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Calix[8]arenes Solid-State Structures: Derivatization and Crystallization Strategies

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1. Introduction

The macrocycles known as calix[*n*]arenes, where *n* represents the number of phenolic units bridged by methylene groups, represent ideal building blocks in supramolecular chemistry for the development of scaffolds with a preorganized structure, a well-defined cavity size, and modifiable positions for the introduction of a variety of functional groups, as shown in Fig. 1 (Böhmer, 1995; Asfari et al., 2001). The development of novel calixarene derivatives with the capability to act as receptors, sensors, catalysts, or ion transporters designed for specific purposes has been exploited to a great extent with the smaller member of the family calix[4]arene, and to a lesser degree with calix[6]arene. In the particular case of calix[4]arenes, the ease of modification by introduction of several types of functional groups at the phenolic rim has led to the development of numerous examples of versatile compounds (Baklouti et al., 2006; Baldini et al., 2007). The variety of derivatives reported to date is related to the well established synthetic protocols, which allow the preparation of calix[4]arenes with regio- and atropisomeric control by deprotonation of the phenolic OH groups with specific alkali-metal bases. These synthetic methods have been extended to the more recently developed thiacalix[4]arenes, which feature sulfur atoms as bridging groups between the phenolic components.

The development of systems based on the larger members of the calixarene and thiacalixarene families, namely calix[8]arene and thiacalix[8]arene (from now on referred to indiscriminately as calix[8]arenes), has been slow relative to its smaller analogues. This is likely due to the number of phenolic OH and aromatic positions available for functionalization, for which the regioselective introduction of substituents remains a challenging synthetic task. As a consequence, reports on crystallographically characterized calix[8]arene derivatives are relatively sparse. While the solution structures can be determined by a variety of methods, notably NMR spectroscopy, crystallographic characterization still represents the most reliable proof of the spatial arrangement of the macrocycles, particularly when the mobility of the large calix[8]arene is concerned. The limited availability of structural data is likely related to the large number of degrees of freedom present in the larger macrocycles, which does not allow the long-range ordering required for single-crystal formation. A search of the Cambridge Structural Database affords 89 structures of methylene-bridged calix[8]arenes, compared to the numbers of the four- and six-member macrocycles (Table 1).

p-R-calix[4]arene   *p*-R-calix[6]arene
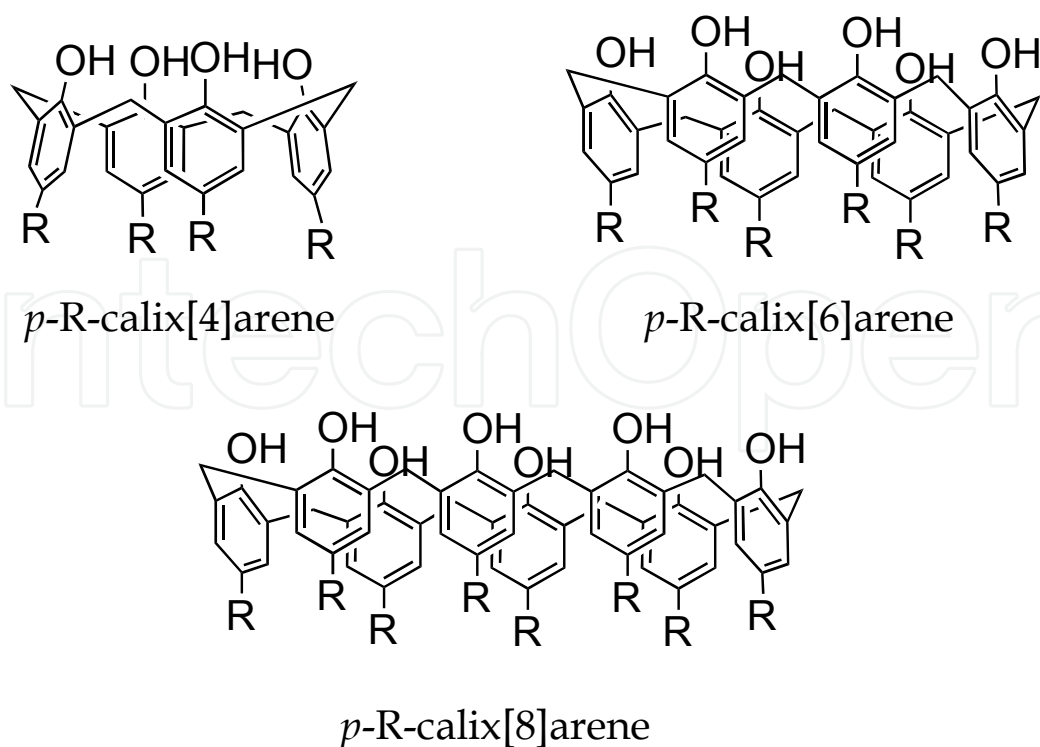

p-R-calix[8]arene

Fig. 1. Schematic representation of calix[*n*]arenes

The current chapter covers the synthetic strategies that have proven successful for the preparation of calix[8]arene derivatives amenable for structural characterization. One of them involves the formation of anionic derivatives, which are obtained by deprotonation of the phenolic OH groups, and render the calix[8]arenes as ligands towards main group and transition metals. Formally anionic phenolate derivatives have also been obtained by elimination of HCl from the reaction of calix[8]arenes with oxophilic transition-metal chlorides. These strategies have resulted in the prevalence of structural information on the 8-member macrocycles in which the calix[8]arene framework becomes rigid due to the formation of multiple oxygen-metal-oxygen bridges (Redshaw, 2003).

Compound	Number of structures
Calix[4]arene	2227
Calix[6]arene	283
Calix[8]arene	89

Table 1. Crystallographic structures reported in the CSD.

The other general strategy described in this chapter is the one involving the introduction of intramolecular covalent bridges to limit the conformational flexibility of calix[8]arenes (Geraci et al., 1995). In this respect, the use of cesium salts has allowed the regioselective introduction of covalent bridges to the 1 and 5 phenolic positions of *p-tert*-butylcalix[8]arene (Cunsolo et al., 1994). The importance of 1,5-substitution (or 1,5-3,7 substitution) resides in the high symmetry of such derivatives, relative to 1,2- or 1,4- derivatives, which appears to result in better packing interactions. In this context, we will discuss the introduction of nitrogen-containing spanning elements, which could lead to the development of new types

of receptors, as well as for the binding of non-oxophilic metals within the calixarene cavity. These include our recently reported 1,5-disubstituted *p-tert*-butylcalix[8]arene by introduction of a 2,6-dimethylpyridyl group (Hernández & Castillo, 2009). A general overview on the crystallization techniques for each type of calix[8]arenes derivative accompanies the discussion.

2. Discussion

Original reports on the synthesis of the parent *p-tert*-butylcalix[8]arene date back to 1955 (Cornforth et al., 1955), where it was described as a high-melting solid with a proposed octameric structure, based on osmometry and mass spectrometry (Gutsche & Muthukrishnan, 1978; Muthukrishnan & Gutsche, 1979). Unambiguous structural assignment as an octaphenol-containing macrocycle by X-ray crystallography was initially precluded by solvent loss from the plates obtained by recrystallization from chloroform. It therefore seemed necessary to obtain calix[8]arene derivatives that did not lose solvent readily under ambient conditions, in order to afford single crystals amenable for structural characterization.

One property of calix[8]arene that was inferred from the structure of its smaller congener calix[4]arene is its large macrocyclic cavity, although crystallographic characterization was needed in order to corroborate it. Confirmation of its large cavity size in the solid state made it an attractive alternative to crown ethers for the potential binding of large cationic species. Among other possibilities, this property placed it as an ideal candidate for the selective binding of oxophilic heavy metals, including alkali, alkaline earth, lanthanide and actinide metals through the phenolic oxygen atoms. It is therefore natural that some of the first crystallographically characterized calix[8]arene derivatives consisted of metal complexes where the usually flexible structure of the macrocycle becomes relatively rigid due to the presence of multiple oxygen-metal ion-oxygen bridges. These types of derivatives were extended to *p*-block elements, including metals and non-metals such as phosphorus, germanium and bismuth.

