CHAPTER 2

Host-guest Chemistry: an Introduction

2.1 Supramolecular chemistry

Supramolecular chemistry has been defined as the 'chemistry of molecular assemblies and of the intermolecular bond' by one of its leading proponents, Jean-Marie Lehn, who shared the Nobel prize in 1987 [1]. Other broadly accepted definitions are 'chemistry beyond the molecule', 'the chemistry of the noncovalent bond' and 'nonmolecular chemistry' [2]. Inclusion phenomena, host-guest chemistry or molecular recognition are used interchangeably with supramolecular chemistry which origins from the lock and key mechanism of biological catalysis proposed by Emil Fischer in 1894 [3].

Supramolecular chemistry is a chemistry of multi-component molecular assemblies of higher complexity that result from the association of structural units or chemical species which are held together by a variety of weaker (non-covalent) interactions, which forms 'supermolecule' or aggregates of molecules [4, 5]. Supramolecular chemistry focuses on molecular design for achieving complementarity between single molecular hosts and guest, recognition, self-assembly, preorganisation and self replication [5]. Thus, supramolecular chemistry is a highly interdisciplinary field that encompass organic chemistry and synthetic procedures for molecular construction; coordination chemistry and metal ion ligand complexes; physical chemistry for experimental and theoretical studies of interactions; biochemistry and biological processes which relate to substrate binding and recognition; and materials science of solids [4].

Supramolecular chemistry can be divided into two main groups; (i) host-guest chemistry and (ii) self-assembly, Figure 2.1. Host–guest chemistry is a study of large 'host' molecules that are capable of enclosing smaller 'guest' molecules *via* non-covalent which includes electrostatic interactions, hydrogen bonding, π–π interactions, dispersion interactions and hydrophobic or solvophobic effects [5]. Molecular recognition by a host molecule depends on the degree of structural and electronic complementarity between host and guest where structural complementarity is associated

with the presence of a cavity or cleft in the host incorporating fixed or semi-fixed binding sites that are correctly aligned for binding to the guest while electronic complementarity involves binding sites on the host and guest that are compatible with their electron density distributions [6]. The interplay between the nature and shape of the respective potential energy surfaces of the two molecules in a host-guest system will control the molecular recognition and binding strength. Closer arrangement of binding sites for guest molecules reflects in higher association constant for the respective host-guest complex [6]. Appropriate preorganisation of the bonding sites promotes spontaneous self-assembly for supramolecular entity in complexation as well as determines the stability of the guest molecule [6].

Self-assembly is a spontaneous and reversible association of two or more components to form a larger, non-covalently bound aggregate of supramolecular species[5, 6]. The growths of crystals, the formation of liquid crystals, the spontaneous generation of synthetic lipid bilayers, the synthesis of metal co-ordination complexes and the alignment of molecules on existing surfaces are some of the examples of self-assembly in chemical systems [6].

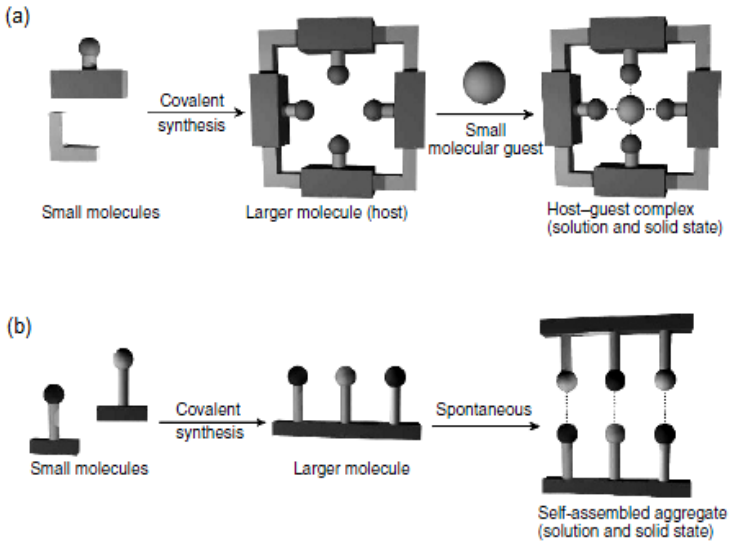


Figure 2.1. Supramolecular system from molecular building blocks: (a) host-guest complexation and (b) self assembly [5].

2.1.1 Intermolecular interactions

In molecular recognition electrostatic interaction between polar molecules is relatively stronger and direction dependent. Hydrogen bonds represent a particular type of electrostatic interaction i.e. an attractive interaction between a proton donor and a proton acceptor. The term hydrogen bond was introduced in 1920 which describe the internal structure of water [6]. Pimentel and McClellan [7] define a hydrogen bond as the interaction between a functional group A-H and an atom or a group of atoms B in the same or different molecules when:

i) there is indication of bond formation (association or chelation)

ii) there is indication that this new bond linking A-H and B specifically involves the hydrogen atom already bonded to A.

The common hydrogen bond donor groups are C-H, H-H, O-H, S-H, P-H, F-H, Cl-H, Br-H and I-H while acceptor groups include N, O, P, S, F, Cl, Br and I as well as alkenes, alkynes, aromatic π-clouds and transition metals [8]. There is a weaker category of hydrogen bond, which is type C-H···A (where A= F, O, N, Cl, Br, I) [8, 9, 10]. Most hydrogen bonds are relatively strong and has highly directional nature, hydrogen bond has been described as ‘masterkey interaction in supramolecular chemistry’, thus makes them ideal in achieving complementarity in supramolecular systems [2]. Systems with weaker (longer) hydrogen bonds exhibit greater inclination of bond angles showing larger deviation from linearity, for example N-H···N bonds appearing to be more likely bent than O-H···O bonds [6].

π-Facial interactions can be a classical donor-acceptor hydrogen bond as well as a π-π bonded system [11, 12, 13]. These interactions are weak however they often act in a co-operative manner with other intermolecular interactions which provide precise orientation within a given supramolecular architecture. Van der Waals interactions act

between the molecules at distances generally larger than the sum of their electron clouds and although these forces are weak but their total collective contribution to complex stability can be significant [6]. π-π Interactions have long been observed in biological systems such as stabilising DNA through vertical base-pair interactions and in the intercalation of drugs into the grooves of DNA as well as in many synthetic host-guest systems [6, 14]. The occurrence of π-π interactions can be explained by solvophobic [15], electron donor-acceptor [15], as well as atomic models [17]. Hunter and Sanders [18], in 1990, proposed a conceptually simple model for π-systems based on electrostatic and van der Waals forces and they proved many characteristics of such interactions such as the 'offset' face-to-face and edge-to-face arrangements, Figure 2.2 for both neutral and polarised π-systems which predicts the nature of π-π interactions and form a basis for efficient host-guest systems.

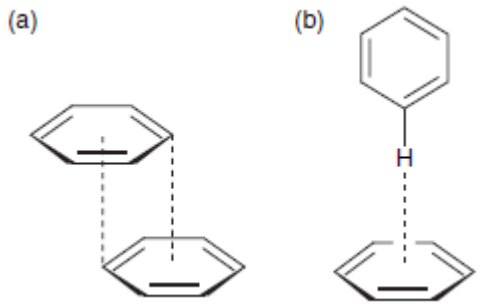


Figure 2.2. (a) Offset face-to-face and (b) edge-to-face arrangements.

Hunter and Sanders [18] have developed six simple rules that apply to π-stacked aromatic systems:

i) π-π repulsion dominates in aligned face-to-face π-stacked geometries

ii) π-σ attraction dominates in edge-on (T) geometries

iii) π-σ attraction dominates in π-stacked geometries

iv) For interactions between highly charged atoms, charge-charge interactions dominates

v) A favourable interaction with a neutral or weakly polarised site requires the following π-polarisation: (a) a π-deficient atom in a face-to-face geometry; (b) a π-deficient atom in the vertical T-group in the edge-on (T) geometry; and (c) a π-rich atom in the horizontal T-group in the edge-on (T) geometry

vi) A favourable interaction with a neutral or weakly polarised site requires at least one of the following σ-polarisation: (a) a positively charged atom in a face-to-face geometry; (b) a positively charged atom in the vertical T-group in the edge-on geometry; or (c) a negatively charged atom in the horizontal T-group in the edge-on geometry.

Hydrophobic binding is common in supramolecular chemistry and it is defined as the association of non-polar regions of host and guest molecules in aqueous or protic media[6]. Solvation effect is important in mediating the strength of hydrophobic binding for host-guest formation and molecular recognition particularly for large molecules[19, 20]. Complex formation involving hydrophobic binding will be accompanied by partial or full desolvation of host and guest and the strength of solvation of the separated entities will affect the stability of the resulting complex [6].

2.2 Calixarene chemistry

2.2.1 Overview of Calixarene chemistry

Macrocyclic compounds, which are recognize as calixarenes were first synthesized by Adolph von Baeyer in 1872 as hard resinous product of the reaction of formaldehyde with phenol in the presence of strong acids [21-23]. Due to limitations to the analytical tools at that time, he was unable to isolate and characterize the pure material from the reaction. Later in 1894, two German chemists, L. Lederer [24] and O.Manasse [25], succeeded in isolating *o*-hydroxymethylphenol and *p*-hydroxymethylphenol from the base-induced reaction of formaldehyde with phenol via dehydration process. The reaction then drew the attention of a wealthy chemist Leo Baekeland who then patented a process using phenol-formaldehyde chemistry, named Bakelite which initiated the first large-scale production of a synthetic plastic [26]. It was not until 1944 that Alois Zinke, and his co-worker Erich Zeigler, proposed a cyclic tetrameric structure as a product of the base-induced condensation of *p-tert*-butylphenol and formaldehyde, and assigning the product as "mehrkernmethylenephenolvorbindungen" [27, 28]. The compound is classed as [1n]metacyclophanes (where n is the number of benzene rings)[29]. In 1952, he provided unequivocal proof of this structure and other phenol-formaldehyde products [30]. Petrolite Corporation in Missouri commercialized oxyalkylated alkylphenol-formaldehyde resins as oil demulsifiers and in 1970s "Petrolite Procedures" was established where the procedure involves a reaction of *p-tert*-butylphenol and *p*-formaldehyde in xylene, with small amount of 50% KOH solution yielding high melting insoluble compound [31-33].

The revolutionary work of C. David Gutsche in the late 1970s led to a new interest in the chemistry of phenol-formaldehyde products, with the descriptive name 'calixarene' being introduced [34]. Calixarene is derived from the Greek word *calix* meaning vase, and *arene* indicating the presence of aromatic rings, which is the resemblance of the

bowl-shaped conformation of the smaller calixarenes to a Greek vase called a *calix crater* [35], Figure 2.3.

Calixarenes are a class of cyclooligomers, synthesised by the condensation reaction between a *p*-substituted phenol and formaldehyde. The calixarene host molecules can be synthesized in a number of sizes with a bracketed number positioned between *calix* and *arene* (e.g. calix[n]arene), where n denotes the number of phenolic units linked to each other by methylene bridges for n = 4–8 being the most familiar macrocycles. The most common cyclic tetramer with *p-tert*-butyl substituents is termed *p-tert*-butylcalix[4]arene. Calixarenes are composed of aryl moieties connected through positions ortho to the phenolic groups and possess a well-defined cavity with the wide side defined as upper rim (usually located on the top) while the narrower side is defined as lower rim and a central annulus [36], Figure 2.3. Calixarenes can be functionalised with a wide choice of substituents either on the upper rim and/or the lower rim (O-centres of the phenolic groups) where prefixes are designated along with appropriate numbering.

