"Alternate Alkylation" of *p-tert*-Butylcalix[8]arene in the Presence of Weak Bases

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Alkylation of *p-tert*-butylcalix[8]arene in the presence of weak bases has been investigated using *p*-methylbenzyl bromide as an electrophile and CsF as a weak base in THF/DMF. Initially, a sequence of monoalkylation steps on progressively more alkylated compounds has been carried out, leading to the isolation and characterization of 13 *p*-methylbenzyl ethers ranging from mono- to octasubstituted. Successively, the time course of the composition of the reaction mixture has been determined at regular time intervals by chromatographic analysis and products isolation, in order to have a semiquantitative dynamic picture of the whole process. The reaction path goes mainly through the formation of mono-, 1,3-di-, 1,3,5-tri-, 1,3,5,7-tetra-, 1,2,3,5,7-penta-, 1,2,3,4,5,7- and 1,2,3,5,6,7-hexa-, and heptasubstituted derivatives. This result agrees with an "alternate alkylation" mechanism based on the preferential formation of monoanions stabilized by two flanking hydrogen bonds. However, the isolation of appreciable amounts of 1,2,4-tris(*p*-methylbenzyl) ether indicates that less stable monoanions can also be formed, possibly due to either temporary conformational preferences or the conformational mobility of the calix[8]arene macrocycle, resulting in a less effective hydrogen-bonding stabilization of anionic intermediates.

Introduction

In the last few years, interest for calixarenes[1] has grown exponentially due to their importance in supramolecular chemistry[2] as well as the multiplicity of practical applications, actual or potential, that range from the construction of ion-selective electrodes[3] and the purification of fullerenes (C_{60} and C_{70}) by selective complexation[4] to the production of materials with nonlinear optical properties[5] and the removal of cesium from nuclear waste.[6]

The chemistry of these compounds is an interesting example of reactivity modification, due to mutual interaction, of one out of many identical functional groups within the same molecule. In fact, the close spatial proximity of the phenol groups leads to the formation of a "circular hydrogen bond"[1] and consequently to a dramatic increase of the first proton dissociation.[7] Moreover, when calixarenes act as nucleophiles in substitution reactions, the reactivity is strongly influenced, and under suitable conditions, products with unexpected substitution patterns are obtained. For example, proximal[8] and diametrical[9] alkylation of calix[4]arenes or 1,4-disubstitution and 1,2,4,5-tetrasubstitution of calix[6]arenes[10,11] can be achieved in high yields, whereas 1,2,3- or 1,3,5-trialkylated calix[6]arenes are obtained with lower yields.[11–14] The factors governing these reactions undoubtedly are related to the strength of the base and the possibility of forming mono- or polyanions of different stability,[2,15] the metal template effects,[16] the conformational behavior,[17] and the different solubility of intermediates. However, in many instances, the reaction outcome is as yet not well-understood, providing "interesting intellectual challenges".[10b]

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(1) (a) Gutsche, C. D. *Calixarenes*; Royal Society of Chemistry: Cambridge, 1989. (b) *Calixarenes: A Versatile Class of Macrocyclic Compounds*; Vicens, J., Böhmer, V., Eds.; Kluwer: Dordrecht, 1991.

(2) Shinkai, S. *Tetrahedron* **1993**, *49*, 8933–8968.

(3) Cobben, P. L. H. M.; Egberink, R. J. M.; Bomer, J. G.; Bergveld, P.; Verboom, W.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1992**, *114*, 10573–10582.

(4) (a) Atwood, J. L.; Koutsantonis, G. A.; Raston, C. L. *Nature* **1994**, *368*, 229–231. (b) Suzuki, T.; Nakashima, K.; Shinkai, S. *Chem. Lett.* **1994**, 699–702. (c) Williams, R. M.; Zwier, J. M.; Verhoeven, J. W.; Nachtegaal, G. H.; Kentgens, A. P. M. *J. Am. Chem. Soc.* **1994**, *116*, 6965–6966.

(5) Kelderman, E.; Derhaeg, L.; Heesink, G. J. T.; Verboom, W.; Engbersen, J. F. J.; van Hulst, N. F.; Persoons. A.; Reinhoudt, D. N. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1075–1077.

(6) Ungaro, R.; Casnati, A.; Ugozzoli, F.; Pochini, A.; Dozol, J.-F.; Hill, C.; Rouquette, H. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1506–1509.

(7) Araki, K.; Iwamoto, K.; Shinkai, S.; Matsuda, T. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 3480–3485.

(8) Bottino, F.; Giunta, L.; Pappalardo, S. *J. Org. Chem.* **1989**, *54*, 5407–5409. Groenen, L. C.; Ruël, B. H. M.; Casnati, A.; Timmerman, P.; Verboom, W.; Harkema, S.; Pochini, A.; Ungaro, R.; Reinhoudt, D. N. *Tetrahedron Lett.* **1991**, *32*, 2675–2678.

(9) (a) Gutsche, C. D.; Dhawan, B.; Levine, J. A.; No, K. H.; Bauer, L. J. *Tetrahedron* **1983**, *39*, 409–426. (b) 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*, 7567–7575. (c) van Loon, J.-D.; Arduini, A.; Coppi, L.; Verboom, W.; Pochini, A.; Ungaro, R.; Harkema, S.; Reinhoudt, D. N. *J. Org. Chem.* **1990**, *55*, 5639–5646. (d) Collins, E. M.; McKervey, M. A.; Madigan, E.; Moran, M. B.; Owens, M.; Ferguson, G.; Harris, S. J. *J. Chem. Soc., Perkin Trans. 1* **1991**, 3137–3142.

(10) (a) Rogers, J. S.; Gutsche, C. D. *J. Org. Chem.* **1992**, *57*, 3152–3159. (b) Kanamathareddy, S.; Gutsche, C. D. *J. Org. Chem.* **1992**, *57*, 3160–3166.

(11) Neri, P.; Foti, M.; Ferguson, G.; Gallagher, J. F.; Kaitner, B.; Pons, M.; Molins, M. A.; Giunta, L.; Pappalardo, S. *J. Am. Chem. Soc.* **1992**, *114*, 7814–7821. (b) Neri, P.; Pappalardo, S. *J. Org. Chem.* **1993**, *58*, 1048–1053.

(12) (a) Casnati, A.; Minari, P.; Pochini, A.; Ungaro, R. *J. Chem. Soc., Chem. Commun.* **1991**, 1413–1414. (b) Janssen, R. G.; Verboom, W.; Reinhoudt, D. N.; Casnati, A.; Freriks, M.; Pochini, A.; Ugozzoli, F.; Ungaro, R.; Nieto, P. M.; Carramolino, M.; Cuevas, F.; Prados, P.; de Mendoza, J. *Synthesis* **1993**, 380–386.

