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Design and Synthesis of Transition Metal and Inner Transition Metal Binding Calixarenes

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Abstract: Calixarenes, macrocycles containing a preorganized central cavity, are often used to bind molecular and ionic guests. Though these guests are mostly limited to alkali metal or organic cations, and solvents, it is possible to assemble transition metal coordination complexes from calixarene derivatives. This review will illustrate how careful design strategies can be employed to devise target compounds and focus on synthetic approaches to prepare the desired calixarene derivatives.

Keywords: Calixarene, oxacalixarene, azacalixarene, thiacalixarene, transition metal, macrocycle.

1. INTRODUCTION

The ability to design ligands to target specific metals is a particular strength of synthetic organic chemistry. One of the greatest challenges is to differentiate between metals with very similar properties. This is particularly difficult when the metal has no binding preferences and is a common problem when considering ligands for alkali metals (Na^+, K^+, etc) and alkaline earth metals (Mg^{2+}, Ca^{2+}, etc). Fortunately the transition metals have well-defined preferences in terms of ideal chelating geometries and donor atoms with almost all falling into one of three coordination geometries: octahedral (six coordinate), tetrahedral and square planar (four coordinate). Nature observes these preferences, for example when proteins fold around transition metals to form metalloenzymes, and uses them when a structural element is required as is seen in the tetrahedral zinc finger motif of some gene regulatory proteins.

Two approaches can be taken to bind transition metals. The easiest is to find a small molecule, such as oxalic acid or ethylenediamine, which can bind to one or more metal coordination sites and form a complex. A more complicated approach is to incorporate the donor atoms within a macrocyclic framework. In doing so the donor atoms are preorganized for a metal of a particular size and preferred geometry. While the resulting macrocycle lacks the flexibility that multiple small ligands have when approaching the metal, this can offer an advantage in terms of size-based selectivity. A preorganized cavity also gives the complex greater stability through the 'macrocyclic effect'. This is an extension of the chelate effect observed when an increasing number of donor groups are incorporated into a flexible ligand. If a metal cation is bound to six unidentate ligands, e.g. ammonia, the reduction in entropy is much greater than if the same metal was bound by a single ligand with six appropriately spaced donor atoms. In the former case each ligand can be replaced independently but in the latter each donor atom is linked by a carbon backbone to at least one other which reduces its freedom to leave the metal. By combining several donor atoms in a preorganized macrocycle it is even harder for the metal to exchange ligands. As a consequence many ligands have been designed and synthesized to take advantage of the macrocyclic effect.

Constraining the positions of heteroatoms in a macrocycle's backbone is one way to preorganize the donor atoms. One such class of metal-binding macrocycles that has received attention over recent years is that of the calixarenes. Calixarenes are composed of phenolic subunits, as shown in Fig. (**1**), and have further possibilities for functionalization [1]. Ordinarily the bridge between the phenolic moieties is $–CH_2$-, however, in thiacalixarenes it is –S- and in oxacalixarenes and azacalixarenes it is $–CH_2OCH_2$- and –

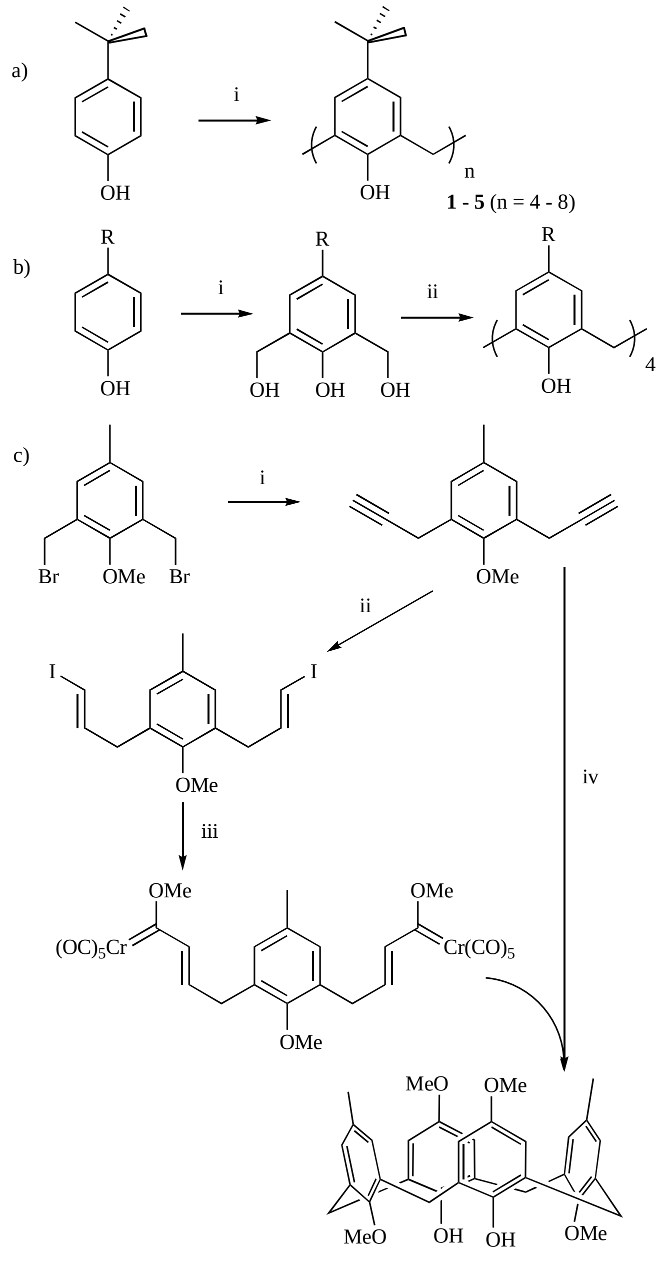

Fig. (1). Synthesis of calix[n]arenes: **a**) i) CH_2O/NaOH then heat in Ph_2O [6], **b**) i) CH_2O/NaOH, ii) reflux in *o*-xylene [7], **c**) i) TMS-C≡C-MgBr/CuBr, $AgNO_3$/KCN, ii) Cp_2ZrHCl, *N*-iodosuccinate, iii) t-BuLi, $Cr(CO)_6$, Me_3OBF_4, iv) 1,2-dichloroethane, reflux [8].

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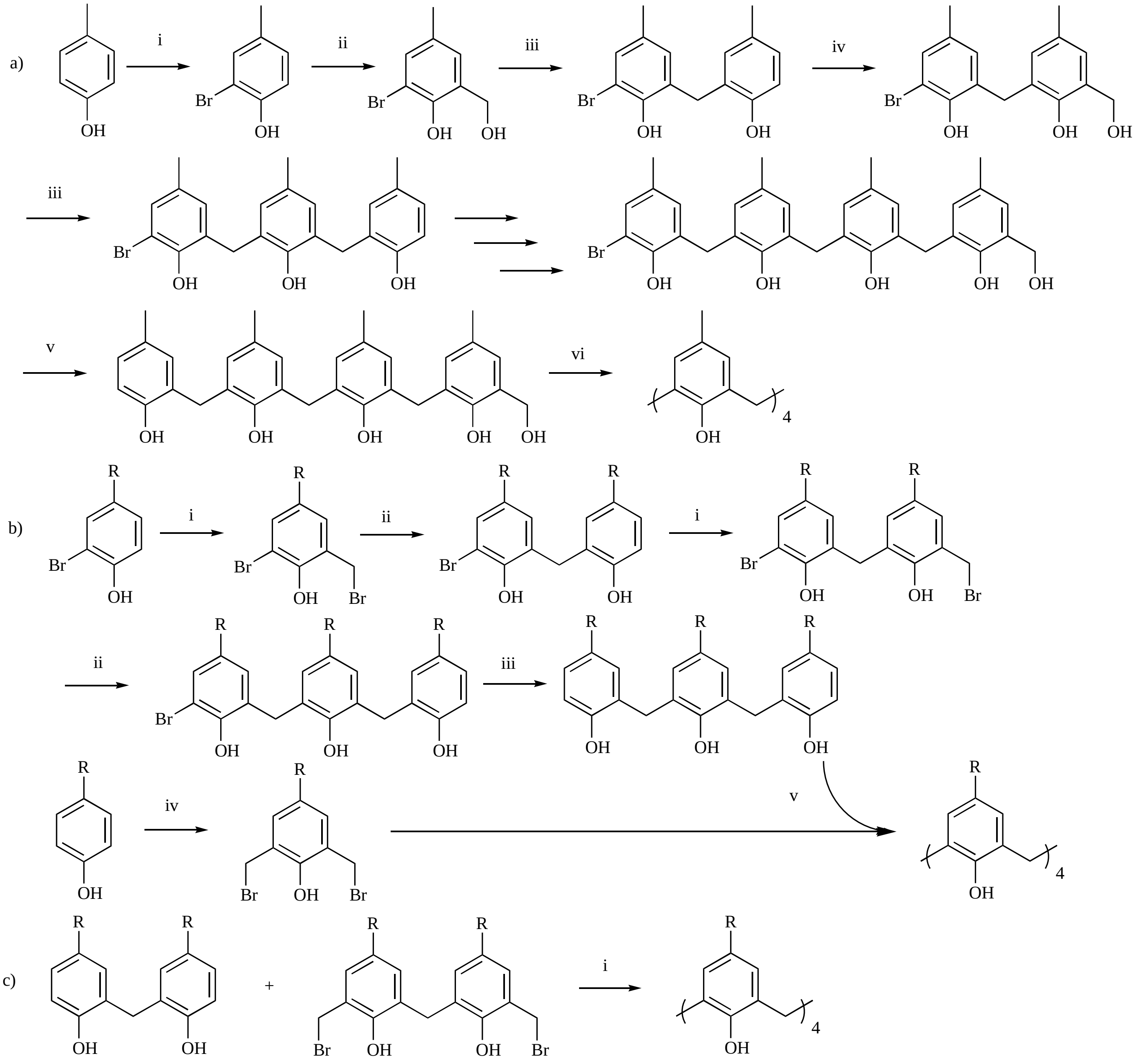


Fig. (2). Linear synthesis of calix[4]arenes: **a**) i) $Br_2/CHCl_3$; ii) $CH_2O/NaOH$, iii) *p*-cresol, HCl (cat.); NaOH, Pd/C, iv) $CH_2O/NaOH$; CO_2 to precipitate, v) NaOH, Pd/C, vi) AcOH, HCl [5], **b**) i) $CH_2O/HBr/AcOH$, ii) 4-R-phenol, heat, iii) KOH, Pd/C, iv) $CH_2O/NaOH$, isolate product, then HBr in AcOH, v) AcOH, reflux, high dilution [9b], **c**) i) $TiCl_4$, dioxane [9c].

$CH_2N(R)CH_2$- respectively. In these compounds the donor atoms are preorganized in the traditional manner. Calixarenes contain phenolic oxygen atoms on their lower rims which can act as a secondary binding region for metals. Again, the thiol analogues are known and have very different metal affinities from the parent compounds. Furthermore, the lower rim phenols can be derivatized to incorporate other metal-binding substituents such as pyridyl groups or carboxylic acids. Finally, depending on the nature of the upper rim group in the 4-position, a variety of coordinating substituents can also be introduced there.

