Study on the Alkylation of *p-tert*-Butylcalix[8]arene. Partially *O*-Alkylated Calix[8]arenes

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Reactions of *p-tert*-butylcalix[8]arene (**1**) with various alkylating agents, including *para*-substituted benzyl bromides, *tert*-butyl bromoacetate, and 2-chloro-*N*,*N*-dimethylacetamide, were carried out in THF–DMF in the presence of a base. With strong bases (NaH or BaO/$Ba(OH)_2$) octasubstituted derivatives were obtained, usually in good yield, while in the presence of weak bases (K_2CO_3 or CsF) more or less complicated reaction mixtures were obtained, wherefrom 1,3,5,7-tetraethers with C_4 symmetry were isolated in yields up to 49%. The eight equivalent $ArCH_2Ar$ groups of these compounds give rise to a singlet in the ^{1}H-NMR spectrum, indicating a conformational freedom of the macrocycle, as confirmed by VT-NMR studies. The origin of the 1,3,5,7-regioselectivity can be explained, assuming that alkylation proceeds *via* a sequence of alternating monodeprotonation and alkylation steps. In each individual monodeprotonation step, those phenoxide monoanions are formed preferentially which are stabilized by two flanking hydrogen bonds. However, this cannot be the whole explanation. In fact, when methyl iodide was used as the electrophile in the reaction with **1**, the main products were the 1,2,4-trimethoxy and 1,2,3,4-tetramethoxy derivatives, whereas the 1,3,5,7-tetramethyl ether was not detected in the reaction mixture. This finding leads us to believe that in the reaction with MeI some factor other than stability of oxyanions prevails, possibly the molecular dimension of the electrophile. This seems to be confirmed by the observation that *n*-butyl iodide, of intermediate dimension between MeI and arylmethyl bromides, gives alkylation products typical of both reaction courses.

Introduction

In the last decade the chemistry of calixarenes has been investigated in many directions using essentially the smallest members of this class of macrocyclic compounds, calix[4]arenes.[1] As a result of these efforts, synthetic procedures for their regio- and stereoselective (conformation-selective) functionalization at either the lower[2] or upper rim[3] have been established. Recent extensions of these studies to calix[6]arenes have revealed a rather different behavior, hardly to be foreseen on the basis of knowledge of the chemistry of the smaller analogoues.[4,5] Nevertheless, clear guidelines are now emerging for their regioselective alkylation at the lower rim.[4,5] Still less is known about calix[8]arenes.

Due to the large dimension of their annulus, calix[8]-arenes have a certain propensity to give 1:2 host–guest[6] or bimetallic complexes.[7] For the same reason they appear particularly attractive for the synthesis of molecular receptors for compounds of biomedical interest, such as peptides,[8] sugars,[9] and pharmaceuticals.[10] In order to obtain effective molecular receptors from calix[8]arenes, priority should be given to two points of considerable interest: (i) selective introduction of suitable functional groups and (ii) reduction of the conformational mobility of the macrocycle. With reference to the first point, we have started an investigation aimed at the selective functionalization at the lower rim of *p-tert*-butylcalix[8]-

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Table 1. Compound Yield in the Alkylation of *p-tert*-Butylcalix[8]arene in Dry THF/DMF (10:1) at Reflux

entry	base (equiv)	electrophile (equiv)	time (h)	isolated compd (%)
1	BaO (16)/$Ba(OH)_2$ (8)	*p-t*-Bu-BnBr (8)	72	**3a** (80)
2	NaH (16)	BnBr (8)	8	**3b** (90)
3	NaH (16)	*p*-CN-BnBr (8)	6	**3c** (85)
4	BaO (16)/$Ba(OH)_2$ (8)	*p*-NO_2-BnBr (8)	6	**3d** (90)
5	K_2CO_3 (32)	*p*-CN-BnBr (32)	12	**3c** (95)
6	CsF (16)	*p-t*-Bu-BnBr (8)	96	**3a** (90)
7	K_2CO_3 (16)	*p-t*-Bu-BnBr (8)	20	**4a** (41)
8	K_2CO_3 (16)	*p*-Me-BnBr (8)	6	**4b** (23)
9	K_2CO_3 (16)	BnBr (8)	6	**4c** (20)
10	K_2CO_3 (8)	*p*-CN-BnBr (4)	9	**4d** (10)
11	K_2CO_3 (8)	*p*-NO_2-BnBr (4)	23	**4e** (15)
12	CsF (16)	*p-t*-Bu-BnBr (8)	16	**4a** (43)
13	CsF (16)	*p*-Me-BnBr (8)	12	**4b** (38)
14	CsF (16)	BnBr (8)	13	**4c** (28)
15	CsF (8)	*p*-CN-BnBr (4)	94	**4d** (20)
16	CsF (8)	*p*-NO_2-BnBr (4)	31	**4e** (45)
17	CsF (8)	*p*-Br-BnBr (4)	32	**4f** (28)
18	CsF (16)	$BrCH_2CO_2$-*t*-Bu (8)	7	**4g** (49)
19	CsF (16)	$BrCH_2CONMe_2$ (8)	16	**4h** (20)
20	K_2CO_3 (16)	MeI (8)	7	**5** (68)
21	CsF (16)	MeI (8)	22	**5** (30), **7** (21)
22	K_2CO_3 (16)	*n*-BuI (8)	72	**4i** (30), **5a** (25)
23	CsF (16)	*n*-BuI (8)	15	**4i** (20), **5a** (15)

arene, since the large majority of the reported *O*-substituted derivatives of this compound are octasubstituted.[11] The few known partially *O*-substituted derivatives, apart from the trivial cases of monosubstitution, have uncertain substitution patterns.[12-13]

As the natural extension of a preliminary paper from our group,[14] we report here full experimental data on the synthesis and characterization of several *p-tert*-butylcalix[8]arenes partially substituted with different groups. In addition, a mechanism that explains their preferential formation is discussed.

Results and Discussion

In the present study *p-tert*-butylcalix[8]arene (**1**) has been alkylated using *para*-substituted benzyl bromides (*p*-X-BnBr), *tert*-butyl bromoacetate, 2-chloro-*N,N*-dimethylacetamide, methyl iodide, and *n*-butyl iodide in THF–DMF (10:1). The reactions were carried out at reflux temperature in the presence of a base (NaH, BaO/$Ba(OH)_2$, K_2CO_3, Na_2CO_3, or CsF). The effect of each base is discussed separately in the sequel and the results are reported in the synoptical Table 1. Finally, the reactions with alkyl iodides are treated separately in view of their different course.

Alkylation of *p-tert*-Butylcalix[8]arene (1) in the Presence of NaH or BaO/$Ba(OH)_2$. Arylmethylation of **1** in the presence of excess NaH or BaO/$Ba(OH)_2$ with 8 equiv of *p*-X-benzyl bromide afforded octabenzyl derivatives **3a–d** in almost quantitative yields (Scheme 1 and Table 1). The ^{1}H-NMR spectra of these compounds display

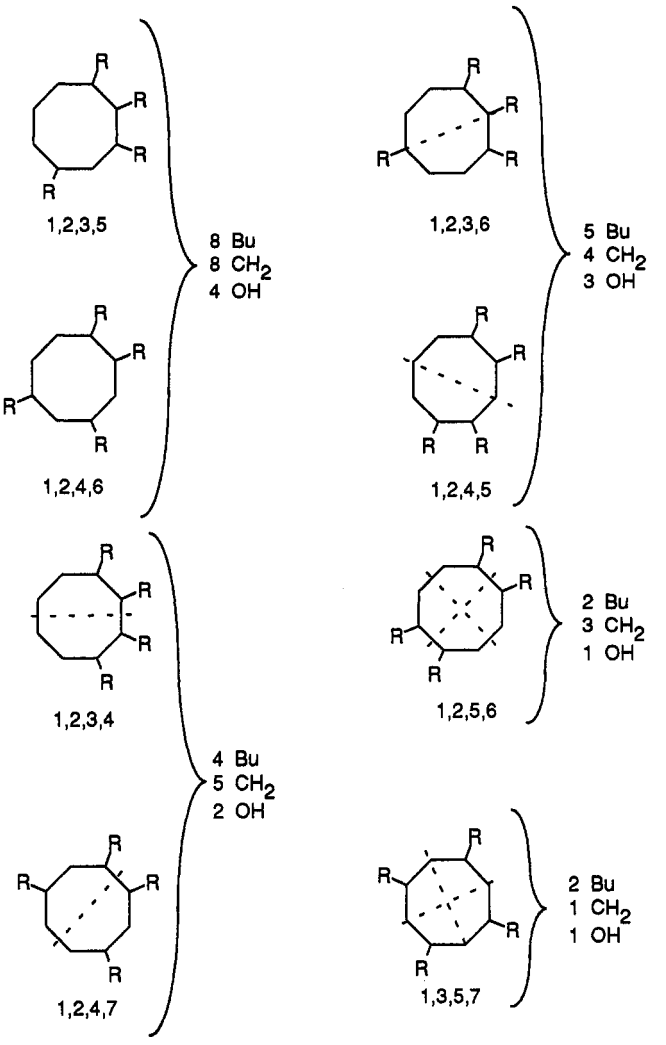

Figure 1. Schematic representation of the eight possible tetrasubstituted regioisomers of a calix[8]arene. The number of expected NMR resonances, assuming conformational mobility, for *t*-Bu, $ArCH_2Ar$, and OH groups, are reported in each case.

only a few resonances due to the equivalence of the eight arylbenzyloxy units and to the conformational flexibility of the macrocycle that is testified by the appearance of the bridging methylene signals as singlets. In some instances the flexibility is somewhat reduced, as indicated by the broadening of the signals in question. Accordingly, the ^{13}C-NMR spectra show the expected signals for the repeating unit of the macrocycle, with the bridging methylene in the range 30.2–30.4 ppm, the *tert*-butyl group at 31.2–31.3 and 34.0–34.1 ppm, and the oxymethylene carbon at 73.2–74.4 ppm.