(13) (a) Neri, P.; Rocco, C.; Consoli, G. M. L.; Piattelli, M. *J. Org. Chem.* **1993**, *58*, 6535–6537. (b) Neri, P.; Consoli, G. M. L.; Cunsolo, F.; Piattelli, M. *Tetrahedron Lett.* **1994**, *35*, 2795–2798.

(14) (a) Moran, J. K.; Roundhill D. M. *Inorg. Chem.* **1992**, *31*, 4213–4215. (b) Moran, J. K.; Georgiev, E. M.; Yordanov, A. T.; Mague, J. T.; Roundhill D. M. *J. Org. Chem.* **1994**, *59*, 5990–5998.

(15) Pappalardo, S.; Giunta, L.; Foti, M.; Ferguson, G.; Gallagher, J. F.; Kaitner, B. *J. Org. Chem.* **1992**, *57*, 2611–2624.

(16) Iwamoto, K.; Fujimoto, K.; Matsuda, T.; Shinkai, S. *Tetrahedron Lett.* **1990**, *31*, 7169–7172; *Corrigendum* **1991**, *32*, 830.

(17) Iwamoto, K.; Araki, K.; Shinkai, S. *J. Org. Chem.* **1991**, *56*, 4955–4962. Iwamoto, K.; Araki, K.; Shinkai, S. *Tetrahedron* **1991**, *47*, 4325–4342.

0022-3263/95/1960-4126$09.00/0

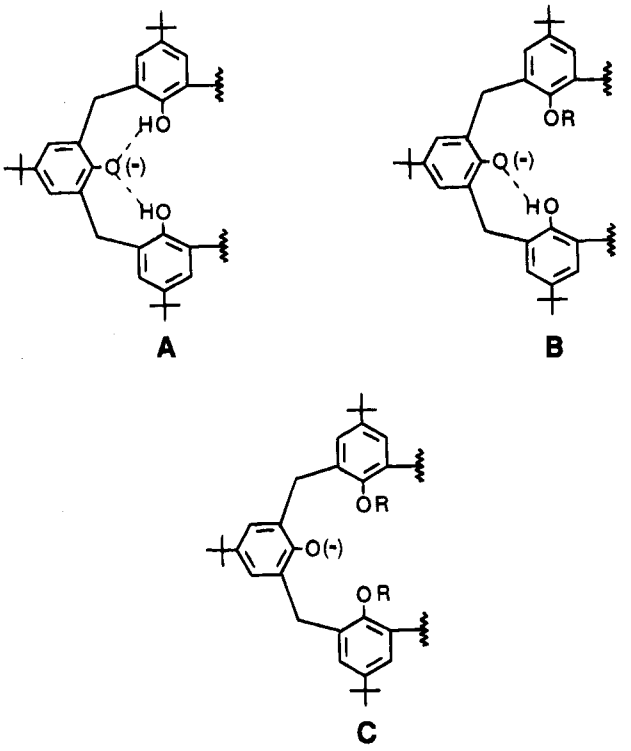
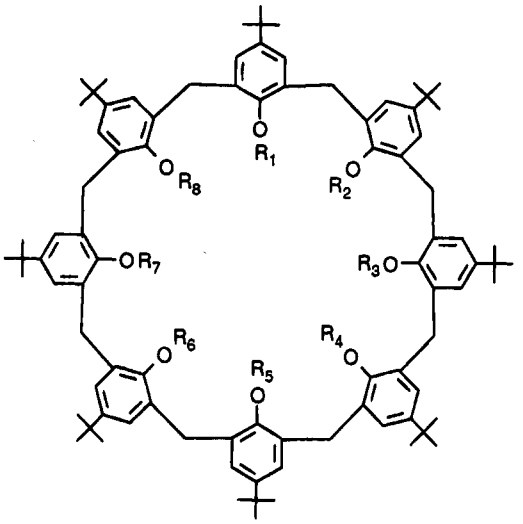


Figure 1. Hydrogen-bonding stabilization of calixarene monoanions.

Recently, we reported that alkylation of *p-tert*-butylcalix[8]arene (**C8**) in the presence of weak bases (K_2CO_3 or CsF) in THF/DMF affords, in yields up to 49%, 1,3,5,7-tetrasubstituted derivatives.[18] These compounds possess C_4 symmetry and therefore are particularly promising for the design of preorganized calix[8]arene-based hosts.[19] In order to explain the origin of this type of substitution, we have suggested a mechanism analogous to that proposed previously for calix[4]arenes,[9c] which assumes the formation of only monoanions when the reaction is carried out in the presence of weak bases. A sequence of monodeprotonation steps, each followed by a monoalkylation step, occurs preferentially at those positions, giving rise to monoanions more stabilized by contiguous hydrogen bonds (the order of stability of anions **A**–**C** in Figure 1 should be **A** > **B** > **C**). On this basis, it is expected that, in the second alkylation step, only three disubstituted derivatives (1,3-, 1,4-, and 1,5-) are formed (Figure 2), and following the same principle, one can extend the pathway to progressively more alkylated compounds, until exhaustive alkylation is achieved. With most of the electrophiles, products having alkylated phenol rings in alternate positions have been isolated, and we propose the name of "alternate alkylation" for this reaction course.

From the reaction of **C8** with methyl iodide in analogous conditions, we have isolated the 1,2,4-trimethyl and 1,2,3,4-tetramethyl ethers.[18b] In this case, a deviation from the alternate alkylation appears to occur, for which an explanation has not been given.[20] In order to shed light on these facts, we have examined the alternate alkylation of *p-tert*-butylcalix[8]arene with a typical electrophile, *p*-methylbenzyl bromide, and we report here the results obtained. In the course of this study, we have isolated and characterized several partially substituted derivatives, ranging from mono- to heptaalkylated compounds, in many instances representing the first examples of a calix[8]arene with a given substitution pattern.

Chart 1



Compd	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8
C8	H	H	H	H	H	H	H	H
1	MBn	H	H	H	H	H	H	H
$\mathbf{2}_{1,3}$	MBn	H	MBn	H	H	H	H	H
$\mathbf{2}_{1,4}$	MBn	H	H	MBn	H	H	H	H
$\mathbf{2}_{1,5}$	MBn	H	H	H	MBn	H	H	H
$\mathbf{3}_{1,3,5}$	MBn	H	MBn	H	MBn	H	H	H
$\mathbf{3}_{1,3,6}$	MBn	H	MBn	H	H	MBn	H	H
$\mathbf{3}_{1,2,4}$	MBn	MBn	H	MBn	H	H	H	H
$\mathbf{4}_{1,3,5,7}$	MBn	H	MBn	H	MBn	H	MBn	H
$\mathbf{5}_{1,3,5}$	MBn	MBn	MBn	H	MBn	H	MBn	H
$\mathbf{6}_{1,3}$	MBn	MBn	MBn	MBn	MBn	H	MBn	H
$\mathbf{6}_{1,5}$	MBn	MBn	MBn	H	MBn	MBn	MBn	H
7	MBn	MBn	MBn	MBn	MBn	MBn	MBn	H
8	MBn	MBn	MBn	MBn	MBn	MBn	MBn	MBn

MBn ≡ *p*-methylbenzyl

Results and Discussion

We have previously demonstrated that treatment of *p-tert*-butylcalix[8]arene with *para*-substituted benzyl bromides using K_2CO_3 in THF/DMF under reflux gives 1,3,5,7-tetraethers in yields that depend on the electrophile reactivity.[18a] Successively, it was evidenced that the use of CsF as base in most cases improves the yields and allows for extension of the reaction to very reactive electrophiles such as 2-haloacetyl derivatives.[18b] The increase in yields was related to the weakness of the base,

(18) (a) Neri, P.; Geraci, C.; Piattelli, M. *Tetrahedron Lett.* **1993**, *34*, 3319–3322. (b) Neri, P.; Battocolo, E.; Cunsolo, F.; Geraci, C.; Piattelli, M. *J. Org. Chem.* **1994**, *59*, 3880–3889.