In this review examples of each type of transition metal-binding calixarene will be summarized. In addition to the classic *d*-block transition metals, the lanthanides, or inner transition metals, and actinides are amenable to complexation by calixarenes as well and will therefore also be considered in this review. Synthetic routes to upper and lower rim substituted calixarenes will be described and the affinities for different metal discussed.

2. CALIXARENE SYNTHESIS

Calixarenes (Fig. (**1a**)) were probably first prepared by von Baeyer; his paper of 1872 notes the formation of solid products from phenol-formaldehyde condensation [2]. Later their formation was investigated by Zinke [3], also as part of research focused on the Bakelite process, and by Cornforth, who found that certain derivatives had antitubercular properties and was the first to link different properties to different conformers [4].

The first rational route to calixarenes came in 1958 when Hayes and Hunter from the research department of Bakelite Ltd prepared 4-methylcalix[4]arene from a linear precursor (Fig. (**2a**)) in an

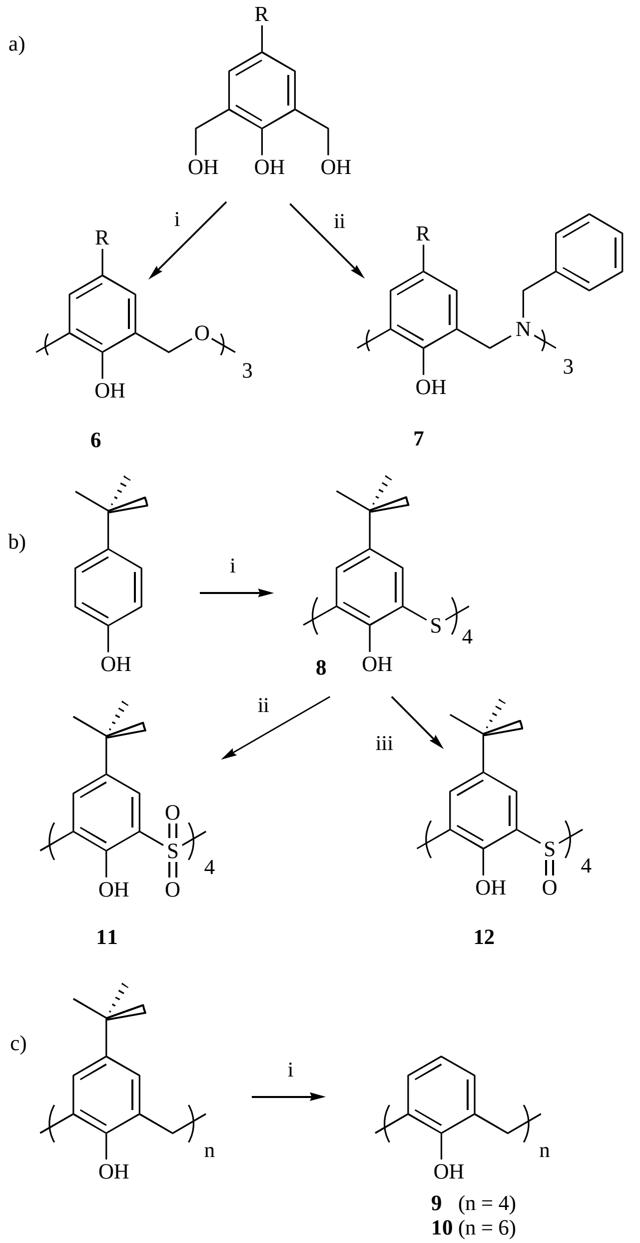


Fig. (3). a) Oxacalix[3]arenes, azacalix[3]arenes and thiacalixarenes; i) acid, *o*-xylene, reflux, ii) benzylamine, toluene, reflux, [12, 13], **b**) i) S_8, ii) $H_2O_2/CF_3CO_2H/ CHCl_3$, iii) H_2O_2, [14], **c**) i) $AlCl_3$, phenol, toluene [16].

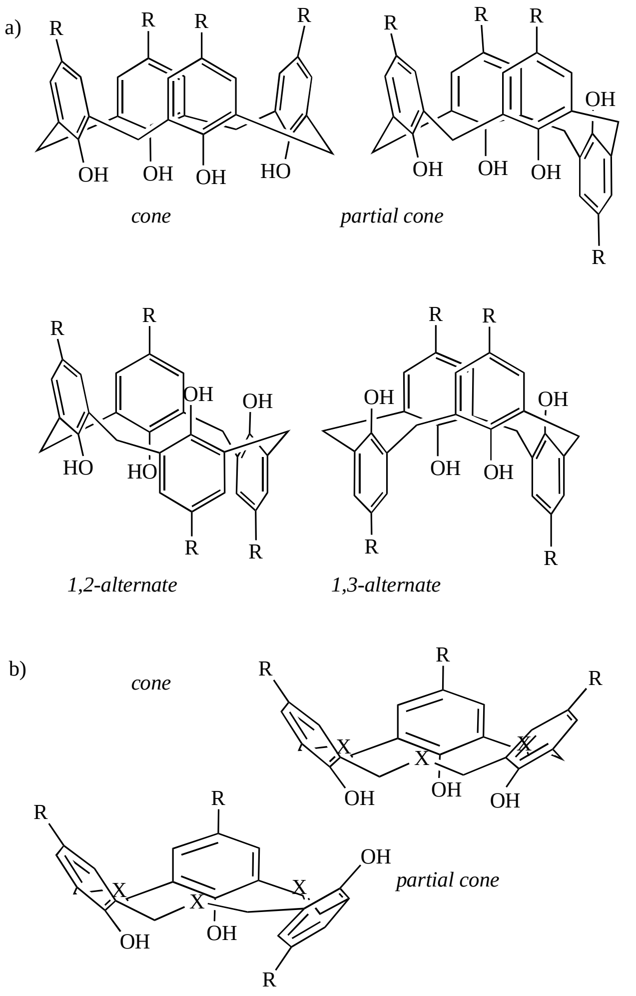


Fig. (4). Calixarene conformations: **a**) calix[4]arenes, **b**) oxa- and azacalix[3]arenes (X = O and NR, respectively).

eight-step synthesis [5]. There was little interest shown in the calixarenes until the inclusion properties of crown ethers and similar compounds were exploited in the late 1970s and early 1980s as part of the 'supramolecular chemistry' movement. Once it was realised that the calixarenes had rigid central cavities not unlike those of the cyclodextrins, into which guest species could fit, there was renewed interest in the compounds. They were championed particularly by Gutsche who coined the term 'calixarene' (from the Greek: *calix*, cup or chalice, plus *arene*) [6]. The Gutsche group reported the single step syntheses of 4-t-butylcalix[n]arenes in 1981 where n extends from 4 to 8 (compounds **1** to **5** respectively, Fig. (**1a**)). Other routes have been found to calix[4]arenes such as the dehydration of bis(methylol)-4-t-butylphenol (Fig. (**1b**)) [7] and an unusual application of chromium carbonyl chemistry to initiate ring formation as in Wulff's method that involves the formation of two of the aromatic rings through triple benzannulation of a Fischer carbene complex (Fig. (**1c**)) [8]. The Böhmer group, and others, have followed a stepwise approach (Fig. (**2b**)) to introduce a variety of functional groups [9]. Efficient routes have also been found to calix[5]- and [7]arenes (**2**, **4**) [10, 11] as well as more unusual compounds such as the oxacalix[3]arenes (**6**) and azacalix[3]arenes (**7**) and thiacalixarenes (**8**) (Fig. (**3**)) [12-14]. The general synthesis of calix[n]arenes involves base-catalyzed condensation between a phenol derivative and formaldehyde at high temperatures [15]. This appears to form oligomers that cyclise to give calix[8]arenes and then pinch and cleave to form two calix[4]arenes. Removal of the t-butyl groups of the parent calixarene, as detailed below, leads to the more conformationally mobile calix[4]arenes (**9**) and calix[6]arenes (**10**) [16].

Calixarenes can adopt a number of conformers, shown in Fig. (**4**), as the phenolic moieties are able to rotate through the macrocyclic annulus. Those with three phenolic rings can adopt a *cone* or *partial cone* conformation depending on the orientation of the phenolic rings [17]. These conformers are observed for azacalix[3]arenes and oxacalix[3]arenes: the syntheses of calix[3]arenes, though reported, have never been repeated [18]. Calix[4]arenes are by far and away the most commonly encountered members of the family and can adopt *cone*, *partial cone*, *1,2-alternate* and *1,3-alternate* conformers [1a]. Depending on the upper and lower rim substituents, these may be able to interconvert or may be frozen in one particular conformer. As the size of the calixarene increases the number of conformers, and ease with which they may be interconverted, increases. Unless stated otherwise, the examples given in this review will be *cone* conformers; their con-

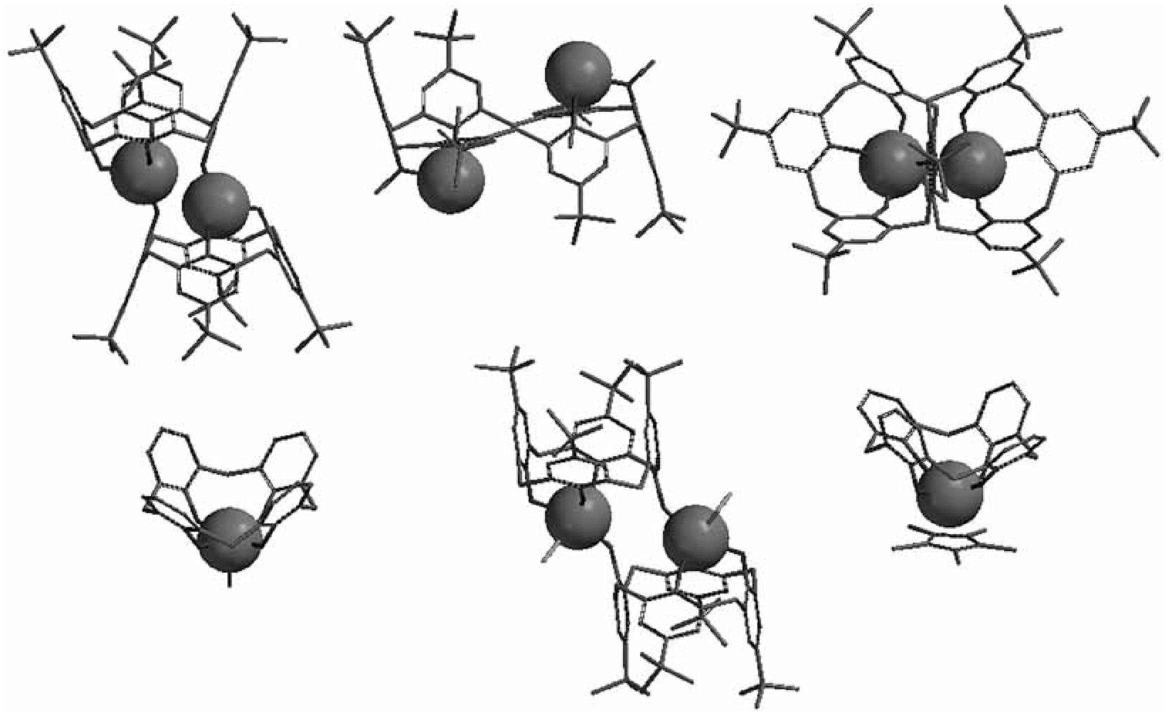


Fig. (5). Calixarene complexes: (top, l to r) $\mathbf{1}_2\cdot\mathrm{Ti}_2$, $\mathbf{3}\cdot\mathrm{Ti}_2$, $\mathbf{5}\cdot\mathrm{Ti}_2$, (bottom, l to r) $\mathbf{9}\cdot\mathrm{WO}$, $\mathbf{1}_2\cdot(\mathrm{TaCl}_2)_2$, $\mathbf{9}\cdot\mathrm{TaCp}^*$ (hydrogen atoms, solvent and other ligands removed for clarity).

vergent binding sites are preorganized for metal binding and are most commonly associated with metal complexation.

