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Synthesis and Properties of Pyridinocalixarenes*

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Abstract. Several facets of pyridinocalixarene chemistry have been investigated including reaction pathways for their formation from the base-catalyzed alkylation of the parent calixarenes with PicCl·HCl, effect of the nature and identity of the base on regio- and stereoselective *O*-alkylations, creation of molecular asymmetry in calix[4]arenes and enantiomeric resolution, conformation and conformational mobility, and complexation.

Key words: Regio- and stereoselective *O*-alkylations, conformation and conformational mobility, inherently chiral calix[4]arenes and enantiomeric HPLC resolution, *N*-oxide ligands and complexes.

1. Introduction

Readily available calixarenes are currently enjoying considerable interest in host–guest or supramolecular chemistry as three-dimensional building blocks for the design of new lipophilic receptors and carriers with specific properties [1, 2]. The architecture of this class of compounds is such that they simultaneously possess a potential hydrophobic cavity, suitable for the inclusion of small organic molecules, and a hydrophilic site (hydroxyl groups) very attractive for chemical modification. The chemistry of calix[4]arenes, i.e. the smallest members of this family, has been disclosed in the last few years, and general procedures have been developed for regio– [3–13] and stereoselective [14–19] functionalizations at the lower rim. The larger calix[n]arenes (n = 5–8) have received less attention, mainly because of a higher degree of functionality and flexibility which complicate their chemistry, and only very recently useful guidelines are emerging for the selective functionalization of these substrata [20–25].

Functionalization of calixarenes by the base-catalyzed *O*-alkylation with α-halomethyl-*N*-heterocyclic reagents has been recently introduced in order to extend the coordination chemistry of calixarenes to transition metals [7, 26, 27]. This review deals with the synthesis and properties of calixarenes endowed with pyridine pendant groups at the lower rim, derivable from *p-tert*-butylcalix[n]arenes (n = 4, 6, 8) by direct *O*-alkylation with 2-(chloromethyl)pyridine hydrochloride (PicCl·HCl) in the presence of base. The influence of the molar ratios between the reactants and the nature of the base applied on the product distribution and

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conformational outcome is emphasized. Furthermore, the discovery of regioselective *syn-proximal* (1,2)-di-*O*-alkylation of calix[4]arenes [7–13] has opened new perspectives toward the synthesis of atropisomeric inherently chiral calix[4]arenes, owing to the nonplanar structure of these compounds. Most of the chiral derivatives here described can be optically resolved into their antipods by enantioselective HPLC methods. The locked conformation of pyridinocalix[4]arenes and fluxional properties of the larger calixarene homologues is discussed. Further chemical transformations of the title compounds and their potentialities are briefly outlined.

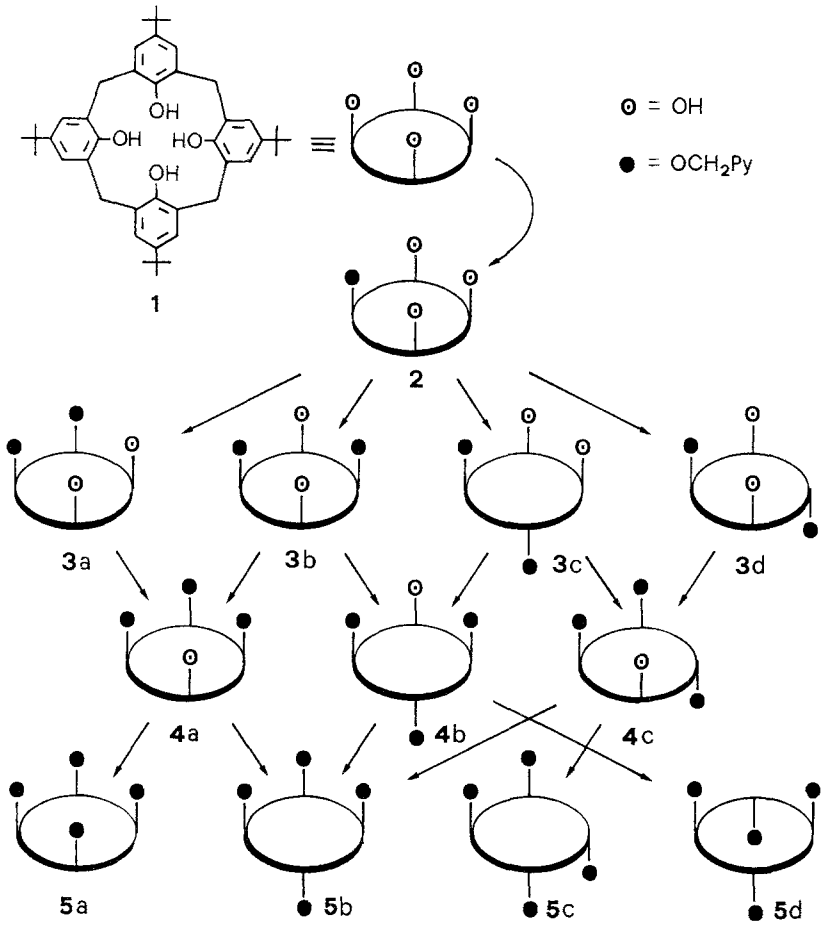
2. Pyridinocalix[4]arenes

A schematic representation of the twelve pyridino homologues derivable from *p-tert*-butylcalix[4]arene **1** and possible reaction pathways for their formation are shown in Scheme 1. Of these compounds, only *anti*-(1,2) and *anti*-(1,3)-di-*O*-alkylated regioisomers **3c** and **3d** have not been reported yet. The remainder have been obtained either by direct *O*-alkylation of the parent calix[4]arene **1** or by alkylation of an appropriate precursor. The mechanism of alkylation of calix[4]arene **1** with PicCl·HCl is based on product analysis of stepwise alkylation experiments, and MM2 calculations of the involved intermediates and their anions [18].