The use of limiting amounts of base and alkylating agent invariably led to very complex reaction mixtures containing unreacted *p-tert*-butylcalix[8]arene. Due to the severe tailing of **1**, the chromatographic separation was always very difficult and only minute amounts of impure products could be isolated.

Alkylation of 1 in the Presence of K_2CO_3. The use of K_2CO_3 led to reaction mixtures from which 1,3,5,7-tetrabenzyl derivatives **4a–e** (which on TLC plates usually are the slowest-migrating compounds) were isolated by chromatography (Scheme 1).[14] These tetraethers are easily recognized from the appearance in their ^{1}H-NMR spectra of two 1:1 signals for the *tert*-butyl groups of the

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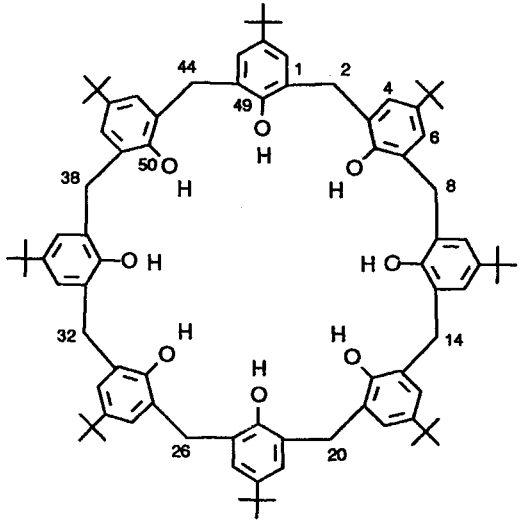
Scheme 1



1

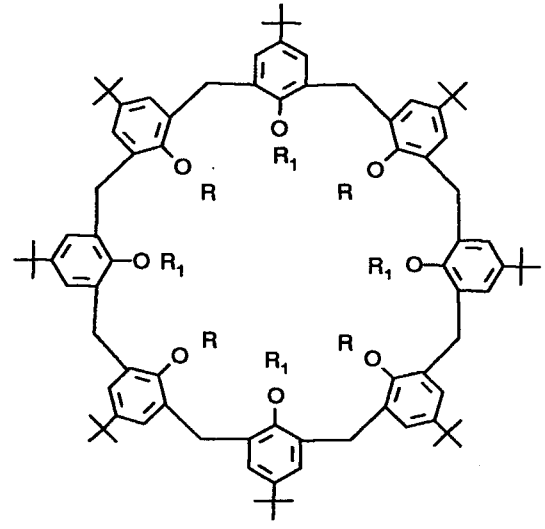
+ R-X

2a-i

THF/DMF
Reflux

Base
see Table I

a *p*-*t*-Bu-BnBr
b *p*-Me-BnBr
c BnBr
d *p*-Br-BnBr
e *p*-CN-BnBr
f *p*-NO_2-BnBr
g $BrCH_2COO$-*t*-Bu
h $ClCH_2CONMe_2$
i *n*-BuI



3a-d

R = R_1

a *p*-*t*-Bu-Bn
b Bn
c *p*-CN-Bn
d *p*-NO_2-Bn

4a-i, R = H

R_1

a *p*-*t*-Bu-Bn
b *p*-Me-Bn
c Bn
d *p*-NO_2-Bn
e *p*-CN-Bn
f *p*-Br-Bn
g CH_2COO-*t*-Bu
h CH_2CONMe_2
i *n*-Bu

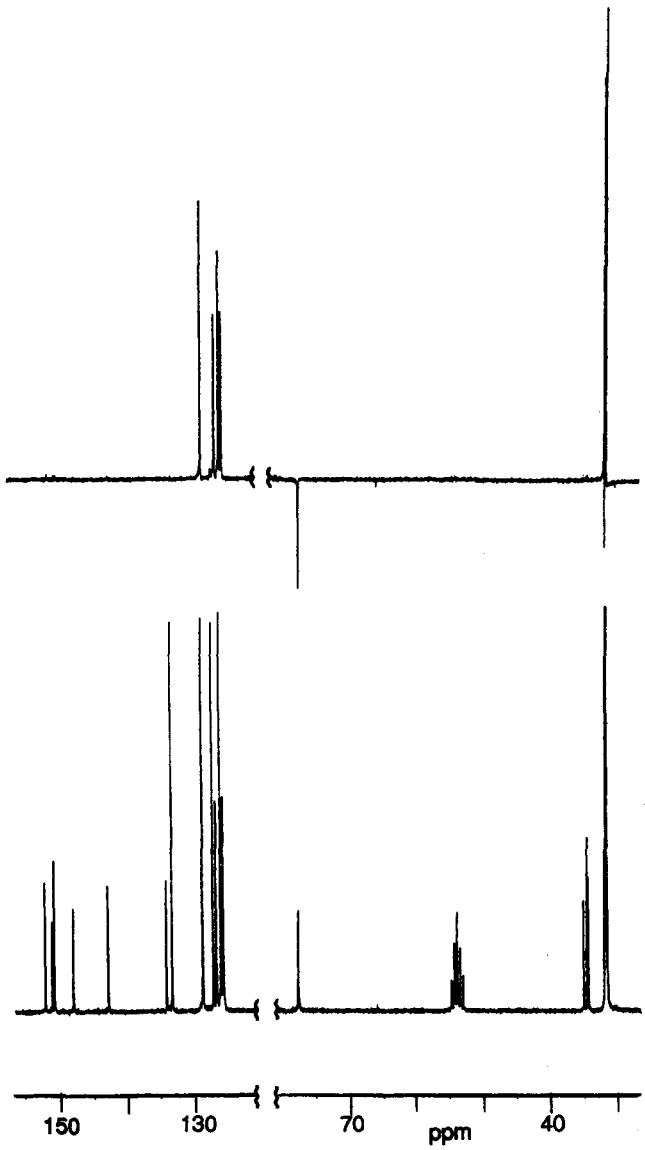
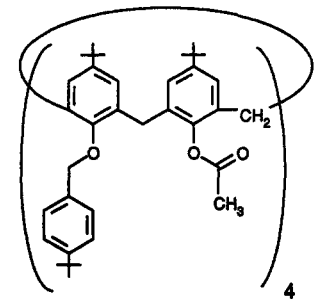


Figure 2. DEPT (top) and BB-decoupled (bottom) ^{13}C-NMR spectra of 1,3,5,7-tetraether **4a** (CD_2Cl_2).

calix[8]arene skeleton and from the presence of only a singlet for the $ArCH_2Ar$. In fact, among the eight tetrasubstituted regioisomers of a calix[8]arene (Figure 1), only the one with 1,3,5,7-pattern is expected to give rise to the above-mentioned NMR features, if complete conformational freedom is assumed. In VT-^{1}H-NMR studies a coalescence, related to the transition between frozen conformation(s) and free conformational interconversion, was observed at low temperatures.[15] The ^{13}C-NMR spectra are fully compatible with the highly symmetrical structures and show the expected resonances for two symmetrically linked *p-tert*-butylaryl units as exemplified by the spectrum of **4a** shown in Figure 2. The single $ArCH_2Ar$ signal occurs between 29.1 and 31.7 ppm, in some instances obscured by one of the two intense *tert*-butyl resonances (31.1–31.7 ppm). The oxymethylene carbon resonates in the range 77.4–75.6 ppm and accidental isochrony with $CDCl_3$ signals is also observed in some cases.

(15) In the case of compound **4a** the coalescence occurred at 240 K in $CDCl_3$ solution and, since spectra at low temperatures were not well-resolved, only a rough value (ca. 11.6 kcal/mol) for the energy barrier could be evaluated, using a maximum signal separation of 60 Hz for the *tert*-butyl signals.

1,3,5,7-Tetraethers **4a–e** are possible precursors for the synthesis of octasubstituted calix[8]arenes with alternating groups at the lower rim. Thus, **4a** by overnight treatment with Ac_2O/Py is quantitatively converted into the tetraacetyl derivative **4aAc**. This synthetic route could be further expanded by removal of benzyl groups upon treatment with debenzylating agents (Me_3SiBr) and reintroduction of new functional groups leading, in principle, to heteroditopic hosts.[16]



4

4aAc

Scrutiny of Table 1 (entries 7–11) indicates that the overall yield of the 1,3,5,7-tetrabenzyl ether is somehow related to the electronic effect of the substituent at the para position of the benzyl bromide. In fact, benzyl bromides bearing electron-withdrawing groups (CN, NO_2) afford very complex reaction mixtures, from which 1,3,5,7-tetraethers can be isolated, albeit in scanty yields (10–15%), only when limiting amounts of base and electrophile are used. This behavior can be explained by considering that an increase of electron-withdrawing effect results in increased reactivity and loss of regioselectivity. Conversely, electron-donating groups reduce the reactivity of the electrophile that thus became more selective. The very reactive α-haloacetyl derivatives under the same conditions afford intractable reaction mixtures.

