Functionalization of *p-tert*-Butylcalix[6]arene by Alkylation with 2-(Chloromethyl)pyridine Hydrochloride

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A study of the base-catalyzed alkylation of *p-tert*-butylcalix[6]arene (1) with 2-(chloromethyl)-pyridine in DMF has led to the isolation and identification of 10 of the 12 possible pyridinyl homologues of 1. The identity of the base applied and molar ratios between the reactants play an important role in determining the product distribution. Regioselective 1,2,4,5-tetra-O-alkylation is realized with NaH as the base, while the use of BaO/$Ba(OH)_2$ affords in high yield 1,4-diether 5, which is isolated as a barium complex. The reactions with limiting amounts of alkylating agent and K_2CO_3 produce invariably complex mixtures with 1,2,3-triether 6 as the major product. The structure of the products has been established by elemental analysis, FAB (+) mass spectral measurements, and NMR techniques. [(2-Pyridylmethyl)oxy]calix[6]arene homologues show in most cases broadened ^{1}H-NMR spectra at rt, which sharpen at higher temperatures, allowing for a distinction between the various regioisomers. FAB (+) mass spectra and some NMR features arising from the substitution patterns at the lower rim are discussed.

Introduction

Calixarenes are cavity-containing molecules that are the focus of considerable interest in the field of supramolecular chemistry as three-dimensional building blocks for new host molecules with desired properties.[1] So far extensive work has been carried out on the smallest members of this family, i.e. calix[4]arenes, and general procedures have been developed for the selective functionalization at either the upper and lower rim.[2]

Despite their greater potential, the larger calix[6]arenes have received little attention, mainly because of a higher degree of functionality and flexibility which complicate their chemistry and make isolation and characterization of the products an often difficult task. As a matter of fact, sporadic examples of partial functionalization (mixtures of regioisomers of unknown composition) at the lower rim of calix[6]arenes are known,[3] and only recently 1,3,5-tri-O-alkylated calix[6]arenes[4] and a fundamental study on the products of aroylation[5] and arylmethylation[6] of calix-[6]arenes have been reported.

Following previous studies concerning the synthesis, structure, and conformation of calixarenes bearing pyridinyl pendant groups at the lower rim as potential ligands for transition metals,[7] we have investigated the direct functionalization of *p-tert*-butylcalix[6]arene by alkylation with 2-(chloromethyl)pyridine hydrochloride (PicCl·HCl). We have found that by tuning the reaction conditions (amount of electrophile, base, solvent) it is possible to isolate in variable yield 10 of the 12 possible pyridinocalix-[6]arene homologues (Chart I). In this paper we report the synthesis and structural characterization of these compounds. The results obtained provide an additional contribution toward the elucidation of the mechanisms governing the lower-rim alkylation of calix[6]arenes.

Results and Discussion

Alkylation of *p-tert*-butylcalix[6]arene (1) with PicCl·HCl (2–30 equiv) was carried out in anhydrous *N,N*-dimethylformamide (DMF) at 60 °C or CH_3CN at reflux temperature for 16–24 h in the presence of base (NaH, K_2CO_3, or BaO/$Ba(OH)_2$). Table I summarizes the product composition as a function of the molar ratios between the reactants and the identity of the base applied. Exhaustive alkylation reactions were clean, while reactions with limiting amounts of electrophile led in most cases to very complex reaction mixtures, which could be eventually separated into the pure components by careful column chromatography (SiO_2, a gradient of AcOEt in cyclohexane as the eluent), followed in some istances by preparative TLC (Table I). The molecular weights of the pure components were deduced by microanalytical data and FAB (+) MS, their structures being firmly established by ^{1}H- and ^{13}C-NMR spectroscopy.

Syntheses. Treatment of *p-tert*-butylcalix[6]arene (1) with a large excess of PicCl·HCl (30 equiv) and NaH (75 equiv) in DMF afforded 1,2,4,5-tetra-O-alkylated compound 11 (61%),[7c] along with minor amounts of pentaether 12 (5%) and hexaether 13 (8%). The selective formation

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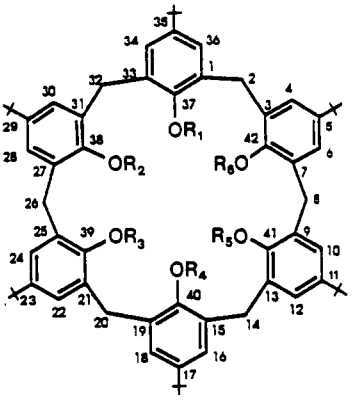
Chart I



Compd	R_1	R_2	R_3	R_4	R_5	R_6
1	H	H	H	H	H	H
2	Pic	H	H	H	H	H
3	Pic	Pic	H	H	H	H
4	Pic	H	Pic	H	H	H
5	Pic	H	H	Pic	H	H
6	Pic	Pic	Pic	H	H	H
7	Pic	Pic	H	Pic	H	H
8	Pic	H	Pic	H	Pic	H
9	Pic	Pic	Pic	Pic	H	H
10	Pic	Pic	Pic	H	Pic	H
11	Pic	Pic	H	Pic	Pic	H
12	Pic	Pic	Pic	Pic	Pic	H
13	Pic	Pic	Pic	Pic	Pic	Pic

Table I. Product Composition in the Base-Catalyzed Lower-Rim Alkylation of *p-tert*-Butylcalix[6]arene (1 mmol) with PicCl·HCl[a]

PicCl·HCl mmol	base (mmol)	product distribution (%)
30	NaH (75)	11 (61), 12 (5), 13 (8)
28	K_2CO_3 (56)	12 (4), 13 (81)
4	K_2CO_3 (8)	3 (3), 5 (2), 6 (51), 7 (trace), 9 (<1), 11 (1)
3	K_2CO_3 (6)	2 (<1), 3 (8), 5 (11), 6 (35), 7 (2), 8 (1), 9 (trace), 11 (1)
2	K_2CO_3(4)	2 (5), 3 (16), 5 (12), 6 (38)
2	BaO (4)/$Ba(OH)_2$ (2)	5·Ba (80)

[a] Dry DMF was used as solvent except for the reaction with 3 mmol of PicCl·HCl, which was carried in acetonitrile.

of 11 is in agreement with the results reported by Gutsche for the NaH-catalyzed aroylation and arylmethylation of 1.[5,6]

Exhaustive alkylation to hexaether 13 was realized in 81% yield by treating 1 with PicCl·HCl (28 equiv) and anhydrous K_2CO_3 (56 equiv) in DMF, using a slight modification of the procedure reported by Shinkai.[8] The reaction produced also small amounts of the pentaether 12.

