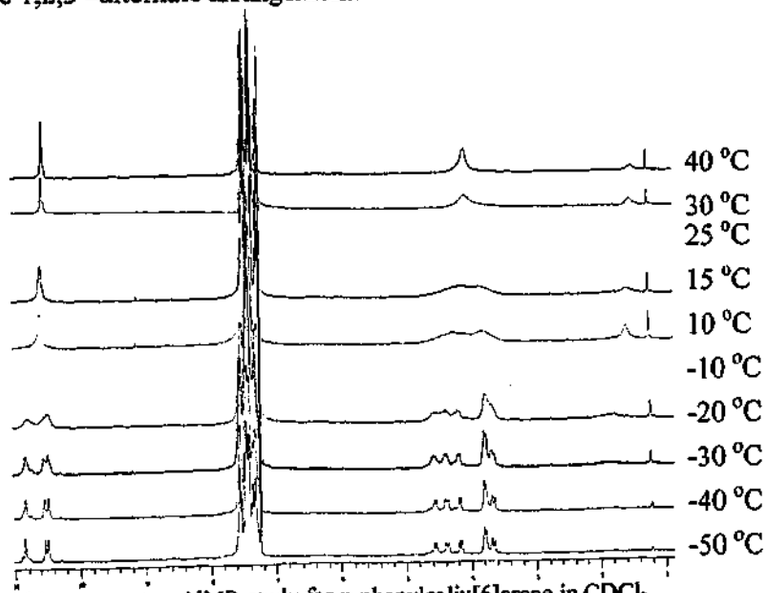


Figure 3.5 Variable temperature NMR study for *p*-phenylcalix[6]arene in $CDCl_3$.

3.2.3.2 VT-^{1}H NMR for *p*-H and *p*-^{t}Bu-calix[10]arene

The availability of *p*-^{t}Bu-calix[10]arene, prepared by careful temperature control of the one–pot condensation reaction and the availability of calix[10]arene by the general de-*tert*-butylation reaction encouraged the study of their conformational behaviour in solution at different temperatures. The solution study of these large container molecules was undertaken in an attempt to understand the factors influencing their conformational flexibility.

At ambient temperature, the ^{1}H NMR spectrum o [illegible]camer, **10**^{tBu}, shows a sharp singlet at δ = 9.12 ppm for the phenolic prot[illegible] [illegible]ystems observed for the bridging methylene groups, Figure 3.6. In low [illegible] of the experiment **10**^{tBu} remains freely mobile and flexible thro[illegible] range where the smaller calixarenes become less mobile. The [illegible]e protons are seen to coalesce at about 238 K (T_C), corresponding to t[illegible] low $\Delta G^{\ddagger}$ value of 10.70 kcal mol^{-1}.

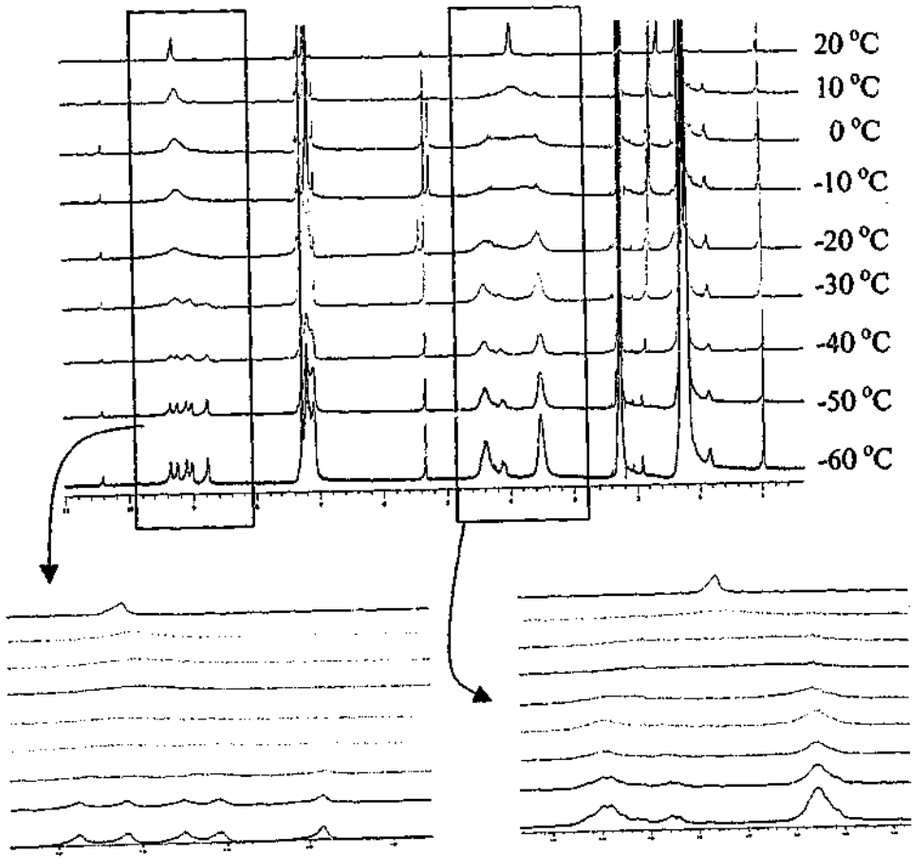


Figure 3.6 Variable temperature NMR study for *p*-^{t}Bu-calix[10]arene in $CDCl_3$.

The large cavity of the decamer and the relatively unhindered rotations of the phenolic units through the annulus for the phenolic units, shows that the formation of a well-ordered structure is only possible at very low temperatures (-35°C). At -60°C the ^{1}H NMR spectrum shows five sharp peaks (δ 8.6 - 9.6 ppm) in the hydroxy region, each integrating for two protons, suggesting that the adopted conformation has a mirror plane of symmetry. The observed δ-shift range for the OH-groups suggests that the hydroxyls are still engaged in strong intramolecular bonding. The solid state structure of $\mathbf{10}^{\mathbf{tBu}}$ was established by X-ray crystallography and is in good agreement with the observed behaviour in solution, reflecting the possibility that the flexibility of $\mathbf{10}^{\mathbf{tBu}}$ results in a structure where the phenolic groups interact strongly *via* hydrogen bonding. The molecule adopts a pinched-cone conformation (boat-like conformation), with two planes of symmetry, consistent with the five singlets observed for the hydroxy groups at low temperatures Figure 3.7(b). The short O···O distances of 2.747 Å, 2.765 Å and 2.941 Å (all under 3 Å) suggest there is strong hydrogen bonding around the ring, Figure 3.7(a). The X-ray data were collected at 123(1) K on an Enraf-Nonius KappaCCD single crystal diffractometer with Mo-K_α radiation (λ = 0.71073 Å). The structure was solved by direct methods with SHELXS-97 and refined by full matrix least-squares on F^2 using SHELXL-97. All non-hydrogen atoms were refined anisotropically, and C-H hydrogens were included at geometrically estimated positions. Two of the three crystallographically distinct *tert*-butyl groups were disordered, with one having a methyl group disordered over two sites, and the other having all methyl groups disordered over two sites at half occupancies. The calculated density of 0.860 g cm^{-1} is very low and the crystal is likely to be highly solvated, however residual electron density was diffuse and could not be modelled as solvent molecules. The SQUEEZE routine in PLATON[19] was applied which calculated a potential solvent volume of 4099.7 Å^3. Refinement with the adjusted data lowered R_1 from ~12% to ~6%. *p*-^{t}Bu-calix[10]arene: $C_{110}H_{140}O_{10}$, Mr = 1622.2, orthorhombic, *Fmm*2, a = 32.0865(10), b = 32.1477(10), c = 12.1460(3) Å, V = 12528.7(6) Å^3, Z = 4, ρ = 0.860 g cm^{-1}, μ = 0.054 mm^{-1} (no correction), colourless plate, 0.38 x 0.32 x 0.08 mm, θ_{max} = 22.48°, 38435 reflections measured, 4129 unique reflections (R_{int} = 0.079), 286 parameters, R_1 = 0.0606 (on 3449 observed data [$I > 2\sigma(I)$]), wR_2 = 0.1647 (all data), S = 1.036.

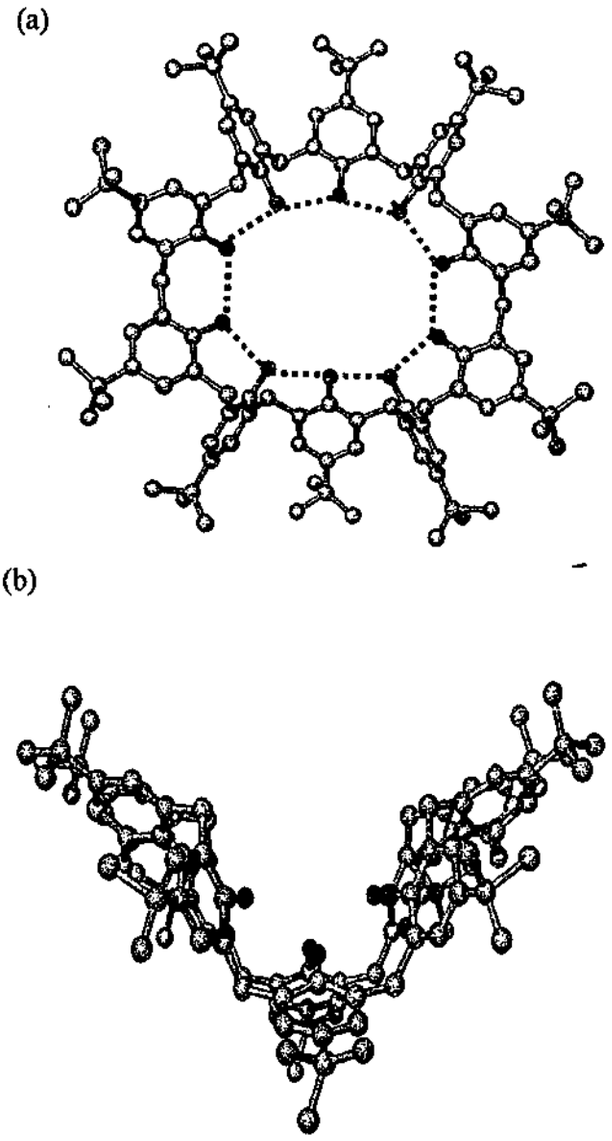


Figure 3.7 Molecular structure of $\mathbf{10}^{^{t}Bu}$ showing circular H-bonds as red dotted lines (a), side view showing $\mathbf{10}^{^{t}Bu}$ adopting the pinched-cone conformation (b).

The removal of *tert*-butyl groups renders the macrocycle $\mathbf{10}^{H}$ more flexible compared to the same macrocycle bearing bulkier *tert*-butyl groups, showing the importance of the *para* substituents contributing in fixing the macrocycle at a given conformation. This observation is supported by the VT-NMR experiment, the spectrum showing only one single peak for the hydroxys, which starts broadening at –40°C but without splitting even at –60°C, Figure 3.8. The presence of one peak for the hydroxys at 9.4 ppm is indicative of strong hydrogen bonding network. It is therefore concluded that

calix[10]arene, unlike *p*-^{t}Bu-calix[10]arene, adopts a centre of symmetry with a possible pleated loop conformation.

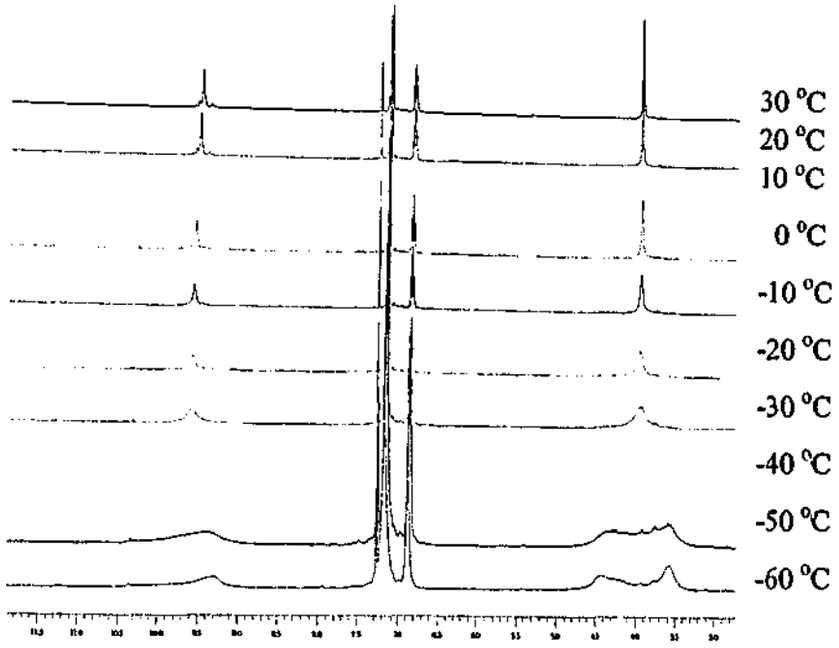


Figure 3.8 Variable temperature ^{1}H NMR study for calix[10]arene in $CDCl_3$.

3.2.4 *p*-Benzylcalix[4]arene/Fullerene C_{60} complex

The structure of *p*-benzylcalix[4]arene was established using X-ray diffraction data and shown to be an inclusion complex with water sandwiched between calixarenes in the columnar array, Figure 3.9. The water resides in the cavity of the cone conformation, hydrogen bonded to the lower rim hydroxyl groups of two calixarenes. This is different to the water inclusion complex of sulfonated calix[4]arene where the water in the cavity has the O-H groups of the water inclusion complex H-bonded (H$\cdots\pi$) to adjacent aromatic rings.[59,60] Another structural feature is the columnar π-stacking of the 1:1 H_2O:calixarene 'supermolecules'.

Crystals for X-ray structural determination were grown from a moist acetone/2-propanol solution of *p*-benzylcalix[4]arene affording [*p*-benzylcalix[4]arene].$[H_2O]_{0.5}$: $C_{56}H_{48}O_{4.5}$, space group *P4/n*, a = 19.070(3), b = 19.070(3), c = 5.6631(11) Å, V = 2059.4(6) Å^3, T = 173(2) °K, ρ_{calcd} = 1.279 gcm^{-1}, μ = 0.080 cm^{-1} (no correction), Z = 4, Mo K_α radiation, $2\theta_{max}$ = 50° (1484 observed, $I > 2\sigma(I)$), 139 parameters, no restraints, R_1 = 0.0455, wR_2 = 0.1245 (all data), Data were collected at 173(1) K on an Enraf-

Nonius Kappa CCD diffractometer. The structure was solved by direct methods (SHELXS-97) and refined with a full matrix least-squares refinement on F^2 (SHELXL-97), Hydrogens included at calculated positions, $S = 1.079$.

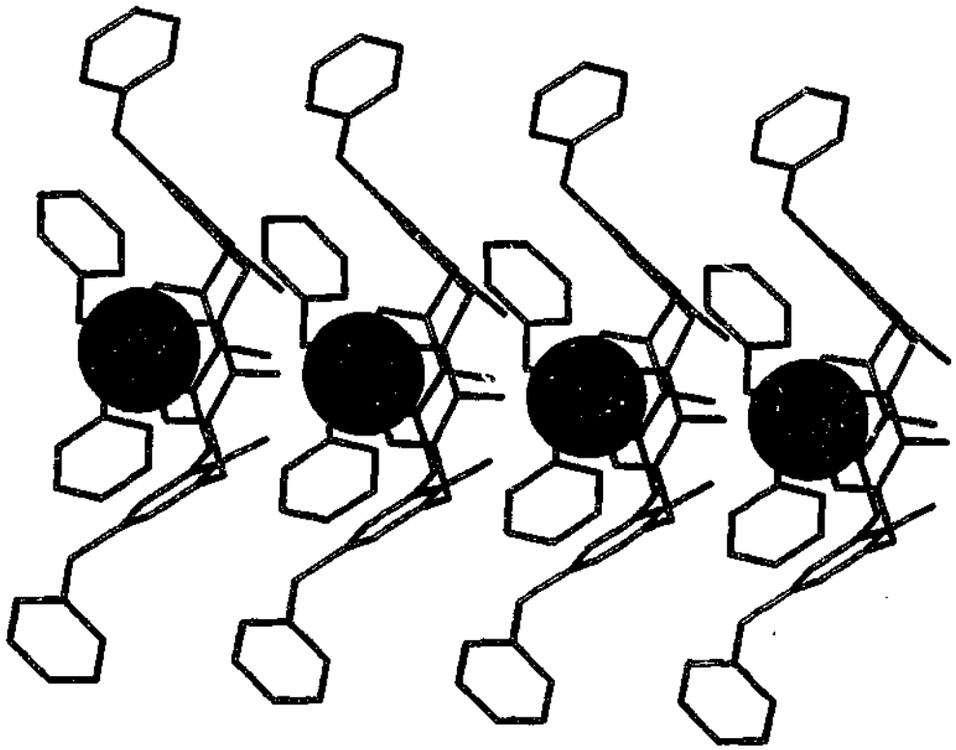


Fig.3.9 Molecular structure of *p*-benzylcalix[4]arene showing the inclusion of water within a self inclusion leading to π···π stacked columnar array (The oxygen atoms of the included water molecules are represented as red space-filling spheres and hydrogen atoms have been omitted for clarity).

A C_{60}/*p*-benzylcalix[4]arene complex was prepared by slow evaporation of an equimolar toluene solution of both components. While crystals suitable for X-ray-diffraction studies were obtained, the structural elucidation has not been complete due to weak data from small crystals. Access to synchrotron data is important to obtain data for adequate refinement of the structure. Nevertheless, preliminary solution of the structure shows *p*-benzylcalix[4]arene forms a 1:1 complex with C_{60} similar to those reported by Atwood *et al.*[61,62] for *p*-iodocalix[4]arene benzyl ether and *C*-ethylphenylcalix[4]resorcinarene where the fullerenes form columnar arrays. Indeed the cell dimensions are remarkably similar for the 1:1 complex of C_{60} with *C*-ethylphenylcalix[4]resorcinarene (tetragonal, a = b = 18.9296(7), c = 27.2702(13) Å,[61] *c.f.* tetragonal, space group (I_4), a = b = 19.2183(3), c = 27.7911(6) Å for [*p*-benzylcalix[4]arene.C_{60}]).

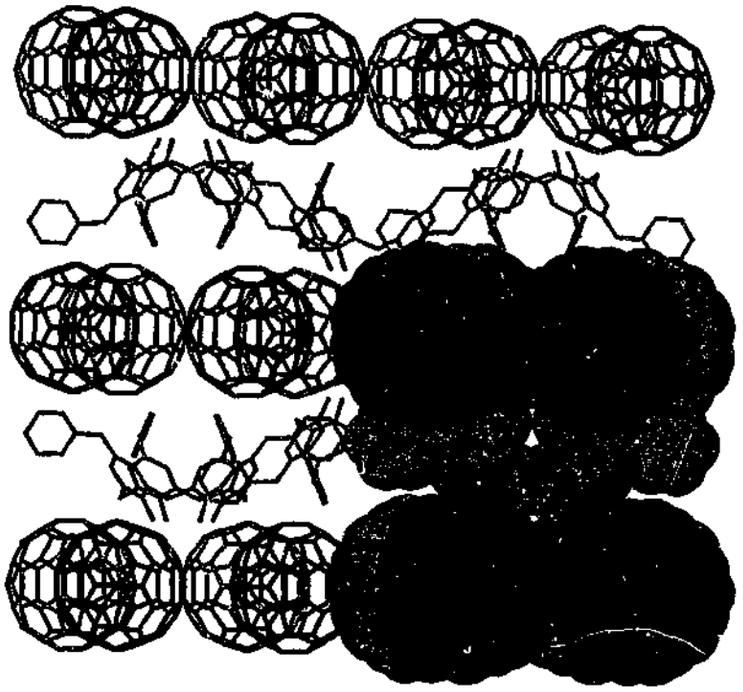


Figure 3.10 Projection of the packing diagram of [C_{60}/*p*-benzylcalix[4]arene] viewed along [100] plane showing the alternating sheets of close contact fullerenes and the alternating layers of *p*-benzylcalix[4]arene molecules.

The striking feature of the overall structure is the ordering of C_{60} molecules, forming layered arrays intercalated by *p*-benzylcalix[4]arene. The fullerene layers consists of alternating sheets of C_{60} along the *c* axis, separated by the calixarene layers (Figure 3.10). The alternating fullerene sheets are offset to each other in the *a,b* plane by 30.34° The space around each fullurene is associated with inter-fullerene interactions in the *a,b* plane. Each fullerene has contacts at the van der Waals limit to five other fullerenes, with centroid-centroid distances of 9.93-9.98 Å (Figure 3.11). Packing of the fullerenes in the *a,b* plane is not hexagonal close packing, but is such to create columns presumably filled with disordered toluene molecules.

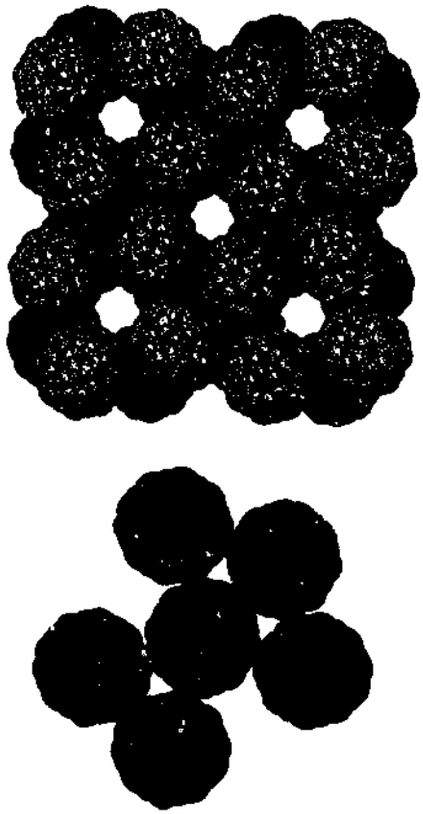


Figure 3.11 Projections along the *c* axis showing the alternating layers of C_{60} (top) and the close contact fullurenes (bottom) in C_{60}/*p*-benzylcalix[4]arene structure (the calixarenes are removed for clarity).

The calixarene molecules reside on a C_4 symmetry axis and, within each calixarene monolayer, there are two distinct molecular orientations related by inversion centres. These two orientations are rotated by 90° relative to one another, building planar alternating rows of calixarenes in 'up and down' arrangement as illustrated in Figure 3.12. The calixarene bilayer consists of two of such monolayers associated with one another in a head-to-head fashion separated by fullerene molecules, *i.e.* where the upper rim of each calixarene molecule in one layer faces the upper rim of a calixarene molecule of the second layer (Figure 3.10). Despite the lack of inclusion of C_{60} in the calixarene cavity, *p*-benzylcalixarene has induced fullerene packing in a highly organised array. The benzyl *para* groups of the calixarenes are of importance in generating this high order. The space fill shows the insertion of the benzyl *para* substituent in between the layers of C_{60} molecules (Figure 3.10). Five close contacts of C_{60} molecules is also found in the structure of Ni(TMTAA)C_{60}, although here the fullerenes form a corrugated rather than a flat sheet.[63]

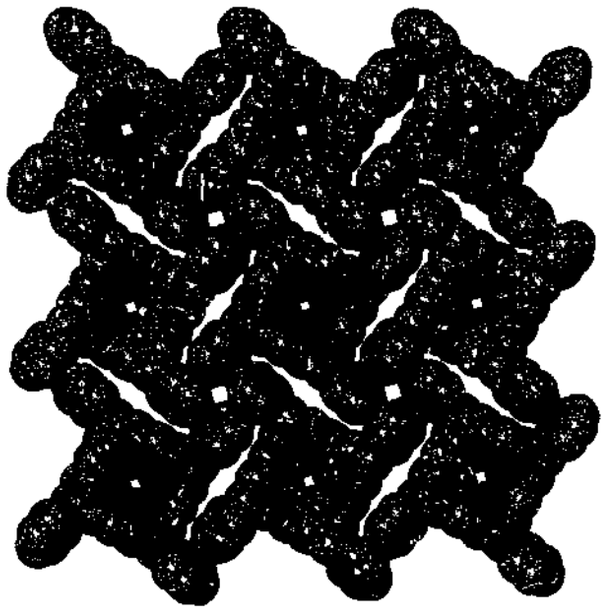
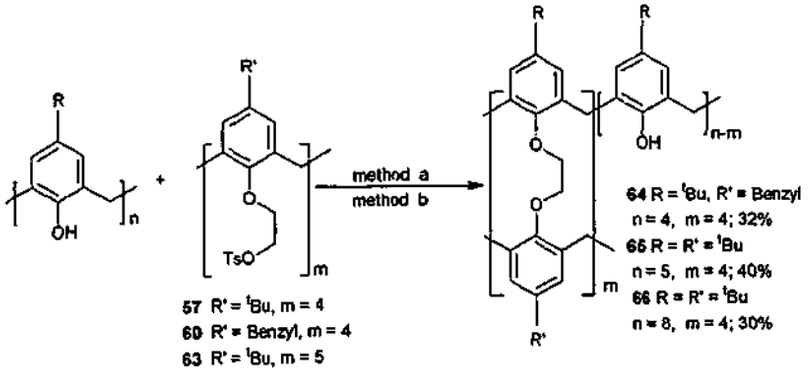


Figure 3.12 The calixarene layer viewed along the *c* axis in the 1:1 C_{60}/*p*-benzylcalix[4]arene structure showing the calixarene layer and the alternating rows of calixarenes in an up and down arrangement.

3.3 Molecularly linked calixarenes

Calixarenes can be modified by substitution of the upper and lower rims. Particular interest surrounds the lower rim fuctionalisation in the preparation of fused calixarenes as divergent receptors. Lower rim derivatisation of calix[4,5,6 and 8] was carried out with the aim of forming the building blocks necessary for the coupling of two calixarene molecules. The strategy adopted to build these fused calixarenes centred around lower rim functionalisation of one calixarene followed by a subsequent condensation with another calixarene, Scheme 3.2.



Scheme 3.2

The synthesis of these receptors involves a series of reactions starting with the building blocks *p*-alkyl-calix[n]arenes (n = 4 to 10, alkyl = ^{t}Bu; n = 4 – 8, alkyl = Benzyl; n = 4 – 8, alkyl = Phenyl) followed by the derivatisation at the lower rim with specific functionality. These calixarenes have the specific feature of being conformationally mobile in solution, which is an impediment in the preparation of the desired derivatives fixed in the cone conformation. This conformational flexibility involves the rotation of the aryl groups around the axis that links the *meta* carbon atoms to the bridging methylene groups, in a direction that bring the phenolic hydroxy groups through the annulus of the macrocyclic ring. The degree of flexibility varies from one ring system to another and generally the rate of the conformational flexibility is greater for large calixarenes due to weaker hydrogen bonding between the hydroxy groups. The larger and bulkier *para* substituents intervene in reducing this conformational interconversion especially in small ring systems such as *p*-alkyl-calix[4]arene where the hyroxy groups are engaged in a strong hydrogen bonding. For all the calixarenes, only the calix[4]arene and calix[5]arene are the most likely to accommodate the hydroxy groups in the same plane to form the cone conformation which is needed to construct the linked calixarene, divergent receptors. The derivatives fixed in the cone conformation of *p*-^{t}Bu-calix[4]arene and *p*-benzylcalix[4]arene have been prepared and consequently four divergent receptors have been generated with *p*-^{t}Bu-calix[4]arene linked to *p*-^{t}Bu-calix[5]arene, **65**, and have been structurally authenticated. The preparation of these fused calixarenes is sought at forming heterotopic divergent-host molecules having two *exo*-hydrophobic cavities and etheral cage at the middle, thus providing cavities for dual inclusion in addition to a central cage for metal complexation (Figure 3.12). The synthesis of lower rim derivative precursors to fused calixarenes is presented, together with the discussion of their conformational behaviour in solution and in the solid state.

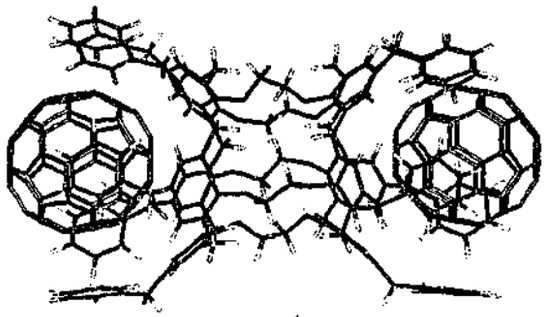
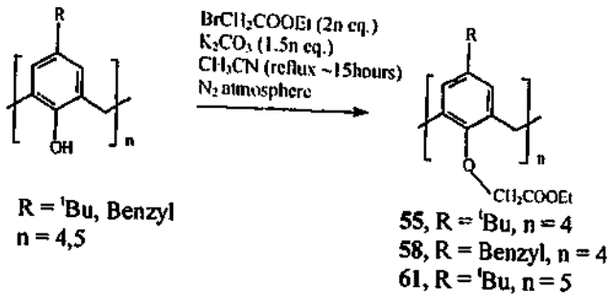


Figure 3.12 Molecular modelling of the divergent receptor based on fused *p*-benzylcalix[5]arenes with the inclusion of C_{60} molecules.

3.3.1 Precursors syntheses

The general synthesis of the lower rim derivatives of calixarenes and the factors governing their conformational control have been well established for the tetramer, calix[4]arene (section 1.4.3). Similarly, calix[5]arene functionalisation has been carried out with the appropriate adjustment of the reaction conditions and reagents stoichiometry.[64-67] Factors governing the conformational outcome of the pentamer are not currently well understood, the lower rim introduction of alkyl groups larger than *n*-propyl are observed to be sufficiently bulky to hinder the interconversion mechanism, thus "locking" the calixarene into a given configuration.[64] The O-rim alkylation of the tetramer affords derivatives which are generally in the cone conformation. The tetra-(ethoxy-carbonyl-methoxy) **55**, **58** tetra-(hydroxy-ethanoxy) **56**, **59** and the tetra-(tosylate-ethanoxy) **57**, **60** of *p*-^{t}Bu-calix[4]arene and *p*-benzylcalix[4]arene respectively have been prepared and been shown to adopt the cone conformation. In order to test the effect of the *para* substituents on the lower rim functionalisation of calix[4]arene, the ester derivative tetra-(ethoxy-carbonyl-methoxy) of calixarene was prepared and found to also adopt the cone conformation. In contrast, the penta O-rim alkylated derivatives of calix[5]arene adopt a number possible conformations (Figure 1.16).

Unlike the advances in the functionalisation of calix[4]arene which is possible with a paticular conformation (cone, 1,2-alternate or 1,3-alternate), calix[5]arene with its larger cavity and greater number of possible conformations results in an unpredictable mixture of conformers. It is anticipated that the importance of the first derivatisation as a deciding step in the preparation of derivatives of the pentamer in the desired cone conformation is paramount. The penta-ester derivative of *p*-^{t}Bu-calix[5]arene **61** was prepared using a large excess of K_2CO_3 and bromoethyl acetate in a concentrated solution of acetonitrile and was obtained as a single conformer, following the general procedure illustrated in Scheme 3.3. The conformation of the ester derivative **61** was assigned on the basis of characteristic ^{1}H and ^{13}C NMR patterns of the bridging methylene groups.[64] The preorganised cone conformation was established by the appearance of the two pairs of doublets for the methylene protons and a singlet for the methylene carbons as conclusive proof for the cone structure of compound **61**. The lower rim functionalisation for larger calix[n]arenes (n = 6, 8) has also been attempted, producing the non-cone conformation derivatives.

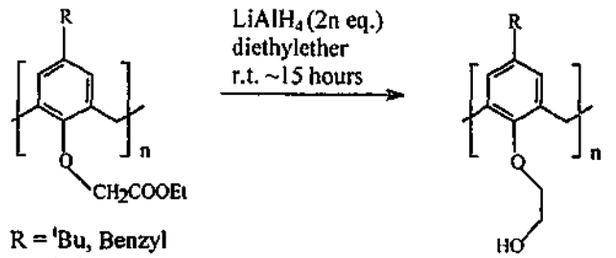


R = ^{t}Bu, Benzyl
n = 4,5

55, R = ^{t}Bu, n = 4
58, R = Benzyl, n = 4
61, R = ^{t}Bu, n = 5

Scheme 3.3

The syntheses of compounds **62** and **63** involved adaptation of literature procedures,[68] with their structures established in the solid state. The reduction of the ester groups of **61** yielded compound **62** following an adaptation of a literature procedure,[68] Scheme 3.4.



R = ^{t}Bu, Benzyl
n = 4, 5

56, R = ^{t}Bu, n =4
59, R = Benzyl, n = 4
62, R = ^{t}Bu, n =5

Scheme 3.4

The penta-(hydroxy-ethanoxy) of *p*-^{t}Bu-calix[5]arene **62** crystallised as a potassium complex, [K(CH_3OH)(**62**)]Br.solvent (see below) with a methanol molecule bound to the metal centre in the cavity, Figure 3.13. The potassium is hepta coordinated, involving only four phenoxy oxygens, two of the associated terminal OH groups, which are associated with five membred chelate rings, and the oxygen of methanol included in the cavity. Hence, the potassium is offset relative to the centroid of the phenoxy oxygens, showing that the cation is too small to involve the fifth ethanoloxy group in its coordination sphere. Consequently, compound **62** has a distorted cone conformation described by the tilt angles of the aryl moieties relative to the plane formed by the phenoxy oxygens of the calix[5]arene, which are 40.41°, 93.19°, 53.41°, 59.85° and 91.76°, Figure 3.13.

Crystals of [K(CH_3OH)(**62**)]Br.solvent diffracted extremely weakly with only *ca* 25% observed data and hence should be regarded as a preliminary investigation and full details are not presented. Structural details shown in Fig.3.13. Crystals are trigonal (hexagonal), $R\ \bar{3}$, a = 35.3037(10) , c = 28.5278(6) Å.

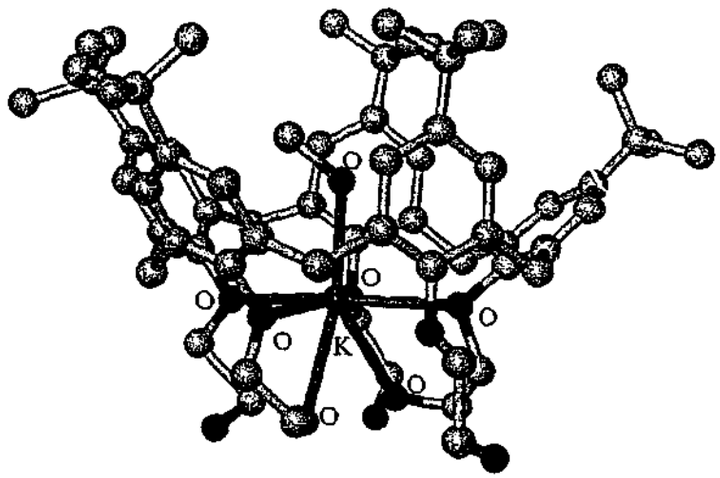
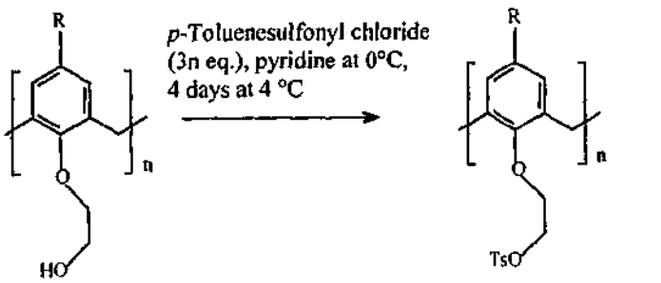


Figure 3.13 Molecular structure of the potassium complex of *p*-^{t}Bu-calix[5]arene derivative **62**, enforced in the cone conformation. The average of the K— O distances is of 2.819 Å.

The subsequent tosylation reaction was carried out following the reported procedure (Scheme 3.5) and afforded the penta-(tosylate-ethanoxy) derivative **63** in the cone conformation also necessary for the formation of bis-calix[5]arene.



R = ^{t}Bu, Benzyl
n = 4, 5

57, R = ^{t}Bu, n = 4
60, R = Benzyl, n = 4
63, R = ^{t}Bu, n = 5

Scheme 3.5

The structure of the penta-(tosylate-ethanoxy) *p*-^{t}Bu-calix[5]arene, **63**, shows a distortion in the cone conformation with the self inclusion of one *para* substituent *tert*-

butyl group leaning towards the cavity, with a tilt angle of the phenol plane with respect to the phenoxy oxygens plane of 115.05° with the lower rim ethyltosylate group protruding out. The remaining four phenolic moieties have tilt angles of 47.62°, 79.15°, 83.44° and 37.38° indicating that the aryls are in an alternating in-and-out arrangment, Figure 3.14. Compound **63** crystallises in a triclinic, $P\bar{1}$ space group, a = 14.154(3), b = 19.042(4), c = 20.780(4) Å, α = 64.68(3), β = 75.15(3), γ = 72.46(3), V =4774.2(2) Å^3, Z = 2, ρ = 1.254 g cm^{-1}, μ = 0.190 mm^{-1} (no correction), colourless, 0.15 x 0.15 x 0.12 mm, θ_{max} = 25.0°, 43539 reflections measured, 16683 unique reflections (R_{int} = 0.132), 1216 parameters, R_1 = 0.1185 (on 7671 observed data [$I > 2\sigma(I)$]), wR_2 = 0.3056 (all data), S = 1.044. One ^{t}Bu group and one tosylate group were disordered over two sites with one disordered tosylate site refined isotropically as rigid body refinement.