Alkylation of 1 in the Presence of CsF. On the basis of the above consideration, we concluded that the strength of the base should have a similar effect, weak bases increasing the regioselectivity of the reaction. Indeed, the use of CsF, considered weaker than K_2CO_3,[17] resulted in a general increase of the yields of 1,3,5,7-tetrasubstituted derivatives (Table 1, entries 12–19).[18] This effect was particularly evident with the strongest electrophiles, *p*-NO_2-BnBr and *p*-CN-BnBr, for which the yields rose from 10–15% to 20–45%. Furthermore, in the case of *tert*-butyl bromoacetate and 2-chloro-*N,N*-dimethylacetamide, the reaction mixtures, intractable when K_2CO_3 was used, were easily separated when the reactions were carried out in the presence of CsF, and 1,3,5,7-tetraester **4g** and the 1,3,5,7-tetraamide **4h** were isolated in moderate yield (49 and 20%, respectively).

It should be noted that the signals in the ^{1}H-NMR spectrum of tetraamide **4h** are significantly broader than in the other 1,3,5,7-derivatives, indicating a reduced conformational flexibility of the macrocycle. This is

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(17) See for instance ref 4d, and, for a general discussion on the use of fluorides as bases, Clark, J. H. *Chem. Rev.* **1980**, *80*, 429.

(18) A similar yield-increasing effect by using CsF instead of K_2CO_3 was also observed in the direct monoalkylation of calix[4]arenes: Groenen, L. C.; Ruël, B. H. M.; Casnati, A.; Verboom, W.; Pochini, A.; Ungaro, R.; Reinhoudt, D. N. *Tetrahedron* **1991**, *47*, 8379.

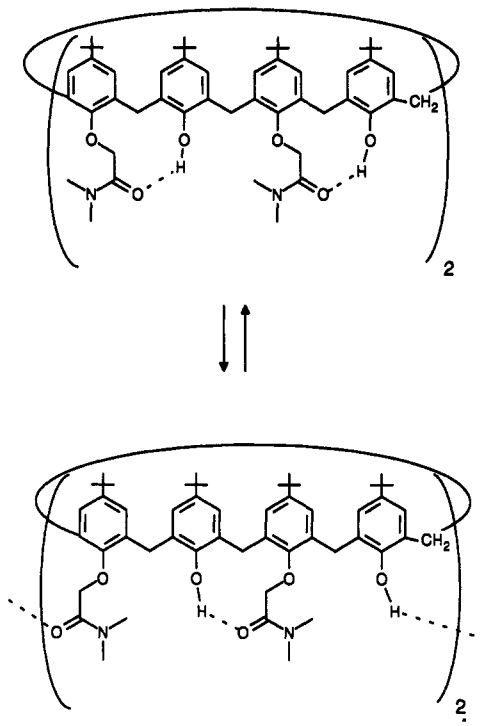


Figure 3. Equilibrium between clockwise and anticlockwise oriented H-bonds in 1,3,5,7-tetraamide **4h**.

attributable to the presence of intramolecular hydrogen bonds between hydroxyl and amide groups, as deduced from the downfield postion (9.11 ppm) of the OH signal in the ^{1}H-NMR spectrum. At room temperature these hydrogen bonds can flip rapidly, in the NMR time scale, between a clockwise and anticlockwise orientation (Figure 3). Freezing of this motion makes observable the new cycles determined by the hydrogen bonds. Accordingly, the low-temperature spectrum of **4h** shows an OH signal further shifted to 9.37 ppm, two AB systems (4.08 and 3.76 ppm, J = 16.8 Hz; 3.85 and 3.43 ppm, J = 14.5 Hz) corresponding to $ArCH_2Ar$ groups *exo* or *endo* with respect to each newly-formed cycle, and four broad aromatic signals (7.20, 6.99, 6.94, and 6.67 ppm, 4 H each). The *tert*-butyl and *N*-Me signals are only marginally affected. The oxymethylene singlet becames a narrow AB system (4.70 and 4.66 ppm, J = 10.0 Hz) passing through a coalescence temperature (T_c) of 268 K from which an energy barrier of 13.4 kcal/mol was determined. Above T_c the ^{1}H-NMR spectra of **4h** are compatible with an average D_{4h} structure, that upon cooling becames frozen in a C_4 conformation that should exists as an enantiomeric pair.

Proposed Mechanism for the Alkylation of 1 in the Presence of Weak Bases. As a general conclusion from the above experimental data, the origin of the 1,3,5,7-regioselectivity has to be ascribed to the discriminating ability of the electrophiles toward anionic intermediates of different stability and appears to be independent of metal template effect. Indeed, the reaction outcome was not modified significantly when Na_2CO_3 was used instead of K_2CO_3, the only difference being a longer reaction time possibly due to the lower solubility of the former.

By analogy with the alkylation mechanism proposed for calix[4]arenes (that in similar conditions afford distal disubstituted derivatives),[2,3a,19] it is plausible that for calix[8]arenes in the presence of weak bases only a monoanion can be formed, which undergoes subsequent alkylation. From the monoalkylated species four different monoanions can be derived by removal of a proton from each of the positions 2,3,4, or 5. If position 2 was involved, the oxyanion would be stabilized by a single hydrogen bond and accordingly its concentration in the reaction mixture would be negligible.[20] Instead, the other three possible monoanions, all of them stabilized by two hydrogen bonds, would form preferentially and thus lead to the 1,3-, 1,4-, and 1,5-disubstituted derivatives (Figure 4). Following the same line of reasoning, two trisubstituted compounds are to be expected, namely the 1,3,5-(from both 1,3- and 1,5-disubstituted compounds) and the 1,3,6-isomer (from both 1,3- and 1,4-disubstituted isomers). The 1,3,6-derivative, which can only give monoanions stabilized by a single hydrogen bond, should not undergo further alkylation,[21] whereas the 1,3,5-trisubstituted isomer, through a monoanion stabilized by two hydrogen bonds, could evolve giving the 1,3,5,7-tetrasubstituted compound (Figure 4). Further reaction, necessarily implying the formation of nonstabilized anions, has low a probability and occurs slowly, giving, after prolonged time, the octasubstituted derivative.[22]

Alkylation of 1 with Methyl Iodide. The above-outlined alkylation mechanism should be independent of the nature of the alkylating agent. However, when we used methyl iodide as the electrophile, a different behavior was observed.

With K_2CO_3 as the base, a trimethoxy derivative, $C_{91}H_{118}O_8$ (elemental analysis and FAB(+) MS) was obtained in 68% isolated yield (Table 1, entry 20).[23] This compound was assigned structure **5** (Chart 1) on the basis of the following considerations. The ^{1}H-NMR spectrum contained three discrete MeO signals (3.76, 3.84, and 3.88 ppm) and six *tert*-butyl signals (1.03, 1.07, 1.22, 1.23, 1.24, and 1.25 ppm) in a 1:1:1:1:1:3 ratio, indicating an asymmetric substitution pattern. The ^{13}C-NMR spectrum, due to extensive overlapping, showed only 53 sufficiently resolved peaks out of the expected 91. Among them, three OMe signals at 61.7, 62.0, and 62.2 ppm, and 16 lines between 140 and 155 ppm (characteristic of aromatic quaternary carbons bearing oxygen or *tert*-butyl group) were clearly seen (Figure 5), indicating an asymmetric trisubstitution. At this point two alternative structures, namely 1,2,4-trimethyl ether **5** and its 1,2,5-isomer **6** (Chart 1), had to be considered since among the five regioisomers of a trisubstituted calix[8]arene, only these are asymmetric (Figure 6). The final choice was made on the following basis. It is well documented that in the parent calixarenes the contiguous hydroxyls from a very strong intramolecular "circular" hydrogen bond that stabilizes the cone, pinched cone, and pleated-loop conformations of calix[4]arene, calix[6]arene, and calix[8]arene, respectively.[1] This is reflected in the downfield shift of the OH signals in the ^{1}H-NMR spectrum.[1,20]

(19) Dijkstra, P. J.; Brunink, J. A. J.; Bugge, K.-E.; Reinhoudt, D. N.; Harkema, S.; Ungaro, R.; Ugozzoli, F.; Ghidini, E. *J. Am. Chem. Soc.* **1989**, *111*, 7565. Grootenhuis, P. D. J.; Kollman, P. A.; Groenen, L. C.; Reinhoudt, D. N.; van Hummel, G. J.; Ugozzoli, F.; Andreetti, G. D. *J. Am. Chem. Soc.* **1990**, *112*, 4165.

(20) Araki, K.; Iwamoto, K.; Shinkai, S.; Matsuda, T. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 3480.

(21) Products from some reaction mixtures were also isolated having ^{1}H-NMR spectra commensurate with a 1,3,6-trisubstitution, but due to the ambiguity with 1,2,3- and 1,3,5-substitution patterns (see Figure 6) they await definitive structural characterization.

