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Chemistry of Calix[7]arenes

Marco Martino and Placido Neri*

Dipartimento di Chimica, Università di Salerno, Via S. Allende 43, I-84081 Baronissi (Salerno), Italy

Abstract: Calix[7]arenes, of intermediate size between the corresponding hexamers and octamers, are of comparable interest for the synthesis of molecular receptors for medium-sized guests. At this regard current information concerning their synthesis, exhaustive and selective functionalisation, intramolecular bridging, conformational features, and supramolecular properties is reviewed. These data are of particular relevance for the design of new calix[7]arene-based hosts of interesting potentialities in supramolecular chemistry.

Keywords: Calixarenes, Calix[7]arenes, synthesis, functionalisation, conformation, intramolecular bridging, supramolecular chemistry.

Dedicated to Professor Adolfo Zambelli on the Occasion of his 70th Birthday

1. INTRODUCTION

In the past two decades considerable attention has been devoted to the chemistry of the phenols/formaldehyde cyclic oligomers, which were named *calixarenes* by Gutsche [1], in relation to the cone-shaped structure of the smaller tetrameric member of the family (Fig. **1**). In fact, due to the presence of variously shaped cavities in their structures, these macrocycles have gained a prominent position in supramolecular chemistry [2], mainly linked to their complexing ability toward cations, anions, and neutral molecules, often displayed with very remarkable and unparalleled selectivity [3]. In addition, they have found widespread applications in several other areas, which include chemosensors, transport, catalysis, bioorganic chemistry, luminescent probes, self-assembly, crystal engineering, and supramolecular devices [3].

The synthesis of calixarenes, by base-induced condensation of *p*-alkylphenols with formaldehyde, was developed in the 1970s, by Gutsche and coworkers [1,4] who re-interpreted the results of original discovery of the reaction by Zinke [5] in the 1940s. These procedures have made the so-called “major” [6] calix[*n*]arenes (*n* = 4, 6, 8) readily accessible in good and reproducible yields [7], and consequently have allowed their study and the subsequent exploitation in the mentioned areas of supramolecular chemistry [3].

In contrast, the “minor” [4] odd homologues (*n* = 5, 7), often obtained only as *by-products* of even-membered macrocycles, had remained largely less studied because of the lack of efficient preparation procedures. However, in the past decade improved synthetic procedures have been reported [8] allowing significant advances in the study of their properties, which already appear of particular interest [3]. This *mini-review* surveys the chemistry and properties of the calix[7]arene macrocycle with main focus on its synthesis and chemical modifications.

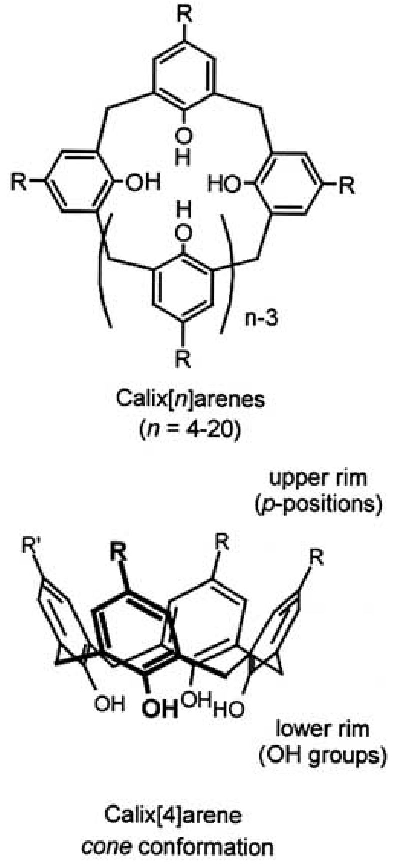

Fig. (1). Structure of calix[*n*]arenes.

2. SYNTHESIS OF CALIX[7]ARENE MACROCYCLES

Notwithstanding there is no large difference in thermodynamic stability among the major calixarenes [9] and the corresponding cyclic heptamer, no synthetic procedures of comparable efficiency are currently available

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*Address correspondence to this author at the Dipartimento di Chimica, Università di Salerno, Via S. Allende 43, I-84081 Baronissi (Salerno), Italy; Tel: +39 089 965 258/965 283; E-mail: neri@unisa.it

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for calix[7]arene macrocycle. This can be ascribed to a kinetic control of the cyclisation step [9], which may be influenced either by a template effect of the metal cation present in the reaction mixture or by the conformational predisposition of the linear oligomer likely driven by the intramolecular H-bond. Among the three general types of synthesis of calixarene macrocycles (one-pot, stepwise and fragment condensation) [3] the one-pot procedures have been mainly used for the synthesis of calix[7]arenes, which can be either base-induced or acid-catalysed. An historical example of stepwise synthesis is also known [10a].

2.1 Base-Induced Syntheses

Several calix[7]arenes **1a-j** bearing different substituents at the *para* positions of the aromatic rings (the so-called *upper rim*) have been obtained by base-induced condensation of the corresponding *p*-substituted phenols.

The first synthesis of this kind, reported in 1982, by Nakamoto and Ishida [11], concerns the preparation of *p-tert*-butylcalix[7]arene **1a**, in 6% yield, by condensation of *p-tert*-butylphenol with formaldehyde in 1,4-dioxane in the presence of KOH. Subsequently, it was found that longer reaction times (up to 30 h), under similar conditions, reduce the yield to ca. 4% [12].

Other *p*-alkylcalix[7]arenes **1b**, obtained by reaction of the corresponding *p*-alkylphenol, with formaldehyde, KOH or NaOH in benzene or xylene, at 100-120 °C for 30-100 h, were patented in 1984 [13] and 1999 [14]. In addition, Nakamoto and coworkers [15] reported the preparation of *p-n*-alkylcalix[7]arenes **1c** from *p-n*-octyl, *p-n*-nonyl-, or *p-n*-dodecylphenol and formaldehyde in xylene at 130 °C in the presence of NaOH. The products were separated from the corresponding calix[6,8]arenes, present in the reaction mixture, by fractional crystallisation and column chromatography.

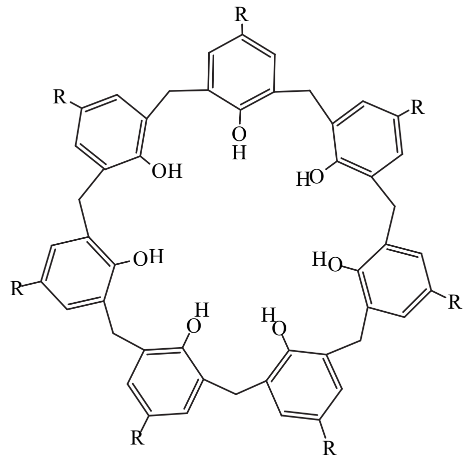
The syntheses of *p*-phenyl- (**1d**) [16] and *p*-(*p*-tolyl)calix[7]arene (**1e**) [16a] were mentioned in 1984-85 [16]. Subsequently (1989), Asfari and Vicens [17] reported the first *p*-methyl- (**1f**) and *p*-ethylcalix[7]arene (**1g**) obtained in 22 and 27% yield, respectively, by KOH-promoted condensation of pertinent phenols with formaldehyde in tetralin. Reaction times were very short (2 h for **1f** and 45 min for **1g**). Further reports [14,18] concerning the synthesis of **1f** suggest that longer reaction times lower the yields.

The synthesis of *p-tert*-butylcalix[7]arene **1a**, was improved up to 17% yield in 1995, by Lamartine and coworkers [19], by reacting *p-tert*-butylphenol, 37% aqueous formalin, KOH or LiOH in refluxing xylene, for 2 h. In this work the influence of several parameters on the yield was examined in detail. For instance, it was found that the dropwise addition of phenol or reaction times longer than 4 h reduce the amount of **1a** favoring the corresponding calix[8]arene. The relative amount of phenol and formalin was also of particular relevance and a statistical analysis showed that better results are obtained using 1 g of phenol per 10 mL of formalin.