3. UNMODIFIED CALIXARENES

The simplest binding mode that calixarenes can adopt is through the lower rim phenolic oxygen atoms. This favours those transition metals with hard acid properties (e.g. $\mathrm{Ti}^{\mathrm{III}}$, $\mathrm{Ti}^{\mathrm{IV}}$, $\mathrm{Zr}^{\mathrm{IV}}$, $\mathrm{Nb}^{\mathrm{IV}}$, $\mathrm{Ta}^{\mathrm{IV}}$, $\mathrm{Mo}^{\mathrm{VI}}$, W^{VI}, vanadyl [VO^{2+}], uranyl [$\mathrm{UO}_2{}^{2+}$]), as shown in Fig. (**5**), and those with a preferred geometry that matches that of the calixarene (e.g. octahedral or square planar metals and calix[4]arenes, tetrahedral or trigonal planar species and oxa- or azacalix[3]arenes or calix[6]arenes).

3.1. Calix[4]arenes

Several simple transition metal complexes have been prepared from **1** in which the metal coordinates to the lower rim oxygen atoms or bridges between two calixarenes through oxo-coordination. Reaction with $\mathrm{Ti}^{\mathrm{IV}}(\mathrm{NMe}_2)_4$ in toluene deprotonates the calixarene, liberating HNMe_2, leading to a dimeric structure in which the titanium coordinates in a tetrahedral geometry to three phenolic oxygen atoms of one macrocycle and one from a second macrocycle shown in Fig. (**5**) [19]. The same paper reports that similar structures are seen when the calixarenes are treated with $\mathrm{N(SiMe}_3)_2$ and complex iron or cobalt. Reaction with Eu^{3+} also results in a bridged 2:2 complex [20]. As zirconium is in the same group as titanium it might be expected to form a similar complex, however, it does not appear to do so but will react with **1** when two opposite phenol groups are methylated [21]. Selective methylation of the opposite phenolic rings is achieved by refluxing the parent calix[4]arene in dry acetone, or acetonitrile, with two equivalents of TsOMe, or MeI, in the presence of $\mathrm{K_2CO_3}$ [22]. The pentachlorides of niobium and tantalum form 1:1 complexes in which it is believed that three phenolic groups are deprotonated and the fourth engages in a weak interaction with a metal dichloride fragment [23]. Dimers similar to those formed by titanium, though with extra ligands as niobium and tantalum are six-coordinate, are also observed [23]. Reaction of **1** or **9** with W^{VI} or $\mathrm{Mo}^{\mathrm{VI}}$ leads to complete deprotonation and coordination of the metal to all four phenolic oxygens. In the case of the tungsten complex the metal-bound oxygen is retained giving a monomeric structure [24]. When the same reaction is carried out on calix[4]arenes with bulky alkyl groups attached to their upper rims via a diazo coupling reaction the resulting complex is able to self-assemble into a multimolecular stack in which the W=O moiety is included within the cavity of the next macrocycle [25]. Unusual variations on the well-known organometallic tantalum and niobium 'piano stool' compounds have been prepared through the reaction of their cyclopentadienyl (Cp), or pentamethylcyclopentadienyl (Cp*), metal trichlorides with **9** (Fig. (**5**)). In traditional piano stool compounds the cyclopentadienyl group forms the 'seat' while carbonyl groups act as the 'legs'; in these variants the metals coordinate to four deprotonated calixarene phenol groups [26].

3.2. Calix[6]arenes

Titanium reacts with **3** to form two different structures. With the parent compound a dimer is formed, held together by four metal centres [27]; the hexamethylated analogue forms a monomeric structure that binds two titanium centres [28].

3.3. Calix[8]arenes

Titanium also reacts with **5** in a 2:1 stoichiometry via the alkoxide [29] or from titanocene [30]. Zirconium, vanadium (as VO^{2+}) [31] and europium [32] are thought to form similar complexes, and molybdenum has been shown to adopt the same structure when it reacts with calix[8]arene [33].

3.4. Oxacalix[3]arenes

Oxacalix[3]arenes, **6**, have $-\mathrm{CH_2OCH_2}-$ bridges in place of the $-\mathrm{CH_2}-$ bridges in calixarenes and are consequently more flexible [12]. Their threefold symmetry and larger central cavity makes them ideal as ligands for lanthanides and actinides as well as transition metals that favour facial coordination. Unlike the

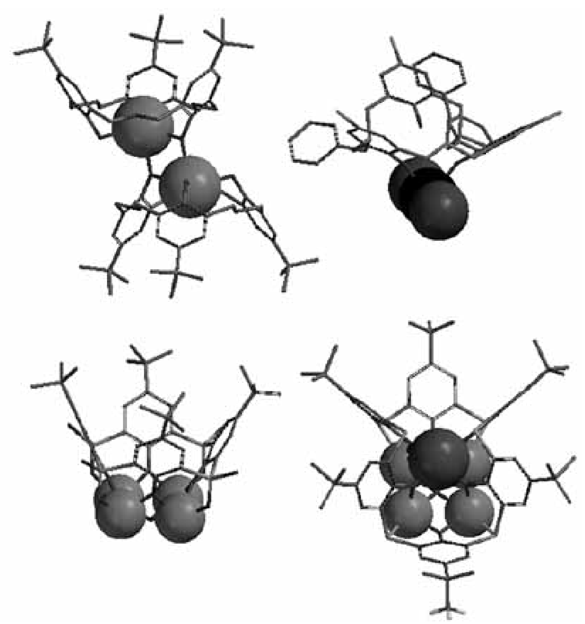


Fig. (6). Calixarene complexes: (top, l to r) **6a**$_2$·Ln$_2$, **7c**·UO$_2$, (bottom, l to r) **12**·Co$_4$, **13**·Ni$_4$Co (hydrogen atoms, solvent and other ligands removed for clarity).

calix[n]arenes, which are usually synthesized as the 4-t-butyl derivative, oxacalix[3]arenes having one of several different substituents in the 4-position can be formed readily from the appropriately substituted phenol, though in variable yields [34]. Linear syntheses, rather than the usual acid promoted cyclocondensations, have also been devised to synthesize oxacalix[3]arenes with combinations of substituents in the 4-position [35].

Binding of Ti^{IV} to **6a** has been proposed based on an exhaustive variable temperature NMR study of ligand exchange reactions which indicates a 1:1 complex in which the macrocycle is completely deprotonated [36]. The crystal structure of a titanium complex with the 4-methyl derivative, **6b**, confirmed the hypothesis; the same derivative also bound the VO^{2+} in a similar manner [37]. The latter appeared to stack through μ-oxo-bridged linear chains where the vanadyl moiety is bound within the macrocyclic cavity in contrast to the 'exo' geometry proposed for similar calix[4]arene analogues [26]. The reaction of Sc^{3+} with **6a** yields a crystalline 2:2 complex (Fig. (**6**)) [38] as do the analogous Lu^{3+}, Y^{3+} and La^{3+} complexes [39]. Both **6a** and **6b** have an ideal disposition of phenolic oxygens to bind UO$_2^{2+}$ [40]. The methyl (**6c**) and i-propyl (**6d**) derivatives bind Re(CO)$_3$ though, unusually, the metal deprotonates and then binds through only two of the available phenolic groups [41].

3.5. Azacalix[3]arenes

By analogy to oxacalix[3]arenes the azacalix[3]arenes, **7**, possess –CH$_2$NRCH$_2$- bridges where R is typically a benzyl group. The 4-substituent on the phenolic rings is typically a t-butyl, methyl or chloro group. These compounds have been investigated with particular reference to their potential to bind trivalent lanthanide and UO$_2^{2+}$ ions (Fig. (**6**)). The predominant motif is 1:1 coordination with the metal at the centre of the macrocyclic cavity: the 4-chloro-*N*-benzyl derivative, **7c**, binds Nd^{3+} [42], Yb^{3+} [43] and UO$_2^{2+}$ [44] in this manner. A complex involving two ligands and one Yb^{3+} cation has also been crystallographically characterized [43].

3.6. Thiacalixarenes

4-t-Butylthiacalix[4]arene, **8**, was first reported in 1997 [14] and would seem to be an ideal ligand for metals requiring soft donor atoms. Indeed this seems to be so, as it has been shown to quantitatively extract metal cations of soft to intermediate character such as Co^{2+}, Ni^{2+}, Cu^{2+} and Zn^{2+} [45]. By way of contrast the oxidized sulfone analogue, in which the bridge is –SO$_2$- (**11**), fails to have any significant affinity for these cations, binding preferentially to hard metals. The intermediate sulfoxide with an –SO- bridge (**12**) binds not only hard metal cations but also Co^{2+}, Ni^{2+} and Zn^{2+}. Strangely, the affinity for Cu^{2+} is not restored.

Crystal structures show how different donors allow thiacalixarenes to bind a wide variety of metals: 'hard' Zr^{IV} forms a 2:2 dimer binding solely to the phenolic oxygen atoms and bridging methanol molecules [46] whereas Zn^{2+} forms a 3:4 cluster, binding to both oxygen and sulfur atoms [47] and Co^{2+} ions are bound to all available heteroatoms as a 4:1 complex [48].

Due to their extensive array of donor atoms, thiacalix[6]arenes (**13**) are able to bind transition metal clusters as in the case of the 5:1 Co^{2+} complex and the mixed 5:1 clusters containing combinations of Co^{2+}, Ni^{2+}, Mn^{2+} and Cu^{2+} [49]. The general structures of **14** to **18** are shown in Fig. (**7**).

3.7. Other Calixarenes

Many variations on the calixarene skeleton are available, many as by-products of other syntheses. Foremost among these are the expanded calix[4]arenes where either -CH$_2$N(CH$_2$C$_6$H$_5$)CH$_2$- or -CH$_2$OCH$_2$- has replaced one or more of the -CH$_2$- bridges. 4-t-Butylbishomooxacalix[4]arene (**14**) [6] binds UO$_2^{2+}$ with 1:1 stoichiometry [50] (as does 4-methyltetrahomodioxacalix[4]arene (**15**) [43] and 4-methyl-*N*-benzyltetrahomodiazacalix[4]arene (**16**) [44, 51]) and Eu^{3+} as a 2:2 dimer [52]. 4-t-Butyltetrahomodioxacalix[4]arene (**17**) binds UO$_2^{2+}$ with 2:1 stoichiometry [53] and 4-t-butyloctahomotetraoxacalix[8]arene (**18**), being much larger and more flexible, also binds UO$_2^{2+}$ but with 4:1 stoichiometry [54].