(22) For instance, exhaustive benzylation with *p-tert*-Bu-BnBr in the presence of CsF required 96 h (entry 6, Table 1).

(23) The methylation products are sparingly soluble and difficult to separate by column chromatography. Therefore, preparative TLC was used in their purification.

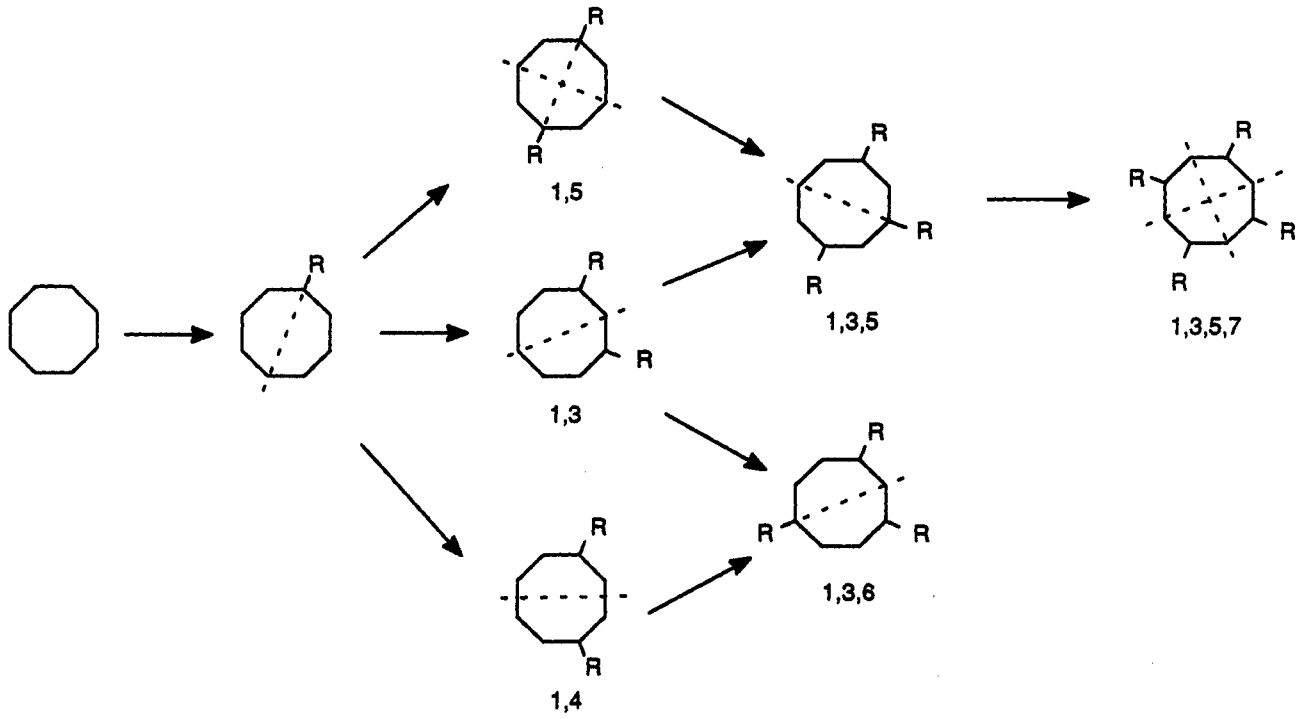


Figure 4. Proposed mechanism for the alkylation of **1** in the presence of weak bases.

Typical values of *p-tert*-butylcalix[n]arene[20] are 10.34 ppm for $n = 4$; 10.50 ppm for $n = 6$; and 9.60 ppm for $n = 8$. Shinkai has pointed out[20] that in partially *O*-substituted calix[4]arenes, isolated hydroxyls ("non-hydrogen-bonded") resonate at 6.20–7.20 ppm, while OH groups involved in an H-bond by only one side ("half-hydrogen-bonded") resonate around 8.5 ppm. Finally, "full-hydrogen-bonded" hydroxyls resonate at values close to that of the parent unsubstituted calix[4]arene.[24,25] Consequently, the presence of five discrete OH resonances (D_2O exchangeable) of the same relative intensity in the ^{1}H-NMR spectrum of **5** (Figure 5) at 9.10 and 9.08 ("fully-bonded"), 8.86 and 8.74 ("half-bonded"), and 7.67 ppm ("non-bonded") is clear-cut evidence of the assigned structure.[26,27]

When CsF was used as the base in the methylation of **1**, besides **5**, an additional compound of lower R_f was isolated by TLC in 21% yield (Table 1, entry 21). The

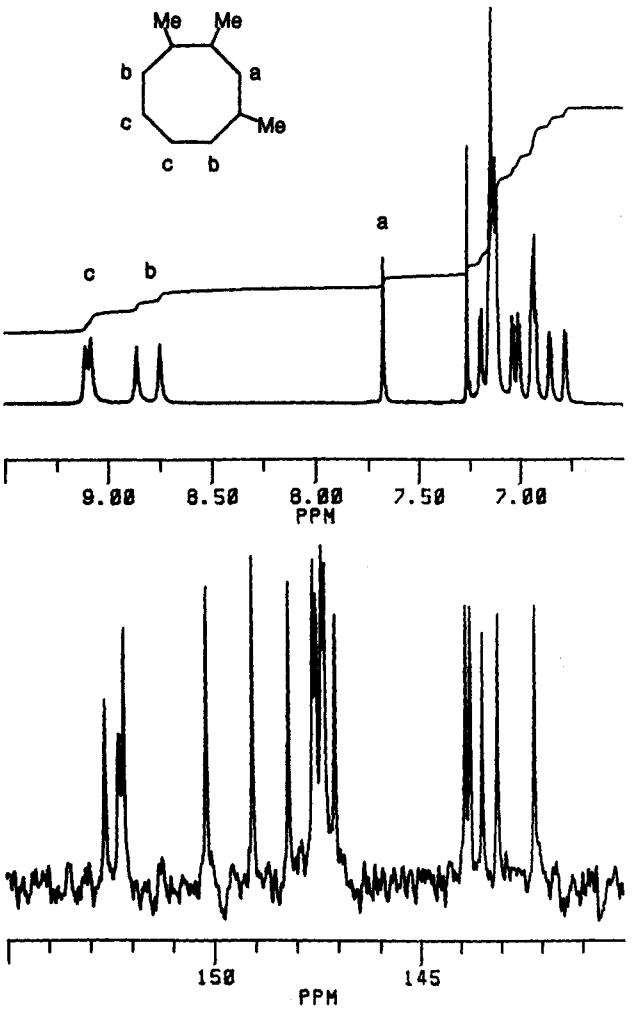


Figure 5. Key NMR spectral features of 1,2,4-trimethoxy derivative **5**: top, aromatic and OH region of ^{1}H NMR spectrum; bottom, region of ^{13}C-NMR spectrum showing the resonances of aromatic carbons bearing oxygen or *tert*-butyl.

(24) For example, the OH chemical shift of the 4 partially methylated *p-tert*-butylcalix[4]arenes are (ppm)[20] 9.54 (2 H) and 10.13 (1 H), monomethoxycalix[4]arene; 7.19 (2 H), 1,3-dimethoxycalix[4]arene; 8.60 (2 H, syn OH), 7.28 (2 H, anti OH), 1,2-dimethoxycalix[4]arene;[2a] 6.20 (1 H), trimethoxycalix[4]arene.

(25) In agreement with these findings, the "non-hydrogen-bonded" hydroxyls of the 1,3,5,7-tetrasubstituted derivatives **4a–g** appear within 7.07 and 7.41 ppm.

(26) Very recently the OH chemical shift has also been used as a probe in the structure assignment of regioisomers of calix[5]crown ethers: Kraft, D.; Arnecke, R.; Böhmer, V.; Vogt, W. *Tetrahedron* **1993**, *49*, 6019.

(27) An independent discrimination between structures **5** and **6** could be obtained considering the five products obtainable by monomethylation in each case. From **5** these tetramethyl derivatives are (cf. Figure 1) 1,2,3,5 and 1,2,4,6 (asymmetrical), 1,2,4,5 (2-fold symmetry element bisecting aromatic rings), 1,2,3,4 and 1,2,4,7 (2-fold symmetry element bisecting bridging methylenes). Those obtainable from **6** are 1,2,3,5, 1,2,4,6, 1,2,4,5 (as for **5**), 1,2,3,6 (2-fold symmetry element bisecting aromatic rings) and 1,2,5,6 (two orthogonal 2-fold symmetry elements bisecting $ArCH_2Ar$ groups). Comparison between these structures indicates that compounds having a 2-fold symmetry element bisecting $ArCH_2Ar$ groups can only be obtained from **5**, whereas the highly symmetric 1,2,5,6-isomer can only be derived from **6**. Subjecting **5** to monomethylation[19] in the presence of 1.2 equiv of CsF, a tetrasubstituted compound having a two-fold symmetry bisecting $ArCH_2Ar$ groups (deduced from its ^{1}H-NMR spectrum) was obtained (*inter alia*), thus giving an additional proof of structure **5**. This tetrasubstituted derivative was later positively identified as **7** (*vide infra*).