2.1. Exhaustive *O*-alkylation and conformer distribution

Tetrakis[(2-pyridylmethyl)oxy]calix[4]arene conformers **5a–d** are obtained by subjecting the parent calix[4]arene **1** to a large excess of PicCl·HCl in anhydrous dimethylformamide (DMF) in the presence of a base. The conformational outcome of the reaction strongly depends upon the identity and strength of the base applied. The reaction with NaH is stereoselective and produces only the cone conformer **5a** (80%) [7, 18]. By using weaker bases, such as alkali metal carbonates, mixtures of conformers are obtained, and with Cs_2CO_3 it is possible to isolate after careful chromatography the four possible cone **5a** (9%), partial cone **5b** (54%), 1,2-alternate **5c** (1–2%) and 1,3-alternate **5d** (18%) conformers [18, 28].

Stereochemical assignments follow from distinctive proton and carbon NMR spectral patterns arising from each conformation. Selected ^{1}H-NMR regions of the four extreme conformations of tetra-substituted calix[4]arenes are illustrated in Figure 1, and are in agreement with the spectral patterns reported by Gutsche for calix[4]arene conformers [29]. The ^{13}C-NMR resonances of both $ArCH_2Ar$ and OCH_2Py groups provide a further diagnostic tool for distinguishing among the various conformers. Consistently with the single rule proposed by de Mendoza *et al.* for the determination of the conformation of calix[4]arenes [30], the signals of the methylene groups connecting two adjacent phenyl moieties in a *syn* orientation (e.g., in the cone conformation) appear at 30.7 ± 0.8 ppm, and those of the OCH_2Py groups linked to them at 76.4 ± 2.2 ppm; on the other hand, they show up at



Scheme 1.

38.2 ± 1.0 ppm and 70.8 ± 1.8 ppm, respectively, when both phenyl moieties are *anti* oriented (e.g., in the 1,3-alternate conformation) [18].

Cone and partial cone structures **5a** and **5b** have been further confirmed by single-crystal X-ray analyses [18]. In both compounds a methanol of solvation is hydrogen bonded to one pyridine N atom and is *exo* to the calix cavity. In the partial cone conformer **5b** the conformation adopted is such that the pendant OCH_2Py group of the 'inverted' aryl ring lies in, and effectively fills, the calix cavity produced by the remaining three aryl rings. Self-inclusion phenomena (i.e., inclusion of flexible substituents within the calix cavity) are not uncommon in calixarene chemistry, especially in the larger analogues [31]. Studies in solution (1D and 2D NMR) and *in vacuo* (MM2 calculations) are in agreement with the conformation found in the solid state [18].

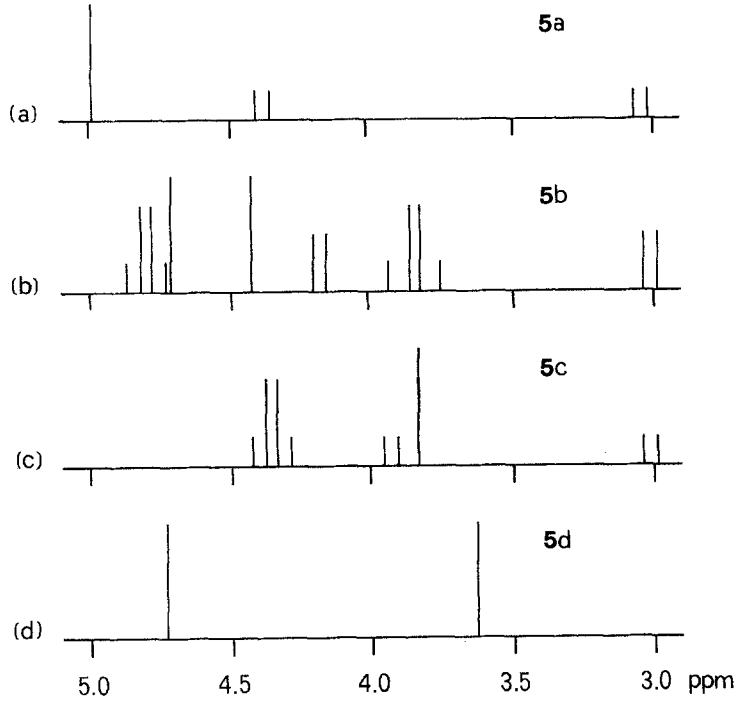


Fig. 1. Schematic representation of the observed methylene and oxymethylene ^{1}H-NMR patterns for tetrakis[2-pyridylmethyl)oxy]calix[4]arene cone (a), partial cone (b), 1,2-alternate (c), and 1,3-alternate (d) conformers **5a–d**.

2.2. PARTIAL *O*-ALKYLATION. REGIO- AND STEREOSELECTIVITIES

Increased calix[4]arene/PicCl·HCl molar ratios and diminished reaction times give mixtures of products representing various stages of alkylation; nevertheless, under appropriate reaction conditions (solvent, base, temperature, reaction time) selective functionalization can be realized. Accordingly, monoalkylated derivative **2** is generated in 59% yield by reaction of **1** with PicCl·HCl in toluene at 70°C for 20 h in the presence of NaH [32]. When alkylation of **1** is conducted with 2.2 equiv. of PicCl·HCl in dry DMF in the presence of NaH (10 equiv.), *syn-proximal* di[(2-pyridylmethyl)oxy]calix[4]arene regioisomer **3a** is obtained in up to 85–90% yield [7, 33]. Conversely, substitution of alkali metal carbonates (Na_2CO_3 or K_2CO_3) for NaH affords regioselectively the *syn-distal* (1,3)-regioisomer **3b** in 50–60% yield, even in the presence of an excess of electrophile [18, 26]. Similarly, alkylation of de-*tert*-butylated calix[4]arene with 2-bromomethyl-6-hydroxymethylpyridine (2 equiv.) and K_2CO_3 (1 equiv.) in refluxing acetonitrile gives the *syn-distal* di-*O*-alkylated derivative as an intermediate in the synthesis of a calix[4]arene cryptand [27].