4. INTRODUCTION OF BINDING SITES AT THE UPPER RIM

There is a vast literature concerning the modification of calix[n]arenes at the upper rim for, though it is possible to prepare 4-methyl- and 4-phenylcalixarenes [55] directly, most derivatization starts from the appropriate 4-t-butylcalix[n]arene. The t-butyl group can be removed by retro-Friedel-Crafts acylation, effected by aluminium trichloride [16], leaving the calix[n]arene open to Mannich reactions [56], sulfonation [57], halogenation [9b], and Claisen rearrangement of lower rim *O*-allyl substituents to the 4-position [16, 58]. Alkylation of the phenolic oxygens allows direct nitration of 4-t-butylcalix[n]arenes [59] leading to the possibility of reduction to the corresponding amine [60]. Further derivatization is then possible by a number of routes such as diazonium salt or Schiff base formation, to mention but two examples. Not all of these approaches generate calix[n]arenes with suitable donor groups to bind transition metals, nevertheless, several interesting compounds have been prepared.

Both calix[n]arenes and thiacalix[n]arenes appear to be amenable to these methods, however, the oxa- and azacalix[n]arenes are less robust. In particular, the ether and amine links are cleaved by aluminium trichloride which rules out any route that requires de-t-butylation. It is preferable to incorporate upper rim functionality directly through condensation of the appropriate 2,6-bis(hydroxymethyl)phenol precursor.

4.1. Upper Rim Amines

Introduction of upper rim amine functionality (Fig. (**8**)) was first reported by Gutsche in a 1988 paper where he laid out the different strategies available [56]. The interaction of *cone* 4-(2-aminoethyl)calix[4]arene (**19**) with transition metals (Ni^{2+}, Cu^{2+},

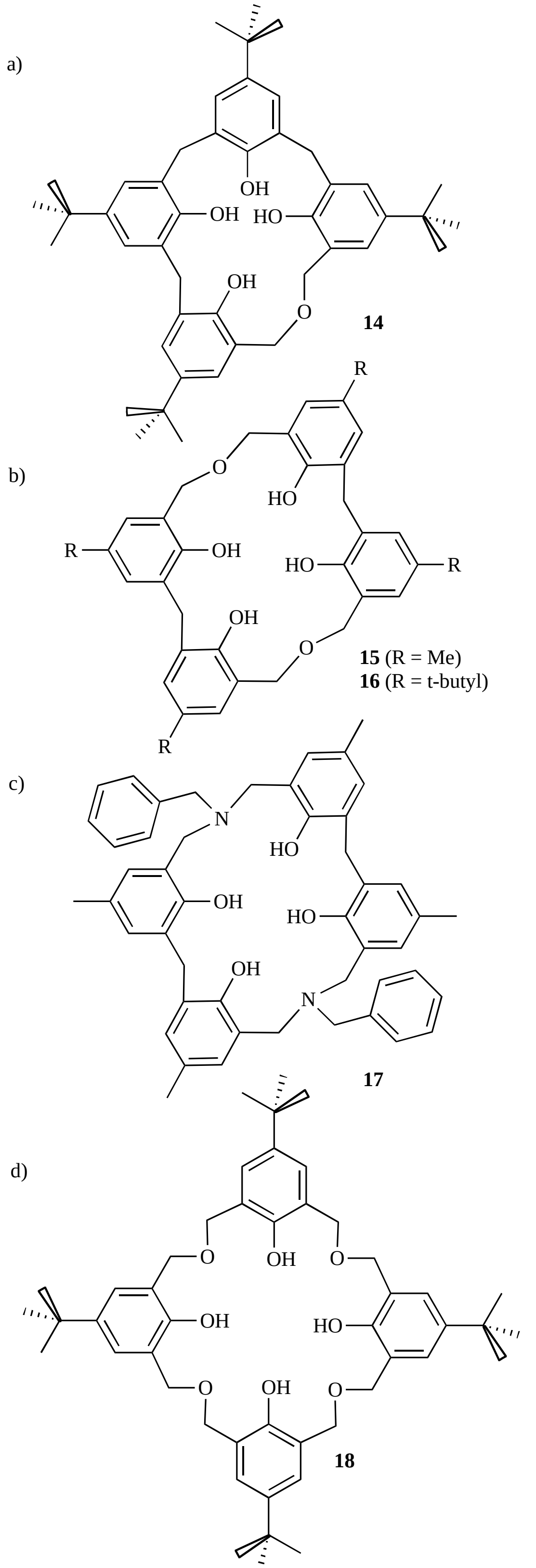


Fig. (7). Homooxa- and azacalixarenes: **a**) 4-t-butyl-bishomooxacalix[4]arene, **b**) tetrahomodioxacalix[4]arenes, **c**) 4-methyl-*N*-benzyl-tetrahomodiazacalix-[4]arene, d) 4-t-butyloctahomotetraoxacalix[8]arene.

Pd^{2+}, Co^{2+} and Fe^{2+}) was investigated but it was believed that the substituents were too flexible to bind well. More rigid bipyridyl groups have been introduced to a calix[4]arene (**20**) by Beer [61], via amide coupling, in order to bind ruthenium prior to coordination of further bipyridines. The resulting compound gives a selective electrochemical response to $H_2PO_4^-$ in the presence of competing anions. Similarly, reaction of 4-aminocalix[6]arene (**21**) with chloroglyoxime forms the hexaglyoxime derivative (**22**) which binds Ni^{2+}, Cu^{2+} and Co^{2+} [62].

Many enzymes, particularly hydrolases, employ twin metal centres that work in a concerted fashion and it has been one goal of calixarene chemists to synthesize derivatives that mimic this type of activity [63]. This challenge was taken up by the Reinhoudt group with respect to a nuclease mimetic calixarene. Calix[4]arene (**9**) was protected at the lower rim, mono- or diformylated and reacted with methylamine. The amine was treated with 2-(bromomethyl)-6-(hydroxymethyl)pyridine and the free alcohol reacted with methylamine hydrochloride to produce derivatives with one or two diaminopyridyl metal-binding sites [64]. Zn^{2+} complexes, generated *in situ* by the addition of the metal in acetonitrile/HEPES buffer, exhibited high catalytic activity but only when two zinc ions were present (**23**).

Another goal of calixarene research is to devise a metal-binding derivative that responds when a specific guest is complexed. Recently a calixarene has been reported that binds selectively to Cu^{2+} and signals the event by fluorescing at 355 nm. The calix[4]arene (**24**) incorporates four upper rim iminoquinoline subunits and is prepared by protecting the phenols, nitrating the upper rim, reducing the tetraamine, and forming the Schiff base [65].

Oxacalix[3]arenes have three fold symmetry that has the potential to be employed in enzyme mimicry or sensing applications, however, the introduction of metal ligating groups in the 4-position can have some interesting consequences. Reaction of 4-bromooxacalix[3]arene (**6e**) with ethyl 2-bromoacetate and then with diethyl-4-pyridylborane generates 4-pyridyl upper rim derivative **25** (Fig. (**9**)). This compound has been used to form a dimeric molecular capsule held together by three Pd(II) centres linked through the pyridyl groups [66].

4.2. Upper Rim Sulfonates

Despite the extensive interest in the water-soluble sulfonatocalix[n]arenes there has been little evidence of direct sulfonate-transition metal binding. A majority of complexes formed involve the calixarene acting as a ‘second sphere’ ligand as the metals’ primary coordination sites are occupied by water or other small ligands. The sulfonatocalixarenes provide useful scaffolds, often as polyanions, that organize the complex transition metal cations and promote crystallization from aqueous solution. 4-Sulfonatocalix[4]arene (**26**) [67, 68] (Fig. (**10**)) has been investigated for many years with a specific focus on metal binding in water. Examples of such complexes include $[Cu(H_2O)_4(pyridine)_2]^{2+}$ [67], $[Ni(H_2O)_5(pyridine)]^{2+}$ [69] though only one lanthanide complex appears to show direct coordination [70].

4.3. Upper Rim Phosphonates and Phosphines

Reaction of calix[4]arene (**9**) with chloromethyl *n*-octyl ether in the presence of $SnCl_4$ introduces chloromethyl groups in the 4-position. Subsequent reaction with triethylphosphite followed by hydrolysis gives a phosphonic acid derivative (**27**) [71]. The calix[6]arene analogue (**28**) has also been prepared and shown to bind Eu^{3+} and Am^{3+} [72].

Lithiation of bromocalix[4]arene, protected at the lower rim, followed by treatment with chlorodiphenylphosphine results in the formation of diphenylphosphinecalix[4]arenes [73, 74]. Diphenylphosphinecalix[4]arene methyl ether (**29**) binds Cu^{2+} as a 1:2 complex and extracts Hg^{2+}, Cu^{2+}, Cd^{2+}, Zn^{2+} and Ni^{2+} with decreasing efficacy though all are extracted in preference to alkali metals [73].