Increased calix[6]arene/PicCl·HCl molar ratios gave complex mixtures of products representing various stages of alkylation. When 1 was reacted with PicCl·HCl (2 equiv) in the presence of K_2CO_3 (4 equiv), a mixture was produced from which four compounds have been isolated. These were identified as the monoether 2 (5%), 1,2-diether 3 (16%), 1,4-diether 5 (12%), and 1,2,3-triether 6 (38%). Attempts to isolate the 1,3-diether 4 have been unsuccessful, although a very weak spot of what is believed to be the missing di-O-alkylated regioisomer was present in the TLC plate of the crude reaction mixtures.

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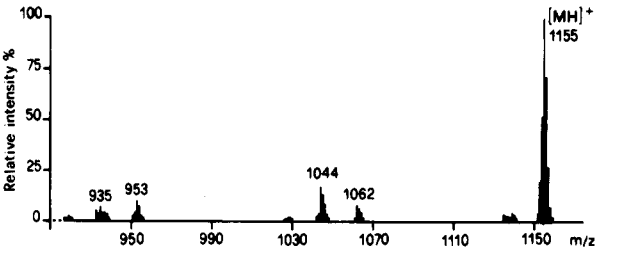


Figure 1. The FAB (+) mass spectrum of 1,2-diether 3.

By increasing the amount of electrophile to 4 equiv, monoether 2 disappeared totally, diethers were still present in ca. 5% overall yield, 1,2,3-tri-O-alkylated 6 accumulated up to 51% along with very small amounts of the 1,2,4-tri-O-alkylated regioisomer 7 (<1%), while a low-yield conversion to tetraethers 9 and 11 was also observed.

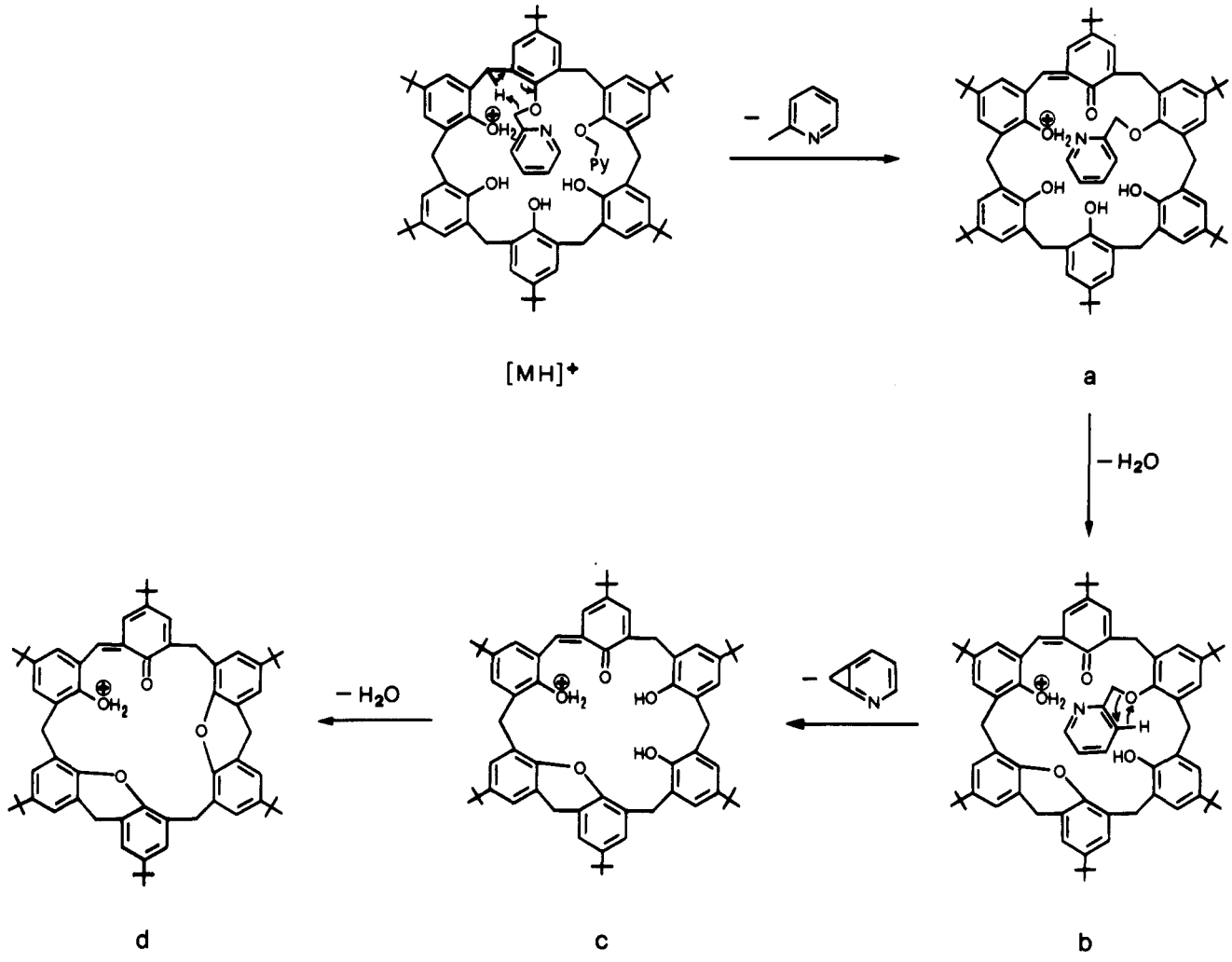
1,2,3,4-Tetra-O-alkylated regioisomer 9 was independently synthesized as the sole product (35%) by subjecting 6 to PicCl·HCl (1 equiv) in anhydrous DMF at room temperature in the presence of NaH.

The alkylation of 1 with PicCl·HCl in the presence of BaO/$Ba(OH)_2$ produced a sparingly soluble material in 80% yield. TLC analysis of the product showed a single spot corresponding to 1,4-diether 5. However, an analytical sample, obtained by recrystallization from DMF, gave microanalytical data consistent with the formulation 5Ba·2DMF. This composition is substantiated by ^{1}H-NMR spectroscopy and by the FAB (+) MS, which shows the molecular ion at m/z 1291 (3.4% relative intensity), in addition to the peaks characteristic of the ligand (see below). Thermal gravimetric analysis (TGA) of the barium complex confirmed the presence of two DMF molecules, which are released at 130–170 °C, while the product decomposed over 390 °C. The formation of a labile K^+ complex has been hypothesized by Gutsche[6] to account for the selective 1,4-di-O-alkylation of 1 when using Me_3-SiOK, Me_3COK, or KH as the base.