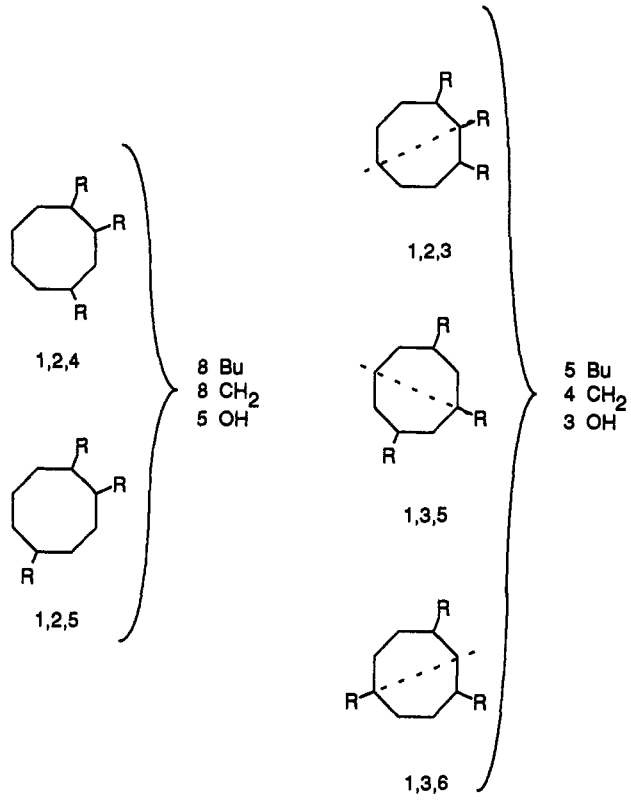
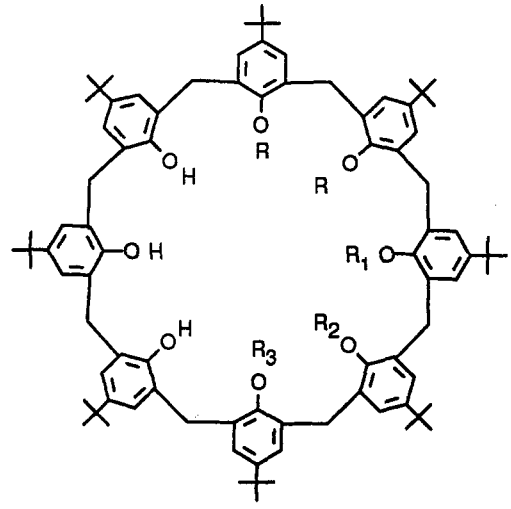


Figure 6. The five possible trisubstituted regioisomers of a calix[8]arene and their expected NMR resonances.

Chart 1



Compd	R	R_1	R_2	R_3
5	Me	H	Me	H
5a	*n*-Bu	H	*n*-Bu	H
6	Me	H	H	Me
7	Me	Me	Me	H

structure of 1,2,3,4-tetramethoxycalix[8]arene (**7**) (Chart 1) was assigned to this compound on the basis of the following considerations. The tetrasubstitution was evidenced by the molecular formula $C_{92}H_{120}O_8$ (elemental analysis and FAB(+) MS). Moreover, in the ^{1}H-NMR spectrum of **7**, two methoxyl singlets, each integrating for 6 H, appeared at 3.50 and 3.70 ppm (Figure 7B), while the four hydroxyls were illustrated by two 2 H broad singlets (D_2O exchangeable) at 8.51 and 8.85 ppm (Figure 7A). The presence of four *tert*-butyl signals at δ 1.14, 1.19, 1.232, and 1.235 in a 1:1:1:1 intensity ratio, as well as of five singlets for the $ArCH_2Ar$ groups at 3.82, 3.84, 3.87, 4.03, and 4.04 ppm in a 2:2:1:2:1 intensity ratio (Figure 7B), indicated the conformational mobility and the presence of a binary symmetry element bisecting the calix[8]arene macrocycle through two opposite $ArCH_2Ar$ groups. This type of symmetry finds an unequivocal confirmation in the ^{13}C-NMR spectrum of **7** since two methoxyl signals are seen at 60.5 and 61.9 ppm, while in the low-field region eight signals due to oxygen- and *t*-Bu-bearing aromatic carbons are clearly seen (Figure 7C), accounting for four couples of equivalent aromatic rings. An examination of Figure 1 shows that, among the eight tetrasubstituted derivatives, only the 1,2,3,4- and the 1,2,4,7-regioisomers are compatible with these spectral features. Structure **7** was chosen since two OH signals are seen (Figure 7A) at 8.51 and 8.85 ppm in its ^{1}H-NMR spectrum (the alternate structure with 1,2,4,7-substitution pattern implies one signal below and one above 8 ppm). The signal at higher

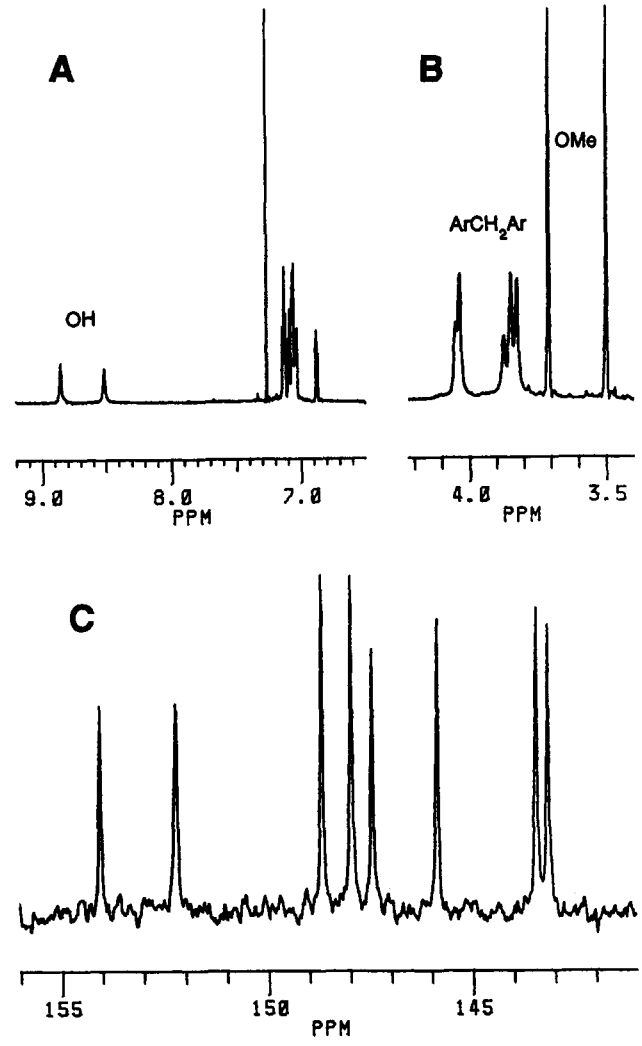


Figure 7. Key NMR spectral features of 1,2,3,4-tetramethyl ether **7**: aromatic and OH region (A) and $ArCH_2Ar$ and OMe region (B) of ^{1}H-NMR spectrum; region of ^{13}C-NMR spectrum of aromatic carbons bearing oxygen or *tert*-butyl (C).

field can confidently be assigned to the symmetry-related hydroxyls at positions 5 and 8 ("half-hydrogen-bonded" OH) and the one at lower field to the "fully-hydrogen-bonded" hydroxyls at positions 6 and 7.

In brief, in the same experimental conditions in which *p*-X-BnBr or α-haloacetyl derivatives react with *p-tert*-butylcalix[8]arene to yield 1,3,5,7-tetrasubstituted compounds, MeI has a certain preference for contiguous substitution leading to 1,2,4-trimethoxycalix[8]arene (**5**) and 1,2,3,4-tetramethoxycalix[8]arene (**7**).[28] This and the absence of 1,3,5,7-tetramethoxycalix[8]arene from the reaction mixture evidence that in methylation a mechanism is operating which is different from that outlined above for the other electrophiles. Since molecular dimension of the attacking electrophile appeared a possible controlling factor in methylation, we were persuaded to examine the reaction with a larger alkyl iodide, namely *n*-butyl iodide.

Alkylation of 1 with *n*-Butyl Iodide. Alkylation of **1** with *n*-BuI was carried out in the presence of either K_2CO_3 or CsF as base. The outcome of the reaction was very similar in both cases, and from the reaction mixtures two compounds were isolated by chromatography (Table 1, entries 22 and 23). The more polar of the two was positively identified as 1,3,5,7-tetrabutoxycalix[8]arene (**4i**) from the presence in the ^{1}H-NMR spectrum of two signals in a 1:1 ratio for the *tert*-butyl groups at 1.10 and 1.19 ppm, one 16-H singlet related to the $ArCH_2Ar$ groups at 3.91 ppm, and four multiplets at 0.82 (12 H), 1.44 (8 H), 1.83 (8 H), and 3.88 ppm (8 H) attributable to four equivalent *n*-butyl groups.

The less polar compound was assigned structure **5a** (Chart 1) on the basis of the presence of five OH resonances of the same intensity at 7.71, 8.62, 8.95, 9.06, and 9.12 ppm in the ^{1}H-NMR spectrum, giving a pattern closely reminiscent to that observed in the spectrum of **5**. In addition, three resonances for nonequivalent *n*-butyls were observed at 0.77, 0.82, and 0.91 ppm. The asymmetric substitution pattern was also confirmed by the ^{13}C-NMR spectrum, which in the 140–155 ppm region shows 15 out of 16 resonances of aromatic quaternary carbons bearing an oxygen or *t*-Bu group.