(19) Cunsolo, F.; Piattelli, M.; Neri, P. *J. Chem. Soc., Chem. Commun.* **1994**, 1917–1918.

(20) After the initial submission of this paper, we observed that the 1,3,5,7-tetramethyl ether of **C8** is also formed (as an isoluble material) in these conditions: Cunsolo, F.; Consoli, G. M. L.; Piattelli, M.; Neri, P. *Tetrahedron Lett.*, in press.

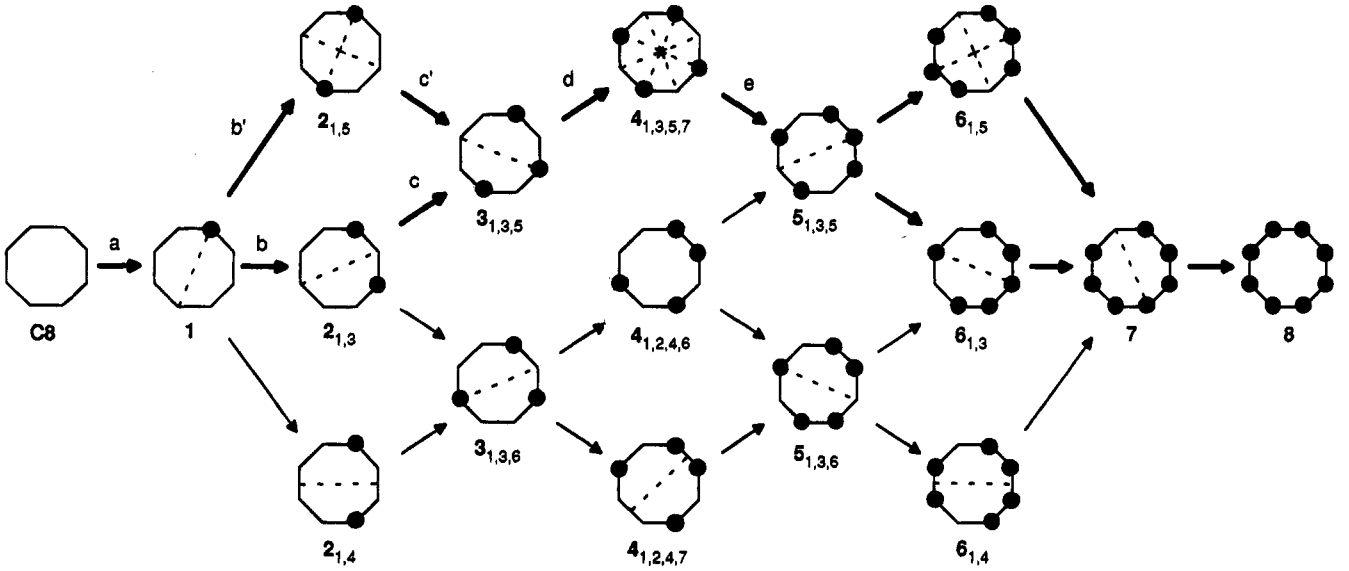


Figure 2. Possible routes for alternate alkylation of a calix[8]arene in the presence of weak bases. The thick arrows refer to the main pathway leading to the products isolated in the alkylation of **C8** with *p*-methylbenzyl bromide in the presence of CsF.

deprotonation occurring at those positions that give more stabilized monoanions. In this connection, it is to be noted that, according to common opinion, fluoride anions are not able to attain complete deprotonation of phenolic OH but, forming strong hydrogen bonds with acidic protons, are able to produce partially charged intermediates.[21,22] In contrast, we have observed that the addition of solid K_2CO_3 or CsF to a *p-tert*-butylcalix[8]arene solution results in an upfield shift of all the signals in the ^{1}H-NMR spectrum, attributable to the formation of a monoanionic species with either base.[23] In any event, even if partially charged intermediates would be formed, the above general considerations should retain their validity.

In order to study the mechanism of the alkylation in the presence of weak bases, we decided to examine in some detail the behavior of a typical electrophile, *p*-methylbenzyl bromide, in a CsF-catalyzed reaction. The choice was based on the observation that the presence of the methyl group, resonating in an empty region of the ^{1}H-NMR spectrum, would have greatly facilitated the structural characterization of the products, reducing possible accidental isochronies.[24] Since separation and identification of the intermediates from a very complex mixture appeared to be a difficult task, we decided to investigate the course of the reaction by carrying out a succession of monoalkylation steps on progressively more alkylated compounds. In each single step, the reaction mixture was more tractable than in a polyalkylation, and characterization of the products could benefit from simple chemical correlations. Subsequent work was devoted to the study of the time course of the distribution of products during alkylation under standard conditions, to have a semiquantitative dynamic picture of the whole process.

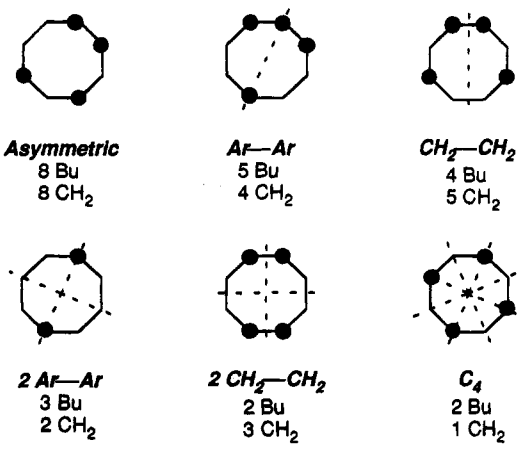
Monoalkylation of C8. It has been recently demonstrated that direct monoalkylation of calix[4]arenes can be achieved in moderate to good yield by using a limiting amount of a weak base and a large excess of electrophile.[21] We have now applied these conditions to the monobenzylation of **C8**, and by using 1.2 equiv of CsF and 10 equiv of *p*-methylbenzyl bromide, we obtained the monobenzyl derivative **1** in 50% yield. The ^{1}H-NMR spectrum of **1** contains four signals for *t*-Bu groups instead of the expected five, due to the accidental isochrony of two of them. The $ArCH_2Ar$ groups give rise to a broad hump in the 3.5–4.2 ppm region, indicating a slow conformational interconversion, due to the presence of seven contiguous OH groups that allow for the formation of a "broken" circular hydrogen bond only slightly less stable than that of the parent **C8** (the energy of

(21) Groenen, L. C.; Ruël, B. H. M.; Casnati, A.; Verboom, W.; Pochini, A.; Ungaro, R.; Reinhoudt, D. N. *Tetrahedron* **1991**, *47*, 8379–8384.