In 1996, Yamagishi *et al.* [20] reported the synthesis of *p*-methoxycalix[7]arene **1h**, by *t*-BuOK-promoted condensation of *p*-methoxyphenol and paraformaldehyde in tetralin, obtaining calix-hydroquinone derivatives.

In 1997, Ungaro and coworkers [21] studied the condensation of *p*-benzyloxyphenol with paraformaldehyde obtaining calix[7]arene **1i** as by-product besides the calix[8]arene main product. In particular, **1i** was formed in 21% yield using KOH as base, while NaOH and LiOH gave 6 and 17% yield, respectively.

In 1999, Thuéry *et al.* [22] obtained *p*-benzylcalix[7]arene **1j** in *ca.* 16% yield, utilising *p*-benzylphenol, paraformaldehyde and a 14 M KOH solution in tetralin at 180-185 °C. In the same year, Raston and coworkers [23] have shown that **1j** can be obtained in 5-10% yield, besides the corresponding cyclic pentamer, by ultra-high intensity grinding (UHIG) of pure *p*-benzylcalix[6 or 8]arenes in the presence of KOH and molecular sieves (4 Å). The results suggest that the products are not formed through a simple disproportionation mechanism. Better yields of **1j** (15-20%), along with *p*-benzylcalix[10]arene, were obtained by KOH-promoted direct condensation of *p*-benzylphenol and paraformaldehyde in tetralin under more forcing conditions.



1a-j

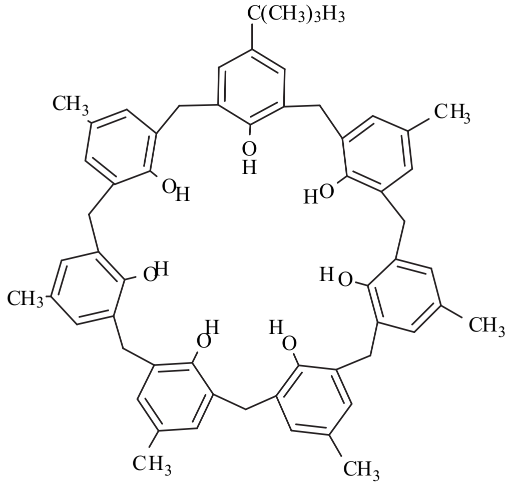
	R	Ref.
a	*t*-Butyl	6,11,12,19
b	Alkyl (C_{1-12})	13,14
c	*n*-Alkyl (C_8, C_9, C_{12})	15
d	Phenyl	16
e	*p*-Tolyl	16a
f	Methyl	14,17,18
g	Ethyl	17
h	Methoxyl	20
i	Benzyloxy	21
j	Benzyl	22,23

2.2 Acid-Catalyzed Synthesis

The single example of acid-catalysed synthesis of a calix[7]arene (**1a**), obtained along with the so-called “large” calix[*n*]arenes (*n* > 8), was reported in 1999, by Stewart and Gutsche [6]. In this work the formation of *p-tert*-butylcalix[*n*]arenes by condensation of *p-tert*-butylphenol with *s*-trioxane or paraformaldehyde was studied using three different solvent/acid-catalyst systems (AcOH/HCl, toluene/TsOH, and $CHCl_3$/TsOH). Almost quantitative yields in terms of mixture of calix[*n*]arenes were obtained with $CHCl_3$/TsOH system using *s*-trioxane as the HCHO source. Under these conditions the optimal yields of calix[7]arene **1a** (up to 25%) were obtained using a *p-tert*-butylphenol/*s*-trioxane/TsOH molar ratio of 1/1.15/0.1 and a *p-tert*-butylphenol/chloroform concentration of 5-10% wt/mL. The crude reaction mixture containing calix[4-20]arenes can be fractionated using a series of precipitation/dissolution cycles. *p-tert*-Butylcalix[7]arene **1a** is one of the most soluble *p-tert*-butylcalixarenes in common organic solvents; therefore, it can be isolated and then purified by crystallisation, after precipitation of the other “major” and “minor” calixarenes.

2.3 Stepwise Synthesis

The so-called “stepwise synthesis” [10b] is based on the non-convergent multi-step growing of a linear oligomer that is cyclised in the last step. This approach has the advantage of the direct construction of a calixarene macrocycle carrying different substituents at the upper rim. However, it is time-consuming and suffers from overall low yields due to large number of steps. By using this approach the first historical preparation of a calix[7]arene was reported by Kämmerer and Happel in 1980 [10a]. The synthetised compound **1k**, bearing one *tert*-butyl and six methyl substituents at the *para* positions, was obtained in 62% yield in the last cyclisation step.



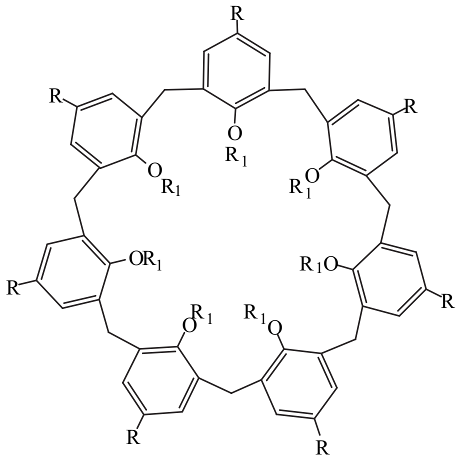
1k

3. EXHAUSTIVE FUNCTIONALISATION

A very interesting aspect of calixarene chemistry is their easy chemical modification, which can be used to profoundly alter the chemical and supramolecular properties of the parent macrocycle. This represents a great advantage for calixarenes, with respect to other macrocyclic hosts (for example, cyclodextrins and crown-ethers) used in supramolecular chemistry [2], that over the years has led to a very large variety of derivatives [3]. The chemical modification of calixarenes is commonly performed by functionalisation at the *para* positions of the aromatic rings (the *upper rim*) or at the phenolic hydroxyls (the *lower rim*), but, more or less occasionally, transformations involving the *meta* positions, bridging methylenes, oxidation or reduction of phenol rings have also been carried out [3]. In the case of calix[7]arenes only the two former modifications have been reported.

3.1 Exhaustive Functionalisation at the Lower Rim

p-tert-Butylcalix[7]arene **1a** has been exhaustively methylated at the lower rim by treatment with MeI in the presence of Cs_2CO_3 in acetone to give heptamethoxy-calix[7]arene **2a** in 90% yield [24]. In addition **1a** has been alkylated with ethyl bromoacetate/K_2CO_3 in acetone to give **2b** in high yield [25]. Ester derivative **2b** was then easily converted to the corresponding heptacarboxylic acid **2c** [25b].



2a-g

R	R_1	Ref.
a *t*-Bu	Me	24
b *t*-Bu	CH_2COOEt	25
c *t*-Bu	CH_2COOH	25b
d Me	$COCH_3$	18a,26
e Alkyl (C_{1-12})	OCH_2CH_2OH	14
f Alkyl (C_{1-12})	$OCH_2CH_2OCOCH{=}CH_2$	14
g OBn	OCH_2CONRR'	21b

p-Methylcalix[7]arene **1f** has been transformed into the corresponding heptacetate **2d** [18a, 26], while calixarenes **1b** were converted into the heptakis(2-hydroxyethoxy) derivatives **2e** [14]. The latter in turn were fully esterified to the heptaacrylic derivatives **2f** [14].

Alkylation at the lower rim of *p*-benzyloxycalix[7]arene **1i**, to give several *N,N*-disubstituted-acetamido derivatives (**2g**), was reported in a patent by Dozol *et al.* [21b].

3.2 Exhaustive Functionalisation at the Upper Rim

Functionalisation at the upper rim of calixarenes is usually performed by modification of the *p*-substituents of directly synthesised OH-bearing macrocycles. The most common way [27] concerns the removal of *tert*-butyl groups of **1a**, by transalkylation to a suitable acceptor, to give *p*-H-calix[7]arene **3a** [28]. The freed *p*-position of the latter can then be modified with a series of further reactions.