The concomitant formation of 1,2,4-tributyl ether **5a** and 1,3,5,7-tetrabutyl ether **4i** indicates that in butylation both mechanisms, typified by the reactions with methyl iodide and, respectively, benzyl bromide, are in competition and lend support to the hypothesis that the molecular dimension of the electrophile plays a role in the alkylation of *p-tert*-butylcalix[8]arene.

Conclusions

Alkylation of *p-tert*-butylcalix[8]arene (**1**) with *para*-substituted benzyl bromides, *tert*-butyl bromoacetate, and 2-chloro-*N*,*N*-dimethylacetamide in the presence of weak bases (K_2CO_3 or CsF) affords several partially *O*-substituted derivatives. In most cases the main product, isolated in yield up to 49%, is the 1,3,5,7-tetraether having C_4 symmetry and conformational freedom. Formation of this type of derivative can be explained by assuming that alkylation proceeds through alternating steps of monodeprotonation and alkylation and that monodeprotonation occurs with preferential formation of phenoxide monanions stabilized by two flanking hydrogen bonds. When methyl iodide is used as electrophile, the main products are the 1,2,4-trimethoxy and the 1,2,3,4-tetramethoxy derivatives, while the 1,3,5,7-tetramethyl ether is completely absent from the reaction mixture. Since this "anomalous" behavior could be ascribed to the smaller dimension of MeI as compared to those of the arylmethyl bromides, an electrophile with intermediate dimension, *n*-butyl iodide, was reacted with **1** in the same experimental conditions. The reaction mixture in this case contained products typical of both mechanisms, thus supporting the contention that stability of monoanions is not the only factor controlling the reaction course and that dimension of the electrophile also plays a role. However, a detailed investigation is needed to prove the proposed mechanism and to find a convincing explanation of the behavior of MeI and possibly other small electrophiles.

The selective alkylation of *p-tert*-butylcalix[8]arene described in the present work is a first step toward the understanding of the chemistry of this macrocyclic compound, and the resulting products are potentially useful for the development of new classes of receptors for large molecules. Studies in this direction are currently being carried out in our laboratory.

Experimental Section

General Comments. Melting points are uncorrected. NMR spectra were taken on a Bruker AC-250 spectrometer operating a 250.13 (^{1}H) and 62.9 (^{13}C) MHz, at 295 K using $CDCl_3$ solutions with Me_4Si as internal standard (unless otherwise indicated). FAB(+) MS spectra were recorded on a VG-ZAB 2-SE, using 3-nitrobenzyl alcohol as matrix.[29] Elemental analyses were obtained from the Institute of Pharmaceutical Chemistry of the University of Catania. Column chromatography (CC) was performed using silica gel (Kieselgel 60, 63–200 μm, Merck). All chemicals were reagent grade and were used without further purification. Anhydrous DMF and THF were purchased from Aldrich; *p-tert*-butylcalix[8]arene (**1**) was either from a commercial source or prepared following a literature procedure.[30]

General Procedure. A suspension of 0.5 g (0.385 mmol) of *p-tert*-butylcalix[8]arene (**1**) in 44 mL of THF/DMF (10:1 v/v) was refluxed under stirring until a clear solution was obtained (20 min); then the appropriate amount of base (Table 1) was introduced and stirring was continued for additional 20 min under nitrogen. A solution of the alkylating agent (3.08 or 1.54 mmol, Table 1) in 6 mL of THF was then added. The progress of the reaction was followed by TLC and stirring was maintained under reflux until the starting calix[8]arene **1** was no longer detected in the reaction mixture (the reaction time for each electrophile is reported in Table 1). Most of the organic solvent was removed under vacuum to leave a residue which was suspended in 0.1 N HCl (100 mL). The insoluble material was collected by filtration, washed with MeOH (10 mL), and dried. In methylations, the addition of acid was followed by extraction with CH_2Cl_2, washing with H_2O, and drying (Na_2SO_4). The crude product was purified by cromatography.

5,11,17,23,29,35,41,47-Octa-*tert*-butyl-49,50,51,52,53,54,55,56-octakis[(4-*tert*-butylbenzyl)oxy]calix[8]arene (3a) was prepared following the general procedure (entry 1, Table 1) and purified by CC (CH_2Cl_2/*n*-hexane 1:4): 609 mg (80%), white powder, mp 236–238 °C; R_f = 0.62 (CH_2Cl_2/*n*-hexane 2:3); ^{1}H NMR δ 0.93, 1.16 (s, 72 H each), 4.12 (s, 16 H), 4.59 (s, 16 H), 6.70 (s, 16 H), 7.16 and 7.22 (AB, J = 8.1 Hz, 32 H);

(28) It is noteworthy that in the alkylation of *p-tert*-butylcalix[6]arene the 1,3,5-trisubstitution has been observed only in the reaction with methyl iodide[4a,d] and not with various other alkylating agents.[4b,c,5] In addition, see footnote 4 in Kanamathareddy, S.; Gutsche, C. D. *J. Am. Chem. Soc.* **1993**, *115*, 6572.

(29) In the FAB(+) MS spectra of compounds **4a–f** the molecular peak is very weak and often is lost in the background noise. On the contrary, the tetraacetyl derivative **4aAc** and the remaining partially substituted derivative (**4g–i**, **5**, **5a**, and **7**) give FAB(+) MS spectra where the molecular ion peak is the base peak.

(30) Munch, J. H.; Gutsche, C. D. *Org. Synth.* **1989**, *68*, 243.

^{13}C NMR δ 30.3 (t), 31.3 (q), 34.0, 34.3 (s), 74.4 (t), 125.1, 126.1, 127.6 (d), 133.0, 134.8, 145.9, 150.2, 152.9 (s). Anal. Calcd for $C_{176}H_{232}O_8$: C, 85.38; H, 9.44. Found: C, 85.25; H, 9.53.

5,11,17,23,29,35,41,47-Octa-*tert*-butyl-49,50,51,52,53,54,-55,56-octakis(benzyloxy)calix[8]arene (3b)[31] (entry 2, Table 1): CC (CH_2Cl_2/*n*-hexane 1:4), 693 mg, (90%), white powder, mp 205–208 °C; R_f = 0.26 (CH_2Cl_2/*n*-hexane 2:3); ^{1}H NMR δ 1.00 (s, 72 H), 4.09 (s, 16 H), 4.49 (s, 16 H), 7.01 (s, 16 H), 6.94–7.08 (overlapped, 40 H); ^{13}C NMR δ 30.2 (t), 31.3 (q), 34.1 (s), 74.5 (t), 125.9, 127.3, 127.4, 128.1 (d), 133.0, 137.5, 146.0, 152.9 (s). Anal. Calcd for $C_{144}H_{160}O_8$: C, 85.67; H, 7.98. Found: C, 85.48; H, 7.57.

5,11,17,23,29,35,41,47-Octa-*tert*-butyl-49,50,51,52,53,54,-55,56-octakis[(4-cyanobenzyl)oxy]calix[8]arene (3c) (entry 3, Table 1): CC (CH_2Cl_2), 725 mg (85%), white powder, mp 255–256°C; R_f = 0.51 (Et_2O/CH_2Cl_2 2:48); ^{1}H NMR δ 0.59 (s, 72 H), 3.52 (s, 16 H), 4.19 (s, 16 H), 6.54 (s, 16 H), 6.73 and 6.86 (AB, J = 7.9 Hz, 32 H); ^{13}C NMR δ 30.2 (t), 31.2 (q), 34.0 (s), 73.3 (t), 112.0, 118.3 (s), 126.1, 127.2, 131.9 (d), 142.5, 142.8, 146.7, 154.4 (s). Anal. Calcd for $C_{152}H_{152}N_8O_8$: C, 82.27; H, 6.90; N, 5.04. Found: C, 82.55; H, 7.01; N, 4.98.

5,11,17,23,29,35,41,47-Octa-*tert*-butyl-49,50,51,52,53,54,-55,56-octakis[(4-nitrobenzyl)oxy]calix[8]arene (3d) (entry 4, Table 1): CC (CH_2Cl_2/*n*-hexane 3:2), 823 mg (90%), yellow powder, mp 241–242 °C; R_f = 0.55 (CH_2Cl_2/*n*-hexane 4:1); ^{1}H NMR δ 0.97 (s, 72 H), 3.96 (s, 16 H), 4.62 (s, 16 H), 6.95 (s, 16 H), 7.13 and 7.79 (AB, J = 8.6 Hz, 32 H); ^{13}C NMR δ 30.4 (t), 31.2 (q), 34.1 (s), 73.2 (t), 123.3, 126.2, 127.1 (d), 132.6, 144.4, 146.9, 147.1, 152.4 (s). Anal. Calcd for $C_{144}H_{152}N_8O_{24}$: C, 72.70; H, 6.44; N, 4.71. Found: C, 72.57; H, 6.29; N, 4.65.