(22) Clark, J. H. *Chem. Rev.* **1980**, *80*, 429–452.

(23) Solid K_2CO_3 or CsF was added to a solution (acetone-d_6 or THF-d_8) of **C8** and the ^{1}H-NMR spectrum recorded. In the four cases, very similar upfield shifts were observed: $\Delta\delta$ = 0.27–0.30 (ArH), 0.10–0.11 ($ArCH_2Ar$, broadened), and 0.05–0.06 (*t*-Bu). For other studies on calixarene anions, see: Gutsche, C. D.; Iqbal, M.; Nam, K. C.; See, K. A.; Alam, I. *Pure Appl. Chem.* **1988**, *60*, 483–488. Gutsche, C. D.; Alam, I.; Iqbal, M.; Mangiafico, T.; Nam, K. C.; Rogers, J.; See, K. A. *J. Inclusion Phenom. Mol. Recognit. Chem.* **1989**, *7*, 61–72. Harrowfield, J. M.; Ogden, M. I.; Richmond, W. R.; Skelton, B. W.; White, A. H. *J. Chem. Soc., Perkin Trans. 2* **1993**, 2183–2190.

(24) The 28 partially substituted calix[8]arenes can be grouped as follows, in accordance with the number and type of symmetry elements: (a) asymmetrical, (b) one symmetry element bisecting opposite aromatic rings (Ar–Ar symmetry), (c) one symmetry element bisecting opposite $ArCH_2Ar$ groups (CH_2–CH_2 symmetry), (d) two orthogonal Ar–Ar elements of symmetry, (e) two orthogonal CH_2–CH_2 elements of symmetry, and (f) one C_4 axis of symmetry. Assuming free conformational mobility of the macrocycle, the number of the expected NMR resonances for *t*-Bu and $ArCH_2Ar$ groups is identical within each group as indicated below.



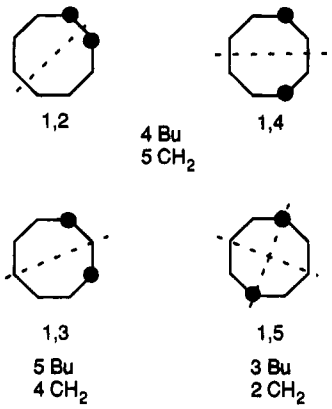


Figure 3. Schematic representation of the four possible disubstituted (or hexasubstituted) regioisomers of a calix[8]-arene. The circles indicate the two substituted aromatic rings or, in the case of hexasubstitution, the two OH-bearing rings. The number of expected resonances for *t*-Bu and $ArCH_2Ar$ groups of conformationally mobile derivatives are given in each case.

activation for the latter was estimated to be 15.7 kcal/mol).[25] Raising the temperature to 320 K resulted in the transformation of the shapeless signal into four sharp singlets at 3.74, 3.81, 3.94, and 3.99 ppm, as expected from the Ar–Ar symmetry of the molecule. The signals of the *t*-Bu groups were also resolved into five singlets (1.20, 1.21, 1.22, 1.25, and 1.27 ppm) of relative intensity 2:2:2:1:1.

Monoalkylation of Mono(*p*-methylbenzyl)calix[8]-arene 1. According to the proposed mechanism, it is expected that monoalkylation of **1** should occur only at positions 3, 4, or 5, producing three of the four possible disubstituted derivatives. TLC of the reaction mixture showed, in addition to unreacted **1**, four spots with R_f = 0.63, 0.54, 0.47, and 0.35. The fastest migrating compound was identified as 1,3-dibenzylcalix[8]arene $\mathbf{2}_{1,3}$ on the basis of its ^{1}H-NMR spectrum.[26] The presence of five *t*-Bu resonances (1.09, 1.10, 1.20, 1.21, and 1.24 ppm) in a 1:1:2:2:2 intensity ratio is indicative of a structure possessing Ar–Ar symmetry characteristic of the 1,3-disubstitution. In fact, the 1,2- and 1,4-disubstituted derivatives are both characterized by CH_2–CH_2 symmetry, whereas the 1,5-diether has two orthogonal Ar–Ar planes of symmetry (Figure 3). As observed for **1**, the ^{1}H-NMR signals related to the bridging methylenes in $\mathbf{2}_{1,3}$ appear as a hump that at 336 K resolves into four singlets (3.78, 3.82, 3.90, and 3.97 ppm) of the same intensity. The equivalence of the two *p*-methylbenzyl groups is reflected in the presence of two singlets at 2.30 and 4.80 ppm for the methyls and the OCH_2 groups, respectively.

The second compound in order of increasing polarity (R_f = 0.54) was also a disubstituted derivative, as confirmed by elemental analysis. The presence of four *t*-Bu signals at 1.04, 1.09, 1.10, and 1.12 ppm (1:1:1:1