2.1 Description of solid-state structures
2.1.1 Unfunctionalized calix[8]arenes

Although chronologically the parent *p-tert*-butylcalix[8]arene was not the first calix[8]arene to be structurally characterized due to loss of solvent molecules when crystallized from chloroform, it was obtained shortly after the first report of a calix[8]arene derivative; crystals stable enough towards solvent loss were successfully obtained from the high-boiling (115 °C) solvent pyridine (Gutsche et al., 1985). Subsequent reports include the chloroform and acetonitrile clathrates (Schatz et al., 2001; Dale et al., 2003), as well as a new determination of the pyridine-derived crystals (Huang et al., 2001); the structure of calix[8]arene with H atoms in the *para* positions also includes a molecule of the solvent pyridine (Zhang & Coppens, 2001). The aforementioned cases are described as clathrates despite the pleated loop conformation adopted by the macrocycle (Fig. 2), which is favored by the maximization of intramolecular hydrogen bonding. This configuration lacks a well-defined, deep cavity for inclusion to take place, although the incipient guest molecules may interact via hydrogen bonds, particularly in the case of pyridine.
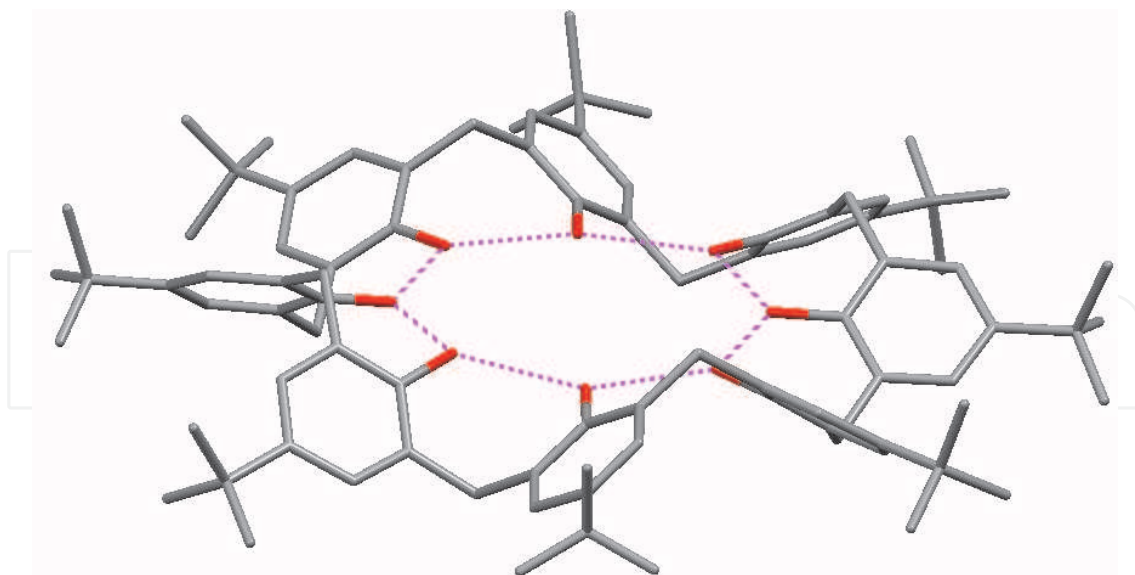
Fig. 2. Depiction of the pleated loop conformation of *p-tert*-butylcalix[8]arene with intramolecular hydrogen bonds shown in magenta (generated from Schatz et al., 2001)

Among calix[8]arenes without substituents at the phenolic positions that have been structurally characterized, the compound obtained by condensation of silyl-protected bisphenol A with formaldehyde resulted in the *p*-2-(4-hydroxyphenyl)propylcalix[8]arene (Ahn et al., 2000). Crystallization involved isopropyl ether diffusion into an acetone solution of the macrocycle, and the presence of *n*-Bu$_4$NBF$_4$ appeared to be necessary although its role is not understood. A related compound is the *p*-cumylcalix[8]arene analogue (Ettahiri et al., 2003), which was obtained by slow evaporation from dimethylsulfoxide (DMSO) solution in an alternate conformation, with two phenolic units up and two down around the macrocycle. In addition to the high boiling point of the solvent (189 °C), four molecules of DMSO form hydrogen bonds with the OH moieties, thus stabilizing the crystalline arrangement. A more recent example of an unsubstituted calix[8]arene features two deprotonated phenolic units in 1 and 3 positions of the macrocycle, and was obtained from an octasilylated precursor by fluoride attack with 2 equivalents of *n*-Bu$_4$NF$^.$(H$_2$O). This reaction results in the formation of (*p-tert*-butylcalix[8]arene-2H)(*n*-Bu$_4$N)$_2$, which was crystallized from a mixture of the polar aprotic solvent dimethylformamide (DMF, b.p. 153 °C), and acetone in a 10:1 ratio (Martínez-Alanis and Castillo, 2005). The macrocycle adopts a conformation that is very similar to the pleated loop described for the parent *p-tert*-butylcalix[8]arene, with one tetrabutylammonium cation hosted within the cavity probably due to electrostatic interactions with the phenolate units.

2.1.2 Octasubstituted calix[8]arene derivatives

Initial motivation for the preparation of calix[8]arene derivatives arose from the need to substantiate its octameric structure by X-ray crystallography. Naturally, the most easily accessible derivatives are the phenolic *O*-octasubstituted compounds, which circumvent the problem of selectively introducing a limited number of functional groups at the phenolic positions. As mentioned in section 2.1.1, chronologically the first successful attempt to obtain a stable, crystalline derivative was the report of *p-tert*-butylcalix[8]arene acetylated at all the phenolic oxygen atoms (Andreetti et al., 1981). The octasubstituted derivative was

crystallized from the high-boiling acetic acid (118 °C), which likely prevented the problems associated with the loss of crystallization solvent observed for the parent *p-tert*-butylcalix[8]arene. In what would later become a recurring observation, the *p-tert*-butyl groups were disordered over at least two positions with occupancy factors close to 0.5 each. Analogous octasubstituted compounds represent some of the first examples of structurally characterized calix[8]arene derivatives, with a growing number reported in recent years. The initial report of the completely acetylated calix[8]arene was followed by the structure of the octa-*O*-substituted macrocycle with 1,1,3,3-tetramethylbutyl substituents in the *para* phenolic positions (Ungaro et al., 1985). This compound was crystallized from the polar solvent mixture acetone/methanol in a 1:1 ratio, although no guest molecules are present in the structure; this is probably due to the self-inclusion of four of the *O*-(2-methoxy)ethyl substituents filling the macrocyclic cavity. Shortly afterwards the *para*-H methyl ether analogue (Coleman et al., 1986), in which a clathrate was obtained by ethyl ether diffusion into a deuterated chloroform solution, was also reported. The molecules of $CDCl_3$ were described as being partially hosted within the calixarene cavity, and it is important to note that data were collected with the crystals kept in a sealed capillary with the mother liquor. This likely prevented loss of the relatively volatile chloroform, which does not appear to be tightly bound to the calixarene.

O-methylated derivatives abound among structural reports, with different substituents such as *t*-Bu, Br, and NO_2 at the *para* positions of the phenol. The former was crystallized from chloroform solution as the clathrate (Bolte et al., 2002). Crystals of the *p*-bromo derivative have been obtained from CCl_4 (Baudry et al., 2003) and tetrahydrofuran (Bolte et al., 2003), in both cases by slow evaporation of solvents resulting in two molecules of each being hosted within the macrocyclic cavities. The *p*-nitro analogue crystallized from tetrahydrofuran (THF), but the solvent molecules in the structure are not included within the cavities (Podoprygorina et al., 2003); instead, two nitro groups on nitroanisole units opposite to each other in the macrocycle fill the cavity. The molecules of THF present in the structure fill the voids between stacks of the calix[8]arenes, which are stabilized by π-π interactions. In a related *p*-Br octa-*O*-butyl calix[8]arene, crystal packing appears to be promoted by Br-π interactions (Perret et al., 2007). The absence of solvent molecules in the latter structure is explained by the orientation of six butoxy groups towards the macrocyclic cavity.