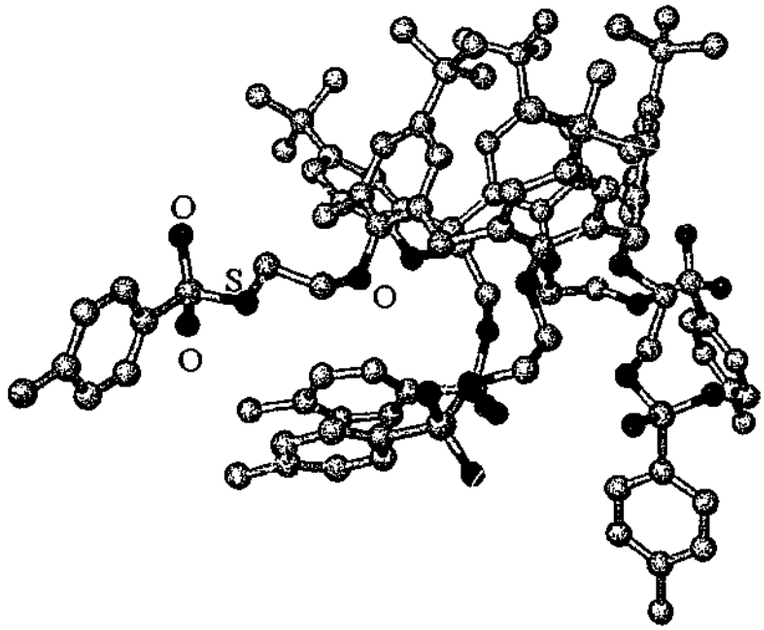


Figure 3.14 Molecular structure of the per-tosylated derivative of *p*-^{t}Bu-calix[5]arene, **63** in a distorted cone conformation.

3.3.2 Bis-calixarenes

The methodology used was an adaptation of a previously reported procedure,[68] consisting of complete esterification of a calix[4]arene, followed by reduction to the hydroxyethyleneoxy compound and tosylation prior to the condensation reaction with calix[n]arenes to form bis-calixarenes,[69] which presumably is driven by steric and proximity effects, Scheme 3.2. Bis-calixarene **64** was prepared in 32% yield, by condensation of *p*-^{t}Bu-calix[4]arene and the per-tosylated derivative of *p*-

benzylcalix[4]arene, **60** under an inert atmosphere and high dilution in acetonitrile in the presence of K_2CO_3 for 3 days. Under similar reaction conditions, bis-calixarenes **65** and **66** were prepared in 40% and 30% yields respectively, *i.e.* condensing *p*-^{t}Bu-calix[n]arene (n = 5, 8) and their per-tosylated derivative of *p*-^{t}Bu-calix[4]arene, **57**[68].

In considering of the cone conformation requirement for building tubular bis-calixarenes, *p*-benzylcalix[4]arene derivatives been prepared, **58**, **59** and **60**, as precursors to bis-calixarene, **64**. Compound **64** was isolated by triturating the crude reaction mixture in a hot ethanol/water mixture to remove unreacted starting materials, filtration followed by chromatography of the resulting solid, using 1:1 dichloromethane/hexane, isolated from the first and second fractions.

Bis-calixarene **65** was produced as a single product and was easily isolated from the mixture by first heating the crude reaction mixture in ethanol/water and filtering it hot, to remove unreacted materials, followed by flash chromatography. In general, the good solubility of the new bis-calixarenes in organic solvents impeded their isolation by crystallisation methods. The more polar unreacted starting materials can be removed and recycled if desired, by heating the crude reaction mixture in an appropriate solvent mixture. For instance, unreacted *p*-^{t}Bu-calix[8]arene in the preparation of bis-calixarene **66** was precipitated using an ethyl acetate/hexane mixture and any remaining crude product was subject to chromatography on a silica gel column using dichlromethane hexane 1:1 to elute the bis-calixarene, made facile by the high polarity of the pertosylated derivative of *p*-^{t}Bu-calix[4]arene, **57**. ^{1}H NMR data is in agreement with their tubular structures showing several doublets AB spin resonances, which is indicative of fixed conformations of the calixarene moieties.

It is noteworthy that bis-calixarene, **66** was formed as two isomers in a 1:1 ratio (NMR integrations) but their separation was unsucsseful. NMR data is consistent with the presence of a symmetrical isomer A with two sets of AB spin systems from fixed conformations for *p*-^{t}Bu-calix[4]arene and *p*-^{t}Bu-calix[8]arene units in the macrocycle and a lower symmetry isomer B with broad peaks. The hydroxy region of the spectrum provide additional structural information; isomer A has a broad singlet for the free hydroxys at 8.80 ppm in contrast to isomer B with four singlets at 9.25, 9.35, 9.40, 9.45 ppm suggestive of the existence of a strong hydrogen bonding array. There are other possible structures for isomer B, also with four different environments for the unbound hydroxy groups. However, in considering the pleated loop conformation of free *p*-^{t}Bu-

calix[8]arene, the proximity effect factor and the relatively short length of the ethyl linkages, in addition to the high values observed for chemical shifts for the unbound hydroxys, which are within range of the chemical shift for hydroxys of *p*-^{t}Bu-calix[8]arene (*c.f.* 9.6 ppm), the most likely structure for isomer B is that shown in Figure 3.15.

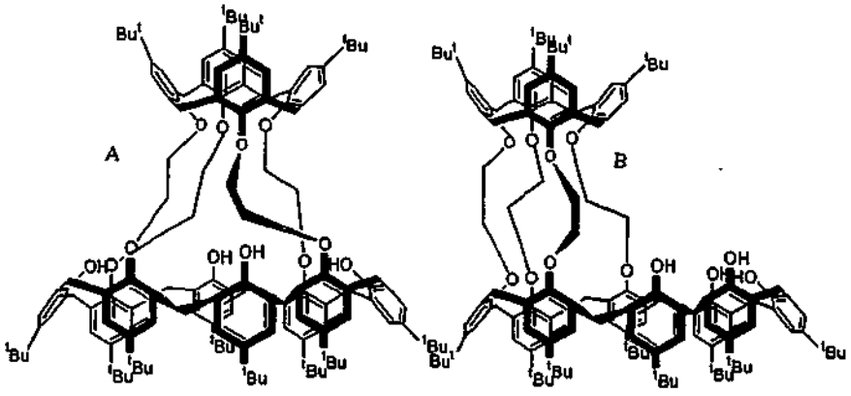


Figure 3.15 Structural representation of the isomers of bis-calixarene **66**.

The NMR spectroscopy of bis-calixarene **65** proved difficult to assign the structure unambiguously due to the large number of protons involved within the overlaping regions. Along with mass spectrometry and microanalyses, the presence of several doublets between 2.5 and 5.5 ppm, five singlets for the *tert*-butyl groups and four broad doublets and a multiplet for the aromatic protons, suggested that bis-calixarene **65** has high symmetry. The ^{1}H NMR was consistent with the structural rigidity of the molecule with both calixarene moieties in the bis-calixarene adopting the cone conformation, having fewer multiplets arising from the protons of the ethylene bridging linkers in addition to one singlet for the remaining unbound hydroxy proton. The compound has been structurally authenticated (Figure.3.16) in the solid state confirming the NMR prediction and serves as a guide to establish the structures of the other fused calixarenes in conjunction with mass spectrometry and microanalyses.

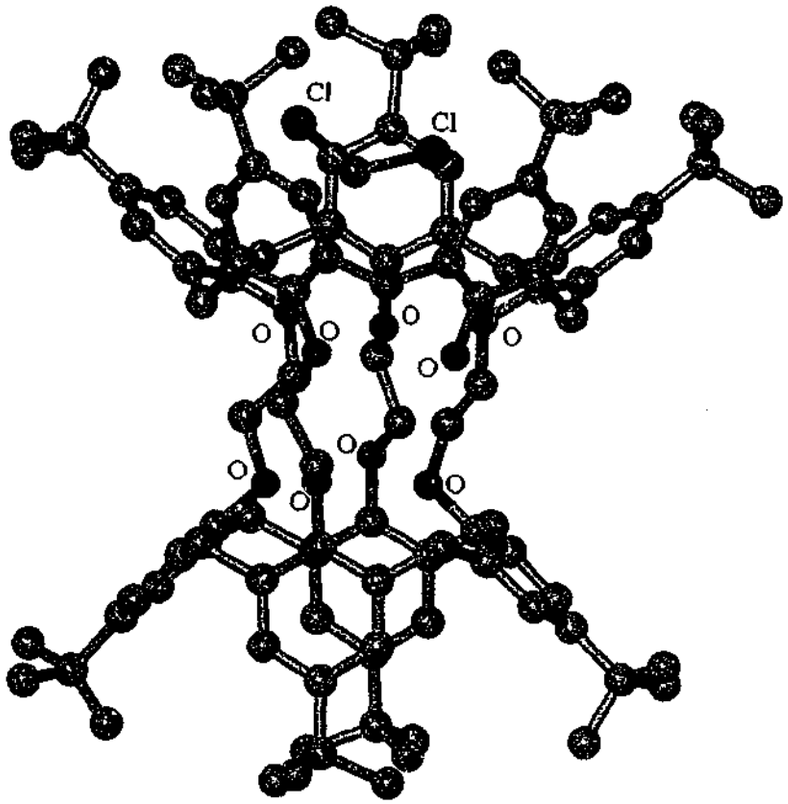


Figure 3.16 Molecular structure of *p*-^{t}Bu-[4]arene 'linked' to *p*-^{t}Bu-calix[5]arene; bis-calixarene **65** with a molecule guest of CH_2Cl_2.

Bis-calixarene **65** crystallises in the triclinic, space group $P\bar{1}$ with a dichloromethane molecule included in the cavity of the calix[5]arene moiety, both C-H groups being directed towards the centres of two aromatic rings (1,3). The short C-H···Aryl centroids distances are 2.96 Å and 2.87 Å, indicating that dichloromethane molecule is tightly bound within the cavity of the calix[5]arene. Similar to the inclusion of methylene chloride in *p*-^{t}Bu-calix[4]arene attached to Al(III) centers in a bis-calixarene complex.[38] The same calix[5]arene has a distorted cone conformation with tilt angles relative to the plane of the phenolic oxygens of 28.99°, 93.74°, 25.09°, 89.35° and 72.36°. In contrast, the calix[4]arene moiety retains a symmetrical cone conformation similar to that in the bis-calix[4]arene reported by Beer *et al.*[69]; with tilt angles of 39.82°, 68.91°, 35.69° and 84.91°. The crystal packing diagram shows the bis-calixarene forming an infinite linear array, with calix[5]arenes and calix[4]arenes moieties in a head to head arrangement at the van der Waals limit, with packing to adjacent linear arrays giving an overall honeycomb arrangement, Figure 3.17.

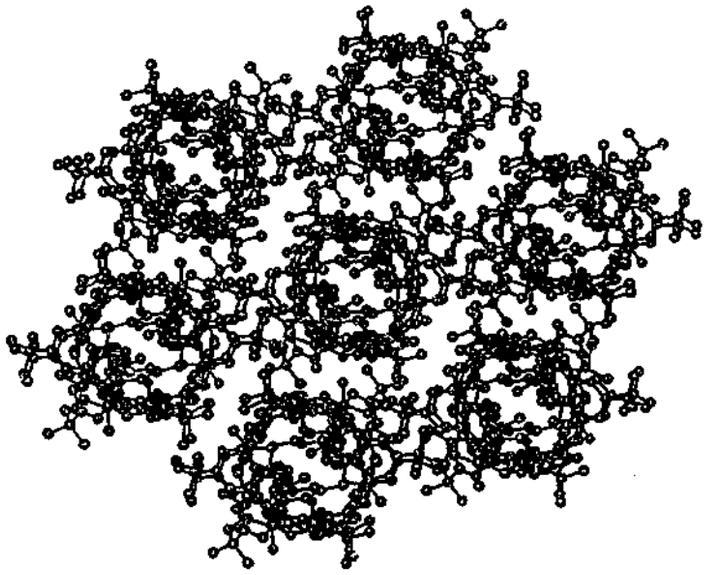


Figure 3.17 Crystal packing diagram for the stacked bis-calixarenes **65** forming tubular arrays within the crystal lattice (hydrogens and solvent molecules are removed for clarity).

3.3.3 Tris-calixarenes

To further investigate the condensation reaction of pertosylated derivative of *p*-^{t}Bu-calix[4]arene with different ring size *p*-^{t}Bu-calix[n]arenes (n = 4, 5, 6 ,8), the condensation reaction of the pertosylated derivative, **57** with *p*-^{t}Bu-calix[6]arene under the previousely outlined reaction conditions was investigated. This resulted in the formation of the tris-calixarene **67** isolated in 26% yield, consisting of two *p*-^{t}Bu-calix[6]arenes joined to a *p*-^{t}Bu-calix[4]arene base by ethylene linkages. The ESI-MS analysis shows the presence of the molecular ions $[M+H]^+$ and $[M+Na]^+$ of the tris-calixarene **67**. However, the ^{1}H NMR experiment proved inconclusive in assigning the structure. The presence of several doublet AB spin system resonances and a single broad singlet at 8.6 ppm accounts for the eight free hydroxy protons, showing strong hydrogen bonding engagement, suggesting that both *p*-^{t}Bu-calix[6]arenes are connected to *p*-^{t}Bu-calix[4]arene base in a similar fashion. Hence, the proposed mode of attachement of the *p*-^{t}Bu-calix[6]arene units to *p*-^{t}Bu-calix[4]arene is **I** or **II**, presented in Figure 3.18. It is likely that the *p*-^{t}Bu-calix[6]arenes are in the 'pinched' cone conformation, linked *via* ehtylene linkers to *p*-^{t}Bu-calix[4]arene, forced into the 1,3 alternate conformation to overcome otherwise steric compression, *ie.* structure **I**.

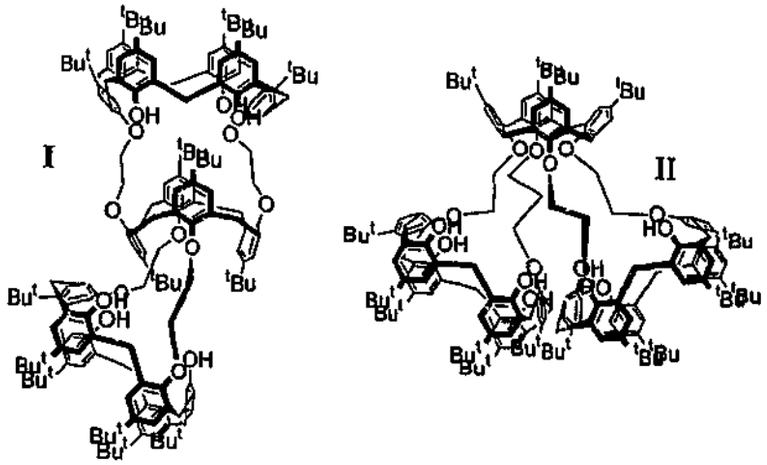
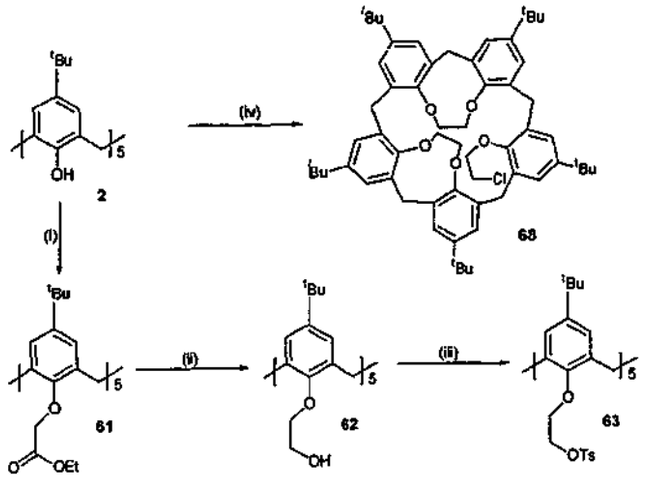


Figure 3.18 The two possible isomeric structures for tris-calixarene **67**.

The coupling reaction of the penta-tosylate-ethyleneoxy of *p*-^{t}Bu-calix[5]arene with another calix[5]arene to form the target compound bis-calix[5]arene was unsuccessful, even with the coupling reaction being performed under high dilution, at different reaction conditions, different temperatures and using metal templates (Na^+or K^+). The use of NaH or K-selectride as the base instead of K_2CO_3 followed by addition of **63** at low temperature prior to reflux resulted in only recovering the starting materials.

A more direct approach involving *p*-^{t}Bu-calix[5]arene and chloroethyltosylate with K_2CO_3 produced a rather unexpected compound, 1,2-3,5 proximal *p*-^{t}Bu-calix[5]di-crown, **68** in good yield (60%), with the remaining hydroxyl bearing chloroehanoxy fuctionality set up for further elaboration, but no presence of bis-calixarenes (Scheme 3.6).



Scheme 3.6 *Reagents and conditions*: (i) K_2CO_3, $BrCH_2CO_2Et$, CH_3CN, 24 hrs, Reflux. (ii) $LiAlH_4$, $(C_2H_5)_2O$, 24 hrs, RT. (iii)TsCl, Pyridine, 2 days, 0 °C. (iv) K_2CO_3, $ClCH_2CH_2OTs$, CH_3CN, 48 hrs, Reflux.

This is presumably a consequence of higher reactivity of the carbon bearing the tosyl group compared to the carbon bearing the chlorine in the chloroethyltosylate reagent. The former carbon centres react in the first instance to form the intermediate tri-chloroethanoloxy of *p*-^{t}Bu-calix[5]arene, which undergoes self condensation. Also, the 1,3-alternate conformation can be accounted for by the involvement of the tosyl groups in the reaction, as for the behaviour established in calix[4]arene chemistry.[12] Finally, the favoured proximal conformation can be explained by the short length of the ethylene spanner, generating a non-cone immobilised 1,2-3,5 proximal ^{t}Bu-calix[5]di-crown, Figure 3.19, as established by an X-ray structure determination. The compound crystallises with included iso-propanol solvent molecule and water, the overall composition being **[68]**$_4$(*iso*-propanol)$_{6.5}$(H_2O)$_2$: $C_{263.5}H_{341.5}Cl_4O_{28.5}$, Mr = 4106.67, triclinic, $P\bar{1}$, a = 19.1047(5), b = 21.9058(3), c = 31.8410(8) Å, α = 90.268(1), β = 91.758(1), γ = 112.179(1)°, V =12331.9(5) Å^3, Z = 2, ρ = 1.106 g cm^{-1}, μ = 0.112 mm^{-1} (no correction), colourless, 0.20 × 0.15 × 0.10 mm, θ_{max} = 27.88°, 82575 reflections measured, 53357 unique reflections(R_{int} = 0.061), 2611 parameters, R_1 = 0.1413 (on 25726 observed data [$I > 2\sigma(I)$]), wR_2 = 0.3925 (all data), S = 1.027. Solvent propanol and water molecules were refined isotropically. One chloro atom was modelled as disordered over two sites at 80:20 occupancy.

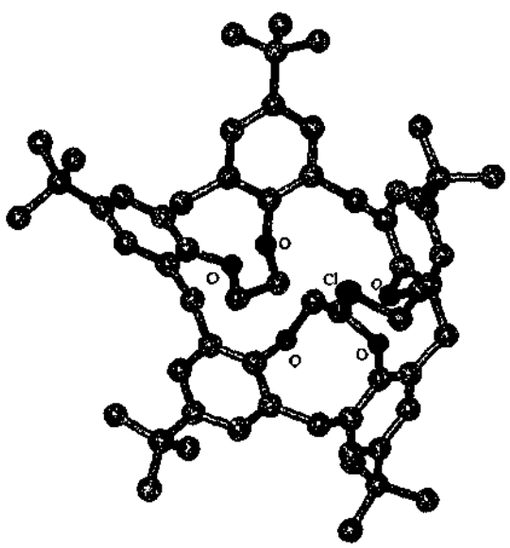


Figure 3.19 Molecular structure of 1,2-3,5 proximal *p*-^{t}Bu-calix[5]di-crown, **68** from the X-ray structure determination of (**68**)$_4$(*iso*-propanol)$_{6.5}$(H_2O)$_2$.

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SULFONATED CALIXARENES: RESULTS AND DISCUSSION

4.1 Introduction

Water soluble calixarenes are becoming an increasingly important class of compound in the field of supramolecular chemistry. They allow the study of the interactions involved in host-guest recognition processes in water. The most studied sulfonated calix[4]arenes are able to complex a variety of metal and organic cations in water.[1-5] The binding of cations in water involves electrostatic forces, van der Waals and hydrophobic effects, and the electron rich aromatic ring can also be involved in cation-π, π-π interactions. These studies give a deeper understanding of the type of forces involved, and are important in the design of receptors mimicking biological systems.[6,7]

p-Sulfonato-calix[n]arenes have been widely investigated and shown to have remarkable inclusion properties, being capable of forming supramolecular architectures of high complexity.[8-11] Nevertheless, there is a still an interest in preparing water soluble species based on other calixarene systems and the investigation of their inclusion properties. Thus the *p*-phenylcalix[n]arenes (n = 4, 5, 6, 8), *p*-cumylcalix[n]arenes (n = 4, 6) and *p*-benzylcalix[n]arenes (n = 4, 5, 6, 7, 8) families were sulfonated, producing new classes of water soluble calix[n]arenes. *p*-Phenylcalix[5, 6]arene sulfonates and their analogues *p*-benzylcalix[5, 6]arene compounds in particular have inclusion properties favoring inclusion of rod shaped carotenoids (*trans*-ß-carotene, asthaxantin) and globular molecules such as fullerene C_{60}, enabling their solubilisation in aqueous media. The resulting non-covalent host-guest compiexes are of current scientific and technological interest for their chemical, physical and biological properties.[12-15]

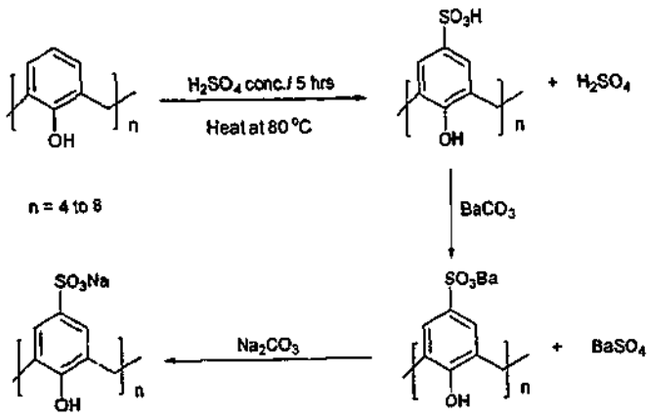
The inclusion complexes of these sulfonated calix[5, 6]arenes with C_{60} fullerene allows the study of C_{60} molecules in water;[15] the C_{60} in the supermolecule exhibit essentially the same electronic spectra as those of the free C_{60}. Biologically active molecules such as *trans*-ß-carotene and asthaxathin also form supramolecular complexes with sulfonated *p*-phenyl- and *p*-benzyl-calix[5, 6]calixarenes in water. Such non-covalent association achieve water solubility of these lipophilic molecules with retention of their

original electronic spectra and stability within the supermolecule.[16] This chapter includes characterization, studies of the aggregation behaviour of these novel sulfonated calixarenes and their complexes in water using UV-vis spectrometry, light scattering measurements, powder X-ray diffraction and NMR techniques.

4.2 Sulfonated calix[n]arenes

4.2.1 Synthesis of *p*-sulfonato-calix[n]arenes

Traditionally sulfonated calixarenes[17] were prepared by reacting calixarenes with an excess of neat sulfuric acid for a few hours at 80°C until no insoluble material was detected in the reaction mixture. However, this approach necessitates the conversion of the sulfonated calixarenes to their sodium salts due to the fact that the sulfonic acids are very difficult to isolate from neat sulfuric acid and can be hygroscopic. This conversion is achieved by neutralizing the excess of sulfuric acid using barium carbonate. The resulting barium sulfate is removed from the reaction mixture by filtration and the filtrate is treated with sodium carbonate to pH 9, for counter cation exchange. The crude sodium sulfonated calixarene is then treated with activated charcoal before precipitating it from methanol, Scheme 4.1.

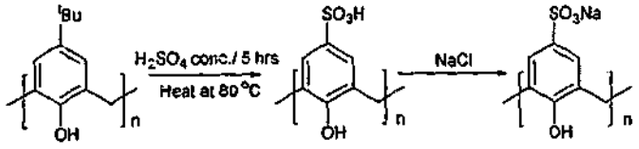


Scheme 4.1

A more direct method for the synthesis of sulfonated calixarenes developed by the Atwood group[18] involves the *ipso* substitution of *tert*-butyl groups by sulfonate groups with elimination of isobutylene. The procedure involves reacting the *p*-^{t}Bu-calixarenes with an excess of neat sulfuric acid, then the reaction mixture is poured into a large concentrated solution of brine. The salting effect of brine precipitates the sodium sulfonate of the calixarenes contaminated with small amounts of sodium chloride. Further treatment

of the crude product with charcoal and adjustment of the pH of the solution affords either the tetra sodium (neutral pH) or the penta sodium salt (pH 9) sulfonated calixarene, Scheme 4.2. The drawbacks of this and the above synthetic methods are that the product is prone to contamination with inorganic salts and there are difficulties in isolating the sulfonic acids of the calixarenes from the sulfuric acid solution.

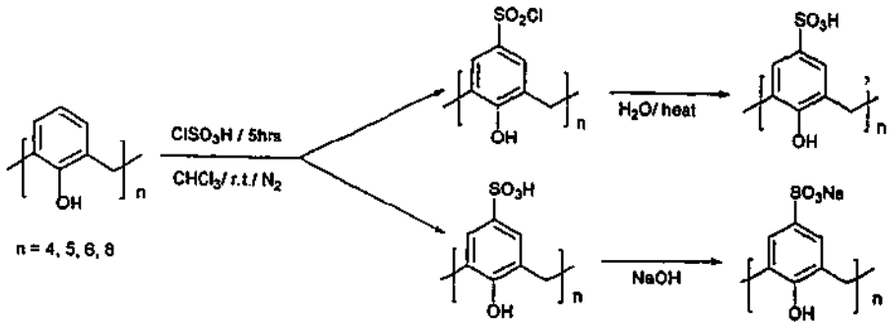
The accessibility of analytically pure sodium sulfonates of these calixarenes requires multiple crystallisations, and allowing the aqueous solutions of the sulfonated calixarenes to stand for some time. Nevertheless, the latter procedure was used for the preparation of sulfonated calixarenes with removal of the inorganic salts contaminating the product using osmotic dialysis. The experiment consisted of pouring a crude aqueous solution of a sodium salt of sulfonated calixarene into a dialysis tubing (Visking, size 8 Inf Dia 32/32" – 25.4 mm : 3μ) and the filled tube is stored in a large volume of deionised water for a week, discarding water daily and replacing it with fresh batch. This procedure was attempted for a sodium sulfonted calix[5]arene (1 g in 10 ml of water). The contents of the dialysis tubing was poured into a flask, and removal of water *in vacuo* afforded an amber solid. Trituration of the solid with methanol (20 ml) followed by filtration afforded pure sodium *p*-sulfonated calix[5]arene, as the hepta sodium salt.



Scheme 4.2

The previous procedures are regarded as the major routes to the sodium sulfonated calixarenes. Alternatively, the sulfonic acids of calixarenes were produced by using the chlorosulfonic acid approach, which consisted of adding chlorosulfonic acid dropwise to a chloroform solution of calixarene at 0°C with the biphasic mixture then stirred at room temperature for 5 hours under an inert atmosphere. The reaction mixture was then poured into an ice-cold water and the organic phase separated and treated separately affording the chlorosulfonyl derivative, isolated in pure form. Subsequent hydrolysis of the latter produced pure sulfonic acids of the calixarenes, with facile elimination of hydrochloric acid bi-product. The aqueous layer was brought to dryness under reduced pressure and the pure sulfonic acid calixarene was obtained by precipitation using dry acetone or dry ether. The chlorosulfonation route is a general procedure for all calix[n]arenes affording pure

sulfonic acids of calix[n]arenes with the added advantage of intercepting the chlorosulfonyl derivatives for further elaboration (such as conversion to sulfamides or sulfones), Scheme 4.3. Conveniently, the sodium salts of all these sulfonic acid derivatives of calix[n]arenes can be easily prepared by simple acid-base titration using 1 *M* sodium hydroxide solution at neutral pH. Removal of water to dryness under reduced pressure and addition of methanol to the crude residue precipitates the corresponding sodium salt of the sulfonated calix[n]arenes.



Scheme 4.3

Another approach to obtain the free sulfonic acids of calix[n]arenes from the sodium salt analogues involved the use of ion exchange chromatograhy. The technique was performed using a cation exchange resin (AG 50W-X2 Resin 200-400 mesh hydrogen form) and the procedure consisted of preparing a column packed with a resin, eluted first with 1 *M* HCl then water. A solution of the sodium salt of sulfonato-calix[4]arene (1 g in 10 ml H_2O) was added to the column and eluted with 50 ml of water. During elution, the resin acted as a support substituting the sodium ions with hydrogen ions and the collected solution was brought to dryness under reduced pressure affording the sulfonic acid of calix[4]arene.

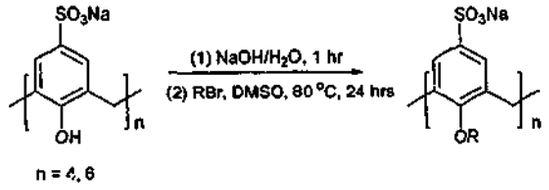
4.2.2 Lower rim derivatisation of *p*-sulfonato-calix[n]arenes

In order to increase the hydrophilicity of the sulfonated calixarenes and to achieve control over their conformational flexibility, alkyl groups were introduced to the lower rim using reported procedures.[17,19] *p*-Sulfonato-calix[4]arene is conformationally mobile in solution with ^1H NMR in D_2O giving a singlet for the methylene protons. Considering the cone conformation requirement to assemble capsular structures based on two or more sulfonated calixarenes (section 4.3.2) for selective encapsulation of organic molecules, the lower rim alkylation was aimed at 'locking' *p*-sulfonato-calix[4]arene into the cone conformation. The lower rim derivatisation was carried out using two approaches.

The first approach consisted of adding a solution of alkyl bromide (10 equiv.) in DMSO to a solution of *p*-sulfonato-calix[4]arene and sodium hydroxide (5 equiv.) in water, stirring for an hour the reaction mixture was heated at 80°C for 24 hours, Scheme 4.4. The reaction mixture was then allowed to cool to room temperature and the product precipitated on the addition of a large volume of ethanol.

The second approach involved complete alkylation of the lower rim of calix[4]arene by the appropriate alkyl halide followed by the sulfonation using sulfuric acid. Work up of the reaction mixture afforded the tetra alkylated derivatives *p*-sulfonato-calix[4]arene, $Et4^{SO_3Na}$, **48**, and $npr4^{SO_3Na}$, **49**. The hexa-(octadecanoxy)-*p*-sulfonato-calix[6]arene(octadecane6^{SO_3Na}), **50**, was prepared using an adaptation of the former approach.

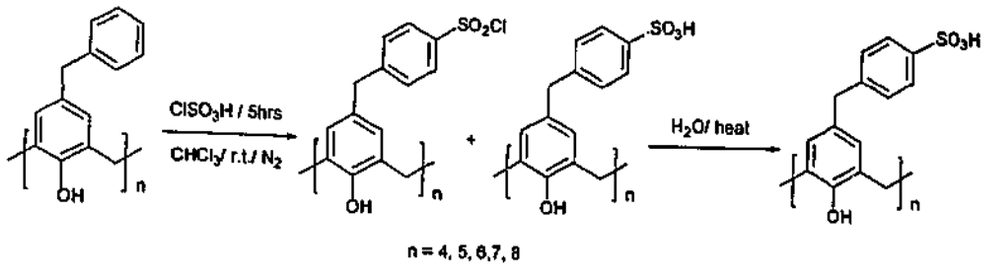
The tetra alkylated derivatives both proved to preferentially adopt the cone conformation in water, by exhibiting an AB spin system arising from the bridging methylene protons (^{1}H NMR in D_2O). In contrast, the hexa alkylated derivative **50** bearing long alkyl chain at lower rim shows a singlet for methylene protons indicative of a fluxional non-cone conformation.



Scheme 4.4

4.2.3 Synthesis of novel sulfonated calix[n]arenes derived from *p*-benzyl, *p*-phenyl and *p*-cumyl phenol.

Sulfonic acids of *p*-benzylcalix[n]arenes (n = 4 – 8), sulfonic acids of *p*-cumylalix[n]arenes (n = 4, 6) and sulfonic acids of *p*-phenylcalix[n]arenes (n = 4, 5, 6, 8) were synthesized using the same approach as for the calix[n]arene systems. The adaptation of the chlorosulfonation route to the *p*-benzylcalixarenes, cumylalix[n]arenes and *p*-phenylcalix[n]arenes systems produced the chlorosulfonyl derivatives, which were hydrolysed to the corresponding sulfonic acids. It is noteworthy, that the electrophilic aromatic substitution of chlorosulfonic acid is regioselective, incorporating chlorosulfonyl groups selectively at the *para* position of the benzyl, cumyl and phenyl groups, Scheme 4.5. The *ortho* positions of the terminal aromatic rings are also electronically activated for substitution but presumably this is sterically disfavoured.



Scheme 4.5

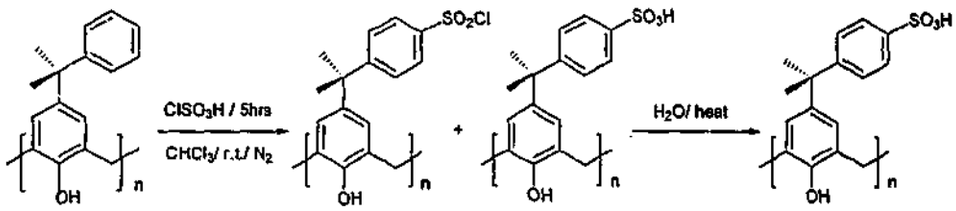
The electrophilic substitution reaction on monosubstituted benzene ring can be directed either to the *ortho*, *meta* or *para* position. The group already in the ring determines which position the new group will take. Generally, the groups which are *meta* directing are deactivating and those which are *ortho-para* directing are activating.[55] The orientation and reactivity effects of each group are explained on the basis of resonance and field effects on the stability of the intermediate arenium ion. Any group that has an electron–donating field effect in principal should have an activating effect and *ortho-para*-directing role. The sulfonation of the benzyl group of the calixarene can be regarded somewhat as a sulfonation of toluene if ignoring the calixarene core, thus the sulfonation in principal should occur not only at *para* position but at the *ortho* position as well. However, in fact the calixarene core should not be ignored at all and sterically could be the origin of the *para* directing outcome of these reactions. A given group causes the same general kind of orientation–predominately *ortho-para* or predominately *meta*–whatever the nature of the electrophilic reagent. Table 4.1 summarises the orientation of nitration in a number of substituted benzenes as an example for the elecrophilic substitution reaction.[56]

Table 4.1 Orientation of nitration of C_6H_5-Y (Isomers yield %)[56]

Y	*Ortho*	*Meta*	*Para*
OH	50-55	trace	45-50
CH_3	58	4	38
Cl	30	trace	70
NO_2	6.4	93.3	0.3
CHO	-	-	72

The synthesis of all these novel sulfonic acids calixarenes was in high yield, using the biphasic approach. The chlorosulfonyl intermediates could be intercepted and isolated in good yields when the reaction was performed under anhydrous conditions (Scheme 4.5).

Sulfonation of *p*-benzylcalix[n]arenes using sulfuric acid was unsuccessful, with recovering of starting material from the reaction mixture. When *p*-benzylcalix[n]arene was heated in concentrated sulfuric acid, a product was isolated from the reaction mixture but was difficult to characterise. This may suggest that in the biphasic approach, the chlorosulfonation reaction occurs at the interface with selective attack of the exposed aromatic *para* position of benzyl groups. Similar reasoning is also applicable to the mode of attack of chlorosulfonic acid of the *para* position of the cumyl and phenyl substituents in *p*-cumyl and *p*-phenyl calix[n]arenes, Scheme 4.6 and Scheme 4.7 respectively.



Scheme 4.6

The ^{1}H NMR of these sulfonic acids is in accordance with their assigned structure. For instance, there is an AA'XX' for the aromatic protons of the *para* substituted benzyl groups and a singlet for the aromatic rings constituting the calixarene core along with a broad singlet accounting for both the bridging methylene protons and the methylenes of the *para* benzyl groups, Figure 4.1. The ^{13}C NMR is also consistent with their structure showing a singlet for the carbon of the bridging methylene protons at about 31 ppm and a singlet for the carbon of the methylenes of the *para* benzyl groups at 40 ppm. Furthermore, the ESI-MS analysis shows the presence of the molecular ion $[M+Na]^{+}$ for all these sulfonic acids.