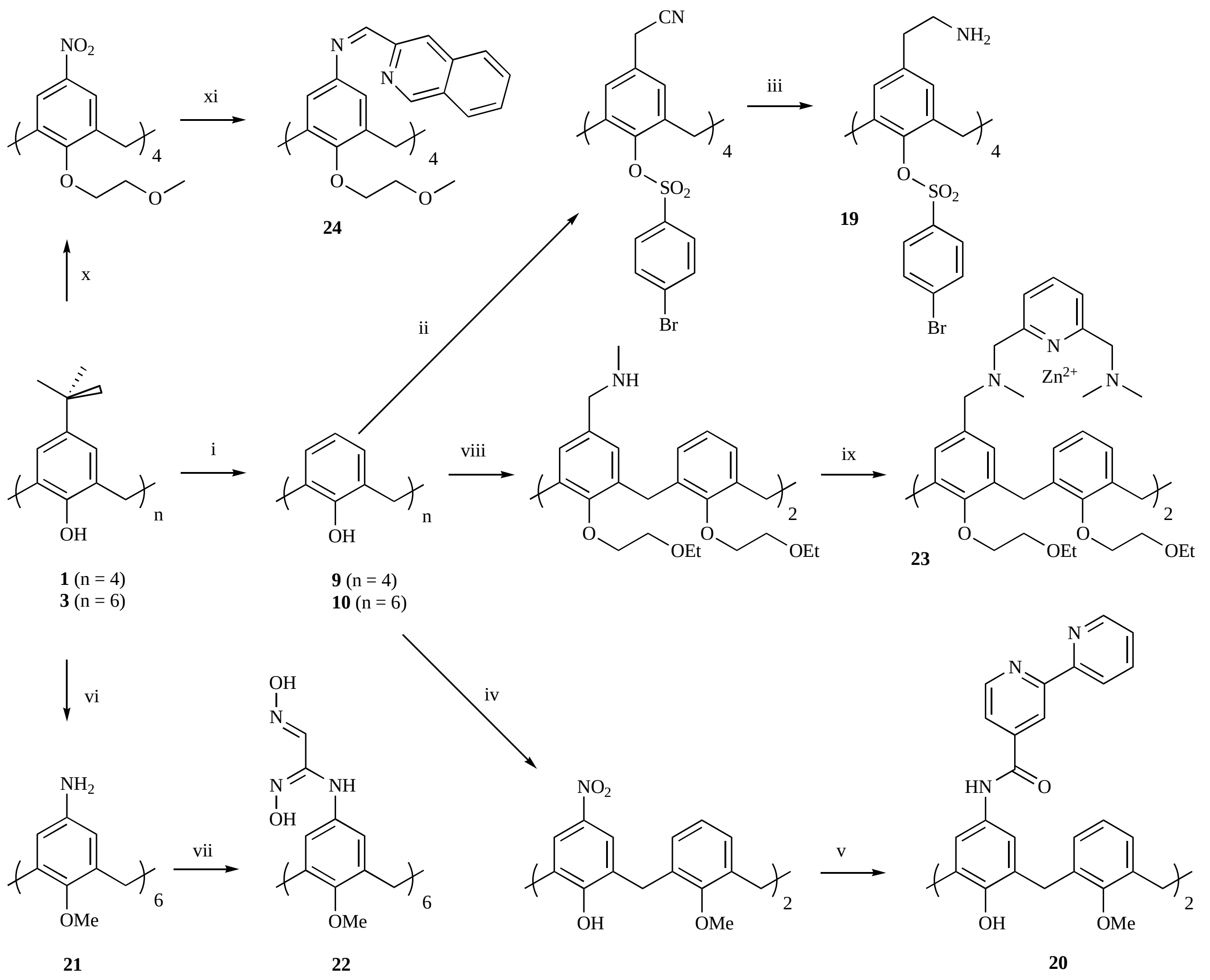


Fig. (8). General upper rim modifications of calixarenes **1** and **3**: i) $AlCl_3$, phenol, toluene [16], ii) $CH_2O/HNMe_2/AcOH$, MeI/NaCN/DMSO, NaH/4-bromobenzenesulfonyl chloride, iii) B_2H_6/THF [56], iv) K_2CO_3/MeI, 65% $HNO_3/AcOH$, v) NH_2NH_2/Raney Ni, 4-chlorocarbomyl-2,2'-bipyridine/Et_3N [61], vi) 100% $HNO_3/AcOH$, K_2CO_3/MeI, NH_2NH_2/Raney Ni, vii) *anti*-chloroglyoxime/base [62], viii) K_2CO_3/2-ethoxybromoethane, $SnCl_4/Cl_2CHOCH_3$, $MeNH_2/H_2$/10%Pd/C, ix) 2-(bromomethyl)-6-(hydroxymethyl)pyridine/ K_2CO_3, $SOCl_2$, $K_2CO_3/HNMe_2{\cdot}HCl$, Zn^{2+} [64], x) K_2CO_3/methoxyethyl tosylate, 100% $HNO_3/AcOH$, xi) NH_2NH_2/Raney Ni, 2-quinolinecarbaldehyde [65].

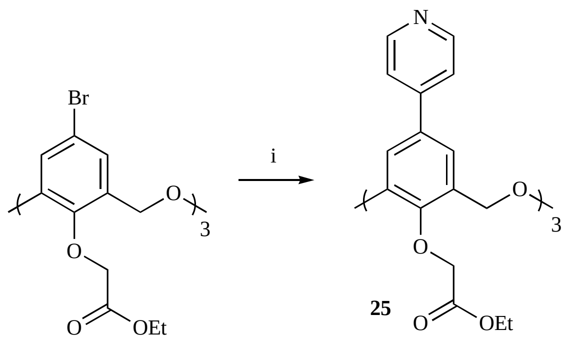


Fig. (9). Introduction of a pyridyl group to the upper rim of an oxacalix[3]arene: i) diethylpyridylborane [66].

Phosphinic acid can be introduced directly in the 4-position illustrated by **30** in Fig. (**11**). The Raston group have used this compound to form nanorafts in both the gas and solution phase. Although metal complexes of this calixarene have yet been prepared it clearly has the potential to be exploited for this purpose [75].

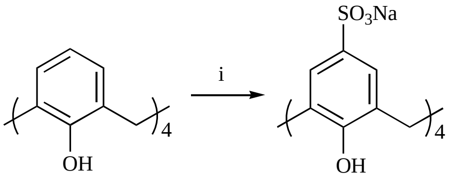


Fig. (10). Sulfonation of calix[4]arene at the upper rim: i) H_2SO_4, 60°, ii) $BaCO_3$, Na_2CO_3 [67].

4.4. Upper Rim Carboxylic Acids

Calix[4]arenedicarboxylic acid (**31**), prepared quantitatively from the dialdehyde, is an interesting addition to the list of upper rim functionalized calixarenes [76] (Fig. (**12**)). Despite the common use of carboxylates to bind transition metals these compounds have yet to be utilized as ligands perhaps due to the stability of their hydrogen bonded dimers [77].

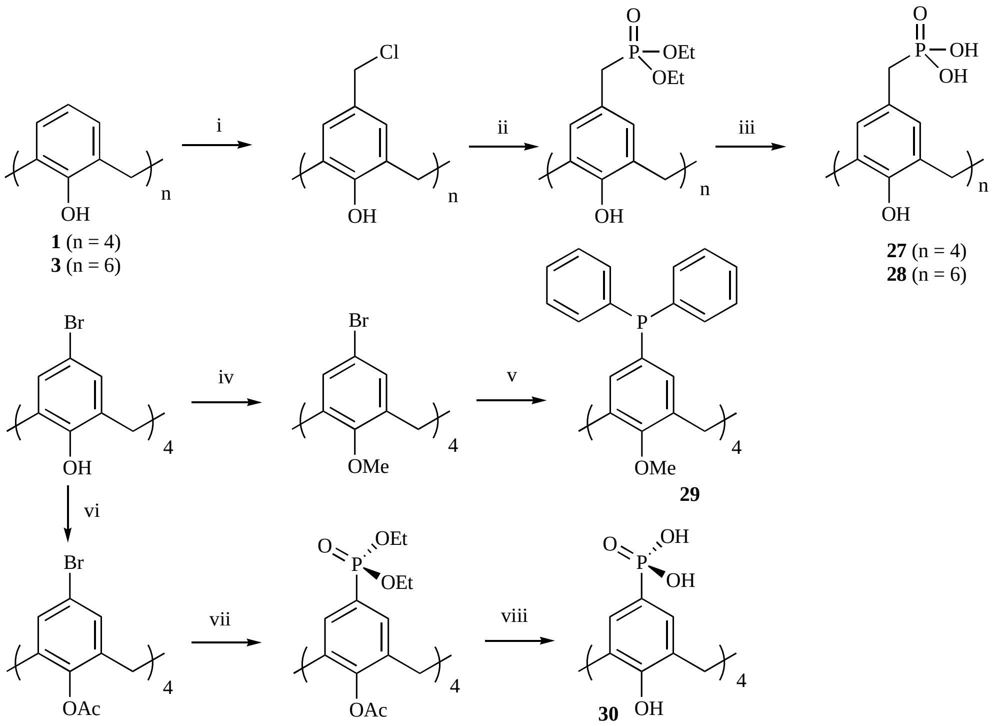


Fig. (11). Introduction of phosphorus to the upper rim of calixarenes: i) chloromethyl *n*-octyl ether/$SnCl_4$, ii) $P(OEt)_3$, iii) H_2O [70], iv) NaOMe, v) BuLi, chlorodiphenylphosphine [73], vi) Ac_2O/NaOAc, vii) $P(OEt)_3/NiCl_2/PhCN$, viii) $KOH/THF/H_2O/MeOH$, $Me_3SiBr/MeCN$ [75].

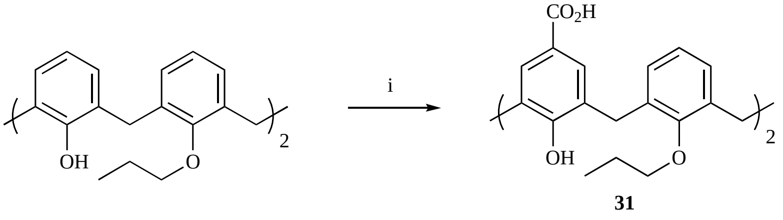


Fig. (12). Introduction of carboxylic acids at the upper rim of calix[4]arene: i) $SnCl_4/Cl_2CHOMe$, H_2NSO_3H, $NaClO_2$ [76].

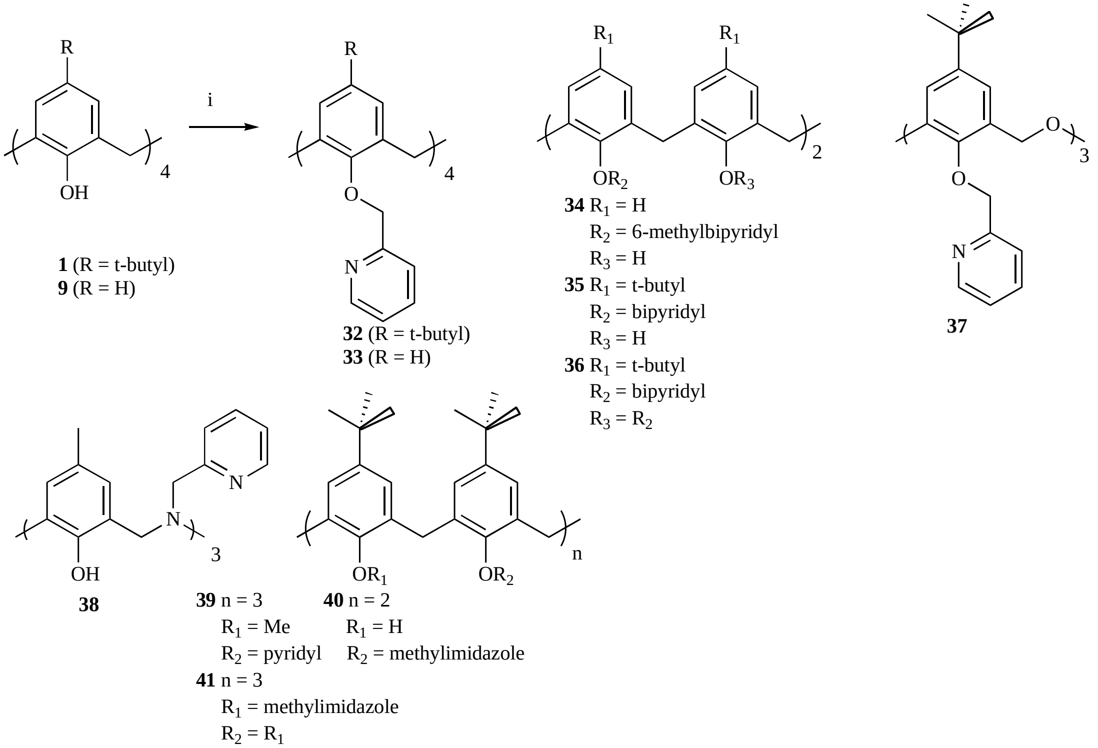


Fig. (13). Lower rim pyridyl and imidazole substituents: i) picolyl chloride·HCl/base [94].