The *p*-OH octapropylated calix[8]arene derivative has been crystallized from pyridine/water (Leverd et al., 2000), as well as from acetone (Leverd et al., 2000a). In both cases, the structures are stabilized by the presence of H-bonds between the solvent molecules and the *para*-hydroxy groups. The cavities are partially filled by the self-inclusion of *O*-propyl groups in both reports, with no solvent molecules hosted inside. Two final examples of octasubstituted calix[8]arene feature the ester groups –CH_2CO_2Et (Volkmer et al., 2004; Yan et al., 2009), and although it is not explicitly reported in the latter, in the former case the compound was crystallized from ethanol. These derivatives differ in the *p*-(1,1,3,3-tetramethylbutyl) and *p-t*-Bu substituents, with both adopting the familiar cone conformation commonly observed for calix[4]arenes, and two phenolic units on opposites ends of the macrocycle tilted towards the cavity. The ester groups attached to these phenol moieties are self-included, thus rendering the presence of ethanol within the cavity unnecessary. Nonetheless, the former structure does contain 2 hydrogen-bonded solvent molecules.

2.1.3 Calix[8]arene complexes with alkali and alkaline-earth metals

The ion-binding and transporting properties of calixarenes have been of particular interest for the development of novel derivatives analogous to the crown ethers. In this context, the oxygen-rich environment of calixarenes is ideal for the preparation of the oxophilic alkali and alkaline-earth metal complexes; in the case of calix[8]arenes, speculation on their potential to support polynuclear assemblies received confirmation from the initial solid-state characterization of a dipotassium complex (Clague et al., 1999). The macrocycle adopts a pinched conformation, with phenolic OH groups bridging the potassium ions at the pinch (Fig. 3). Surprisingly, the formally anionic oxygen atoms are located furthest from the K^+ ions; although this disposition of oxygen donors may seem counter-intuitive, it has been observed in related Cs^+ systems (Hernández & Castillo, 2009). This arrangement appears to be favored by intra-calixarene hydrogen bonds, with further stabilization by molecules of ethanol that was employed as solvent in combination with diethyl carbonate. In addition, molecules from the solvent mixture also play a role in coordinating to the cations. A related potassium complex featuring two K^+ ions sandwiched between two monoanionic calix[8]arenes (Bergougnant et al., 2005) was crystallized from the water/THF interface. In contrast to the dipotassium complex described by Clague and coworkers, in the complex reported by Bergougnant et al. the phenolate is bound directly to the K^+ ion, while the molecules of water present in the structure form H-bonded clusters.

The water/THF interfacial strategy for the crystallization of mono- and dianionic *p-tert*-butylcalix[8]arenes with alkali metal cations has been exploited by the group of Fromm (Bergougnant et al., 2007). The method consists of the dissolution of the metal carbonates in water, while the calix[8]arene is suspended in THF and then layered on top of the aqueous solutions. For the lighter alkali metals Li and Na, dianionic calix[8]arene complexes of general formula $M_2(calix[8]arene-2H)(THF)_x(H_2O)_y$ were obtained, whereas the heavier congeners K-Cs afforded monoanionic complexes of the type $M(calix[8]arene-H)(THF)_x(H_2O)_y$. In the latter, the relatively flat conformation of the macrocycles resulted in stacks that incorporate the alkali cations and water molecules aligned with the phenolic OH groups, thus generating inorganic channel-like structures.

Mixed alkali/alkaline-earth complexes have been obtained with *p-i*-Pr and *p-i*-Bu-calix[8]arenes from DMF. The crystallization method was not clearly stated, although it appears that the crystals formed on standing after 72 hours (Clague et al., 1999a). It is quite evident that the macrocycle becomes rigid upon metal complexation, since all the calixarene O atoms are involved in coordination to the four Li^+ and two Sr^{2+} cations in both structures; moreover, six of the macrocyclic oxygen donors act as Li-O-Sr bridging ligands. Bimetallic strontium complexes have also been prepared from octasubstituted calix[8]arenes (Casnati et al., 2000), with all carbonyl *O*-atoms of the eight amides present coordinating to the Sr^{2+} cations, which are additionally chelated by six of the eight phenolic oxygen atoms. Although the complexes differ in the *p*-substituents of the calix[8]arenes (*p*-OMe and *p-t*-Bu), as well as in the identity of the counter anions (picrate and chloride), the ¾ cone (or flattened partial-cone) conformations adopted by the macrocycles are very similar, likely with a similar degree of rigidity. A synergistic effect appears to be responsible for the coordination of the second strontium cation, since both reactions were initially attempted with a 1:1 molar ratio of calix[8]arene to Sr salt. In the case of the picrate, crystals were obtained from a solvent mixture that included acetic acid, which ultimately chelates the cations, fills the voids defined by the calixarene and the diethyl amide arms, and stabilizes the free picrates via H-bonds. In the latter case one chloride ligand remains coordinated to each strontium cation, while the extended structure is stabilized by H-bonded water and methanol molecules.
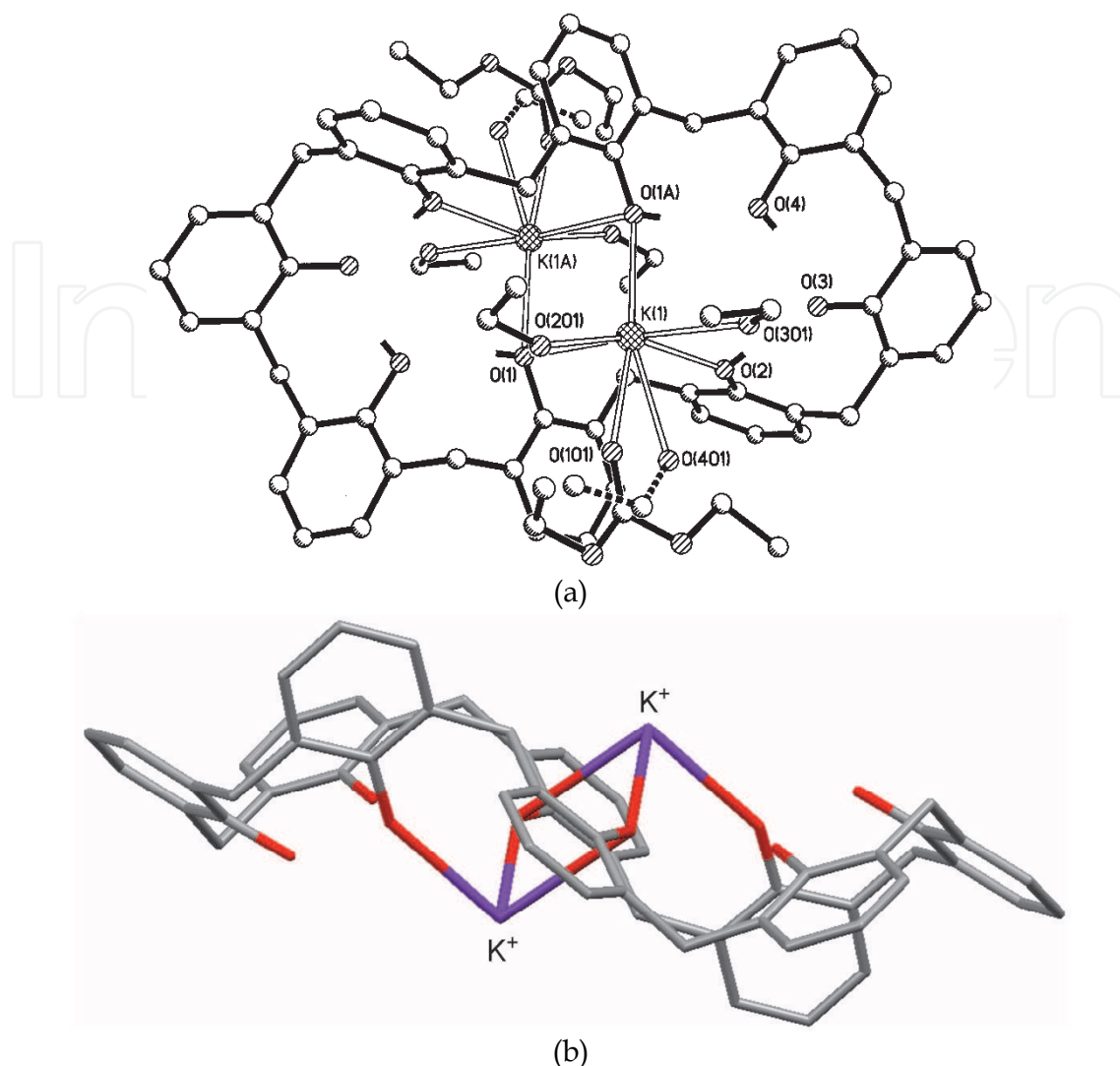
(a)

(b)

Fig. 3. a) Solid-state structure of the K+ complex of dianionic *p-tert*-butylcalix[8]arene (Clague et al., 1999); b) Side view of the pinched conformation, *p-t*-Bu groups and solvent molecules removed for clarity

In addition to the aforementioned complexes, a monometallic structure with Ca^{2+} and doubly deprotonated *p-tert*-butylcalix[8]arene has been reported (Harrowfield et al., 1991). In this example, only two adjacent phenoxide oxygen atoms coordinate to the metal, as well as solvent molecules of DMF (crystals were obtained by cooling a hot DMF solution of the complex). This results in high mobility for the calcium cation and apparent eight-fold symmetry, as evidenced by ^1H NMR spectroscopy in solution.