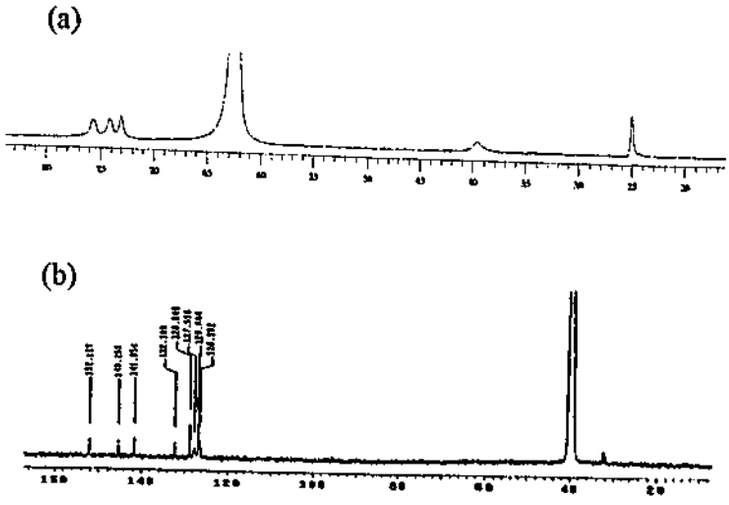


Figure 4.2. (a) ^{1}H NMR spectra of the octa-sulfonic acid of *p*-phenylcalix[8]arene in d_6-DMSO. (b) ^{13}C NMR spectra of the octa-sulfonic acid of *p*-phenylcalix[8]arene in d_6-DMSO.

The sodium sulfonates analogues of all these novel sulfonic acids were prepared in a similar fashion as for the parent sulfonic acids of calixarenes. Titration with 1 *M* sodium hydroxide until pH 7, followed by the removal of water *in vacuo* from the neutralised solution and addition of methanol resulted in precipitation of the sodium salts.

These novel water soluble calixarenes were very difficult to crystallise compared to their *p*-sulfonato-calixarenes analogues, which crystallise readily with many complexes structurally authenticated in the solid state using X-ray diffraction data.[1-11] Their characterisation was obtained by ^{1}H and ^{13}C NMR spectroscopy and mass spectrometry. The amorphous nature (powder X-ray diffraction) of these newly prepared compounds may be due to the extra benzyl, cumyl and phenyl groups attached to the calixarene core, engaging the individual molecules to form large aggregates. These aromatic *para*-substituents in principle extend the cavity, giving rise to more hydrophobic character, altering their chemical behaviour with respect to the parent *p*-sulfonato-calixarenes. For instance, higher coordination metals such lanthanides form precipitates and gels instantaneously with sulfonic acids of benzylcalix[n]arenes. It is likely that these gels are a result of complexation of the metal with the sulfonate groups coordinating a number of *p*-benzylcalixarenes sulfonates *via* electrostatic cohesive forces. The formation of gels is not observed with the *p*-sulfonato-calixarenes.[10]

These novel sulfonated calixarenes also show greater solubility in organic solvents such as acetone, alcohols and tetrahydrofuran. The increased hydrophilicity in these

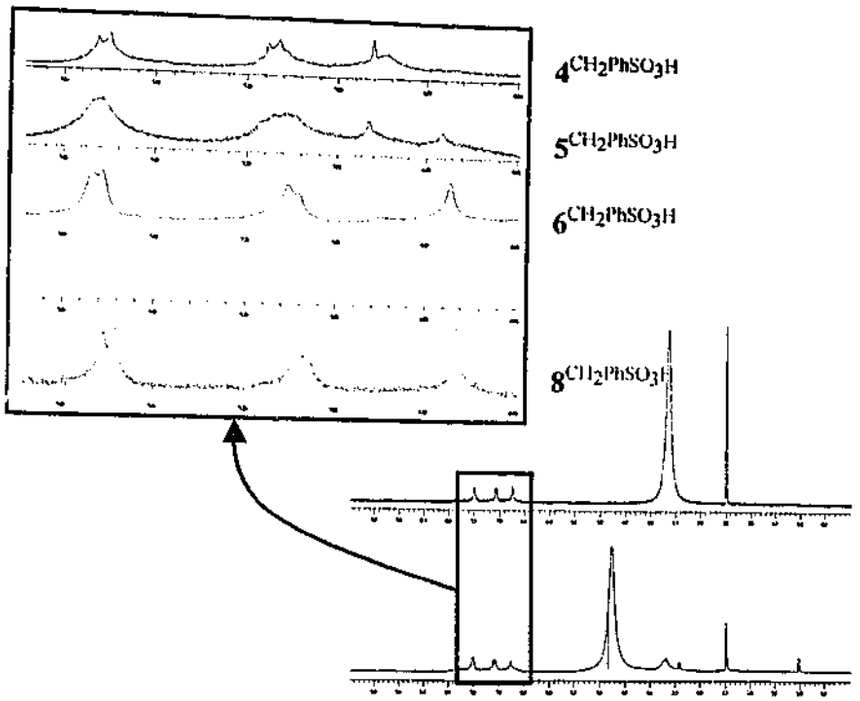
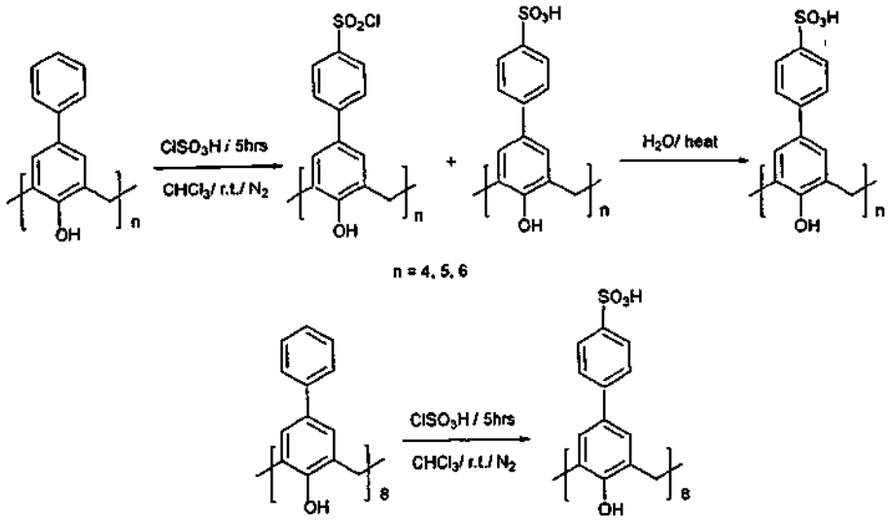


Figure 4.1 300 MHz ^{1}H NMR of the sulfonic acids of *p*-benzylcalix[n]arenes (n = 4, 5 ,6 ,7, 8) in d_6- DMSO.

In a similar fashion, sulfonic acids of *p*-phenylcalix[n]arenes (n = 4 – 8) and *p*-cumylcalix[n]arenes (n = 4, 6) were characterised using ^{1}H and ^{13}C NMR, IR and mass spectrometry. The ^{1}H and ^{13}C NMR of *p*-phenylcalix[n]arenes display similar resonance signals to the parent sulfonic acids of calix[n]arenes with a broad singlet for $ArCH_2Ar$ (~ 4 ppm) and a singlet (~ 7.3 ppm); an AA'XX' system (7.3-7.6 ppm) for the aromatic region and one resonance for the bridging methylene carbons at about 32 ppm Figure 4.2.



Scheme 4.7

sulfonated calixarenes enable them to solubilise large organic chromophore and hydrophobic fullurenes in aqueous medium. Overall, these benzyl, cumyl and phenyl groups extend the surface area for confinement of large guest molecules. The increase in the hydrophobic character to these calixarenes is expected to encourage the hydrophobic host-guest complexation in aqueous media.

4.3 Molecular/Ionic capsules

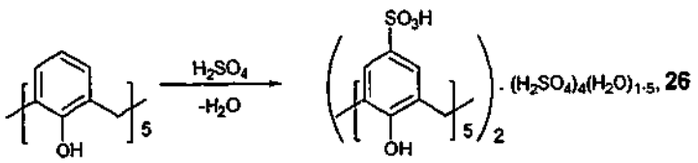
4.3.1 Molecular capsule based on *p*-sulfonato-calix[5]arene

Highly charged water soluble sulfonated calix[4,5,6,8]arenes form a diverse range of complexes and structural types depending on the counter ion/degree of protonation.[2,3,5,8,10,20-27] The bowl shaped *p*-sulfonatocalix[4,5]arenes, can form clay like bilayer structures which show remarkable inclusion properties encompassing ionic guests and molecules[2,3,23] including water in the hydrophobic cavity associated with $H_2O\cdots\pi$-aromatic hydrogen bonding.[5] In addition, *p*-sulfonatocalix[4]arenes forms superanions or ionic capsules in water at low pH in which two calixarenes shroud an 18-crown-6 molecule bearing sodium and two *trans*-water molecules, or a tetra-protonated cyclam molecule, the counter ions being chromium(III) oligomeric species.[8] This work relates to a surge in contemporary studies on the formation of self assembled molecular capsules using hydrogen bonding,[28-35] and the formation of other ionic capsules held together by coordination interactions.[36,39]

Herein the synthesis and structural characterisation of a molecular capsule comprised of two calix[5]arenesulfonic acid molecules which encapsulate two sulfuric acid molecules as a hitherto unknown hydrogen bonded dimmer is described. Treatment of calix[5]arene with sulfuric acid then cooling the brown solution to –15°C for several weeks gave the corresponding *para* substituted penta-sulfonic acid isolated as a mixed sulfuric acid/water adduct, (calix[5]arenesulfonic acid)$(H_2SO_4)_4(H_2O)_{1.5}$, **26**, Equation 4.1. The composition of the material was established from single crystal X-ray diffraction data collected at 123 K from a prismatic crystal of dimensions 0.25 x 0.20 x 0.15 mm. The crystal was mounted on a glass capillary under oil and quickly transferred under a stream of cold nitrogen showing a loss of clarity during mounting, indicating a degree of deterioration. The structure was solved by direct methods with SHELXS-97 and refined by full matrix least-squares on F^2 using SHELXL-97. (Calix[5]arenesulfonic acid)$(H_2SO_4)_4(H_2O)_{1.5}$: $C_{35}H_{49}O_{37.5}S_9$, M_r = 1358.28 g mol^{-1}, triclinic, space group $P\bar{1}$,

a = 11.7770(3), b = 15.9118(4), c = 16.0580(4) Å, α = 105.459(1), β = 90.871(1), γ = 105.767(1)°, U = 2778.68(12) Å^3, Z = 2, ρ_{calc} = 1.623 g cm^{-1}, μ = 0.464 mm^{-1}, 2.6 < 2θ < 55.0, 57663 reflections measured, 12660 unique reflections (R_{int} = 0.073), 7156 observed ($I > 2\sigma(I)$), 846 parameters, 2 restraints, R_1 = 0.1267 (observed data), wR_2 = 0.4012 (all data), S = 1.384. The C-H hydrogen atoms of the calixarene were fixed at geometrically estimated positions with a riding refinement. Two sulfuric acid groups (including the guest molecule) were fully ordered, however other sulfuric acid sites and the waters were disordered and given partial occupancies. Two disordered sulfuric acid groups were modelled with S-O bond lengths restrained to chemically reasonable values.

The samples appeared uniform but attempts to isolate the crystals were compounded by the extremely fragile, hygroscopic and indeed deliquescent nature of the material on their removal from the mother liquor. The decomposed material can be converted to the corresponding sodium salt, as a derivative of compound **26** (yield 50%). NMR studies to ascertain the formation of the capsules in d_6-DMSO and other solvents were inconclusive. While sulfuric acid is normally regarded as the reagent of choice for sulfonating calixarenes, the formation of a sulfuric acid adduct of a calixarene, indeed a host-guest complex, is without precedent.



Equation 4.1

The structure of **26** is shown in Figure 4.3. The compound crystallises in space group $P\bar{1}$ with one supermolecule or molecular capsule, [$(H_2SO_4)_2 \subset$(calix[5]arenesulfonic acid)$_2$], in the unit cell and thus the capsules lie on inversion centres. In addition to the capsule the unit cell contains six sulfuric acid molecules, disordered over several positions with partial occupancies and three water molecules of crystallisation, also disordered, forming an intricate hydrogen bonded network. In contrast the two encapsulated sulfuric acid molecules are fully occupied and show no positional disorder. There are several salient features of the capsule.

The calixarenes are in the cone conformation, although two of the phenol groups disposed in the 1,3 positions in the calixarene ring are noticeably more tilted away from the principle axis of the calixarene than the other phenolic groups. The tilt angles relative to

the plane defined by the five phenolic O-centres are sequentially 150.8, 113.0, 148.7, 125.5 and 123.7°. The most tilted phenol group is hydrogen bonded to a sulfuric acid molecule in the cavity of the calixarene, with O...O separation 2.90 Å. While the precision of the structure precluded location of the hydrogen atoms, the O...O distances in general are indicative of hydrogen bonding interactions.

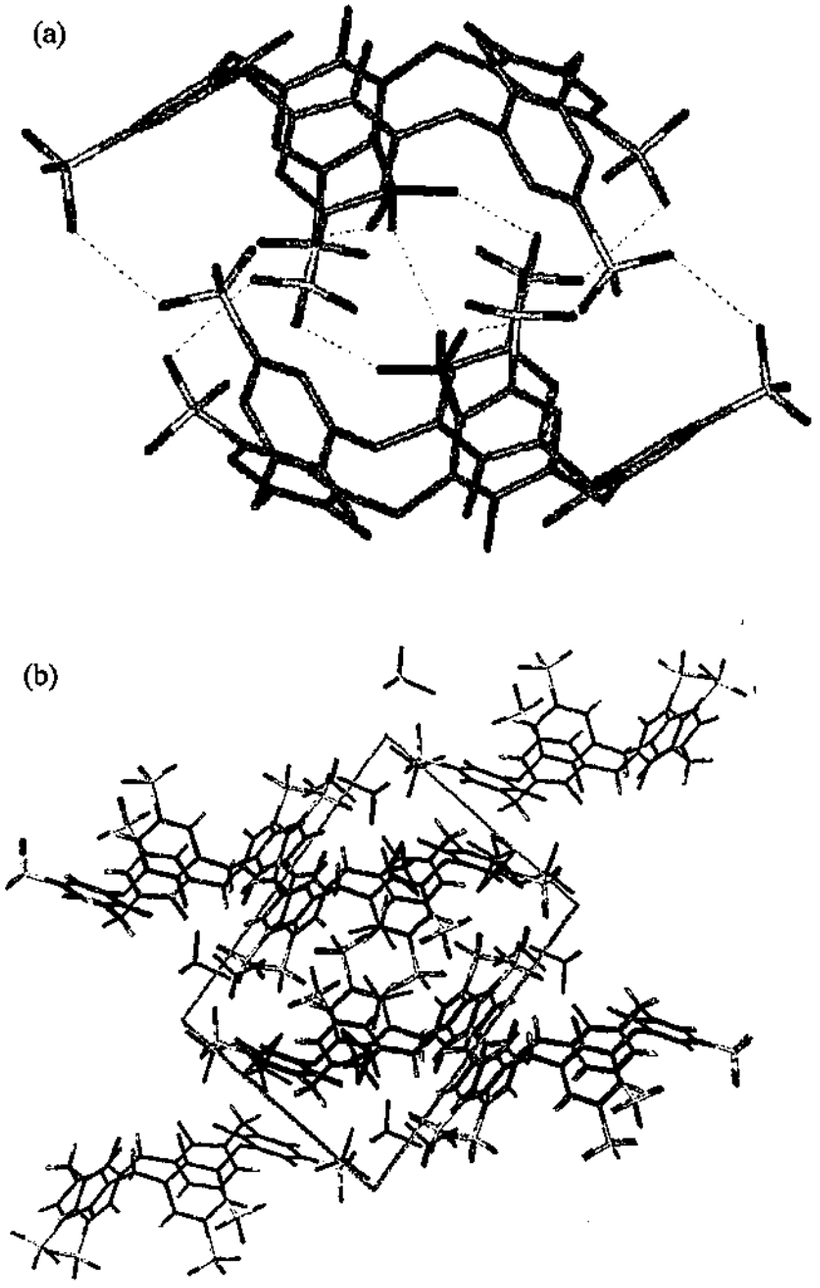


Figure 4.3 (a) Molecular structure of capsule of $[(H_2SO_4)_2 \subset (\text{calix[5]arenesulfonic acid})_2]$; dotted lines represent potential H-bonds, (b) packing diagram with unit cell projection.

Other features of the capsule are that it is flattened in the direction of the principle axes of the calixarenes and that the calixarenes are slipped relative to each other, Figure 4.3. This gives the snug fit of the sulfuric acid dimer in the capsule with one sulfuric acid molecule in each of the cavities of the calixarenes and hydrogen bonding of the sulfonic acid groups of one calixarene with the other. There are four such inter-calixarene (intracapsule) hydrogen bonds, Figure 4.3, at O...O separations 2.63 and 2.65 Å, and this almost results in inter-digitation of the sulfonic acid groups of one calixarene with those of the other calixarene. The binding of the sulfuric acid molecules is driven by four hydrogen bonding interactions per molecule, one for each of the oxygen centres of each sulfuric acid molecule. The oxygen centre residing deepest in the cavity has a hydrogen bond to one of the phenolic O-centres which is skewed furthest from the average cone conformation. Two others are to sulfonic groups of the other calixarene, at 2.38 and 2.79 Å, this also is a manifestation of the flattened nature of the capsule. The other hydrogen bond involves an oxygen atom of its centro-symmetric related sulfuric acid molecule at O...O distance 2.60 Å.

The single hydrogen bond linking the sulfuric acid dimer is particular noteworthy in the context of the structure of crystalline sulfuric acid. Here there is a continuous two dimensional puckered sheet-like array of acid molecules held together by hydrogen bonding interactions such that each oxygen in the tetrahedral arrangement of O-atoms around each sulfur forms a single hydrogen bond to another sulfuric acid molecule (O...O separation 2.62 Å).[40,41] Thus the present structure has two adjacent sulfuric acid molecules interacting with each other through vertices of the tetrahedra analogous to the continuous structure of sulfuric acid itself. Furthermore the S-O...O angles are similar, 109.9 Å *c.f.* 120.4° in **26**. This is also the type of hydrogen bonding in the few sulfuric acid adducts which have been structurally authenticated.[42-45] Alternative hydrogen bonding modes are possible including face-to-face linking of the tetrahedra.

The structure of compound **26** is notably different from that of the corresponding sodium salt where the calixarenes do not form molecular capsules,[2,26] and also a lanthanide complex (see later). This is in direct contrast to the only other structurally authenticated calixarenesulfonic acid, {calix[6]arenesulfonic acid}.23H_2O, which is isostructural with its corresponding Na^+ salt, and has the calix[6]arene in a double partial cone conformation effectively excluding the possibility of capsule formation.[46]

The results herein extend the range of molecular capsules which can be assembled using the principles of supramolecular chemistry, from the initial studies on calix[4]arene[8] to the larger calix[5]arene. Success here suggests that a range of species may be encapsulated, depending on interaction complementarity between the molecules and with calixarenes and between the calixarenes. It is likely that the larger calix[5]arene has greater flexibility, able to form a flattened, slipped structure, as in **26**, or an expanded structure able to encapsulate larger molecules, beyond the crown ether in the above calix[4]arene studies.[8] This may include C_{60} noting that two linked calix[5]arenes can encapsulate the fullerene[47] and there is therefore the possibility of water solublisation of the fullerene at least at low pH to overcome any electrostatic repulsion between ionised calixarenesulfonic acid molecules in the capsule (see later).

4.3.2 Ionic capsule based on *n*-propyloxy-*p*-amino-calix[4]arene and *n*-propyloxy-*p*-sulfonato-calix[4]arene

Molecular/ionic capsules are of interest in building large polyhedral structures similar to those in biological systems, trapping and stabilising molecules, and for novel function such as drug delivery, separation problems and chemical transformations.[28-35] This concept was persuasive in the preparation of ionic capsule based on charged calixarenes, the negatively charged sulfonato-calixarene and the positively charged amino-calixarene.

p-Sulfonato-calix[4]arene is shaped like a truncated cone with hydrophilic upper and lower rims separated by a hydrophobic mid-region. The solid state packing arrangements of structures involving this molecule are dominated by these strongly structure-directing topological and electronic characteristics. Indeed, early work by Atwood *et al.*[2,22] showed that the preferred packing motif in the solid state consists of an up-down arrangement to form bi-layers (Figure 2.3). This arrangement is also consistent with the behaviour of organic compounds in water, where they tend to associate through hydrophobic interactions.[48]

The host-guest complexation of sulfonated calixarenes in water is primarily governed by the charge and by the size of the hydrophobic cavity.[49,50] The charge factor implies that anionic calixarenes tend to bind cationic guest molecule by using negatively charged sulfonates groups or the electron rich cavity whereas cationic calixarenes bind anionic guest molecules. The host-guest interaction requires (but not always) a preorganised cavity to facilitate the inclusion process. In solution, *p*-sulfonato-

calix[4]arene is conformationally mobile and lacks the required predisposed cavity due possibly to the repulsive forces between the anionic sulfonate groups. The ^{1}H NMR spectra at ambient temperature in D_2O is supportive of this flexibility showing a singlet for the bridging methylene protons. Inded this flexibility may favour the inclusion of the guest molecule, although, the building of inonic capsule, such as illustrated in Figure 4.4, requires rigid cavity water soluble calixarenes that can act as a molecular trap for organic guest molecules.

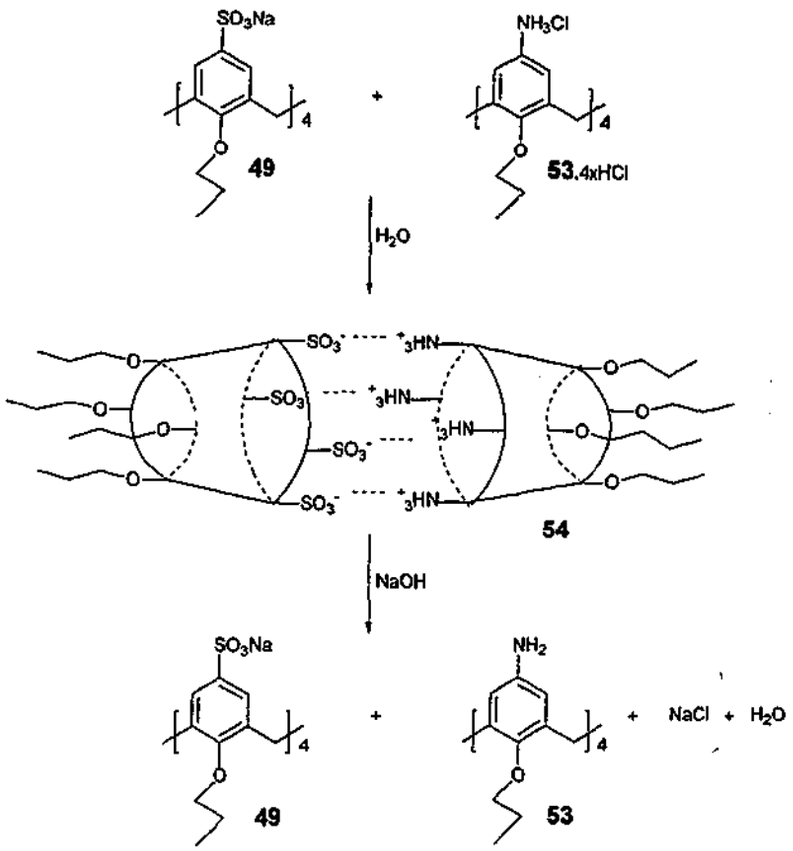
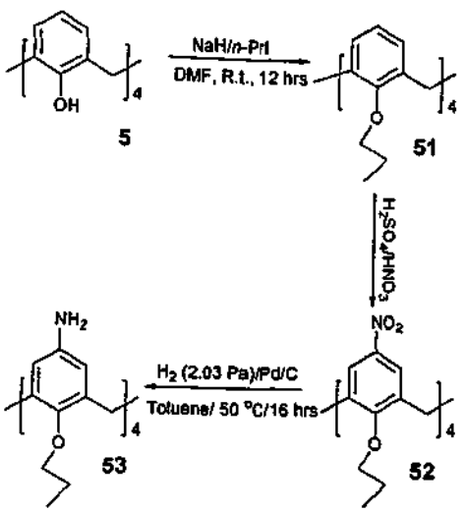


Figure 4.4 Schematic representation of the ionic capsule composed of negatively and positively charged calixarenes showing pH dependency.

The introduction of *n*-propyl groups at the lower rim locks the *p*-sulfonato-calix[4]arene into the cone conformation, achieved using the method illustrated in Scheme 2.4. The cone conformation of the *n*-propyloxy-*p*-sulfonato-calix[4]arene **49** was established by ^{1}H NMR spectroscopy where the methylene protons exhibit a pair of doublets. The synthesis of the amino-calix[4]arene **53** was carried out by nitrating the cone O-*n*-propyloxy-calix[4]arene **51** followed by reduction of the nitro groups, Scheme 4.8.

The prepared amino-calix[4]arene was also confirmed adopting the cone conformation, and was made water soluble by conversion to its hydrochloric salt in 1 *M* hydrochloric acid.



Scheme 4.8

The formation of the ionic capsule was demonstrated by addition of an equi-molar solution of *p*-sulfonato-calix[4]arene **49** and the hydrochloric salt of the *p*-amino-calix[4]arene **53** generated *in situ*. Upon mixing, a white precipitate formed which was collected by filtration and dried in a dessicator overnight to afford the ionic capsule **54**. The solid was insoluble in most solvent and therefore difficult to characterise NMR spectroscopy. IR of the solid shows the presence of $-SO_3^-$ and NH functionalities respective for the two components. The ionic capsule formed redissolves on the addition of base with NMR in basic solution establishing a 1:1 ratio of the two components. Clearly the electrostatic attraction of the two oppositely charged sets of functional groups from different calixarenes (most likely associated with N^+–H···$^-$O–S hydrogen bonding) contribute in the assemble of the proposed capsule.

4.3.3 Capsule based on coordination chemistry

The coordination selectivity exhibited by calixarenes towards rare earth cations has been widely investigated because of its implications for separation science.[51] Particular interest is given to the interactions with a highly charged water soluble *p*-sulfonato-calixarenes.[52,53]

Reaction of Na_5[*p*-sulfonato-calix[5]arene] with lanthanum nitrate hydrate ($La(NO_3)_3.xH_2O$) or ytterbium nitrate hydrate ($Yb(NO_3)_3.xH_2O$) in water resulted in needles upon standing in air for over four weeks in. The crystals of the ytterbium complex were too small for single X-ray structure determination. The stucture of the lanthanum complex (yellow pale crystals) was partially resolved. Difficulties were encountered in obtaining meaningful data for this compound, the structure was refined isotropically, and the R factor is very high. Preliminary results, however, estimate the composition to be [*p*-sulfonato-calix[5]arene]$_2La_2Na_4(H_2O)_{25}$. The unit cell parameters are a = 15.2489(3), b = 18.7219(3), c = 22.1122(4); α = 89.6120(10), β = 71.6060(10), γ = 74.6990(10), V = 5757.70(18); Z = 2.

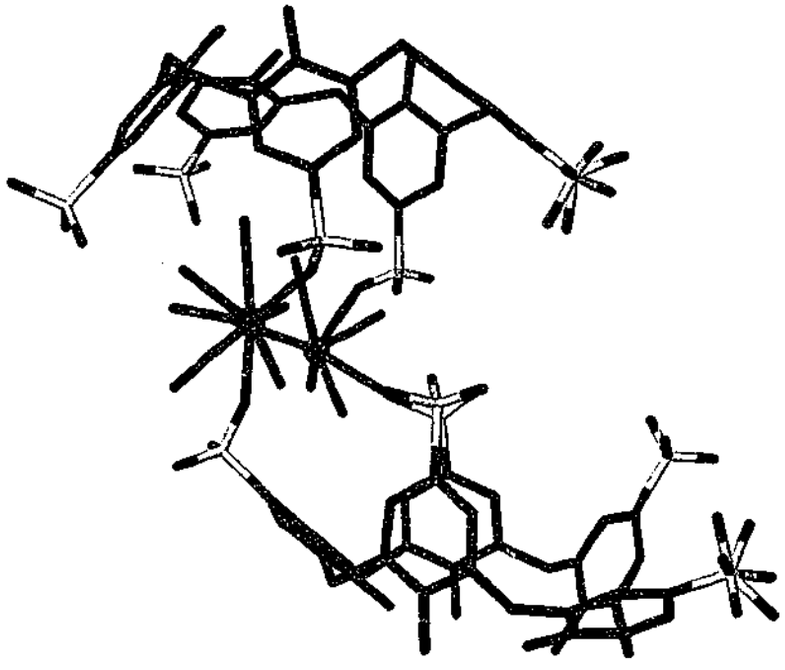


Figure 4.6 Diagram of the partly resolved crystal structure of [*p*-sulfonato-calix[5]arene]$_2La_2Na_4(H_2O)_{25}$ showing lanthanide coordination by calixarene.

The structure here is regarded as a slipped capsule held together by coordination of two lanthanides centres through sulfonate groups, one from each calixarene, Figure 4.6. This contrasts with a more symmetrical capsule held together by hydrogen bonding, for the sulfuric acid encapsulated structure (see above).

4.4 Supramolecular complexation of novel sulfonated calixarenes

In aqueous medium, amphiphilic compounds tend to aggregate so that they can reduce the surface area in contact with water molecules. The energy gain thus obtained is

the origin of the hydrophobic force,[48] which is responsible for the complexation of lipophilic molecules inserted into the central part of the amphiphile. This concept suggests that the shape of the hydrophobic molecule and the aggregation morphology can be partly regulated by the shape of the included guest molecule. In the same context, *p*-benzylcalix[5, 6]arenes sulfonates **37**, **38** and *p*-phenylcalix[5, 6]arenes **45**, **46** are found to form complexes with lipophilic molecules *trans*-β-carotene, astaxanthin and fullerene C_{60} in water, plate 4.1.

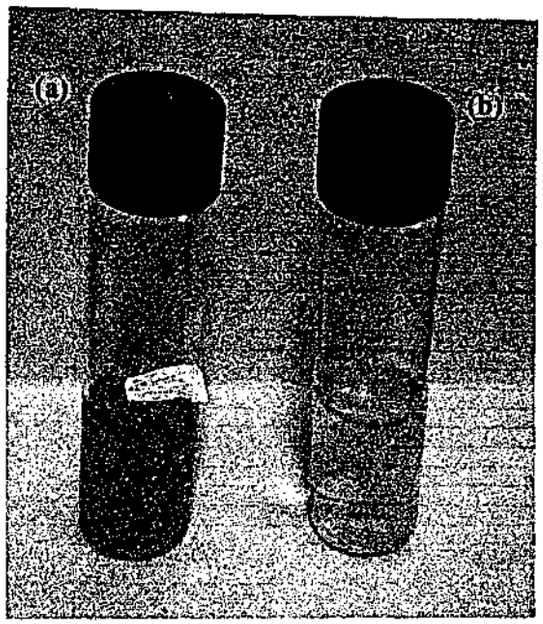


Plate 4.1 (a) Brown transluscent aqueous solution of sulfonated *p*-benzylcalix[5]arene/C_{60} complex, (b) Orange transparent aqueous solution of sulfonated *p*-benzylcalix[5]arene/*trans*-β-carotene complex.

In the lack of conclusive analysis such as X-ray crystallography for these complexes, preliminary results on the type and the mode of the interactions involved were based on IR, UV-vis, ^{1}H NMR and light scattering experiments.

4.4.1 *p*-Benzylcalix[n]arene sulfonates

A set of experiments were carried out involving the mixing of equimolar quantities of *p*-benzylcalix[n]arene sulfonates (n = 4, 5, 6, 7, 8) and *trans*-β-carotene. The solid mixture was ground together until a uniform powder was obtained (*ca.* 1 min). Grinding was continued after adding distilled water for another minute. The resulting slurry was twice filtered with standard filter paper and once with 0.2 μm porosity filter paper affording a clear transparent solution, Figure 4.7. From all the calixarene studied using grinding experiments, only *p*-benzylcalix[n]arene sulfonates (n = 5, 6) **37**, **38** afforded intense coloured orange solutions, Plate 4.1(b). However, *p*-benzylcalix[n]arene sulfonates

(n = 4, 8) take up a trace of *trans*-β-carotene supported by the formation of faint yellow solutions. Likewise, *p*-benzylcalix[5,6]arenes form also complexes with astaxanthin, and they are prepared as for *trans*-β-carotene. Figure 4.8 shows the structure of the rod shaped carotenoid guest molecules consisting of conjugated olefinic backbone.

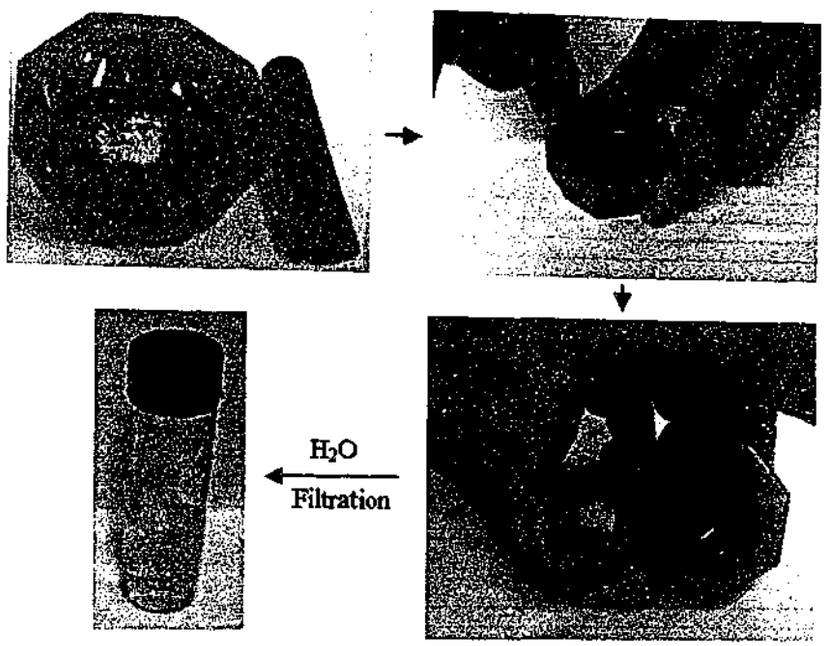
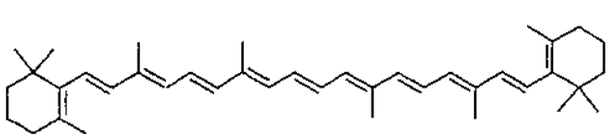
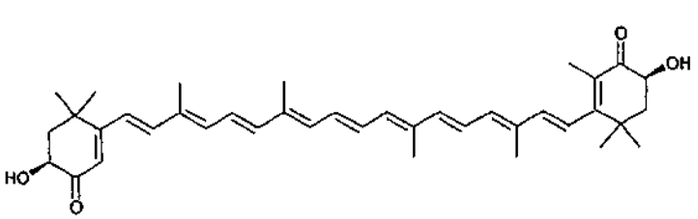


Figure 4.7 Schematic representation of the grinding experiment of sulfonated *p*-benzylcalix[5]arene and *trans*-β-carotene.



trans-β-Carotene



Astaxanthin

Figure 4.8 The structural representation of *trans*-β-carotene and astaxanthin.

Similar results were obtained when grinding *p*-benzylcalix[n]arene sulfonates (n = 5, 6) and C_{60} fullurene for (*ca.* 1 min) resulting in a brown paste, Figure 4.9. Upon addition of distilled water, grinding was continued for an additional minute. The resulting slurry was twice filtered with standard filter paper and once with 0.2 μm porosity filter paper affording brown-yellow solutions of C_{60} in water but not for the other calixarenes, Plate 4.1(a).

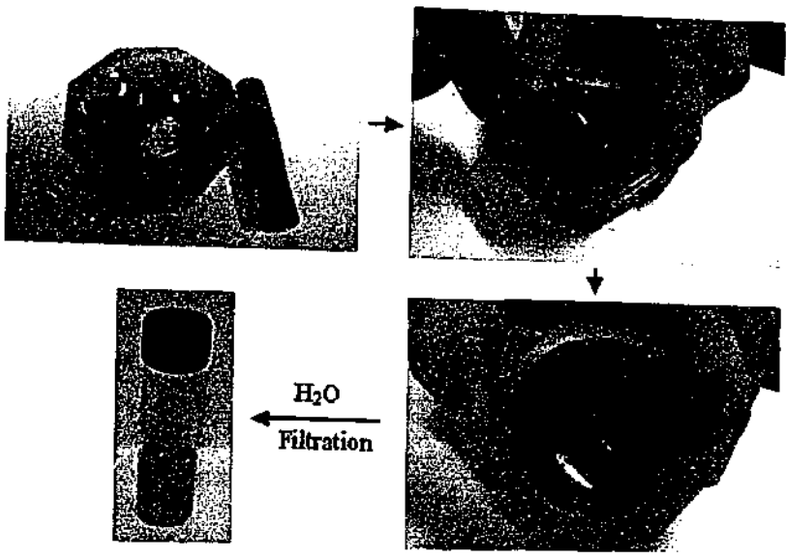


Figure 4.9 Schematic representation of the grinding experiment of sulfonated *p*-benzylcalix[5]arene and C_{60}.

4.4.2 *p*-Phenylcalix[n]arene sulfonates

Sulfonated *p*-phenylcalix[5, 6]arenes show similar interactions with *trans*-β-carotene and C_{60}. The preparation of the complexes of sulfonated *p*-phenylcalix[5, 6]arenes with *trans*-β-carotene and with fullerene C_{60} was achieved by the grinding method described previously for the sulfonated *p*-benzylcalix[5, 6]arenes, Figure 4.7 and Figure 4.9. The carotenoid complexes resulted in bright orange solution clearly containing *trans*-β-carotene in water and brown solution of C_{60} in water. In the *trans*-β-carotene/sulfonated *p*-phenylcalix[6]arene, the UV-vis spectra show the characteristic band of *trans*-β-carotene as shown in Figure 4.10.