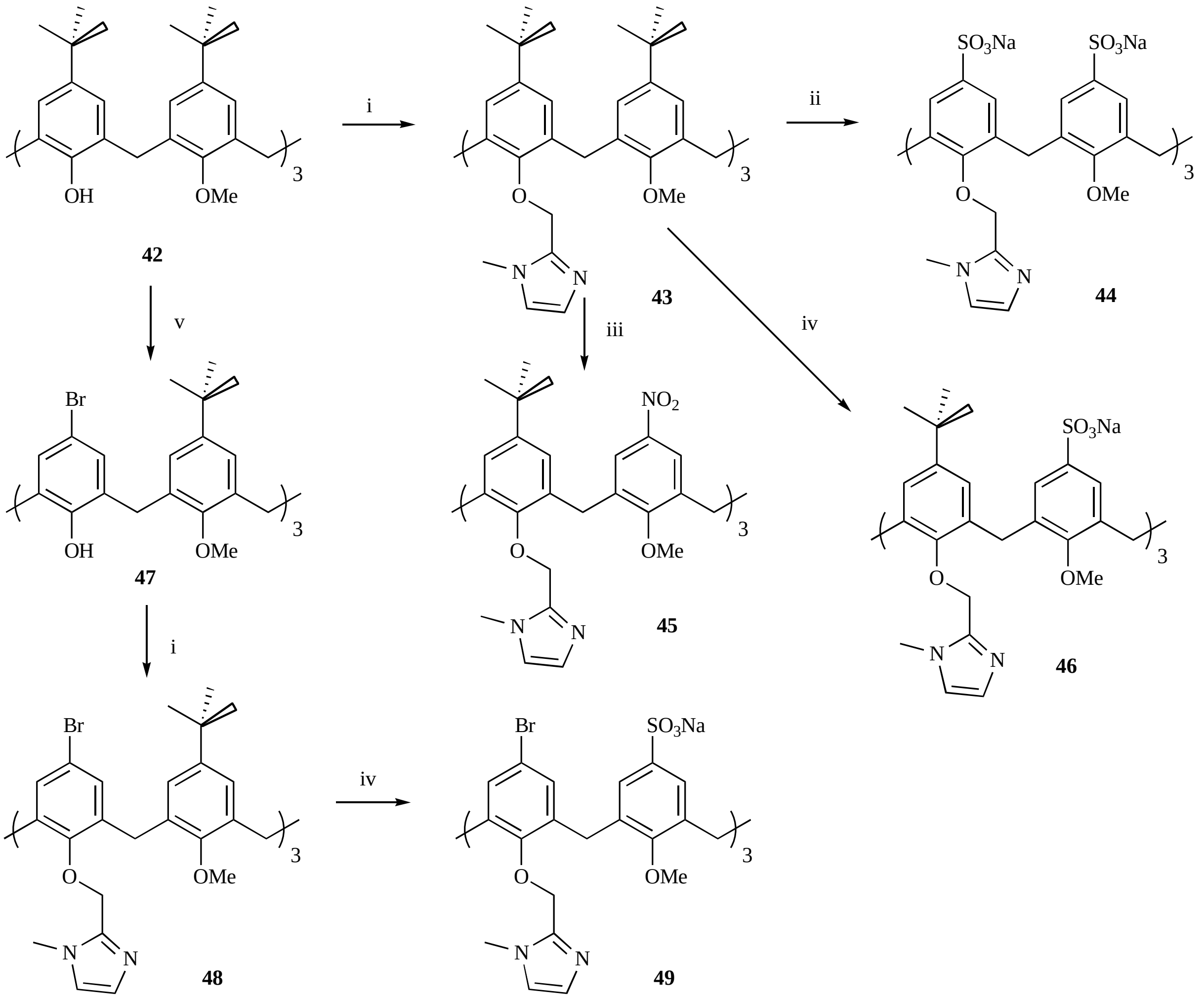


Fig. (14). Reactions of calix[6]arenes: i) NaH/2-chloromethyl-1-methyl-*1H*-imidazole·HCl [104a], ii) H_2SO_4 (conc.), iii) HNO_3/AcOH, iv) HSO_3Cl, base, v) $AlCl_3$, NBS [106].

5. INTRODUCTION OF BINDING SITES AT THE LOWER RIM

Lower rim modification, and in particular the formation of pendent aryl ethers, is by far and away the major strategy used to introduce binding sites for transitional metals. The ease with which the aryl ethers are formed opens up numerous possibilities including the incorporation of nitrogen donors in pyridyl [78], imidazole [79], acetamide [78b, 80, 81], ethylamine [81], pteridine [82], hydroxamate [83], bipyridine [84] and triazacyclononane [85] substituents. Figs. (**13**), (**14**) and (**15**) illustrate the general approaches available. Similarly, oxygen donors can be introduced as esters and ethers [86], carboxylic acids [87] and ketones [88]. Reaction of calixarenes with chlorodiphenylphosphine, under various conditions and degrees of lower rim protection, introduces pendent diphenylphosphine moieties [89]. Methyl phosphine oxides can also be formed [90], as can diethylphosphonates [91], through reaction with the appropriately activated precursor. Finally, the use of sulfur as a pendent donor has been limited, however, the thiol analogue of 4-t-butylcalix[4]arene has been prepared [92] and shown to be an excellent ligand for mercury [93]. Routes to these other lower rim derivatives are shown in Figs. (**16**) and (**17**).

5.1. Nitrogen-Containing Lower Rim Substituents

One of the earliest methods to introduce pendent nitrogen donors, from the Pappalardo group, was through reaction of **1** or **9** with NaH in DMF followed by an excess of picolyl chloride·HCl [94]. This approach produced the tetrasubstituted *cone* conformer in 72% yield for calix[4]arene (**32**) and 80% for the 4-t-butyl parent (**33**). Further work by the group [95] confirmed that the *cone* products were formed exclusively in the presence of sodium cations. When K^+ or Cs^+ salts were used instead a mixture of *cone*, *partial cone* and *1,3-alternate* conformers resulted with a minority of the product in the *cone* conformer. Stepwise alkylation was achieved through reaction of four equivalents of picolyl chloride·HCl with the respective calix[4]arenes with the products isolated by column chromatography. The 4-t-butylcalix[6]- and [8]arene analogues have also been prepared, in 81% and 24% respectively, and the latter appears to have a high affinity for UO_2^{2+} [96].

The Beer group has taken this approach slightly further by attaching two lower rim 6-methylbipyridine substituents to opposite phenols of calix[4]arene (**34**) [97]. As expected the compound bound Cu^+ as an orange 1:1 complex, however, mass spectrometric evidence for the 2:2 complex was also found. Similarly, the Ungaro group prepared **1** with two and four pendent 2,2-bipyridyls (**35**, **36**) which complexed Eu^{3+} and Tb^{3+} to give luminescent species [98].

Introduction of pendent methylpyridine moieties into oxacalix[3]arenes proceeds by an analogous process (**37**) [78b, 99]; methylpyridine can be incorporated at the nitrogen bridgeheads of methylazaxalix[3]arenes through condensation of 2,6-bis(hydroxymethyl)-4-methylphenol with 2-picolylamine to give the azacalix[3]arene in 29% yield (**38**) [100]. Perhaps surprisingly these pyridyl-containing derivatives have yet to be investigated as potential transition metal binding agents. There is one exception. In 1998 the Reinaud group published the synthesis ofa 4-t-butylcalix[6]arene derivative where three alternate phenolic groups were methylated prior to treatment with picolyl choride (**39**) and investigated its Cu^+ binding [101]. The crystal structure of the copper complex shows the metal coordinated by all three picolyl groups. It is held within the calixarene's central cavity where an acetonitrile molecule binds to give the metal's preferred tetrahedral geometry.

In Nature, the imidazole group is ubiquitous as a transition metal binding motif and, consequently, is an ideal candidate to introduce into calixarene chemistry. While two and four imidazole groups have been appended to 4-t-butylcalix[4]arene (**40**, **41**) [102, 103], it is the trisubstituted 4-t-butylcalix[6]arene derivative has attracted more attention [79, 104]. The Reinaud group has again pioneered the use of the calix[6]arene scaffold, this time to generate a trimethyltris(imidazole) derivative that binds both Zn^{2+} [104b] and Cu^+ [104c] in a tetrahedral environment. The synthesis starts with the regioselective C_{3v} symmetric 4-t-butylcalix[6]arenetrimethylether (**42**) [105] which is deprotonated with NaH in tetrahydrofuran. Subsequent reaction with a large excess of 2-chloromethyl-1-methyl-*1H*-imidazole·HCl forms the target compound (**43**) in 84% after column chromatography. In order to make the compound more water soluble several strategies have been employed with direct hexasulfonylation (**44**) or *ipso*-nitration (**45**) of the tris(imidazole) both being successful. *Ipso*-chlorosulfonylation followed by hydrolysis results in the formation of the tri-t-butyltrisulfonato derivative (**46**). Alternatively, starting from **42**, de-t-butylation of the three unsubstituted phenols by $AlCl_3$ followed by bromination with *N*-bromosuccinamide produces the tribromo-tri-t-butylcalix[6]arenetrimethylether (**47**). Reaction with 2-chloromethyl-1-methyl-*1H*-imidazole·HCl generates the tris(imidazole) derivative (**48**) which is now amenable to sulfonation following removal of the remaining three t-butyl groups (**49**) [106].

One of the first substituents to be attached to the lower rim of **1** was the *N*,*N*-diethylacetamide moiety. The synthesis is straightforward: the calixarene is dissolved in tetrahydrofuran and deprotonated with an excess of NaH then a three fold excess of 1-chloro-*N*,*N*-diethylacetamide is added. Following reflux and workup the product, in the *cone* conformation, is isolated in 95% yield as white crystalline needles (**50**) [107]. Since the original report the di- and trisubstituted derivatives of **1** have been prepared [108, 109], as have the tri- and hexasubstituted analogues of **3** [110] and the derivatives of **6a** [78b, 80b, 111]. Originally calixarenes with *N*,*N*-diethylacetamide substituents were investigated as receptors for alkaline metal cations [107, 111], however, they have a far more interesting chemistry with lanthanides [108, 112] and transition metals [109, 113, 114]. Fe^{2+}, Ni^{2+}, Cu^{2+} and Zn^{2+} cations are all bound within the central cavity of the calixarene and interact primarily with the amide carbonyl oxygens; Fe^{2+} and Ni^{2+} also interact with the phenolic oxygens. Tb^{3+} shows a strong luminescent response when encapsulated by the tetraacetamides but Eu^{3+} is less affected [112]. To improve the luminescent properties of lanthanide complexes based on the calixarene framework other groups have been appended including naphthalene (**51**), phenanthrene (**52**) and triphenylene (**53**) [115]. Eu^{3+} and Tb^{3+} were particularly responsive to the triphenylene antenna.

The binding of *cone* 4-t-butyloxacalix[3]arenetris(*N*,*N*-diethylacetamide) (**54**) to transition and other metals has been investigated [116]. Results show a preference in the order $Pb^{2+} > Ca^{2+} \approx Zn^{2+} > Na^+ > Ba^{2+} \approx Ag^+ \approx K^+$ which seems to indicate a preference for the divalent cations, independent of their nature and size. Although it appears that binding in solution is within the central cavity, the crystal structure of the Hg^{2+} complex shows that two calixarenes bind an Hg_2Cl_4 dimer between them through carbonyl and ether oxygens directed away from the central cavity [114]. In general **54** is a weaker extractant than the tetraacetamides of **1** and **14** [117, 118], presumably due to its higher conformational flexibility.

The Roundhill group also used the amide approach to enhance lanthanide luminescence by incorporating lower rim acetamide groups into both 4-t-butylcalix[4]- and [6]arenes (**55**, **56**) [81]. The acetamides were then reduced by borane to yield the 2-aminoethoxy analogues (**57**, **58**). It was demonstrated that **55** and **58** gave the greatest fluorescence lifetime enhancement in the presence of Tb^{3+}.