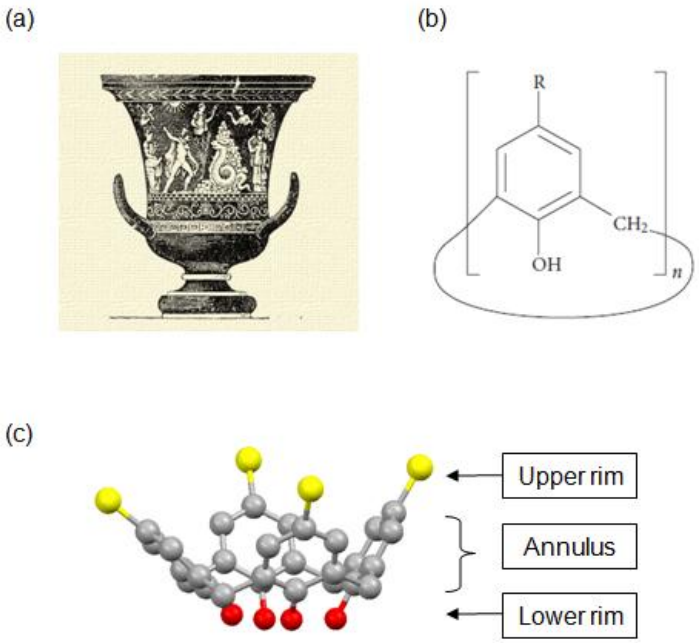


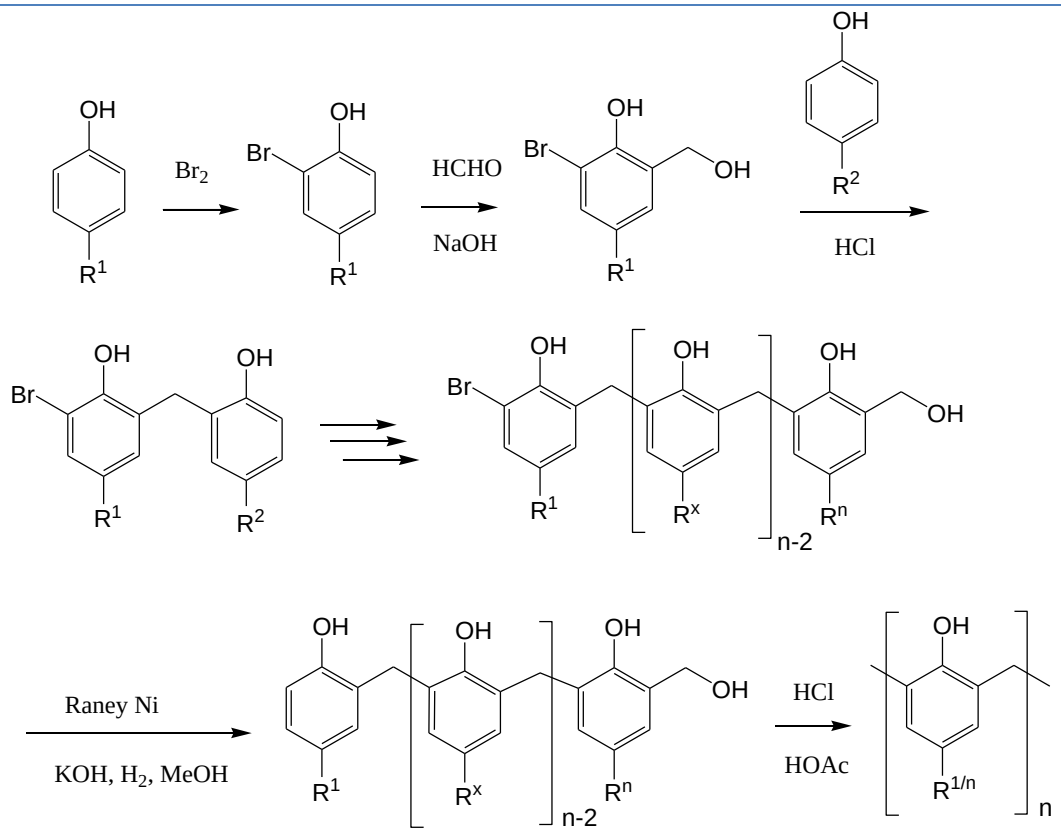
Figure 2.3. (a) Calix *crater*, (b) calix[n]arene and (c) representation of calix[4]arene in cone conformation showing upper and lower rim.

2.2.2 Synthesis

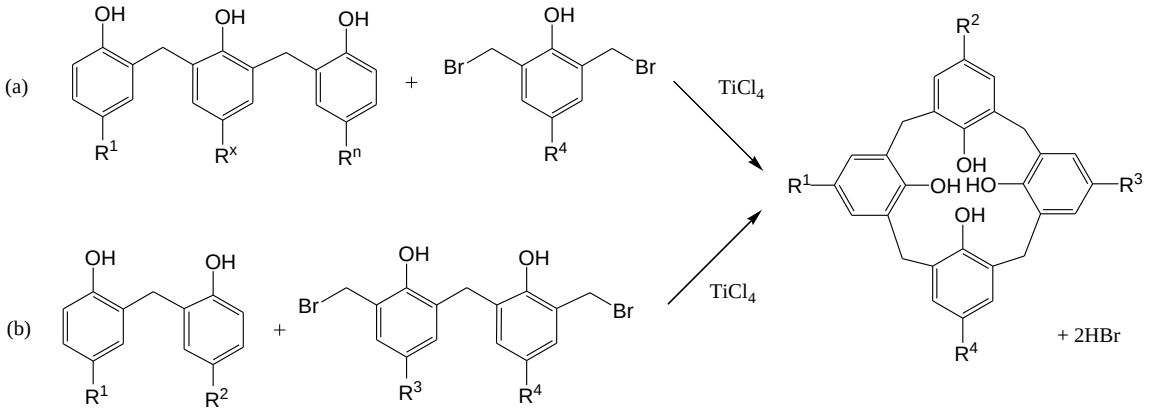
Convergent stepwise and base-induced one-step procedures are commonly used in preparing calixarenes [37]. Greater range of *p*-substituted calixarenes can be obtained by the stepwise synthesis through individual arylation steps, while the calixarenes obtained from a one-pot synthesis yields the same substituent in all of the *p*-positions. Other synthesis procedure available includes fragment condensation synthesis which is useful for making *p*-substituted calixarenes.

The stepwise synthesis of calixarenes by Hayes and Hunter [38, 39], Scheme 2.1, allows access to a greater range of *p*-substituted calixarenes through the use of individual arylation steps but the process is rather long and tedious, generally produced lower yields [40-45]. Using the procedure established by Hayes and Hunter, Kämmerer [42] succeeded in improving this procedure to produce *p*-hexamethyl-*p*-butyl-calix[7]arene in 16 steps with an overall 62% yield. In general the synthesis involves protection of one of the ortho sites by bromination yielding an *o*-bromo-*p*-alkylphenol. Then a series of alternating hydroxymethylation and condensation steps are used to build up the linear oligomer to the desired length. The oligomer is then deprotected by dehalogenation and cyclised under dilute conditions to give the cyclic product.

Preparation of calixarenes is via fragment condensation using performed well defined fragments [46]. The major advantage of this procedure is that it is convergent rather than a non-convergent stepwise procedure and fewer steps are required although it leads to restriction in the degree of variation in the p-substituents. The precursors are commonly synthesised in a stepwise manner and primarily in a "3+1" [47] approach or "2+2" [48] manner to give calix[4]arenes, Scheme 2.2. "3+1" convergent stepwise synthesis involves symmetrical linear trimer which is condensed with a 2,5-*bis*-halomethyl phenol, and the condensation step is ideally performed using large excess of $TiCl_4$ which circumvent the need for high dilution [47].



Scheme 2.1. General procedure for stepwise synthesis of *p*-substituted calix[n]arene [49].



Scheme 2.2. General procedure for: (a) "3+1" and (b) "2+2" fragment condensation to synthesize *p*-substituted calix[n]arene [49].

The early synthesis procedures for preparation of calixarenes were not reproducible and led to unpredictable yields of the desired product and difficulty in separating the mixtures. However the synthesis has been improved when Gutsche introduced the one-step synthesis of calixarenes through the condensation of *p-tert*-butylphenol with formaldehyde under basic conditions which yielded cyclic tetra-, hexa-, or octamer (four, six or eight *tert*-butylphenol units) [50]. Gutsche also showed the importance of the base catalyst concentration at various temperatures influence the outcome of the reaction [51]. The yield of cyclic tetramer is optimized at around 0.03 mol equivalents of the base (with respect to the phenol) however at higher concentrations cyclic hexamer forms as the major product with maximum yield at around 0.4 mol equivalents of base, Figure 2.4. The temperature of the reaction is also an important consideration as lower temperature lead to formation of cyclic octamer as major product [52]. According to this observation and investigations, it has been documented that the octamer is the kinetic-controlled product, while the tetramer is the thermodynamic-controlled product. Another noteworthy factor is the influence of the cation introduced in the reaction where Na favours the formation of cyclic octamer while K, Rb or Cs favours the formation of cyclic hexamer.

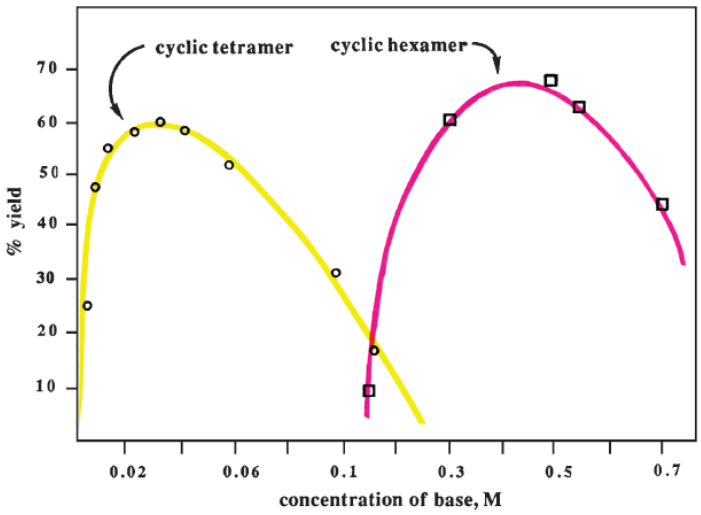
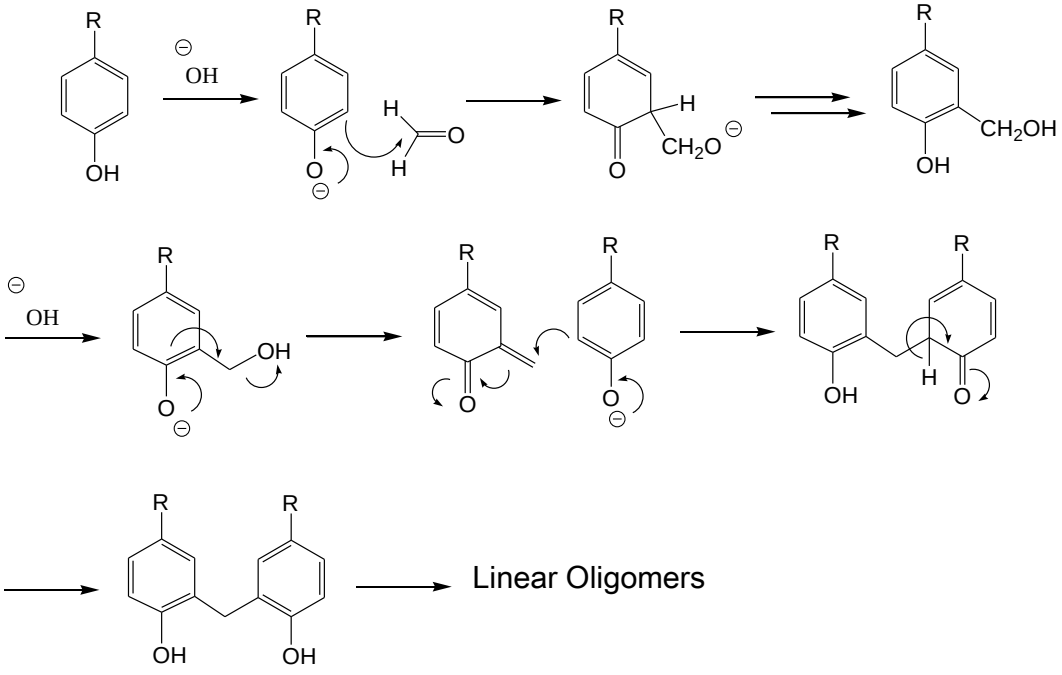


Figure 2.4. Influence of base concentration on the yield of *p-tert*-butylcalix[4]arene [51].

2.2.3 Mechanism of calixarene formation

The mechanism of base-induced oligomerization of phenols begins with the formation of a phenoxide which acts as a carbon nucleophile and the nucleophilic attack is on the highly reactive carbonyl group of formaldehyde to yield hydroxymethyl phenol, Scheme 2.3. The hydroxymethyl phenol can be converted to *o*-quinonemethide intermediates that consequently react with a phenolate ion in a Michael-like process to give diarylmethyl compounds. The diarylmethyl compound continues to undergo a similar set of transformation to form linear oligomers that are the precursors to the calixarene formation. The mechanism for the conversion of the linear oligomers to calixarene is complicated and has been shown that there are at least three dozen linear oligomers prior to cyclization [50, 53].



Scheme 2.3. Based catalysed mechanism for the formation of linear oligomers prior to cyclization [54].