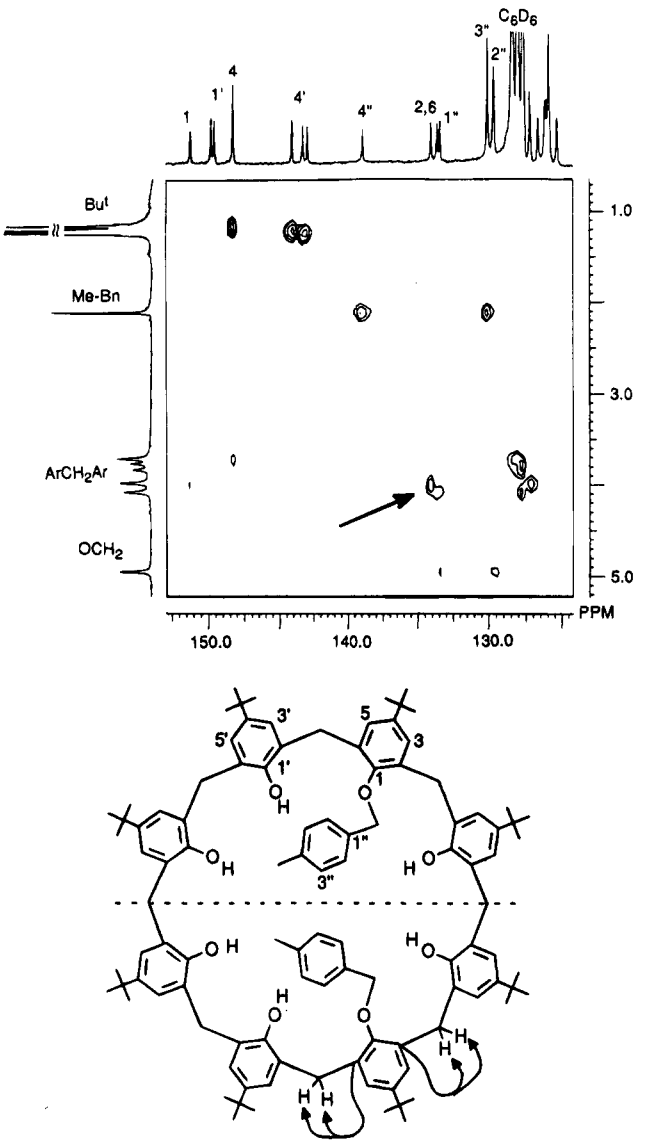


Figure 4. Section of the ^{1}H–^{13}C long-range HETCOR NMR spectrum of $\mathbf{2}_{1,4}$ (C_6D_6, 307 K). The assignments in the ^{13}C-NMR spectrum (top trace) are given according to the bottom structure, where primed numbers refer to any OH-bearing ring. The arrows indicate diagnostic correlations between bridgehead carbons and $ArCH_2Ar$ protons.

intensity ratio) indicated a structure with CH_2–CH_2 symmetry. This inference was confirmed by the presence of three OH signals (8.71, 9.31, and 9.41 ppm, 1:1:1 ratio) and by the appearance, in the spectrum at 307 K, of five singlets for the $ArCH_2Ar$ groups at 3.59, 3.65, 3.71, 3.86, and 3.96 ppm in a 2:1:1:2:2 ratio. Since this symmetry is consistent with either a 1,2- or a 1,4-disubstitution pattern (Figure 3), to discriminate between the two possibilities, a 2D heteronuclear NMR study was carried out. Although extensive overlapping in the aromatic region precluded a complete signal assignment, all the carbon resonances above 129 ppm were assigned through a combination of 2D correlations and chemical shift arguments. The latter were based on the observation that the quaternary carbon resonances of a phenol ring upon alkylation experience a downfield displacement, and in particular, the bridgehead carbons move from the crowded region at 126–128 to ca. 133 ppm.[27] The assignments given on top of Figure 4 are based on this consideration and the analysis of 2D ^{1}H–^{13}C long-range correlations. The presence of cross-peaks between the

(25) Gutsche, C. D.; Bauer, L. J. *J. Am. Chem. Soc.* **1985**, *107*, 6052–6059.

(26) To give an immediate insight into the substitution pattern of calix[8]arenes, throughout the present paper, we used a modified version of the nomenclature system introduced by Shinkai (Otsuka, H.; Araki, K.; Shinkai, S. *J. Org. Chem.* **1994**, *59*, 1542–1547). The bold-faced number indicates the number of substituents, while the subscript refers to the location of the substituents. Thus, $\mathbf{3}_{1,3,6}$ indicates a 1,3,6-trisubstituted compound. For the sake of simplicity, in the case of penta- and hexasubstituted compounds, the subscripts refer to the unsubstituted aromatic rings.

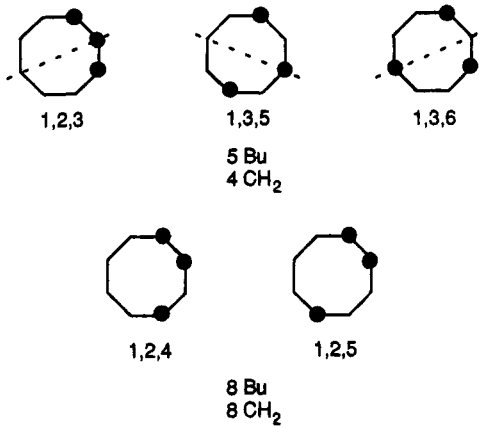


Figure 5. Five possible trisubstituted (or pentasubstituted) regioisomers of a calix[8]arene with their expected resonances.

aromatic bridgehead carbons of the alkylated phenol rings and two $ArCH_2Ar$ proton singlets of 4 H intensity (Figure 4) clearly indicated that the alkylation site is flanked by two rings each bearing a free OH group. Therefore, the compound in question was identified as 1,4-bis(*p*-methylbenzyl)calix[8]arene $\mathbf{2}_{1,4}$.

The third compound (R_f = 0.47) was assigned the structure of 1,5-bis(*p*-methylbenzyl)calix[8]arene $\mathbf{2}_{1,5}$, since, in its ^{1}H-NMR spectrum, three singlets at 1.13, 1.157, and 1.164 ppm (2:1:1 ratio) for the *t*-Bu groups indicated two orthogonal Ar–Ar planes of symmetry (Figure 3). Accordingly, the $ArCH_2Ar$ protons appeared as two 1:1 singlets (3.61 and 3.93 ppm) in the 310 K spectrum, while the OH signals were seen as two 2:1 singlets at 8.41 and 8.51 ppm.

The slowest migrating spot contained two trisubstituted derivatives, $\mathbf{3}_{1,3,5}$ and $\mathbf{3}_{1,3,6}$, whose structure was elucidated as will be discussed below. Therefore, the monoalkylation of monobenzylcalix[8]arene **1** affords 1,3-, 1,4-, and 1,5-disubstituted derivatives, whereas the 1,2-isomer does not form in appreciable amounts.

Monoalkylation of Bis(*p*-methylbenzyl)calix[8]arenes. According to the proposed mechanism, monoalkylation of dibenzyl ether $\mathbf{2}_{1,5}$ is expected to give the 1,3,5-trisubstituted derivative only. Actually, two compounds were isolated from the reaction mixture, one of which was identified as the known 1,3,5,7-tetrabenzyl ether $\mathbf{4}_{1,3,5,7}$,[18] whereas the second one was a trisubstituted derivative with Ar–Ar symmetry. In accordance with the anticipated structure, its ^{1}H-NMR spectrum, upon the temperature being raised to 325 K, shows five resonances for *t*-Bu groups at 1.07, 1.13, 1.22, 1.28, and 1.30 ppm of intensity ratio 1:2:1:2:2 and four equal intensity singlets at 3.81, 3.97, 4.00, and 4.07 ppm. Moreover, the *p*-methylbenzyl substituents give rise to two 2:1 singlets in the Me (2.07 and 2.08 ppm) and OCH_2 (4.74 and 4.80 ppm) regions, respectively. Although the NMR data cannot distinguish per se between the three trisubstituted regioisomers possessing Ar–Ar symmetry (Figure 5), the structure of $\mathbf{3}_{1,3,5}$ was confidently assigned to the isolated triether considering that the other two isomers

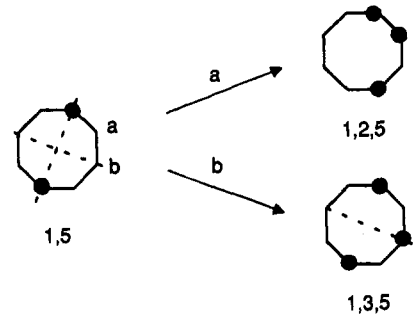


Figure 6. Possible monoalkylation products of compound $\mathbf{2}_{1,5}$.