5,11,17,23,29,35,41,47-Octa-*tert*-butyl-49,51,53,55-tetrahydroxy-50,52,54,56-tetrakis[(4-*tert*-butylbenzyl)oxy]calix[8]arene (4a) (entry 12, Table 1): CC (LiChroprep Si-60, 25-40 μm, CH_2Cl_2/*n*-hexane, 2:3), 317 mg (43%), white powder, mp 153–155 °C; R_f = 0.47 (CH_2Cl_2/*n*-hexane 1:1); ^{1}H NMR δ 1.05, 1.16, 1.32 (s, 36 H each), 3.85 (s, 16 H), 4.92 (s, 8 H), 6.97, 6.98 (s, 8 H each), 7.38 (s, 4 H), 7.42 and 7.43 (AB, J = 8.7 Hz, 16 H); ^{13}C NMR (CD_2Cl_2) δ 31.55, 31.58, 31.7 (q), 31.68 (t), 34.2, 34.5, 34.9 (s), 77.4 (t), 125.5, 125.9, 126.6, 128.6 (d), 127.1, 133.1, 133.9, 142.6, 147.9, 150.6, 150.9, 151.8 (s). Anal. Calcd for $C_{132}H_{168}O_8$: C, 84.2; H, 8.99. Found: C, 84.02; H, 8.71.

5,11,17,23,29,35,41,47-Octa-*tert*-butyl-49,51,53,55-tetrahydroxy-50,52,54,56-tetrakis[(4-methylbenzyl)oxy]calix[8]arene (4b) (entry 13, Table 1): CC (CH_2Cl_2/*n*-hexane 2:3), 249 mg (38%), white powder, mp 127–130 °C; R_f = 0.49 (CH_2Cl_2/*n*-hexane 3:2); ^{1}H NMR δ 1.03, 1.16 (s, 36 H each), 2.34 (s, 12 H) 3.85 (s, 16 H), 4.85 (s, 8 H), 6.95, 6.98 (s, 8 H each), 7.14 and 7.36 (AB, J = 7.5 Hz, 16 H), 7.38 (s, 4 H); ^{13}C NMR δ 21.2 (q), 29.6 (t), 31.2, 31.5 (q), 33.8, 33.9 (s), 77.0 (t), 124.9, 126.1, 128.6, 129.3 (d), 126.4, 132.4, 133.5, 138.0, 142.0, 147.2, 150.3, 150.5 (s). Anal. Calcd for $C_{120}H_{144}O_8$: C, 84.06; H, 8.46. Found: C, 83.91; H, 8.37.

5,11,17,23,29,35,41,47-Octa-*tert*-butyl-49,51,53,55-tetrahydroxy-50,52,54,56-tetrakis(benzyloxy)calix[8]arene (4c) (entry 14, Table 1): CC (CH_2Cl_2/*n*-hexane 3:2), 180 mg (28%), yellow powder, mp 150–153 °C; R_f = 0.15 (CH_2Cl_2/*n*-hexane 1:1); ^{1}H NMR δ 1.05, 1.17 (s, 36 H each), 3.86 (s, 16 H), 4.88 (s, 8 H), 6.97, 6.99 (s, 8 H each), 7.24–7.45 (overlapped, 20 H), 7.41 (s, 4 H); ^{13}C NMR δ 31.28 (t), 31.22, 31.5 (q), 33.8, 34.0 (s), 77.1 (t), 124.99, 126.15, 128.3, 128.4, 128.5 (d), 126.3, 132.4, 136.1, 142.0, 147.3, 150.3, 150.6 (s). Anal. Calcd for $C_{116}H_{136}O_8$: C, 83.98; H, 8.26. Found: C, 83.83; H, 8.19.

5,11,17,23,29,35,41,47-Octa-*tert*-butyl-49,51,53,55-tetrahydroxy-50,52,54,56-tetrakis[(4-cyanobenzyl)oxy]calix[8]arene (4d) (entry 15, Table 1): CC (Et_2O/CH_2Cl_2 1:99), 135 mg (20%), yellow powder, mp 145–147 °C; R_f = 0.14 (CH_2Cl_2); ^{1}H NMR δ 1.05, 1.19 (s, 36 H each), 3.91 (s, 16 H), 4.89 (s, 8 H), 6.96, 6.97 (s, 8 H each), 7.31 (s, 4 H), 7.37 and 7.38 (AB, J = 8.9 Hz, 16 H); ^{13}C NMR δ 31.3 (t), 31.1, 31.5 (q), 33.9, 34.1 (s), 75.7 (t), 111.8, 118.5 (s), 125.2, 126.3, 127.9, 132.3 (d), 125.7, 132.2, 141.1, 142.3, 148.2, 150.1 (s). Anal. Calcd for $C_{120}H_{132}N_4O_8$: C, 81.97; H, 7.56; N, 3.18. Found: C, 81.77; H, 7.40; N, 3.05.

(31) For completeness we report here physicochemical data of this previously described compound.[11c]

5,11,17,23,29,35,41,47-Octa-*tert*-butyl-49,51,53,55-tetrahydroxy-50,52,54,56-tetrakis[(4-nitrobenzyl)oxy]calix[8]arene (4e) (entry 16, Table 1): CC (CH_2Cl_2/cyclohexane 3:1), 323 mg (45%), yellow powder, mp 139–141 °C; R_f = 0.19 (CH_2Cl_2/cyclohexane, 3:1); ^{1}H NMR δ 1.04, 1.18 (s, 36 H each), 3.84 (s, 16 H), 4.94 (s, 8 H), 6.96, 6.98 (s, 8 H each), 7.07 (s, 4 H), 7.49 and 8.08 (AB, J = 8.5 Hz, 16 H); ^{13}C NMR δ 29.1 (t), 31.16, 31.52 (q), 33.9, 34.1 (s), 75.6 (t), 123.7, 125.1, 126.4, 128.4 (d), 126.0, 132.2, 142.5, 143.2, 147.6, 148.0, 149.9, 150.2 (s). Anal. Calcd for $C_{116}H_{132}N_4O_{16}$: C, 75.78; H, 7.23; N, 3.04. Found: C, 75.61; H, 7.19; N, 2.98.

5,11,17,23,29,35,41,47-Octa-*tert*-butyl-49,51,53,55-tetrahydroxy-50,52,54,56-tetrakis[(4-bromobenzyl)oxy]calix[8]arene (4f) (entry 17, Table 1): CC (CH_2Cl_2/cyclohexane 2:3), 213 mg (28%), yellow powder, mp 138–139 °C; R_f = 0.45 (CH_2Cl_2/cyclohexane 1:1); ^{1}H NMR δ 1.03, 1.19 (s, 36 H each), 3.86 (s, 16 H), 4.82 (s, 8 H), 6.95, 7.00 (s, 8 H each), 7.28 and 7.45 (AB, J = 8.5 Hz, 16 H), 7.22 (s, 4 H); ^{13}C NMR δ 30.9 (t), 31.2, 31.5 (q), 33.9, 34.0 (s), 76.2 (t), 125.0, 126.2, 130.0, 131.7 (d), 122.4, 126.3, 132.3, 135.1, 142.2, 147.5, 150.1, 150.3 (s). Anal. Calcd for $C_{116}H_{132}O_8Br_4$: C, 70.58; H, 6.74. Found: C, 70.41; H, 6.67.

5,11,17,23,29,35,41,47-Octa-*tert*-butyl-49,51,53,55-tetrahydroxy-50,52,54,56-tetrakis[[(*tert*-butoxycarbonyl)-methyl]oxy]calix[8]arene (4g) (entry 18, Table 1): CC (gradient Et_2O in $CHCl_3$), 330 mg (49%), white powder, mp 151–162 °C; R_f = 0.21 (CH_2Cl_2/*n*-hexane 3:1); ^{1}H NMR δ 1.01, 1.18, 1.41 (s, 36 H each), 3.92 (s, 16 H), 4.38 (s, 8 H), 6.89, 6.97 (s, 8 H each), 7.20 (s, 4 H); ^{13}C NMR δ 27.9, 31.2, 31.5 (q), 29.0 (t), 33.9, 34.1 (s), 71.9 (t), 82.7 (s), 125.3, 125.9 (d), 126.1, 132.2, 141.9, 147.5, 150.3, 151.1, 168.1 (s); FAB (+) MS *m/z* 1777 (100, MNa^+). Anal. Calcd for $C_{112}H_{152}O_{16}$: C, 76.68; H, 8.73. Found: C, 76.59; H, 8.62.

5,11,17,23,29,35,41,47-Octa-*tert*-butyl-49,51,53,55-tetrahydroxy-50,52,54,56-tetrakis[[[(*N*,*N*-dimethylamino)-carbonyl]methyl]oxy]calix[8]arene (4h) (entry 19, Table 1) (300 mg of KI were added to allow for halide exchange): CC (AcOEt/cyclohexane 2:3), 126 mg (20%), white powder, mp >250 °C; R_f = 0.2 (AcOEt/cyclohexane 2:3); ^{1}H NMR δ 1.07, 1.31 (s, 36 H each), 1.96, 2.78 (s, 12 H each), 4.03 (s, 16 H), 4.30 (s, 8 H), 6.82, 7.17 (s, 8 H each), 9.18 (s, 4 H); ^{13}C NMR δ 29.6 (t), 31.5 (q), 33.8, 34.2 (s), 34.6, 35.5 (q), 71.6 (t), 124.1, 126.9 (d), 127.4, 132.6, 141.6, 146.8, 149.9, 153.7, 169.5 (s); FAB (+) MS *m/z* 1639 (100, MH^+). Anal. Calcd for $C_{104}H_{140}N_4O_{12}$: C, 76.24; H, 8.61; N, 3.41. Found: C, 76.33; H, 8.52; N, 3.32.