Some of the components of the precursor mixture may be involved in the transformation of both the *p-tert*-butylcalix[6 and 8]arene to *p-tert*-butylcalix[4]arene in yields of 75% or higher under the conditions of the Modified Zinke–Cornforth procedure. Under base-induced conditions, the kinetic-controlled product, *p-tert*-butylcalix[8]arene, is produced in the first step, but ultimately *p-tert*-butylcalix[4]arene is produced in relatively high yield as the final product and it is understood that the *p-tert*-butylcalix[8]arene undergoes transformation during refluxing with diphenyl ether at the second stage of a thermodynamic-controlled process. Gutsche and coworkers speculated that the transformation of cyclic octamer to cyclic tetramer might follow a ‘‘molecular mitosis’’ pathway wherein the cyclic octamer pinches together to form a figure-eight conformer which then splits into a pair of cyclic tetramers, Figure 2.5. However, there are other possible competing pathways such as fragmentation-recombination processes. A study was carried out to test the molecular mitosis hypothesis, where a 50:50 mixture of fully deuterated and fully protiated of *p-tert*-butylcalix[8]arenes was refluxed to yield a product distribution indicating both processes were active pathways for formation of *p-tert*-butylcalix[4]arene [55, 56]. The mechanism for *p-tert*-butylcalix[6]arenes has been postulated as involving a linear hexamer intermediate rather than a pair of linear trimers [57].

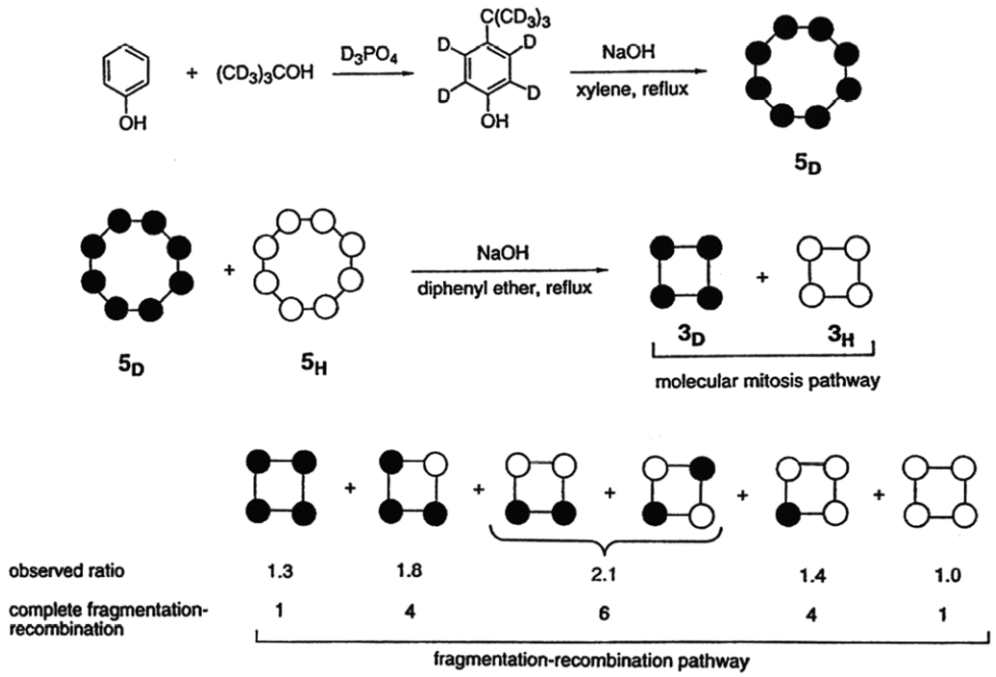


Figure 2.5. Overview of the molecular mitosis mechanism test. (Black and white circles represents deuterated and protonated residues respectively) [56].

2.2.4 Conformations of calixarenes

The free rotations of the methylene groups (Ar-CH_2-Ar) between phenolic groups result in variable conformations where the hydroxyl groups or *p*-substituents rotate independently through the annulus. The spatial orientation of each phenolic unit depends on the function of reaction conditions, the number of phenols linked together, degree of substitution, and the length of the linkage between phenols. Calix[4]arene can adopt four limiting conformational isomers, designated as the cone, partial cone (*paco*), 1,2-alternate (1,2-alt), or 1,3-alternate (1,3-alt) conformation [36], Figure 2.6.

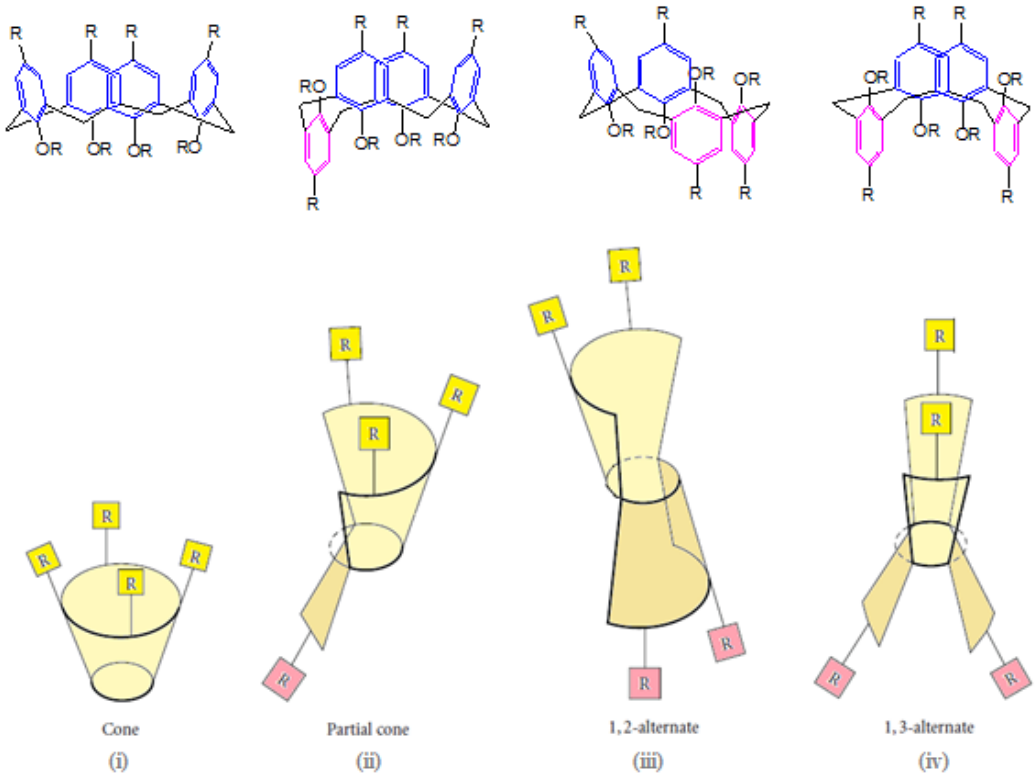


Figure 2.6. Four possible conformations of calix[4]arene [36].

Proton nuclear magnetic resonance (^{1}H NMR) measurements of several calixarenes in solution show that they mainly exist in the cone conformation due to the strong intramolecular hydrogen bonding among OH groups, Figure 2.7, nevertheless they are conformationally mobile at room temperature [2, 58]. ^{1}H NMR spectra in the 3.5-5.0 ppm region provides distinct pattern for conformational analysis, as the conformational changes result in a splitting pattern in the ^{1}H NMR spectrum of calix[4]arene. The pattern for cone conformation is a pair of doublets for the bridging methylene protons indicating an AB spin system. The patterns for the other conformers are: two pairs of doublets or one pair of doublets and one singlet for partial cone; one singlet and two doublets for 1,2-alternate; and one singlet for 1,3-alternate. Table 2.1 summarizes the ^{1}H and ^{13}C NMR resonances for the four possible conformations of *p-tert*-butylcalix[4]arene.

Table 2.1 ^{1}H and ^{13}C NMR resonances for the four different conformations of *p-tert*-butylcalix[4]arene (s= singlet, d= doublet; J= 12 Hz) [59].

	^{1}H NMR			^{13}C NMR			
Conformation	ArH	CH_2	$C(CH_3)_3$	Ar	CH_2	$\underline{C}(CH_3)_3$	$C(\underline{C}H_3)_3$
Cone	1s	1d	1s	4	1	1	1
paco	2s and 2d or 4s (ratio 1:1:1:1)	2d or 1d and 1s (ratio 1:1)	3s (ratio 1:2:1)	12	2	3	3
1,2-alt	2s (ratio 1:1)	1s and 2d (ratio 1:1)	1s	4	2	1	1
1,3-alt	1s	1s	1s	4	1	1	1

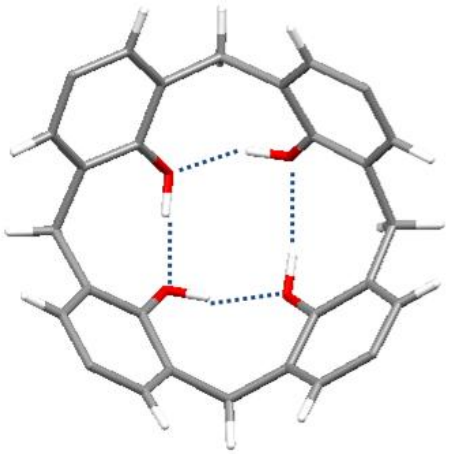


Figure 2.7. Lower rim intramolecular hydrogen bonded interactions in calix[4]arene, which stabilise the cone conformation.

Calix[5]arenes can adopt the same four possible conformations, the cone, partial cone, 1,2-alternate and 1,3-alternate conformations and usually adopt the cone conformation both in solution and the solid state. Calix[6]arene can exist in eight conformations described as distorted cone, compressed cone, pinched cone, double partial cone, winged, 1,2,3-alternate, 1,3,5-alternate and distorted 1,2,3-alternate [55]. Bott and co-workers [60] showed that the conformation of calix[6]arene in the solid state depends on the solvent from which the compound is crystallized. For example, a pinched cone conformation in which all of the OH groups are intramolecularly

hydrogen bonded in a cyclic array will be preferred when the solvent (e.g. benzene) cannot engage in hydrogen bonding with the OH groups of the calixarene. However, solvent (e.g. acetone, DMSO) which can disrupt the intramolecular hydrogen bonding forces the calixarene to restrict in a distorted 1,2,3-alternate conformation. The much larger annulus of the calix[8]arenes have 16 possible conformations and the numerous other conformations make these marocyclic molecules more flexible and complicated than calix[4]arenes. Generally calix[8]arenes crystallized in the pleated loop conformation and the structure allows maximal hydrogen bonding with the OH groups lying above and below the average plane of the molecule [61].

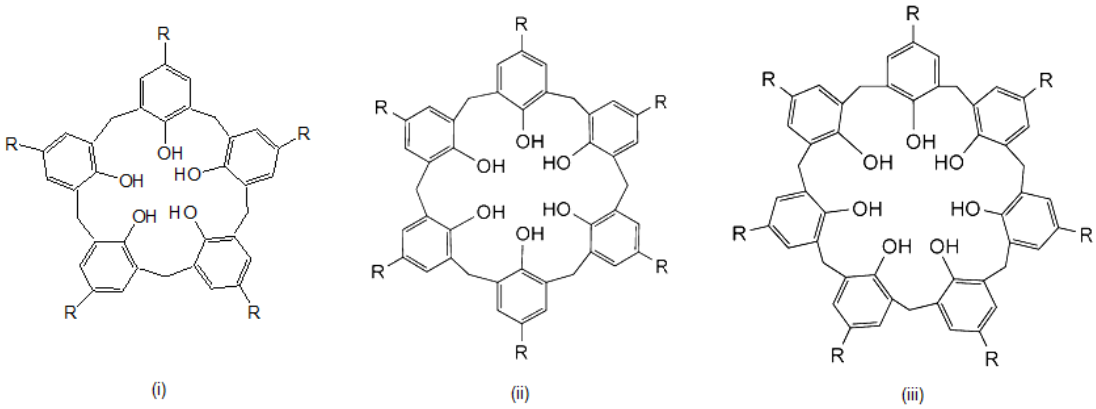


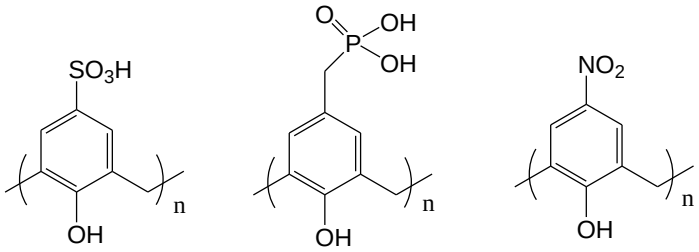
Figure 2.8. (i) Calix[5]arene, (ii) calix[6]arene and (iii) calix[7]arene.

2.2.5 Water soluble calixarenes

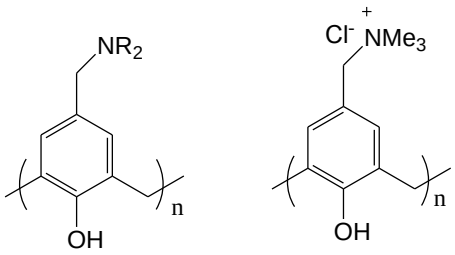
Calixarenes are inherently insoluble in aqueous media which makes them incompatible to be used in any biological context as water is the solvent where most biological processes take place. As a result synthesis of water-soluble derivatives is necessary to extend their utility for example in substrate-binding studies in aqueous solution where synthetic water-soluble receptors can be used in mimicry of natural processes such as specific recognition of bioactive molecules (antigens, microbial/viral pathogens, nucleotides) or enzymatic transformation of substrates [62]. Water-soluble calixarenes also demonstrate remarkable inclusion properties in aqueous solution and in the solid state with various guest molecules of different sizes and shapes such as inorganic ions, organic molecules, amino acids, hormones and peptides. In aqueous solutions, water-soluble calixarenes have potential to bind much more strongly to organic guests than in lipophilic media because of the hydrophobic effect [2]. Other potential applications of these molecules are building up new synthetic materials which are of interest in nanochemistry as well as surfactants to water-solubilise biomolecules such as carotenoids [63] as well as carbon rich nanomaterials such as fullerenes [64, 65] and carbon nanotubes [66, 67].