The first of them was reported by Shinkai and coworkers [29] in 1986, and concerned the synthesis of *p*-sulfonatocalix[7]arene derivatives **3b**.

Subsequently, Gutsche and Alam in 1988 [30], reported the functionalisation of *p*-H-calix[7]arene based on the Mannich/*p*-quinone-methide route [31], which involves treatment of **3a** with formaldehyde and a secondary amine to give the Mannich base, quaternarisation, and nucleophilic substitution (via the putative *p*-quinone-methide intermediate). In this way, water soluble calix[7]arenes bearing dialkylamino (**3c**) or carboxylic (**3d-e**) groups were prepared [30].

p-Mercurocalix[7]arenes **3g** were obtained by Regen and coworkers [12] by *O*-alkylation of **3a** with *n*-BuBr or *n*-$C_{16}H_{33}Br$ to give **3f**, which in turn were mercurated by treatment with $Hg(OCOCF_3)$ in $CHCl_3$.

Recently, Lamartine and coworkers [28] reported the one-pot preparation of *p*-acetylcalix[7]arene **3h** from *p-tert*-butylcalix[7]arene **1a**, which underwent an $AlCl_3$-catalysed de-*tert*-butylation with a modified Gutsche's procedure [27] to give **3a** as intermediate. The latter was then acylated *in situ* by slow addition of CH_3COCl to give **3h** in an overall 49% yield.

p-H-calix[7]arene **3a** was also converted into phenylazocalix[7]arene **3i** (21% yield) [32] by treatment with benzenediazonium tetrafluoroborate in THF in the presence of pyridine.

Calix[7]arene heptahydroquinone derivative **3j** was obtained by BBr_3-mediated demethylation [20] of the parent *p*-methoxycalix[7]arene **1h**. In a similar way, palladium-catalysed debenzylation of **1i** opened the way to calix[7]arene heptahydroquinone derivatives **3l** variously alkylated at the upper rim [21b].

4. SELECTIVE FUNCTIONALISATION

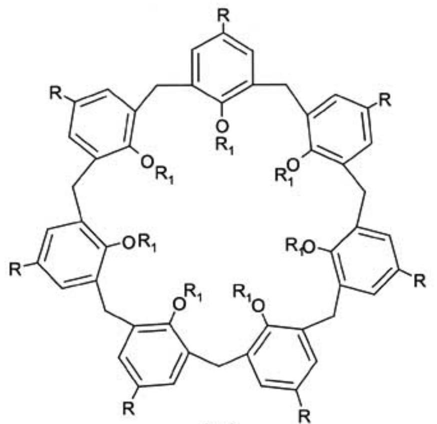
The chemical modification of calixarenes can be carried out in a selective manner at both the lower and upper rim, thus further expanding the variety of possible derivatives. In this way, suitable functional groups can be placed on specific positions along the macrocycle leading to more sophisticated changes of their chemical and supramolecular properties [3]. Selective modification of the lower rim is readily obtainable by direct etherification or esterification and usually relies on the different reactivity of phenolic OH groups influenced by intramolecular hydrogen bonds, cation templation, or sterical bulkiness [3,33].

Instead, selective modification of the upper rim is usually hardly obtainable by direct methods, such as aromatic electrophilic subtitution, because of the undifferentiated reactivity of phenol rings at the various positions [3]. Therefore, selective *p*-substitution is commonly achieved by transferring at the upper rim the selectivity already obtained at the lower rim, exploiting the different reactivity of *O*-substituted versus unsubstituted phenol rings [3,34].

As concerns calix[7]arenes there is only one example of selectively *p*-substituted derivative, which, however, was obtained by stepwise synthesis (see section 2.3), whereas the first examples of partially *O*-substituted compounds have been recently reported by our group [24].

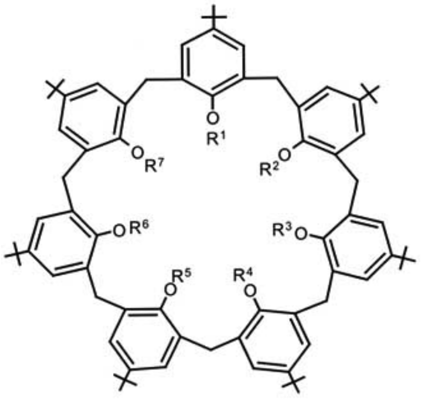
4.1 Selective Functionalisation at the Lower Rim

Partial substitution at the lower rim of *p-tert*-butylcalix[7]arene **1a** has been obtained by weak-base-promoted *O*-alkylation or *O*-acylation in analogy to what was found for other calixarenes [24]. In particular, methylation of **1a** in the presence of CsF, $KHCO_3$, or K_2CO_3 allowed the synthesis of mono- (**4a**), 1,3- (**4b**) and 1,4-dimethoxycalix[7]arene (**4c**), in yields up to 42, 14, and 32%, respectively. Interestingly, the reaction conducted in



3a-l

	R	R_1	Ref.
a	H	H	11,28,30,33
b	SO_3R (R=H,NH_4,Alkylammonium,metal)	H,C_1-$_{18}$,*n*-alkyl	29
c	$CH_2N(CH_2CH=CH_2)_2$	H	30
d	CH_2CH_2COOH	H	30
e	$CH_2CH(COOEt)_2$	H	30
f	H	*n*-C_4H_9, *n*-$C_{16}H_{33}$	11
g	$HgOCOCF_3$	*n*-C_4H_9, *n*-$C_{16}H_{33}$	11
h	COMe	H	28
i	N=N-Ph	H	33
j	OH	H	20
l	OH,alkoxy,aryloxy arylalkoxy,cycloalkoxy, $O(CH_2)_m[O(CH_2)_p]_qOR''$	OCH_2CONRR'	21b



4a $R^1 = Me$, $R^{2-7} = H$
4b $R^{1,3} = Me$, $R^{2,4-7} = H$
4c $R^{1,4} = Me$, $R^{2,3,5-7} = H$

5a $R^{1,2,4,6} = Me$, $R^{3,5,7} = H$
5b $R^{1,2,4,6} = p\text{-}CH_2C_6H_4Bu^t$, $R^{3,5,7} = H$
5c $R^{1,2,4,6} = CH_2C_6H_5$, $R^{3,5,7} = H$
5d $R^{1,2,4,6} = n\text{-}Pr$, $R^{3,5,7} = H$
5e $R^{1,2,4,6} = COC_6H_5$, $R^{3,5,7} = H$

the presence of 4 equiv of K_2CO_3 afforded 1,2,4,6-tetramethoxycalix[7]arene **5a** in 88% yield.

The extension of these conditions to other alkylating or acylating agents, such as *p-tert*-butylbenzyl bromide, benzyl bromide, *n*-propyl iodide, and benzoyl chloride, revealed that 1,2,4,6-tetra-*O*-substituted calix[7]arenes **5b-e** can be obtained in 50-72% yield, indicating the generality of the procedure [24]. This finding is particularly surprising if it is considered that 16 partially substituted calix[7]arene derivatives are possible (Fig. **2**).

Identification of the substitution pattern of partially derivatised calix[7]arenes is not always straightforward from their 1D NMR spectra. In fact, among the 16 possible derivatives only two are asymmetrical, namely those with $3_{1,2,4}$ and $4_{1,2,3,5}$ pattern, which can then be unequivocally identified. All the remaining derivatives possess a symmetry plane bisecting an aromatic ring and the opposite $ArCH_2Ar$ group (Ar—CH_2 symmetry). Therefore, they would give rise to very similar symmetrical NMR spectra showing always four $ArCH_2Ar$ and four *t*-Bu signals in a 2:2:2:1 ratio (under the assumption of conformational mobility), thus impeding the assignment of substitution pattern based only on symmetry considerations.

Additional information to discriminate among the possible regioisomers for a given derivative can be derived from the ^1H NMR chemical shifts of phenolic hydroxyls. In fact, it is now well established that in the calixarene family the strength of intramolecular hydrogen-bond increases with the number of consecutive OH groups reaching a maximum in the "circular H-bond" of the parent unsubstituted calixarene [35]. Concomitantly, an increase in the chemical shift of OH groups is observed to reach values higher than 10 ppm for some "circular" systems. On this basis, phenolic hydroxyls can be easily classified as "isolated", "singly-H-bonded", or "doubly-H-bonded", according to the number of flanking H-bonds with proximal OH groups [36].