The structure of **3a** has been elucidated by single-crystal X-ray analysis. Compound **3a** adopts a relatively distorted cone conformation in the solid state, creating

a hydrophobic cavity which is large enough to accommodate an ethanol molecule with the hydroxyl end of the molecule directed out of the calix cavity [34].

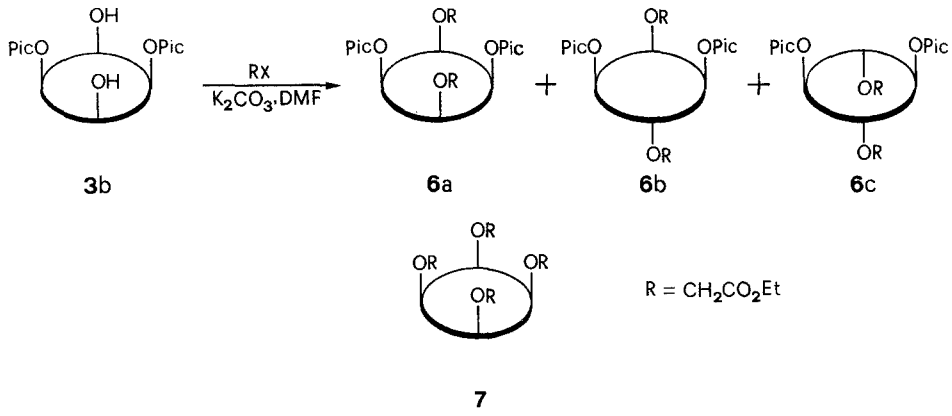
Although theoretically four different disubstituted regioisomers **3a–d** can exist (Scheme 1), direct substitution on the parent calix[4]arene **1** in the presence of the above bases regioselectively affords **3a** or **3b**, with no trace of the other two possible *anti* regioisomers. However, the isolation of tetra-*O*-alkylated 1,2-alternate conformer **5c** in the Cs_2CO_3-catalyzed exhaustive alkylation of **1** suggests that the obvious *anti*-(1,2)- or *anti*-(1,3)-di-*O*-alkylated precursors are transient species under the experimental conditions employed [35].

In order to gain an insight into the origin of conformational isomers in the base-catalyzed exhaustive alkylation of **1** with PicCl·HCl, stepwise alkylation reactions with regioisomers **3a** and **3b** have been carried out in DMF by varying the electrophile molar ratio, reaction time and base (alkali metal carbonates) [18]. Alkylation of **3a** with one equivalent of PicCl·HCl affords stereoselectively tri-*O*-alkylated cone conformer **4a** in high yield, irrespective of the nature of the base used. *Syn-distal* regioisomer **3b** was proved to be less reactive under analogous reaction conditions, and alkylation with Cs_2CO_3 gave tri-*O*-alkylated partial cone conformer **4c** (34%, based on unreacted **1**) as the main product, along with minor amounts of cone **4a** (11%). Alkylation of each of the two di-*O*-alkylated regioisomers with an excess of electrophile and base has shown that in the final substitution step the template effect of the base plays an important role in determining the conformational outcome of the reaction: the conformation of the tri-*O*-alkylated precursor(s) (cone and/or partial cone) is completely retained with Na^+ cation in the base, mainly retained with K^+, and completely inverted (cone to partial cone) and/or partial cone to 1,3-alternate) with Cs^+. Since *syn*-1,2 and *syn*-1,3-di-*O*-alkylated intermediates **3a, b** can be generated *in situ* with excellent regioselectivity during the one-pot exhaustive alkylation of the parent calix[4]arene **1** with excess PicCl·HCl, the reaction can be easily driven to the desired conformer(s) by a proper choice of the base [18].

2.3. BIS(SYN-PROXIMALLY) AND BIS(SYN-DISTALLY) FUNCTIONALIZED CALIX[4]ARENES

Di-*O*-alkylated regioisomers are a potential source of calix[4]arenes with mixed ligating groups at the lower rim. Reinhoudt has reported that functionalization of the free hydroxyl groups of *syn-proximal* di-*O*-alkylated calix[4]arenes affords a variety of cone bis(*syn-proximally*) functionalized calix[4]arenes [13]. Cation complexation studies on these derivatives have shown that subtle changes in regioselective functionalization influences the selectivity for Na^+ considerably.

Alkylation of (1,2)-di[(2-pyridylmethyl)oxy]calix[4]arenes in THF in the presence of NaH produces the *achiral* bis(*syn-proximally*) functionalized calix[4]arenes (cone conformers) in good yield [18]. On the other hand, when alkylation of **3a** is conducted in DMF in the presence of Cs_2CO_3, *chiral* partial cone structures are



Scheme 2.