It is possible to modify both upper and lower rims with groups containing positive or negative charges, or with neutral but highly hydrophilic moieties to facilitate the solubility properties [62]. In 1984, Ungaro and co-workers introduced the first example of water-soluble calixarene, the tetracarboxylic acid of *p-tert*-butylcalix[4]arene which the lower rim is functionalized with four carboxylic groups [68]. In the same year, Shinkai reported the synthesis of the first sulfonated calixarene, followed by an improved preparation for *p*-sulfonatocalix[6]arene [69]. *p*-Sulfonatocalixarenes are characterised by a remarkable solubility in water that is nearly independent of the pH. Further investigation of the sulfonated calixarenes lead to the discovery of anionic

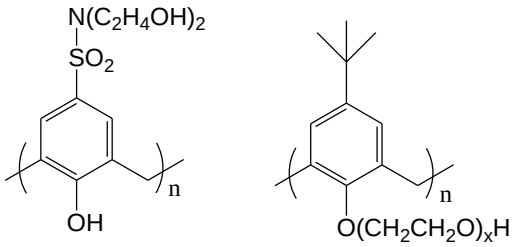
water-soluble derivatives containing nitro [70], phosphonic acid [71,72], and boronic acid moieties [73, 74]. Phosphonic acid groups on the upper rim of calix[n]arenes lead to compounds soluble under basic conditions while boronic acids functional groups have favourable interactions with saccharides in the presence of alkali metal ions. Other cationic water-soluble calixarenes contain tetraalkylammonium groups and primary amines [75,76] whereas neutral water-soluble calixarenes have sulphonamides [77] and sugars [78] as the functional groups.



Anionic calixarenes



Cationic calixarenes

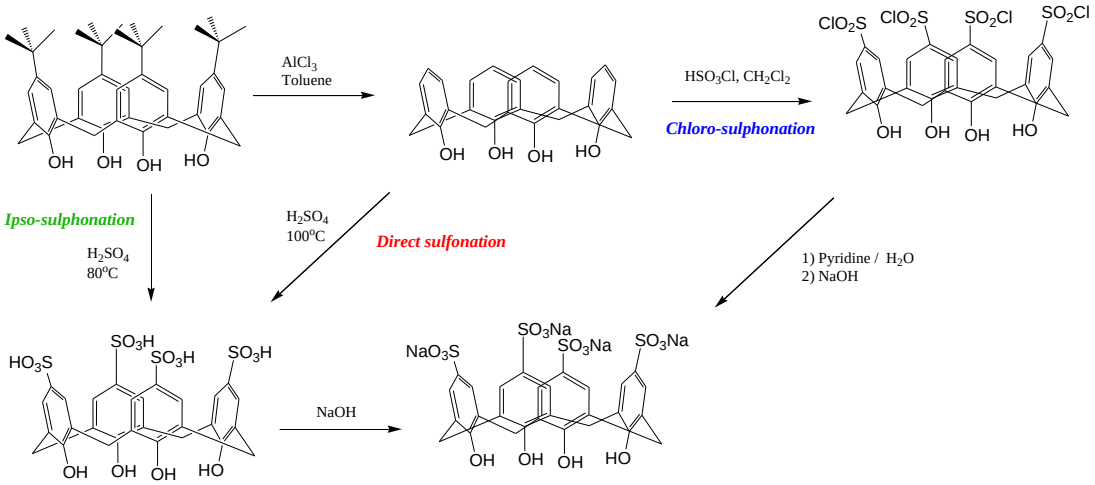


Neutal calixarenes

Figure 2.9. Examples of anionic, cationic and neutral calixarenes.

2.2.6 Sulfonated calix[n]arenes

Functionalisation at the upper rim calixarenes can be achieved by three synthesis routes, Scheme 2.4. The first method involves the removal of the *tert*-butyl group or de-*tert*-butylation from the *tert*-butyl-calix[n]arenes by a reverse Friedel-Crafts reaction [79]. The Lewis acid-catalyzed de-*tert*-butylation is performed using $AlCl_3$ in toluene with a small amount of phenol which acts as a better acceptor molecule than toluene for the *tert*-butyl groups. This reverse Friedel-Crafts reaction is an effective method for transalkylation which removes unwanted alkyl group from calix[n]arenes. The product *p*-H-calix[n]arene can then undergo electrophilic substitution with a range of different electrophiles at the *para* position. The *p*-sulfonatocalix[n]arenes can be prepared by treating the *p*-H-calix[n]arene with an excess of concentrated sulfuric acid, which is known as direct sulfonation [69, 80]. The second route involves direct *ipso*-substitution of the *tert*-butyl groups by the electrophile, a procedure developed by Atwood *et al.*, which bypass the need to remove the *tert*-butyl groups in a separate step [81]. However the drawback of this route is not all electrophiles are applicable. *p*-Sulfonatocalix[n]arenes can also be produced by chlorosulfonation method involving chlorosulfonic acid and *p*-H-calix[n]arene [82, 83].



Scheme 2.4. Synthesis of *p*-sulfonatocalix[4]arene [84].

2.2.7 General structural motifs of sulfonated calix[4]arene

2.2.7.1 Bilayers

p-Sulfonatocalix[4]arene, commonly as the sodium salt is highly water-soluble and often in the cone conformation stabilised by intramolecular hydrogen bonding which is consistent with the deprotonation of the phenoxy anion. Thus, cone conformer of *p*-sulfonatocalix[4]arene possess hydrophilic upper and lower rims, whereas the cavity is essentially hydrophobic which is known to serve as a flexible molecular container to accommodate various guests. The sodium salt of *p*-sulfonatocalix[4]arene pentaanion usually assembles into highly ordered multilayer structure (*p*-sulfonatocalix[4]arene·5 Na^{+}. $12H_20$), which consists of organic layers each formed by 'up–down' cone conformer of calixarenes in the crystalline material. The structure very much resembles naturally occurring organic clay minerals or bio-organic bilayer structure where the calixarene hydrophobic segment alternates with the hydrophilic layers comprised of intercalating layers of water molecules and sodium ions [85], Figure 2.11. Interestingly, the sum of the distances between the calixarene bilayers is spanned to 13.7 Å, and this maybe be compared with sodium vermiculite (15.0 Å) and smectite (14.4-15.6 Å). The structures of sulfonated calixarene and hydrated sodium vermiculite have close similarities which they consist layers of covalent material with hydrated cations in between [85].

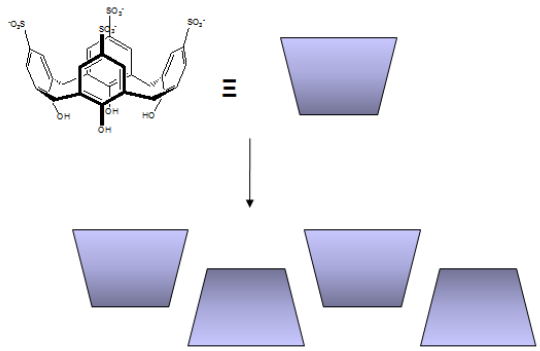


Figure 2.10. Cartoon representation of typical bilayer arrangement for *p*-sulfonatocalix[4]arene.

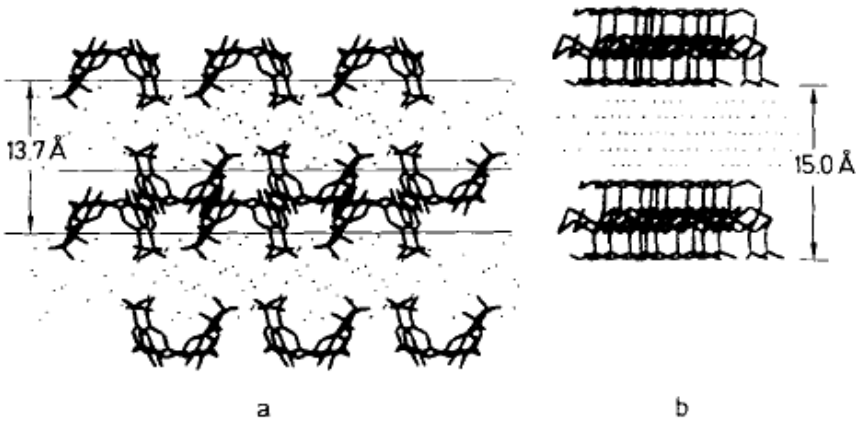


Figure 2.11. a) Bilayer structure of *p*-sulfonatocalix[4]arene · 5 Na^+. $12H_2O$ in the crystal and b) layer structure of hydrated sodium vermiculite [85].

Remarkably, in the presence of solely water, the sodium salt of *p*-sulfonatocalix[4]arene complexes strongly to a water molecule that is embedded within the calixarene cavity, Figure 2.12. This structure was resolved by Atwood [86] and provided the first evidence for O-H···π hydrogen bonds from water to the π cloud of the aromatic nuclei, a phenomenon thought to stabilise protein tertiary structures in biological systems. The intracavity water molecule donates both of its protons to hydrogen bonds to opposite faces of the calixarene cavity with O-H···π–centroid separations of 2.38 and 2.50 Å.

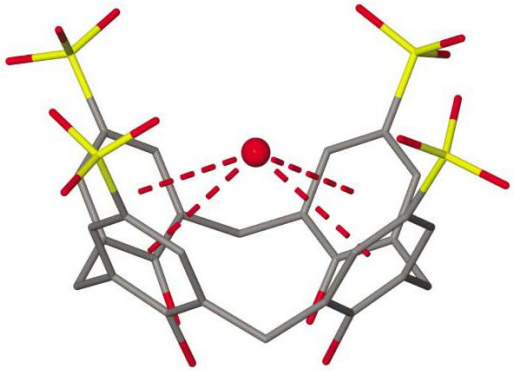


Figure 2.12. Projection of the calixarene showing the water molecule in the cavity of a sulfonated calixarene [87].

Subsequently, binding and structural studies concerning *p*-sulfonatocalix[4]arene have been extended to include a wide range of inorganic cations. Bonal and Morel-Desrosiers *et al.* [88, 89] investigated the binding affinities and thermodynamics of *p*-sulfonatocalix[4]arene with various kinds of metal (Na^+, K^+, Rb^+, Cs^+, Ag^+, Tl^+, NH_4^+, Ca^{2+}, Mg^{2+}, La^{3+}, Nd^{3+}, Sm^{3+}, Eu^{3+}, Gd^{3+}, Dy^{3+}, Yb^{3+}) using isothermal titration calorimetry method and the results showed *p*-sulfonatocalix[4]arene has much weak binding abilities for monovalent cations and moderate strong binding abilities for divalent and trivalent cations. The divalent and trivalent metal ions are hydrated to more extent than the monovalent ions and are relatively stable in association with calixarene outer-sphere involving strong electrostatic interactions outside the cavity [90]. Malfreyt and co-workers studied the complexes of *p*-sulfonatocalix[4]arene with rare-earth metal ions in aqueous solution using molecular dynamics simulations and demonstrated that the outer-sphere complex formed with the lanthanide cations preserves the calixarene conformational flexibility in the complex [91].

The formation of the bilayer structure being built by *p*-sulfonatocalix[4]arenes is stable in the presence of monovalent and multivalent metal ions. The variation of alkali metal cations reflects a decreasing trend in the degree of hydration [92], for example the stoichiometries obtained for *p*-sulfonatocalix[4]arene salts from sodium to cesium cations are Na_5(*p*-sulfonatocalix[4]arene] · $12H_2O$, K_5[*p*-sulfonatocalix[4]arene] · $8H_2O$, Rb_5[*p*-sulfonatocalix[4]arene] · $5H_2O$ and Cs_5[*p*-sulfonatocalix[4]arene] · $4H_2O$.