An alkylation experiment on 1 was also conducted in refluxing CH_3CN (1 day) using 3 equiv of PicCl·HCl and 6 equiv of K_2CO_3. The reaction afforded a complex mixture similar to those described for the reactions in DMF, with diethers 3 and 5 and triether 6 as the major components. In addition, the reaction furnished very small amounts (<1%) of 1,3,5-tri-O-alkylated compound 8, which could be isolated in a pure form after extensive chromatography. The isolation of 8 confirms that the obvious precursor, i.e. 1,3-diether 4, is a transient species under the experimental conditions employed.

FAB (+) Mass Spectra. The FAB (+) mass spectra of pyridinocalix[6]arene homologues 2–13 display very prominent molecular ion peaks, which provide the base peak in the spectra. A typical FAB (+) mass spectrum, relative to diether 3, is reported in Figure 1. It shows the protonated molecular ion at m/z 1155 (base peak) and less intense fragment ions (6–18% relative intensity) at m/z 1062, 1044, and 953, corresponding to the sequential losses

Scheme I



of 93 (C_6H_7N), 18 (H_2O), and 91 (C_6H_5N) amu from the molecular ion. A possible rationale for the decomposition of **3** is illustrated in Scheme I. The extrusion of 2-picoline (C_6H_7N) from the protonated molecular ion may occur via a six-membered cyclic transition state by migration of a bridged methylene proton to the oxymethylene carbon to produce *o*-quinoid structure **a** (*m/z* 1062). Subsequent elimination of water from two adjacent phenolic OH groups of **a** affords dibenzopyran structure **b** (*m/z* 1044), which suffers the loss of a C_6H_5N moiety via a 5-center migration of the 3-pyridyl proton to the close O atom to generate structure **c** (*m/z* 953). Analogous dibenzopyran structures, obtained by loss of water from the molecular ion, have been proposed by Kämmarer et al. for the EI-induced mass spectral fragmentation of calix[4]arenes.[9] Further elimination of a neutral water molecule from **c** eventually yields bis-dibenzopyran structure **d** (*m/z* 935). The fragmentation pattern is quite uniform in the entire series, and the rationale proposed for the decomposition of **3** well applies to all the compounds examined. Selected ions and their relative abundances for compounds **2–13** are listed in Table S1 in the supplementary material.

NMR Spectral Features. *p-tert*-Butylcalix[6]arene (**1**) is a conformationally flexible molecule, as deduced from the broad singlet for the $ArCH_2Ar$ protons at room temperature, and dynamic ^{1}H-NMR measurements have demonstrated a facile interconversion among various conformers with a coalescence temperature of 11 °C and an inversion barrier of 13.3 kcal/mol in $CDCl_3$.[10] Conversion of **1** to the monoether **2** reduces the conformational mobility, resulting in a set of three pairs of doublets at room temperature for the bridging 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. The oxymethylene carbon resonances have been shown to provide a diagnostic tool for distinguishing among the various conformers of pyridinocalix[4]arenes, a signal around 77 or 71 ppm being indicative for a cone or 1,3-alternate conformation, respectively.[7b] If this rule can be extended to the larger calix[6]arenes, a signal at 77.91 ppm for the oxymethylene carbon of **2** may be suggestive for a cone conformation.

The distinction between di-O-alkylated regioisomers **3** and **5** was apparent from their ^{1}H-NMR patterns. The ^{1}H-NMR spectrum of 1,4-diether **5** in $CDCl_3$ shows a pair of *tert*-butyl resonances in a 2:1 ratio and a five-line pattern in the $ArCH_2Ar$ region which can be analyzed as a pair of broad doublets and a singlet in a ratio of 2:1. Coalescence of the AB system occurs at 320 K in $C_2Cl_4/CDCl_3$ (1:1 v/v), and at 360 K the methylenes show up as two broad singlets. In the barium complex **5**Ba·2DMF the bridged methylenes show up as two pairs of well-resolved doublets in a ratio 2:1, indicating a structure with a binary symmetry element.

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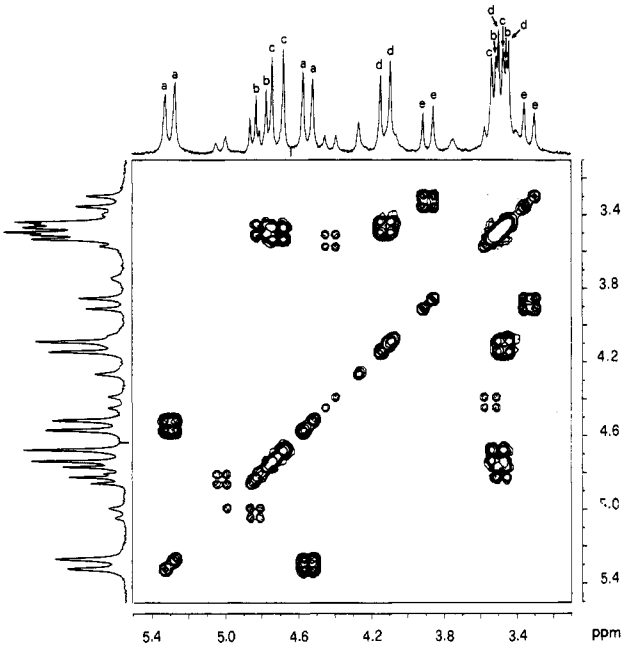

Figure 2. The methylene region of the COSY spectrum (250 MHz, $CDCl_3$, 295 K) of 1,2-diether **3**. Letters a–e refer to the five AB systems belonging to the major conformer, while unlabeled signals of low intensity likely arise from minor conformer(s).