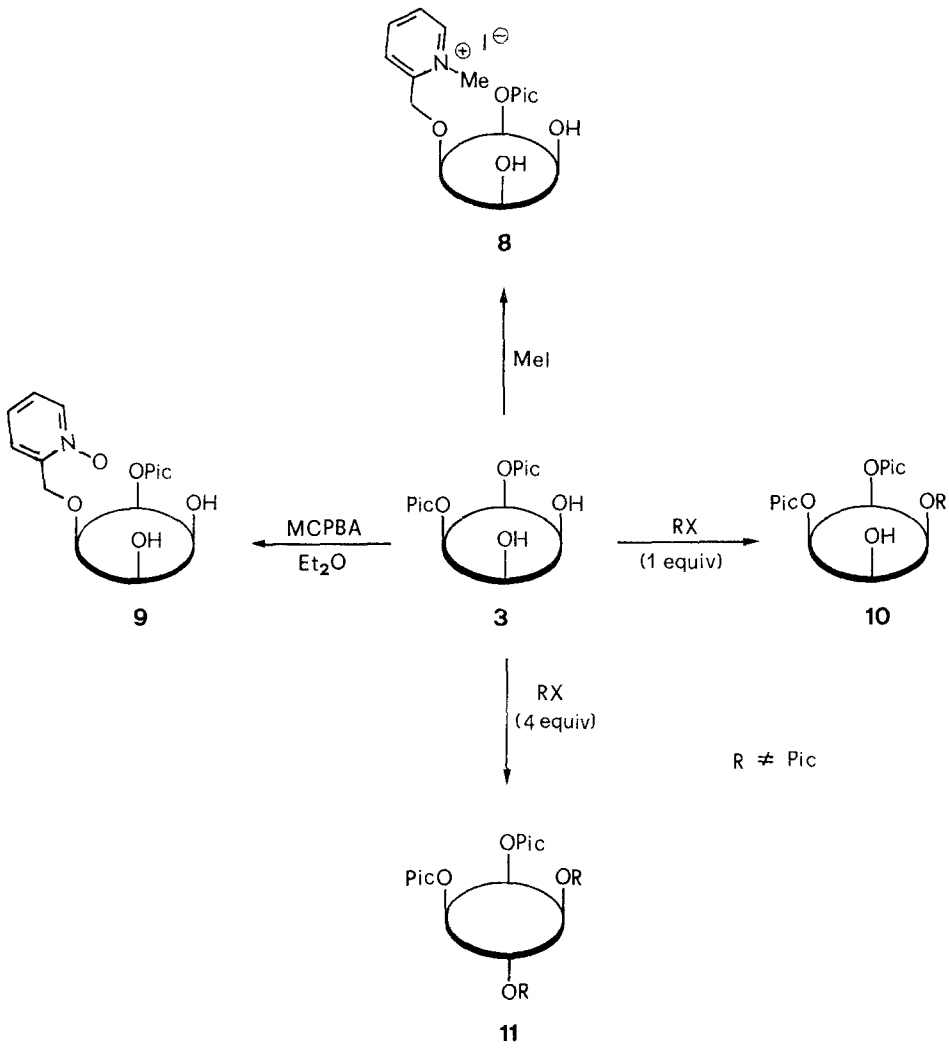
formed preferentially, owing to the absence of symmetry elements [33, 36]. This class of compounds is discussed in detail in the next section.

The alkylation of *syn-distal* regioisomer **3b** with ethyl bromoacetate and K_2CO_3 in DMF produces a mixture of bis (*syn-distally*) tetra-*O*-alkylated cone **6a** (32%), partial cone **6b** (7.7%) and 1,3-alternate **6c** (1.1%) conformers [37, 38], as shown in Scheme 2. Solvent extraction data have indicated that cone **6a** shows a strong metal affinity, comparable to that of cone tetrakis[(ethoxycarbonylmethyl)oxy]calix[4]-arene **7**, and binds not only Na^+ but Li^+, partial cone **6b** shows a poor metal affinity (enhanced K^+ selectivity but lower Ex% values), while 1,3-alternate **6c** has the highest Ex% for K^+ among the three conformational isomers. Thus, metal recognition with calix[4]arene ionophores can be exploited not only on the basis of the nature of binding sites and ring size [39], but also on the basis of conformational changes [37, 38].

2.4. Molecular asymmetry and enantioselective HPLC resolution

Although chiral calix[4]arenes can be generated by simply attaching chiral residues at the upper [40] or lower [41–43] rim of the calixarene skeleton, recent interest has been focused on the possibility of synthesizing 'inherently' chiral calix[4]arenes, which are build up of nonchiral subunits and consequently owe their chirality to the fact that the calixarene molecule is nonplanar. Molecular asymmetry can arise from the substitution pattern at the lower rim and/or conformation. In this respect, Shinkai has recently reported a systematic classification of all possible chiral isomers derivable from calix[4]arene, and delineated some basic concepts for the design and synthesis of chiral derivatives [44].

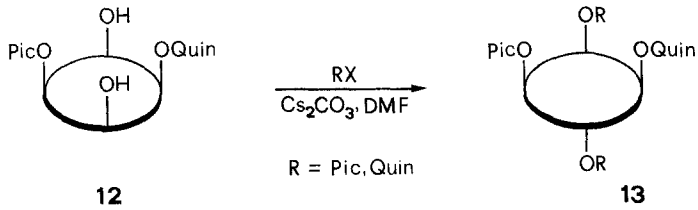
Two strategies have been used for the preparation of inherently chiral calix[4]arenes: the fragment condensation (convergent stepwise synthesis of asymmetric calix[4]arenes from appropriate linear precursors) [45–52] and the lower-rim functionalization of a preformed calix[4]arene [32, 33, 36, 44]. The second strategy



Scheme 3.

is more attractive for practical reasons, and is based on the regio- and stereoselective functionalization of conventional calix[4]arenes at the lower rim.

Syn-proximal di[(2-pyridylmethyl)oxy]calix[4]arene **3a** has proved to be a useful achiral intermediate for the production of inherently chiral derivatives, and some chemical modifications are shown in Scheme 3. Dissolution of **3a** in MeI at room temperature produces the chiral *N*-methylpyridinium derivative **8** in a nearly quantitative yield [18], while MCPBA oxidation in diethyl ether has led to the isolation of the chiral mono-*N*-oxide **9** [53]. The reluctance of **8** to undergo further *N*-alkylation suggests the hypothesis that the lone pair of the residual ring nitrogen is



12 **13**

Scheme 4.

directly involved in a sort of 'self-complex' structure, with the *N*-methylpyridinium cation surrounded by oxygen and nitrogen donor atoms [18].