Atwood and co-workers reported structural motifs involving *p*-sulfonatocalix[4]arene incorporating different trivalent lanthanoid ions [87]. The solid state structures showed the bilayer arrangement which optimises the hydrophobic–hydrophobic π-stacking interactions between adjacent macrocycles. It is noteworthy that the bilayers are linked together through noncovalent interactions with the host molecule rather than direct sulfonate–metal interplay when gadolinium, terbium or thulium cation is incorporated in

the structures. The cavity of a calixarene resides directly above the base of another calixarene and the bilayers are separated by the wide hydrophilic layer consisting aquated lanthanoid ions and disordered water molecules forming two dimensional hydrogen bonded polymers. Two dimensional *p*-sulfonatocalix[4]arene coordination polymer is formed when larger rare earth metal ions are used such as cerium and praseodymium and in this structure the aquated metal ion direct links to the sulfonate group of calixarene. Nevertheless the crystal packing exhibits the bilayer array with the sulfonate and phenolic groups arranged above and below respectively and the hydrophilic layer is narrower as opposed to the two dimensional hydrogen bonded polymers which permits effective hydrogen bonding between the metal ions and calixarene sulfonate groups.

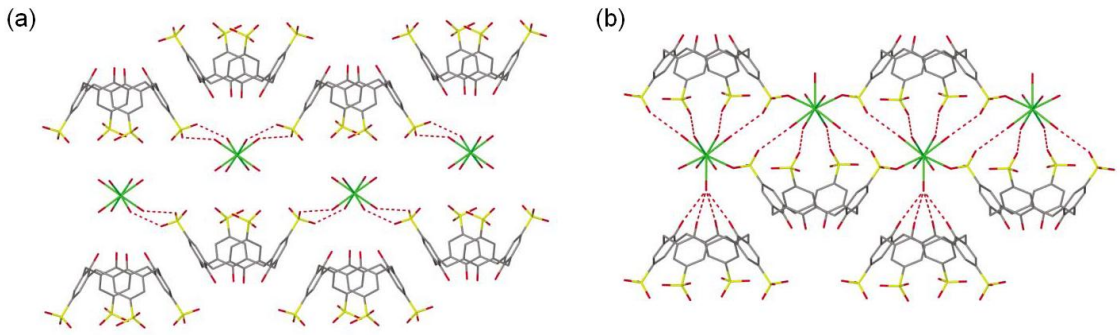


Figure 2.13. (a) 2D hydrogen bonded polymers and (b) 2D coordination polymers [87].

The cone conformation of calixarenes is flexible in its ability to accommodate various guests. Studies on inclusion complexes between *p*-sulfonatocalix[4]arene and a range of organic ammonium cations, such as tetramethylammonium [93], pyridinium [94, 95], adeninium [96], lysine [96, 97] and alkyl di- and tri-ammonium [98]. The first *p*-sulfonatocalix[4]arene–nucleic acid base complex structure is [adeninium]$_4$[*p*-sulfonatocalix[4]arene] · 14H_2O complex, reported by Atwood *et al.* [96]. The retention of the common bilayer structure is observed where the sulfonato groups are directed

into the hydrophilic layer with the adeninium cations resides in between the layer forming hydrogen network, while the calixarene hydrophobic cavity contains a water molecule involved in aromatic π-hydrogen bonding.

Raston *et al.* reported a study of supramolecular complexes involving nucleic bases (e.g. guanine and cytosine) and related compounds (e.g. benzimidazole and 2-hydroxybenzimidazole) with *p*-sulfonatocalix[4]arene [99]. The guanine and benzimidazole complexes demonstrate the same overall bilayer structure with the guest cation perched above the cavity of *p*-sulfonatocalix[4]arene in the hydrophilic layer. In the mixed complex with guanine and cytosine, a cytosine cation resides in the calixarene cavity whereas another cytosine along with a guanine cation positioned *exo* to the calixarene cavity disrupts the usual bilayer structure formation although the sulfonate groups of *p*-sulfonatocalix[4]arene are oriented in opposite directions. In the case of 2-hydroxybenzimidazole the cation is found both *exo* and *endo* to the cavity of *p*-sulfonatocalix[4]arene.

Solid state structures concerning the interactions of *p*-sulfonatocalix[4]arene with positively charged amino acids (e.g. lysine and arginine) have been investigated by Coleman *et al.* [100, 101]. In this context, the inclusion of the hydrophobic alkyl functions into the calixarene cavity occurs. A 1:1 complexation of *p*-sulfonatocalix[4]arene with L-lysine exhibits an intercalation behaviour within the calixarene up-down bilayer system where the chiral cationic organic molecule with a flexible aliphatic side chain can span the bilayer [102]. The crystal structure consists of two crystallographically independent calixarenes and four independent L-lysine where three cations are found to reside within the hydrophilic layer separating the calixarene bilayer, while the remaining molecule spans the bilayer, with all the L-lysine molecules have N-H···O hydrogen bonds with oxygen atoms on the sulfonate groups of the calixarenes from the α- and ε-amino groups. For the complex with D-arginine, the solid-state structure

contains a water channel diagonal to a zig-zag bilayer of the host and the arrangement is stabilised by six π-π interactions. Four crystallographically independent molecules of *p*-sulfonatocalix[4]arene form a cage which accommodates six D-arginines, each with different lateral chain conformations. Among the cations, four have lateral chains included into the calixarene cavities while the other two occupied the independent sites in the cage. Thus, this creates a complicated hydrogen between the polar groups of the D-arginine molecules with fully or partially occupied sites of water molecules and with sulfonate groups of *p*-sulfonatocalix[4]arene [101]. A different supramolecular packing structural design from those observed in the case of L-lysine and D-arginine (usual bilayer or zig-zag bilayer) has been recently reported by Coleman and co-workers. The complex between *p*-sulfonatocalix[4]arene and triethylammonium ligands yields a novel stepped bilayer solid-state packing motif [103]. The structural motif is stabilised by hydrogen bonds between the calixarene molecules and water molecule. C-H···O interactions between methylenic bridges and sulfonate oxygens, and between aromatic carbons and the calixarene sulfonate oxygens were also detected.

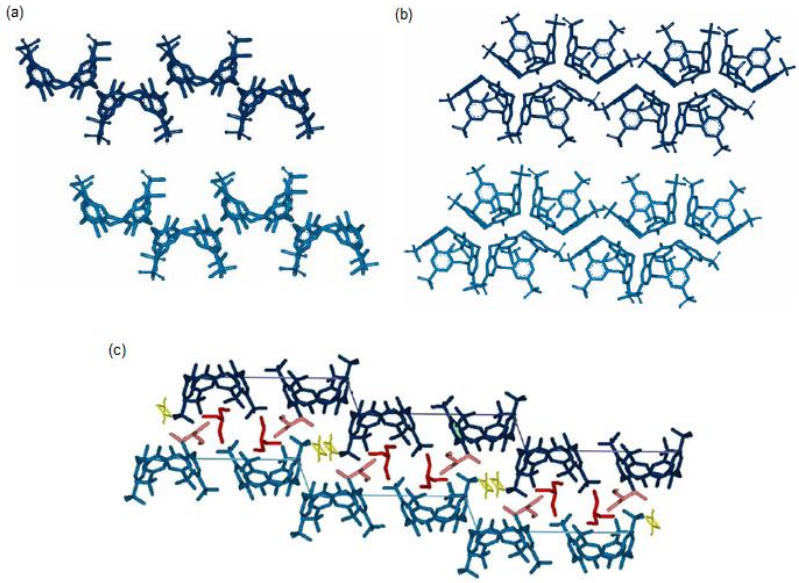


Figure 2.14. (a) Molecular packing showing: (a) typical bilayer, (b) zig-zag bilayer and (c) stepped bilayer structural motif of *p*-sulfonatocalix[4]arene [103].

2.2.7.2 Molecular capsules

Studies on inclusion properties of *p*-sulfonatocalix[4]arene have shown that, in the presence of guest molecules, calixarenes can self-assemble to form dimeric units, host capsules, suitable to include the small organic molecules. The complexes of *p*-sulfonatocalix[4]arene with 1,4-butanediamine (putrescine) and 1,5-pentanediamine (cadaverine) demonstrates that two *p*-sulfonatocalix[4]arene molecules of the opposing layers form a capsule encapsulating two cadaverine diammonium guest molecules or one putrescine and one water molecule within the capsule cavity, yet still retaining the common bilayer motif [98]. The ammonium cation is held by ammonium-sulfonate hydrogen bonds and alkyl-aromatic hydrophobic interactions inside the cavity and with water molecule bridging between the included guest molecules and *p*-sulfonatocalix[4]arene which contributes to the stabilization of the capsule. In the case of much longer ammonium molecule such as 1,5,10-triazadecane (spermidine) and cyclic *cis*-1,2-cyclohexanediamine molecules, partial inclusion of the guest molecule within the cavity is observed being held by similar interactions as putrescine and cadaverine however capsule formation was not present which is attributable to lateral displacement of one layer of the complex with respect to the other. This results in one sulfonate group of calixarene of one layer being positioned above the cavity of calixarene of the opposing layer. The spermidine trication extends outside the *p*-sulfonatocalix[4]arene cavity and forms hydrogen bond to an adjacent *p*-sulfonatocalix[4]arene of the same layer.

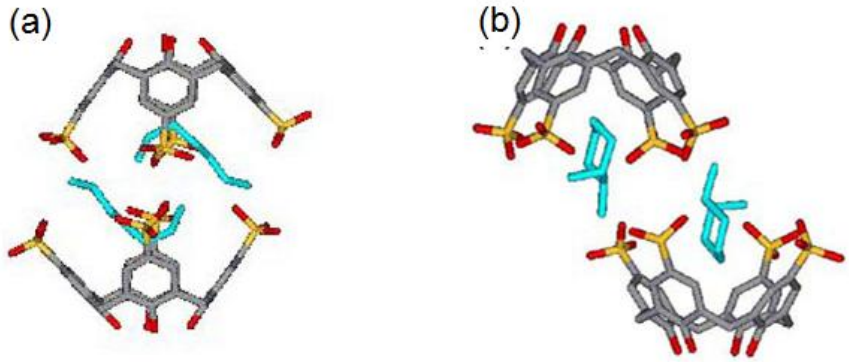


Figure 2.15. (a) Molecular capsule and (b) slipped face to face interaction [98].

In a recent investigation by Raston research group on the ability of two *p*-sulfonatocalix[4]arenes to align face-to-face across the upper rim, sharing a common hydrophobic molecule such as a crown ether, with the ensuing ionic capsules or superanions forming parts of bilayer structures is significant [104-108]. The variables to formation of capsules include the degree of protonation of the calixarenes, the nature of core species within the capsules the polynuclear counterions and other large cations, lanthanide ions, ionic strength, and more [109]. Some noteworthy illustrations of such host-guest chemistry of *p*-sulfonatocalix[4]arene are the inclusion of large globular like guests such as (2.2.2)-cryptand [110] and disc-shaped molecules such as 4,13-diaza-18-crown-6 [111] and cyclam [112] in the protonated forms. This finding has implications in the use of *p*-sulfonatocalix[4]arene as a basis of purifying (*bis*-)amino functionalized molecules such as (di)-aza-crown ethers and cryptands through self-assembly processes, noting some of these molecules are precursors in mixed *cis*-platin derivates for use as novel anti-cancer drugs [113].

Molecular capsule motifs are found when [2H(2.2.2)-cryptand]$^{2+}$ is trapped in a molecular capsule arrangement as part of a 2-D lanthanide coordination polymer [110]. Host-guest complexes with diprotonated 4,13-diaza-18-crown-6 crystallize are readily accessible in the presence of aquated gallium(III) cations residing at the hydrophilic regions of the *p*-sulfonatocalix[4]arenes, thus demonstrating the ability of this system to assemble in the presence of dissimilar polyaquated metal cations [114]. The ionic capsule is without precedence, and its ability to crystallise as a dichromium(III) aqua cation suggests it has potential in forming complexes of a wide range of large cationic species, with ultimate applications in separation science [112]. A key feature of the *p*-sulfonatocalix[4]arene ionic capsules containing 1,4,8,11-tetraazacyclotetradecane (cyclam) is the complementarity of curvature of the cyclam linked within the capsule by an intricate hydrogen bonded array, albeit with some geometrical preorganisational requirements [112]. The capsule itself is not as symmetrical as those containing crown ether [104], with the two bowl cavities offset relative to each other, presumably to maximise hydrogen bonding and for geometrical complementarity between the interacting hydrophobic components of the cyclam and calixarene while the dichromium cations sit at the hydrophilic equator of the capsules [112].