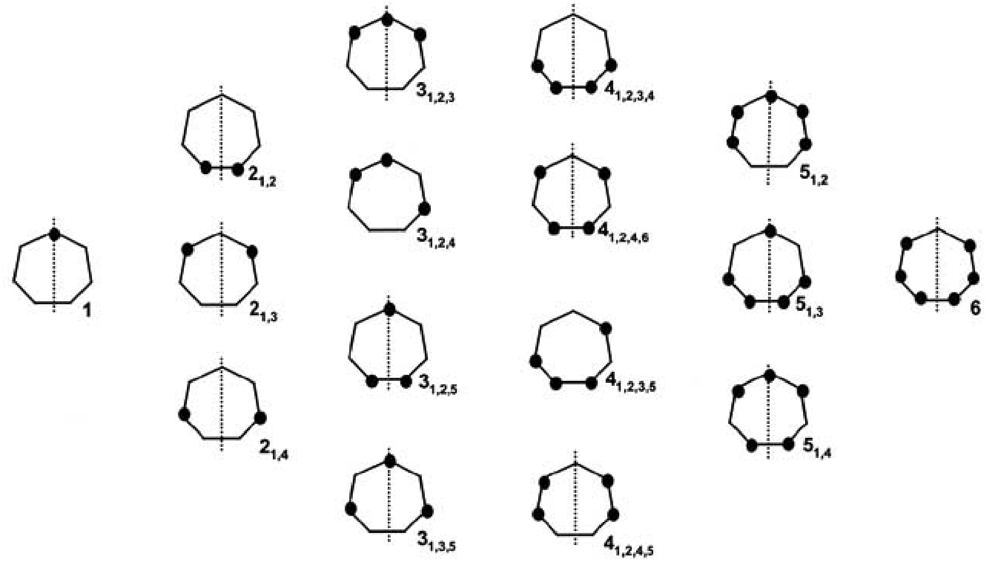


Fig. (2). Schematic representation of all possible partially substituted calix[7]arenes.

An example of this approach is given by structure assignment to 1,3- (**4b**) and 1,4-dimethoxycalix[7]arene (**4c**), which showed "clear-cut" patterns of OH signals [**4b**, δ 7.90 (isolated, 1 H), 8.75 (singly-H-bonded, 2H), 9.59 (doubly-H-bonded, 2 H); **4c**, δ 8.90, 9.44 (singly-H-bonded, 2 H, 2 H), 9.87 (doubly-H-bonded, 1 H)]. In accordance, 1,2,4,6-tetrasubstituted calix[7]arenes **5a-e** showed only isolated OH signals in the 6.61-7.55 ppm range [24].

The surprisingly high regioselectivity of 1,2,4,6-tetrasubstitution of calix[7]arene **1a** can be easily explained, on the basis of current knowledge on weak-base-promoted *O*-alkylation of other calixarenes, in terms of preferential formation of doubly-H-bonded monoanions [24]. In fact, as previously proposed for the *syn*-distal alkylation of calix[4]arenes [37] and for the "alternate alkylation" of calix[8]arenes [38], in the presence of a weak base only monoanions are very likely formed. Therefore, the alkylation proceeds through a sequence of monodeprotonation and monoalkylation steps (Fig. **3**).

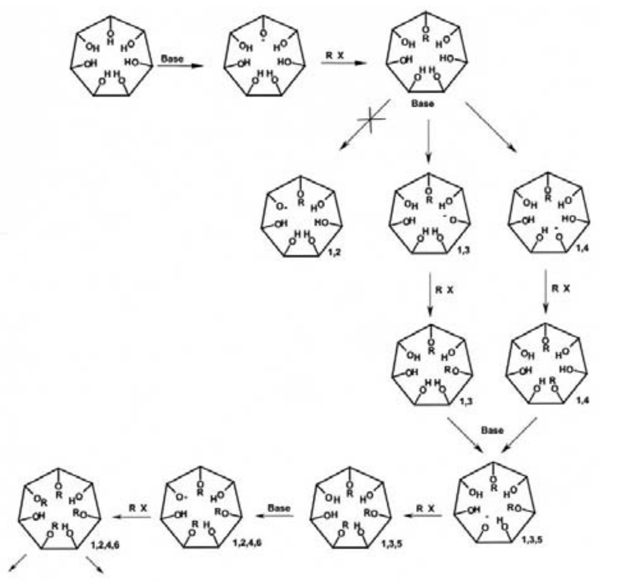


Fig. (3). Plausible pathways for the weak-base promoted alkylation of *p-tert*-butylcalix[7]arene (**1a**) leading to 1,2,4,6-tetra-*O*-substituted derivatives.

Monodeprotonations occur preferentially at those positions that give rise to monoanions more stabilised by double-H-bonds (the order of stability of anions **A-C** in Fig. **4** should be **A** > **B** > **C**). On this basis, after the first monodeprotonation/monoalkylation cycle the two monoanions at positions 3 and 4 should be preferentially formed leading to 1,3- and 1,4-disubstituted derivatives (Fig. **3**). These compounds would convergently give rise to 1,3,5-trisubstituted derivative, which in turn, through the intermediacy of a singly-bonded monoanion of type **B**, would evolve to 1,2,4,6-tetrasubstitution.

The observed high regioselectivity is the highest among those observed for calix[5]-, -[6]- and -[8]arenes [38,39], and it is directly comparable to the well-known *syn*-distal *O*-alkylation of calix[4]arenes [37,40]. This finding can be explained by the convergency of the illustrated reaction pathway.

5. CONFORMATIONAL PROPERTIES

Among the most peculiar features of calixarenes are their stereochemical properties related to the possible relative orientation of aromatic rings. For example, four well-known extreme conformations (*cone*, *partial-cone*, *1,2-alternate*, and *1,3-alternate*) are possible for unalkylated calix[4]arenes [3]. This number increases to eight for a corresponding calix[7]arene if a simple "up" or "down" orientation is assumed, but is even higher if the "out", "inward", and "outward" inclinations of the rings are also considered. In fact, a systematic conformational search for *p*-H-calix[7]arene **3a** revealed 651 energy-minimised structures (local minima) in the 40 kcal/mol energy window from the global minimum [9]. This conformational variability can be considered an aspect usefully exploitable for the production of hosts of various shapes, which, in any case, has to be taken into account in the design process.

5.1 Solid State Conformations

The structure adopted in the solid state by the parent calixarene and their derivatives are representative of the conformational propensity of the macrocycle; therefore, in this section they are examined with specific reference to the geometry of the calix[7]arene skeleton and neglecting other aspects.

Presently eight solid state structures involving a calix[7]arene macrocycle have been determined by X-ray crystallography. In the first, reported in 1991 by Andreetti *et*

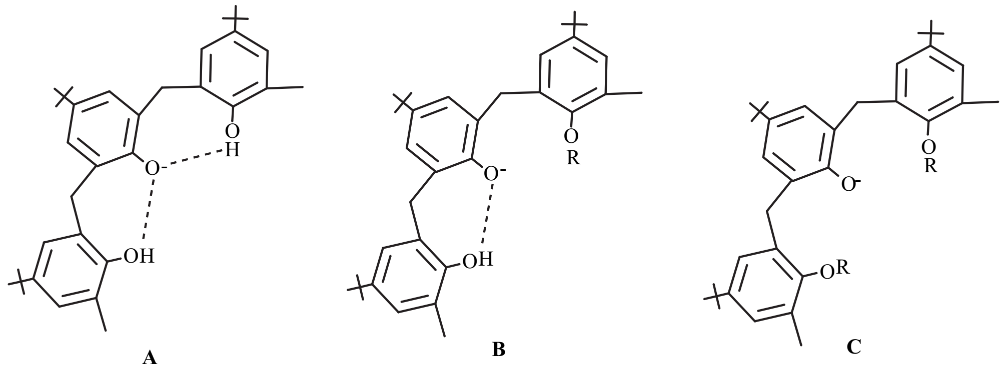


Fig. (4). Hydrogen-bond stabilisation for calixarene monoanions.

al. [41], the conformation assumed by *p-tert*-butylcalix[7]arene **1a** (Fig. **5**), is dictated by the strong intramolecular H-bond formed by phenolic OH groups, all present on the same side of the molecule. It can be described as a combination of a tetrameric (cone-like) and trimeric (3/4-cone-like) substructures. Two intramolecular cavities are consequently formed whose axes are mutually perpendicular. Harada and Shinkai observed that this structure is consistent with the lowest MM3-energy conformation found by means of a systematic conformational search, and defined as *double-cone pinched conformation* [9].