1,2-Diether **3** displays a set of three high-field singlets of equal intensity arising from the *tert*-butyl protons and a well-resolved twenty-line pattern for methylene and oxymethylene protons. These were analyzed as five pairs of doublets in a ratio 2:1:2:2:1, as substantiated by appropriate cross-peaks in the COSY spectrum shown in Figure 2. The ^{1}H-NMR spectrum of **3** displays additional signals of much lower intensity in the *tert*-butyl region along with additional multiplets in the methylene and aromatic regions which may account for the presence of a minor conformer in solution. Coalescence of methylenes occurs at 360 K in $CDCl_3$. The 1,2-substitution pattern is further corroborated by the ^{13}C-NMR spectrum, which displays four resonances at 29.52, 30.76, 32.75, and 33.13 ppm in a rough 1:2:1:2 ratio for the bridging methylenes.

The substitution patterns in tri-O-alkylated regioisomers were deduced by their ^{1}H-NMR spectra at different temperatures. The ^{1}H-NMR spectrum of 1,2,3-tri-O-alkylated compound **6** in CD_2Cl_2 at 290 K showed a set of four resonances for *tert*-butyl hydrogens in a ratio 2:2:1:1 and a nine-line pattern for the bridged methylenes which was ananlyzed as two pairs of doublets and a singlet in a 1:1:1 ratio. The oxymethylene protons appeared as a single broad singlet. In DMSO-d_6 at 355 K the methylene protons showed up as three broad singlets of equal intensity, while the oxymethylene protons split into two broad singlets in a ratio 2:1.

1,2,4- and 1,3,5-tri-O-alkylated regioisomers **7** and **8** displayed broadened ^{1}H-NMR spectra at rt which sharpened at higher temperatures. In **7**, sharpening of the *tert*-butyl resonances with contemporary coalescence of the methylene protons occurred at 305 K, while at 335 K a set of five resonances arising from the *tert*-butyl groups in a ratio 1:1:2:1:1, a sharp singlet and three broad singlets in a ratio 1:3:1:1 for bridging methylenes, and three sharp resonances for oxymethylenes became apparent. Instead **8** at 360 K showed, as expected for a C_3 symmetry, two *tert*-butyl resonances of equal intensity for unalkylated and alkylated rings and single resonances for methylene and oxymethylene protons.

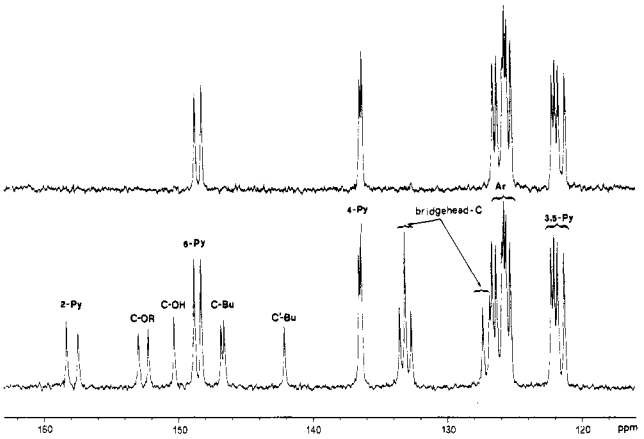

Figure 3. Aromatic regions and partial assignments of DEPT (top) and broad-band decoupled (bottom) ^{13}C-NMR spectra (62.9 MHz, $CDCl_3$, 360 K) of 1,2,3,4-tetraether **9**.

The NMR spectral features and conformational analysis of tetraether **11** have been discussed in a previous paper.[7c] The 1,2,3,4-tetra-O-alkylated regioisomer **9** presents symmetries similar to those of 1,2-diether **1d**. The ^{1}H-NMR spectrum at 360 K ($CDCl_3$) shows the expected three resonances of equal intensity for *tert*-butyl groups, a sharp singlet and three broad singlets for the bridged methylenes in a ratio 1:2:2:1, and two resonances of equal intensity for the oxymethylene protons. The 1,2,3,4-substitution pattern is further substantiated by the ^{13}C-NMR spectra, recorded at 360 K, which show three of the four expected resonances for methylene carbons in a rough 1:1:4 ratio and two signals for oxymethylene carbons. In addition the aromatic region 120–160 ppm exhibits 27 of the 28 expected resonances for sp^2 carbons, which could be partly assigned by a DEPT experiment, as shown in Figure 3.

Although symmetrically related to monoether **2**, pentaether **12** displays a broad ^{1}H-NMR spectrum in $CDCl_3$ at room temperature. Sharp signals were obtained in DMSO-d_6 at 384 K, showing four resonances in a ratio 2:1:2:1 arising from the *tert*-butyl groups, two singlets for bridged methylenes in a ratio 1:2, and three singlets for oxymethylene protons, consistent with the assigned structure.

The ^{1}H-NMR spectrum of hexaether **13** in $CDCl_3$ at rt is broad, while in DMSO-d_6 at 384K it is sharp, and single resonances for *tert*-butyl, methylene, and oxymethylene protons in the expected ratios were obtained. The elevated number of resonances observed in the ^{13}C-NMR spectrum of **13** at rt likely indicates that in solution the molecule exists as a mixture of at least two conformers.

Conclusions

The alkylation of *tert*-butylcalix[6]arene (**1**) with PicCl·HCl in DMF under different reaction conditions (molar ratios of the reactants, base) has led to the isolation and identification of 10 of the 12 possible pyridinocalix[6]arene homologues. Selective 1,2,4,5-tetra- or 1,4-di-O-alkylation is achieved in good yields by using NaH or $BaO/Ba(OH)_2$, respectively, while the reactions with limiting amounts of electrophile and K_2CO_3 afford invariably 1,2,3-tri-O-alkylated derivative as the major product in up to 51% yield.

The substitution pattern for di-, tri-, and tetra-O-alkylated regioisomers was firmly established by NMR spectroscopy. The ^{1}H-NMR spectra at different temperatures, deemed essential for the structural characterization, provide at the present stage only a qualitative picture of the influence of pyridinyl substituent(s) and substitution pattern on the conformational mobility of pyridinocalix[6]arene homologues. As a general trend, the coalescence temperature (T_c) for these systems 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 $T_{c_{1,2,3}} > T_{c_{1,2,4}} > T_{c_{1,3,5}}$), suggesting that hydrogen bonding among hydroxyl groups plays a major role in raising the energy barrier to conformational inversion. Additional studies in order to characterize the conformational behavior of these systems are in progress.