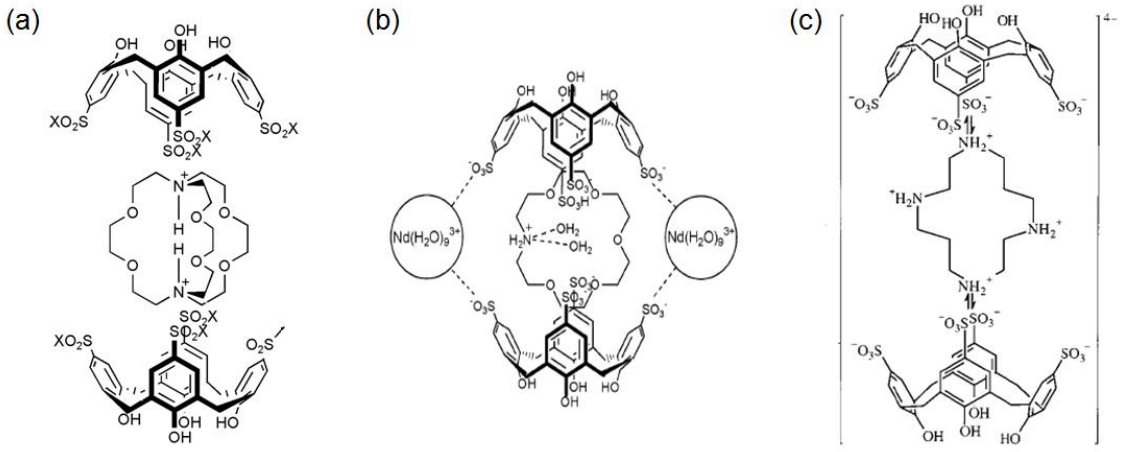


Figure 2.16. Molecular capsule encapsulating (a) (2.2.2)-cryptand, (b) crown ether and (c) cyclam [110,112, 114].

Guo *et al.* also demonstrated the construction of molecular capsules based on *p*-sulfonatocalix[4]arene in the presence of 1,10-phenanthrolinium ion [115] and viologen guest [116]. A face-to-face dimer is formed by the π···π stacking interaction of the bound phenanthrolinium ion with another bound phenanthrolinium molecule stabilized by noncovalent interactions, which results in the formation of the bis-molecular capsule where the -phenanthrolinium dimer acts as a pillar that holds the calixarenes together[115]. In the case of benzyl viologen, the striking feature is that calixarene from a bilayer in line with another bilayer which reflects in the appearance of polymeric capsules, observed in the extended structure [116]. The 4,4′-dipyridinium portion also plays a great role as a linker that holds the capsule units together along the equatorial orientation, leading to the one-dimensional polymerization of capsules [116].

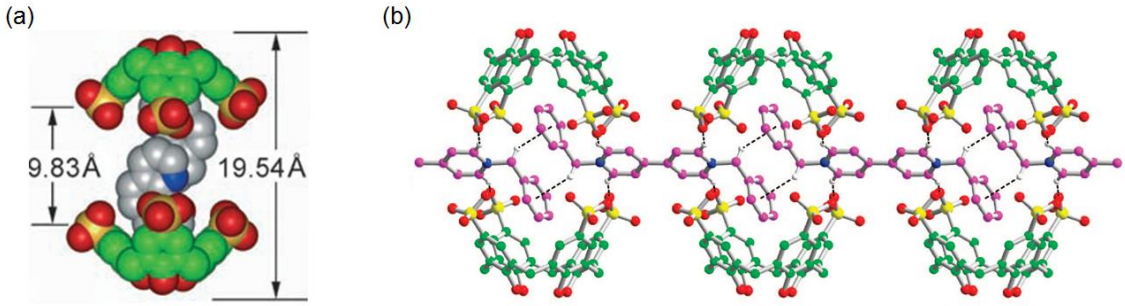


Figure 2.17. Molecular capsule encapsulating (a) phenanthroline and (b) benzyl viologen [115, 116].

2.2.7.3 Russian doll and ferris wheel

Numerous *p*-sulfonatocalix[4]arene capsules take on the form of Russian Matryoshka dolls [109, 117] which are essentially inclusion complexes of inclusion complexes and are unusual examples of second-sphere supramolecular complexation. These 'Russian dolls' are readily formed by combining sodium *p*-sulfonatocalix[4]arene with 18-crown-6 in the presence of lanthanide(III) ions, at low pH, which act to seal the molecular

capsules by coordinating with the sulfonate groups [118]. A degree of structural flexibility is associated with the inclusion of a sodium cation in the crown ether; sodium centres can have two *trans*-water molecules, or two *trans*-oxygen centres from sulfonate groups, one from each calixarene [118]. These sealed 'Russian doll' superanions take on an overall 7- charge and their formation can be associated with selective retrieval of large polynuclear transition-metal aquo species or aluminium Keggin ions from polymeric metallic mixtures [117, 118].

The rare earths have also been shown to form similar 'Russian dolls' with these superanions, and alternative 'Ferris wheels' or hybrids of both with *p*-sulfonatocalix[4]arene and 18-crown-6 host–guest systems [87, 106, 107]. The rare earths can be either (i) present as homoleptic aquated ions, (ii) be bound directly to one or more oxygen centres of sulfonate groups with the coordination sphere satisfied by water molecules, or (iii) be encapsulated as Ln–18-crown-6–H_2O complexes with the presence of additional *exo*-capsule lanthanide cations [117].

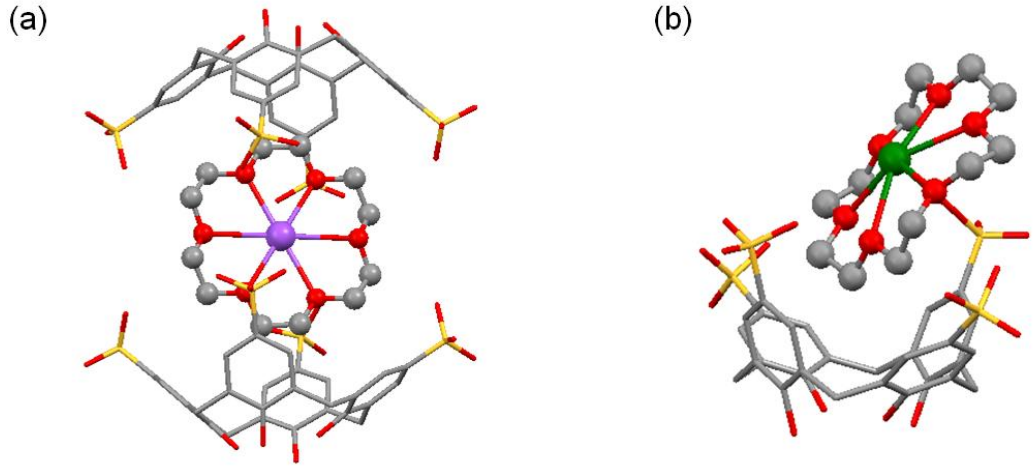


Figure 2.18. (a) "Russian doll" and (b) " Ferris wheel" [105, 107].

2.2.7.4 Spheroids and tubules

The typical up–down antiparallel bilayer packing of *p*-sulfonatocalix[4]arene can be circumvented under certain conditions where the molecules can pack in a parallel manner which in turn can enforce curvature on the resultant supramolecular arrays [117, 119, 120]. Atwood and co-workers demonstrated that *p*-sulfonatocalix[4]arene can generate more complicated structure variations such as large molecular assemblies of large nanometer-scale spheroids (icosahedral and cuboctahedral) [120, 121] or helical tubules [122]. The formation of icosahedral arrangements is general for the lanthanide metals while the formation of the cuboctahedral spheroids is limited to neodymiun, praseodymium, and samarium [117, 120].

When pentasodium *p*-sulfonatocalix[4]arene is treated with pyridine N-oxide and lanthanum nitrate in a 2 : 2 : 1 ratio, the molecular components assemble as C-shaped dimers coordinated through a lanthanum(III) centre and arranged in an up-up radially symmetric fashion along the surface of a sphere in the contrast to up-down fashion when forming a bilayer [117, 121]. The extended structure has 12 calixarene molecules arranged at the vertices of a nanometre scale icosahedron linked through six pairs of C-shaped dimers in a trigonal antiprismatic fashion that the ‘spheroid shell’ is tightly packed with the polar outer-shell surface consists of the sulfonate head groups and the polar inner-shell surface comprises the phenolic hydroxyl groups [117]. In the similar system, nanotubules in helical manner rather than icosahedral arrays obtained when the ratio of the same starting components is changed to 2:8:1 [117, 121]. In this arrangement calixarene molecules are arranged along the surface of a cylinder that is analogous to the spherical assembly having polar tubule core composed of hydrated sodium and lanthanum cations whilst adjacent tubules are linked by *exo* sodium and lanthanum cations that are coordinated to the calixarene upper rim sulfonate groups at the polar outer shell [120, 121].

Replacing 18-crown-6 for pyridine N-oxide, and praseodymium(III) (or neodymium(III) or samarium(III)) triflate for lanthanum nitrate in the ternary *p*-sulfonatocalix[4]arene –guest–Ln system results in a second nanospheroid consisting of 12 calixarene molecules arranged at the vertices of a cuboctahedron [117, 120]. Praseodymium(III) ions are complexed by 18-crown-6 together with two trans-water molecules, and form the core of upper rim to upper rim molecular capsules, similar to the trans-aqua 18-crown-6 complex of sodium [117]. In the extended solid-state structure, these 'Russian dolls' are arranged in the form of cuboctahedra and this introduces the formation of pores in the 'spheroid shell' which are occupied by water molecules [117]. Changing the species from pyridine-N-oxide to 18-crown-6 residing in the calixarene cavity can result in expansion of the spheroid and simultaneously opening up channels in the spheroid shell [117]. The control of pore size and interchangeable spheroid shell structure is reminiscent of the behaviour of the cowpea chloritic mottle virus under specific pH control, a system that can be used to trap molecular material for study within the virion shell [123]. The larger cuboctahedral array appears to allow 'communication' from the *endo*-hydrophilic cavity of the dual solid through hydrophobic channels/pores to *exo* hydrophilic regions via the presence of water molecules within these voids [117].

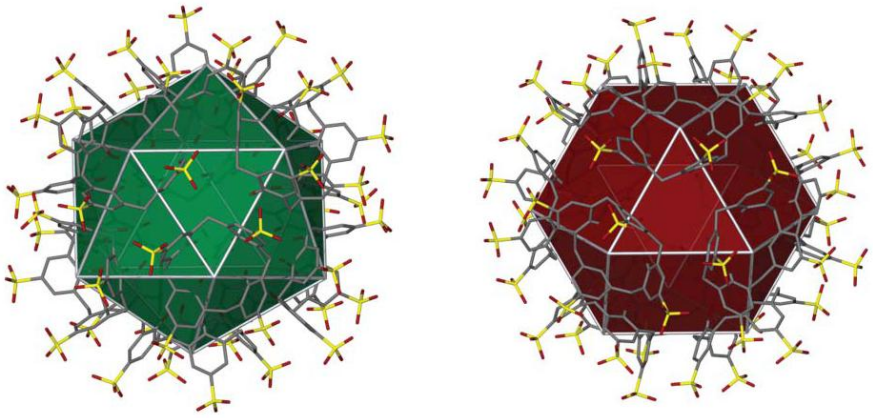


Figure 2.19. (a) The icosahedron (Platonic) and the cuboctahedron (Archimedean) [117].

2.2.7.5 Interlocking of large organic cation

Ionic organic solids based on calixarenes and phosphonium cations have been investigated by Raston *et al.* and the work highlights a remarkable structural versatility, and the exciting potential of building materials with applications in catalysis and supramolecular devices [124]. The reported structures are engage in association with their electrostatic attraction and self association via either π···π or C–H···π interactions as a route to building up new materials [124]. The first structure of tetraphenylphosphonium complexes was reported in 2004 where a pseudo polymorphic tetraphenylphosphonium complexes of *p*-sulfonatocalix[4]arene was observed [125]. The pseudo-polymorphic complexes formed in excess of tetraphenylphosphonium cations have a phenyl group of the cation that snugly fits into the calixarene cavity, which is consistent with electrostatic considerations for the components in the structures, and associated with a disruption of the bilayer arrangement [125]. Hydrophobic phosphonium cations serve to extend the hydrophobic surface and expand the bilayers, effectively augmenting the hydrophobicity of these cations [124]. The pseudo-polymorphic structures differ in the manner of inclusion of the tetraphenyl phosphonium phenyl arm in the calixarene cavity and in the way of which two other tetraphenyl phosphonium cations associate, predominately by only one mode of intermolecular phenyl–phenyl interaction where both structures are lacking in concerted multiple phenyl interactions, with edge-to-face (**ef**) interactions prevalent in one structure while the other is the offset face-to-face (**off**) interactions. Formation of the tetraphenylphosphonium complexes is templated by trivalent lanthanide ions but is not necessarily incorporated into the structures at the expense of the less dense and hydrophilic/organic phosphonium cations [125].

An organic clay-like structure based on the same supramolecular tectons, notably tetraphenylphosphonium cations and *p*-sulfonatocalix[4]arene anions is formed, however in this structure the lanthanide cations are incorporated into the structure with

the calixarene taking on a -5 charge and with water included in the cavity [126]. The phosphonium cations are now arranged within the bilayers in phenyl-embraced columnar arrays, as opposed to the complexes formed in the presence of excess phosphonium cations have the calixarenes arranged in columnar arrays. The overall structure is reminiscent of the arrangement of clay minerals and ion exchange resins [126, 127].