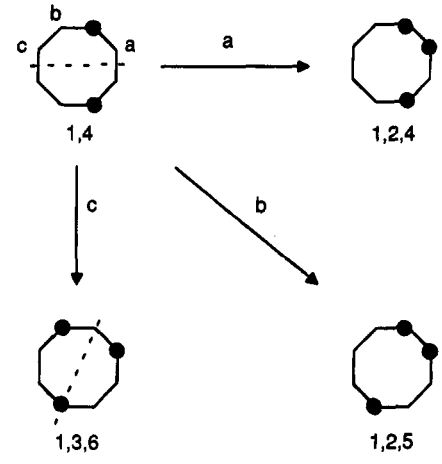


Figure 7. Possible monoalkylation products of compound $\mathbf{2}_{1,4}$.

cannot form upon monoalkylation of $\mathbf{2}_{1,5}$ (Figure 6). Additional evidence came from the result of its monoalkylation, which yielded tetraether $\mathbf{4}_{1,3,5,7}$.

In the monoalkylation of 1,4-dibenzylcalix[8]arene $\mathbf{2}_{1,4}$, a trisubstituted compound was formed, whose Ar–Ar symmetry was evident in the ^{1}H-NMR spectrum in C_6D_6 solution at 340 K, that shows the expected five *t*-Bu singlets (1.11, 1.17, 1.24, 1.26, and 1.27 ppm, 2:1:2:2:1) and four $ArCH_2Ar$ singlets (3.86, 3.96, 4.01, and 4.03 ppm). The three methylbenzyl groups give rise to two singlets in a 2:1 ratio for both the methyls (δ 2.11 and 2.13) and the OCH_2 groups (δ 4.77 and 4.88). This compound was assigned the 1,3,6-trisubstitution pattern, considering that, among the trisubstituted derivatives in principle obtainable from $\mathbf{2}_{1,4}$ (Figure 7), only $\mathbf{3}_{1,3,6}$ possesses Ar–Ar symmetry, the other two being asymmetric.

Monoalkylation of 1,3-dibenzylcalix[8]arene $\mathbf{2}_{1,3}$ afforded both $\mathbf{3}_{1,3,5}$ and $\mathbf{3}_{1,3,6}$ in 23 and 19% yield, respectively.

Alkylations of 1,3,5,7-Tetrakis(*p*-methylbenzyl)calix[8]arene $\mathbf{4}_{1,3,5,7}$. It has been noted that, with excess reagents and an extension of the reaction time, exhaustive alkylation can be obtained even with a base as weak as CsF.[18b] Clearly, this means that alkylation of OH groups not flanked by hydrogen bonds also occurs, albeit slowly, indicating that monoanions of type **C** (Figure 1) can be formed, possibly at very low concentrations. Therefore, further alkylation of $\mathbf{4}_{1,3,5,7}$ appeared to be a clean and unambiguous way to obtain pentasubstituted calix[8]arene $\mathbf{5}_{1,3,5}$. Indeed, this compound was obtained in 48% yield, and its ^{1}H-NMR data were in full agreement with the assigned structure. In fact, five *t*-Bu signals are present at δ 0.85, 1.01, 1.12, 1.19, and 1.22 in a 1:2:2:1:2 intensity ratio, indicative of Ar–Ar symmetry (Figure 5). Due to accidental isochrony, the four expected

(27) This downfield displacement is evidenced by the comparison of the ^{13}C NMR resonances for *p-tert*-butylcalix[8]arene (**C8**) (Gutsche, C. D.; Dhawan, B.; No, K. H.; Muthukrishnan, R. *J. Am. Chem. Soc.* **1981**, *103*, 3782–3792; *Corrigendum* **1984**, *106*, 1891) and those of its octabenzyl derivative **8**: $\Delta\delta$ = 6.1 (*C*-O), 4.5 (*C*-CH_2), 3.3 (Ar*C*H), 1.2 (*C*-Bu^t). Confirmation is obtained from consideration of the ^{13}C NMR data for $\mathbf{4}_{1,3,5,7}$ ($\Delta\delta$ between alkylated and OH-bearing rings: 3.3 (*C*-O), 6.0 (*C*-CH_2), 1.2 (Ar*C*H), 7.7 (*C*-Bu^t)).[18b]

$ArCH_2Ar$ signals appear as three singlets at 3.82, 3.91, and 4.15 ppm in a 2:1:1 ratio, whereas the five *p*-methylbenzyl substituents are clearly separated by the Me signals (δ 2.09, 2.26, and 2.27, 2:1:2) into three 2:2:1 groups.

Since $\mathbf{4}_{1,3,5,7}$ is more easily available than $\mathbf{5}_{1,3,5}$, the dialkylation of the former was considered a viable method for obtaining the two hexaethers having the OH groups in a 1,3 or 1,5 relative position. In practice, a mixture of these two compounds was obtained as a single band by TLC of the crude reaction product that, in addition, contained $\mathbf{5}_{1,3,5}$ and small amounts of hepta- and octa-substituted calix[8]arenes. Separation of the two hexaethers was difficult and was only reached by careful preparative TLC. This is reminiscent of the behavior of two isomeric 2,4-dinitrophenyl hexaethers of *p-tert*-butylcalix[8]arene.[28] Characterization of these compounds was straightforward on the basis of ^{1}H-NMR (Figure 3). Thus, hexakis(*p*-methylbenzyl)calix[8]arene $\mathbf{6}_{1,3}$ was characterized by its Ar–Ar symmetry, revealed by the presence in the spectrum of five *t*-Bu (δ 0.98, 0.99, 1.07, 1.11, and 1.23, 2:2:1:1:2) and four $ArCH_2Ar$ signals (3.80, 3.88, 4.08, and 4.12 ppm, 4 H each). The six substituents give rise to four distinct groups of signals in a 1:2:2:1 ratio, as evidenced by the resonances for the methyls (δ 2.08, 2.20, 2.24, and 2.26, 1:2:1:2) and the OCH_2 groups (4.55, 4.63, 4.71, and 4.80 ppm, 1:2:1:2).

The isomeric $\mathbf{6}_{1,5}$, having two orthogonal Ar–Ar planes of symmetry (Figure 3), was identified by the presence of three *t*-Bu (δ 0.95, 1.03, and 1.22, 2:1:1 ratio) and two bridging CH_2 singlets of the same intensity (3.86 and 4.00 ppm). The high symmetry of the molecule is also reflected in the presence of only two types of benzyl groups in a 2:1 ratio, as evidenced by two singlets in the Me region (δ 2.12 and 2.20, 1:2).