Of the more unusual pendent groups, pteridine [82], hydroxamate [83] and triazacyclononane [84] stand out. Pteridine has been incorporated as a chromophore that has amide and pyridyl functionality (**59**). Despite the binding site being reasonably attractive for transition metals and lanthanides only sodium has elicited a response from the compound. Hydroxamate is found in Nature, where it is often encountered as a motif in Fe^{3+}-binding siderophores. When exhaustively attached to the lower rim of 4-t-butylcalix[6]arene (**60**) it is able to extract UO_2^{2+} in competition with carbonate. The Beer group reacted 4-t-butylcalix[4]arenebis(acetylchloride) (**61**) with two equivalents of *N*,*N'*-dimethyl-1,4,7-triazacyclononane then reduced the resulting diamide (**62**) with $LiAlH_4$ (**63**). The disubstituted calixarene bound two Ni^{2+} cations, one in each triazacyclononane ring, linked by bridging azide anions [85].

5.2. Oxygen-Containing Lower Rim Substituents

A range of oxygen-containing groups can be introduced as lower rim substituents with the formation of the ester often the first step. In the case of **1** this is generally carried out by deprotonating with NaH or K_2CO_3, which favours the formation of the *cone* conformer, or Cs_2CO_3, which leads to the *1,3-alternate* conformer being adopted. Addition of a large excess of $BrCH_2CO_2Et$ results in the formation of the tetraethylacetate (**64**). If required, this can be cleaved to yield the tetraacid (**65**). Lower rim acids can also be prepared directly through reaction with bromoacetic acid or base-assisted cleavage of lower rim amides. Despite the ease with which these derivatives can be made, they have little application as ligands for transition metals. Indeed, the only transition metal that appears to interact with ethers or esters is Ag^+ [119]. Ketones prepared from 4-t-butyldihomooxacalix[4]arene, particularly the t-butyl derivative (**66**) [120], bind Ag^+ but also have reasonable affinities for Cu^{2+} and Zn^{2+}, and show some extraction of Mn^{2+}, Fe^{2+}, Co^{2+}, Ni^{2+} and Hg^{2+} [121]. Calixarene carboxylates have been shown to extract lanthanides, with the best complexing agent being **67**, the octaacid of **5** [87b]. As might be expected tetracarboxylates of **8** bind to the softer transition metals well and the bridging sulfurs can be involved in complexation; affinity is particularly high for Fe^{2+} [122].

4-t-Butyloxacalix[3]arenetris(ethylacetate) (**68**) is formed, in a mixture of *cone* and *partial cone* conformers, by reaction of **6** with $BrCH_2CO_2Et$ in the presence of base [87b, 123]. Treatment of the *cone* conformer with KOH in refluxing ethanol, followed by HCl, generates the related acid (**69**). This compound can also be obtained from **54** [80b] by base catalyzed hydrolysis [124]. The latter route may be preferable as it is possible to form the *cone* conformer of **54** in yields of 40% whereas the yield of the ester analogue is considerably lower. C*one*-**69** has been shown to bind to lanthanides (Yb^{3+}, $Eu^{3+}$and Pr^{3+}) with high stability (log $\beta \approx 20 - 30$) [89b]. Surprisingly the interactions of this compound with other trivalent transition metals, such as Co^{3+}, Fe^{3+} or Mn^{3+}, has yet to be investigated.

5.3. Phosphorus-Containing Lower Rim Substituents

Phosphines are soft bases and ligate a number of soft transition metals, particularly Pt^{II}. Diphosphates, in which phosphorus binds to multiple phenolic oxygens, are prepared from reaction of the parent calix[n]arene with $ClPO(OEt)_2$; the calix[6]arene derivative has been isolated in 50% yield (**70**) [125]. Direct reaction of calix[6]arene with PCl_3 generates *syn* and *anti* isomers in which two phosphorus atoms each bridge three phenolic oxygens (**71**).

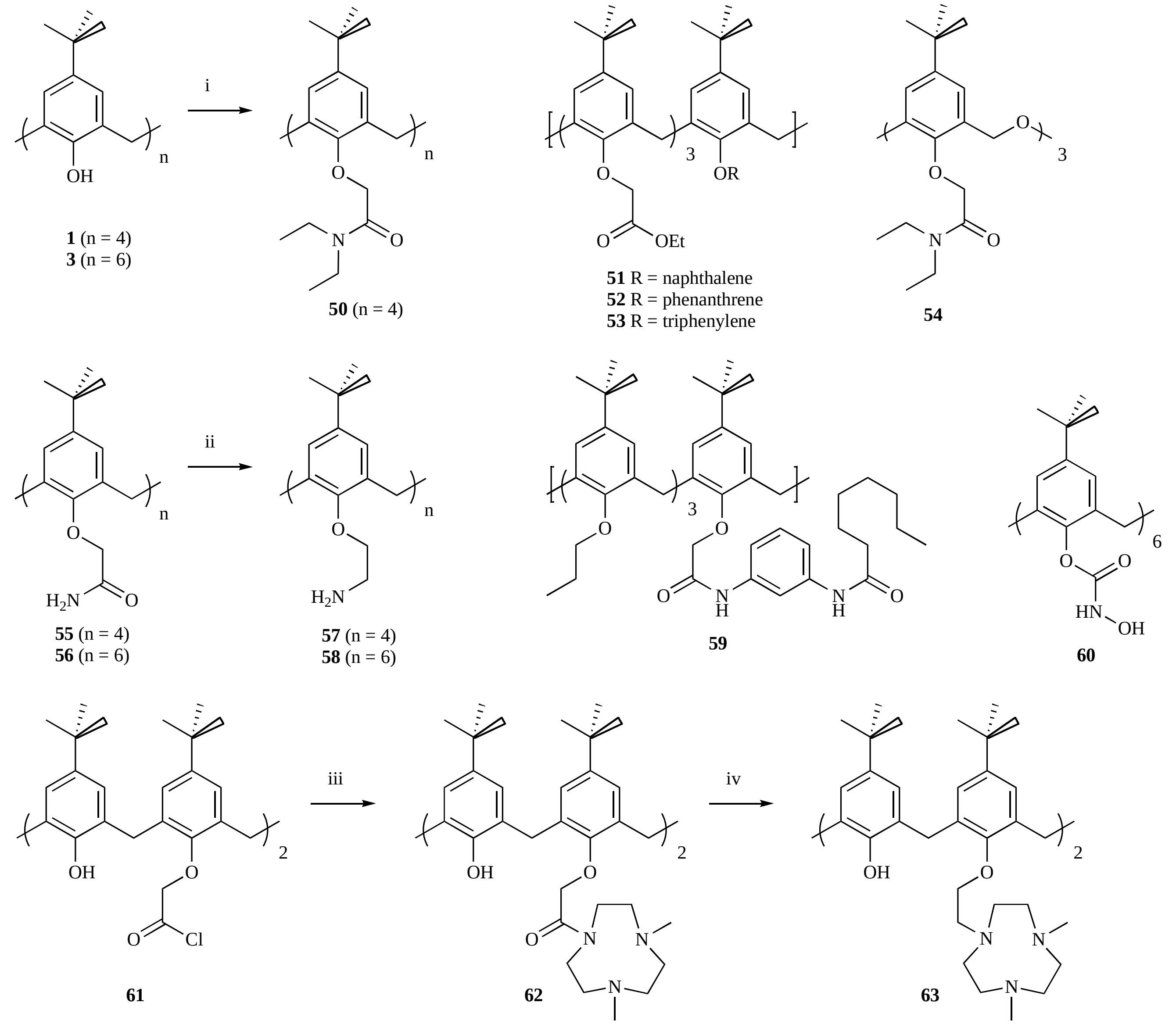


Fig. (15). Lower rim amides and derivatives: i) base/1-chloro-*N*, *N*-diethylacetamide [107], ii) B_2H_6 [82], iii) *N,N'*-dimethyl-1,4,7-triazacyclononane/Et_3N, iv) $LiAlH_4$ [85].

The calixarene is formed in yields of up to 40% and reacts with Pt^{II} and Pd^{II} [126]. Compounds that are more amenable to direct metal coordination include the $–PO(O^iPr)_2$ and $–PPh_2$ derivatives (**72**, **73**), prepared from the chlorophosphate or chlorophosphine. The tetra-substituted derivative of **1** forms an 8:2 complex with CuCl [127] and a 2:1 complex with $Fe^{IV}(CO)_3$ [128]. The Lattman group has been exploring the coordination chemistry of 4-t-butylcalix[5] arenes through the introduction of bridging phosphorus species at the lower rim [129, 130]. These compounds can then react with titanium and zirconium to form complexes such as **74** (Fig. (**16**)).

Oxacalix[3]arenes have been successfully phosphorylated by treating the parent compound with NaH in toluene followed by $Ph_2P(O)CH_2OTs$ and heating at 90ºC for 72 hours (**75**) [131]. The reaction gave the *cone* and *partial cone* conformers in a 4:1 ratio which were separable by column chromatography. The *cone* conformer extracted a range of lanthanide picrates from water to dichloromethane with efficiencies varying from 4% for Y^{3+} to 43% for Pr^{3+}. Reduction of the phosphine oxides was achieved quantitatively using $PhSiH_3$ in refluxing toluene (**76**); the reduced *cone* conformer formed 1:1 complexes with Ag^+, Au^{III}, $Mo^{VI}(CO)_3$ and $Rh^{VI}H(CO)$ with an average C_{3v} symmetry as determined by NMR.

5.4. Thiacalixarenes and Lower Rim Thiols

Reaction of **1** with NaH followed by $ClC(S)Me_2$ in diglyme yields a compound with four dimethylthiocarbamate groups in the *1,2-alternate* conformation [92]. Heating this in *p*-tolyl ether brings about a Newman-Kwart rearrangement; subsequent reduction with $LiAlH_4$ generates **77** which adopts the more stable *1,3-alternate* conformation as shown in Fig. (**17**). The softer sulfur donor atoms, combined with an ideal separation between sulfurs on opposite rings, makes this derivative an ideal ligand for Hg^{2+} which binds in a 2:1 stoichiometry [93]. Reaction of two equivalents of $ClCH_2CH_2SMe$ with **9** yielded a mixture of mono- and 1,3-bis(thiomethylethyloxy)calixarenes that were isolated, after column chromatography, in 22% (**76**) and 4% (**79**) yield, respectively [97]. From ^{13}C NMR shifts of the alkyl carbons it was clear that the disubstituted calixarene bound Ag^+ as the 1:1 complex.