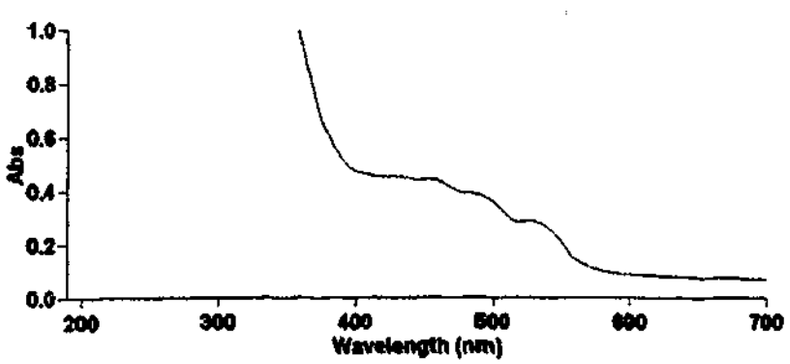


Figure 4.10 UV-vis spectra of sulfonated *p*-phenylcalix[6]arene/*trans*-β-carotene complex in water.

4.4.3 Physical analyses

4.4.3.1 UV-vis spectroscopy

The *trans*-β-carotene complex with sulfonated *p*-benzylcalix[5]arene retains the integerity of the carotenoid, as determined by UV-vis studies which show its characteristic bands without any significant shifts relative to uncomplexed *trans*-β-carotene in methanol. UV-vis experiments for comparison purposes were conducted in methanol since *trans*-β-carotene is insoluble in water, Figure 4.11 (a), (b).

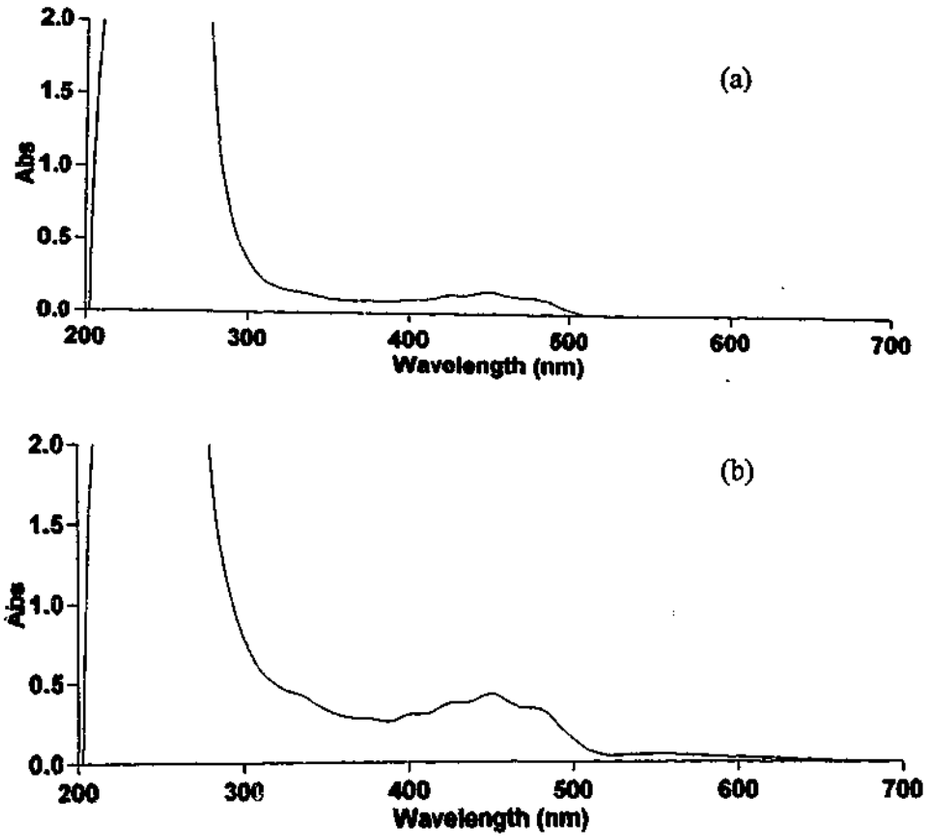


Figure 4.11 (a) UV-vis spectra of *trans*-β-carotene in methanol. (b) UV-vis spectra of sulfonated *p*-benzylcalix[5]arene/*trans*-β-carotene complex in methanol.

In order to establish the composition of the sulfonated *p*-benzylcalix[5]arene /*trans*-β-carotene complex, *p*-benzylcalix[5]arene sulfonate was ground with *trans*-β-carotene at different molar ratios. Upon filtration, the dark red powder, presumably uncomplexed *trans*-β-carotene, were collected and washed with excess of water, dried and weighed. The filtrates were further filtered using 0.2 μm filter paper and the solutions obtained were brought to dryness *in vacuo*. The resuling orange/amber solids were weighed and at all

ratios the uptake of *trans*-β-carotene by the calixarne was estimated at one mole of *trans*-β-carotene to two moles of the calixarenes. UV-vis of these complexes at different molar ratios of *trans*-β-carotene to the calixarene are illustrated in Figure 4.12.

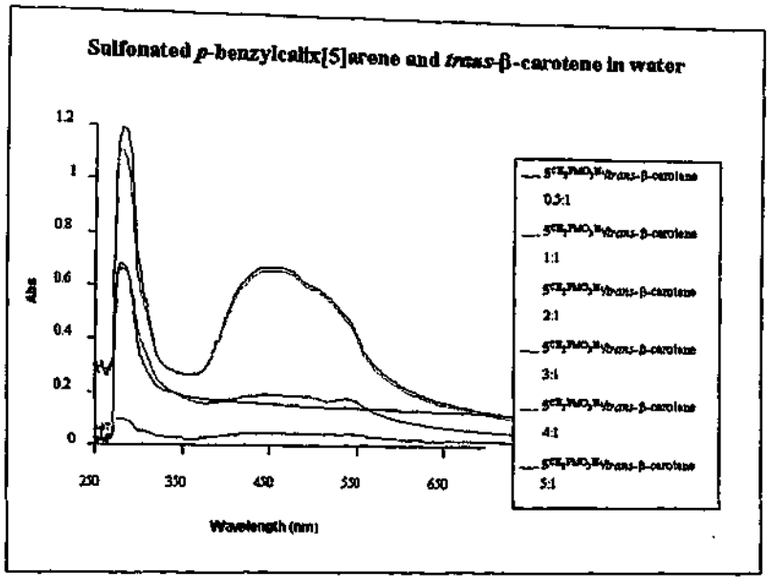


Figure 4.12. UVvis of sulfonated *p*-benzylcalix[5]arene /*trans*-β-carotene complexes at different molar ratios.

The slightly transluscent brown solutions of C_{60} complexes with sulfonated *p*-benzylcalix[5, 6]arenes **37**, **38** and with sulfonated *p*-benzylcalix[5, 6]arenes **45**, **46** were further filtered and the UV-vis spectra of the solutions show the three strong characteristic bands of C_{60} (*i.e.* Figure 4.13). Unfortunately, the solubility limitations of C_{60} particularely in methanol hindered discerning the bands shifts caused by the complex formation. The C_{60} complexes formed show appreciable stability, the solutions retained their brown colour without ocasional precipitations typical of colloidal C_{60} observed with other sulfonated calixarenses $\mathbf{8}^{SO_3H}$, **25** and ocadecane$\mathbf{6}^{SO_3Na}$, **50**.

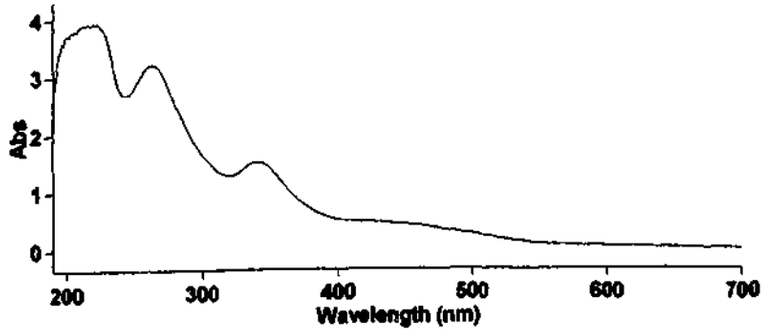


Figure 4.13 UV-vis of sulfonated *p*-benzylcalix[5]arene/C_{60} complex in water.

4.4.3.2 NMR analysis

In order to prove the complex formation and its composition in solution, ^{1}H NMR studies were performed on the *trans*-β-carotene/$5^{CH_2PhSO_3Na}$ complex. The resulted bright orange solution of the complex in water was brought to dryness under reduced pressure affording an orange/amber solid, which was used in the NMR experiment. The ^{1}H NMR spectrum of the complex in D_2O gave broad chemical shifts impeding the analysis of its composition. In contrast, in d_6 DMSO, the chemical shifts become resolved and show the presence of the two components in a nearly 2:1 ratio, Figure 4.14. This finding is consistent with the anticipated encapsulation of *trans*-β-carotene by two $5^{CH_2PhSO_3Na}$ molecules, but is not a definite proof that this is the type of interaction involved. Molecular modelling of the supposed encapsulation mode is depicted in Figure 4.15. Similarly, the ratio of the components in the *trans*-β-carotene/$6^{CH_2PhSO_3Na}$ complex is found to be near 2:1, two sulfonated *p*-benzylcalix[6]arene to one *trans*-β-carotene molecule. Following the same analogy as set previously with alike reservation as to the type of interaction involved, the possible interaction of *trans*-β-carotene with sulfonated *p*-benzylcalix[6]arene derived from molecular modelling experiments is illustrated in Figure 4.16.

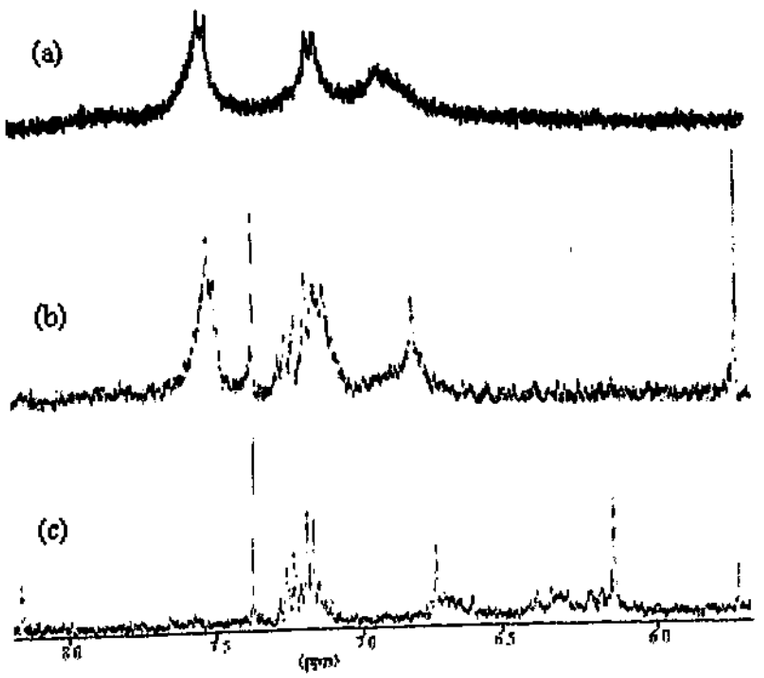


Figure 4.14 300 MHz ^{1}H NMR in d_6 DMSO of depicted region of interest showing (a) $5^{CH_2PhSO_3Na}$ (b) *trans*-β-carotene/$5^{CH_2PhSO_3Na}$ complex, and. (c) *trans*-β-carotene.

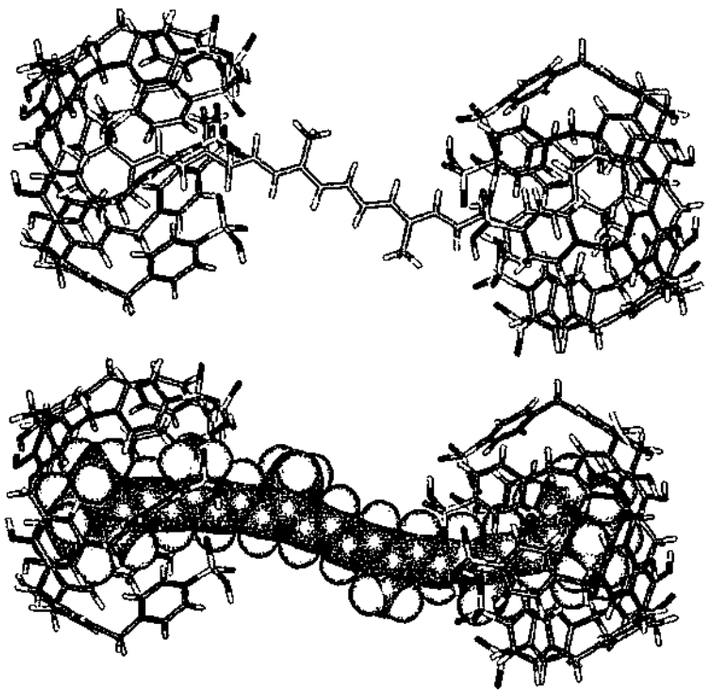
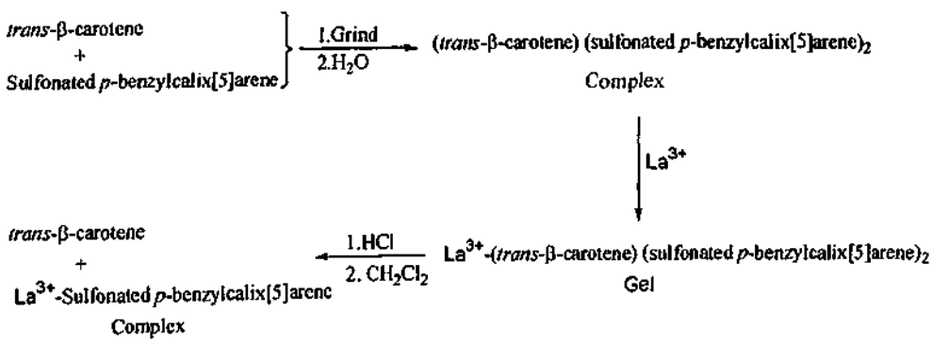


Figure4.15 Molecular model of the possible encapsulation of *trans*-β-carotene with sulfonated *p*-benzylcalix[5]arene.

The stability of the carotenoid *trans*-β-carotene complexes *trans*-β-carotene/$5^{CH_2PhSO_3Na}$ and *trans*-β-carotene/$6^{CH_2PhSO_3Na}$ is striking. Attempt to dissociate these complexes for the retrieval of the carotenoid and to achieve a reversible process was challenging. The extraction methods using an organic solvent were attempted but were unsuccessful. The pursuit in accomplishing the release of the carotenoid from these complexes resulted in a surprising route. Interestingly, the addition of lanthanum salt in the form of $La(NO_3)_3$ to the orange solutions of these complexes resulted in a formation of orange gels instantaneously. The gels were acidified using 1 *M* HCl and by addition of dichlormethane, the extraction of the carotenoid was then achievable, Scheme 4.9.



Scheme 4.9

4.4.3.3 Light scattering

Light scattering measurements using a Brookhaven Instruments with ZetaPlus Particle Sizing Sofware Ver. 2.31, shows that all the aqueous solutions of sulfonated *p*-benzylcalix[n]arenes (n = 4, 5, 6, 7, 8) and sulfonated *p*-phenylcalix[n]arenes (n = 4, 5, 6, 8) were heterogeneous. The particle sizing seems to be consistent using different samples at different concentrations throughout the experiments. Table 4.2 summarises the results obtained from those experiments.

Table 4.2 Results of the particle sizing using light scattering for sulfonated *p*-benzylcalix[n]arenes and sulfonated *p*-phenylcalix[n]arenes.*

Sulfonated calixarene	***Effective Diameter (nm)***	***Sulfonated calixarene***	***Effective Diameter (nm)***	***Sulfonated calixarene***	***Effective Diameter (nm)***
$4^{CH_2PhSO_3Na}$	98	$4^{CH_2PhSO_3H}$	54	4^{PhSO_3H}	60
$5^{CH_2PhSO_3Na}$	225	$5^{CH_2PhSO_3H}$	200	5^{PhSO_3H}	190
$6^{CH_2PhSO_3Na}$	200	$6^{CH_2PhSO_3H}$	174	6^{PhSO_3H}	180
$7^{CH_2PhSO_3Na}$	96	$7^{CH_2PhSO_3H}$	60	8^{PhSO_3H}	145
$8^{CH_2PhSO_3Na}$	144	$8^{CH_2PhSO_3H}$	150	-	-

*Errors ± 10 nm

The complexes obtained from the griding experiments were further filtered using 0.2 μm filter paper and studied using particle size analysis. Molecular modelling of the expected mode of interaction between sulfonated *p*-benzylcalix[6]arene and *trans*-β-carotene is depicted in Figure 4.16

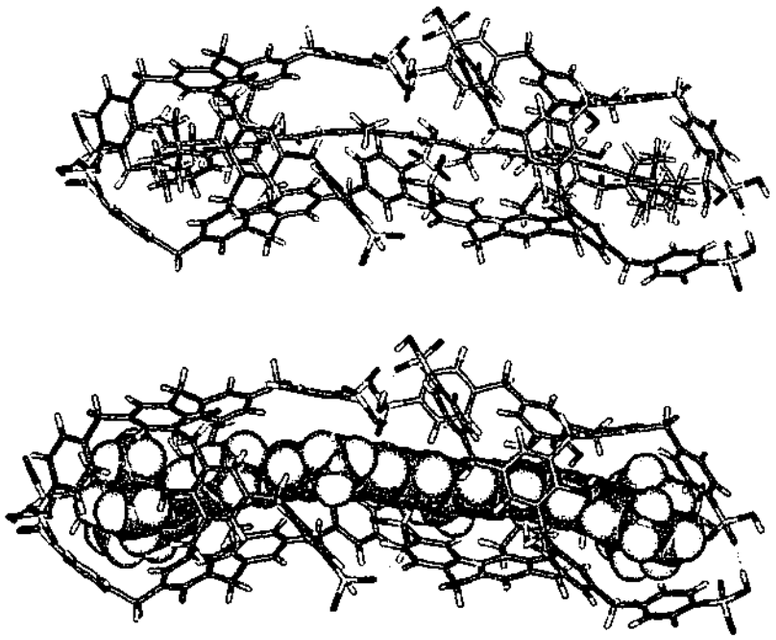


Figure4.16 Molecular model of the possible encapsulation of *trans*-β-carotene with sulfonated *p*-benzylcalix[6]arene.

The particle size distributions in solutions, measured by light scattering indicate that there are other species present with particle size ranging between 30 and 150 nm apart from the effective size of the preponderant specie. The inclusion complex claim arises from the ratio of the components involved (*ca.* 2:1) and the calixarene size preference (sulfonated calix[5,6]arenes). Nevertheless, the acclaimed mode of interaction is inconclusive and more likely require structural authentication for definite proof.

Table 4.3 Effective diameter for sulfonated *p*-benzylcalix[n]arenes with *trans*-β-carotene and with *Asthaxantin.*

Sulfonated calixarene/ trans-β-carotene complex	***Effective Diameter (nm)***	***Sulfonated calixarene/ Asthaxantin complex***	***Effective Diameter (nm)***
trans-β-carotene/**4**^{CH_2PhSO_3Na}	-	*Asthaxantin*/**4**^{CH_2PhSO_3Na}	-
trans-β-carotene/**5**^{CH_2PhSO_3Na}	130	*Asthaxantin*/**5**^{CH_2PhSO_3Na}	137
trans-β-carotene/**6**^{CH_2PhSO_3Na}	140	*Asthaxantin*/**6**^{CH_2PhSO_3Na}	135
trans-β-carotene/**7**^{CH_2PhSO_3Na}	-	*Asthaxantin*/**7**^{CH_2PhSO_3Na}	-
trans-β-carotene/**8**^{CH_2PhSO_3Na}	-	*Asthaxantin*/**8**^{CH_2PhSO_3Na}	-

*Errors ± 10 nm

Table 4.4 Effective diameter for sulfonated *p*-benzylcalix[n]arenes and sulfonated *p*-phenylcalix[n]arenes with C_{60} fullerene.*

Sulfonated calixarene/C_{60} complex	***Effective Diameter (nm)***
$C_{60}/4^{PhSO_3Na}$	-
$C_{60}/5^{PhSO_3Na}$	97
$C_{60}/6^{CH_2PhSO_3Na}$	130
$C_{60}/7^{CH_2PhSO_3Na}$	-
$C_{60}/8^{CH_2PhSO_3Na}$	-

*Errors ± 10 nm

The light scattering experiments reveal that all the sulfonated calixarenes are associated in solution with particle sizes ranging from 54 nm to 200 nm for the sulfonic acids of the *p*-benzyl systems, to 96 to 225 nm for the corresponding sodium salts, Table 4.2. Except for the calix [8]arene system, there is a significant increase in size of the particles for the sodium salts relative to the acids. This may be related to the metal ions effectively linking sulfonated calixarenes together through complexation of sulfonate groups from different supermolecules. In this context it is noted that on addition of lanthanides to the calixarenes (either the acids or the sodium salts) results in the spontaneous formation of gels. This can be explained then by the linking of the aggregates present in solution, beyond complexation within aggregates. Inter- calixarene complexation is highlighted by the structure shown in Figure 4.6, notably the lanthanide complex of *p*-sulfonated calix[5]arene. Moreover, the addition of lanthanide ions to the carotenoid complexes, also affording gels, can be similarly explained, *viz* inter-aggregate complexation as well as intra-aggregate complexation. Perhaps the disruption of the *trans*-β-carotene–calixarene interplay by the lanthanide would explain the release of the guest molecule, as evident by its uptake in an organic solvent (see above), upon addition of the lanthanide.

The light scattering experiments also show a significant reduction in particle size on complexation of the sodium salts of the calixarenes with the carotenoids, but only where there is an appreciable uptake of the carotenoid, notably for the calix[5 and 6]arenes. For

the other systems the particle sizes were not perturbed after treatment with the carotenoids. The same also applies for the complexation of the fullerene.

For the complexes of the carotenoids and C_{60} with the various sulfonated calix[5 and 6]arenes, attempts to grow crystals for X-ray structure determinations were unsuccessful, and in the context of the light scattering experiments revealing large aggregates in solution, this finding is not surprising. Furthermore, removal of the solvent from the solutions containing the host – guest complexes gave what appeared to be glasses. Grinding these residues into powders revealed on X-ray powder diffraction studies that they are amorphous, *i.e.* Figure 4.17(c), and again this is not surprising given the large nano-meter size particles present in solution. Finally attempts to get mass spectrometry data were unsuccessful, using a high resolution fourier transform mass spectrometer. The only peaks present were for the host and guest as separate entities, albeit as metal salts for the former, typical of the originally prepared sodium salts of the calixarenes in question.

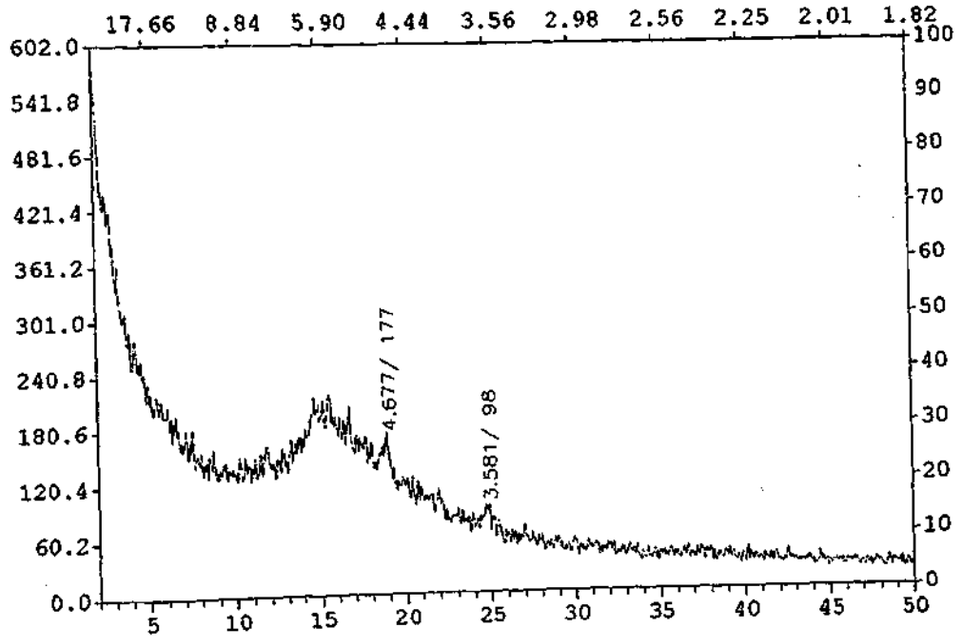


Figure 4.17(a) Powder X-ray diffraction pattern of commercial *trans*-β-carotene.

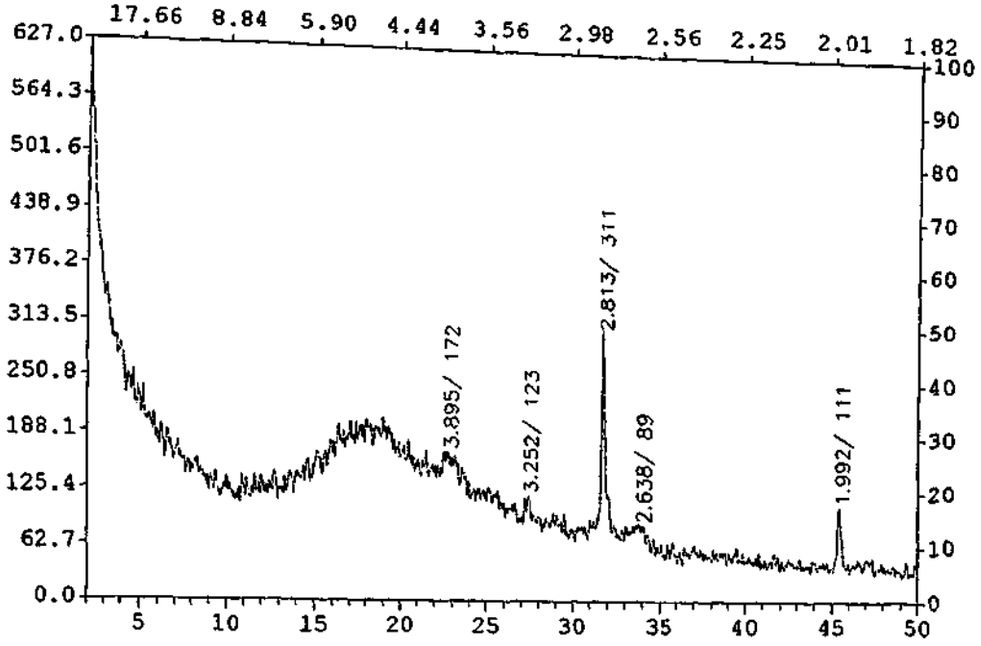


Figure 4.17(b) Powder X-ray diffraction pattern of sulfonated *p*-benzylcalix[5]arene contaminated with NaCl.

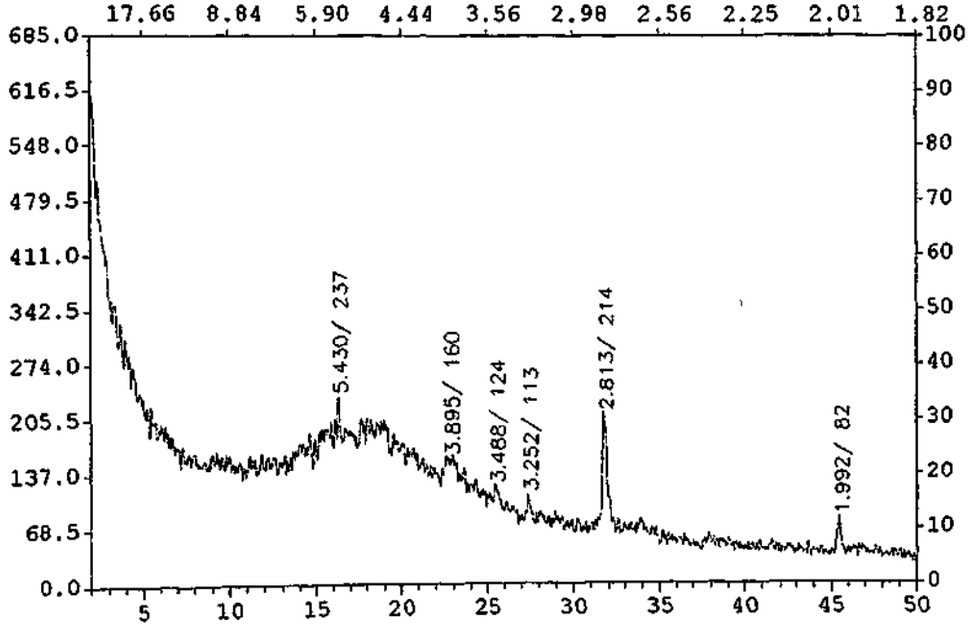


Figure 4.17(c) Powder X-ray diffraction pattern of sulfonate *p*-benzylcalix[5]arene/*trans*-β-carotene complex.

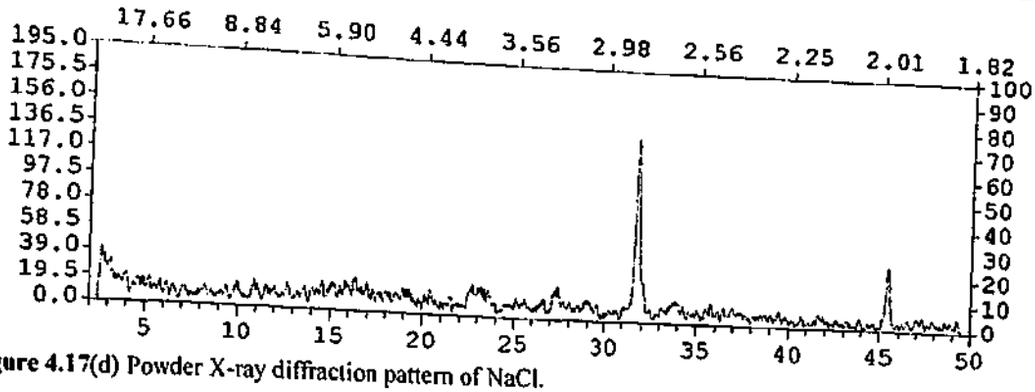


Figure 4.17(d) Powder X-ray diffraction pattern of NaCl.

In turning to a model for the uptake of the caretenoids and fullerenes it is noteworthy that the ratio of host to guest is close to 2:1. For the fullerene case, this can be understood in relation to the structure of the bis-*p*-benzylcalix[5]arene complex of C_{60} which has been structurally authenticated, Figure 4.18.[53]

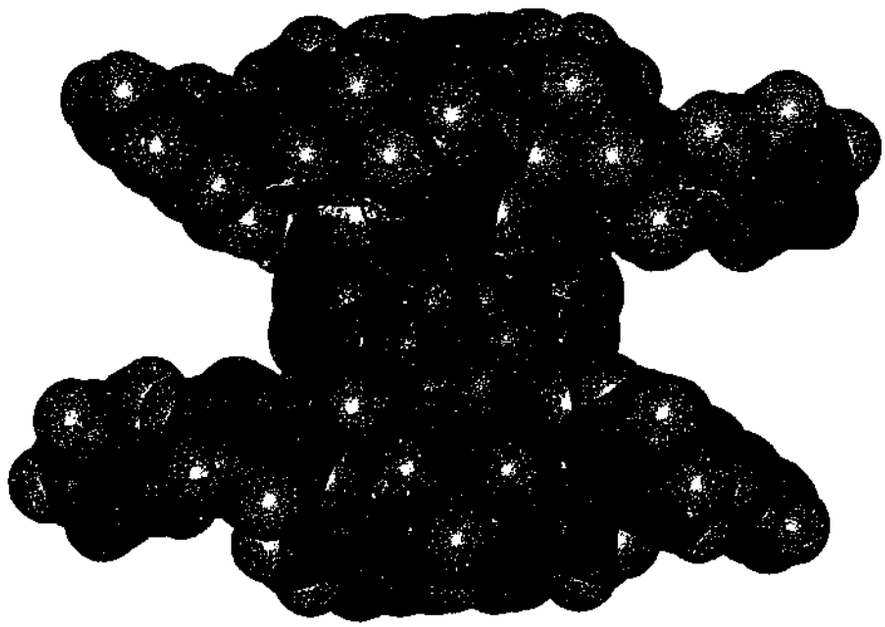


Figure 4.18. The crystal structure of the supermolecule [C_{60} (*p*-benzylcalix[5]arenes)$_2$] showing the encapsulation of C_{60} fullerene by two *p*-benzylcalix[5]arenes.[53]

The two calixarenes shroud the fullerene with the benzyl groups directed away from the core of the supermolecule. If this is the structure of the supermolecule with now the polar sulfonated groups similarly directing away, it is consistent with the 2:1 ratio of the two tectons. There is no structural precedent for carotenoids inclusion complexes with calixarenes, but in order to keep the 2:1 ratio, it is likely that supermolecules are also

present with two calixarenes sourrounding the rod shaped carotenoid. This has been modelled for the sulfonated *p*-benzyl calix[5 and 6]arenes for *trans*-β-carotenene. Thus for both types of included molecules the proposed model is the aggregation of the 2:1 supermolecules into large nano-meter size particles, through hydrophobic-hydrophobic interactions between the calixarenes from adjacent supermolecules, noting the calixarenes have large hydrophobic surface areas, as well as hydrogen bonding interactions, and coordination interplay associated with the sodium ions, Figure 4.19(c). This explains the 2:1 integrity of the host and guest molecules. Alternative models include the aggregation of the caretenoids into a single or multiple arrays surrounded by the sulfonated calixarenes, Figure 4.19(a) and (b) respectively. They can be ruled out on the basis that the ratio is unlikely to be stochiometric, and in the case of the nano-meter size particle of aggregated *trans*-β-carotene surrounded by a layer of sulfonated calixarenes Figure 4.19(a), the ratio of carotenenoid would far exceed that of calixarene, for the size of the particles established.

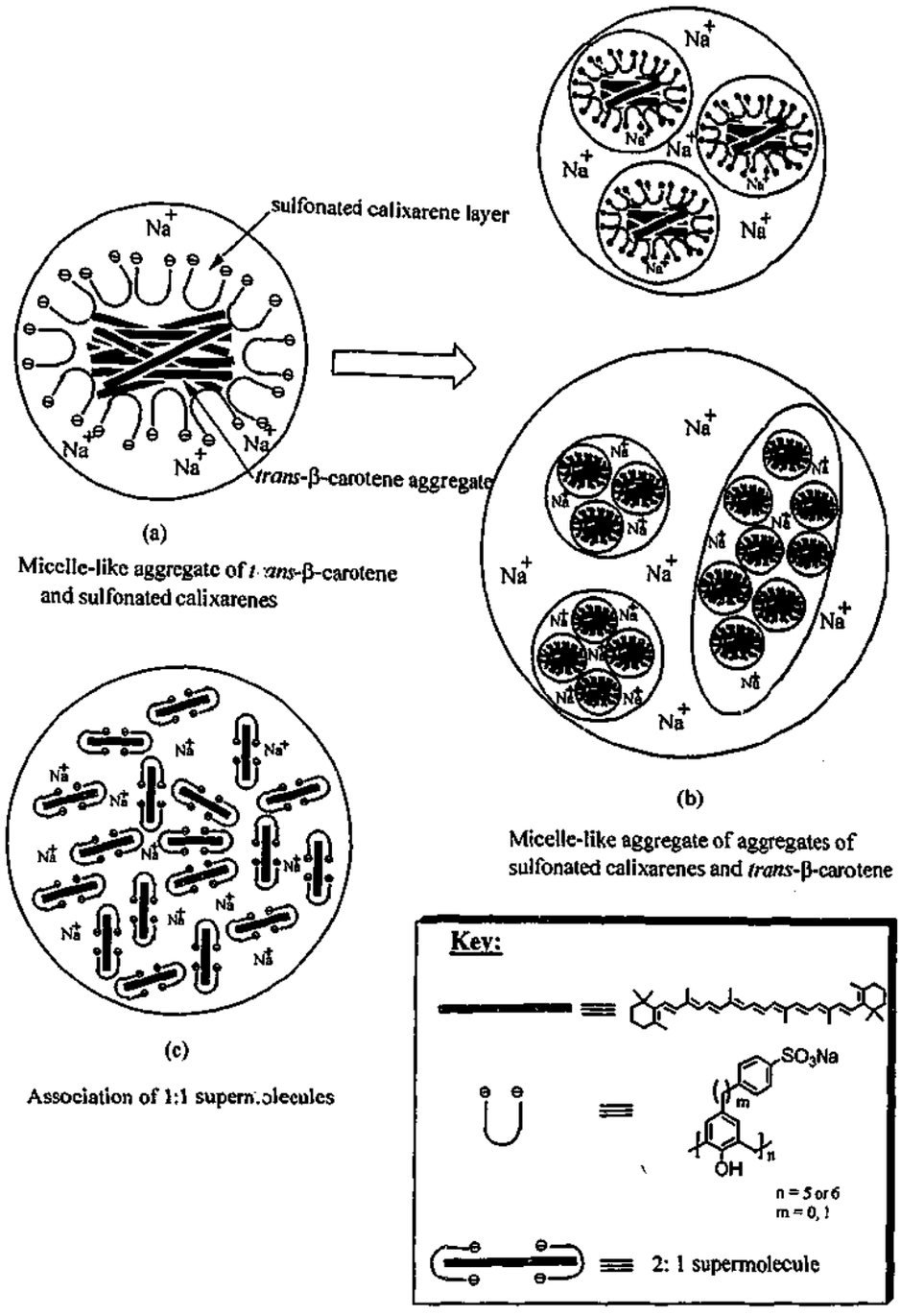


Figure4.18 Models for the the possible encapsulation/aggregation of *trans*-β-carotene with sulfonated *p*-benzyl-, *p*-phenyl-calix[5,6]arene; (a), (b) micellar aggregation and (c) inclusion complex formation and association of the supermolecules by sodium cations.