Heptakis(*p*-methylbenzyl)calix[8]arene **7** can be conveniently prepared (38%) through direct alkylation of **C8** using 32 equiv of base and electrophile. Its ^{1}H-NMR spectrum is commensurate with Ar–Ar symmetry, showing five *t*-Bu resonances (δ 0.92, 0.93, 1.00, 1.05, and 1.17, 1:2:2:2:1) and three $ArCH_2Ar$ singlets (3.84, 4.05, and 4.12 ppm, 1:1:2), whereas the high symmetry of octabenzylcalix[8]arene **8** is apparent from the simplicity of its spectrum at 323 K, which shows five singlets (δ 1.01, *t*-Bu; 2.08, *p*-Me; 4.09, $ArCH_2Ar$; 4.60, CH_2O; and 7.05, ArH) and an AB system (6.80 and 7.06, J = 7.5 Hz) due to the ArH protons of the *para*-substituted benzyl moieties.

At this point, monoalkylation of $\mathbf{3}_{1,3,6}$ seemed of some interest for obtaining products appearing in the lower part of Figure 1. Unfortunately, the small amounts available discouraged any attempt in this direction.

Comparative Features of *p*-Methylbenzyl Ethers of C8. The availability of several partially substituted calix[8]arenes enables us to compare some of their properties. Going from **C8** to $\mathbf{4}_{1,3,5,7}$ through progressively more alkylated derivatives, we observed a gradual increase in polarity, which can be related to the progressive decrease of the number of intramolecular hydrogen bonds. Breaking of intramolecular interactions gives the OH groups the possibility of interacting with the stationary phase, attaining the greatest efficacy in the case of $\mathbf{4}_{1,3,5,7}$ in which four "isolated" hydroxyls are present. Further alkylation then gives rise to compounds with a reduced number of OH groups, paralleled by a decrease in polarity.

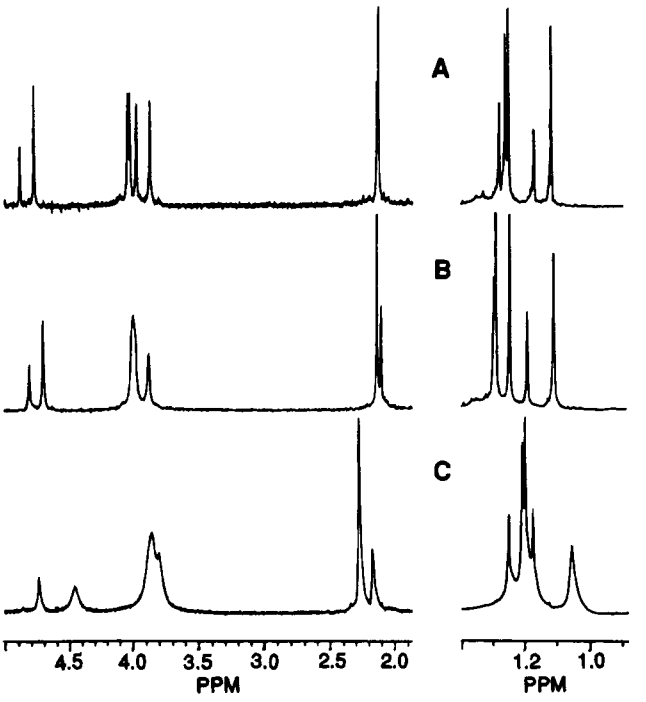


Figure 8. Informative regions of the 250-MHz ^{1}H-NMR spectra of $\mathbf{3}_{1,3,6}$ at 340 K (A) and 295 K (B) in C_6D_6 and at 295 K in $CDCl_3$ (C). In each spectrum, the scales of ppm and intensity are different for the two regions.

The changes in the chemical shifts of the *t*-Bu groups in the ^{1}H-NMR spectrum upon benzylation are also worth mentioning. Comparison between *p-tert*-butylcalix[8]-arene and octakis(*p*-methylbenzyl) ether **8** evidences an upfield shift from 1.24 to 1.01 ppm, attributable to the change of electronic effect passing from a H-bonded OH to an OR group. This shift is easily observable in other partial derivatives and allows for a confident distinction of resonances of *t*-Bu groups attached to OH- or OR-bearing aromatic rings. Thus, pentasubstituted $\mathbf{5}_{1,3,5}$ shows three singlets at 0.85, 1.01, and 1.12 ppm (1:2:2 ratio) attributable to *t*-Bu groups of benzylated rings and two signals at δ 1.19 and 1.22 (1:2 ratio) associable to OH-bearing rings. Comparison of ^{1}H-NMR data of derivatives ranging from tri- to octasubstituted suggests 1.15 ppm as the discriminating value between the two types of rings. However, in addition to a slight deviation for $\mathbf{3}_{1,3,6}$ that can be due to a change in the experimental conditions (solvent and temperature), a complete failure of the rule was observed for mono- and disubstituted derivatives. In these cases, the extensive hydrogen-bonding system still present along the macrocycle may be considered responsible for the strong deviations.

A further interesting point regards the ascertainment of the symmetry of partially derivatized calix[8]arenes by the inspection of NMR spectra. Due to the large number of resonances, extensive overlapping is often observed, particularly for asymmetrically substituted compounds. This and the frequent occurrence of signal broadening caused by the reduced conformational interconversion make the choice of solvent and temperature crucial for observing the expected number of resonances, as exemplified by the ^{1}H-NMR spectra of $\mathbf{3}_{1,3,6}$ (Figure 8) that became well-resolved at 340 K using C_6D_6 as solvent. About the conformational interconversion, we have observed that *para*-substituted benzyl groups are not bulky

(28) Muthukrishnan, R.; Gutsche, C. D. *J. Org. Chem.* **1979**, *44*, 3962–3964.