6. OTHER BINDING MODES

The examples given above cover the majority of calixarene derivatives that have been reported to date. There are, however, a few

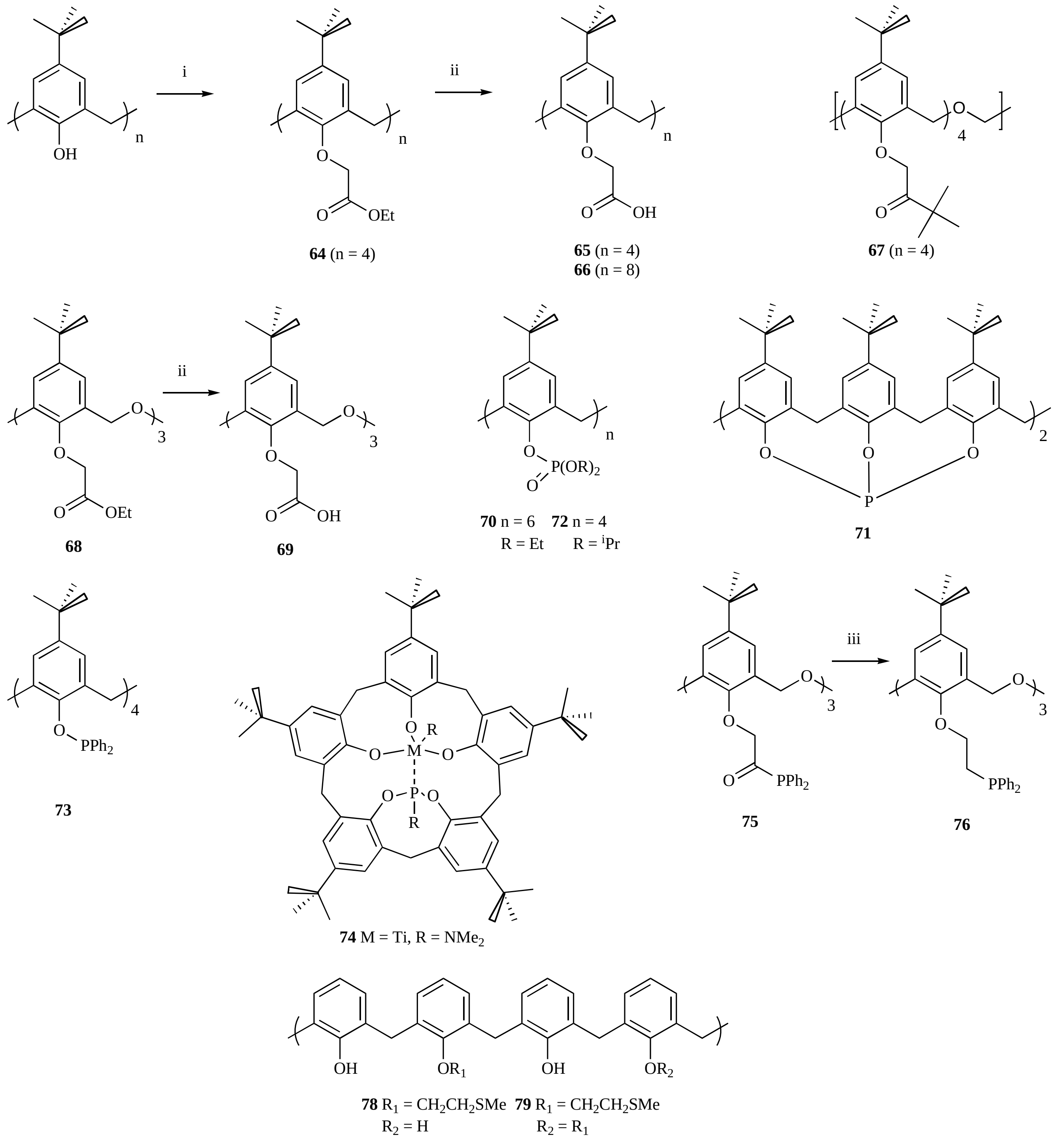


Fig. (16). Oxygen, phosphorus and sulfur containing lower rim substituents: i) base/2-bromoethyl acetate [119], ii) base, iii) $PhSiH_3$ [131].

compounds based on the calixarene structure that bind transition metals in unusual ways that are also worthy of attention.

6.1. Calixcrowns and Calixtubes

Tethering two or more calixarene rings together couples the rigid calixarene annulus to a secondary preorganized binding site. Much work in this direction employs polythers to bind alkali metals, such as Cs^+ which is an important constituent of radioactive waste, and some 'calixcrowns' can also bind Ag^+. The compounds are usually prepared from a calix[4]arene and a polyether ditosylate. Reaction of **1** with pentaethylene glycol ditosylate in the presence of K^+ results in the formation of the singly strapped 4-t-butylcalix[4]arene (**80**) [132]; the analogous reaction between the *1,3-alternate* conformer of **9** and two equivalents of pentaethylene glycol ditosylate in the presence of Cs^+ generates the doubly capped analogue (**81**) [133] that binds Ag^+ [134] (Fig. (**19**)). Indeed, calix[4]arenes appear to have a general affinity for Ag^+; the Shinkai group has shown that simple *O*-propyl derivatives bind the metal in both *cone* and *partial cone* conformations [135].

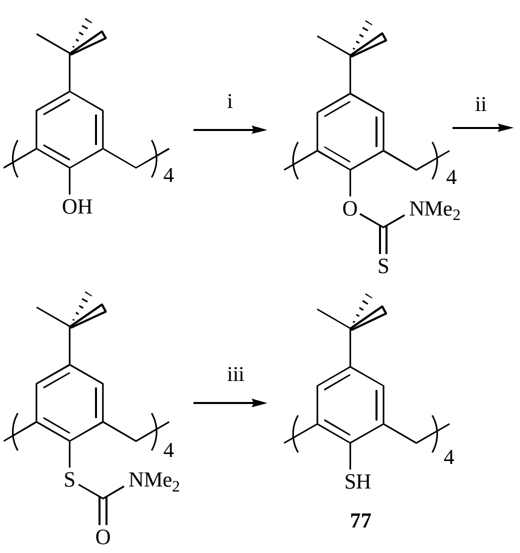


Fig. (17). 4-t-Butylcalix[4]arenethiol synthesis: i) NaH, ClC(S)Me$_2$, ii) heat, iii) LiAlH$_4$ [93].

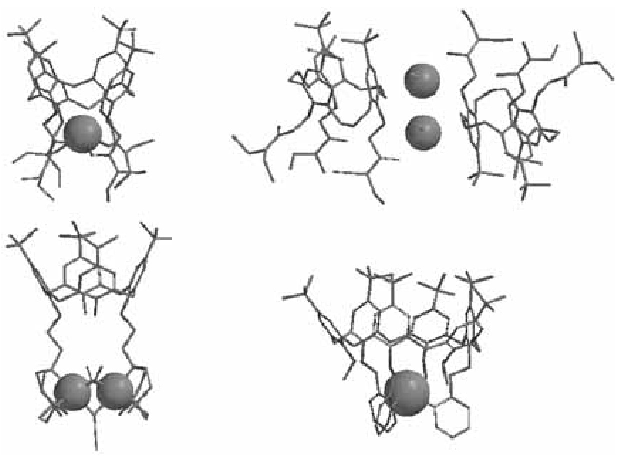
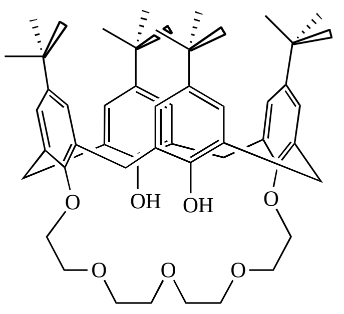


Fig. (18). Calixarene complexes: (top, l to r) **49**·Fe, **53**$_2$·Hg$_2$Cl$_4$, (bottom, l to r) **62**·Ni$_4$, **38**·Cu (hydrogen atoms, solvent and non-coordinating species removed for clarity).

In 1997 the Beer group published the synthesis and potassium binding ability of a bis(calix[4]arene), or calixtube (**82**) [136] as shown in Fig. (**19**). Tetraacetate **64** is reduced to the alcohol by LiAlH$_4$ and tosylated in pyridine at 0°C. The tetratosylate reacts with **1** in the presence of K$^+$ which acts as both the deprotonating and templating agent for the reaction so that four ethyl substituents bridge the two calixarenes in a remarkable 50% yield. An analogue in which **1** is coupled to **9** in 14% yield (**83**) binds Ag$^+$ in a 1:1 stoichiometry [137].



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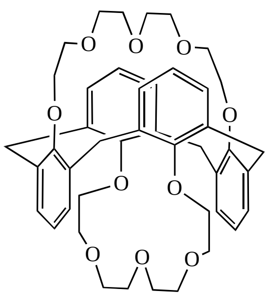

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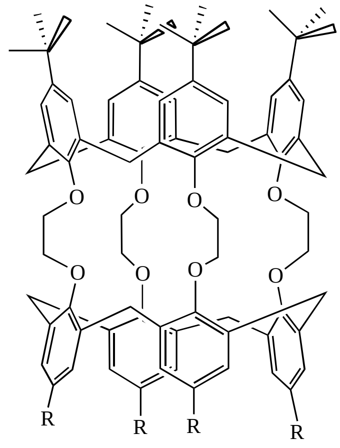
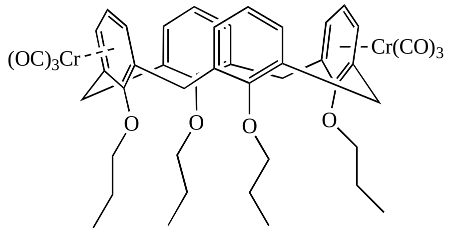


82 R = t-butyl
83 R = H

Fig. (19). Calixcrowns and calixtubes.

6.2. Organometallic Calixarene Derivatives

The aromatic rings of calixarenes would seem like ideal surfaces for organometallic interactions yet it took until 1993 for such an ambition to be realized when the Shinkai group introduced Cr(CO)$_3$ fragments to the exterior of one or two phenolic rings of a calix[4]arenetetrapropyl ether (**84**) in the *cone* conformation [138]. A year later the Atwood group prepared organometallic 'sandwich' complexes where two Cp*Ir^{III} moieties were incorporated into the outer faces of two opposing phenolic rings of **1** to give **85** [139]. The resulting compound reverses the usual electron-rich characteristics of the calixarene cavity making it attractive to anions. When similar reactions were attempted with **9** the reduced steric hindrance allowed four *p*-cymeneRu^{II} or Cp*Ir^{III} moieties to bind externally [140].



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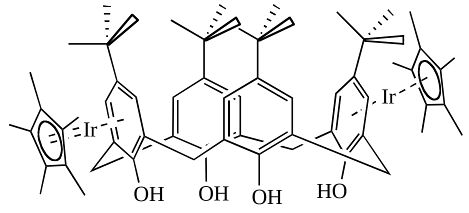

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Fig. (20). Organometallic calixarenes.

CONCLUSIONS

The calixarene framework is ideally suited to bind metal ions. It is rigidly defined in terms of geometric constraints and may be modified to incorporate many groups with the necessary properties for cation binding. This extends not only to simple cations but also to the more demanding requirements of transition metals. Furthermore the calix[4]arenes, and to some extent other members of the family, exist in specific conformers which allow divergent binding motifs to be employed in metal ligation. We have shown that the unmodified calixarenes bind hard transition metals with alkali metal or alkaline earth electronic configurations such as Ti^{IV}, Zr^{IV}, Nb^{V}, Ta^{V}, Mo^{VI} and W^{VI} (all d^0), and trivalent lanthanides. Other oxygen-containing substituents bind metals with full d-shells such as Zn^{2+} and Ag^{+} (both s^0d^{10}) whereas nitrogen and sulfur donor atoms bind a far wider range of transition metals. The syntheses of the calixarene derivatives themselves are rarely particularly challenging, though there are occasionally issues of regioselectivity, but this is perhaps one of the strengths of the development of calixarene-based ligands for transition metals.

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