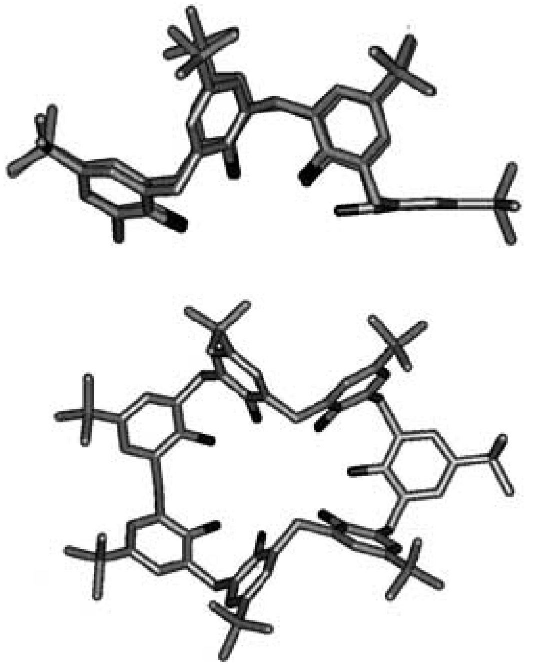


Fig. (5). Side (top) and top (bottom) views of the X-ray crystal structure of *p-tert*-butylcalix[7]arene **1a** (H atoms and the three pyridine solvent molecules are omitted) [41].

Perrin *et al* found a slightly different conformation [42] for *p*-ethylcalix[7]arene **1g** (Fig. **6**), characterised by a more flattened 3/4-cone-like trimeric subunit and by a tetrameric subunit with the two proximal, central phenolic rings inverted with respect to the others. In this way, the tetrameric portion more closely resembles a half calix[8]arene pleated-loop structure [43]. A conformation very similar to this was found for *p*-benzylcalix[7]arene **1j** [23]. In both structures a strong intramolecular H-bond is evidenced by O···O distances in the 2.60-2.74 Å range. Interestingly, the above mentioned conformational search [9] indicated that this *pleated-loop/cone* conformation corresponds to the 19th in increasing order of energy, being less stable by 5.4 kcal/mol with respect to the lowest-energy *double-cone pinched* conformation. It is presumed that this less stable conformation is assumed by **1g** and **1j** because of crystal packing effects.

A difficult classifiable conformation (Fig. **7**) was found in the X-ray structure of heptacarboxylic acid **2c** [25b], in which all calixarene oxygens are on the same side of the molecule with the two distal rings of tetrameric portion "outward" inclined, while the distal aryls of the trimeric subunit are "inward" oriented.

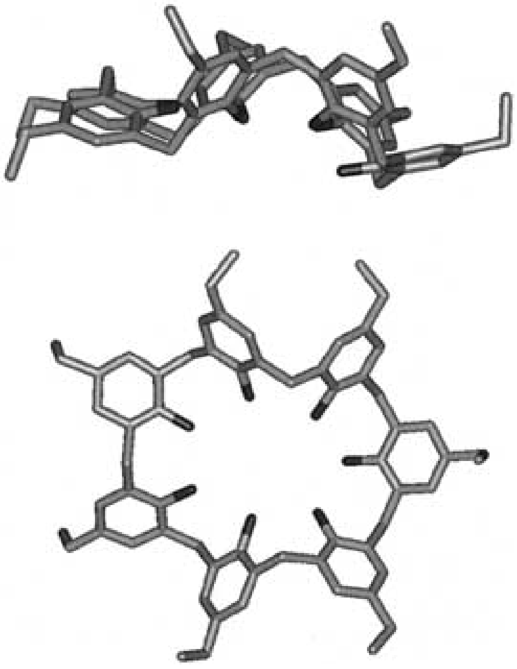


Fig. (6). Side (top) and top (bottom) views of the X-ray crystal structure of *p*-ethylcalix[7]arene **1g** (H atoms omitted) [42].

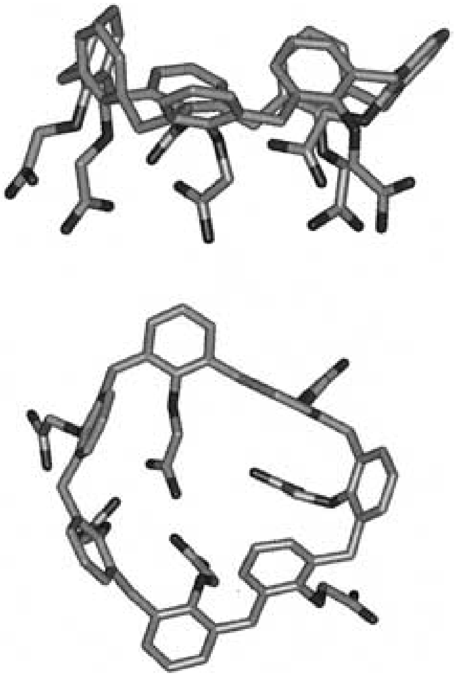


Fig. (7). Side (top) and top (bottom) views of the X-ray crystal structure of *p-tert*-butylcalix[7]arene-heptacarboxylic acid derivative **2c** (H atoms, *tert*-butyl groups, and the five $CHCl_3$ solvent molecules are omitted) [25b].

In a *p-tert*-butylcalix[7]arene/UO_2 complex [44] the conformation adopted by calix[7]arene skeleton was very similar to the *double-cone pinched conformation* of the parent **1a** (Fig. **5**) with two cone-like tetrameric and trimeric subunits. The uranyl cation is bonded at the four oxygens of tetrameric portion, while the trimeric unit is not involved in cation coordination.

A more intricate structure was found for a bis(*p*-benzylcalix[7]arene)/hexauranyl complex [22] (Fig. **8**) in which the calix[7]arene portion was considered as "cluster-keeper" of the hexametallic core. In this instance the calix[7]arene skeleton adopts a conformation in which the trimeric unit is close to the usual 3/4-cone geometry, while in the tetrameric portion the two distal rings are inverted, with respect to the proximal rings, in order to interact with additional metal centers. All seven phenolic oxygens are involved in cation coordination.

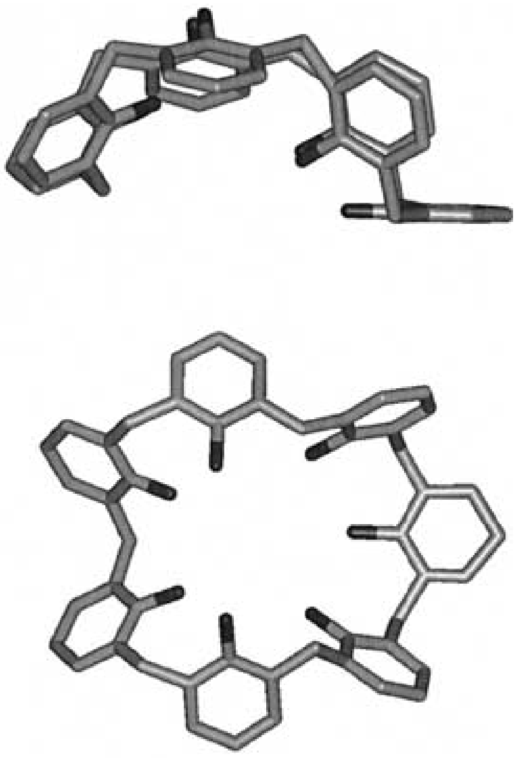


Fig. (8). Side (top) and top (bottom) views of the X-ray crystal structure of the complex formed by *p*-benzylcalix[7]arene **1j** (H_7L) with uranyl cation in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) of formula $(UO_2^{2+})_6(L^{7-})_2(O^{2-})_2(HDABCO^+)_6 \cdot 3CH_3CN \cdot CHCl_3 \cdot 5CH_3OH \cdot 3H_2O$ (H atoms, *p*-benzyl groups, uranyl and $HDABCO^+$ cations, and solvent molecules are omitted) [22].