2.1.4 Calix[8]arene complexes with lanthanide and actinide metals
Lanthanide derivatives are among the first structurally characterized calix[8]arene-metal complexes. As in the case of alkali and alkaline-earth metals, speculation on their potential to act as scaffolds for polymetallic assemblies received early confirmation from the solid-state characterization of a dieuropium complex (Furphy et al., 1987). The macrocycle adopts a pinched conformation similar to that observed in a dipotassium complex (Clague et al., 1999), except for the fact that in the potassium complex there are two phenolic OH groups

bridging the metals, while in the europium case two phenoxide groups bridge the Eu^{3+} ions as depicted in Fig. 4a. Europium is the lanthanide with the highest representation among crystallographically characterized calix[8]arene complexes, with 4 other bimetallic examples reported. The sole exception to this general trend is the monometallic Eu^{3+} complex with a coordinated nitrate, analogous to the Ca^{2+} analogue described in the previous section (Harrowfield et al., 1991). All of the dinuclear complexes are essentially isostructural, whether they are crystallized from DMSO or DMF (Harrowfield et al., 1991a; Harrowfield et al., 1991b). Two of the europium complexes were obtained from *p*-NO$_2$ and *p*-H-calix[8]arenes; the former was crystallized from DMF (Bünzli et al., 1998), while the latter was obtained from DMSO solution (Fleming et al., 2003). The differences in the *para*-substituents do not affect the overall structural arrangement. In all cases the high boiling points and strongly coordinating properties of the solvents appear to be necessary to stabilize the crystal lattice, as well as to complete the coordination environment of the metal centers. Lanthanum and lutetium complexes were obtained from both DMSO and DMF, while the thulium analogue was exclusively crystallized from the former solvent. Finally, the analogous bimetallic praseodymium complex was obtained from DMF solution.

Regarding actinide metals, complexation of uranium and thorium is of particular interest due to the possibility to selectively bind the radioactive metals within the large macrocyclic cavities of calix[8]arene derivatives. Although the reports on uranium complexes far outnumber those of thorium, the latter was the first calix[8]arene-actinide complex to be structurally characterized (Harrowfield et al., 1991c). The structure of the thorium (IV) complex is unique due to the presence of two independent calix[8]arenes in the asymmetric unit with completely different conformations: one calix[8]arene ligand is in a pinched conformation, akin to that observed for the bimetallic lanthanides described above, while a second macrocycle adopts a conformation that approaches that of the free macrocyclic pleated loop; the two calixarenes assemble around Th^{4+} cations to afford a tetrameric core. Recrystallization of the complex from acetone afforded the DMSO/water solvate, with the DMSO molecules hosted within the cavities acting as terminal *O*-ligands towards the metal cations.

Polymetallic complexes have also been obtained from the reactions of uranium (IV) and *p*-H-calix[8]arene; the seemingly random reaction conditions reported (3 equivalents of UCl_4, pyridine or THF as solvents, absence or presence of NaH as base) resulted in bi-, tri- and pentauranium complexes, in one of the cases with 4 sodium ions associated. The trinuclear complex was the first to be reported, and pyridine was employed as solvent due to the poor solubility of the calix[8]arene in other solvents such as THF (Salmon et al., 2006). Pyridine likely solubilizes the macrocycle and facilitates its deprotonation upon metal complexation, resulting in an anionic complex $[U_3Cl_{11}(calix[8]arene-7H)]^{6-}$ that is charge balanced by six pyridinium cations. The latter stabilize the extended structure by H-bonding to phenoxide *O*-atoms, one chloride, and lattice pyridine molecules. In the case of the bi- and pentauranium (IV) complexes, deprotonation of calix[8]arene with NaH promotes the reactions with $U(acac)_4$ and UCl_4, respectively (acac = acetylacetonate). The bimetallic complex consists of polymeric chains connected by multiple Na-O bridges through the acac ligands. The conformation of the macrocycle is described as two partial-cones, fused together in a propeller-like fashion; each partial-cone binds one U^{4+} ion through the oxygen atoms, while a Na^+ ion with a pyridine ligand is hosted within each of the cavities defined by the four phenolic units. Likewise, the conformation of the two anionic calix[8]arenes in

the pentanuclear complex is described as distorted partial-cones. Each calixarene binds two uranium (IV) cations featuring additional chloride and pyridine ligands, while the fifth U^{4+} ion bridges the two calixarene ligands.
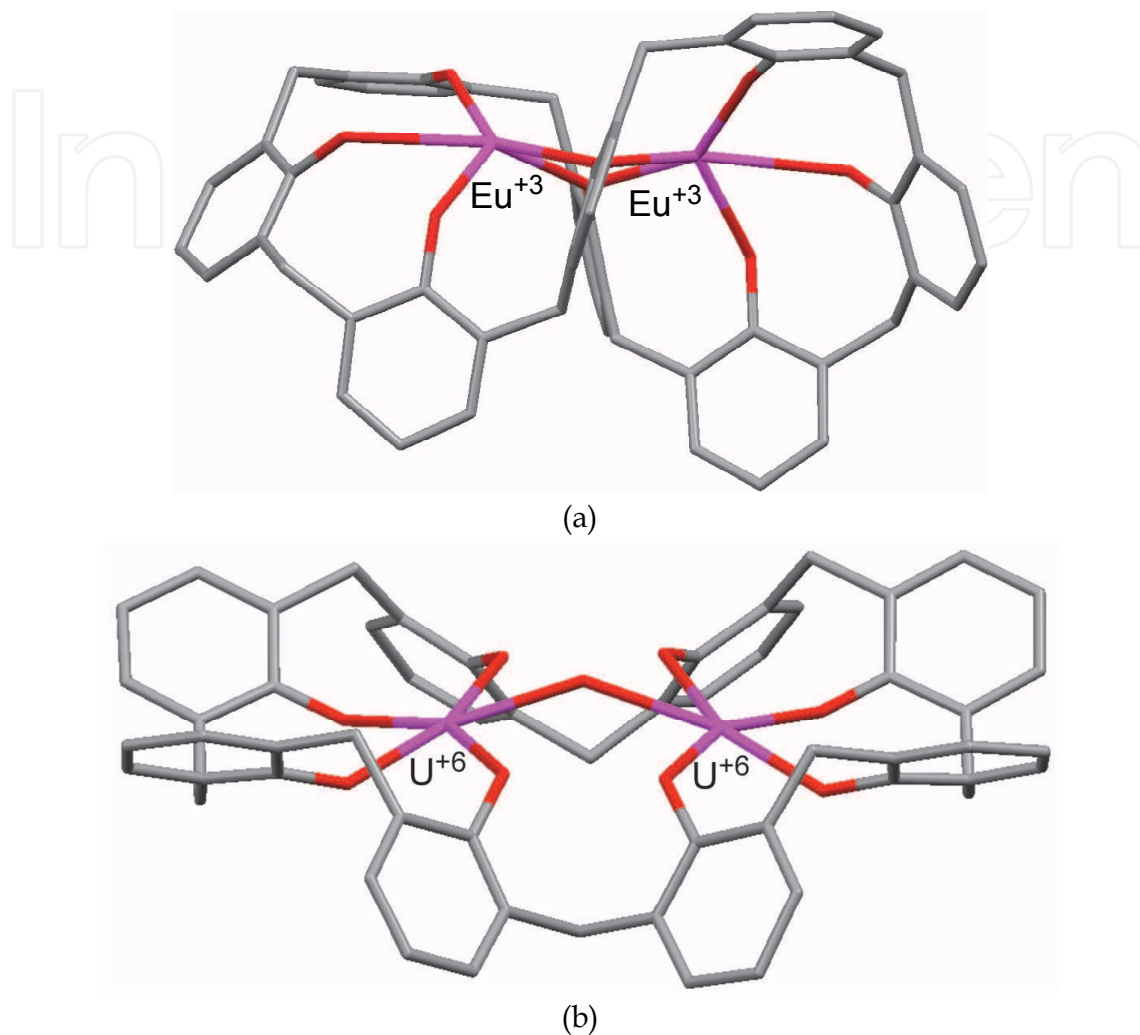