Overall, significant advances have been made in host – guest chemistry of fullerene C_{60} and carotenoids in water, and a reasonable model has been proposed to understand the chemistry. These findings should lead to other advances in the field of supramolecular chemistry of chromophores and fullerenes. This approach has been recently highlited by the work of Matile in the confinement of carotenoid by β-barrels shaped molecules.[54]

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CONCLUSIONS

5.1 Introduction

The vast majority of biochemical reactions involve a high degree of molecular recognition. The understanding of these recognition processes provides insights into the chemistry of life and may contribute in the design of artificial enzymes. The realisation of molecular recognition by synthetic systems was firstly accomplished by the use of Pederson's crown to discriminate between alkali metal ions, metals involved in physiological processes. This discovery became the starting point for the research for other synthetic macrocycles bearing a cavity and able to perform selective host-guest chemistry such as cryptands and spherands. In the last two decades, bowl-shaped molecules "calixarenes" suitable for inclusion phenomena have been introduced and have attracted interest from a broad spectrum of the chemical sciences and beyond. Calixarenes are cavity-shaped molecules consisting of phenol units, connected *via* methylene groups, to form ring systems which can exists in conformations with cavities. The contribution in this thesis is within the framework of molecular recognition and supramolecular chemistry of calixarenes.

Phenol-aldehyde condensations generally result in the formation of a complex mixture of oligomeric products.[1] However, phenols bearing alkyl groups in the *para* position, under specific reaction conditions, afford the macrocyclic calixarenes. Large scale production from inexpensive starting materials, rational choice of cavity size, high thermal and chemical stability, low solubility in many solvents and low toxicity are features of calixarenes.[1,2,3] These molecules find applications in a variety of fields, for example catalyis, enzyme mimics, chemical analysis, ions selective electrodes, phase transfer agents, complexation and separation of organic molecules, accelerators for instant adhesives, stabilisers for organic polymers, incorporation in polymer structures and environmental cleaning.[1,2,3] Such properties render calixarenes a promising third class of macrocyclic hosts in supramolecular chemistry, together with crown ethers and cyclodextrins.

5.2 Calixarenes hosts of choice

5.2.1 Calixarenes synthesis

Most studies have concentrated on *p*-^{t}Bu-calix[n]arenes (n = 4, 6, 8) since they are readily accessible by the general one pot procedure. In contrast, the direct syntheses of calixarenes derived from other *p*-alkylphenols (*ie* *p*-benzylphenol and *p*-phenylphenol) have not been extensively investigated and are generally formed in low yields,[4,5] and this is an impediment to developing their chemistry. The construction of calixarenes with larger/deeper cavities such as *p*-phenylcalix[n]arenes is of interest in confining large molecules and as an entry to new supramolecular arrays. In this context a good procedure has been developed for the synthesis of *p*-benzylcalix[4]arene and *p*-phenylcalix[4,5]arenes with hydrophobic cavities capable of binding large molecules. The research has also achieved the preparation of calixarenes using 'green' approaches as alternative syntheses. The facile production of *p*-benzylcalix[n]arene systems (n = 5 – 8) using a solvent free method is without precedent. Furthermore, the variation in the amount of base catalyst and the type of the base in this condensation preferentially produces a particular ring size. However, the yields are modest and the fine tunning of the reaction conditions is still needed for better performance. Nevertheless, significant advances have been made in this thesis. The selective production and a facile access of the octamers has allowed the conversion to their tetramer analogues using a solid state Ultra High Intensity Grinding (UHIG) process. The work has also improved the yields of *p*-^{t}Bu-calix[5,10]arenes obtained to 20% and 7% yields respectively.

5.2.2 Functionalised Calixarenes

The design of molecular hosts necessarily requires an understanding of the shape and electronic nature of the target guest. Presently, the large C_{60} is a highly symmetrical (spherical) globular molecule, which is relatively electron deficient. In contrast, linear *trans*-β-carotene is a rigid rod, which is electron rich due to the conjugated polyene chain. This conjugated double bond system is highly reactive and generally makes carotenoids one of the least stable class of the isoprenes. While calixarenes without modifications can achieve the complexation of fullerene C_{60} when the appropriate cavity

size is provided, complexation of β-carotene is rather more demanding and requires a design of a fine tuned host molecule.

The calixarenes produced have been functionalised both at the upper and lower rim generating a great number of new derivatives with promising application in supramolecualr chemistry. The novel sulfonated calixarenes derived from *p*-benzylcalix[n]arene and *p*-phenylcalix[n]arenes in particular have n[illegible]ble properties in solubilising C_{60} fullerene and *trans*-β-carotene in w[illegible]gly, these interactions are observed only for *p*-benzylcalix[5,6]arenes sulfonates and *p*-phenylcalix[5,6]arenes sulfonates, while *p*-benzylcalix[illegible]nd *p*-phenylcalix[4,8]arenes sulfonates have minor effects. The [illegible]n the result is in favour with the inclusion of these molecules within [illegible]lixarenes and that *p*-benzyl- and phenyl-calix[5,6]arenes sulfonates presen[illegible]it. *p*-Benzyl- and phenyl-calix[4,8]arenes sulfonates are either too small or too [illegible] for the inclusion to occur. Furthermore, In the case of *p*-benzylcalix[5,6]arenes and *trans*-β-carotene complexes, the molar ratio between the two components is close to two calixarenes to one *trans*-β-carotene.

In the pursuit of host molecule for complexation of rigid rod type molecule such as *trans*-β-carotene, barrel structures have been synthesised consisting of fused calixarenes. The tubular structure has been confirmed by a solid state authentication for *p*-^{t}Bu-calix[4]arene linked to *p*-^{t}Bu-calix[5]arene. The inclusion of *trans*-β-carotene has not been achieved in organic solvents, although, the inclusion chemistry of these type of compounds has not been fully explored. It is apparent that the water soluble *p*-benzyl and phenyl calix[5,6]arenes sulfonates are better hosts for *trans*-β-carotene and C_{60} fullerene because of the hydrophobic effect (large hydrophobic pocket) encouraging the inclusion process.

5.3 Host-Guest chemistry

The formation of host-guest inclusion complexes in solution and in the solid is the result of a series of interactions, involving the host, the guest and the solvent molecules. The principles behind complex or supermolecule formation are in general governed by the concepts of molecular recognition, notably the structural and the electronic

complementarity between the host and guest molecules. Inclusion host-guest formation further requires a cavity of the appropriate dimensions for inclusion, and for this cavity to be readily available to favourably interact with the guest. Furthermore, the host-guest interactions must be cummulative and abundant to overcome and/or replace guest-guest, host-solvent, guest-solvent, and intramolecular host interactions, particularly in the formation of solid-state complexes, given the inherently weak nature of the host-guest interactions involved. These supramolecular interactions are exemplified in the solid state in the present work by both the inclusion of water in *p*-benzylcalix[4]arene structure and sulfuric acid in the calix[5]arene sulfonic acid capsule. In solution, however, these inclusion or host-guest complexes were difficult to establish. Besides the ball-socket type inclusion of calixarenes, they are also regarded as molecular template for generating topological and directional arrangement of the guest molecules, a feature of great importance in crystal engineering and material science. This is apparent from *p*-benzylcalix[4]arene/C_{60} complex where the C_4 symmetry of *p*-benzylcalix[4]arene imposing the special layered arrangement of C_{60} molecules. The dimension of the cavity of *p*-benzylcalix[4]arene is too small to accommodate C_{60} fullerene and thus results in an *exo*-host-guest complex with C_{60} molecules at the van der Waals limit, arranged in flat sheets, albeit not efficient hexagonal close packing. Similar studies have shown that other calix[4]arenes form *exo*-host-guest interactions, with supramolecular interacalation of C_{60} into a calixarene bilayer.[6-8] It is noteworthy that in contrast, *p*-benzylcalix[5]arene has shown to form inclusion complexes with C_{60} where the fullerene is encapsulated within the calixarene cavity.[9] Hence, the novel *p*-phenylcalix[5]arene with deeper and rigid cavity is favoured becoming a possible host for C_{60} fullerene.

5.4 Future directions

The future work could follow the optimisation of the green approaches for the synthesis of calixarenes. Solventless reactions showed success in the preparation of the kinetically favoured octamers. However, the tetramers requiring more forcing conditions are still low yielding and need further fine tunning of their preparation (*e.g.* UHIG, ionic liquids). In respect to the tubular structures, the synthesis of large barrel shape structures based on calix[5]arene to form divergent receptors should be pursued. The precursors to this fusion have already been prepared and further investigation into the coupling

reaction is required. The preparation of water soluble fused calixarenes is worth considering in exploiting the hydrophobic effect for complexation of large hydrophobic molecules.

The complexation of fullerene C_{60} and *trans*-β-carotene by *p*-benzyl and phenyl calix[5,6]arenes sulfonates merit further study as to the effect of the grinding in the inclusion process. The complexes require further analysis such as electron microscopy and binding constant determinations, although it should br noted that the systems are very complex.

In relation to supramolecular chemistry, *p*-phenylcalix[5]arene with larger and deeper cavity would be a potential candidate for inclusion of fullerene and larger globular molecules. The fused calixarene divergent receptors require testing their inophoric properties and further elaboration of their chemistry.

Overall the research undertaken has made a significant contribution to the calixarenes synthesis, supramolecular chemistry of sulfonated calixarenes and has resulted thus far in four publications (see Appendix).

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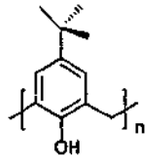
EXPERIMENTAL

General considerations

Reagents and solvents were purchased from Aldrich and used without further purification unless otherwise mentioned. ^{1}H and ^{13}C NMR spectra were performed using Varian 300 MHz or Bruker DRX 300 spectrometers and deuterated solvents were referenced to TMS or TMSP. The infrared spectras were recorded on a Perkin Elmer 1610 FTIR in the range 4000 - 400 cm^{-1} as KBr discs. Mass spectra were recorded on a Bruker BioApex 47e FTMS (4.7 Tesla) fitted with an Analytica electrospray source. Micro-analysis were performed elemental analyses Services (Australia) or (New Zealand). X-ray data was recorded on an Enraf-Nonius KappaCCD or a Siemens SMART CCD diffractometer (173 K).

6.1 Calixarene synthesis

6.1.1 *p-tert*-Butylcalix[n]arenes



1, n = 4
2, n = 5
3, n = 6
4, n = 8

p-^{t}Bu-calix[8]arene, **4** was prepared using a solvent free approach, consisted of heating a slurry of *p*-^{t}Bu-phenol (20.2 g, 134 mmol), NaOH (0.2 g, 5 mml) in 15 ml of formaldehyde at 110 °C for *ca.* 2 hours under a stream of nitrogen. Within few minutes, the heterogenous mixture turned to a pale yellow solution and within one hour, the reaction became viscous as water is removed by means of Dean-Stark-apparatus. Heating and stirring were continued until a thick mass is formed. The reaction was allowed to cool to room temperature affording a hard glassy solid. Trituration of this solid using acetonitrile have precipitated a white solid, which was analysed as *p*-^{t}Bu-calix[8]arene as the sole calixarene, isolated in 30% yield; n = 8, ^{1}H NMR (300 MHz, $CDCl_3$, 30°C, TMS): δ 9.61 (s, 8H, OH), 7.15 (s, 16H, ArH), 4.36 (s, 8H, $ArCH_2Ar$, *J* 15.3 Hz) 3.50 (s, 8H, $ArCH_2Ar$) 1.23 (s, 72H, $C(CH_3)_3$).

p-^{t}Bu-calix[n]arenes, n = 4, 5, 6 were prepared from the above *p*-^{t}Bu-calix[8]arene using an adaptation of the literature procedures:[1,2]

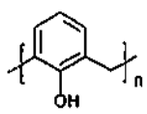
(i) *p*-^{t}Bu-calix[4]arene, **1**: A mixture of *p*-^{t}Bu-calix[8]arene (5 g, 3.85 mmol) and NaOH (0.24 g, 6 mmol) dissolved in 0.5 ml of water was heated to reflux in diphenyl ether (50 ml) for *ca.* 4 hours. The resulting dark brown solution was allowed to cool to room temperature and upon addition of ethyl acetate with additional stirring for 2 hours, resulted in a pale brown crystals which were collected by suction filtration. Further washing with ethyl acetate, followed by recrystallisation from toluene afforded 3 g (60%) of *p*-^{t}Bu-calix[4]arene as glistening crystals. ^{1}H NMR (300 MHz, $CDCl_3$, 30°C, TMS): δ = 10.34 (s, 4H, OH), 7.10 (s, 8H, ArH), 4.30 (s, 4H, $ArCH_2Ar$, *J* 12 Hz) 3.53 (s, 4H, $ArCH_2Ar$) 1.21 (s, 36H, $C(CH_3)_3$).

(ii) *p*-^{t}Bu-calix[5]arene, **2**: A mixture of *p*-^{t}Bu-phenol (11.25 g, 7.48 mmol), paraformaldehyde (7.50 g) and KOH (1.35 g, 2.07 mmol) dissolved in 5 ml of water was heated to reflux in tetralin (150 ml) to 80-85°C and held at this temperature for 1.5 hours under a stream of nitrogen. The reaction flask was then placed in an oil bath preheated to 200°C and the N_2 flow was increased to facilitate the removal of water using a Dean-Stark trap. During this heating period, the internal temperature reached 200°C within 5 min and the colour of the reaction mixture changed from lemon yellow to dark brown as most of the water is eliminated. The reaction mixture was held within 200-210°C range for an additional 3 hours and then allowed to cool to room temperature, whereupon it was filtered and the precipitate was washed with toluene to leave 8 g of an off-white powder. The filtrate was evaporated to dryness *in vacuo* and the residual dark-brown gummy residue was stirred with chloloroform (70 ml) and HCl (1 *M*, 50ml) for half an hour. The biphasic mixture was filtered to give 1 g of a white powder. The chloroform layer was separated and washed with water, dried over $MgSO_4$ and volatiles removed *in vacuo*. The resulting residue was triturated by heating to reflux with acetone (50 ml) for half an hour and filtered hot to leave 0.9 g of white powder. The acetone filtrate was concentrated to 30 ml and allowed to cool to room temperature whereupon small amount of white powder formed and was removed by filtration. The filtrate was allowed to stand for 3 hours, and any subsequent precipitate was removed before refrigerating overnight. At this stage, any additional precipitated powder is removed before storing the filtrate in the freezer (-15°C) for 2 days. *p*-^{t}Bu-calix[5]arene crystallized as

diamond shaped crystals, 1.9 g (15%). ^{1}H NMR (300 MHz, $CDCl_3$, 30°C, TMS): δ = 8.64 (s, 5H, OH), 7.18 (s, 10H; ArH), 3.40-4.20 (br-s, 10H, $ArCH_2Ar$), 1.24 (s, 45H, $C(CH_3)_3$).

(iii) *p*-^{t}Bu-calix[6]arene, **3**: A mixture of *p*-^{t}Bu-phenol (5.0 g, 33 mmol), formaldehyde solution (37%, 7 ml) and KOH (0.75 g, 13.3 mmol) were loaded into a three necked, round bottomed flask equipped with a mechanical stirrer and a Dean-Stark water trap fitted with a condenser. The reaction mixture was stirred and heated to 80-100°C until the mixture became yellow. At this stage, xylene (100 ml) was added and the reaction mixture was stirred and heated to 110°C until all the water had been removed. Then, the reaction mixture was brought to reflux, and a gentle reflux was maintained for 3 hours. The reaction mixture was allowed to cool at room temperature and the white precipitate was filtered and washed with xylene (20 ml). The solid was then dissolved in chloroform (80 ml) and transferred to a separating funnel, washed successively with HCl (1 *M*, 100 ml), H_2O, brine (100 ml) and dried over $MgSO_4$. Chloroform was removed *in vacuo* to *ca.* 20 ml and hot acetone (100 ml) was added. Upon cooling, a white precipitate formed which is filtered to afford *p*-^{t}Bu-calix[6]arene, 3.8 g (75%). ^{1}H NMR (300 MHz, $CDCl_3$, 30°C, TMS: δ 10.50 (s, 6H, OH), 7.15 (s, 12H, ArH), 3.90 (s, 12H, $ArCH_2Ar$), 1.25 (s, 54H, $C(CH_3)_3$).

6.1.2 *p*-H-calix[n]arenes



5, n = 4
6, n = 5
7, n = 6
8, n = 8
9, n = 10

Removal of the *tert*-butyl of *p-tert*-butylcalix[n]arenes (n = 4, 5, 6, 8 and 10) was performed by an adaptation of the literature procedure.[1]

General procedure for the synthesis of p-H-calix[n]arenes: To a heterogenous mixture of a of *p-tert*-butylcalix[n]arene (13.5 mmol) and phenol (18.60 mmol) in anhydrous toluene (100 ml) in the three-necked, round-bottomed flask equipped with a dry N_2 inlet, a mechanical stirrer and a vaccum adaptor with $CaCl_2$ connected to a water aspirator to trap HCl produced during the reaction, was added with vigorous stirring anhydrous $AlCl_3$ (75.02 mmol). Stirring was continued for one hour as the mixture turned deep red with the formation of sticky phase. When TLC showed no presence of starting material and single spot for the product, the reaction mixture was poured into a beaker containing 200 g of crushed ice. The reaction vessel

was rinsed with dichloromethane (100 ml) and crushed ice (*ca.* 100 g) and the washing was added to beaker. After the ice had thawed, the organic phase was separated, washed with 1 *M* HCl (3 x 100 ml), water and dried over $MgSO_4$. Dichloromethane was removed *in vacuo*, and the desired product was precipitated on the addition of diethyl ether (100 ml).

(i) *p*-H-calix[4]arene, **5**: Yield 75%, ^{1}H NMR (300 MHz, $CDCl_3$, 30°C, TMS): δ 10.18 (s, 4H, OH), 7.03 (d, 8H, ArH, *J* 7.6 Hz), 6.95 (t, 4H, ArH, *J* 7.6 Hz), 4.22 (br-s, 2H; $ArCH_2Ar$) 3.60 (br-s, 2H, $ArCH_2Ar$).

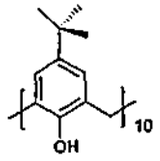
(ii) *p*-H-calix[5]arene, **6**: Yield 72%, ^{1}H NMR (300 MHz, $CDCl_3$, 30°C, TMS): δ 8.92 (s, 5H, OH), 7.22 (d, 10H, ArH, *J* 7.5 Hz), 6.95 (t, 5H, ArH, *J* 7.5 Hz), 3.86 (br-s, 10H, $ArCH_2Ar$).

(iii) *p*-H-calix[6]arene, **7**: Yield 73%, ^{1}H NMR (300 MHz, $CDCl_3$, 30 °C, TMS): δ 10.45 (s, 6H, OH), 7.19 (d, 12H, ArH, *J* 11 Hz), 6.95 (t, 6H, ArH), 3.93 (s, 12H, $ArCH_2Ar$).

(iv) *p*-H-calix[8]arene, **8**: Yield 70%, ^{1}H NMR (300 MHz, $CDCl_3$, 30°C, TMS): δ 9.46 (s, 8H, OH), 7.06 (br-s, 16H, ArH), 6.95 (br-s, 8H, ArH), 4.29 (br-s, 8H, $ArCH_2Ar$), 3.43 (br-s, 8H, $ArCH_2Ar$).

(v) *p*-H-calix[10]arene, **9**: Yield 65%, ^{1}H NMR (300 MHz, $CDCl_3$, 30°C, TMS): δ 9.5 (s, 10H, OH), 7.15 (d, 20H; ArH, *J* 8.3Hz), 6.85 (t, 10H, ArH, *J* 8.3Hz), 3.89 (s, 20H, $ArCH_2Ar$); ^{13}C NMR (300 MHz, $CDCl_3$, 30°C, TMS) δ 32.07 ($ArCH_2Ar$), 122.22 (Ar), 128.30 (Ar), 129.24 (Ar), 149.49 (ArOH). IR: (KBr), ν 567 (w), 751 (s), 833 (w), 908 (w), 959 (w), 1084 (m), 1209 (s), 1256 (s), 1364 (m), 1466 (s), 1592 (m), 2948 (m), 3240 (s) cm^{-1}.

6.1.3 *p-tert*-Butylcalix[10]arene



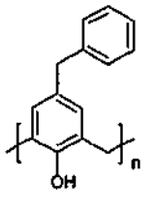
10

The procedure attempted was similar to the literature preparation of *p*-^{t}Bu-calix[5]arene[2] and consist of heating a mixture of *p*-^{t}Bu-phenol (11.25 g, 74.8 mmol), paraformadehyde (7.5 g, 250 mmol) at 80-85°C for 1.5 hours. Upon addition of KOH (1.35 g, 20.7 mmol), the temperature was increased rapidly to 205-210 °C and the reaction mixture

was held at this range for 3 hours. Similar work up procedure was performed as for the isolation of *p*-^{t}Bu-calix[5]arene (12% yield).[2] Successive precipitation with acetone afforded a white solid *p*-^{t}Bu-calix[10]arene in 5% yield, and subsequently the isolation of *p*-^{t}Bu-calix[5]arene (15% yield).

^{1}H NMR (300 MHz, $CDCl_3$, 30°C, TMS): δ 9.21 (s, 5H, OH), 7.12 (s, 10H, ArH), 3.89 (s, 10H, $ArCH_2Ar$), 1.22 (s, 45H, $C(CH_3)_3$); ^{13}C NMR (300 MHz, $CDCl_3$, 30 °C, TMS) δ 34.31 ($C(CH_3)_3$), 32.55 ($ArCH_2Ar$), 31.81 ($C(CH_3)_3$), 125.80 (Ar), 128.05 (Ar), 144.45 (Ar), 147.16 (ArOH).

6.1.4 *p*-Benzylcalix[n]arenes



11, n = 5
12, n = 6
13, n = 7
14, n = 8

The *p*-benzylcalix[n]arenes were prepared by using a modified literature procedure[3] or by a novel solvent free preparation, detailed below:

General procedure for the solvent free syntheses: A mixture of *p*-benzylphenol (20.1 g, 0.109 mol.), 13 ml of formaldehyde solution and catalytic amount of base (sodium hydroxide or potassium hydroxide, introduced as the molar equivalent used of base per mole of the phenolic monomer) was stirred and heated at 110-120°C under a gentle flow of N_2. Within few minutes, the heterogenous mixture turned pale yellow and within one hour the reaction became viscous as water was removed. Heating and stirring were continued until a thick mass formed as a clear beige glassy solid (*ca.* 2 hours). The reaction mixture was allowed to cool to room temperature and the solid heated in a 100 ml of acetonitrile for 15 mins. Upon cooling a white precipitate was formed and collected by filtration and was shown to be *p*-benzylcalix[8]arene. The acetonitrile filtrate was evaporated to dryness *in vacuo* and the residual brown solid dissolved in chloroform (100 ml) and washed successively with HCl (1 *M*, 100 ml), H_2O, brine (100 ml) and dried over $MgSO_4$. Removal of chloroform *in vacuo*, *p*-benzylcalix[n]arenes (n = 5, 6, 7) were separated by fractional crystallisation using acetone.

(i) *p*-benzylcalix[8]arene, **14**: A mixture of *p*-benzylphenol (20.1 g, 0.109 mol.), 13 ml of formaldehyde solution and 0.5 ml of 10 *M* sodium hydroxide (molar ratio of the base to the

phenol 0.045) was stirred and heated at 120°C for *ca.* 2 hours forming a clear beige glassy material). Trituration using acetonitrile gave a white precipitate consisting of *p*-benzylcalix[8]arene as the sole calixarene produced (30%). ^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS): δ = 9.42 (s, 8H, OH), 7.07 (m, 40H, Ph), 6.83 (s, 16H, Ar-H), 3.79 (s, 16H, Ar-CH_2-Ph), 4.22 (d, 8H, Ar-CH_2-Ar), 3.29 (d, 8H, Ar-CH_2-Ar).

(ii) *p*-benzylcalix[7]arene, **13**: Similar procedure was conducted and based on *p*-benzylphenol (20.1 g, 0.109 mol.), 15 ml of formaldehyde solution and 2.8 ml of 10 *M* of potassium hydroxide (0.26 molar ratio of KOH to the phenol). After precipitating *p*-benzylcalix[8]arene present using acetonitrile, the filtrate was dried *in vacuo* and the resulting solid was treated with acetone (30 ml) to precipitate *p*-benzylcalix[7]arene (6.5%). ^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS): δ = 3.83 (s-br, 28H, Ar-CH_2-Ar and Ph-CH_2-Ph), 6.88 (s, 14H, Ar-H), 7.13 (m, 35H, Ph), 10.27 (s, 7H, OH).

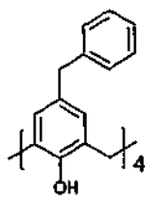
(iii) *p*-benzylcalix[6]arene, **12**: Similar procedure was conducted and based on *p*-benzylphenol (20.1 g, 0.109 mol.), 15 ml of formaldehyde solution and 3.7 ml of 10 *M* of sodium hydroxide (0.34 molar ratio of KOH to the phenol). After precipitating *p*-benzylcalix[8]arene present using acetonitrile, the filtrate was dried *in vacuo* and the resulting solid was triturated with acetone (50 ml) to precipitate *p*-benzylcalix[6]arene (10%). ^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS): δ = 3.81 (s-br, 24H; Ar-CH_2-Ar and Ph-CH_2-Ph), 6.92 (s, 12H; Ar-H), 7.21 (m, 30H; Ph), 10.31 (s, 6H; OH).

(iv) *p*-benzylcalix[5]arene, **11**: Similar approach to the general procedure was conducted using *p*-benzylphenol (20.1 g, 0.109 mol), 15 ml of formaldehyde solution and 3.6 ml of 10 *M* of sodium hydroxide (0.34 molar ratio of KOH to the phenol). The mixture was stirred and heated to 120°C for *ca.* 2 hours until the thick mass had formed. After cooling, *p*-benzylcalix[8]arene was precipitated using acetonitrile and the filtrate was evaporated to dryness *in vacuo*. The residual solid obtained was triturated with acetone (50 ml) to precipitate *p*-benzylcalix[5]arene (15%). ^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS): δ = 3.82 (s-br, 20H; Ar-CH_2-Ar and Ph-CH_2-Ph), 6.93 (s, 10H; Ar-H), 7.21 (m, 25H; Ph), 8.80 (s, 5H; OH).

General procedure for the modified thermal procedure: p-Benzylphenol (19.44 g, 106 mmol) and paraformaldehyde (9 g, 300 mmol) were suspended in tetralin (150 ml) in a 500 ml RBF fitted with a Dean-Stark trap apparatus under a N_2 atmosphere. The mixture was heated to

80°C, at which point aqueous KOH solution (1.4 ml, 14 *M*) was added and the reaction flask was then placed in an oil bath preheated to 200 °C. Within 5 min, the internal temperature reached 200°C and the mixture was kept at this temperature for 4 hours. Upon removal of tetralin *in vacuo*, the remaining caramel coloured product was dissolved in $CHCl_3$ and the solution washed with 1 *M* HCl solution, brine and H_2O. The remaining $CHCl_3$ solution was dried with Na_2SO_4 and removed *in vacuo*. The dark brown product was dissolved and heated in acetone (100 ml) affording a precipitate, which was collected by filtration and shown to be *p*-benzylcalix[8]arene (2.30, 11%). The acetone was removed *in vacuo* and further acetone was added (80 ml). Upon standing, a white precipitate resulted shown to be *p*-benzylcalix[5]arene (3.9 g, 20%). Evaporation followed by acetone addition (80 ml) yielded a precipitate shown to be *p*-benzylcalix[6]arene (3 g, 14%). The filtrate was brought to dryness under *vacuuo* and shown by ^{1}H NMR to be constituted mainly of *p*-benzylcalix[7]arene. The remaining solid was dissolved in 50 ml of acetone and upon refrigerating overnight, a white precipitate deposited, which was shown to be pure *p*-benzylcalix[7]arene (2.50 g, 12%).

6.1.5 *p*-Benzylcalix[4]arene



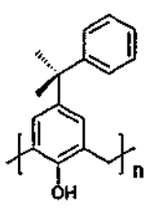
15

p-Benzylcalix[4]arene, **15** was produced in small quantities using the solvent free approach, whereas the thermolysis of *p*-benzylcalix[8]arene gave variable quantities of the calixarene.

A mixture of *p*-benzylphenol (20.1 g, 0.109 mol), 13 ml of formaldehyde solution and 0.5 ml of 10 *M* sodium hydroxide (0.19 g, 0.0049 mol) was stirred and heated at 120°C for *ca.* 2 hours forming a gummy beige material whereupon 165 ml of warm diphenyl ether was added and the contents heated first for 2 hours at 120°C, before ramping the temperature to 260°C over half an hour. Heating to reflux at 260°C was maintained for 3 hours forming a dark amber solution, and the mixture was then allowed to cool to room temperature. Diphenyl

ether was removed *in vacuo* and the viscous material obtained was dissolved in chloroform, washed with washed with 1 *M* HCl (3 x 100 ml), water and dried over $MgSO_4$. Chloroform was removed *in vacuo* affording an amber oil, which crystallizes slowly on standing and upon addition of acetone (150 ml). *p*-Benzylcalix[4]arene was obtained as a micro-crystalline white powder. Yield 60%, m. p. 204.5-205.6°C, MS (ESI^+): m/z 807.34 $[M+Na]^+$, 844.44 $[M(H2O)+K]^+$, $C_{56}H_{48}O_4$ (784.34).^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.39 (d, 4H, Ar-CH_2-Ar, *J* 15 Hz), 3.76 (s, 8H, Ar-CH_2-Ph), 4.18 (d, 4H, Ar-CH_2-Ar), 6.78 (s, 8H; Ar-H), 7.11- 7.30 (m, 20H, Ph), 10.13 (s, 4H, OH), ^{13}C NMR: ($CDCl_3$, 300 MHz) δ 32.1 (Ar-CH_2-Ar), 41.3 (ArCH_2-Ph), 126.2 (Ar), 128.4 (Ar), 128.6 (Ar), 129.0 (Ar) 129.5 (Ar), 134.7 (Ar), 141.3 (Ar), 147.2 (Ar-OH).

6.1.6 *p*-Cumylcalix[n]arenes



16, n = 4
17, n = 6

p-Cumyl-calix[4,6]arenes were prepared using an adaptation of the literature procedure for the synthesis of *p*-benzylcalix[n]arenes.[3]

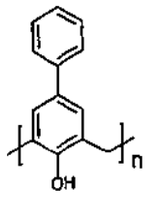
p-Cumylphenol (11.25 g, 53 mmol) and paraformaldehyde (4.5 g, 150mmol) were suspended in tetralin (65 mls) in a 250 ml RBF fitted with a Dean-Stark apparatus under N_2. The mixture was heated to 80°C, aqueous KOH solution (0.7 mls, 14 *M*) was added and the temperature rapidly increased to 200°C. The reaction mixture was kept at this temperature for 4 hours. After allowing the reaction mixture to cool to room temperature, tetralin was removed *in vacuo* and the resulting caramel coloured product was dissolved in chloroform. The chloroform solution was transferred to a separatory funnel and washed successively with 1 *M* HCl solution, brine and H_2O. The chloroform layer was separated and dried over Na_2SO_4. After removal of chloroform *in vacuo*, the resulting dark brown product was dissolved in warm acetone (50 ml) and upon standing, a white precipitate deposited. The solid was collected by filtration and shown to be *p*-cumylcalix[4]arene (1.53 g, 13%). Evaporation of the solvent followed by further addition of acetone (60 ml) yielded a white precipitate upon

standing and was shown to be *p*-cumylcalix[6]arene (1.67 g, 14%). Further standing (2 days) yields a white powder shown to be a mixture of *p*-cumyl[4 and 6]arenes (1.15g).

(i) *p*-Cumyl-calix[4]arene, **16**: ^{1}H NMR (400 MHz, $CDCl_3$, 25°C, TMS): δ = 1.51 (s, 24H, CH_3), 3.34 (d, 4H, Ar-CH_2-Ar, J_{AB} = 13.2 Hz), 4.27 (d, 4H, Ar-CH_2-Ar, J_{AB} 13.2 Hz), 6.85 (s, 8H, Ar-H), 7.11 – 7.25 (m, 20H, Ph), 9.52 (s, 4H, OH); ^{13}C NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 30.7 (CH_3), 31.1 (Ar-CH_2-Ar), 42.3 (Ar-CH_2-Ph), 125.5 (Ar), 126.6 (Ar), 126.8 (Ar), 127.9 (Ar), 128.5 (Ar), 150.4 (Ar(C)-OH); MS (ESI): m/z: 920.3 $[M+Na]^+$; $C_{64}H_{64}O_4$ (897.2): calcd C 85.68, H 7.19; found C 85.67, H 6.21%.

(ii) *p*-Cumyl-calix[6]arene, **17**: ^{1}H NMR (400 MHz, $CDCl_3$, 25°C, TMS): δ = 1.55 (s, 36H, CH_3), 3.37 (br-s, 6H, Ar-CH_2-Ar), 4.08 (br-s, 6H, Ar-CH_2-Ar), 6.86 (s, 12H, Ar-H), 7.12 – 7.26 (m, 30H, Ph), 10.45 (s, 6H, OH); ^{13}C NMR (400 MHz, $CDCl_3$, 25°C, TMS): δ = 31.3 (br, CH_3), 31.3 (br, Ar-CH_2-Ar), 42.7 (Ar-CH_2-Ph), 125.7 (Ar),126.9 (Ar), 127.0 (Ar), 127.8 (Ar), 128.1 (Ar), 150.8 (Ar(C)-OH); MS (ESI): m/z: 1384.3 $[M+K]^+$; $C_{96}H_{96}O_6$ (1344.9): calcd C 85.68, H 7.19%; found C 85.69, H 6.59%.

6.1.7 *p*-Penylcalix[n]arenes



18, n = 4
19, n = 5
20, n = 6
21, n = 8

General procedure for the preparation of p-penylcalix[n]arenes: To a slurry of *p*-phenylphenol (10 g, 58.7 mmol) and 5.5 g of parafomaldehyde in 200 ml of tetralin in a 250 ml round-bottomed flask equipped with a condenser and a Dean-Stark water trap; 2 ml of 15 *M* KOH (26.4 mmol) was added dropwise at 80°C under a stream of nitrogen. The reaction vessel was lowered into a preheated heating mantle at 200°C and kept at this temperature for 2.5 hours. After 1 min the reactants dissolved and after 15min a precipitate began to form. Tetralin was removed *in vacuo* from the cooled reaction mixture and the residue was stirred in 200 ml of warm chloroform containing 2 *M* HCl (250 ml). The chloroform layer was separated, filtered, washed with water and dried ($MgSO_4$) to afford a yellowish solid, after removal of the solvent *in vacuo*. The yellowish solid was triturated in hot methanol, then

filtered to affords 3 g of a beige powder which consisted of a mixture of *p*-phenylcalix[n]arenes (n= 4, 5, 6). The beige solid was then heated in a acetone/methanol mixture (1:0.5) and upon standing 0.80 g (7.4%) of *p*-phenylcalix[6]arene, **20**, precipitated. IR (KBr) ν 3173 cm^{-1} (OH stretching); ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ 4.05 (s-br, 12H, $ArCH_2Ar$), 7.22-7.49 (m, 42H, ArH), 10.57 (s, 6H, OH); ^{13}C NMR (300 MHz, $CDCl_3$, 25°C): δ 32.93 ($ArCH_2Ar$), 127.00 (Ar), 127.15 (Ar), 127.74 (Ar), 128.63 (Ar), 128.84 (Ar), 135.56 (Ar), 140.88 (Ar), 149.35 (Ar-OH), MS (ESI^-): m/z 1091.6 [M-H]; $C_{78}H_{60}O_6$ (1092.43): requires C 85.68, H 5.54; found C 85.40, H 6.30. The filtrate was then evaporated and the residue triturated in acetone/methylene chloride, affording 0.5 g (5%) of a crystalline solid shown to be *p*-phenylcalix[5]arene, **19**. IR (KBr) ν 3282 cm^{-1} (OH stretching); ^1H NMR (300 MHz, $CDCl_3$, 25°C): δ = 4.01 (s-br, 10H, $ArCH_2Ar$), 7.25-7.49 (m, 35H, ArH), 9.11 (s, 5H, OH); ^{13}C NMR (300 MHz, $CDCl_3$, 25°C): δ = 32.14 ($ArCH_2Ar$), 127.00 (Ar), 127.08 (Ar), 127.20 (Ar), 128.36 (Ar), 128.86 (Ar), 135.30 (Ar), 140.88 (Ar), 149.87 (Ar-OH), MS (ESI^+): m/z (%): 933.35 (100) $[M+Na]^+$; $C_{65}H_{50}O_5$ (910.36): requires C 85.68, H 5.54; found C 84.06, H 5.24%, M.P. > 350°C [dec.]. After evaporation of the filtrate, the residue obtained was triturated with acetone affording 1 g (9%) of *p*-phenylcalix[4]arene, **18**. IR (KBr) ν 3200 cm^{-1} (OH stretching); ^1H NMR (300 MHz, $CDCl_3$, 25°C): δ = 3.67 (d, 4H, $ArCH_2Ar$, J_{AB} = 13.5 Hz), 4.38 (d, 4H, $ArCH_2Ar$; J_{AB} = 13.5 Hz) 7.20-7.49 (m, 28H, ArH), 10.43 (s, 4H, OH); ^{13}C NMR (300 MHz, $CDCl_3$, 25 °C,): δ = 31.33 ($ArCH_2Ar$), 127.08 (Ar), 127.12 (Ar), 128.26 (Ar), 128.64 (Ar), 128.90 (Ar), 135.99 (Ar), 140.96 (Ar), 148.69 (Ar-OH), MS (ESI^-): m/z (%): 727.4 (100) $[M-H^+]$; $C_{52}H_{40}O_4$ (728.29): requires C 85.68, H 5.54; found C 85.50, H 6.06.