When **3a** is treated with an electrophile RX (1 equiv.) in anhydrous DMF in the presence of Cs_2CO_3 (1 equiv.) at 60°C for a few hours, racemic *cone* calix[4]arenes **10**, endowed with mixed ligating functionalities in the sequence $A^{\alpha}A^{\alpha}B^{\alpha}C^{\alpha}$ [54] at the lower rim are obtained in 42–93% yield with excellent stereoselectivity [33]. The conformational outcome of this reaction is not affected by metal template effects, but rather is determined by the strong hydrogen bonding stabilization of the phenolate intermediate in the cone conformation. The reaction appears to be general, as demonstrated by the wide variety of binding functionalities (including alkenic, alcoholic, ether, amino, ester, amide, keto, aromatic and *N*-heteroaromatic groups) which can be easily introduced at the lower rim via ether formation [33]. The first chiral calix[4]arene possessing the $A^{\alpha}A^{\alpha}B^{\alpha}C^{\alpha}$ pattern of substituents at the lower rim was obtained by Shinkai by using a different strategy, i.e. a $BaO/Ba(OH)_2$ assisted bis-*O*-propylation of monopyridinocalix[4]arene **2** [32].

Conversely, alkylation of **3a** with an excess of electrophile RX under similar conditions gave the chiral tetra-*O*-alkylated *partial cone* derivatives **11**, possessing an $A^{\alpha}A^{\alpha}B^{\alpha}B^{\beta}$ sequence of substituents at the lower rim [33, 36]. In a similar way, exhaustive alkylation of mixed *syn-distal* **12**, generated from **2** by treatment with 2-chloromethylquinoline hydrochloride (QuinCl·HCl), with either PicCl·HCl or QuinCl·HCl furnished the corresponding chiral partial cone derivatives **13**, having the $A^{\alpha}A^{\alpha}A^{\beta}B^{\alpha}$ pattern of substituents at the lower rim [33], as shown in Scheme 4.

Apart from NMR spectral patterns showing molecular asymmetry, evidence of chirality for cone **10** and partial cone structures **11** and **13** was provided by the addition of Pirkle's reagent (*S*)-(+)-(9-anthryl)-2,2,2-trifluoroethanol to a chloroform solution of each calixarene, which caused doubling of (in principle) all signals.

The direct HPLC separation of most chiral tri-*O*-alkylated calix[4]arenes **10** has been achieved using Chiralcel OD phase, while it was ineffective for partial cone products **11** and **13** [55]. Nevertheless, compound **11** (R = CH_2Quin) could be separated into its entantiomers by using a Chiralpak OP(+) HPLC column [36]. Sufficient amounts of each pair of enantiomers from racemic **10** (R = benzyl) and **11** (R = CH_2Quin) could be obtained to measure their CD spectra. These

are almost mirror images of each other, indicating that the eluates from the two chromatographic peaks are optical isomers.

Among the various factors influencing enantioselection, hydrogen bonding between the residual hydroxyl group of tri-*O*-alkylated compounds and the Chiralcel OD phase seems to play an important role. As a matter of fact, the separation factor of compound **10** (R = benzyl) ($\alpha = 3.45$ under optimum conditions) dramatically drops to 1.24 when the OH group is replaced by a propoxy group [55].

2.5. *N*-OXIDE DERIVATIVES

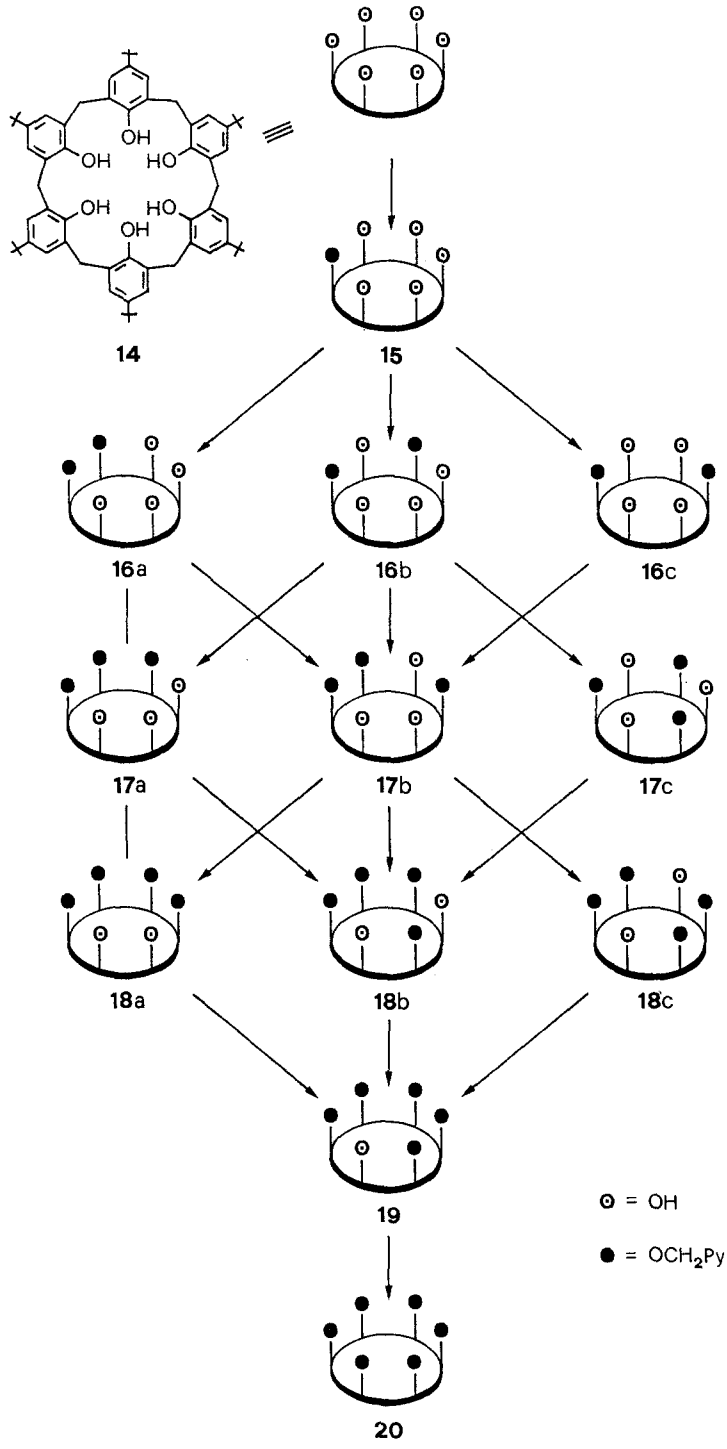
Regio- and conformational isomers of calix[4]arenes bearing pyridine-*N*-oxide pendant groups at the lower rim have been recently synthesized by MCPBA oxidation of appropriate pyridinyl precursors in order to provide different atropisomeric (cone, partial cone, 1,2- and 1,3-alternate) *N*-oxide ligands [53, 56].