(a)

(b)

Fig. 4. a) Eu^{3+} complex of the hexaanionic *p-tert*-butylcalix[8]arene in pinched conformation (from Furphy et al., 1987); b) Pleated loop conformation of the μ-OH-bis(uranyl) complex (from Thuéry et al., 1995), *p-t*-Bu groups and exogenous ligands removed for clarity

Uranyl salts are more predictable in terms of the nuclearity of the complexes formed with calix[8]arene ligands than their uranium (IV) counterparts. A bimetallic complex was obtained by initial deprotonation of *p-tert*-butylcalix[8]arene with excess triethylamine in acetonitrile; two of the four uranyl oxo moieties interact with protonated triethylammonium cations, and the overall structure is characterized by hydrogen-bonded water and acetonitrile molecules (Thuéry et al., 1995). This diuranium (VI) species shares geometric features with one of the macrocycles observed in the structure of the thorium complex reported (Harrowfield et al., 1991c), in which the metal cations are coordinated by four phenolic oxygen atoms each, and bridged only by a hydroxyl ion. The phenolic units adopt a conformation close to that observed for the free *p-tert*-butylcalix[8]arene, which is commonly described as pleated loop, although with a distortion towards a saddle shape

(Fig. 4b). Thus, these complexes differ from the bimetallic lanthanide derivatives, in which phenolic bridges are always present. Nonetheless, the structure appears to be rigid due to the presence of the OH$^-$ bridge between the U^{6+} ions. A related uranyl complex with a very similar structure was reported, with the main difference being the presence of two equivalents of crown ether-encapsulated KOH (Thuéry et al., 2007).

2.1.5 Calix[8]arene complexes with transition metals

As in the case of lanthanides, reactions of transition metals with calix[8]arenes give rise predominantly to bimetallic complexes. This is likely due to the extended bridging that occurs, resulting in macrocycles with reduced flexibility relative to the free calix[8]arenes, making them amenable for crystallization. For example, the first report of a transition metal complex characterized in the solid state consists of a Ti^{4+} dimer (Hofmeister et al., 1989), with a chiral propeller-like macrocyclic conformation that is very similar to that of the Eu^{3+} complexes. Molybdenum and tungsten also give rise to bimetallic complexes in most cases, irrespective of the oxidation state of the metal. The highest oxidation state attainable for molybdenum in the Mo^{6+}-imido complex gives rise to an oxophilic metal center, which coordinates to four phenolates in the complex [(CH$_3$CN)Mo=NAr]$_2$(calix[8]arene-8H), Ar = 2,6-diisopropylphenyl; the macrocycle adopts a twisted conformation with no pinch, thus no bridging phenolates are present (Gibson et al., 1995). Two molecules of acetonitrile, which was employed as solvent for recrystallization of the complex, are bound to the molybdenum ions while hosted within the two cavities defined by each half of the macrocycle. A related tungsten(VI) hydrazido complex (hydrazido = NNPh$_2$$^{2-}$) was structurally characterized by diffraction experiments with synchrotron radiation (Redshaw & Elsegood, 2000). The complex is characterized by a twisted macrocyclic conformation, as well as bridging phenolates in *trans*-positions relative to the hydrazido ligands; the crystals were obtained from an acetonitrile/dichloromethane mixture, both of which are present in the structure as solvate molecules. Replacement of an imido or hydrazido ligand for an oxo moiety results in a very similar macrocyclic conformation in [(CH$_3$CN)W=O]$_2$(*p-tert*-butylcalix[8]arene-8H) (Redshaw & Elsegood, 2003).

The flexibility of the *p-tert*-butylcalix[8]arene backbone was demonstrated in the report of di-, tri- and tetratungsten complexes reported from the reaction with WCl$_6$ (Gibson et al., 2002). The bimetallic complex is of particular interest due to the presence of a W-W triple bond, formed upon reduction of the dinuclear W^{6+} precursor to W^{3+} with sodium amalgam; moreover, the conformation adopted by the macrocycle is unique for transition metal complexes, and was described as two ¾ cones (cups) facing each other. As in the case of many other complexes, crystallization was achieved from acetonitrile solution, which stabilizes the structure by coordination to the sodium cations necessary to charge-balance the anionic ditungsten-calixarene complex.

Although chronologically developed at a later stage, the group 5 metals vanadium and niobium have also been employed in the preparation of bimetallic calix[8]arene-derived complexes. The bimetallic V^{5+}-imido (imido = N-*p*-tolyl^{2-}) complex has a structure similar to that reported for the Ti^{4+} complex described above, with bridging phenoxides in *trans*-positions relative to the imido groups, thus precluding coordination of acetonitrile solvent molecules (Gibson et al., 2001). Likewise, the analogous vanadyl derivative is characterized by bridging phenoxides *trans* to the oxo ligands (Hoppe et al., 2006); this configuration

appears to preclude the presence of voids, thus favoring crystallization from acetonitrile solution upon cooling. The niobium complex reported was prepared from $NbCl_5$ as metal source, and crystallized from hot acetonitrile solution as two polymorphs, only one of which was refined as $(NbCl_2)_2(p\text{-}tert\text{-}butylcalix[8]arene-6H)$. The macrocycle adopts a twisted conformation, and no oxygen bridges between the metal centers are observed; the two OH protons on the phenolic units are H-bonded to acetonitrile molecules in the lattice (Redshaw et al., 2007).

Not surprisingly, late transition metals are hardly represented among structurally characterized calix[8]arene complexes. This is related to the high oxophilicity of the early transition metals in high oxidation states (Ti^{4+}, V^{5+}, Mo^{6+}), compared to the reluctance of the low-valent metals in the late groups of the d-block to bind π-electron rich phenolate donors. Electronic repulsion of the electrons on the oxygen-centered lone pairs with the metal-centered electrons associated to a high d-electron count accounts for their low stability. The first complex of this type required solvothermal conditions in order to afford an anionic dicobalt complex sandwiched between two trideprotonated $p\text{-}tert$-butylcalix[8]arenes, charge balanced by two triethylammonium cations (Petit et al., 2007). In addition to the Co^{2+}, d^7 complex, the second example involves a bimetallic Cu^{2+}, d^9 species coordinated to an octasubstituted calix[8]arene derived from the octaester described in section 2.1.2 (Yan et al., 2009). Four of the eight Schiff base moieties coordinate to the cupric ions through two oxygen and one nitrogen atom each, emphasizing the importance of the nitrogen-containing substituents for the formation of metal complexes involving late transition metals; no solvent molecules (chloroform or petroleum ether) are present in the crystal structure.

2.1.6 Calix[8]arene complexes with *p*-block elements

The oxophilic nature of aluminum was exploited to obtain a trimethylaluminum complex with methylated calix[8]arene, which represents one of the first structurally characterized derivatives (Coleman et al., 1987). Both $p\text{-}t$-Bu and p-H-calix[8]arene methyl ethers react exothermically with 8 equivalents of $AlMe_3$ to afford the hexaaluminum complexes, which were crystallized from benzene and toluene, respectively. The conformations adopted by the macrocycles do not resemble any of the other metal complexes, probably due to the ethereal nature of the phenolic units, which precludes the formation of H-bonds and metal-oxygen-metal bridges. Steric considerations appear to be responsible for the presence of only six trimethylaluminum units. The second report on these types of derivatives with *p*-block elements involves three bridging phosphates, the central one linking the 1 and 5 phenolic positions, with the other two phosphorus atoms bound to three adjacent phenolates (Gloede et al., 2001). Although considerably flattened, the shape of the macrocycle can be described as having two ¾ cups or bowls oriented in opposite directions. Another phosphorus-containing octa-*O*-acetyl derivative features substantially disordered diethoxyphosphonate groups in the *para*-positions of the calixarene (Clark et al., 2008).