Experimental Section

General Comments. Melting points are uncorrected. Multiplicities in ^{13}C-NMR spectra were obtained by DEPT experiments. FAB (+) MS were recorded using 3-nitrobenzyl alcohol as a matrix. Elemental analyses were obtained from the Institute of Pharmaceutical Chemistry of the University of Catania. TGA measurements were performed with heating rates of 10, 4, and 1 °C/min in a dynamic nitrogen atmosphere. The sample weights were in the range 5–10 mg. All chemicals were reagent grade and were used without further purification. Anhydrous DMF and 2-(chloromethyl)pyridine hydrochloride were purchased from Fluka. *p-tert*-Butylcalix[6]arene (1) was prepared by a literature procedure.[11] All reactions were carried out under nitrogen.

5,11,17,23,29,35-Hexa-*tert*-butyl-37,38,39,40,41-pentakis[(2-pyridylmethyl)oxy]-42-hydroxycalix[6]arene (12). A mixture of 1 (0.97 g, 1 mmol), NaH (1.8 g, 75 mmol), and PicCl·HCl (4.92 g, 30 mmol) in anhydrous DMF (30 mL) was reacted as previously described for the preparation of 11.[7c] The solid obtained by dilution with water was triturated with Et_2O (20 mL) to leave a residue from which 11 (61%) and 13 (8%) could be isolated by column chromatography. The Et_2O extract was concentrated and chromatographed on neutral alumina by eluting with cyclohexane–AcOEt (2:1 v/v), to afford 12 (71 mg, 5%) as a glassy solid: R_f = 0.56 (Al_2O_3, cyclohexane/AcOEt, 3:1); ^{1}H-NMR (DMSO-d_6/C_2Cl_4, dual tube, 384 K) δ 1.04, 1.21 [s, $C(CH_3)_3$, 18 H each], 1.13, 1.40 [s, $C(CH_3)_3$, 9 H each], 3.95 (s, $ArCH_2Ar$, 4 H), 4.03 (s, $ArCH_2Ar$, 8 H), 4.87 (s, OCH_2Py, 4 H), 4.97 (s, OCH_2Py, 2 H), 4.99 (s, OCH_2Py, 4 H), 6.80, 7.04, 7.19, 7.36 (d, J = 2.4 Hz, ArH, 8 H), 7.07, 7.14 (s, ArH, 4 H), 7.0–7.1 (m, 5-PyH, 5 H), 7.40–7.55 (m, 3-PyH + 4-PyH, 10 H), 7.65 (s, OH, 1 H), and 8.45–8.52 (m, 6-PyH, 5 H); ^{13}C-NMR ($CDCl_3$, 298 K) δ 31.06 (t, $ArCH_2Ar$), 31.17, 31.28, 31.63 [q, $C(CH_3)_3$], 34.00 [s, $C(CH_3)_3$], 74.94, 75.21 (t, OCH_2Py), 121.43, 121.60, 121.87, 122.27, 124.79, 125.44, 126.00, 126.25, 126.65 (d), 132.55, 132.84 (s, bridgehead-C), 136.52, 136.62 (d, 4-Py) 141.69, 145.95, 146.22 (s), 148.18 (d, 6-Py), 148.31, 148.60 (d, 6-Py), 150.76, 151.80, 152.90 (s), 157.16, and 157.55 (s, 2-Py); FAB (+) MS m/z 1428 (100, MH$^+$). Anal. Calcd for $C_{96}H_{109}N_5O_6$: C, 80.69; H, 7.69; N, 4.90. Found: C, 80.35; H, 7.84; N, 4.86.

5,11,17,23,29,35-Hexa-*tert*-butyl-37,38,39,40,41,42-hexakis-[(2-pyridylmethyl)oxy]calix[6]arene (13). A slight modification of the procedure reported by Shinkai[8] was used. A mixture of *p-tert*-butylcalix[6]arene (1) (0.486 g, 0.5 mmol), PicCl·HCl (2.3 g, 14 mmol), and anhydrous K_2CO_3 (3.86 g, 28 mmol) in dry DMF (25 mL) was stirred at 70 °C for 20 h. After cooling, the mixture was diluted with water to give a precipitate which was collected by filtration and dried. The solid was triturated with cold MeOH (15–20 mL) to remove pentaether 12 (4%), leaving almost pure 13 (0.61 g, 81%). It was dissolved in $CHCl_3$ (25 mL) and passed through a short column (neutral Al_2O_3, eluent cyclohexane–AcOEt, 2:1) to afford 0.54 g (71%) of a white powder: mp >300 °C (lit.[8] mp >300 °C); R_f = 0.32 (Al_2O_3, cyclohexane–AcOEt, 2:1); ^{1}H-NMR (DMSO-d_6, 384 K) δ 1.06 [s, $C(CH_3)_3$, 54 H], 3.89 (s, $ArCH_2Ar$, 12 H), 4.85 (s, OCH_2Py, 12 H), 6.93 (m, 5-PyH, 6 H), 7.03 (s, ArH, 12 H), 7.23 (d, J = 7.6 Hz, 3-PyH, 6 H), 7.37 (m, 4-PyH, 6 H), and 8.32 (d, J = 4.5 Hz, 6-PyH); ^{13}C-NMR ($CDCl_3$, 295 K) δ 30.06, 32.20 32.44 (t, $ArCH_2Ar$), 31.13, 31.46, 31.64 [q, $C(CH_3)_3$], 33.87, 34.03, 34.13 [s, $C(CH_3)_3$], 72.87, 74.66, 75.36 (t, OCH_2Py), 120.78 (d), 121.94 (s), 122.23, 123.76, 123.88, 125.58, 125.76 (d), 126.51 (s), 127.25 (d), 127.58 (s), 127.89 (d), 132.51, 132.66, 133.11, 134.67 (s), 136.51, 137.62 (d, 4-Py), 142.80, 143.03, 145.44 (s), 146.16 (d, 6-Py), 146.54, 146.70 (s), 148.76 (d, 6-Py), 148.98, 149.17, 151.54, 152.42, 152.71 (s), 157.08, 158.04, and 158.71 (s, 2-Py); FAB (+) MS m/z 1520 (100), 1519 (88, MH$^+$).

Partial Alkylation of 1 with PicCl·HCl and K_2CO_3 in DMF. A stirred mixture of 1 (0.97 g, 1 mmol), PicCl·HCl (2 mmol), and K_2CO_3 (0.55 g, 4 mmol) in anhydrous DMF (25 mL) was heated in an oil bath at 60 °C for 24 h. The mixture was diluted with water (80 mL), and the resulting precipitate was collected by filtration and dried. The crude product was dissolved in $CHCl_3$ and purified by column chromatography (SiO_2, a gradient of AcOEt in cyclohexane) to afford the following fractions.