Extraction data of alkali metals with the picrate method have shown that pyridinyl compounds are better ionophores than their *N*-oxide counterparts (deleterious role of hydrogen bonding between *N*-oxide functionalities and water molecules). The highest phase-transfer values are observed for cone conformers, where selectivity follows the order $Na^+ > K^+ > Rb^+ > Cs^+ > Li^+$. In aprotic solvents *N*-oxide ligands are much stronger complexers, and alkali and lanthanide metal complexes have been prepared and characterized. The Eu(III) and Tb(III) complexes of tetra-*N*-oxide cone conformer are fluorescent upon UV light excitation at 312 nm. Unfortunately, these complexes totally lose their luminescence upon addition of water, indicating their modest stability in aqueous medium [56, 57].

3. Pyridinocalix[6]arenes

A schematic representation of the twelve pyridino homologues derivable from *p-tert*-butylcalix[6]arene **14** and possible reaction pathways are shown in Scheme 5. Of these compounds, only diether **16b** and tetraether **18b** have not been isolated yet. The remainder have been obtained either by direct alkylation of **14** or by stepwise synthesis [23, 26, 38, 58]. In contrast to pyridinocalix[4]arenes and calix[6]arenes bearing very bulky substituents at the lower rim [59], no conformational isomerism is observed for these compounds, indicating that the calix[6]arene annulus is large enough to allow the oxygen-through-the annulus rotation of the pyridylmethyloxy groups.

Alkylation of the parent calix[6]arene **14** with PicCl·HCl (0.5–30 equiv.) was investigated in anhydrous DMF at 60°C (and in one case in refluxing CH_3CN) in the presence of base [NaH, K_2CO_3, or $BaO/Ba(OH)_2$]. Exhaustive alkylation reactions are clean, while reactions with limiting amounts of electrophile produce complex reaction mixtures, which can be eventually separated into the puric components by extensive chromatographic means.


OH
OH
HO
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14
15
16a
16b
16c
17a
17b
17c
18a
18b
18c
19
20
⊙ = OH
● = OCH2Py

Scheme 5.

3.1. SYNTHESES

Hexaether **20** is obtained in 81% yield by subjecting **14** to a large excess of PicCl·HCl in the presence of K_2CO_3 [23, 26]. The use of NaH instead of K_2CO_3 affords regioselectively 1,2,4,5-tetraether **18c** (61%), along with pentaether **19** (5%) and hexaether **20** (8%) [23, 38, 58]. The selective formation of **18c** parallels the results reported by Gutsche for the NaH-catalyzed aroylation and arylmethylation of **14** [21, 22].

Conditions for partial alkylation have been found by tuning the amount of electrophile and the identity of the base. Thus, monoether **15** is generated in 55% yield by reacting **14** with PicCl·HCl (0.5 equiv.) and K_2CO_3. Reactions of **14** with increasing amounts of PicCl·HCl (1–4 equiv.) and K_2CO_3 in DMF produce invariably complex mixtures with 1,2,3-triether **17a** as the major product (up to 51%), along with variable amounts of diethers **16a** and **16c** and 1,2,4-triether **17b** as by products. When alkylation of **14** is carried out in CH_3CN, the product distribution is similar to that described in DMF, but in addition a small amount of 1,3,5-triether **17c** could be isolated, suggesting that the obvious precursor, i.e. 1,3-diether **16b**, is a transient species under the experimental conditions employed. The 1,2,3,4-tetraether **18a**, scantly present in the K_2CO_3-catalyzed alkylation products, can be synthesized as the sole product (35%) by treating 1,2,3-triether **17a** with PicCl·HCl (1 equiv.) in the presence of NaH [23].

Alkylation of **14** with PicCl·HCl (2 equiv.) in the presence of $BaO/Ba(OH)_2$ affords regioselectivity the barium complex of 1,4-diether **16a** in 80% yield [23]. The formation of a labile K^+ complex has been hypothesized by Gutsche to account for the selective 1,4-di-*O*-alkylation of **14** when using Me_3SiOK, Me_3COK, or KH as the base [22].

3.2. FLUXIONAL PROPERTIES

p-tert-Butylcalix[6]arene **14** is a conformationally flexible molecule, as deduced from the broad singlet for the $ArCH_2Ar$ protons in the ^{1}H-NMR spectrum at room temperature, and dynamic measurements have demonstrated a facile interconversion among various conformers with a coalescence temperature (T_c) of 11°C and an inversion barrier of 13.3 kcal/mol in $CDCl_3$ [60]. Conversion of **14** to monoether **15** reduces the conformational mobility, resulting in a set of three pairs of doublets at room temperature for the CH_2 protons, which remain invariant up to 345 K in $CDCl_3$, and coalesce at temperatures higher than 360 K, with an estimated $\Delta G > 18$ kcal/mol. If the rule found for pyridinocalix[4]arenes can be extended to the larger calix[6]arene homologues, a signal at 77.91 ppm for the oxymethylene carbon of **15** may be suggestive for a cone conformation [23].