Heavy group 14 and 15 elements are represented by germanium and bismuth in terms of crystallographically characterized calix[8]arenes. One of the Ge^{2+} derivatives assembles from benzene as two rhombic Ge_2O_2 dimers with bridging oxygen donors, as well as one terminal phenolate ligand for each germanium (II) resulting in a tetragermanium-*p*-H-calix[8]arene complex that acquires a deep bowl shape (Wetherby et al., 2007). The lone pair on each Ge^{2+} allows them to act as donors towards $Fe_2(CO)_8$ fragments in a formal oxidation to Ge^{4+}; as a consequence of the oxidation process each resulting germanium (IV) is bound to only two

oxygen atoms from the calixarene. The analogous tetragermanium (II) complex with *p-tert*-butylcalix[8]arene adopts a different conformation, since the bowl shape attained in the *p*-H analogue would result in considerable steric repulsion between *p-t*-Bu substituents on the phenolic units in 1 and 5 positions (Green et al., 2009). The reaction with $Fe_2(CO)_9$ in benzene has a different outcome as well, since only two germanium (II) ions interact with $Fe(CO)_4$ fragments in the product, without any oxidation at Ge taking place.

The first bismuth derivative of *p-tert*-butylcalix[8]arene was obtained from the silylamide $Bi[N(SiMe_3)_2]_3$ by recrystallization from a toluene/THF/acetonitrile mixture (Liu et al., 2004). The solid-state structure is defined by two calix[8]arene-Bi_4 complexes bridged by μ_4-oxo ligands; the macrocycle adopts a pinched cone conformation, with the cavity filled by two molecules of toluene. When the same calix[8]arene was treated with *n*-butyllithium and subsequently with 4 equivalents of $BiCl_3$, an anionic tetrabismuth-tetralithium complex with both phenolate and chloride ligands was formed (Liu et al., 2008). Despite these differences, the macrocyclic conformation can also be described as pinched cone, with one dimethoxyethane (DME) and one THF molecules inside the cavity acting as ligands towards the lithium cations.

2.1.7 Covalently-bridged calix[8]arenes

An alternative strategy for the functionalization of calix[8]arenes that has led to crystalline derivatives is the introduction of bridging organic substituents at the phenolic rim, thus linking two (or four) oxygen atoms. The usefulness of this approach relies on the regioselectivity of the transformation, since the reactions could in principle lead to a complex mixture of isomers. Instead, the methods developed have allowed the introduction of substituents at 1,2-, 1,4- and 1,5-phenolic positions selectively, thus restricting the degrees of freedom of the macrocycle. While the reduced mobility caused by functionalization appears to be beneficial in itself for the crystallization of the organic derivatives, the preorganization seems to also result in an ideal binding pocket for large metal ions. The first type of organic-linked derivative to be structurally characterized is the doubly tetramethylene-bridged *p-tert*-butylcalix[8]arene in 1,5 and 3,7 phenolic positions (Geraci et al., 2000). The idealized symmetry of the macrocycle is D_{2d}, made up of four ¾ cone clefts and filled with one molecule of dichloromethane and two of water.

The template effect observed for cesium in the 1,5-regioselective introduction of substituents was confirmed in the singly 1,5-tetramethylene-bridged derivative of *p-tert*-butylcalix[8]arene, which crystallizes as the CsCl complex (Consoli et al., 2002). Conformationally, the macrocycle has a very similar structure to that of the 1,5:3,7-doubly bridged derivative, with the Cs+ coordinated to all oxygen atoms, as well as two molecules of methanol (employed as solvent together with dichloromethane), one molecule of water, and the chloride counterion. Two additional molecules of water are present in the cavities of the ¾ cone clefts defined by three phenolic units. A related 1,5-tetramethylene-bridged hexa-*O*-(4-*t-Bu*-benzyl) derivative has also been characterized (Consoli et al., 2002a). One of the *t-Bu*-benzyl-substituted phenolic units is tilted towards the cavity, participating in self-inclusion in one of the ¾ cone clefts, while another cleft contains a molecule of CH_2Cl_2 from the methanol/dichloromethane solvent mixture used for crystallization.

The introduction of heteroatoms in the covalent bridges has generated interest due to the potential to bind metal ions different from the frequently observed oxophilic alkali, lanthanide, and actinide metals. A 1,4-regioisomer with a phenanthroyl group has been
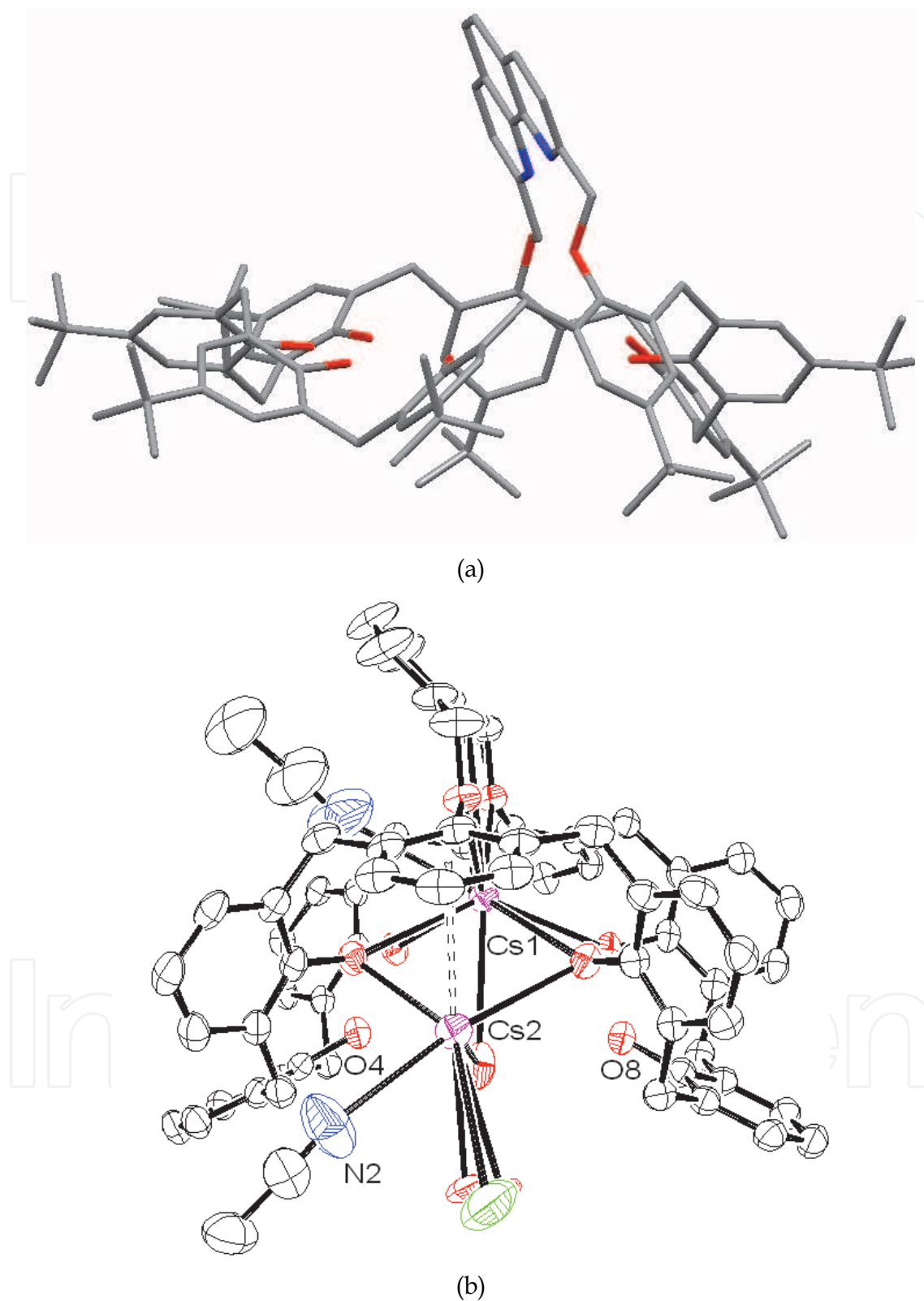
(a)

(b)