Very recently the X-ray crystal structure of a complex formed by *p-tert*-butylcalix[7]arene **1a** (H_7L) with an europium(III) tetracationic cluster of formula $(HO^-)_2(CO_3^{2-})Eu_4(H_3L^{4-})_2 \cdot 6DMSO \cdot 5H_2O \cdot 4CH_3CN$ has been reported [45]. The geometry adopted by the calix[7]arene skeleton also in this case is very similar to the *double-cone pinched conformation* of the parent **1a** (Fig. **5**). The four oxygens of the tetrameric portion and one of the trimeric unit are involved in the coordination of the europium cluster.

5.2 Solution Behavior

The most common parent calix[7]arene **1a** is conformationally mobile in solution, as it is the case for the other parent calixarenes bearing OH groups at the lower rim. In fact, conformational interconversion in calixarenes occurs by the "*oxygen-*" or "*p-substituent-through-the-annulus*" routes (Fig. **9**) and the small dimension of OH group allows its passage through the annulus for all calixarenes including the smaller calix[4]arene [3]. Obviously, the "*p-substituent-through-the-annulus*" route is possible with small-enough groups. As concerns the passage of the common *p-tert*-butyl substituent (e.g. **1a**) it has been demonstrated that it is operative starting from hexameric to larger members [46].

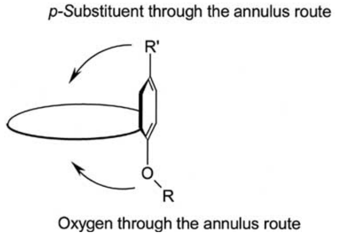


Fig. (9). Possible routes for conformational interconversion in calixarenes.

The mobility of OH-bearing calixarenes is impeded by the presence of a "circular H-bond" and consequently, broad ^1H NMR spectra are observed at room temperature for them [6]. Variable temperature NMR studies (300 MHz, $CDCl_3$) for *p-tert*-butylcalix[4-9]arenes reveal coalescence temperatures [6] in the 11-66 °C range, whose values are directly dependent on the strenth of the "circular H-bond". Among them, *p-tert*-butylcalix[7]arene **1a** shows the penultimate lowest value of 14 °C before that of *p-tert*-butylcalix[6]arene (11 °C), indicating a lower H-bond stability. From the coalescence temperature a free energy of activation for conformational inversion in the 13.1-15.7 kcal/mol range was calculated for *p-tert*-butylcalix[4-9]arenes, being the penultimate lowest value of 13.3 Kcal/mol that of **1a** [6]. Interestingly, at low temperatures (–55 °C) calix[7]arene **1a** gives rise to an asymmetrical spectrum, showing seven equal intensity OH signals, due to a frozen asymmetrical conformation. A similar consideration can also be made for *p*-benzylcalix[7]arene **1j**, which also shows seven OH signals at –80 °C. MM3-calculations indicated that this frozen structure very likely corresponds to a C_1 *double-cone pinched conformation* in which the directionality of intramolecular H-bonds is fixed [9].

The introduction of substituents at the lower rim breaks the continuity of the circular H-bond leading to an increase in conformational mobility [24]. Thus, in the methylation of **1a** a progressive increase of mobility is observed on going from mono- to 1,2,4,6-tetramethoxy derivative **5a**, which shows sharp ^1H NMR spectra at room temperature. In accordance, the "isolated" non-H-bonded hydroxyls appear at 6.61 ppm.

The complete blockage of the "*through-the-annulus*" passages to give discrete calix[7]arene conformational isomers (atropisomers) requires the presence of bulky-enough groups at both rims of the cavity (the usual *p-tert*-butyl substituent, as in **1a**, does not suffice to this end). At the present time the minimal bulkiness requirements for the calix[7]arene macrocycle have not yet been determined, but uncommon bulkier groups can be easily predicted, making this approach less convenient.

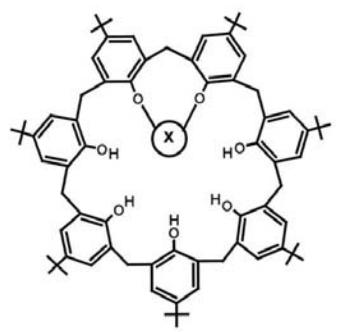
6. INTRAMOLECULAR BRIDGING

The successful applications of calixarenes in several areas of supramolecular chemistry are frequently linked to the three-dimensional pre-organisation of their structure, which improves their recognition abilities [3,47]. Consequently, in the case of calix[7]arenes, as well as for other large homologues, the conformational mobility and variability are considered detrimental for a recognition of the "lock-and-key" type [48], whereas can be considered useful for an "induced-fit" binding [49].

In the first instance a proper shaping of the macrocycle is required, which can be obtained with the insertion of scaffolding elements by intramolecular bridging [50]. Among all the possible bridging and capping modes in principle possible for a calix[7]arene, only the single- and double-bridging at the lower rim have been so far studied.

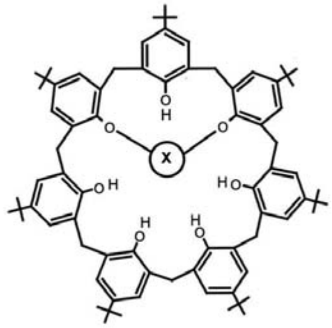
6.1 Single Bridging

The first singly bridged calix[7]arenes have been obtained by direct *O*-alkylation of *p-tert*-butylcalix[7]arene **1a** with bis-electrophiles including $BrCH_2Cl$, oligoethylene glycol ditosylates, and 1,4-bis(bromomethyl)benzene, in the



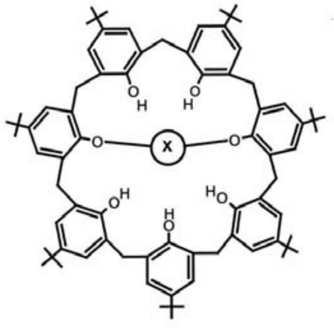
6

a X = CH_2
b X = CH_2CH_2
c X = $CH_2CH_2OCH_2CH_2$
d X = $CH_2(CH_2OCH_2)_3CH_2$



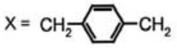
7

a X = $CH_2CH_2OCH_2CH_2$



8

a X = $CH_2CH_2OCH_2CH_2$
b X = $CH_2(CH_2OCH_2)_2CH_2$
c X = $CH_2(CH_2OCH_2)_3CH_2$
d X = $CH_2(CH_2OCH_2)_4CH_2$



e X = $CH_2-C_6H_4-CH_2$

f X = $CH_2CH_2CH_2CH_2$

presence of a base (K_2CO_3 or Cs_2CO_3) [51]. Obviously, this reaction can give rise to three regioisomers intramolecularly bridged at the 1,2-, 1,3-, or 1,4-aromatic rings. It was found that 1,2-bridging was favoured with "short bite" spanning elements, such as dioxamethylene, crown-2, and crown-3, to give derivatives **6a**, **6b**, and **6c** in 15%, 20%, and 25% yield, respectively. Longer bridges failed or only gave very limited amounts of proximal bridging. The 1,3-bridging was more difficult to obtain with all the electrophiles and bases tested, and only 1,3-calix[7]crown-3 **7a** could be obtained in 4% yield. The 1,4-pattern was more easily obtained with several electrophiles in particular when Cs_2CO_3 was used as the base. In this way, 1,4-bridged calix[7]arenes **8a-f** were obtained in 14-72% yields.