The methylene region of 1,2-diether **16a** is characterized by a well-resolved 20-line pattern (five pairs of doublets in the ratio 2 : 1 : 2 : 2 : 1) coalescing at 360 K, while that of the 1,4- regioisomer **16c** displays a 5-line pattern (a pair of broad doublets and a singlet in the ratio 2 : 1) with a T_c of 320 K. In 1,2,3-triether

17a the bridging methylenes show up as a 9-line pattern (two pairs of doublets and a singlet in the ratio 1 : 1 : 1) in CD_2Cl_2, and as three broad singlets of equal intensity in DMSO-d_6 at 355 K. On the other hand, tri-*O*-alkylated regioisomers **17b** and **17c**, as well as their higher homologues **18–20** display broadened ^{1}H-NMR spectra which sharpen at higher temperatures. This behaviour suggests that T_c for pyridinocalix[6]arenes decreases by increasing progressively the degree of substitution at the lower rim; besides, within each series of partially alkylated regioisomers, T_c increases with increasing number of adjacent unalkylated phenol units (e.g. in tri-*O*-alkylated compounds $T_{c1,2,3} > T_{c1,2,4} > T_{c,1,3,5}$), suggesting that hydrogen bonding among hydroxyl groups plays a major role in raising the energy barrier to conformational inversion [23].

The conformational behaviour of 1,2,4,5-tetraether **18c** has been investigated in detail by different techniques that include dynamic NMR spectroscopy, MM2 molecular mechanics calculations and X-ray analysis [58]. From VT-NMR analysis in the range 220–345 K, two coalescence temperatures at 227 ($\Delta G = 11.1$ kcal/mol) and 315 K ($\Delta G = 14.2$ kcal/mol) have been ascertained in $CDCl_3$. Theoretically, 14 different relative orientations of the aromatic rings with respect to the best plane containing the bridging methylenes are possible. The symmetry of NMR signals and NOESY data restricted the possible conformations of **18c** in solution, at temperature below 315 K, to those indicated as A and C in Figure 2. Whereas conformers of type C could be ruled out on the basis of MM2 results showing conformer A as the most stable, conclusive evidence in favour of the existence of conformer A in solution was provided by ^{1}H-NMR and ROESY spectra of **18c** in CD_2Cl_2 at 183 K. The conformation of the lowest energy conformer A can be described as 1,2,4,5-alternate with the OH-bearing phenyl rings in anti orientation with each other. In the solid state a similar conformation A1 is found for **18c**, the only difference being the *syn* orientation of OH$\cdots$O intramolecular hydrogen bonds.

On the basis of the above results, the fluxional behaviour of **18c** can be summarized as shown in Figure 3. At temperatures below 220 K conformer A, having a C_2 axis of symmetry, is predominant and in slow exchange with A1, as illustrated in Figure 2. Above 220 K this equilibrium becomes fast on the NMR time scale, and averaged spectra are obtained consistent with two C_2 axes of symmetry. At temperatures below 315 K conformer D (the third one in the MM2 energy scale), begins to appear as a consequence of the new equilibrium between conformers A and D in the slow exchange rate (Figure 3). The equilibrium between A and D becomes fast, on the NMR time scale, at temperatures above 315 accounting for the second coalescence in the VT-NMR studies. Conformers of type D are believed to be pivotal intermediates in the conformational pathways leading to the other conformers [58].

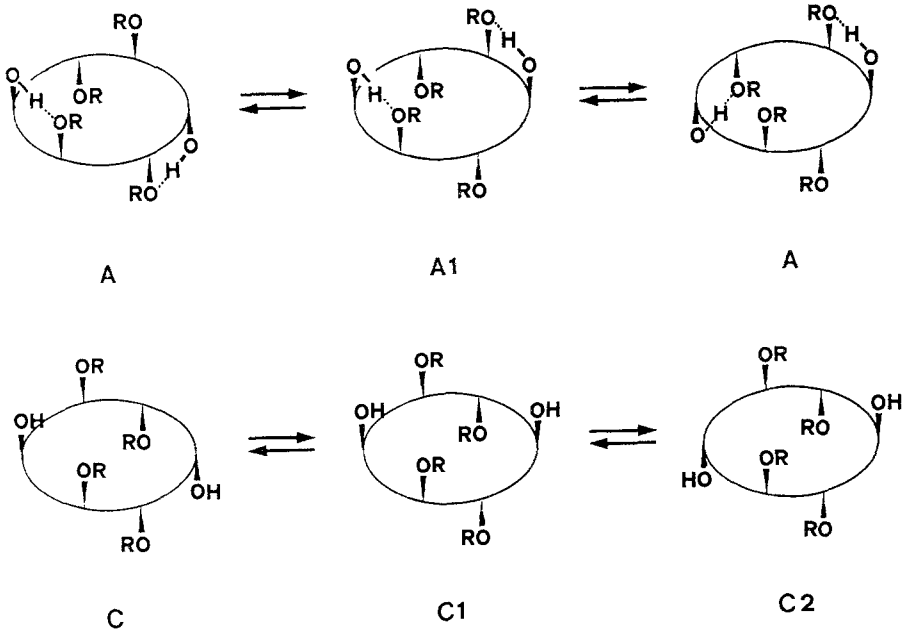


Fig. 2. Schematic representation of the two possible conformations compatible with the NMR spectral properties of **18c** in the temperature range 227–315 K. Reprinted with permission from *J. Am. Chem. Soc.* **114**, 7814 (1992). Copyright 1992 American Chemical Society.