Fig. 5. Comparison of nitrogen-containing bridged *p-tert*-butylcalix[8]arenes in: a) flattened conformation of the 1,4-phenanthroyl (Konrad et al., 2005), and b) 'tub-shaped' conformation of the 1,5-pyridyl-substituted derivative (Hernández & Castillo, 2009)

crystallized from acetonitrile/dichloromethane solvent mixture, and the solid-state structure shows that the macrocycle is in an almost planar conformation stabilized by intracalixarene H-bonds (Konrad et al., 2005). The 1,4-regioselective outcome may be attributed to the use of K$^+$ as templating agent. In contrast, the use of cesium leads to the selective introduction of a 2,6-dimethylenepyridyl spanning element to the 1,5-phenolic positions (Hernández & Castillo, 2009). The conformational template effect of Cs$^+$ was also evidenced in the crystal structure, which contains two cesium cations per macrocycle, with one of them hosted deep inside the macrocyclic cavity, within bonding distance to the pyridyl N-atom. The dicesium complex was crystallized from acetonitrile/dichloromethane by slow evaporation, resulting in both molecules being present in the structure; one molecule of CH_3CN coordinates to each Cs$^+$ cation, while neither of the phenolate O-atoms in the 3 and 7 positions interact with the metal centers. Conformationally, the macrocycle can be described as 'tub-shaped' in an analogous fashion to the 1,5-bridged cesium complex described above (Consoli et al., 2002). Thus, the conformation of covalently-bridged calix[8]arenes is highly influenced by the regioselectivity of the substitution reaction, which is dictated by the templating cation used during the derivatization process, as evidenced in the comparison presented in Fig. 5.

2.1.8 Thia- and *para*-sulfonatocalix[8]arenes

Two novel classes of calix[8]arenes have been developed in recent years, which involve the use of sulfur in either a reduced form as thioether bridging elements between phenolic units, or in an oxidized form as *para*-sulfonate substituents. The former are commonly referred to as thiacalix[*n*]arenes, for which the octamethylated *p-tert*-butylthiacalix[8]arene was crystallized by slow diffusion of CH_3CN into a chloroform solution of the compound (Kon et al., 2002); the octaether adopts a 1,2,3,4-alternate conformation, with two molecules of acetonitrile hosted within the cavity. The parent thiacalix[8]arene was later characterized by X-ray crystallography, the structure being nearly identical to that of *p-tert*-butylcalix[8]arene in the pleated loop conformation (Kondo et al., 2005). A tetrapotassium complex of tetraanionic thiacalix[8]arene has been reported to have a zeolite-like structure, and was crystallized from methanolic solution by slow evaporation as the octasolvate (Kondo et al., 2005a).

Regarding *p*-sulfonatocalix[8]arenes, structural authentication involved the co-crystallization of the decaanion (eight sulfonate and two phenolate groups) in the presence of 4,4'-dipyridine-*N,N'*-dioxide and Eu^{3+} (Dalgarno et al., 2005). Despite the presence of π-stacking interactions and europium-O(sulfonate) coordination, these do not seem to perturb the macrocyclic conformation, which can be best described as the ubiquitous pleated loop. The anionic *p*-sulfonatocalix[8]arene has been crystallized with a variety of inorganic and organic cations, including combinations such as Yb^{3+} and three Ph$_4$P$^+$ cations encapsulated by two anionic *p*-sulfonatocalix[8]arenes (Makha et al., 2006). Ytterbium also favors the encapsulation of the globular [Co(phen)$_3$]$^{3+}$ cation (phen = 1,10-phenanthroline) by the anionic macrocycle in a chalice-like conformation (Smith et al., 2006). Likewise, in the isomorphous structures of [M(phen)$_2$(H$_2$O)]$_2$[M(phen)$_2$]$_2$-*p*-sulfonatocalix[8]arene·2H$_2$O (M = Cu, Zn) the octaanionic calix[8]arene in a 1,2,3,4-alternate conformation encapsulates one [M(phen)$_2$(H$_2$O)]$^{2+}$ in each of the two cone subunits defined by four adjacent phenols; the [M(phen)$_2$]$^{2+}$ complexes join two cones from adjacent calixarenes via M-O(sulfonate) and π-π interactions (Liu et al., 2009). Among organic guests, 1,4-butanediamine and 1,2-*cis*-cyclohexanediamine have been co-crystallized from methanolic solutions by mixing with

aqueous solutions of the *p*-sulfonatocalix[8]arene, followed by slow evaporation (Perret et al., 2006). The solid-state structures determined are characterized by an almost flat versus an 'inverted double partial cone' (1,2,3,4-alternate) conformation, respectively. The latter structure has a 1:2:4 stoichiometry of tetraanionic *p*-sulfonatocalix[8]arene, cyclohexanediammonium, and water, in which the ammonium cations are included deep within the macrocyclic cavity.

2.2 General overview of crystallization conditions

An initial assessment of the observations presented for the different types of calix[8]arenes points to the inherent difficulty in either obtaining adequate crystals, or being able to stabilize them in the absence of guests to fill the voids of the macrocycles. For this purpose, the use of solvents with high boiling points and the capability to form hydrogen bonds facilitates crystal formation and subsequent data collection, particularly in the case of *O*-unsubstituted calix[8]arenes. Moreover, acquisition of diffraction data at low temperature has become standard procedure for the resolution of the solid-state structures of the large macrocycles, since the commonly observed disorder in *t-Bu* groups is minimized, along with thermal motion that might be present in other parts of the molecules, for example in *p*-SO$_3$ groups or in solvates. These general considerations may result in the formation of stable crystals of both parent calix[8]arenes and their derivatives to be taken as a first approach towards successful crystallization and data collection.

Further analysis of the data reveals that octasubstituted derivatives lacking OH groups for hydrogen bonding can generally be crystallized from non-polar solvents. In this class of compounds, some of the phenolic *O*-substituents generally participate in self-inclusion, thus eliminating the need for high-boiling solvents; moreover, solvents with the ability to act as hydrogen bond acceptors are not essential due to the absence of phenolic OH groups available for this kind of interaction. Clathrates can indeed form, but they tend to include solvents such as chloroform, carbon tetrachloride, benzene, toluene, and tetrahydrofuran. Calix[8]arene derivatives with elements of the *p*-block that attain a closed-shell electronic configuration can also be included in this category, since they do not need solvent molecules as auxiliary ligands. This is the case with the aluminum-, phosphorus-, and germanium-containing calix[8]arenes, which were crystallized predominantly from aromatic, non-coordinating solvents. Bismuth deviates from this general rule, probably due to its larger ionic size that results in a tendency to form complexes with higher coordination numbers.