Acetylation of 4a. Compound **4a** (20 mg) was treated with 0.5 mL of Ac_2O and 0.5 mL of pyridine at rt overnight. Excess of reactants was removed under vacuum and **5,11,17,23,29,-35,41,47-octa-*tert*-butyl-49,51,53,55-tetraacetoxy-50,52,-54,56-tetrakis[4-(*tert*-butylbenzyl)oxy]calix[8]arene (4aAc)** was obtained in quantitative yield as a white powder, mp 155–158 °C: ^{1}H NMR δ 1.01, 1.16, 1.29 (s, 36 H each), 1.52 (s, 12 H), 3.83 (s, 16 H), 4.62 (s, 8 H), 6.80, 7.09 (s, 8 H each), 7.31 and 7.33 (AB, J = 8.5 Hz, 16 H); ^{13}C NMR δ 20.0 (q), 31.0 (t), 31.2, 31.3, (q), 34.1, 34.3, 34.5 (s), 75.3 (t), 125.3, 125.5, 126.4, 128.1 (d), 131.9, 132.6, 134.3, 145.6, 146.1, 148.1, 150.9, 152.4, 169.0 (s); FAB (+) MS *m/z* 2050 (100, MH^+). Anal. Calcd for $C_{140}H_{176}O_{12}$: C, 81.98; H, 8.65. Found: C, 81.78; H, 8.46.

5,11,17,23,29,35,41,47-Octa-*tert*-butyl-49,50,51,52,54-pentahydroxy-53,55,56-trimethoxycalix[8]arene (5) (entry 20, Table 1): TLC (SiO_2, Et_2O/CH_2Cl_2 1:99); 48 mg from 70 mg of reaction mixture (68%), white powder, mp 170–172 °C; R_f = 0.64 (CH_2Cl_2); ^{1}H NMR δ 1.03, 1.07, 1.22, 1.23, 1.24, 1.25 (s, 9 H, 9 H, 9 H, 9 H, 9 H, 27 H, respectively), 3.76, 3.84, 3.88 (s, 3 H each), 3.84, 3.92, 3.95, 4.08 (s, 6 H, 2 H, 4 H, 2 H, 2 H, respectively), 6.78 (d, J = 2.3 Hz, 1 H), 6.85 (d, J = 2.3 Hz, 1 H), 6.92–6.93 (overlapped, 3 H), 7.00 (d, J = 2.3 Hz, 1 H), 7.03 (d, J = 2.4 Hz, 1 H), 7.11–7.14 (overlapped, 8 H), 7.19 (d, J = 2.4 Hz, 1 H), 7.67, 8.74, 8.86, 9.08, 9.10 (s, 1 H each); ^{13}C NMR δ 30.1, 31.0, 31.8, 32.2 (t), 31.1, 31.2, 31.3, 31.5, 31.6 (q), 33.9, 34.1, 34.2 (s), 61.7, 62.0, 62.2 (q), 125.2, 125.30, 125.38, 125.40, 125.61, 125.67, 125.8, 126.8 (d), 126.6, 126.9, 127.0, 127.1, 127.3, 127.4, 127.60, 127.63, 127.8, 131.9, 132.4, 132.7, 132.80, 132.85, 142.1, 143.0, 143.4, 143.7, 143.8, 147.0, 147.3, 147.4, 147.5, 147.6, 148.2, 149.0, 150.1, 152.1, 152.2, 152.6 (s); FAB (+) MS

m/z 1339 (100, MH^+). Anal. Calcd for $C_{91}H_{118}O_8$: C, 81.57; H, 8.87. Found: C, 81.48; H, 8.75.

5,11,17,23,29,35,41,47-Octa-*tert*-butyl-49,50,51,52-tetrahydroxy-53,54,55,56-tetramethoxycalix[8]arene (7) (entry 21, Table 1): TLC (SiO_2, Et_2O/CH_2Cl_2 1:99), 15 mg from 70 mg of reaction mixture (21%), white powder, mp 153–155 °C; R_f = 0.32 (CH_2Cl_2); ^1H NMR δ 1.14, 1.19, 1.232, 1.235 (s, 18 H each), 3.50, 3.70 (s, 6 H each), 3.82, 3.84, 3.87, 4.03, 4.04 (s, 4 H, 4 H, 2 H, 4 H, 2 H, respectively), 6.87 and 7.06 (AB, J = 2.3 Hz, 4 H), 7.03, 7.04, 7.07, 7.09, 7.12, 7.13 (d, J = 2.5, 2 H each), 8.51, 8.85 (s, 2 H each); ^{13}C NMR δ 29.7, 30.2, 30.8, 31.8, 32.0 (t), 31.3, 31.5 (q), 33.9, 34.1, 34.2 (s), 60.5, 61.9 (q), 125.3, 125.5, 125.6, 126.0, 127.0 (d), 126.4, 127.3, 127.5, 132.5, 133.0, 133.1, 133.3, 143.1, 143.4, 145.8, 147.4, 147.9, 148.6, 152.2, 154.0 (s); FAB (+) MS *m/z* 1354 (100, MH^+). Anal. Calcd for $C_{92}H_{120}O_8$: C, 81.67; H, 8.93. Found: C, 81.59; H, 8.85.

Monomethylation of 5 To Give 7. Compound **5** (40 mg) was reacted according to the general procedure using 1.2 equiv of CsF and 10 equiv of MeI. Usual workup led to a reaction mixture that was subjected to preparative TLC (SiO_2, Et_2O/CH_2Cl_2 1:99), affording 5 mg of **7**.

5,11,17,23,29,35,41,47-Octa-*tert*-butyl-49,51,53,55-tetrahydroxy-50,52,54,56-tetrabutoxycalix[8]arene (4i) (entry 22, Table 1): CC (CH_2Cl_2/cyclohexane 2:3), 175 mg (30%), white powder, mp 155–156 °C; R_f = 0.35 (CH_2Cl_2/cyclohexane 3:2); ^1H NMR δ 0.81 (t, J = 7.2 Hz, 12 H), 1.10, 1.20, (s, 36 H each), 1.44 (m, 8 H), 1.83 (m, 8 H), 3.88 (t, J = 6.6 Hz, 8 H), 3.91 (s, 16 H), 7.00 (s, 16 H), 7.73 (s, 4 H); ^{13}C NMR δ 13.7 (q), 19.1 (t), 30.1 (t), 31.3, 31.5 (q), 31.9 (t), 33.9, 34.1 (s), 75.2 (t), 124.9, 126.0 (d), 126.6, 132.5, 141.9, 147.1, 150.3, 150.8 (s); FAB (+) MS *m/z* 1523 (100, MH^+). Anal. Calcd for $C_{104}H_{144}O_8$: C, 82.05; H, 9.33; Found: C, 82.13; H, 9.40.

5,11,17,23,29,35,41,47-Octa-*tert*-butyl-49,50,51,52,54-pentahydroxy-53,55,56-tributoxycalix[8]arene (5a) (entry 22, Table 1): CC (CH_2Cl_2/cyclohexane 2:3), 140 mg (25%), white powder, mp 174–175 °C; R_f = 0.54 (CH_2Cl_2/cyclohexane 3:2); ^1H NMR δ 0.77 (t, J = 7.4 Hz, 3 H), 0.82 (t, J = 7.3 Hz, 3 H), 0.91 (t, J = 7.3 Hz, 3 H), 0.99, 1.11, 1.16, 1.23, 1.24, 1.25 (s, 9 H, 9 H, 9 H, 9 H, 27 H, 9 H, respectively), 1.38–1.52 (overlapped, 6 H), 1.70–1.90 (overlapped, 6 H), 3.76–4.06 (overlapped, 22 H), 6.80 and 6.86 (AB, J = 2.3 Hz, 2 H), 6.93 and 7.02 (AB, J = 2.4 Hz, 2 H), 7.02 (d, J = 2.3 Hz, 1 H), 7.02–7.23 (overlapped, 12 H), 7.71, 8.62, 8.95, 9.06, 9.12 (s, 1 H each); ^{13}C NMR δ 13.7, 13.8 (q), 19.0, 19.2 (t), 29.7, 30.1, 31.0 (t), 31.3, 31.5 (q), 31.8, 32.0, 32.1 (t), 33.9, 34.0, 34.2, (s), 74.5, 74.7 (t), 124.9, 125.0, 125.5, 125.8, 126.7, 126.8 (d), 126.5, 126.9, 127.3, 127.6, 132.3, 132.6, 132.8, 141.9, 142.8, 142.9, 143.6, 143.7, 146.9, 147.2, 147.4, 147.6, 148.3, 149.4, 150.3, 151.3, 151.4 (s); FAB (+) *m/z* 1467 (100, MH^+). Anal. Calcd for $C_{100}H_{136}O_8$: C, 81.92; H, 9.34. Found: C, 81.78; H, 9.50.

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Supplementary Material Available: ^1H- and ^{13}C-NMR peak assignments for all new compounds (6 pages). 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.