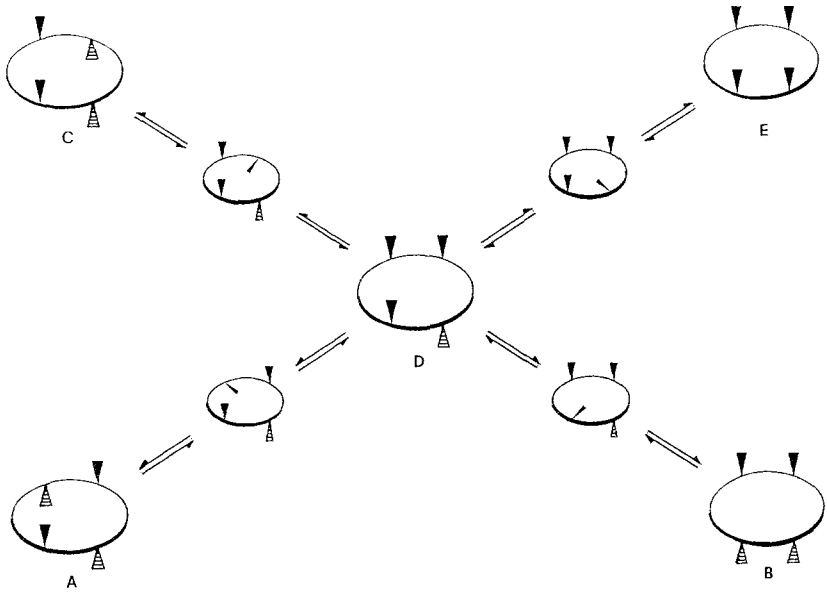
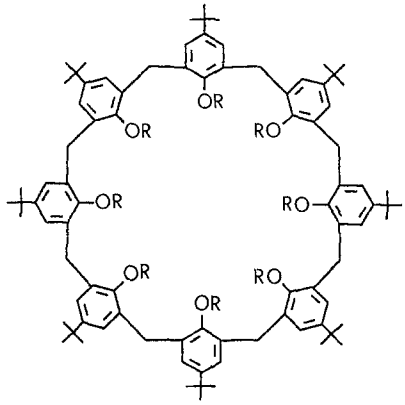


Fig. 3. Proposed mechanism for the conformational interconversions of **18c**. Conformational intermediates are represented by smaller circles where the thinner triangle indicates a pyridine or *tert*-butyl group inside the cavity. Reprinted with permission from *J. Am. Chem. Soc.* **114**, 7814 (1992). Copyright 1992 American Chemical Society.

4. Pyridinocalix[8]arenes

Due to the increased number of OH functionalities, 29 pyridino homologues of *p-tert*-butylcalix[8]arene **21** can exist: one mono-, hepta-, and octa-substituted derivatives, four di-, five tri-, eight tetra-, five penta- and four hexasubstituted regioisomers. The products of the partial alkylation of **21** with PicCl·HCl are hitherto unknown, while fully alkylated octakis[(2-pyridylmethyl)oxy]calix[8]arene **22** has been obtained in 24% yield by using conditions similar to those described for calix[6]arene **20**. From solvent extraction data, Shinkai has shown that compounds **20** and **22** display a high affinity for UO_2^{2+} at elevated temperature (100°C, *o*-dichlorobenzene) [26].



21 R = H
22 R = OCH_2Py

5. Concluding Remarks

The base-catalyzed alkylation of *p-tert*-butylcalix[*n*]arenes (n = 4, 6, 8) with PicCl·HCl has been investigated. Regio- and stereoselective *O*-alkylations have paved the way to atropisomeric inherently chiral calix[4]arenes endowed with mixed ligating functionalities at the lower rim. Tri-*O*-alkylated racemates (compounds **10**) can be optically resolved by enantioselective HPLC, but in order to pursue further studies (chiral recognition, enantioselection) larger quantities of the pure enantiomers are desirable. These may become available by converting **10** into diastereomers upon further alkylation of the residual OH group with suitable optically active derivatizing agents [44].

The properties of calixarene-based host molecules are strongly influenced by the conformation of the calixarene moiety. Pyridinocalix[4]arenes are conformationally inflexible molecules (the introduction of just one pyridylmethyl group at the lower rim suffices to suppress conformational changes), while the larger calix[6]arene homologues show fluxional properties.

Finally, calixarenes endowed with pyridine pendant groups at the lower rim are well suited for the design of receptors containing positively or negatively charged recognition sites by chemical transformations at the pyridine ring nitrogen, and recently a quaternised pyridinocalix[4]arene has been shown to possess molecular recognition for anionic guest species [61].

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28. Spectral data ($CDCl_3$) for **5c**: ^{1}H-NMR δ 1.13 [s, $C(CH_3)_3$, 36H], 3.01, 3.94 (ABq, J = 12.4 Hz, $ArCH_2Ar$, 4H), 3.84 (s, $ArCH_2Ar$, 4H), 4.31, 4.41 (ABq, J = 13.2 Hz, OCH_2Py, 8H), 6.05 (d, J = 7.8 Hz, 3-PyH, 4H), 6.91, 7.25 (ABq, J = 2.2 Hz, ArH, 8H), 6.92 (m, 5-PyH, 4H), 7.06 (td, J = 7.7, 1.7 Hz, 4-PyH, 4H), and 8.25 (d, J = 4.0 Hz, 6-PyH, 4H); ^{13}C-NMR δ 29.88, 39.21 (t, $ArCH_2Ar$), 31.36 [q, $C(CH_3)_3$], 33.97 [s, $C(CH_3)_3$], 74.14 (t, OCH_2Py), 121.49, 122.68 (d, 3,5-Py), 125.28, 125.71 (d, Ar), 132.65, 134.09 (s, bridgehead-C), 136.07 (d,4-Py), 145.12 [s, C_{Ar}—$(CH_3)_3$], 147.66 (d, 6-Py), 153.28 (s, C_{Ar}—OCH_2Py), and 157.65 (s, 2-Py).
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