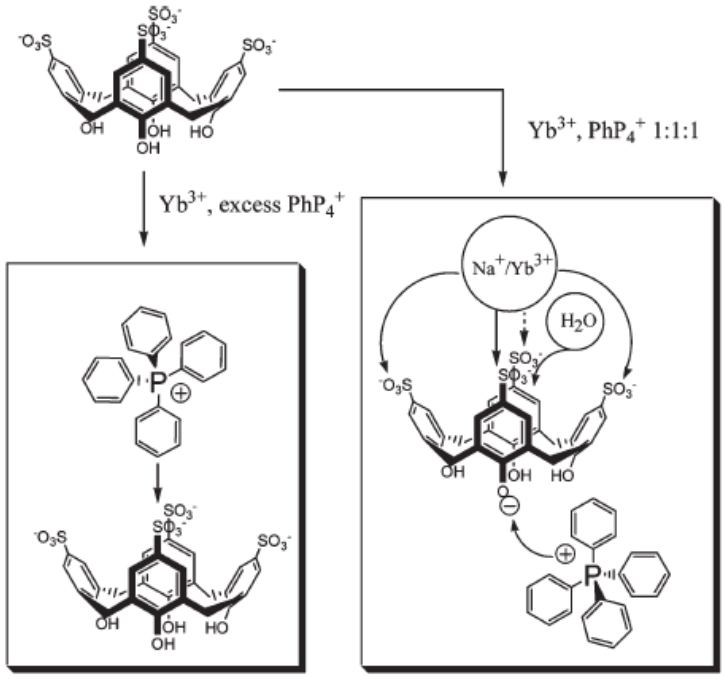


Figure 2.20. Interaction of tetraphosphonium and ytterbium cations with *p*-sulfonatocalix[4]arene at different molar ratios [126].

2.2.8 General structural motifs of sulfonated calix[6]arene

p-Sulfonatocalix[6]arene has larger cavity and possess higher conformational flexibility as compared to *p*-sulfonatocalix[4]arene in which two general conformations are typically observed; 'up–down double partial cone' and 'up–up double cone' [128-132]. Supramolecular structures involving complexation of pyridine *N*-oxide molecule and *p*-sulfonatocalix[6]arene with transition metals (Ni^{2+}) or lanthanides (La^{3+}, Eu^{3+}) demonstrates solid state structures which deviates from the typical bilayer arrangement[130, 133]. With the incorporation of nickel(II) ions *p*-sulfonatocalix[6]arene adopts the double partial cone conformation which acts as a ditopic receptor to two pyridine *N*-oxide molecules with hexaaquanickel(II) cations residing in the hydrophilic regions within the bilayer [133]. When the similar system is replaced with lanthanide(III) metal a corrugated bilayer is formed where there is one pyridine *N*-oxide molecule bound to one metal center [130]. *p*-Sulfonatocalix[6]arene-pyridine *N*-oxide–ytterbium afforded sheet arrangements through intra- and inter-molecular interactions were observed [134]. Two supramolecular tectons were identified: (i) two octacoordinate ytterbium ions bound to opposing sulfonate groups of the calixarene with one pyridine *N*-oxide ligand bound to the metal center while residing in the partial cone of the calixarene and (ii) two lanthanide metal centers are coordinated to opposing sulfonate groups within the calixarene with one pyridine *N*-oxide ligand resides in one partial cone of the calixarene, while another resides in the partial cone of the nearest identical tecton [134].

Variation of stoichiometric amounts of 18-crown-6 and selected lanthanide(III) chlorides reflects in some control on the *p*-sulfonatocalix[6]arene conformation and this has been reported by Raston and co-workers [128]. The calixarene may adopt an 'up-up double cone' conformation or centrosymmetric 'up-down double partial cone' conformation, depending on the ratio of the guest used and the nature of the lanthanide

metal. The calixarene adopts the 'up-up double cone' conformation in the presence of smaller lanthanides, complex has a double "molecular capsule" arrangement with two *p*-sulfonatocalix[6]arenes shrouding two 18-crown-6 molecules, where as when larger lanthanides are introduced, "ferris wheel" arrangement is observed. However in large excess of 18-crown-6 the *p*-sulfonatocalix[6]arene adopts the 'double partial cone' conformation with the calixarene acting as divergent receptor towards disc-shaped crown ether molecules. The formation *bis*-molecular capsule is observed for the complex of *p*-sulfonatocalix[6]arene with tetraphenylphosphonium cations in which the tetraphenylphosphonium cation pair is encapsulated by two calixarenes in the "pinched" "up-up" double cone conformation [129].

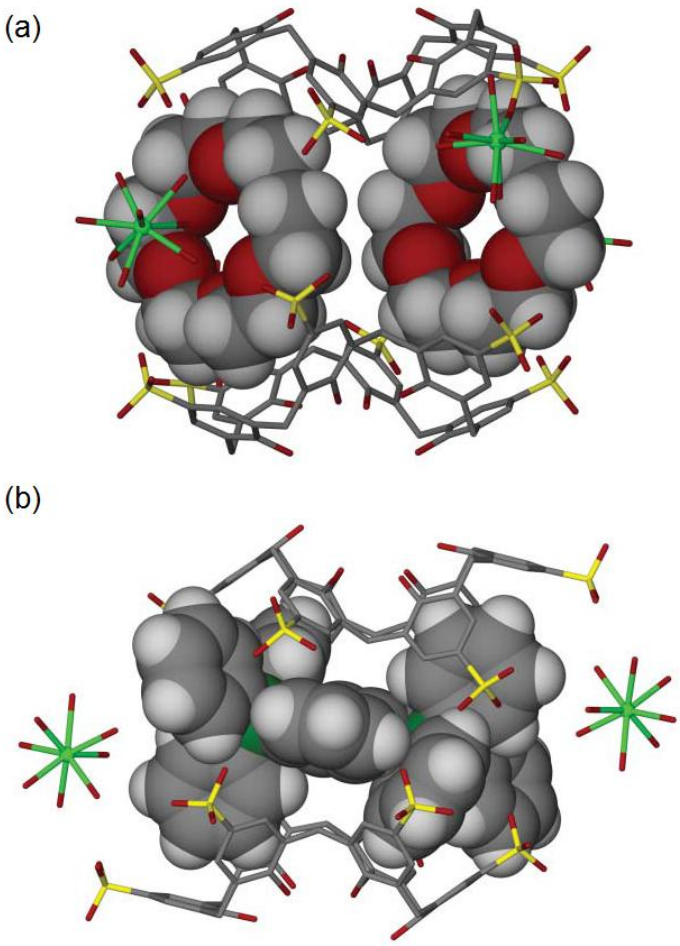


Figure 2.21. *Bis*-molecular capsule arrangement formed by *p*-sulfonatocalix[6]arene shrouding (a) two 18-crown-6 molecules and (b) two tetraphenylphosphonium cations[117].

2.2.9 General structural motifs of sulfonated calix[8]arene

The first supramolecular structure incorporating *p*-sulfonatocalix[8]arene was reported by Raston *et al.* where the calixarene adopts a "pleated loop" conformation which has four "grooves" on either side of the macrocycle and each groove is occupied by a 4,4'-dipyridine-*N*,*N*'- dioxide molecule [135]. The guest molecules with some being europium bound and some non-coordinated interact with the calixarene by a series of π-stacking and C-H···π interactions while the calixarene acts as a linking unit in a complex 3D "wavy brick wall" coordination polymer. Similarly, Raston *et al.* have also established the formation of another complicated structures involving trivalent ytterbium cations and *p*-sulfonatocalix[8]arene [136]. The complex essentially forms skewed "molecular capsule" arrangement consists of two calixarenes, in the pleated loop conformation, effectively shroud three phosphonium ions, with disordered lanthanide ions binding to sulfonate groups as is often observed for many of the lanthanide complexes with smaller sulfonated calixarenes. The structure is complicated, consisting of pseudo molecular capsules of *p*-sulfonatocalix[8]arene forming an overall layered structure where the calixarenes are in bilayer arrangement and the sulfonate groups are alligned on the surface of the capsules creating a criss-crossed large channels filled with water molecules and aquated ytterbium cations forming 2D porous solid [136].

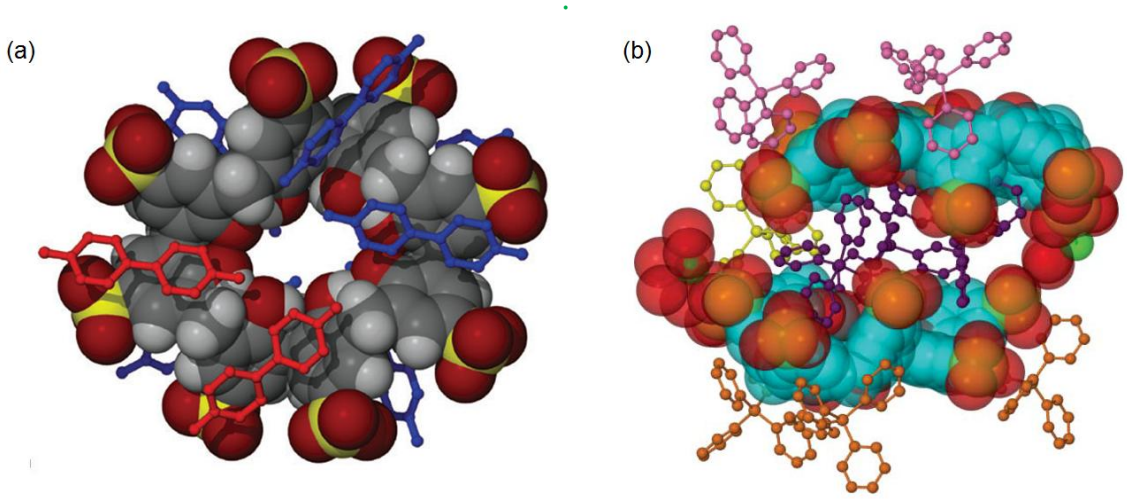


Figure 2.22. (a) 4,4'-dipyridine-N,N'-dioxide molecules in the grooves of the calixarene and complexation with aquated europium(III) ions and (b) 'molecular capsule' based on two calixarenes and three encapsulated tetraphenylphosphonium ions [135, 136].

The first example of *p*-sulfonatocalix[8]arene forming chalice-like cavity in the solid state inclusion of coordination complex involving tris(phenanthroline)cobalt(III) ($[Co(phen)_3]^{3+}$) and trivalent ytterbium cations was reported in 2006 [137]. The encapsulation of globular shaped $[Co(phen)_3]^{3+}$ cation results in a disruption of the calixarene hydrogen bond network associated with the phenolic moieties, and the wrapping of the flexible host around the guest. Two cations are associated externally to each supermolecule and the guest cations are held distant from each other through encapsulation by three calixarenes, with each calixarene in a pleated loop conformation, distorted acting as a heterotritopic receptor for $[Co(phen)_3]^{3+}$ cation. The structure is comprised of a honeycomb lattice of parallel, tubular assemblies with the centre of each tube being occupied by aquated ytterbium ions.

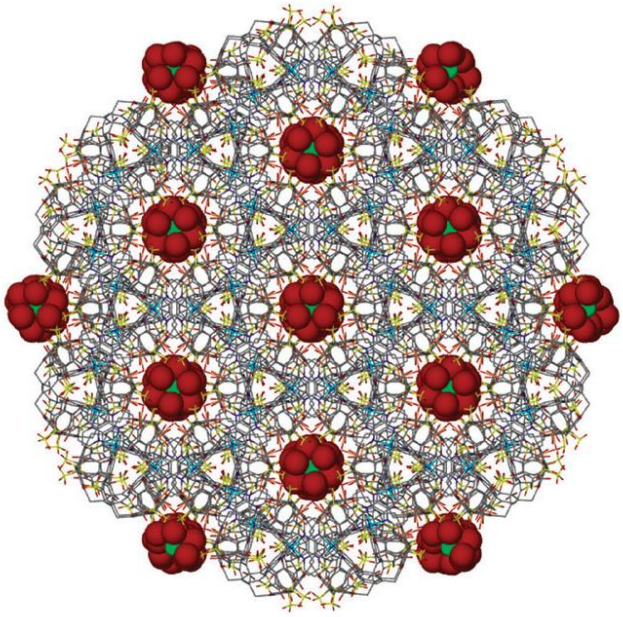


Figure 2.23. Supramolecular array showing the occupation of the channels by aquated ytterbium (III) ions [137].

2.3 Ionic liquids

Main interest to substitution of conventional solvents is renowned to ionic liquid which has its application expanded from electrolytes in electrochemical cells [138-140] to solvents in separation [141-145] and catalytic reactions [146-147]. Paul Walden reported the synthesis and properties of the "first" low melting temperature ionic liquid, ethylammonium nitrate in 1914 which was prepared for electric conductivity measurements [148]. In mid-1970s, room-temperature ionic liquids, alkylpyridinium or 1,3-dialkylimidazolium haloaluminate salts were discovered by research groups in Colorado State University and in the Air Force Academy [149]. Ionic liquid is attractive due to its unique properties such as large liquidus range, negligible vapour pressures at room temperature and high solvating capacity for organic, inorganic and organometallic compounds which makes it a good candidate as alternatives to volatile organic solvents. Ionic liquids are ionic salts in molten state at room temperature and often labelled as 'designer solvents' because their physicochemical properties can be fine tuned by the choice of the cation and/or the anion which can be designed for a particular application[150-152].