Fraction A gave **5,11,17,23,29,35-hexa-*tert*-butyl-37-[(2-pyridylmethyl)oxy]-38,39,40,41,42-pentahydroxycalix[6]arene (2)** (53 mg, 5%): mp >260 °C dec; R_f = 0.82 (cyclohexane–AcOEt, 2:1); ^{1}H-NMR ($CDCl_3$, 295 K) δ 1.08, 1.15 [s, $C(CH_3)_3$), 9 H each], 1.19, 1.21 [s, $C(CH_3)_3$, 18 H each], 3.43–3.54 (m, $ArCH_2Ar$, 6 H), 3.90 (d, J = 13.9 Hz, $ArCH_2Ar$, 2 H), 4.09 (d, J = 14.1 Hz, $ArCH_2Ar$, 2 H), 4.38 (d, J = 13.7 Hz, $ArCH_2Ar$, 2 H), 5.26 (s, OCH_2Py, 2 H), 6.97 (s, ArH, 2 H), 7.03–7.09 (m, ArH, 10 H), 7.26 (bt, J = 5.6 Hz, 5-PyH, 1 H), 8.08 (m, 3-PyH + 4-PyH, 2 H), 8.57 (d, J = 4.5 Hz, 6-PyH, 1 H), and 9.53 (bs, OH, 5 H); ^{13}C-NMR ($CDCl_3$, 295 K) δ 31.24, 31.42, 31.58, [q, $C(CH_3)_3$], 32.41, 32.68, 33.24 (t, $ArCH_2Ar$), 33.96, 34.27 [s, $C(CH_3)_3$], 77.91 (t, OCH_2Py), 121.49, 123.18 (d, 3,5-Py), 125.55, 126.01, 126.30 (d, Ar), 126.77, 126.93, 127.47, 127.67, 132.41 (s, bridgehead-C), 137.93 (d, 4-Py), 143.73, 144.57, 146.58, 148.07 (s), 149.08 (d, 6-Py), 149.29, 149.75 (s), and 156.77 (s, 2-Py). FAB (+) MS m/z 1064 (100, MH$^+$). Anal. Calcd for $C_{72}H_{89}NO_6$: C, 81.24; H, 8.43; N, 1.31. Found: C, 80.94; H, 8.33; N, 1.12.

Fraction B provided **5,11,17,23,29,35-hexa-*tert*-butyl-37,38-bis[(2-pyridylmethyl)oxy]-39,40,41,42-tetrahydroxycalix[6]arene (3)** (185 mg, 16%): mp 202–203 °C; R_f = 0.75 (cyclohexane–AcOEt, 2:1); ^{1}H-NMR ($CDCl_3$, 295 K) δ 1.13, 1.29, 1.32 [s, $C(CH_3)_3$, 18 H each], 3.33, 3.87 (AB q, J = 14.1 Hz, $ArCH_2Ar$, 2 H), 3.46, 4.11 (AB q, J = 14.1 Hz, $ArCH_2Ar$, 4 H), 3.47, 4.79 (AB q, J = 13.6 Hz, $ArCH_2Ar$, 2 H), 3.50, 4.70 (AB q, J = 15.3 Hz, $ArCH_2Ar$, 4 H), 4.54, 5.29 (AB q, J = 13.6 Hz, OCH_2Py, 4 H), 6.9–7.2 (m, ArH + 5-PyH, 14 H), 7.49 (d, J = 7.6 Hz, 3-PyH, 2 H) 7.68 (dt, J = 7.7, 1.5 Hz, 4-PyH, 2 H), and 8.48 (d, J = 4.9 Hz, 2 H); ^{13}C-NMR ($CDCl_3$, 295 K) δ 29.52, 30.76, 32.75, 33.13 (t, $ArCH_2Ar$), 31.13, 31.38, 31.59 [q, $C(CH_3)_3$], 32.38, 33.97, 34.25 [s, $C(CH_3)_3$], 74.19 (t, OCH_2Py), 121.70, 122.43 (d, 3,5-Py), 124.34, 125.63, 126.08, 126.25 (d), 127.50 (s, bridgehead-C), 127.87 (d), 132.36, 133.75 (s, bridgehead-C), 137.13 (d, 4-Py), 143.09, 143.42, 146.74 (s), 147.78 (d, 6-Py), 147.98, 149.10, 151.23 (s), and 158.50 (s, 2-Py); FAB (+) MS m/z 1155 (100, MH$^+$). Anal. Calcd for $C_{78}H_{94}N_2O_6$: C, 81.07; H, 8.20; N, 2.42. Found: C, 81.10; H, 8.52; N, 2.54.

Fraction C yielded the regioisomer **5,11,17,23,29,35-hexa-*tert*-butyl-37,40-bis[(2-pyridylmethyl)oxy]-38,39,41,42-tetrahydroxycalix[6]arene (5)** (140 mg, 12%): mp >300 °C; R_f = 0.67 cyclohexane–AcOEt, 2:1); ^{1}H-NMR ($CDCl_3$, 295 K) δ 1.22 [s, $C(CH_3)_3$, 36 H], 1.26 [s, $C(CH_3)_3$, 18 H], 3.76 (s, $ArCH_2Ar$, 4 H), 3.79, 4.17 (AB q, J = 12.5 Hz, $ArCH_2Ar$, 8 H), 4.94 (bs, OCH_2Py, 4 H), 7.02, 7.07 (d, J = 2.3 Hz, ArH, 4 H each), 7.18 (bs, ArH, 4 H), and 6.69, 6.81, 6.92, 7.97 (bs, PyH, 2 H each); ^{1}H-NMR (C_2Cl_4/$CDCl_3$, 1:1 v/v, 360 K) δ 1.19 [s, $C(CH_3)_3$, 36 H], 1.22 [s, $C(CH_3)_3$, 18 H], 3.78 (s, $ArCH_2Ar$, 4 H), 3.94 (bs, $ArCH_2Ar$, 8 H), 4.82 (s, OCH_2Py, 4 H), 6.96, 7.02 (d, J = 2.4 Hz, ArH, 4 H each), 7.08 (s, ArH, 4 H), 6.7–7.1 (bm, 3,4,5-PyH, 6 H), and 8.17 (bs, 6-PyH, 2 H); ^{13}C-NMR (C_2Cl_4/$CDCl_3$, 1:1 v/v, 350 K) δ 29.83, 32.36 (t, $ArCH_2Ar$), 31.67 [q, $C(CH_3)_3$], 32.76, 33.96 [s,

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$C(CH_3)_3$], 77.50 (t, OCH_2Py), 121.86, 122.46 (d, 3,5-Py), 125.64, 125.78, 126.43 (d), 126.74, 127.45, 127.74 (s, bridgehead-C), 133.21 (s), 137.03 (d, 4-Py), 142.69, 147.55 (s), 148.38 (d, 6-Py), 149.63 (s), and 156.88 (s, 2-Py); FAB (+) MS *m/z* 1155 (100, MH^+). Anal. Calcd for $C_{78}H_{94}N_2O_6$: C, 81.07; H, 8.20; N, 2.42. Found: C, 80.88; H, 8.26; N, 2.38.