For calix[8]arene derivatives with phenolic OH groups and calix[8]arene-metal complexes with open-shell electronic configurations, solvents that can act as electron pair donors towards hydrogen atoms or electron-deficient metal centers are of key importance. Among the solvents that meet the criteria of high boiling points and electron donor capabilities, acetonitrile, dimethylformamide, dimethylsulfoxide, and in some instances pyridine, have been the most successful for the crystallization of calix[8]arenes. Their properties appear to be better suited than those of methanol or ethanol, which are only represented in a few solid-state structures, despite the comparable polarity of the alcohols and the aprotic solvents (Flick, 1998). While alcoholic solvents can act as both donors and acceptors in H-bonding interactions, the former property (with the alcohol as H-donor) does not seem to be crucial in the stabilization of most calix[8]arene crystal lattices. A disadvantage in the use of polar aprotic solvents may be the low solubility of some macrocyclic derivatives, but a co-solvent can be employed to dissolve the calix[8]arenes in appreciable quantities for crystallization.
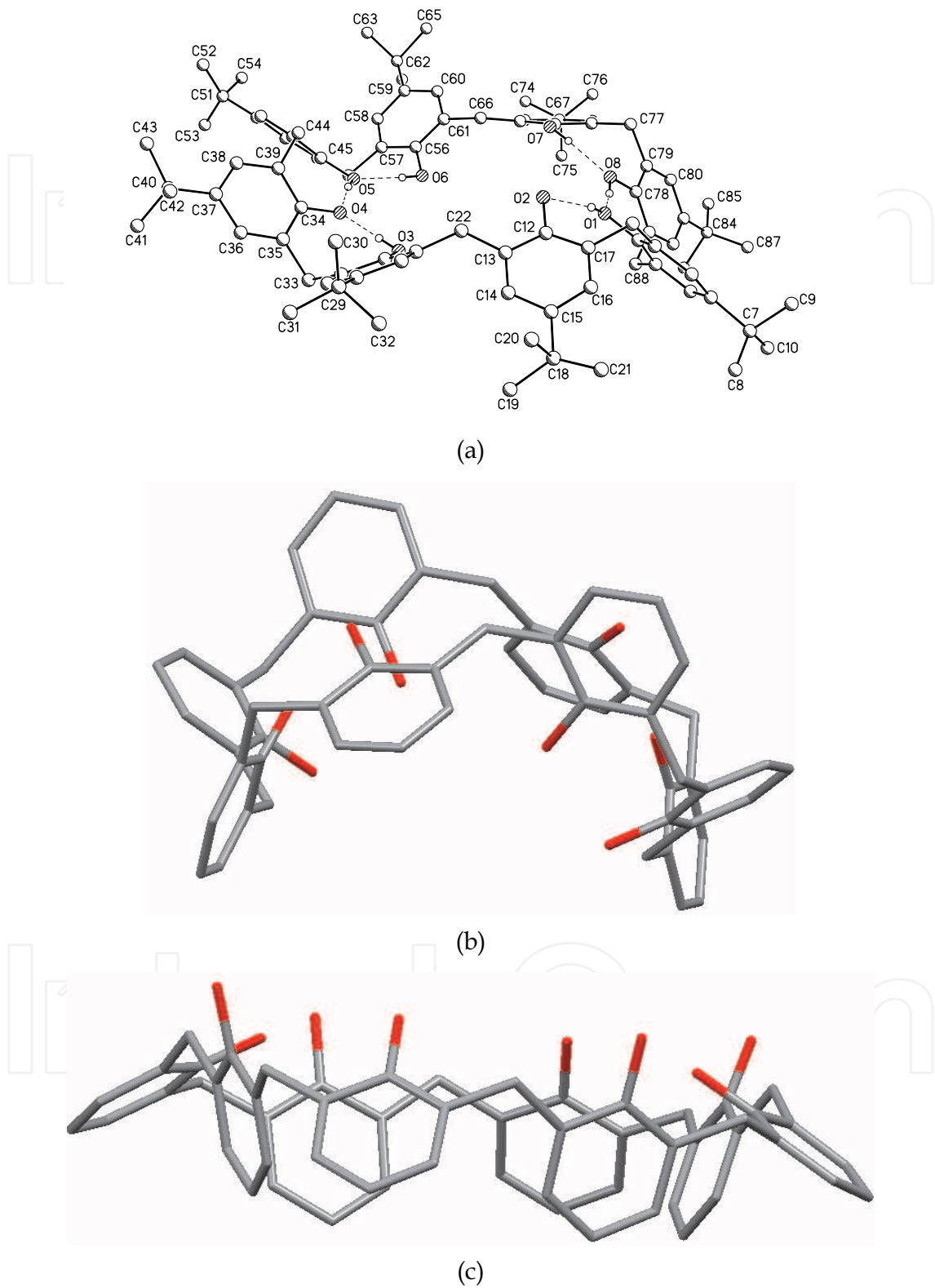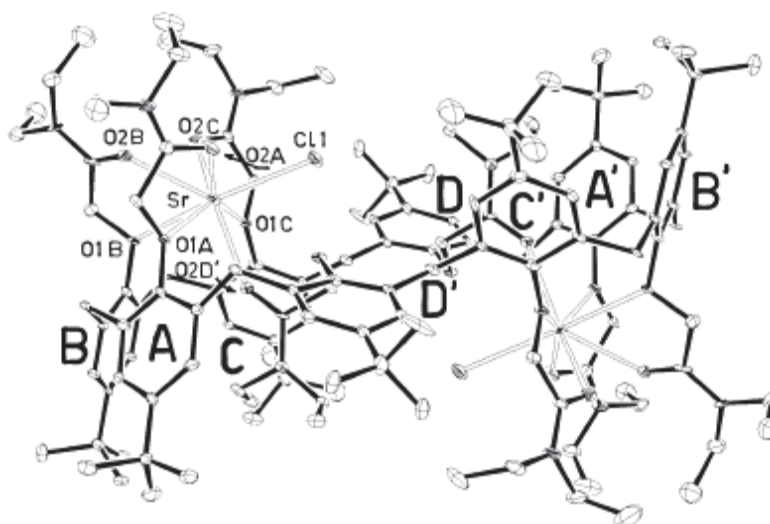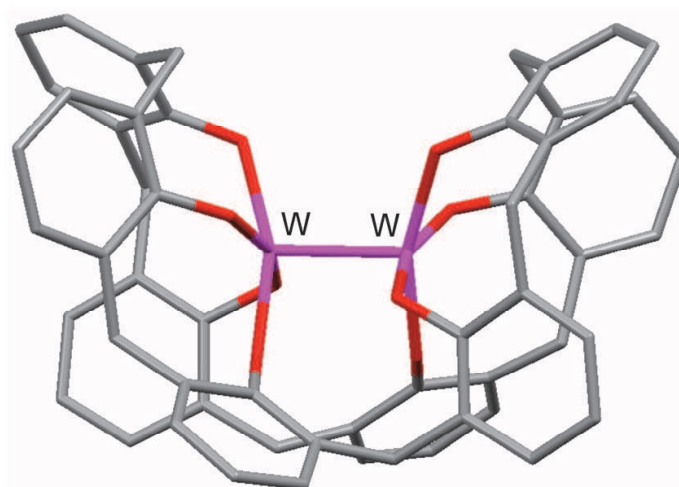
(a)

(b)

(c)

Fig. 6. Conformation adopted by the large macrocycles in the solid state: a) Pleated loop (from Martínez-Alanis and Castillo, 2005); b) 1,2-alternate (Ettahiri et al., 2003); c) cone (Volkmer et al., 2004)

(a)

(b)

(c)

Fig. 7. Conformation adopted by the large macrocycles in the solid state: a) ¾ Cones facing away (from Casnati et al., 2000); b) ¾ cones facing each other (Gibson et al., 2002); c) 1,2,3,4-alternate (from Liu et al., 2009)

For this purpose, volatile solvents such as acetone or dichloromethane are ideal, since slow evaporation tends to result in saturated solutions of the desired compounds predominantly in the high-boiling solvent. Alternatively, heating solutions of the calix[8]arene derivatives followed by slow cooling may result in crystal formation. These guidelines apply for unsubstituted and partially substituted calix[8]arenes with phenolic OH groups, including the covalently bridged derivatives, thiacalixarenes, and complexes with electron-deficient metals. Regarding water as a solvent, most macrocycles are insoluble with the exception of *p*-sulfonatocalix[8]arene, providing the opportunity to further test the interfacial technique.

Finally, a summary of the calix[8]arene conformations determined in the solid state is presented in Figs. 6 and 7, complementing those already presented in previous sections. While it is expected that the macrocycles characterized in the future will adopt one of the conformations herein included, novel structures cannot be ruled out, including variations and intermediate structures related to those already described in the current Chapter.

3. Conclusions

Solid-state characterization of calix[8]arene derivatives involves subtle details, but general trends emerge from an analysis of the reported structures. Complete functionalization at the penolic rim with substituents capable of filling the cavity by self-inclusion may result in derivatives that can be crystallized from non-polar solvents. This method may also be applied to calix[8]arenes with light *p*-block elements. Introduction of organic bridges at the phenolic OH groups, together with complex formation of alkali, alkaline earth, and open-shell (*d*- and *f*-block) metals may result in crystalline derivatives primarily from polar aprotic solvents that can H-bond to the remaining OH functional groups, and coordinate to the electron-deficient metals. The presence of solvent molecules is stabilized by collection of diffraction data at low temperature, although crystal formation appears to be facilitated by slow evaporation of solvent, rather than by cooling. These general guidelines should serve as a first approximation for crystal growth of calix[8]arene derivatives.

4. Acknowledgment

5. References

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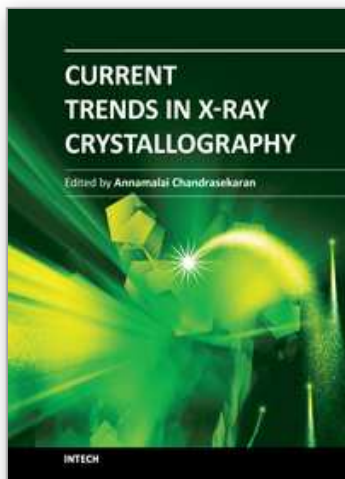
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