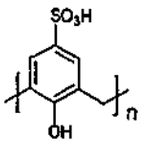
The chloroform insoluble solid recovered by filtration was heated to reflux in methanol for 2 hours and filtered hot to leave a white powder of *p*-phenylcalix[8]arene, **21** (4.1 g, 38%).

IR (KBr) ν 3173 cm^{-1} (OH stretching); ^1H NMR (300 MHz, DMF-d_7, 25 °C): δ 4.06 (s-br, 16H, $ArCH_2Ar$), 7.10 (t, 8H, PhH), 7.20 (t, 16H, PhH), 7.40 (s, 16H, ArH), 7.40-7.44 (m, 16H, PhH), 9.60 - 10.50 (br-s, 8H, OH).

6.2 Calixarene derivatives synthesis

6.2.1 Sulfonated calix[n]arenes

6.2.1.1 Sulfonic acids of calix[n]arenes



22, n = 4
23, n = 5
24, n = 6
25, n = 8

To an ice cooled solution of calix[n]arene in anhydrous dichloromethane (30 ml) was added dropwise 20 equivalents of chlorosulfonic acid ($ClSO_3H$). Stirring was continued at 0 °C for 1 hour after which the ice bath was removed and stirring continued at room temperature overnight. The reaction mixture was poured onto ice water (100 ml), the dichloromethane was removed under reduced pressure and the aqueous phase boiled for 2 hours. The water was then evaporated under reduced pressure and the residue was recrystallised from methanol/acetone to afford the sulfonic acid of calix[n]arene as hydroscopic solids.

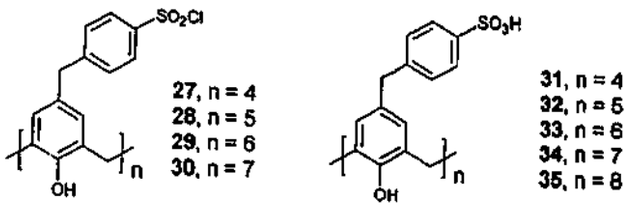
(i) Sulfonic acid of calix[4]arene, **22**: Yield 90%, ^{1}H NMR ($CDCl_3$, 300 MHz, 25°C) δ 7.19 (s, 8H, ArH), 3.60 (s, 8H, $ArCH_2Ar$), ^{13}C NMR ($CDCl_3$, 300 MHz, 25°C) δ 30.64 ($ArCH_2Ar$), 126.66 (Ar), 128.20 (Ar), 135.89 (Ar), 151.60 (Ar).

(ii) Sulfonic acid of calix[5]arene, **23**: Yield 80%, ^{1}H NMR ($CDCl_3$, 300 MHz, 25°C) δ 7.51 (s, 10H, ArH), 3.60 (s, 10H, $ArCH_2Ar$), ^{13}C NMR ($CDCl_3$, 300 MHz, 25°C) δ 29.54 ($ArCH_2Ar$), 125.56 (Ar), 128.30 (Ar), 134.79 (Ar), 151.50 (Ar).

(iii) Sulfonic acid of calix[6]arene, **24**: Yield 80%, ^{1}H NMR ($CDCl_3$, 300 MHz, 25°C) δ 7.04 (s, 12H, ArH), 3.45 (s, 12H, $ArCH_2Ar$), ^{13}C NMR ($CDCl_3$, 300 MHz, 25°C) δ 29.21 ($ArCH_2Ar$), 124.98 (Ar), 127.45 (Ar), 133.87 (Ar), 151.57 (Ar).

(iv) Sulfonic acid of calix[8]arene, **25**: Yield 80%, ^{1}H NMR ($CDCl_3$, 300 MHz, 25°C) δ 7.54 (s, 16H, ArH), 4.05 (s, 16H, $ArCH_2Ar$), ^{13}C NMR ($CDCl_3$, 300 MHz, 25°C) δ 29.54 ($ArCH_2Ar$), 125.24(Ar), 127.13 (Ar), 134.27 (Ar), 152.34 (Ar).

6.2.1.2 Sulfonic acids of *p*-benzylcalix[n]arenes



Synthesis of chlorosulfonyl and sulfonic acid of p-benzylcalix[4]arene, **27** *and* **31**: To a solution of *p*-benzylcalix[4]arene (0.4 g, 0.51 mmol) dissolved in 20 ml of dry dichloromethane, was added dropwise1 ml of chlorosulfonic acid. The biphasic mixture was stirred at room temperature for *ca.* 5 hrs with formation of viscous amber coloured material. The reaction mixture was poured over ice, and the organic phase was separated, treated successively with 1 *M* sodium bicarbonate (x 2), brine solution (x 2), water and dried ($MgSO_4$) affording tetra chlorosulfonyl of *p*-benzylcalix[4]arene, **27**. Yield 56 %, dec. 180 - 195 °C; IR (KBr) ν 3224 (OH), 1173 and 1096 (SO_2 sym.), 1033 and 989 (SO_2 assym.) cm^{-1}; MS (ESI^+): m/z 1201.9 $[M+Na]^+$, 1218.1 $[M+K]^+$, $C_{56}H_{44}O_{12}S_4Cl_4$ (1179.01). ^1H NMR ($CDCl_3$, 300 MHz) δ 3.45 (d, 4H, Ar-CH_2-Ar, J_{AB} 13.2 Hz), 3.87 (s, 8H, Ar-CH_2-Ph), 4.24 (d, 4H, Ar-CH_2-Ar), 6.79 (s, 8H, Ar-H), 7.36 (AA'XX', 8H, Ph-H, *J* 9.6 Hz), 7.94 (AA'XX', 8H, Ph-H), 10.15 (s, 4H; OH); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 32.1 (Ar-CH_2-Ar), 41.3 (ArCH_2-Ph), 127.4 (Ar), 128.7 (Ar), 129.8 (Ar), 130.1 (Ar) 132.7 (Ar), 142.4 (Ar), 147.9 (Ar), 149.7 (Ar-OH).

The aqueous phase was filtered and treated with activated charcoal (x 2) leaving a clear light amber solution. Water was evaporated affording a deliquiscent light gray solid, which was recrystallized from acetone to afford sulfonic acid of *p*-benzylcalix[4]arene, **31**. ^1H NMR (d_6-DMSO, 300 MHz) δ 3.68 (s, 8H, Ar-CH_2-Ph), 4.08 (br-s, 8H, Ar-CH_2-Ar), 6.25 (s. br; COH/SOH, shifts downfield with increasing concentration of H_2SO_4), 6.88 (s, 8H, Ar-H), 7.15 (AA'XX', 8H, Ph-H), 7.53 (AA'XX', 8H, Ph-H), ^{13}C NMR (d_6-DMSO, 300 MHz) δ 49.2 (Ar-CH_2-Ar), 49.5 (ArCH_2-Ph), 126.2 (Ar), 128.7 (Ar), 129.1 (Ar), 129.7 (Ar) 134.2 (Ar), 143.2 (Ar), 145.3 (Ar), 148.2 (Ar-OH); MS (ESI^+): m/z 1105.2 $[M+H]^+$, 1127.2 $[M+Na]^+$, $C_{56}H_{48}O_{16}S_4$ (1104.2); m.p.= dec. 166-170°C.

Data for the chlorosulfonyl of *p*-benzylcalix[5]arene, 28: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.97 (br-s, 20H, Ar-CH_2-Ar and Ar-CH_2-Ph), 6.92 (s, 14H, Ar-H), 7.29 (AA'XX', 10H, Ph-H, *J* 9.3 Hz), 7.78 (AA'XX', 10H, Ph-H), 8.85 (s, 5H; OH).

Data for the chlorosulfonyl of *p*-benzylcalix[6]arene, 29: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.87 (br-s, 24H, Ar-CH_2-Ar and Ar-CH_2-Ph), 6.83 (s, 12H, Ar-H), 7.27 (AA'XX', 12H, Ph-H, *J* 8.3 Hz), 7.84 (AA'XX', 12H, Ph-H), 10.30 (br-s, 6H; OH).

Data for the chlorosulfonyl of *p*-benzylcalix[7]arene, 30: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.95 (br-s, 24H, Ar-CH_2-Ar and Ar-CH_2-Ph), 6.89 (s, 12H, Ar-H), 7.33 (AA'XX', 12H, Ph-H, *J* 8.3 Hz), 7.90 (AA'XX', 12H, Ph-H), 10.37 (s, 7H; OH)

General procedure for the preparation of compounds **32**, **33**, **34** *and* **35**: To an ice cooled solution of *p*-benzylcalix[n]arene in dry dichloromethane (20 ml) was added dropwise 10 equivalents of chlorosulfonic acid. The biphasic mixture was stirred initially at 0°C for half an hour prior to the removal of the ice bath and continuation of stirring at room temperature for *ca.* 5 hours. At this stage, the reaction mixture turned turbid with formation of viscous amber coloured material. The reaction mixture was poured onto ice-cooled water, and dichloromethane was removed *in vacuo*. The remaining aqueous phase was boiled for 2 hours with activated charcoal. Filtration followed by removal of water *in vacuo* gave an amber residue, which was recrystallized from acetone or from a mixture of methanol/acetone to afford the sulfonic acid of *p*-benzylcalix[n]arenes.

Data for the sulfonic acid of *p*-benzylcalix[5]arene: ^{1}H NMR (300 MHz, d_6-DMSO, 25°C): δ = 3.65 (br, 10H, Ar-CH_2-Ar), 3.69 (s, 10H Ar-CH_2-Ph), 6.50 (s-br, COH/SOH, shifts downfield with increasing concentration of H_2SO_4), 6.88 (s, 10H, Ar-H), 7.15 (AA'XX', 10H, PhH, *J* 9Hz), 7.53 (AA'XX', 10H, PhH); ^{13}C NMR (300 MHz, d_6-DMSO, 25°C): δ 31.56 (Ar-CH_2-Ar), 40.50 (ArCH_2-Ph), 126.17(Ar), 128.34 (Ar), 128.6 (Ar), 128.9 (Ar) 132.19 (Ar), 143.6 (Ar), 144.7 (Ar), 149.84 (Ar-OH); IR (KBr) ν 3415 (OH), 1169 and 1121 (SO_3 sym.), 1035 and 1009 (SO_3 assym.) cm^{-1}; MS (ESI^+): m/z 1381.23 $[M+H]^+$, 1403.21 $[M+Na]^+$, $C_{70}H_{60}O_{20}S_5$ (1656.3), m.p.= dec. 230 °C

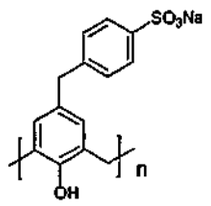
Data for the sulfonic acid of *p*-benzylcalix[6]arene: ^{1}H NMR (300 MHz, d_6-DMSO, 25°C): δ = 3.63 (br, 12H, Ar-CH_2-Ph), 3.67 (s, 12H, Ar-CH_2-Ar), 6.27 (s-br, COH/SOH, shifts

downfield with increasing concentration of H_2SO_4), 6.73 (s, 12H, Ar-H), 7.07 (AA'XX', 12H, PhH, *J* 8.3 Hz), 7.49 (AA'XX', 12H, PhH); ^{13}CNMR (300 MHz, d_6-DMSO, 25°C): δ 31.56 (Ar-CH_2-Ar), 40.50 (ArCH_2-Ph), 126.17 (Ar), 128.34 (Ar), 128.6 (Ar), 128.9 (Ar) 132.9 (Ar), 143.6 (Ar), 144.7 (Ar), 149.8 (Ar-OH); IR (KBr) ν 3497 (OH), 1171 and 1069 (SO_3 sym.), 1033 and 1006 (SO_3 assym.) cm^{-1}; MS (ESI^+): m/z 1679.7 $[M+Na]^+$; $C_{84}H_{72}O_{24}S_6$ (1656.3); m.p.= dec. 265 °C

Data for the sulfonic acid of *p*-benzylcalix[7]arene: ^{1}H NMR (300 MHz, d_6-DMSO, 25°C): δ 3.70 (br, 14H, Ar-CH_2-Ph), 3.73 (s, 14H, Ar-CH_2-Ar), 5.16 (s-br, COH/SOH, shifts downfield with increasing concentration of H_2SO_4), 6.76 (s, 14H, Ar-H), 7.10 (AA'XX', 14H, PhH, *J* 8.2 Hz), 7.52 (AA'XX', 12H, PhH); ^{13}CNMR: (300 MHz, d_6-DMSO, 25 °C): δ 31.03 (Ar-CH_2-Ar), 40.50 (ArCH_2-Ph), 125.75 (Ar), 128 (Ar), 128.2 (Ar), 128.5 (Ar) 129.9 (Ar), 142.9 (Ar), 144.9 (Ar), 150 (Ar-OH); IR (KBr) ν 3420 (OH), 1170 and 1069 (SO_3 sym.), 1031 and 1008 (SO_3 assym.) cm^{-1}; MS (ESI^+): m/z 2010.7 $[M+2K]^+$, $C_{98}H_{84}O_{28}S_7$ (1932.3), m.p.= dec. 191°C

Data for the sulfonic acid of *p*-benzylcalix[8]arene: ^{1}H NMR (300 MHz, d_6-DMSO, 25 °C): δ 3.69 (br, 16H, Ar-CH_2-Ar), 3.75 (s, 16H, Ar-CH_2-Ph), 4.90 (s-br, COH/SOH, shifts downfield with increasing concentration of H_2SO_4), 6.73 (s, 16H, Ar-H), 7.10 (AA'XX', 16H, PhH, *J* 6.6 Hz), 7.54 (AA'XX', 12H, PhH); ^{13}CNMR: (300 MHz, d_6-DMSO, 25 °C): δ 30.9 (Ar-CH_2-Ar), 40.50 (ArCH_2-Ph), 125.6 (Ar), 127.74 (Ar), 127.9 (Ar), 128 (Ar) 132.13 (Ar), 142.78 (Ar), 144.73 (Ar), 149.65 (Ar-OH); IR (KBr) ν 3406 (OH), 1167 and 1123 (SO_3 sym.), 1035 and 1009 (SO_3 assym.) cm^{-1}; MS (ESI^+): m/z 2231.5 $[M+Na]^+$, $C_{112}H_{96}O_{32}S_8$ (2208.36), m.p.= 180°C (dec).

6.2.1.3 Sodium salt of sulfonato-*p*-benzylcalix[n]arenes



36, n = 4
37, n = 5
38, n = 6
39, n = 7
40, n = 8

General procedure: The sodium salt sulfonates of *p*-benzylcalix[n]arenes were prepared by titration of sulfonic acid analogues with 1 *M* sodium hydroxide to neutral pH. Treating the crude with methanol or with ethanol/acetone mixture precipitated the sodium sulfonates of *p*-benzylcalix[n]arenes.

Sodium sulfonates of *p*-benzylcalix[4]arene: ^{1}H NMR (CD_3OD, 300 MHz) δ 3.81 (br-s, 16H, Ar-CH_2-Ar and Ar-CH_2-Ph), 4.82 (s, 4H, COH), 6.90 (s, 8H, Ar-H), 7.22 (AA'XX', 8H, Ph-H), 7.73 (AA'XX', 8H, Ph-H), m.p.= dec. 200 - 210°C.

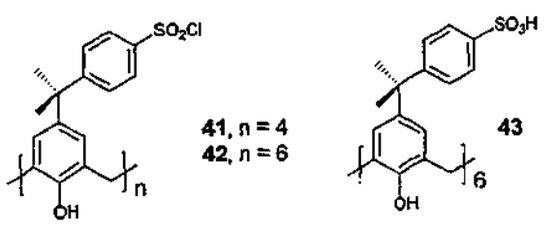
Sodium solfonates of *p*-benzylcalix[5]arene: ^{1}HNMR (300 MHz, d_6-DMSO, 25°C): δ 3.72 (br-s, 20H; Ar-CH_2-Ar and Ar-CH_2-Ph), 6.83 (s, 10H; Ar-H), 7.16 (AA'XX', 10H, Ph-H; *J* 7.3 Hz), 7.52 (AA'XX', 10H, Ph-H); IR (KBr) ν 3459 (OH), 1126 (SO_3 sym.), 1041 and 1011 (SO_3 assym.) cm^{-1}; MS (ESI$^+$): m/z 1527.1 $[M+K]^+$ $C_{70}H_{55}O_{20}S_5Na_5$ (1490.1), m.p.= dec. 300 °C.

Sodium solfonates of *p*-benzylcalix[6]arene: ^{1}HNMR (300 MHz, d_6-DMSO, 25°C): δ 3.72 (br-s, 24H, Ar-CH_2-Ar and Ar-CH_2-Ph), 6.83 (s, 12H, Ar-H), 7.16 (AA'XX', 12H, Ph-H, *J* 9.4 Hz), 7.52 (AA'XX', 12H, Ph-H); IR (KBr) ν 3419 (OH), 1174 (SO_3 sym.), 1069 and 1007 (SO_3 assym.) cm^{-1}.

Sodium solfonates of *p*-benzylcalix[7]arene: ^{1}HNMR (300 MHz, d_6-DMSO, 25°C): δ 3.68 (br-s, 14H, Ar-CH_2-Ar) 3.73 (s, 14H Ar-CH_2-Ph), 6.81 (s, 14H, Ar-H), 7.11 (AA'XX', 14H, Ph-H, *J* 6.6 Hz), 7.54 (AA'XX', 12H, Ph-H), IR (KBr) ν 3441 (OH), 1188 (SO_3 sym.), 1042 and 1011 (SO_3 assym.) cm^{-1}.

Sodium solfonates of *p* -benzylcalix[8]arene: ^{1}HNMR (300 MHz, d_6-DMSO, 25°C): δ 3.72 (br, 32H, Ar-CH_2-Ar and Ar-CH_2-Ph), 6.82 (s, 16H, Ar-H), 7.15 (AA'XX', 16H, Ph-H, *J* 8.6 Hz), 7.52 (AA'XX', 16H, Ph-H), IR (KBr) ν 3461 (OH), 1126 (SO_3 sym.), 1030 and 1011 (SO_3 assym.) cm^{-1}.

6.2.1.4 Chlorosulfonyl and sulfonic acid of *p*-cumylcalix[n]arenes

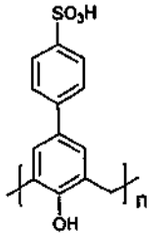


General procedure: To a solution of *p*-cumylcalix[4]arene (0.4g, 0.51 mmol) dissolved in 20 ml of dry dichloromethane, 1ml of chlorosulfonic acid was added dropwise. The biphasic mixture was stirred at room temperature for *ca.* 5 hours with formation of viscous amber coloured material. The reaction mixture was poured over ice, and a white precipitate was collected and shown to be the chlorosulfonyl of *p*-cumylcalix[4]arene, **41**. Yield 70%, MS (ESI^+): m/z 1311.2 $[M+Na]^+$, $C_{64}H_{60}O_{12}S_4Cl_4$ (1288.2); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.30 (s, 24H, CH_3), 3.40 (d, 4H, Ar-CH_2-Ar, J_{AB} 15 Hz), 4.34 (d, 4H, Ar-CH_2-Ar), 6.8 (s, 8H, Ar-H), 7.25 (AA'XX', 8H, Ph-H, *J* 6.1 Hz), 7.75 (AA'XX', 8H, Ph-H), 9.60 (s, 4H; OH).

Data for the chlorosulfonyl of *p*-cumylcalix[6]arene, 42: Yield 60%, MS (ESI^+): m/z 1955.2 $[M+Na]^+$, 1971.0 $[M+K]^+$, $C_{96}H_{90}O_{18}S_6Cl_6$ (1932.3). ^1H NMR ($CDCl_3$, 300 MHz) δ 1.29 (s, 36H, CH_3), 3.45 (br-s, 6H, Ar-CH_2-Ar), 4.13 (br-s, 6H, Ar-CH_2-Ar), 6.86 (s, 12H, Ar-H), 7.38 (AA'XX', 12H, Ph-H, *J* 8.85 Hz), 7.85 (AA'XX', 12H, Ph-H), 10.55 (s, 6H; OH), ^{13}C NMR ($CDCl_3$, 300 MHz) δ 23.5 (CH_3), 29.10 (Ar-CH_2-Ar), 41.6 (Ar-$C(CH_3)_2$-Ph), 123.4 (Ar), 125.2 (Ar), 126.1 (Ar), 126.5 (Ar) 140.3 (Ar), 141.6 (Ar), 149.8 (Ar), 155.0 (Ar-OH).

General procedure for the preparation of sulfonic acids of p-cumylcalix[n]arene: compound **42** was heated to reflux in a mixture of acetone/water (5:1) for 3 hours and filtered hot. The filtrate was concentrated *in vacuo* and the resulting solid was dissolved in hot methanol. Filtration followed by removal of methanol afforded sulfonic acid of *p*-cumylcalix[6]arene, **43**. IR (KBr) ν 3424 (OH), 1180 (SO_3 sym.), 1070 and 1008 (SO_3 assym.) cm^{-1}; ^1H NMR (CD_3OD, 300 MHz) δ 1.27 (s, 36H, CH_3), 3.77(s, 12H, Ar-CH_2-Ar), 5.2 (s-br; COH/SOH, shifts downfield with increasing concentration of H_2SO_4), 6.77 (s, 12H, Ar-H), 7.43 (AA'XX', 12H, Ph-H, *J* 8.7 Hz), 7.85 (AA'XX', 12H, Ph-H)

6.2.1.5 Sulfonic acid of *p*-phenylcalix[n]arene



44, n = 4
45, n = 5
46, n = 6
47, n = 8

General procedure for **44**, **45** *and* **46**: To a solution of *p*-phenylcalix[5]arene (0.4 g, 0.51 mmol) dissolved in 20 ml of dry chloroform was added dropwise 1 ml of chlorosulfonic acid

at 0°C under argon. The mixture was stirred at room temperature for *ca.* 12 hrs to form a bright rose biphasic mixture. This was poured over ice, and the aqueous phase separated and treated with activated charcoal (x 2) leaving a clear light greenish solution. Water was then removed *in vacuo* affording a deliquiscent green solid and upon addition of acetone/methanol mixture a fine gray precipitate formed which was filtered over celite to afford sulfonic acid of *p*-phenylcalix[5]arene.

(i) **Sulfonic acid of *p*-phenylcalix[5]arene:** IR (KBr) ν 2900, 3413 (OH), 1174 (SO_3 sym.), 1007 and 1068 (SO_3 assym.) cm^{-1}; ^1H NMR (300 MHz, d_6-DMSO, 25°C): δ 7.58 (AA'XX', 10H, PhH), 7.46 (AA'XX', 10H, PhH), 7.40 (s, 10H Ar-H), 6.27 (s-br, COH/SOH, shifts downfield with increasing concentration of H_2SO_4), 3.91 (br, 10H; Ar-CH_2-Ar). ^{13}C NMR (300 MHz, d_6-DMSO, 25°C): δ = 31.48 ($ArCH_2Ar$), 126.42 (Ar), 126.66 (Ar), 127.82 (Ar), 128.75 (Ar), 132.40 (Ar), 141.55 (Ar), 145.52 (Ar), 151.75 (Ar-OH).

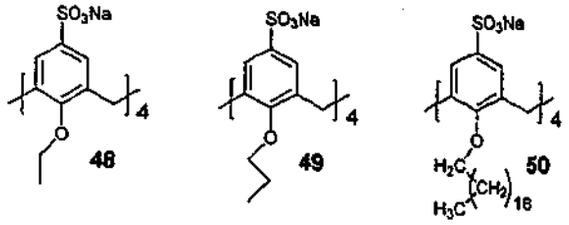
(ii) **Sulfonic acid of *p*-phenylcalix[4]arene:** IR (KBr) ν 2910, 3421 (OH), 1171 (SO_3 sym.), 1004 and 1059 (SO_3 assym.) cm^{-1}; ^1H NMR (300 MHz, d_6-DMSO, 25°C): δ 7.6 (AA'XX', 8H, PhH), 7.4 (AA'XX', 8H, PhH), 7.27 (s, 8H Ar-H), 5.74 (s; COH/SOH, shifts downfield with increasing concentration of H_2SO_4), 4.01 (br-s, 8H; Ar-CH_2-Ar); ^{13}C NMR (300 MHz, d_6-DMSO, 25°C): δ = 31.66 ($ArCH_2Ar$), 125.92 (Ar), 126.70 (Ar), 127.48 (Ar), 128.73 (Ar), 131.90 (Ar), 141.34 (Ar), 146.40 (Ar), 152.80 (Ar-OH).

(iii) **Sulfonic acid of *p*-phenylcalix[6]arene:** IR (KBr) ν 2953, 3441 (OH), 1173 (SO_3 sym.), 1007 and 1067 (SO_3 assym.) cm^{-1}; ^1H NMR (300 MHz, d_6-DMSO, 25°C): δ 7.52 (AA'XX', 12H, PhH; *J* 6.3 Hz), 7.43 (AA'XX', 12H, PhH), 7.32 (s, 12H; Ar-H), 8.75 (s-br, COH/SOH, shifts downfield with increasing concentration of H_2SO_4), 3.85 (br, 12H; Ar-CH_2-Ar); ^{13}C NMR (300 MHz, d_6-DMSO, 25°C): δ 31.68 ($ArCH_2Ar$), 126.25 (Ar), 126.40(Ar), 127.35 (Ar), 128.75 (Ar), 132.95 (Ar), 143.01 (Ar), 145.52 (Ar), 151.70 (Ar-OH).

Preparation procedure of **47:** *p*-phenylcalix[8] arene (2 g, 1.37 mmol) was stirred at 80°C in 10 ml of neat sulfuric acid for *ca* 12 hours, whereupon cooling the reaction mixture was poured over ice, then the aqueous mixture was filtered and treated with activated charcoal (x 2) leaving a clear light greenish solution. Water was removed *in vacuo* affording a deliquiscent light green solid, which was recrystallized from acetone to afford the per-sulfonic

acid of *p*-phenylcalix[8]arene. IR (KBr) ν 2900, 3200 (OH), 1176 (SO_3 sym.), 1006 and 1068 (SO_3 assym.) cm^{-1}; ^1H NMR (300 MHz, d_6-DMSO, 25°C): δ 7.56 (AA'XX', 16H, PhH), 7.42 (AA'XX', 16H, PhH), 7.30 (s, 16H, Ar-H), 6.25 (s-br; COH/SOH, shifts downfield with increasing concentration of H_2SO_4), 3.95 (br-s, 16H, Ar-CH_2-Ar); ^{13}C NMR (300 MHz, d_6-DMSO, 25°C): δ 32.03 ($ArCH_2Ar$), 126.35 (Ar), 126.64 (Ar), 127.55 (Ar), 128.64 (Ar), 132.19 (Ar), 141.65 (Ar), 145.25 (Ar), 152.11 (Ar-OH).

6.2.2 O-alkylated *p*-sodium sulfonato-calix[n]arenes



General procedure for the introduction of alkyl groups at the lower rim of sulfonated calix[n]arenes[4]: To a sodium salt of sulfonated calix[n]arene in water (20 ml) was added an aqueous solution of sodium hydroxide (10 equivalents of NaOH in 10 ml of water). The mixture was stirred until it became homogenous, whereupon a solution of the appropriate alkyl bromide or alkyl iodide (12 equivalents) in DMSO (60 ml) was added and the reaction mixture heated to 80°C for 24 hours. Upon cooling to room temperature the crude product was precipitated upon addition of methanol, which was collected by filtration and dissolved in water (20 ml) and filtered to remove any insoluble material. Volatiles were removed *in vacuo* and the resulting solid washed with hot methanol (x 3) to remove NaBr or NaI by-product. The solid was once again dissolved in water (20 ml) and upon addition of a large volume of ethanol the product precipitated. Filtration followed by drying of the collected solid *in vacuo* afforded the *O*-alkylated derivative of sulfonated calixarene.

Alternative procedure to preparing the O-alkylated sulfonated calix[n]arenes: To an *O*-alkylated derivative of *p*-H-calix[n]arene (*e.g.* **51**) was added a solution of concentrated sulphuric acid (20 ml, 50 equivalents molar excess) and the mixture heated at 80°C for *ca.* 5 hours until no water insoluble material was evident. After cooling, the reaction mixture was poured onto ice-cold water and neutralised with $BaCO_3$. Precipitated $BaSO_4$ was removed by filtration and then Na_2CO_3 was added to the filtrate to exchange the countercation (pH 8-9).

The solution was then treated with charcoal (x 2), filtered hot and the filtrate concentrated *in vacuo*. The resulting residue is dissolved in water (20 ml) and upon addition of ethanol (100 ml) a precipitate formed and filtered off to afford *O*-alkylated derivative of sulfonated calixarene.

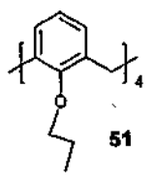
Compound **48**:Yield 54%, ^{1}H NMR (D_2O, 300 MHz, 25°C) δ 1.50 (t, 12H, CH_3, *J* 6 Hz), 3.45 (d, 4H, $ArCH_2Ar$, *J* 12 Hz), 4.05 (q, 8H, OCH_2, *J* 6 Hz), 4.42 (d, 4H, $ArCH_2Ar$), 7.40 (s, 8H, ArH).

Compound **49**:Yield 70%, ^{1}H NMR (D_2O, 300 MHz, 25°C) δ 1.01 (t, 12H, CH_3, *J* 6 Hz), 1.95-2.00 (m, 8H, OCH_2CH_2), 3.40 (d, 4H, $ArCH_2Ar$, *J* 13 Hz), 3.99 (t, 8H, OCH_2, *J* 7 Hz), 4.50 (d, 4H, $ArCH_2Ar$, *J* 13 Hz), 7.33 (s, 8H, ArH).

Compound **50**Yield 40%, ^{1}H NMR (D_2O, 300 MHz, 25°C) δ 0.83 (s-br, 12H, CH_3), 1.10-1.50 (m, 192H, $-(CH_2)_{16}$), 3.92 (br-s, 12H, $ArCH_2Ar$), 4.6 (m, 12H, OCH_2), 7.48 (s, 12H, ArH).

6.2.3 O-alkylated derivatives

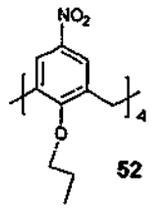
6.2.3.1 *n*-Propyloxy-*p*-H-calix[4]arene



51

The following procedure is representative for the synthesis of several *O*-alkylated *p*-H-calix[n]arene[5]: To a mixture of calix[4]arene (4.0 g, 9.4 mmol) and sodium hydride (3.9 g, 98.0 mmol) in 100 ml of dry *N,N*-dimethylformamide under inert atmosphere, 1-iodopropane (9.2 ml, 94.4 mmol) was added in small portions and the reaction mixture was stirred at room temperature overnight. A 2 *M* HCl (100 ml) was added to the reaction mixture and the resulting precipitate was filtered and the product recrystallised from methanol. ^{1}H NMR ($CDCl_3$, 300 MHz, 25°C) δ 0.94 (t, 12H, CH_3, *J* 7.5 Hz), 1.86 (q, 8H, OCH_2, *J* 7.2 Hz), 3.10 (d, 4H, $ArCH_2Ar$, *J* 13.5 Hz), 3.80 (t, 8H, CH_3, *J* 7.5 Hz), 4.40 (d, 4H, $ArCH_2Ar$), 6.50 (t, 4H, ArH, *J* 6 Hz), 6.55 (d, 8H, ArH, *J* 6 Hz).

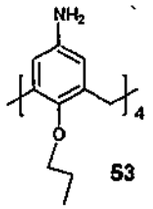
6.2.3.2 *n*-Propyloxy-*p*-nitro-calix[4]arene



52

The following nitration procedure was adapted from literature procedure for several tetra-alkoxy-calix[4]arene[6]: To a cooled dichloromethane solution of *n*-propyloxy of *p*-H-calix[4]arene (0.53 g, 0.9 mmol) and concentrated sulfuric acid (1.1 ml, 14.3 mmol), 1.5 ml of nitric acid (70%) was added at 0°C and the reaction mixture stirred until the dark red colour disappears. The reaction mixture was poured into 100 ml of water and the organic layer separated and dried over Na_2SO_4. Filtration of the sodium sulfate and removal of the solvent *in vacuo* resulted in an orange soild. The residue was recrystallised from methanol to afford the tetra-*n*-propyloxy-tetra nitro-calix[4]arene in 80% yield. ^{1}H NMR ($CDCl_3$, 300 MHz, 25°C) δ 1.01 (t, 12H, CH_3, *J* 7.5 Hz), 1.90 (q, 8H, OCH_2CH_2, *J* 7.5 Hz), 3.41 (d, 4H, $ArCH_2Ar$), 3.96 (t, 8H, OCH_2-, *J* 7.2 Hz), 4.53 (d, 4H, $ArCH_2Ar$), 7.60 (s, 8H, ArH).

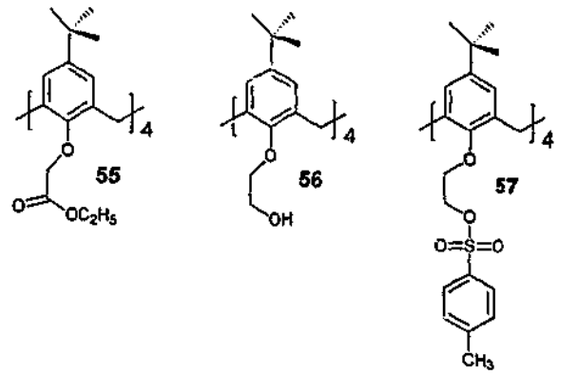
6.2.3.3 *n*-Propyloxy-*p*-amino-calix[4]arene



53

n-Propyloxy-*p*-nitro-calix[4]arene (0.034 g, 0.044 mmol) and 0.023 g of 10% Pd/C in toluene (30 ml) were placed in an autoclave under a 2.03 Pa hydrogen pressure at 50 °C for 16 hours. After cooling and filtration of the catalyst, the resulting amber solution was evaporated to dryness to leave an amber residue. The residue was recrystallised from methanol affording the tetra-*n*-propyloxy tetra amino-calix[4]arene in 70% yield. IR (KBr) ν 3345, [2968, 2925, 2873, 2850] (NH), 1608, 1468 (NH) cm^{-1}, ^{1}H NMR ($CDCl_3$, 300 MHz, 25°C) δ 0.89 (t, 12H, CH_3, *J* 7.3 Hz), 1.78 (q, 8H, OCH_2CH_2, *J* 7.5 Hz), 2.85 (d, 4H, $ArCH_2Ar$, *J* 13.5 Hz), 3. 24 (br-s, 8H, -NH_2), 3.65 (t, 8H, OCH_2-, *J* 7.3 Hz), 4.25 (d, 4H, $ArCH_2Ar$, *J* 13.5 Hz), 6.06 (s, 8H, ArH).

6.2.3.4 O-alkylated *p*-^{t}Bu-calix[4]arene derivatives



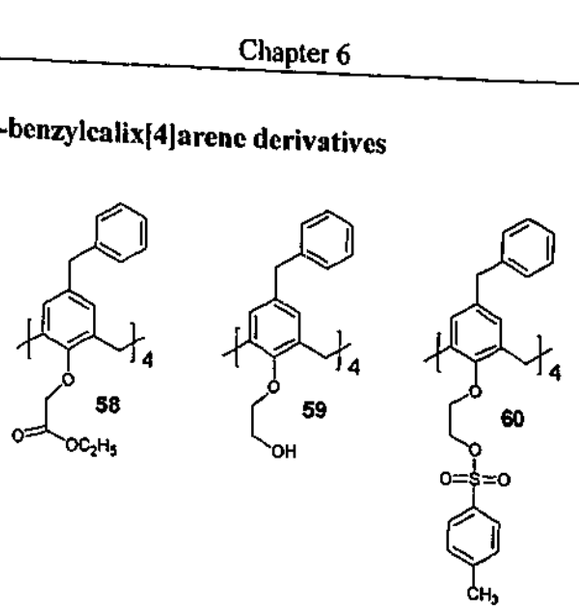
Compound **55**, **56** and **57** were prepared following the literature procedure.[7,8]

Compound **1** furnished **55** in 75% yield, ^{1}H NMR (300 MHz, $CDCl_3$, 30°C, TMS): δ 1.05 (s, 36H, $C(CH_3)_3$), 1.24 (t, 12H, $-CH_3$, *J* 7.2 Hz), 3.15 (d, 4H, Ar-CH_2-Ar, *J* 13.2 Hz), 4.15 (q, 8H, OCH_2CH_3, *J* 7.2 Hz), 4.78 (s, 8H, $ArOCH_2$-), 4.80 (d, 4H, Ar-CH_2-Ar) 6.75 (s, 8H, Ar-H).