The structure assignment for intrabridged calix[7]arenes **6-8** presents difficulties similar to those discussed above for partially *O*-substituted calix[7]arenes **4-5**, owing to their common Ar—CH_2 symmetry. Therefore, also in this case the classification of OH groups as "isolated", "singly-H-bonded", and "doubly-H-bonded", based on their chemical shift, was largely used to the same end. In addition, in some instances an independent demonstration of the bridging pattern was obtained by means of 2D NMR (HSQC and HMBC experiments).

The conformational behaviour of singly bridged calix[7]arenes **6-8** closely resembles that of the analogue calix[8]arene derivatives [52]. In fact, they have a higher mobility with respect to the parent **1a**, because the bridging element partially breaks the stabilising "circular H-bond". In contrast, the bridged calix[6]arene analogues are conformationally blocked on the NMR time scale due to the smaller dimension of their annulus [53]. However, VT NMR studies reveal that bridged calix[7]arenes are slightly less mobile than calix[8]arene analogues bearing an identical bridge [51].

6.2 Double Bridging

In principle, twelve regioisomers are possible for a calix[7]arene double-bridged with two identical elements (Fig. **10**). With the exception of three asymmetrical isomers, namely the 1,2:3,5, 1,2:3,6, and 1,3:2,5, all of them possess an Ar—CH_2 symmetry making them hardly distinguishable by simple symmetry considerations.

The first doubly bridged calix[7]arenes have been obtained by direct *O*-alkylation of *p-tert*-butylcalix[7]arene **1a** with 1,4-diodobutane, mono- or diethylene glycol ditosylates, in the presence of Cs_2CO_3, to give 1,4:2,3-bis-bridged derivatives **9a-c** in 53-76% yield [54]. Interesting was also the alkylation of the preformed 1,4-tetramethylene-bridged calix[7]arene **8f** with $BrCH_2Cl$, oligoethylene glycol ditosylates, or 1,2-bis(bromomethyl)benzene, which afforded 1,4:2,3-bis-bridged derivatives **9d-h** with mixed spanning elements in 30-75% yield.

Also in this case structure assignment was complicated by the common Ar—CH_2 symmetry, and required the use of the chemical shift of OH groups to discriminate among all the possible bridging patterns [54]. Thus, the presence of two OH signals at 8.55 and 9.40 ppm (2:1) in the ^1H NMR spectrum of 1,4:2,3-calix[7]bis-crown-3 **9b**, attributable to singly-H-bonded and doubly-H-bonded hydroxyls, respectively, limited the number of compatible bridging pattern to three, namely 1,2:3,4, 1,4:2,3 and 1,3:2,4. Among these, the 1,4:2,3-bridging pattern was assigned on

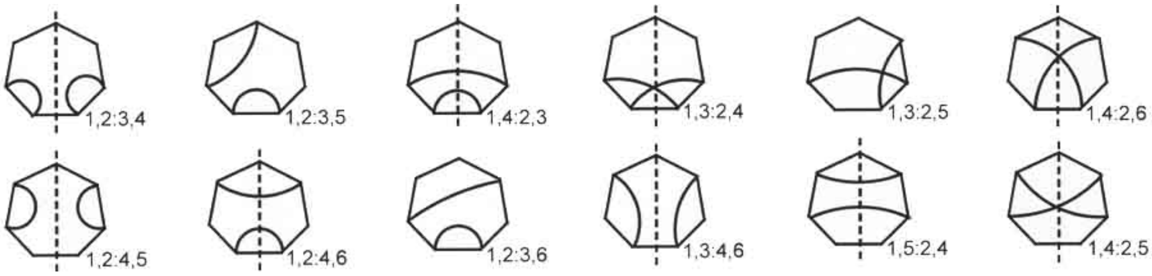
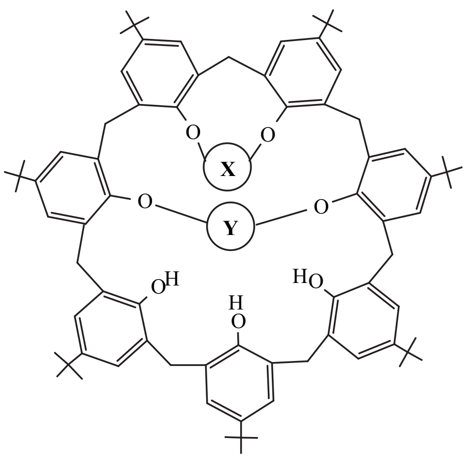
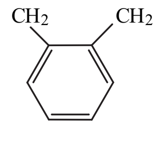


Fig. (10). Schematic representation of the possible 12 doubly intrabridged derivatives of a calix[7]arene.



9

	X	Y
a	CH_2CH_2	CH_2CH_2
b	$CH_2CH_2OCH_2CH_2$	$CH_2CH_2OCH_2CH_2$
c	$CH_2CH_2CH_2CH_2$	$CH_2CH_2CH_2CH_2$
d	CH_2	$CH_2CH_2CH_2CH_2$
e	CH_2CH_2	$CH_2CH_2CH_2CH_2$
f	$CH_2CH_2OCH_2CH_2$	$CH_2CH_2CH_2CH_2$
g	$CH_2(CH_2OCH_2)_2CH_2$	$CH_2CH_2CH_2CH_2$
h		$CH_2CH_2CH_2CH_2$

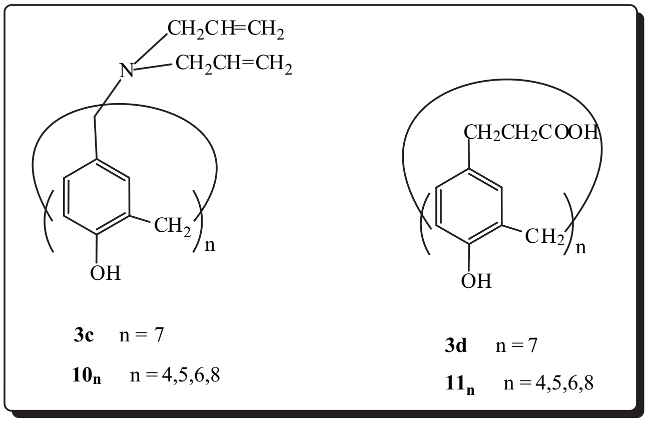
the basis of chemical correlations with known compounds. In fact, alkylation of previously isolated 1,2-calix[7]crown-3 **6c** and 1,4-calix[7]crown-3 **8a**, with diethylene glycol ditosylate afforded **9b** in 60 and 70% yields, and thus demonstrating that both the 1,2- and 1,4-crown-3 bridges were present in its structure. The same 1,4:2,3-bridiging pattern was assigned to the other derivatives **9a-h** by using similar arguments [54].

As concerns the conformational features of bis-bridged calix[7]arenes **9a-h**, VT NMR studies demonstrated that, with the exception of **9d**, conformational interconversion is inhibited by the presence of the two bridges. The *syn* relative orientation of the bridges was indicated by the presence of typical AX systems for pertinent ArCH$_2$Ar groups and was confirmed by means of COSY and NOESY 2D NMR experiments [54].

7. SUPRAMOLECULAR AND MISCELLANEOUS PROPERTIES

As mentioned in the introduction, calixarene derivatives have found a large number of applications in supramolecular chemistry and in other more technological areas. The majority of work has been done on the more common even-membered "major" calixarenes and in particular on calix[4]arenes. In this respect, obviously, calix[7]arenes are significantly less investigated, but other interesting potentialities can be expected providing that a fine control of their chemistry is reached.