Fraction D gave **5,11,17,23,29,35-hexa-*tert*-butyl-37,38,39-tris[(2-pyridylmethyl)oxy]-40,41,42-trihydroxycalix[6]arene (6)** (0.47 g, 38%): mp 222–225 °C; R_f = 0.56 (cyclohexane–AcOEt, 2:1); ^{1}H-NMR (CD_2Cl_2, 290 K) δ 0.86, 1.18 [s, $C(CH_3)_3$, 18 H each], 1.26, 1.38 [s, $C(CH_3)_3$, 9 H each], 3.40 (m, $ArCH_2Ar$, 8 H each), 4.25 (d, *J* = 16.7 Hz, $ArCH_2Ar$, 2 H), 4.65 (d, *J* = 14.7 Hz, $ArCH_2Ar$, 2 H), 4.81 (s, OCH_2Py, 6 H), 6.35, 6.86, 6.97, 7.01, 7.10, 7.36 (s, ArH, 2 H each), 7.1–7.8 (m, PyH, 9 H), 8.10 (d, *J* = 4.9 Hz, 6-PyH, 1 H), and 8.44 (d, *J* = 4.1 Hz, 6-PyH, 2 H); ^{1}H-NMR (DMSO-d_6, 355 K) δ 0.96, 1.17 [s, $C(CH_3)_3$, 18 H each], 1.08, 1.10 [s, $C(CH_3)_3$, 9 H each], 3.67, 3.88, 4.01 (bs, $ArCH_2$-Ar, 4 H each), 4.73 (s, OCH_2Py, 2 H), 4.96 (s, OCH_2Py, 4 H), 6.86, 6.93, 6.99, 7.30 (bs, ArH, 12 H), 7.2–7.8 (bm, PyH, 9 H), 8.46 and 8.57 (bs, 6-PyH, 3 H); ^{13}C-NMR ($CDCl_3$, 298 K) δ 30.20, 32.30, 32.53 (t, $ArCH_2Ar$), 31.23, 31.60, 31.70, 31.74 [q, $C(CH_3)_3$], 33.96, 34.02, 34.23, 34.38 [s, $C(CH_3)_3$], 72.96, 74.68, (t, OCH_2Py), 121.05, 122.05, 122.43, 123.98 (d, 3,5-Py), 125.70, 125.85 (d, Ar), 126.64 (s), 127.31 (d, Ar), 127.72 (s), 127.96 (d, Ar), 132.77, 133.19, 134.71 (s, bridgehead-C), 136.84, 137.77 (d, 4-Py), 142.91, 143.14 (s), 146.26 (d, 6-Py), 146.69, 146.82 (s), 148.67 (d, 6-Py), 149.12, 149.27, 151.64, 152.54 (s), 157.98, and 158.76 (s, 2-Py); FAB (+) MS *m/z* 1246 (100, MH^+). Anal. Calcd for $C_{84}H_{99}N_3O_6$: C, 80.92; H, 8.00; N, 3.37. Found: C, 81.30; H, 8.28; N, 3.42.

By using 4 equiv of PicCl·HCl and 8 equiv of K_2CO_3, the yield of 1,2- and 1,4-dialkylated regioisomers **3** and **5** decreased to 2–3%, while that of 1,2,3-trialkylated calix[6]arene **6** increased to 51%. The reaction gave also sym-tetraalkylated compound **11** (1%) and very small amounts (<1%) of **7** and **9**.

5,11,17,23,29,35-Hexa-*tert*-butyl-37,38,40-tris[(2-pyridylmethyl)oxy]-39,41,42-trihydroxycalix[6]arene (7): mp 155–158 °C; R_f = 0.44 (cyclohexane–AcOEt, 2:1); ^{1}H-NMR ($CDCl_3$, 335 K) δ 0.99, 1.00, 1.27, 1.28 [s, $C(CH_3)_3$, 9 H each], 1.20 [s, $C(CH_3)_3$, 18 H], 3.73 (, $ArCH_2Ar$, 2 H), 3.91, 3.96, 4.15 (bs, $ArCH_2$-Ar, 10 H), 4.69, 4.93, 4.95 (s, OCH_2Py, 6 H), 6.6–7.6 (m, ArH + PyH, 21 H), 8.28 (m, 6-PyH, 2 H), and 8.56 (d, *J* = 3.5 Hz, 6-PyH, 1 H); ^{13}C-NMR ($CDCl_3$, 340 K) δ 29.71 (t, $ArCH_2Ar$), 31.27, 31.30, 31.42, 31.58, 31.68 [q, $C(CH_3)_3$], 32.30 (t, $ArCH_2Ar$), 33.98, 34.15, 34.68, 34.96 [s, $C(CH_3)_3$], 75.25, 75.51, 75.57 (t, OCH_2Py), 121.61, 121.92, 122.24, 122.33, 122.85 (d, 3,5-Py), 124.95, 125.27, 125.49, 125.83, 126.34, 126.46, 126.80, 126.95, 127.34 (d, Ar), 132.52, 132.83 (s, bridgehead-C), 136.56, 136.91 (d, 4-Py), 142.40, 142.87, 146.97, 147.15, 147.30 (s), 148.22, 148.67 (d, 6-Py), 150.10, 150.84, 151.57 (s), 156.57, 156.74, and 156.91 (s, 2-Py); FAB (+) MS *m/z* 1246 (100 MH^+). Anal. Calcd for $C_{84}H_{99}N_3O_6$: C, 80.92; H, 8.00; N, 3.37. Found: C, 80.55; H, 8.12; N, 3.46.