Compound **55** furnished **56** in 85% yield, ^{1}H NMR (300 MHz, $CDCl_3$, 30°C, TMS): δ 1.06 (s, 36H, $C(CH_3)_3$), 3.18 (d, 4H, Ar-CH_2-Ar, *J* 12.9 Hz), 3.25 (br-s, 4H, OH), 3.97 (q, 16H, -OCH_2CH_2O-, *J* 3.6 Hz), 4.30 (d, 4H; Ar-CH_2-Ar, *J* 12.9 Hz), 6.83 (s, 8H;Ar-H).

Compound **56** furnished **57** in 86% yield, ^{1}H NMR (300 MHz, $CDCl_3$, 30°C, TMS): δ 1.03 (s, 36H, $C(CH_3)_3$), 2.41 (s, 12H, O_3SAr-CH_3), 3.00 (d, 4H, Ar-CH_2-Ar, *J* 12.9 Hz), 4.06 (t, 8H; O-CH_2CH_2OTos, *J* 4 Hz), 4.20 (d, 4H, Ar-CH_2-Ar), 4.39 (t, 8H, O-CH_2CH_2OTos, *J* 4 Hz) 6.65 (s, 8H; Ar-H), 7.27 (AA'XX', 8H, SO_3ArH, *J* 8.4 Hz), 7.80 (AA'XX', 8H, SO_3ArH, *J* 8.4 Hz).

6.2.3.4 O-alkylated *p*-benzylcalix[4]arene derivatives



Derivatives of *p*-benzylcalix[4]arene **58**, **59** and **60** were prepared using procedures similar to those employed for reactions involving *p*-^{t}Bu-calix[4]arene.[7,8]

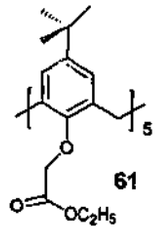
Tetra-(ethoxy-carbonyl-methoxy)-*p*-benzylcalix[4]arene, 58: A mixture of anhydrous potassium carbonate (3.4 g, 24.7 mmol), *p*-benzylcalix[4]arene (3.22 g, 4.1 mmol) and bromoethylacetate (3.6 mls, 32.9 mmol) in dry acetonitrile (150 ml) was heated to reflux under nitrogen for 24 hours. The acetonitrile was removed *in vacuo* and the product extracted into dichloromethane (50 ml), washed with 2 *M* HCl solution, brine, water, and dried with $MgSO_4$ to afford a light amber oil. Addition of warm diethyl ether (50 ml) to the oily residue yielded **58** as a white precipitate (2.8 g, 60%). m.p. = 150 °C, ^{1}H NMR (300 MHz, $CDCl_3$, 30°C, TMS): δ 1.21 (t, 12H, -CH_3 *J* 6Hz), 2.60 - 3.80 (s-br, 4H, Ar-CH_2-Ar), 3.50 - 4.30 (s-br, 4H, Ar-CH_2-Ar), 4.13 (s-br, 16H; Ar-CH_2Ph, -O-CH_2-CH_3), 4.50 (s-br, 8H, ArOCH_2-), 6.40 – 7.10 (s-br, 8H, Ar-H), 6.9 - 7.25 (m, 20H, Ar-H); ^{13}C NMR (300 MHz, $CDCl_3$, 30°C, TMS) δ = 14.5 (CH_3), 30.0 (Ar-CH_2-Ar), 40.8 (Ar-CH_2-Ph), 61.1 (ArO-CH_2-R), 71.2 (O-CH_2-Me), 125.7 (Ar), 128.3 (Ar), 128.7 (Ar), 129.9 (Ar), 130.3 (Ar), 133.55 (Ar), 137.57 (Ar), 142.16 (Ar), 154.3 (Ar(C)-OR), 169.9 (C=O), MS (ESI^{+}): m/z 1716.8 $[M+Na]^{+}$; $C_{72}H_{72}O_{12}$ (1128.50), calcd C 76.57, H 6.43%; found C 76.95, H 6.37%.

Tetra-(hydroxy-ethanoxy)-*p*-benzylcalix[4]arene, 59: $LiAlH_4$ (0.75 g, 19.8mmol) was added in small portions at 10 °C to a supension of the tetra-ester of *p*-benzylcalix[4]arene (2.8 g, 2.47 mmol) in diethyl ether (50ml) and the mixture was stirred overnight at room temperature. 2 *M* HCl (50 ml) was then added in small portions until a precipitate formed

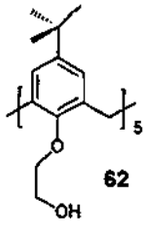
which was filtered and the organic layer dried over $MgSO_4$. The solvent was removed *in vacuo*, and the crude product was crystallized from dichloromethane/isopropanol to give tetra-ethanoloxy of *p*-benzylcalix[4]arene, **59** as white needle crystals(1 g, 42%). m.p. = 220-222°C, ^{1}H NMR (300 MHz, $CDCl_3$, 30 °C, TMS): δ 3.12 (d, 4H, Ar-CH_2-Ar, *J* 14.6 Hz), 3.65 (s, 8H, Ar-CH_2-Ph), 3.95 (s, 16H, -OCH_2CH_2O-), 4.28 (d, 4H Ar-CH_2-Ar), 6.55 (s, 8H,Ar-H), 7.01 – 7.30 (m, 20H, Ph); ^{13}C NMR (300 MHz, $CDCl_3$, 30°C, TMS): δ 30.52 (Ar-CH_2-Ar), 41.6 (Ar-CH_2-Ph), 61.88 (O-CH_2CH_2-), 78.20 (O-CH_2CH_2-), 126.15 (Ar), 128.55 (Ar), 128.77 (Ar), 129.48 (Ar), 134.6 (Ar), 135.67 (Ar), 141.68 (Ar), 153.5 (Ar), MS (ESI): m/z 983.3 $[M+Na]^+$, $C_{64}H_{64}O_8$ (960.46), calcd C 79.96, H 6.72%; found C 81.06, H 6.80%.

Tetra-(tosylate-ethanoxy)-*p*-benzylcalix[4]arene, 60: *p*-Toluenesulfonyl chloride (1.38 g, 7.2 mmol.) was added at 0°C to a solution of tetra-(ethanoloxy)-*p*-benzylcalix[4]arene (0.58 g, 0.6 mmol.) in pyridine (20 ml), whereupon the clear solution was stored at –20°C for 2 days. The reaction mixture was poured into ice cold 2 *M* HCl (100 mL) and the precipitate collected by filtration. The solid was dissolved in dichloromethane (50 ml), washed successively with HCl, brine and dried over $MgSO_4$. Removal of the solvent under reduced pressure, followed by crystalization from isopropanol/methanol afforded the pertosylated derivative of *p*-benzylcalix[4]arene. Yield: (0.68 g, 72%), M.p. = 131 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 30°C, TMS): δ = 2.88 (d, 4H; Ar-CH_2-Ar, J_{AB} 15 Hz), 3.62 (s, 8H; Ar-CH_2-Ph), 4.06 (t, 8H; O-CH_2CH_2OTos, ^3J = 4.3 Hz), 4.18 (d, 1H; Ar-CH_2-Ar), 4.36 (t, 8H; O-CH_2CH_2OTos) 6.42 (s, 8H; Ar-H), 7.0–7.25 (m, 20H; Ph), 7.24 (d, 8H; Tos, J_{AX} 9.3 Hz), 7.72 (d, 8H; Tos); ^{13}C NMR (300 MHz, $CDCl_3$, 30°C, TMS): δ = 22.0 (CH_3), 31.0 (Ar-CH_2-Ar), 41.6 (Ar-CH_2-Ph), 69.9 (O-CH_2CH_2), 72.0 (O-CH_2CH_2), 126.1 (Ar), 128.1 (Ar), 128.5 (Ar), 128.8 (Ar), 129.1 (Ar), 130.1 (Ar), 133.1 (Ar), 134.5 (Ar), 135.1 (Ar), 141.8 (Ar), 144.9 (Ar), 153.6 (Ar), MS (ESI): m/z(%): 1599.48 (100) $[M+Na]^+$; $C_{92}H_{88}O_{16}S_4$ (1576.49): calcd C 70.03, H 5.63%; found C 69.7, H 5.04%.

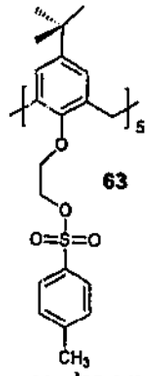
6.2.3.5 O-alkylated *p*-^{t}Bu-calix[5]arene derivatives:



61



62



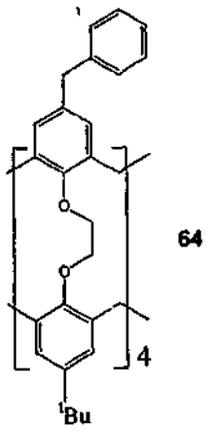
63

Penta-(ethoxy-carbonyl-methoxy)-^{t}Bu-calix[5]arene, **61**: ^{1}H NMR (300 MHz, $CDCl_3$, 30°C, TMS): δ 0.98 (s, 36H, $C(CH_3)_3$), 1.26 (t, 12H, $-CH_3$, *J* 7.2 Hz), 3.30 (d, 4H, Ar-CH_2-Ar, *J* 14.4 Hz), 4.17 (q, 8H, OCH_2CH_3, *J* 7.2 Hz), 4.60 (s, 8H, $ArOCH_2$-), 4.76 (d, 4H, Ar-CH_2-Ar, 14.4 Hz), 6.85 (s, 8H, Ar-H).); ^{13}C NMR (300 MHz, $CDCl_3$, 30°C, TMS) δ = 14.5 (CH_3), 30.7 ($C(CH_3)_3$), 31.7 (Ar-CH_2-Ar), 34.3 ($C(CH_3)_3$), 60.8 (ArO-CH_2-CH_3), 71.1 (ArO-CH_2-CH_3), 125.7 (Ar), 126.0 (Ar), 133.5 (Ar), 145.8 (Ar), 152.3 (Ar), 170.2 (C=O).

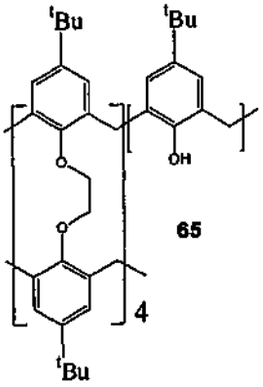
6.3 Molecularely linked calixarenes

6.3.1 Bis-calixarenes

6.3.1.1 *p*-^{t}Bu-calix[4]arene linked to *p*-benzyl-calix[4]arene and *p*-^{t}Bu-calix[4]arene linked to *p*-^{t}Bu-calix[5]arene



64



65

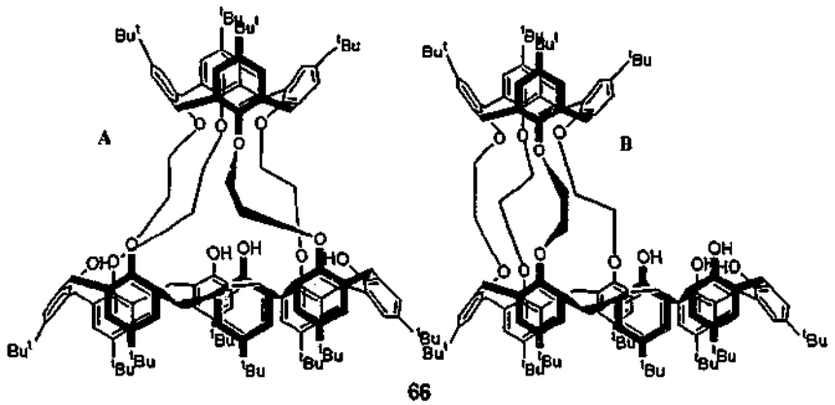
Pertosylated derivative of *p*-^{t}Bu-calix[4]arene or pertosylated derivative of *p*-benzylcalix[4]arene in acetonitrile was added dropwise to a stirred suspension of *p*-^{t}Bu-calix[n]arene (n = 4, 5, 6, 8) with potassium carbonate, in dry acetonitrile under nitrogen and the reaction mixture was brought to reflux for 3 days. Acetonitrile was removed under *vaccuo* and the residue was heated in an appropriate solvent mixture and filtered hot to eliminate the unreacted starting pertosylates. The crude mixture was then dissolved in chloroform, washed successively with 1 *M* HCl, brine solution, water and dried over Na_2SO_4. Filtration followed by concentration *in vacuo* yielded a solid, which was subjected to chromatography on a silica gel column using dichloromethane/hexane eluent to isolate the bis- or tris-calixarenes.

***p*-Benzylcalix[4]arene linked to *p*-^{t}Bu-calix[4]arene, 64**: Pertosylated derivative of *p*-benzylcalix[4]arene 60 in acetonitrile was added dropwise to a stirred suspension of *p*-^{t}Bu-calix[4]arene with potassium carbonate, in dry acetonitrile under nitrogen and the reaction mixture was heated to reflux for 3 days. Acetonitrile was removed in *vacuo* and the residue was heated in ethanol/water and filtered hot. The crude mixture was then dissolved in chloroform, washed successively with 1 *M* HCl, brine solution, water and dried over Na_2SO_4. Filtration followed by concentration of the solvent afforded a solid, which was subjected to chromatography on a silica gel column using dichloromethane/hexane (1:1) to isolate the bis-calixarene. Yield 32%, ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.85 (s, 36H, CH_3), 3.20 (d, 4H, Ar-CH_2-Ar), 3.28 (d, 4H, Ar-CH_2-Ar, J_{AB} 15 Hz), 3.92 (s, 8H, Ar-CH_2-Ph), 4.43 (s, 8H, O-CH_2-), 4.55 (s, 4H, Ar-CH_2-Ar), 4.56 (d, 4H, Ar-CH_2-Ar, J_{AB} 15 Hz)), 6.33 (s, 8H, O-CH_2-), 6.54 (s, 8H, Ar-H), 6.88 (s, 8H, Ar-H), 7.01 – 7.30 (m, 20H, Ph); MS (ESI^+) m/z: 1559.8 $[M+Na]^+$; 1575.8 $[M+K]^+$; $C_{108}H_{112}O_8$ (1561.06): calcd C 84.33, H 7.34 %; found C 84.30, H 7.80 %.

***p*-^{t}Bu-calix[4]arene linked to *p*-^{t}Bu-calix[5]arene, 65**: Pertosylated derivative of *p*-^{t}Bu-calix[4]arene in acetonitrile was added dropwise to a stirred suspension of *p*-^{t}Bu-calix[5]arene with potassium carbonate, in dry acetonitrile under nitrogen and the reaction mixture was brought to reflux for 3 days. Acetonitrile was removed *in vacuo* and the residue was heated in ethanol/water and filtered hot. The crude mixture was then dissolved in chloroform, washed successively with 1 *M* HCl, brine solution, water and dried over Na_2SO_4. Filtration followed by removal of the solvent in *vacuo* afforded a solid, which was subjected to chromatography on a silica gel column using dichloromethane/hexane (1:1) to isolate the biscalixarene. ^{1}H

NMR (300 MHz, $CDCl_3$): δ 1.07 (s, 18H, CH_3), 1.14 (s, 18H, CH_3), 1.19 (s, 9H, CH_3), 1.23 (s, 18H, CH_3), 1.24 (s, 18H, CH_3), 3.00 (d, 1H), 3.23 (d, 2H), 3.33 (d, 4H), 3.43 (d, 2H), 3.74 (m, 2H), 3.95 (d, 2H), 4.28 (d, 4H), 4.36 (d, 2H), 4.48 (d, 2H), 4.63(d, 4H), 4.79 (d, 4H), 4.83 (d, 2H), 5.06 (d, 1H), 6.80 (s, 2H, Ar-H), 6.90 (s, 8H, Ar-H), 7.03 (s, 2H, Ar-H), 7.05 (s, 2H, Ar-H), 7.10 (s, 2H, Ar-H), 7.24 (s, 2H, Ar-H), 7.90 (s, 1H, ArOH); MS (ESI^+): m/z 1564.99 $[M+H]^+$; 1583.01 $[M+Na]^+$; 1597.02 $[M+K]^+$; $C_{107}H_{134}O_9$ (1564.23): calcd C 82.16 H 8.63%; found C 81.95 H 9.23%.

6.3.1.2 *p*-^{t}Bu-calix[4]arene linked to *p*-^{t}Bu-calix[8]arene



66

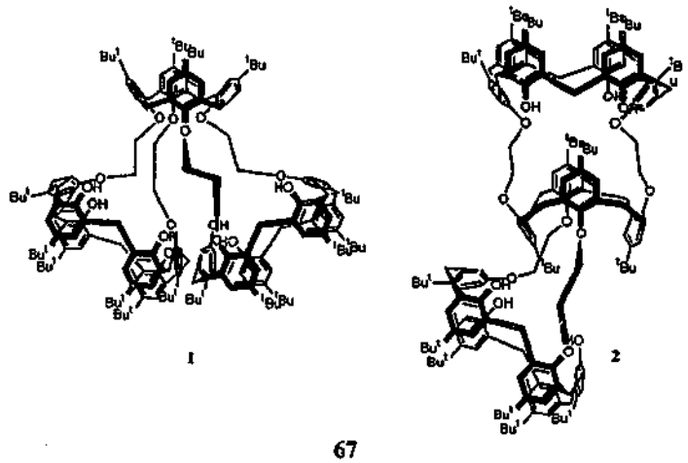
The synthesis of bis-calixarene, *p*-^{t}Bu-calix[4]arene linked to *p*-^{t}Bu-calix[8]arene, **66** was conducted in a similar fashion to the general procedure to making fused calixarenes mentioned above. The bis-calixarene was produced in two isomeric forms with the proposed structures shown above. MS (ESI^+): m/z: 1559.82 $[M+Na]^+$; 1575.81 $[M+K]^+$; $C_{140}H_{176}O_{12}$ (2049.31) calcd C 81.98 H 8.66%; found C 81.25 H 9.47%.

Isomer A: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.23 (s, 36H, CH_3), 1.24 (s, 36H, CH_3), 1.26 (s, 36H, CH_3), 3.19 (d, 4H, Ar-CH_2-Ar, J_{AB} 13.6 Hz), 3.51 (d, 4H, Ar-CH_2-Ar, J_{AB} 15.6 Hz), 3.70 (br-m, 4H, Ar-CH_2-Ar), 4.30 (br-s, 8H, ArO-CH_2-), 4.51 (d, 4H, Ar-CH_2-Ar, J_{AB} 13.6 Hz), 4.70 (br-m, 4H, Ar-CH_2-Ar), 4.90 (d, 4H, Ar-CH_2-Ar, J_{AB} 15.6 Hz), 5.30 (s, 8H, ArO-CH_2-), 7.14 (s, 8H, Ar-H), 7.14 (s, 8H, Ar-H), 7.15 (s, 8H, Ar-H), 8.80 (br-s, 4H, ArOH).

Isomer B: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.80 - 1.35 (m, 108H, CH_3), 3.18 (br-d, 4H, Ar-CH_2-Ar), 3.60 – 4.40 (br-m, 16H, Ar-CH_2-Ar; 16H, ArO-CH_2-CH_2-OAr), 4.65 (br-d, 4H, Ar-CH_2-Ar), 6.30 – 7.30 (m, 72H, Ar-H), 9.25, 9.35, 9.40, 9.45 (s, 1H, ArOH)

6.3.2 Tris-calixarene

6.3.2.1 *p*-^{t}Bu-calix[4]arene linked to *p*-^{t}Bu-calix[6]arene



1 2

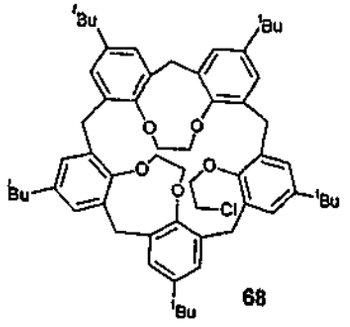
67

The synthesis of tris-calixarene, *p*-^{t}Bu-calix[4]arene linked to *p*-^{t}Bu-calix[6]arene **67** was conducted in a similar fashion to the general procedure to making fused calixarenes mentioned above. From the steric requirement, it is unlikely that the structure is comprised of the central calyx[4]arene in the 1,3 alternate conformation with calix[6]arene on either side (structure **2**).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.7 – 1.40 (m, 144H, CH_3), 2.78 (d, 2H), 3.10 (d, 2H), 3.12 (d, 2H), 3.20 (d, 2H), 3.23 (d, 2H), 3.31 (d, 4H), 3.40 (d, 2H), 3.59 (m, 4H), 3.72 (m, 4H), 3.83 (d, 2H), 3.72 (d, 2H), 4.05 (m, 4H), 4.29 (d, 2H), 4.31 (d, 2H), 4.40 (d, 2H), 4.56 (d, 4H), 4.79 (d, 2H), 4.96 (d, 2H), 4.98 (d, 2H), 7.60 – 7.20 (m, 32H, Ar-H), 8.60 (br-s, 8H, ArOH); MS (ESI$^+$): m/z 2700.53 $[M+H]^+$; 2722.59 $[M+Na]^+$; 2755.63 $[M(CH_3OH)+Na]^+$; $C_{184}H_{232}O_{16}$ (2699.85): calcd C 81.86 H 8.66%; found C 79.85 H 9.01%.

6.3.3 Calixcrown

6.3.3.1 1,2-3,4-dicrown,5-chloroethanoxy-*p*-^{t}Bu-calix[5]arene



68

A suspension of *p*-^{t}Bu-calix[5]arene (0.3 g, 0.66 mmol) and potassium carbonate (0.35 g, 2.5 mmol) in dry acetonitrile (30ml) was heated and stirred under nitrogen for half hour. Chloroethyltosylate (0.21 g, 0.89 mmol) was added and the reaction mixture brought to reflux for four days. Acetinitrile was removed *in vacuo* and crude product was dissolved in chloroform, washed with 2 *M* HCl solution, brine, water, and dried over $MgSO_4$. Crystallisation from propan-2-ol/dichloromethane afforded 4-chloroethanoxy- 1,2-3,5-di-crown-*p*- ^{t}Bu-calix[5]arene **68** in 60% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.00 – 1.40 (m, 45H, CH_3), 3.07 (d, 1H, Ar-CH_2-Ar, *J* 15.6 Hz), 3.17 (d, 2H, Ar-CH_2-Ar, *J* 14.3 Hz) 3.24 – 3.38 (m, 6H, Ar-CH_2-Ar; O-CH_2CH_2-), 3.41 (d, 2H, Ar-CH_2-Ar, *J* 15.6 Hz) 3.84 – 4.40 (m, 6H, O-CH_2-CH_2-), 4.35 (br-d, 1H, Ar-CH_3-Ar) 4.49 (d, 2H, Ar-CH_2-Ar, *J* 15.6 Hz), 4.67 (d, 2H, Ar-CH_2-Ar, *J* 14.3 Hz), 6.30 – 7.40 (m, 10H, Ar-H). MS (ESI^+) m/z: 947.53 $[M+Na]^+$; $C_{61}H_{77}O_5Cl$ (925.7) calcd C 79.17, H 8.39 %; found C 78.53, H 8.10 %.

6.4 Supramolecular interactions

6.4.1 Complex formation in the solid state

6.4.1.1 Synthesis of *p*-benzylcalix[4]arene/H_2O complex (15. H_2O)

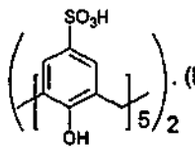
Crystals of **15** for X-ray structural determination were grown from a moist acetone/2-propanol solution of *p*-benzylcalix[4]arene affording [*p*-Benzylcalix[4]arene].$[H_2O]_{0.5}$: $C_{56}H_{48}O_{4.5}$, space group *P4/n*, a = 19.070(3), b = 19.070(3), c = 5.6631(11) Å, V = 2059.4(6) Å^3, T = 173(2) °K, ρ_{calcd} = 1.279 gcm^{-1}, μ = 0.080 cm^{-1} (no correction), Z = 2, Mo K_α radiation, $2\theta_{max}$ = 50° (1484 observed, $I > 2\sigma(I)$), 139 parameters, no restraints, R_1 = 0.0455, wR_2 = 0.1245 (all data), Data were collected at 173(1) K on an Enraf-Nonius Kappa CCD

diffractometer. The structure was solved by direct methods (SHELXS-97) and refined with a full matrix least-squares refinement on F^2 (SHELXL-97), Hydrogens included at calculated positions, S = 1.079.

6.4.1.2 Synthesis of *p*-benzylcalix[4]arene/C_{60} complex (15.C_{60})

Equimolar amounts of *p*-benzylcalix[4]arene and C_{60} were dissolved in warm (60°C) toluene. The solutions were mixed, cooled to room temperature and allowed to evaporate slowly. Large dark crystals were deposited within 3 weeks. A single representative crystal was used in the structural determination and data was collected on a Siemens SMART CCD diffractometer. Preliminary results shows that the complex crystallizes in the tetragonal space group (*I4/m*) with cell dimensions a = 19.2133(8) Å, b = 19.2133(8) Å, c = 27.7788 (11) Å; V = 10253.83(6) Å^3.

6.4.1.3 Calix[5]arene sulfonic acid molecular capsule



. $(H_2SO_4)_4(H_2O)_{1.5}$, **26**

Synthesis: *p*-H-calix[5]arene (0.25 g, 0.47 mmol) was treated with 98% sulfuric acid (3 ml) at 80°C for 10 hours, and the resulting brown solution cooled then stored at –15°C for several weeks whereupon colourless deliquescent crystals deposited. Single crystal structure analysis showed it has the composition (calix[5]arenesulfonic)$(H_2SO_4)_4(H_2O)_{1.5}$. ^{1}H NMR (d_6-DMSO, 300 MHz, 25°C) δ 7.15 (s, 10H, ArH), 6.22 (s-br, COH/SOH), 3.85 (s, 10H, $ArCH_2Ar$). ^{1}H-NMR of H_2SO_4 (d_6-DMSO) δ 12.32 (s, SOH).

Crystallography: A prismatic crystal of dimensions 0.25 x 0.20 x 0.15 mm was mounted on a glass capillary under oil and quickly transferred to under a stream of cold nitrogen. The crystal lost clarity during mounting, indicating a degree of deterioration. X-ray data were collected at 123(1) K on an Enraf-Nonius KappaCCD single crystal diffractometer with MoK_a radiation (λ = 0.71073 Å). Data was corrected for Lorentzian and polarisation effects, but not absorption. The structure was solved by direct methods with SHELXS-97 and refined by full matrix least-squares on F^2 using SHELXL-97. (Calix[5]arenesulfonic acid)$(H_2SO_4)_4(H_2O)_{1.5}$: $C_{35}H_{49}O_{37.5}S_9$, M_r = 1358.28 g mol^{-1}, triclinic, space group $P\bar{1}$, a = 11.7770(3), b =

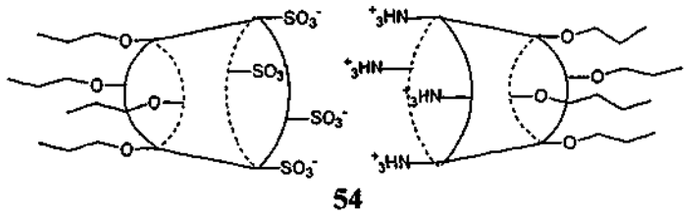
15.9118(4), c = 16.0580(4) Å, α = 105.459(1), β = 90.871(1), γ= 105.767(1)°, U = 2778.68(12) Å^3, Z = 2, ρ_{calc} = 1.623 g cm^{-1}, μ = 0.464 mm^{-1}, 2.6 < 2θ < 55.0, 57663 reflections measured, 12660 unique reflections (R_{int} = 0.073), 7156 observed ($I > 2\sigma(I)$), 846 parameters, 2 restraints, R_1 = 0.1267 (observed data), wR_2 = 0.4012 (all data), S = 1.384. C-H hydrogen atoms of the calixarene were fixed at geometrically estimated positions with a riding refinement. Two sulfuric acid groups (including the guest molecule) were fully ordered, however other sulfuric acid sites and the waters were disordered and given partial occupancies. Two disordered sulfuric acid groups were modelled with S-O bond lengths restrained to chemically reasonable values.

6.4.1.4 *p*-Sulfonato-calix[5]arene slipped capsule

Reaction of equimolar amounts of Na_5[*p*-sulfonato-calix[5]arene] and lanthanum nitrate hydrate ($La(NO_3)_3.xH_2O$) in water resulted in needles upon standing in air for over four weeks. Difficulties were encountered in obtaining meaningful data for this compound, the structure was refined isotropically, and the R factor is very high. The stucture was partially resolved and preliminary results, however, estimate the composition to be [*p*-sulfonato-calix[5]arene]$_2La_2Na_4(H_2O)_{25}$. The unit cell parameters are a = 15.2489(3) Å, b = 18.7219(3) Å, c = 22.1122(4) Å; α = 89.6120(10), β = 71.6060(10), γ = 74.6990(10)°, V = 5757.70(18) Å^3.

6.4.2 Superamolecular chemistry in solution

6.4.2.1 Ionic capsule based on n-propyloxy-*p*-amino-calix[4]arene and n-propyloxy-*p*-sulfonato-calix[4]arene



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The characteristic N-H absorptions of the amino compound **53** was further confirmed by a simple conversion to the hydrochloride salt, IR (KBr) ν 3423, 2950, 2927, 2875 (N-H),

1604, 1466 (N-H) cm^{-1}. To a 2 ml light amber aqueous solution of the ammonium chloride of **53** (10 mg, 0.0145 mmol) was added to a 2 ml light green aqueous solution of **49** (15.4 mg, 0.0145). and upon mixing, a white precipitate formed which was collected by filtration and dried in a dessicator overnight affording **54**. IR (KBr) ν 3425, 3250, 2969 (N-H, SO_3), 1638, 1469, 1380 (N-H, SO_3), 1179, 1122, 1046 (SO_3) cm^{-1}. The solid was insoluble in most solvents and therefore difficult to characterize. However, the ionic capsule formed redissolves on addition of 1 *M* solution of NaOH before dissociates preserving the 1:1 ratio of the two components.

6.4.2.2 Sulfonated *p*-benzylcalix[5,6]arene/trans-β-carotene and *p*-penylcalix[5,6]arene/trans-β-carotene complexes

General procedure for the preparation of the samples: A sample of *p*-benzylcalix[5]arene/*trans*-β-carotene complex was prepared by a solid state grinding experiment. Commercial *trans*-β-carotene (2 mg, 3.7 10^{-3} mmol) was mixed in a mortar with penta-sodium sulfonato-*p*-benzylcalix[5]arene, **37** (6 mg, 4.02 10^{-3} mmol). The solid mixture was grinded until a uniform powder was obtained (*ca.* 1 min). Grinding was continued after adding 2 ml of distilled water for another minute. The resulting orange slurry was twice filtered affording a transparent clear orange solution.

6.4.2.3 Sulfonated *p*-benzylcalix[5,6]arene/C_{60} and sulfonated *p*-penylcalix[5,6]arene/C_{60} complexes

General procedure for the preparation of the samples: The sample of *p*-benzylcalix[5]arene/C_{60} complex was prepared by a solid state grinding experiment. Commercial fullurene C_{60} (7.4 mg, 10.2 mmol) was mixed in a mortar with penta-sodium sulfonato-*p*-benzylcalix[5]arene, **37** (30.7 mg, 20.07 10^{-2} mmol). The solid mixture was grinded until a uniform powder was obtained (*ca.* 1 min). Grinding was continued after adding 2 ml of distilled water for another minute. The resuling deep brown slurry was filtered twice with affording a transparent clear brown solution.

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M. Makha, C. L. Raston, *Chem. commun.,* (2001), *submitted*
M. Makha, M.J. Hardie, P. J. Nichols and C. L. Raston *Prekin trans 1*, (2001), to be *submitted*

Confinement of dimeric sulfuric acid in a self-assembled molecular capsule: $[(H_2SO_4)_2 \subset (\text{calix[5]arenesulfonic acid})_2]$

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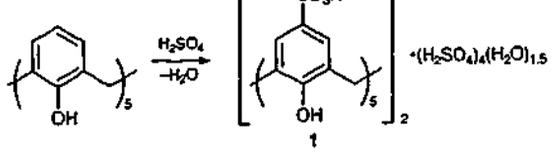
Self-assembled molecular capsules are formed on crystallisation of calix[5]arenesulfonic acid resulting from treating calix[5]arene with sulfuric acid; the calix[5]arenesulfonic acid molecules dimerise *via* hydrogen bonding through the sulfonic acid groups, shrouding two hydrogen-bonded sulfuric acid molecules as the supermolecule $[(H_2SO_4)_2] \subset [(\text{calix[5]arenesulfonic acid})_2]$.

Highly charged water soluble sulfonated calix[4,5,6,8]arenes form a diverse range of complexes and structural types depending on the counter ion/degree of protonation.[1–13] We recently showed that *p*-sulfonatocalix[4]arenes form superanions or ionic capsules in water at low pH in which two calixarenes shroud an 18-crown-6 molecule bearing sodium and two *trans*-water molecules, or a tetra-protonated cyclam molecule, the counter ions being chromium(III) oligomeric species.[12,13] This work relates to a surge in contemporary studies on the formation of self-assembled molecular capsules using hydrogen bonding,[14–18] and the formation of other ionic capsules held together by coordination interactions.[19,20] In general, molecular/ionic capsules are of interest in building large polyhedral structures similar to those in biological systems, trapping and stabilising molecules, and for novel functions such as drug delivery, separation problems and chemical transformations.[14–20]

We now report the synthesis and structural characterisation of a molecular capsule comprised of two calix[5]arenesulfonic acid molecules which encapsulate two sulfuric acid molecules as a hitherto unknown hydrogen bonded dimer. Treatment of calix[5]arene† with sulfuric acid then cooling the brown solution to −15 °C for several weeks gave the corresponding *para*-substituted penta-sulfonic acid isolated as a mixed sulfuric acid/water adduct, (calix[5]arenesulfonic acid)-$(H_2SO_4)_4(H_2O)_{1.5}$ **1** (Scheme 1). The composition of the material was established from single crystal X-ray diffraction data collected at 123(1) K.[24] The samples appeared uniform but attempts to isolate the crystals were compounded by the extremely fragile, hygroscopic and indeed deliquescent nature of the material on removal from the mother liquor. The decomposed material can be converted to the corresponding sodium salt, as a derivative of compound **1** (yield 50%). NMR studies to ascertain the formation of the capsules in DMSO-d_6 and other solvents were inconclusive. While sulfuric acid is the reagent of choice for sulfonating calixarenes,[1–13] the formation of a sulfuric acid adduct of a calixarene, indeed a host–guest complex, is without precedence.

Details of the structure of **1** are shown in Fig. 1.‡ The compound crystallises in space group $P\bar{1}$ with one supermolecule or molecular capsule, $[(H_2SO_4)_2 \subset (\text{calix[5]arenesulfonic acid})_2]$, in the unit cell and thus the capsules lie on inversion centres. In addition to the capsule the unit cell contains six sulfuric acid molecules, disordered over several positions with partial occupancies, and three water molecules of crystallisation, also disordered. The capsules and solvent molecules form a 1D hydrogen bonded network. In contrast the two symmetry equivalent encapsulated sulfuric acid molecules are fully occupied. The S–O bond lengths indicate that S–OH/S=O disorder is likely for the encapsulated sulfuric acids, with one S=O and one S–OH linkage clearly identifiable and the remaining S–O bonds similar within estimated standard deviations. There are several salient features of the capsule. The calixarenes are in the cone conformation, although two of the phenol groups disposed in the 1,3 positions in the calixarene ring are noticeably more tilted away from the principle axis of the calixarene than the other phenolic groups. The tilt angles relative to the plane defined by the five phenolic O-centres are sequentially 150.8, 113.0, 148.7, 125.5 and 123.7° (tilt angle defined as angle from arene centroid to centroid of O_5 plane at the phenolic oxygen). The most tilted phenol group is hydrogen bonded to a sulfuric acid molecule in the cavity of the calixarene, with an O···O separation of 2.92 Å. While the precision of the structure precluded location of the hydrogen atoms, the O···O distances in general are indicative of hydrogen bonding interactions.