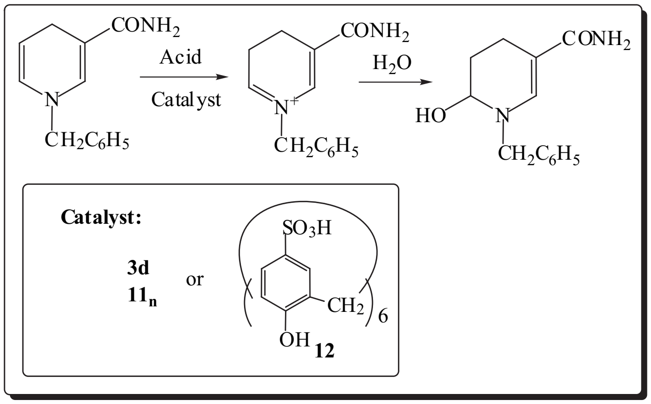
The complexing abilities of water soluble *p*-(diallylaminomethyl)calix[7]arene **3c** and *p*-(2-carboxyethyl)calix[7]arene **3d** [30], in comparison with that of the corresponding calix[*n*]arene homologues $\mathbf{10_n}$ and $\mathbf{11_n}$ (*n* = 4, 5, 6, 8), toward aromatic hydrocarbons ranging in size from durene to decacyclene, have been investigated using a solid-liquid extraction procedure. The larger calix[7]- and –[8]arene derivatives are able to interact with large hydrocarbons such as pyrene and perylene, but unable to interact with the larger coronene or decacyclene. The experimental results were explained in terms of size matching using space-filling CPK models. The association constants of **3c** and **3d**, in acidic or basic aqueous solutions, respectively, ranged from 10^3 to 10^4 M^{-1}.



3c n = 7
$\mathbf{10_n}$ n = 4,5,6,8

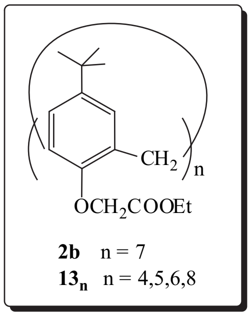
3d n = 7
$\mathbf{11_n}$ n = 4,5,6,8

The catalytic ability of *p*-(2-carboxyethyl)calix[*n*]arenes **3d** and $\mathbf{11_n}$ (*n* = 5,6,8), in comparison with that of *p*-sulfonatocalix[6]arene **12**, for the following reaction [55] were studied following the change in absorptivity at 350 nm [30].



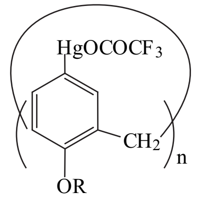
The experimental data demonstrated that the best catalytic activity in the series of *p*-(2-carboxyethyl)calix[*n*]arenes $\mathbf{11_n}$ was obtained with the hexameric compound, which in turn was considerably less efficient than *p*-sulfonatocalix[6]arene **12** previuosly studied by Shinkai and coworkers [56]. The lower catalytic efficiency of calix[7]arene derivative **3d** was attributed to the reduced pre-organisation resulting from the high conformational mobility [30].

The alkali-metal ion transport across a phospholipid bilayer membrane of a series of calix[*n*]arenes (*n* = 4-8) bearing CH$_2$COOEt groups at the lower rim (**2b** and $\mathbf{13_n}$) [25a] has been investigated using the voltage clamp method. In accordance with the known complexing abilities of these systems [57], the tetramer $\mathbf{13_4}$ was found to be a selective Na$^+$ carrier, while the pentamer $\mathbf{13_5}$ preferred K$^+$ over Na$^+$, both the hexamer $\mathbf{13_6}$ and heptamer **2b** show a Cs$^+$ selectivity, whereas the octamer $\mathbf{13_8}$ did not showed ion transport ability. The Cs$^+$/Rb$^+$ transport selectivity was higher for the hexamer $\mathbf{13_6}$ with respect to the heptamer **2b**, which showed the following selectivity order Cs$^+$>Rb$^+$≈K$^+$>Na$^+$>Li$^+$.



2b n = 7
$\mathbf{13_n}$ n = 4,5,6,8

Mercurocalix[*n*]arenes (*n* = 4-7) **3g** and $\mathbf{14_n}$ [12] were used in a work aimed at the preparation of *perforated monolayers* constituted by thin-film composite membranes bearing a two-dimensional oriented network of *molecular pores*. This could be used for unique molecular separations governed by the effective diameter and polarity of each monomolecular porous unit. The monolayer properties of calix[7]arene derivatives **3g** [12] were exactly analogous to those seen for the calix[6]arene series $\mathbf{14_6}$. In particular, hexadecyl derivative yielded a limiting area of 195 ± 5 Å^2 that was in excellent agreement with that predicted for a parallel orientation of the calixarene base (201 Å^2). However, a greater compressibility was observed for calix[7]arene monolayer with respect to calix[4-6]arene analogues, probably due to the higher conformational mobility of the calix[7]arene framework.



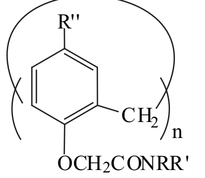
R = n-C_4H_9, n-$C_{16}H_{33}$

3g n = 7
14$_n$ n = 4,5,6

Calix[6 and 7]arenes are promising high-resolution negative electron-beam resist [58] (resolution of the order of 10 nm) due to their low molecular weight. The sensitivity of calix[7]arene was higher than that of calix[6]arene because of its higher molecular weight. Thin layers constituted of calix[7]arenes were also used for image pattern formation by means of etching-off with a high energy beam [59].

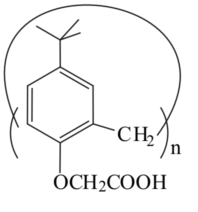
Solutions of hydroquinone-based calix[7]arene derivatives **3l** and **15$_n$** in *o*-nitrophenylhexyl ether were used to extract cobalt, strontium, cesium, europium and sodium isotopes from aqueous nitric acid solutions simulating nuclear waste [21b].

R'' = OH, alkoxy, aryloxy, arylalkoxy, cycloalkoxy, $O(CH_2)_m[O(CH_2)_p]_qOR'''$



3l n = 7
15$_n$ n = 6,7,8

Calix[7]arene-based ligands **2c** and **16$_n$** were used to extract trivalent lanthanides and actinides from water to chloroform and xylene [25b]. In the series of calix[*n*]arenes (*n* = 4-7) the order of extractability, was $Am^{3+} > Nd^{3+} > Eu^{3+} > Tb^{3+} > Dy^{3+} > Er^{3+} > Yb^{3+}$, which was not influenced by the molecular dimension. The extraction of Am^{3+} improved with *n*, in particular when $CHCl_3$ was used as solvent.



2c n = 7**16$_n$** n = 4,5,6

Calix[7]arenes **2f** bearing *p*-alkyl chains (C_{1-12}) and derivatised with (meth)acryloyl groups [14], *via* polyoxyethylene or polyoxypropylene polymer, gave films with excellent heat resistance, hardness, and adhesion.

8. CONCLUSIONS

The chemistry of the calix[7]arenes has been less well studied than that of the even-membered calix[4,6, and 8]arenes as well as the odd-membered calix[5]arenes. Very likely this is due to the lack of well-established, large-scale preparation procedures for the parent macrocycle, in addition to the prospect of a complex chemistry and high conformational mobility.

On the other hand, the dimension of their annulus, of intermediate size between the corresponding hexamers and octamers, makes them at least of comparable interest for the synthesis of molecular receptors for medium-sized guests. This potentiality is likely improved by the fact that calix[7]arenes probably represent the upper limit in the calix[*n*]arene series for the existence of preformed intramolecular cavities available for the complexation of suitable guests.

Similar to the case of calix[5]arenes, the recent reports of improved synthetic procedures for the parent *p-tert*-butylcalix[7]arene has encouraged a more methodological investigation of the chemistry of this macrocycle. Notwithstanding that research efforts along these lines are very recent, clear and useful information concerning the chemical and conformational propensity of this macrocycle are already emerging. From one point of view, these data already provide useful information for a more complete understanding of the chemical behaviour of the calixarene family, but they can also be considered of particular relevance for the creation of new species with great potential in supramolecular chemistry.

ACKNOWLEDGEMENTS

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