The design of ionic liquids usually consists of bulk organic cations with low symmetry, weakly interacting with mononuclear or polynuclear anions [153]. Particularly asymmetrical cations such as ammonium [154-156], imidazolium [157-160], pyridinium [161-163], pyrrolidinium [164], and phosphonium [165] have been widely studied. Pertaining to the anions, mononuclear anions such as BF_4^-, PF_6^-, $N(CF_3SO_2)_2^-$, $CF_3SO_3^-$, SCN^-, $N(CN)_2^-$, $C(CN)_3^-$, etc. usually form neutral and stoichiometric ionic liquids [153]. The strong anion–cation electrostatic interaction is believed to be the major source of interaction in an IL and will vary depending on the charge distribution within an anion[166]. The physicochemical spectrum of the ionic liquid is larger than that of organic solvents and has been predominantly published [153]. Variation of combined

cation and anion determines the properties of the ionic liquid with studies showed that the anion has the dramatic effect on the water miscibility properties while the modification of alkyl substituents of the cation could change the hydrophobicity and the viscosity of the ionic liquid, with densities and surface tension varied as well [141, 167, 168].

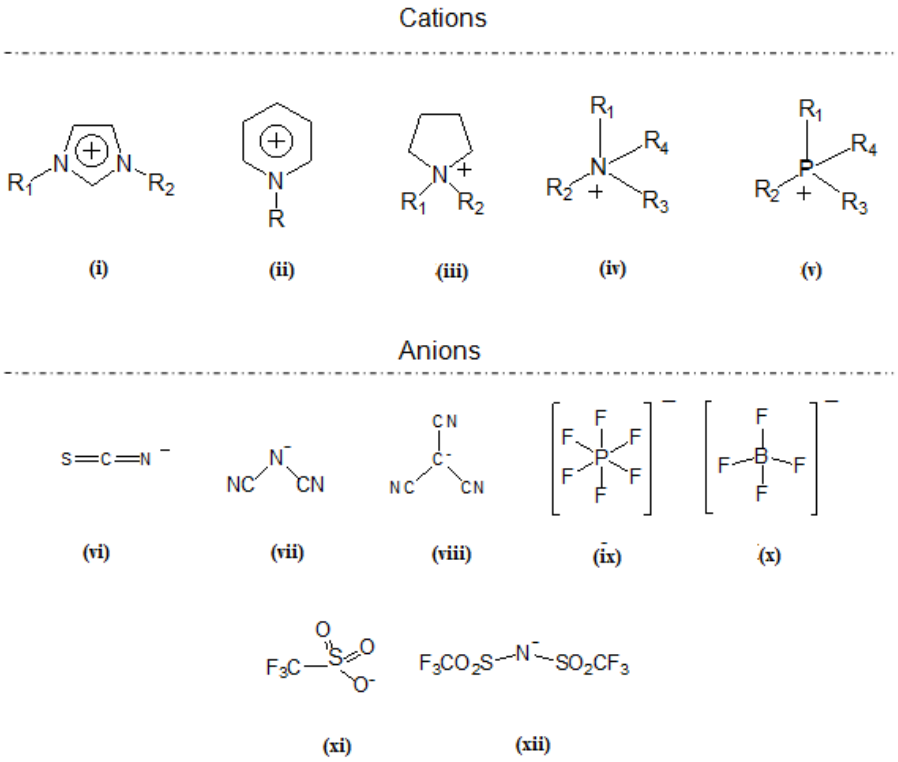


Figure 2.24. Imidazolium (**i**), pyridinium (**ii**), pyrrolidinium (**iii**), ammonium (**iv**), phosphonium (**v**), SCN^- (**vi**), $N(CN)_2^-$(**vii**), $C(CN)_3^-$ (**viii**), PF_6^-(**ix**), BF_4^- (**x**), $CF_3SO_3^-$(**xi**), $N(CF_3SO_2)_2^-$(**xii**).

Imidazolium-based ionic liquids are commonly used and they can act both as hydrogen bond acceptors (anion) and donors (cation) and expected to interact with solvents with both accepting and donating sites, such as water [150]. The solubility of water in imidazolium-based ionic liquids is dependent on both the cation and anion hydrophobicity (structure and chain length) through the hydrogen bonding ability [150]. Therefore, imidazolium-based ionic liquids exhibit medium range ordering and have microphase segregation between polar and non-polar domains depending to the solute–solvent affinity [169]. In aqueous solutions the water molecules form strong hydrogen bonds with the anion rather than with the cation [170].

1-Alkyl-3-methylimidazolium [$C_n$mim] salts possess amphiphilic character which can induce the aggregation behaviour similar to that showed by cationic surfactants [171]. 1-Butyl-3-methylimidazolium cation, $[C_4mim]^+$ in combination with hydrophilic anions like Cl^-, Br^-, $[CF_3SO_3]^-$ or $[BF_4]^-$ are miscible with water, however when combined with $[C(CN)_3]^-$, $[PF_6]^-$ or $[N(SO_2CF_3)_2]^-$ it will results in phase splitting at room temperature [150]. It is also noteworthy that when the alkyl side chain of the cation becomes sufficiently long, the ionic liquid–water system can lead to phase split which then can self-assemble to form micelles and lyotropic liquid crystals, as in the case of 1-octyl-3-methylimidazolium tetrafluoroborate [150]. Hardacre *et al.* [172] studied the organisation of ionic liquid molecules and suggested the existence of a long-range structure in which the anions and cations are arranged alternately. The crystal of imidazolium ionic liquids is formed by anions surrounded by columns of imidazolium cations which arranged into hydrophilic channel assembled by hydrophobic interactions between *n*-alkyl groups of the alkyl cation.

Golovanov *et al.* [173] reported the interionic interactions analysis of 1,3-dialkylimidazole based ionic liquids containing the Br^- anion in the crystalline state. The analysis of the crystal packing revealed three main types of the supramolecular

arrangement of the ions in the crystalline state: chains, layers, and three dimensional frameworks, Figure 2.25. The crystal structure of 1,3-diisopropylimidazolium cation consists of chains formed through the CH···Br contacts with the hydrogen atoms of the imidazole ring, the hydrophobic alkyl substituents forming the outer surface of the chains. The coordination polyhedron of the anion is not completely filled by contacts with the cation but can be additionally coordinated by external solvent molecules on the crystal surface. The crystal packing consisting of layers was found in the crystals containing ionic liquids 1-ethyl-3-methylimidazolium and 1,3-dipropylimidazolium, while bulkier alkyl substituents of imidazolium cation such as 3-methyl-1-propylimidazolium and 1-butyl-3-methylimidazolium prefer to form a three-dimensional framework containing channels filled by alkyl substituents where in all cases the crystal structures are stabilized by CH···Br interaction.

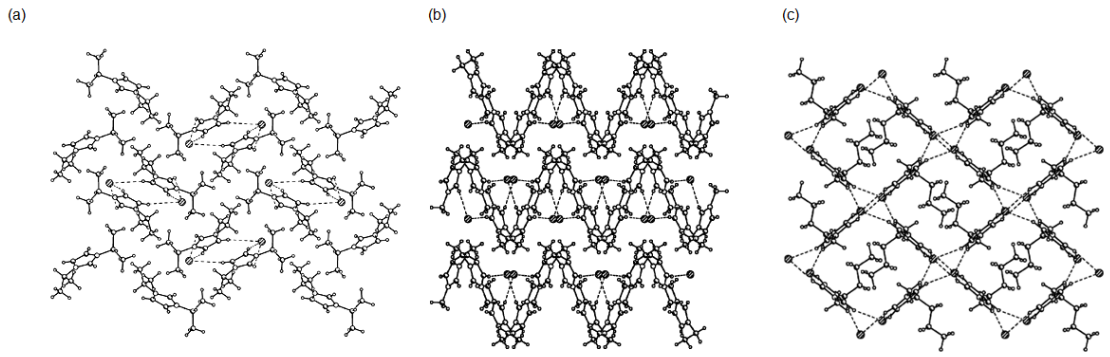


Figure 2.25. Crystal packings of dialkylimidazolium cation, illustrating the supramolecular arrangement of molecules as (a) chains, (b) layers and (c) 3-D framework [173].

2.3.1 Synthesis

Imidazolium-based ionic liquids are commonly prepared in an inert and dry atmosphere of dinitrogen, in two-steps synthesis which generally derived from a corresponding common precursor, the 1-alkyl-3-methylimidazolium halide [174, 175]. The precursor is prepared by quaternization reaction of the 1-methylimidazole with functionalized alkyl halide to afford the corresponding functionalized imidazolium halides in usually good yield. The following step involves the anion exchange reaction, where the precursor is either reacted with a Group 1 metal salt, in particular a sodium salt, or a silver salt of the desired anion in a metathetic reaction, or in an acid-base neutralization reaction. The metathetic and acid-base method is conducted in water at room temperature or organic solvents. Depending on the nature of the anion, the resulting ionic liquid forms either a biphasic system with water, or a homogeneous solution. For ionic liquid which forms biphasic system with water, an aqueous extraction is necessary to remove the halide resulting in halide-free ionic liquids. However for water-miscible ionic liquids, the metathetic reaction involves the removal of water under reduced pressure, addition of trichloromethane, and repeated cooling to precipitate the metal halide followed by several filtration steps. The procedures of the water-miscible ionic liquids prepared by the acid-base method includes repetitive addition of water and removal of water/acid under reduced pressure [175].

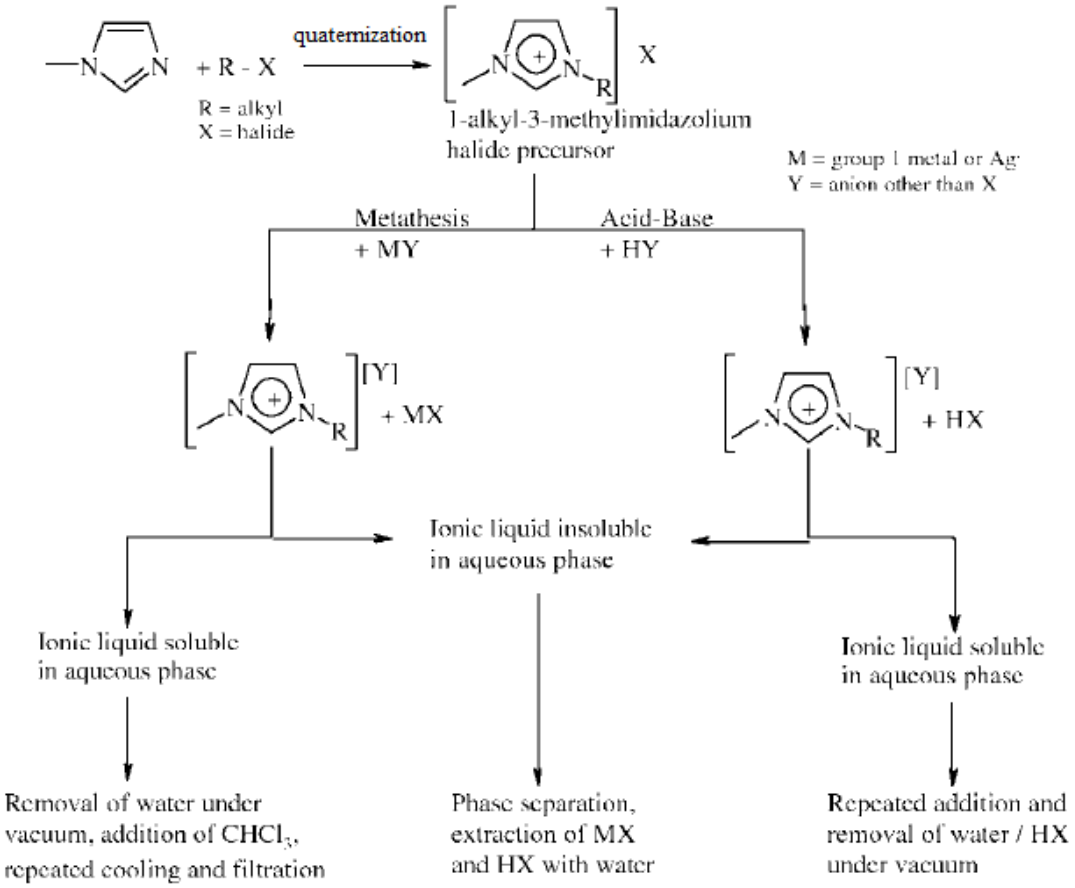


Figure 2.26. Preparation and work-up procedures for ionic liquid synthesis. [175]