5,11,17,23,29,35-Hexa-*tert*-butyl-37,38,39,40-tetrakis[(2-pyridylmethyl)oxy]-41,42-dihydroxycalix[6]arene (9): mp 154–156 °C; R_f = 0.17 (cyclohexane–AcOEt, 2:1); ^{1}H-NMR ($CDCl_3$, 360 K) δ 1.06, 1.07, 1.26 [s, $C(CH_3)_3$), 18 H each], 3.66, 4.08 (s, $ArCH_2Ar$, 2 H each), 3.79, 4.03 (bs, $ArCH_2Ar$, 4 H each), 4.59, 4.82 (s, OCH_2Py, 4 H each), 6.8–7.4 (m, ArH + PyH, 24 H), 8.15 (d, *J* = 4.3 Hz, 6-PyH, 2 H), and 8.43 (d, *J* = 4.2 Hz, 6-PyH, 2 H); ^{13}C-NMR ($CDCl_3$, 360 K) δ 27.00 29.67, 32.18 (t, $ArCH_2Ar$) 31.35, 31.69 [q, $C(CH_3)_3$], 33.99, 34.21 [s, $C(CH_3)_3$], 74.89, 76.43 (t, OCH_2Py), 121.33, 121.84, 122.09, 122.30 (d, 3,5-Py), 125.34, 125.65, 125.83, 125.95, 126.40, 126.70 (d, Ar), 126.88, 127.38, 132.72, 133.19, 133.57 (s, bridgehead-C), 136.43, 136.59 (d, 4-Py), 142.14, 146.61, 146.83 (s), 148.34, 148.84 (d, 6-Py), 150.34, 152.26, 152.99 (s), 157.49, and 158.35 (s, 2-Py); FAB (+) MS *m/z* 1337 (100, MH^+). Anal. Calcd for $C_{90}H_{104}N_4O_6$: C, 80.80; H, 7.84; N, 4.19. Found: C, 80.92; H, 7.95; N, 4.26.

Calix[6]arene **9** was obtained as the sole product (35%) by treatment of **5** with PicCl·HCl (1 equiv) in anhydrous DMF at rt in the presence of NaH for 16 h.

Partial Alkylation of 1 with PicCl·HCl and BaO/$Ba(OH)_2$. Compound **1** (1 mmol) was reacted with PicCl·HCl (2 mmol) and BaO (4 mmol)/$Ba(OH)_2$ (2 mmol) in DMF (25 mL) at 60 °C for 24 h. Usual workup gave a solid which was dissolved in a large volume of $CHCl_3$ and dried (Na_2SO_4). Evaporation of the solvent afforded crude **5**·Ba complex (80%) that was recrystallized from DMF to give **5**Ba·2DMF: ^{1}H-NMR ($CDCl_3$, 295 K) δ 1.07 [s, $C(CH_3)_3$, 18 H], 1.28 [s, $C(CH_3)_3$, 36 H], 2.89, 2.96 (s, Me_2NCHO, 6 H each) 3.24, 4.08 (AB q, *J* = 13.0 Hz, $ArCH_2Ar$, 4 H), 3.28, 4.27 (AB q, *J* = 12.9 Hz, $ArCH_2Ar$, 8 H), 5.37 (s, OCH_2Py, 4 H), 6.97, 7.06, 7.07 (s, ArH, 4 H each), 6.9–7.4 (m, 3,4,5-PyH, 6 H), 8.02 (s, Me_2NCHO, 2 H), and 8.30 (d, *J* = 4.5 Hz, 6-PyH, 2 H); FAB (+) MS *m/z* 1291 (3.4, MBa^+). Anal. Calcd for $C_{78}H_{92}BaN_2O_6$·2DMF·H_2O: C, 69.33; H, 7.48; N, 3.85. Found: C, 69.60; H, 7.47; N, 3.76.

Partial Alkylation of 1 with PicCl·HCl and K_2CO_3 in CH_3CN. A mixture of **1** (0.97 g, 1 mmol), PicCl·HCl (0.49 g, 3 mmol), and K_2CO_3 (0.83 g, 6 mmol) in CH_3CN (50 mL) was refluxed for 24 h. After cooling, the solvent was evaporated to give a residue which was partitioned between water and $CHCl_3$. The organic extract was washed with water, dried (Na_2SO_4), and concentrated. The product was dissolved in $CHCl_3$ and chromatographed (SiO_2 column, a gradient of AcOEt in cyclohexane as the eluent) to give in the order mono-O-alkylated **2** (<1%), di-O-alkylated **3** (8%), and **5** (11%), tri-O-alkylated **6** (35%), followed by small amounts (1–2%) of triethers **7** and **8** and tetraethers **11** and **9**. Fractions containing **7** and **8** were further purified by preparative TLC (cyclohexane–AcOEt, 3:1, eluted twice).

5,11,17,23,29,35-Hexa-*tert*-butyl-37,39,41-tris[(2-pyridylmethyl)oxy]-38,40,42-trihydroxycalix[6]arene (8): mp 201–203 °C; R_f = 0.29 (cyclohexane–AcOEt, 3:1); ^{1}H-NMR ($CDCl_3$, 360 K) δ 1.03, 1.20 [s, $C(CH_3)_3$, 27 H each], 3.91 (bs, $ArCH_2Ar$, 12 H), 4.88 (s, OCH_2Py, 6 H), 6.91, 7.00 (s, ArH, 6 H each), 7.23 (s, OH, 3 H), and 7.1–8.1 (m, PyH, 12 H); ^{13}C-NMR ($CDCl_3$, 360 K) δ 31.42, 31.69 [q, $C(CH_3)_3$], 32.08 (t, $ArCH_2Ar$), 34.30, 34.95 [s, $C(CH_3)_3$], 76.35 (t, OCH_2Py), 122.46, 122.67 (d, 3,5-Py), 125.85 (d, Ar), 127.58, 133.25 (s, bridgehead-C), 136.75 (d, 4-Py), 147.01 (s), 148.96 (d, 6-Py), 151.69 (s), and 159.23 (s, 2-Py); FAB (+) MS *m/z* 1246 (100 MH^+). Anal. Calcd for $C_{84}H_{99}N_3O_6$: C, 80.92; H, 8.00; N, 3.37. Found: C, 80.68; H, 8.13; N, 3.31.

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Supplementary Material Available: Table S1 listing selected ions and their relative abundances in the FAB (+) MS of compounds **2**, **3**, **5–9**, and **11–13** (1 page). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.