Other features of the capsule are that it is flattened in the direction of the principle axes of the calixarenes, and that the calixarenes are slipped relative to each other (Fig. 1). This gives



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Scheme 1

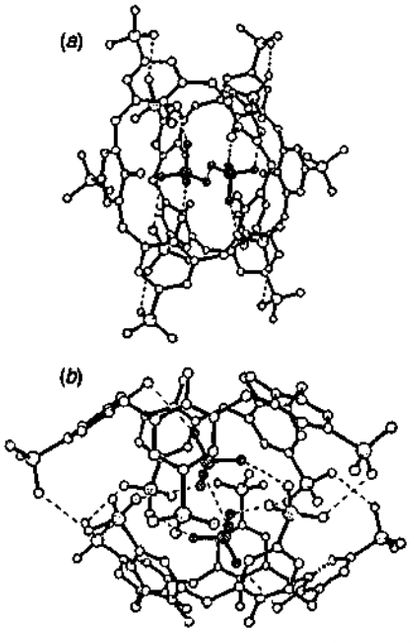

Fig. 1 Projections of the molecular capsule $[(H_2SO_4)_2 \subset (\text{calix[5]arenesulfonic acid})_2]$ in the structure of **1** showing (*a*) the alignment of the calixarenes and sulfuric acid molecules in the capsule involving hydrogen bonding, and (*b*) the flattening of the molecular capsule. Hydrogen bonds are shown as dashed lines and the sulfuric acid molecules are cross-hatched.

a snug fit of the sulfuric acid dimer in the capsule, with one sulfuric acid molecule in each of the cavities of the calixarenes, and hydrogen bonding of the sulfonic acid groups of one calixarene with the other. There are four such inter-calixarene (intracapsule) hydrogen bonds (Fig. 1) at O···O separations of 2.62 and 2.64 Å, with inter-digitation of some of the sulfonic acid groups of one calixarene with those of the other calixarene. The binding of the sulfuric acid molecules is driven by four hydrogen bonding interactions per molecule, one for each of the oxygen centres of each sulfuric acid molecule. The oxygen centre residing deepest in the cavity has a hydrogen bond to one of the phenolic O-centres which is skewed furthest from the average cone conformation. Two others are to sulfonic groups of the other calixarene, at 2.39 and 2.79 Å, and this also is a manifestation of the flattened nature of the capsule. The other hydrogen bond involves an oxygen atom of its centrosymmetric related sulfuric acid molecule at an O···O distance of 2.63 Å.

The single hydrogen bond linking the sulfuric acid dimer is particular noteworthy in the context of the structure of crystalline sulfuric acid. Here there is a continuous two-dimensional puckered sheet-like array of acid molecules held together by hydrogen bonding interactions such that each oxygen in the tetrahedral arrangement of O-atoms around each sulfur forms a single hydrogen bond to another sulfuric acid molecule (O···O separation 2.62 Å).[21] Thus the present structure has two adjacent sulfuric acid molecules interacting with each other through vertices of the tetrahedra analogous to the continuous structure of sulfuric acid itself. Furthermore the S–O···O angles are similar (109.9 *cf.* 120.4° in 1). This is also the type of hydrogen bonding in the few sulfuric acid adducts which have been structurally authenticated.[22] Alternative hydrogen bonding modes are possible including face-to-face linking of the tetrahedra. Effectively we have stabilised a dimer of a similar spatial arrangement as two adjacent sulfuric acid molecules in the continuous structure.

The structure of compound 1 is notably different from that of the corresponding Na salt where the calixarenes do not form molecular capsules.[3,9] This is in direct contrast to the only other structurally authenticated calixarenesulfonic acid, {calix[6]arenesulfonic acid}.$23H_2O$, which is isostructural with its corresponding Na salt, and has the calix[6]arene in a double partial cone conformation, effectively excluding the possibility of capsule formation.[23]

The results herein extend the range of molecular capsules which can be assembled using the principles of supramolecular chemistry, from the initial studies on calix[4]arene[12,13] to the larger calix[5]arene. Success here suggests that a range of species may be encapsulated, depending on interaction complementarity between the molecules and with calixarenes and between the calixarenes. It is likely that the larger calix[5]arene has greater flexibility, able to form a flattened, slipped structure, as in 1, or an expanded structure able to encapsulate larger molecules, beyond the crown ether in the above calix[4]arene studies.[12,13]

Support of this research from the Australian Research Council is gratefully acknowledged.

Notes and references

† *Synthesis:* *p-tert*-Butylcalix[5]arene was prepared by the literature method (ref. 24) and debutylated by standard procedures (ref. 25). Calix[5]arene (0.25 g, 0.47 mmol) was treated with 98% sulfuric acid (3 ml) at 80 °C for 10 h, and the resulting brown solution cooled then stored at −15 °C for several weeks, whereupon colourless crystals of deliquescent (calix[5]arenesulfonic)$(H_2SO_4)_4(H_2O)_{1.5}$ deposited which proved difficult to isolate in an analytically pure form. δ_H(DMSO-d_6) 7.15 (s, ArH), 6.22 (s, broad, COH/SOH, shifts downfield with increasing [H_2SO_4]), 3.85 (s, $ArCH_2Ar$). For H_2SO_4: δ_H(DMSO-d_6) 12.32 (s, SOH).

‡ *Crystal data* for 1: A prismatic crystal of dimensions 0.25 × 0.20 × 0.15 mm was mounted on a glass capillary under oil and quickly placed under a stream of cold nitrogen. The crystal lost clarity during mounting, indicating a degree of deterioration. X-Ray data were collected at 123(1) K on an Enraf-Nonius KappaCCD single crystal diffractometer with Mo-Kα radiation (λ = 0.71073 Å). Data was corrected for Lorentzian and polarisation effects, but not absorption. The structure was solved by direct methods with SHELXS-97 and refined by full-matrix least-squares on F^2 using SHELXL-97. (Calix[5]arenesulfonic acid)$(H_2SO_4)_4(H_2O)_{1.5}$: $C_{35}H_{49}O_{37.5}S_9$, M_r = 1358.28 g mol^{-1}, triclinic, space group $P\bar{1}$, a = 11.7770(3), b = 15.9118(4), c = 16.0580(4) Å, α = 105.459(1), β = 90.871(1), γ = 105.767(1)°, U = 2778.68(12) Å^3, Z = 2, ρ_{calc} = 1.623 g cm^{-1}, μ = 0.464 mm^{-1}, 2.6 < 2θ < 55.0, 57663 reflections measured, 12660 unique reflections (R_{int} = 0.073), 7156 observed [$I > 2\sigma(I)$], 846 parameters, 2 restraints, R_1 = 0.1267 (observed data), wR_2 = 0.4012 (all data), S = 1.384. C–H hydrogen atoms of the calixarene were fixed at geometrically estimated positions with a riding refinement. A number of the sulfuric acid molecules and the waters were disordered and given partial occupancies. Two disordered sulfuric acid groups were modelled with restrained S–O bond lengths. CCDC 182/1459. See http://www.rsc.org/suppdata/cc/1999/2409/ for crystallographic data in .cif format.

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TETRAHEDRON LETTERS

Direct synthesis of calixarenes with extended arms: *p*-phenylcalix[4,5,6,8]arenes and their water-soluble sulfonated derivatives

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Abstract—*p*-Phenylcalix[4,5,6,8]arenes have been isolated from the base catalysed condensation of *p*-phenylphenol with formaldehyde in tetralin, and selectively converted to the corresponding sulfonated derivatives using sulfuric or chlorosulfonic acids.

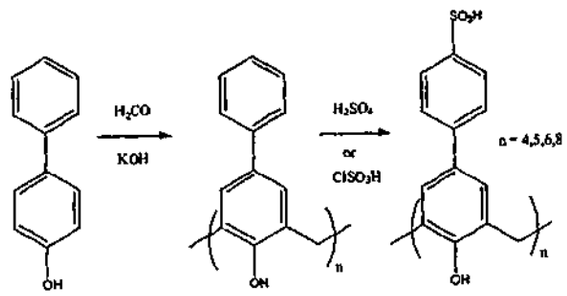
Macrocyclic calixarenes are noted for their diversity and flexibility in supramolecular chemistry, having attracted attention in the last two decades as candidates in mimicking the structure or function of enzymes, crystal engineering, separation science and molecular recognition.[1–3] For example, calix[4,5]arenes and their *p*-sulfonate derivatives have been shown to bind a wide range of molecules and ions.[4,5] Constructing calixarenes with larger/deeper cavities is of interest in confining large molecules and as an entry to new supramolecular arrays. In this context *p*-phenylcalix[*n*]arenes are potential candidates; for $n=4$ and 5, rigid hydrophobic cavities capable of binding large molecules are likely. However, they are not readily available. In the search for deep-cavity calixarenes, various researchers have introduced groups other than Bu^t at the *para* position of calix[4]arene such as benzoyl[7] and piperidinomethyl moieties.[6]

Some procedures for the preparation of *p*-phenylcalix[*n*]arenes have been reported, including the synthesis of *p*-phenylcalix[6 and 8]arenes using a one-pot synthesis involving condensation of *p*-phenylphenol and formaldehyde, with 10 and 7% isolated yields, respectively.[7] However, there is no detailed report on the synthesis of *p*-phenylcalix[4 and 5]arenes using this approach.[7]

There are a few reports using indirect approaches, on the synthesis of *p*-phenylcalix[4]arene, notably by Gutsche et al. using a stepwise route;[8,9] by Anduini et al. using mercury- or thallium-containing calix[4]arene,[10] and by Atwood et al. starting from the *tetra*-methylether of *p*-bromocalix[4]arene, employing the Suzuki palladium-catalysed reaction of arylboronic acids.[11] Also, there is a report on the synthesis of *p*-phenylcalix[5]arene by a '3+2' fragmentation condensation.[12]

Herein we report the direct synthesis of *p*-phenylcalix[*n*]arenes, $n=4$, 5, 6 and 8, which have been isolated in relatively moderate yields (Scheme 1).

In addition, we report the synthesis and characterisation of their water soluble sulfonate derivatives, which have exciting possibilities as phase transfer catalysts, in transport processes and more.



Scheme 1. Synthesis of *p*-phenylcalix[*n*]arenes and their sulfonated analogues.

* Corresponding author.

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PII: S0040-4039(01)01218-7

It is well known that base-catalysed condensation reactions of *p*-substituted phenols with formaldehyde depends on temperature (and temperature gradient), the type of base and molar ratio of phenol to base.[13]

In the present study we systematically varied the ratio of phenol to potassium or sodium hydroxide, with all reactions conducted in tetralin. A higher molar ratio of base (KOH, ca. 0.45)[14] is required to achieve the optimal production of *p*-phenylcalix[4]arene, whereas *p*-phenylcalix[5]arene preparation is optimized at 0.045. Results of the optimisation experiments are summarised in Table 1.

The *p*-phenylcalixarenes were sulfonated either by a direct method using sulfuric acid, as described in the literature for other classes of calixarenes[15] or by chlorosulfonation.[17] The exception is the case of $n=8$, where the former method is preferred because of solubility considerations of the starting material.[16] The lipophilic character of these novel sulfonic acids with appreciable solubilities in polar solvents render their isolation rather difficult and multiple precipitations from ether/ethanol or acetone/ethanol mixtures were required. They were characterised by ^{1}H and ^{13}C NMR spectroscopy and display similar resonance signals to the parent sulfonic acids of calix[*n*]arenes; a broad singlet for $ArCH_2Ar$ (~4 ppm) and a singlet (~7.3 ppm), an AA'XX' system (7.3–7.6 ppm) for the aromatic region and one resonance for the bridging methylene carbons at about 32 ppm[17] (Figs. 1a and 1b).

All sulfonic acids of *p*-phenylcalix[*n*]arenes can be easily converted to the corresponding sodium salts by simple titration with sodium hydroxide.[18]

Table 1. Molar ratio of base to phenol and the resulting isolated yields of *p*-phenylcalix[*n*]arenes

Molar ratio	% Yields			
Base:phenol	$n=4$	$n=5$	$n=6$	$n=8$
0.045 NaOH	0	3	10	30
0.045 KOH	3	15	11	18
0.18 NaOH	0	0	0	0
0.18 KOH	0	2	8	0
0.45 NaOH	2	5	10	20
0.45 KOH	10	5	7.4	38
0.75 NaOH	0	0	0	0
0.75 KOH	0	0	0	0

Figure 1a. ^{1}H NMR spectra of the octa-sulfonic acid derivative of *p*-phenylcalix[8]arene in DMSO-d_6.

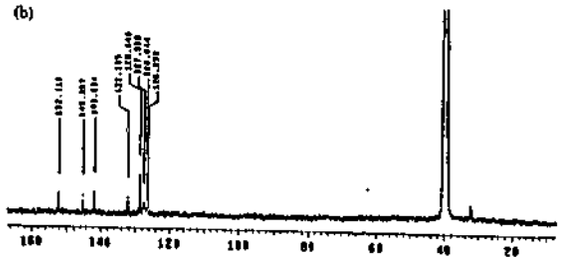

Figure 1b. ^{13}C NMR spectra of the octa-sulfonic acid derivative of *p*-phenylcalix[8]arene in DMSO-d_6.

Overall we have established a simple, direct route to *p*-phenylcalix[*n*]arenes and their sulfonated derivatives. The inclusion/self assembly chemistry of these large macromolecules is currently under investigation.

Acknowledgements

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14. To a slurry of *p*-phenylphenol (10 g, 58.7 mmol) and 5.5 g of paraformaldehyde in 200 ml of tetralin in a 250 ml round-bottomed flask equipped with a condenser and a Dean–Stark water trap; 2 ml of 15 M KOH (26.4 mmol)

was added dropwise at 80°C under a stream of nitrogen. The reaction vessel was lowered into a 200°C preheated heating mantle and kept at this temperature for 2.5 h. After 1 min the reactants dissolved and after 15 min a precipitate began to form. Tetralin was evaporated in vacuo from the cooled reaction mixture and the residue was stirred in 200 ml of warm chloroform containing 2 M HCl (250 ml). The chloroform layer was separated, filtered, washed with water and dried ($MgSO_4$) to afford a yellowish solid, after removal of the solvent. The yellowish solid was triturated in refluxing methanol, filtration affords 3 g of a beige powder which consisted of a mixture of *p*-phenylcalix[*n*]arenes ($n=4$, 5 and 6). The beige solid was then heated in an acetone/methanol mixture and upon standing 0.80 g (7.4%) of *p*-phenylcalix[6]arene precipitated: IR (KBr) 3173 cm^{-1} (OH stretching); ^1H NMR (300 MHz, $CDCl_3$, 25°C): $\delta=4.05$ (s-br, 12H; $ArCH_2Ar$), 7.22–7.49 (m, 42H; ArH), 10.57 (s, 6H; OH); ^{13}C NMR (300 MHz, $CDCl_3$, 25°C): $\delta=$ 32.93 ($ArCH_2Ar$), 127.00 (Ar), 127.15 (Ar), 127.74 (Ar), 128.63 (Ar), 128.84 (Ar), 135.56 (Ar), 140.88 (Ar), 149.35 (Ar-OH), MS (ESI^-): *m/z* (%): 1091.6 (100) [$M-H^+$], 1092.3 (68) [M], 1093.5 (33) [$M+H^+$]; $C_{78}H_{60}O_6$ (1092.43): requires C, 85.68; H, 5.54; found: C, 85.40; H, 6.30. The filtrate was then evaporated and the residue triturated in acetone/methylene chloride, affording 0.5 g (5%) of a crystalline solid shown to be *p*-phenylcalix[5]arene: IR (KBr) 3282 cm^{-1} (OH stretching); ^1H NMR (300 MHz, $CDCl_3$, 25°C): $\delta=4.01$ (s-br, 10H; $ArCH_2Ar$), 7.25–7.49 (m, 35H; ArH), 9.11 (s, 5H; OH); ^{13}C NMR (300 MHz, $CDCl_3$, 25°C): $\delta=32.14$ ($ArCH_2Ar$), 127.00 (Ar), 127.08 (Ar), 127.20 (Ar), 128.36 (Ar), 128.86 (Ar), 135.30 (Ar), 140.88 (Ar), 149.87 (Ar-OH), MS (ESI^+): *m/z* (%): 933.35 (100) [$M+Na^+$]; $C_{65}H_{50}O_5$ (910.36): requires C, 85.68; H, 5.54; found: C, 84.06; H, 5.24; mp >350°C [dec.]. After evaporation of the filtrate, the residue obtained was triturated with acetone affording 1 g (9%) of *p*-phenylcalix[4]arene: IR (KBr) 3200 cm^{-1} (OH stretching); ^1H NMR (300 MHz, $CDCl_3$, 25°C): $\delta=3.67$ (d, 4H; $ArCH_2Ar$; $J_{AB}=13.5$ Hz), 4.38 (d, 4H; $ArCH_2Ar$; $J_{AB}=$ 13.5 Hz) 7.20–7.49 (m, 28H; ArH), 10.43 (s, 4H; OH); ^{13}C NMR (300 MHz, $CDCl_3$, 25°C,): $\delta=31.33$ ($ArCH_2Ar$), 127.08 (Ar), 127.12 (Ar), 128.26 (Ar), 128.64 (Ar), 128.90 (Ar), 135.99 (Ar), 140.96 (Ar), 148.69 (Ar-OH), MS (ESI^-): *m/z* (%): 727.4 (100) [$M-H^+$]; $C_{52}H_{40}O_4$ (728.29): requires C, 85.68; H, 5.54; found: C, 85.50; H, 6.06.

Chromatographic separation of *p*-phenylcalix[4,5,6]-arenes can also be achieved on a silica gel column using acetone/methylene chloride/hexane as eluents at ratios of 1:1:2 with R_f values of 0.23, 0.64 and 0.46, respectively. The chloroform insoluble material (5.7 g) contaminated with *p*-phenylphenol was triturated several times with hot acetone/chloroform to give 4.1 g (38%) of a white solid *p*-phenylcalix[8]arene.

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16. 2 g of *p*-phenylcalix[8] arene was stirred at 80°C in 10 ml of neat sulfuric acid for ca. 12 h whereupon cooling, the reaction mixture was poured over ice, then the aqueous mixture was filtered and treated with activated charcoal (×2) leaving a clear light greenish solution. Water was evaporated affording a deliquiscent light green solid, which was crystallized from acetone to afford the per-sulfonic acid of *p*-phenylcalix[8]arene. IR (KBr): ν(OH) 2900; 3200 cm^{-1}; $\nu_a(SO_2)$ 1006–1068 cm^{-1}; $\nu_s(SO_2)$ 1176 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6, 25°C): $\delta=7.56$ (br-d, 16H; PhH_{AX}), 7.42 (br-d, 16H; PhH_{AX}), 7.30 (s, 16H; Ar-H), 6.25 (s. br; COH/SOH, shifts downfield with increasing [H_2SO_4]), 3.95 (br, 16H; $Ar\text{-}CH_2\text{-}Ar$). ^{13}C NMR (300 MHz, DMSO-d_6, 25°C): $\delta=32.03$ ($ArCH_2Ar$), 126.35 (Ar), 126.64 (Ar), 127.55 (Ar), 128.64 (Ar), 132.19 (Ar), 141.65 (Ar), 145.25 (Ar), 152.11 (Ar-OH).

17. **General procedure for $n=4$, 5 and 6:** To a solution of *p*-phenylcalix[5]arene (0.4 g, 0.51 mmol) dissolved in 20 ml of dry chloroform, 1 ml of chlorosulfonic acid was added dropwise at 0°C under argon. The mixture was stirred at room temperature for ca. 12 h to form a bright rose biphasic mixture. The reaction mixture was poured over ice, and the aqueous phase was separated and treated with activated charcoal (×2) leaving a clear light greenish solution. Water was then evaporated affording a deliquiscent green solid and upon addition of acetone/methanol mixture, a fine gray precipitate formed which was filtered over Celite to afford sulfonic acid of *p*-phenylcalix[5]arene. IR (KBr): ν(OH) 2900; 3413 cm^{-1}, $\nu_a(SO_2)$ 1007–1068 cm^{-1}; $\nu_s(SO_2)$ 1174 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6, 25°C): $\delta=7.58$ (br-d, 10H; PhH_{AX}), 7.46 (br-d, 10H; PhH_{AX}), 7.40 (s, 10H; Ar-H), 6.27 (s. br; COH/SOH, shifts downfield with increasing [H_2SO_4]), 3.91 (br, 10H; $Ar\text{-}CH_2\text{-}Ar$). ^{13}C NMR (300 MHz, DMSO-d_6, 25°C): $\delta=31.48$ ($ArCH_2Ar$). 126.42 (Ar), 126.66 (Ar), 127.82 (Ar), 128.75 (Ar), 132.40 (Ar), 141.55 (Ar), 145.52 (Ar), 151.75 (Ar-OH).

Sulfonic acid of *p*-phenylcalix[4]arene: IR (KBr): ν(OH) 2900; 3421 cm^{-1}, $\nu_a(SO_2)$ 1004–1059 cm^{-1}; $\nu_s(SO_2)$ 1171 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6, 25°C): $\delta=7.6$ (br-d, 8H; PhH_{AX}), 7.4 (br-d, 8H; PhH_{AX}), 7.27 (s, 8H; Ar-H), 5.74 (s; COH/SOH, shifts downfield with increasing [H_2SO_4]), 4.01 (br-s, 8H; $Ar\text{-}CH_2\text{-}Ar$). ^{13}C NMR (300 MHz, DMSO-d_6, 25°C): $\delta=31.66$ ($ArCH_2Ar$), 125.92 (Ar), 126.70 (Ar), 127.48 (Ar), 128.73 (Ar), 131.90 (Ar), 141.34 (Ar), 146.40 (Ar), 152.80 (Ar-OH).

Sulfonic acid of *p*-phenylcalix[6]arene: IR (KBr): ν(OH) 2953; 3441 cm^{-1}, $\nu_a(SO_2)$ 1007–1067 cm^{-1}; $\nu_s(SO_2)$ 1173 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6, 25°C): $\delta=7.52$ (d, 12H; PhH_{AX}; $J_{AX}=6.3$ Hz), 7.43 (d, 12H; PhH_{AX}; $J_{AX}=$ 6.3 Hz), 7.32 (s, 12H; Ar-H), 8.75 (s. br, COH/SOH, shifts downfield with increasing [H_2SO_4]), 3.85 (br, 12H; $Ar\text{-}CH_2\text{-}Ar$). ^{13}C NMR (300 MHz, DMSO-d_6, 25°C): $\delta=31.68$ ($ArCH_2Ar$), 126.25 (Ar), 126.40 (Ar), 127.35 (Ar), 128.75 (Ar), 132.95 (Ar), 143.01 (Ar), 145.52 (Ar), 151.70 (Ar-OH).

18. Sodium sulfonates of *p*-phenylcalix[4]arene, IR (KBr): ν(OH) 3475 cm^{-1}, $\nu_a(SO_2)$ 1008–1042 cm^{-1}; $\nu_s(SO_2)$ 1126; 1452 cm^{-1}, ^1H NMR (300 MHz, DMSO-d_6, 25°C): $\delta=$ 7.56 (d, 8H; PhH_{AX}; $J_{AX}=7.2$ Hz), 7.44 (d, 8H; PhH_{AX}), 7.37 (s, 8H; Ar-H), 3.91 (br-s, 8H; $Ar\text{-}CH_2\text{-}Ar$).

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Synthesis of *p*-benzylcalix[4]arene and its sulfonated water soluble derivative

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p-Benzylcalix[4]arene is formed in good yield by a direct "one pot" reaction involving *p*-benzylphenol and formaldehyde, selectively converted to the corresponding chlorosulfonyl and sulfonate analogues.

There is a growing interest in cyclooligomeric compounds called calix[*n*]arenes.[1] These bowl shaped (usually $n = 4, 5$) or more flexible ($n \geq 6$) macrocycles can form a diverse range of molecular assemblies. The synthesis of calixarenes has been widely investigated by Gutsche *et al.* and others, leading to well-established procedures for their preparation in reasonable yields.[2–8] However, these focus mainly on *p*-^{t}Bu- calix[*n*]arenes derived from base or acid catalysed condensation of *p*-^{t}Bu-phenol and formaldehyde, leading to the major calixarenes ($n = 4$, 5, 6, and 8) and other higher calixarenes.[2,3] In contrast, the direct syntheses of calixarenes derived from other *p*-alkylphenols are not extensively investigated and are generally formed in low yields;[6] this is an impediment to developing their chemistry. Base catalysed condensation of *p*-benzylphenol and formaldehyde, for example, leads to a mixture of *p*-benzylcalix-[5,6,8]arenes in 33%, 16% and 12% yields respectively,[5–7] as well as *p*-benzylcalix[7 and 10]arenes,[4,9,10] with no evidence for the formation of the *p*-benzylcalix[4]arene. Herein we report the synthesis of *p*-benzylcalix[4]arene as the first 'major' calixarene of the *p*-benzylcalix[*n*]arene family now available in good yield. The calix[4]arene is new and its availability offers scope for further elaboration such as *O*-alkylation, aromatic substitution of the benzyl groups, and as a receptor molecule, both aspects being established herein with the synthesis of the water soluble sulfonated *p*-benzylcalix[4]arene and the formation of a discrete 1:1 complex of the calixarene with C_{60} (Scheme 1).

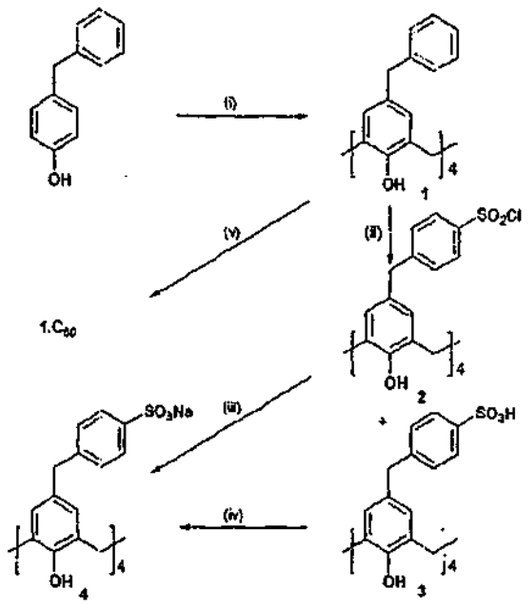
The rigid cone structure of the phenolic-containing array with the flexibility of the benzyl moieties, offers scope for complexation of a range of substrates, of varying shape and electronic characteristics.

The base induced condensation reaction of *p*-benzyl phenol and formaldehyde, proceeds smoothly and quickly relative to the similar condensation of its *p*-^{t}Bu-phenol analogue.[2] Oligomerization of *p*-benzylphenol formed at 120 °C using aqueous formaldehyde as the reaction medium with a catalytic amount of sodium hydroxide, affording a clear beige glass, consisting exclusively of *p*-benzylcalix[8]arene as the sole calixarene formed (tlc, NMR), with the consumption of all the starting phenol. Other products presumably are linear oligomers, noting that corresponding oligomers are formed in the condensation of *p*-^{t}Bu-phenol. Upon addition of diphenyl ether to this material and increasing the temperature quickly to 260 °C over half-an-hour and holding the temperature at reflux for 3 hours affords *p*-benzylcalix[4]arene, **1** in 60% isolated yield.†

It is noteworthy that the outcome of the reaction changes dramatically when either the ramping period or the reflux temperature is altered. For instance when the ramping is over one hour instead of half-an-hour and the reflux temperature is 220 °C instead of 260 °C and even over an extended period of reflux (10 h) the conversion to *p*-benzylcalix[4]arene accounts for only 16% of the starting material.

The organic free solvent condensation to give the *p*-benzylcalix[8]arene also depends on the reaction conditions, notably, the molar ratio of the base to *p*-benzylphenol and the amount of formaldehyde used. Interestingly, this reaction always gives *p*-benzylcalix[8]arene in varying amounts which is easily separated, precipitating from the reaction mixture upon addition of acetonitrile. The mother liquor contains a mixture of *p*-benzylcalix[4,5,6,7]arenes which can be recycled and, if desired, separated (Table 1).

The ready availability of compound **1** allowed the preparation of the water soluble sulfonated derivative. This adds a novel lipophilic and highly charged calixarene to the expanding



Scheme 1 Reagents and conditions: (i) Ph_2O, NaOH, 260 °C, 3 h; (ii) Anh. DCM, $ClSO_2H$, rt, 5 h, Argon; (iii) Py-H_2O, $NaHCO_3$, 100 °C; (iv) NaOH; (v) C_{60}, Tol.

Table 1 Product distributions of the free solvent base induced condensation of *p*-benzylphenol (10 g) and formaldehyde (15 ml) using different molar ratios of base to *p*-benzylphenol at 110 °C

Molar ratio	*p*-BenzylCalix[*n*]arene distributions
0.045 NaOH	$n = 8$, 30%[a]
0.045 KOH	$n = 8$, 30%[a]
0.26 NaOH	$n = 8 > 6 > 4 > 7$
0.26 KOH	$n = 8 > 7 > 4$
0.34 NaOH	$n = 8 > 5 > 4$
0.34 KOH	$n = 6 > 5 > 8$

[a] Isolated yield, no other calixarenes present.

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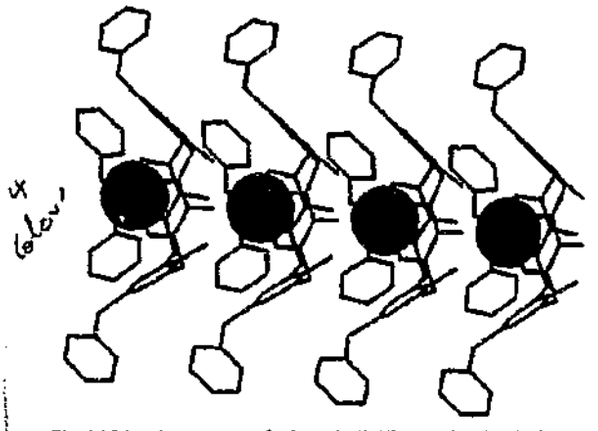

Fig. 1 Molecular structure of *p*-benzylcalix[4]arene showing the inclusion of water within a self inclusion leading to a columnar array (hydrogen atoms have been removed for clarity).

chemistry of the water soluble calixarenes. The sulfonated *p*-benzylcalix[4]arene was prepared using the chlorosulfonation approach, isolated either in 60% yield as the sulfonic acid **3**, which slowly absorbs moisture as a deliquescent solid or as the sodium salt **4**. The chlorosulfonyl analogue, **2** can be intercepted and isolated in 30% yield (this yield can be improved under dry forcing reaction condition).†

The structure of *p*-benzylcalix[4]arene (Fig. 1) was established using diffraction data,‡ and shown to be an inclusion complex with water sandwiched between calixarenes in a columnar array, Fig. 1. The water resides deep in the cavity of the cone conformation, hydrogen bonded to the lower rim hydroxy groups. This is different to the water inclusion complex of sulfonated calix[4]arene with water in the cavity whereby the O–H groups are H-bonded (H···π) to adjacent aromatic rings.[11,12] Another structural feature is the columnar π-stacking of the 1:1 supermolecules.

The C_{60} inclusion complex of **1** was prepared by slow evaporation of an equimolar toluene solution of both components. While crystals suitable for X-ray-diffraction studies were available, solution of the structure has proved elusive. Nevertheless, the structure is likely to be similar to those reported by Atwood *et al.*[13,14] where the fullerenes form columnar arrays. Indeed the cell dimensions are remarkably similar for the 1:1 complex of C_{60} with *C*-ethylphenylcalix[4]resorcinarene (tetragonal, $a = b = 18.9296(7)$, $c = 27.2702(13)$ Å,[13] and tetragonal, $a = b = 19.2183(3)$, $c = 27.7911(6)$ Å for $1.C_{60}$). Moreover, the similarity of the two cells supports the assignment of the 1:1 ratio of the two components.

In conclusion, we have demonstrated the accessibility of *p*-benzylcalix[4]arene in good yield and its water soluble sulfonated derivatives, opening the challenge to expand and diversify the chemistry. Moreover, the results give insight into the advantage of organic solvent free oligomerisation reactions.[15,16]

We are grateful to the Australian Research Council for support of this work.

Notes and references

† *Synthesis* of compound **1**. *p*-Benzylcalix[4]arene was prepared by an adapted method described in ref. 2. A mixture of *p*-benzylphenol (20.1 g, 0.109 mol.), 13 ml of formaldehyde solution and (0.19 g, 0.0049 mol.) of 10 M sodium hydroxide was stirred and heated at 120 °C for *ca.* 2 h forming a gummy beige material. 165 ml of warm diphenyl ether was added and the contents were heated first for 2 h at 120 °C, before ramping the temperature to 260 °C over half-an-hour. Refluxing at 260 °C was maintained for 3 h forming a dark amber solution, and the mixture then allowed to cool to rt. Diphenyl ether was evaporated and the viscous material obtained was washed and dried *in vacuo* affording an amber oil which crystallized slowly on standing, and upon addition of acetone (150 ml), *p*-benzylcalix[4]arene, **1** was obtained as a micro-crystalline white powder. Yield 60%, mp 204.5–205.6 °C, MS (ESI$^+$): *m/z* 807.34 [M.Na$^+$], 844.44 [M(H2O).K$^+$], $C_{55}H_{48}O_4$ (784.34). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.39 (d, 4H, Ar-CH_2-Ar), 3.76 (s, 8H, Ar-CH_2-Ph), 4.18 (d, 4H, Ar-CH_2-Ar), 6.78 (s, 8H; Ar-H), 7.11–7.30 (m, 20H, Ph), 10.13 (s, 4H, OH), ^{13}C NMR: ($CDCl_3$, 300 MHz) δ 32.1 (Ar-CH_2-Ar), 41.3 (ArCH_2-Ph), 126.2 (Ar), 128.4 (Ar), 128.6 (Ar), 129.0 (Ar) 129.5 (Ar), 134.7 (Ar), 141.3 (Ar), 147.2 (Ar-OH). *Synthesis* of compounds **2** and **3**. To a solution of *p*-benzylcalix[4]arene (0.4g, 0.51 mmol) dissolved in 20 ml of dry dichloromethane, 1 ml of chlorosulfonic acid was added dropwise. The biphasic mixture was stirred at rt for *ca.* 5 h with formation of a viscous amber coloured material. The reaction mixture was poured over ice, and the organic phase was separated, treated successively with 1 M sodium bicarbonate (× 2), brine solution (× 2), water and dried ($MgSO_4$) affording the tetrachlorosulfonyl of *p*-benzylcalix[4]arene, **2**. Yield 56%, dec. 180–195 °C, MS (ESI$^+$): *m/z* 1201.9 [M.Na$^+$], 1218.1 [M.K$^+$], $C_{56}H_{44}O_{12}S_4Cl_4$ (1179.01). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.45 (d, 4H, Ar-CH_2-Ar, J_{AB} 13.2 Hz), 3.87 (s, 8H, Ar-CH_2-Ph), 4.24 (d, 4H, Ar-CH_2-Ar), 6.79 (s, 8H, Ar-H), 7.36 (AA′XX′, 8H, Ph-H), 7.94 (AA′XX′, 8H, Ph-H), 10.15 (s, 4H; OH), ^{13}C NMR ($CDCl_3$, 300 MHz) δ 32.1 (Ar-CH_2-Ar), 41.3 (ArCH_2-Ph), 127.4 (Ar), 128.7 (Ar), 129.8 (Ar), 130.1 (Ar) 132.7 (Ar), 142.4 (Ar), 147.9 (Ar), 149.7 (Ar-OH). The aqueous phase was filtered and treated with activated charcoal (× 2) leaving a clear light amber solution. Water was evaporated affording a deliquescent light grey solid, which crystallized from acetone to afford the sulfonic acid of *p*-benzylcalix[4]arene, **3**. Yield 80% dec. 166–170 °C, MS (ESI$^+$): *m/z* 1105.2 [M.H$^+$], 1127.2 [M.Na$^+$], $C_{56}H_{48}S_4O_{16}$ (1104.2). ^{1}H NMR (d_6-DMSO. 300 MHz) δ 3.68 (s, 8H; Ar-CH_2-Ph), 4.08 (br s, 8H, Ar-CH_2-Ar), 6.25 (br s, COH/SOH, shifts downfield with increasing [H_2SO_4]), 6.88 (s, 8H, Ar-H), 7.15 (AA′XX′, 8H, Ph-H), 7.53 (AA′XX′, 8H, Ph-H), ^{13}C NMR (d_6-DMSO, 300 MHz) δ 49.2 (Ar-CH_2-Ar), 49.5 (ArCH_2-Ph), 126.2 (Ar), 128.7 (Ar), 129.1 (Ar), 129.7 (Ar) 134.2 (Ar), 143.2 (Ar), 145.3 (Ar), 148.2 (Ar-OH). Compound **4** was prepared by titration of compound **3** with 1 M sodium hydroxide to neutral pH. Treatment with methanol afforded sodium sulfonates of *p*-benzylcalix[4]arene, **4**, dec. 200– 210 °C. ^{1}H NMR (CD_3OD, 300 MHz) δ 3.65-3.95 (m, 8H, Ar-CH_2-Ar), 3.81 (s, 8H, Ar-CH_2-Ph), 4.82 (s, 4H, COH), 6.90 (s, 8H, Ar-H), 7.22 (AA′XX′, 8H, Ph-H), 7.73 (AA′XX′, 8H, Ph-H).

‡ *Crystal data*. Crystals of **1** for X-ray structural determination were grown from a moist acetone–propan-2-ol solution of *p*-benzylcalix[4]arene affording {*p*-benzylcalix[4]arene}·{H_2O}$_{0.5}$: $C_{56}H_{49}O_{4.5}$, space group $P4/n$, $a = 19.070(3)$, $b = 19.070(3)$, $c = 5.6631(11)$ Å, $V = 2059.4(6)$ Å^3, $T = 173(2)$ K, $\rho_{calc.} = 1.279$ g cm^{-3}, $\mu = 0.080$ cm^{-1} (no correction), $Z = 2$, Mo-K_α radiation, $2\theta_{max} = 50°$ (1484 observed, $I > 2\sigma(I)$, 139 parameters, no restraints, $R_1 = 0.0455$, $wR_2 = 0.1245$ (all data). Data were collected at 173(1) K on an Enraf-Nonius Kappa CCD diffractometer. The structure was solved by direct methods (SHELXS-97) and refined with a full matrix least-squares refinement on F^2 (SHELXL-97), hydrogens included at calculated positions, $S = 1.079$. CCDC 172616. See http://www.rsc.org/suppdata/cc/b1/b106161p/ for crystallographic data in .cif or other electronic format.

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