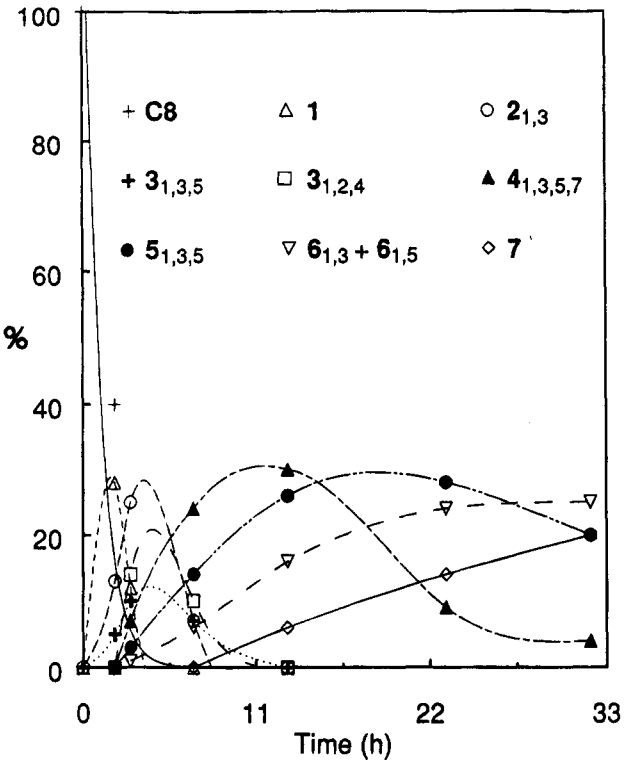


Figure 9. Time course of the distribution of products in the alkylation of *p-tert*-butylcalix[8]arene in THF/DMF with *p*-methylbenzyl bromide and CsF (1:8:16 molar ratio).

enough to hinder the "oxygen through the annulus" pathway.[18b] Since it has been recently shown that, in *p-tert*-butylcalix[6]arenes, inversion of a phenol ring can occur via the "*tert*-butyl through the annulus" route,[29] a complete conformational fixing of the larger *p-tert*-butylcalix[8]arene by simple monofunctional derivatization at the lower rim appears impossible, because the latter route will always be operating.

Time Course Dependence of the Distribution of Products in the Alkylation of *p-tert*-Butylcalix[8]arene. At this point, the availability of several well-characterized partially derivatized calix[8]arenes allowed us to undertake a semiquantitative study of the composition of the reaction mixture as a function of time under the experimental conditions normally adopted for preparative purposes (**C8**, CsF, *p*-MeBnBr, 1:16:8 molar ratio, in 10:1 THF/DMF at reflux). These conditions differ widely from those we used in the monoalkylation reactions (molar ratio of 1:1.2:10). In preliminary experiments, the variation of the distribution of products as a function of the time (Figure 9) was followed by TLC analysis at regular time intervals (30 min). Preparative runs were then carried out and quenched after selected reaction times in order to separate the products by preparative TLC, to identify their structures by spectral methods, and to estimate their relative abundance. It was thus observed that, after 1 h, the reaction mixture contains mainly unreacted **C8**, **1**, and $\mathbf{2}_{1,3}$ and, in addition, very low amounts (less than 3% each) of other di- and trisubstituted derivatives. At the end of the second hour, these minor components became isolable and were identified as $\mathbf{2}_{1,4}$, $\mathbf{2}_{1,5}$, and $\mathbf{3}_{1,3,5}$. Successively, $\mathbf{4}_{1,3,5,7}$ became detectable, and after 3 h, the starting calix[8]arene had disappeared. Then, the pentasubstituted derivative $\mathbf{5}_{1,3,5}$ became detectable, and after 5 h, the monobenzyl derivative **1** had completely disappeared. Soon afterward, a mixture of hexasubstituted $\mathbf{6}_{1,3}$ and $\mathbf{6}_{1,5}$ was seen in TLC, along with an unknown compound that was isolated in appreciable yields (ca. 10%) at the seventh hour. This compound was assigned the structure of $\mathbf{3}_{1,2,4}$ on the basis of the following considerations. The asymmetric trisubstitution was indicated by the presence in the ^{1}H-NMR spectrum of three MeBn groups at 2.25, 2.26, and 2.29 ppm (1:1:1) and by three resonances for oxymethylenes at 4.78, 4.82, and 4.96 ppm. Due to a partial overlap, only five singlets (δ 1.00, 1.08, 1.15, 1.22, and 1.23, 1:1:1:1:4) were seen in the *t*-Bu region and six resonances (δ 3.79, 3.84, 3.86, 3.89, 3.92, and 4.18, 2:2:1:1:1:1) instead of eight for the $ArCH_2Ar$ groups. Discrimination between the 1,2,4- and 1,2,5-pattern (Figure 5) was possible on the basis of the chemical shift of the OH groups. In fact, four D_2O-exchangeable signals at δ 7.47, 8.70, 8.77, and 9.04 in a 1:1:1:2 ratio were seen in the ^{1}H-NMR spectrum, similar to what was observed previously for 1,2,4-trimethoxy-*tert*-butylcalix[8]arene.[18b]

After its appearance, $\mathbf{4}_{1,3,5,7}$ steadily accumulated in the reaction mixture, reaching the highest concentration between the seventh and tenth hour. At the thirteenth hour, the concentration of pentasubstituted $\mathbf{5}_{1,3,5}$ was near that of $\mathbf{4}_{1,3,5,7}$, while heptasubstituted **7** became detectable. From this time forward, a steady decrease in the concentration of $\mathbf{4}_{1,3,5,7}$ (and successively of $\mathbf{5}_{1,3,5}$) was observed, paralleled by a continuous enrichment of the reaction mixture in hexa- and heptasubstituted derivatives. After 96 h, the octabenzyl derivative **8** was still undetectable. Therefore, preparation of the fully alkylated compound required a large excess of base and electrophile (at least 32 equiv each) or a stronger base (e.g. NaH). In the latter case, it can be obtained in 78% yield.

According to Figure 2, on a purely statistical basis, the three dialkylated derivatives $\mathbf{2}_{1,3}$, $\mathbf{2}_{1,4}$, and $\mathbf{2}_{1,5}$ would be formed in a 2:2:1 ratio. In practice, in the experimental conditions adopted, the 1,3-disubstituted derivative is isolated in higher yields, and after 2 h, it accounts for 80% of the total fraction of the disubstituted derivatives. Further evolution of the reaction takes place through $\mathbf{3}_{1,3,5}$, leading to $\mathbf{4}_{1,3,5,7}$. Since alkylation of the latter requires formation of less stable anions of type **C** (Figure 1), the tetraether tends to accumulate and is slowly converted into the pentasubstituted derivative $\mathbf{5}_{1,3,5}$.[30] Further alkylation of $\mathbf{5}_{1,3,5}$, which also involves the intermediacy of a **C**-type anion, proceeds still more slowly, yielding the hexasubstituted derivatives $\mathbf{6}_{1,3}$ and $\mathbf{6}_{1,5}$ in a 3:1 ratio, not far from the statistical value of

(29) Otsuka, H.; Araki, K.; Sakaki, T.; Nakashima, K.; Shinkai, S. *Tetrahedron Lett.* **1993**, *34*, 7275–7278. van Duynhoven, J. P. M.; Janssen, R. G.; Verboom, W.; Franken, S. M.; Casnati, A.; Pochini, A.; Ungaro, R.; de Mendoza, J.; Nieto, P. M.; Prados, P.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1994**, *116*, 5814–5822. Kanamathareddy, S.; Gutsche, C. D. *J. Org. Chem.* **1994**, *59*, 3871–3879.

(30) The diametrical dialkylation of calix[4]arenes occurs with regioselectivity higher than 1,3,5,7-tetraalkylation of calix[8]arenes.[9] This means that the passage through anions of type **C** of 1,3-dialkoxycalix[4]arenes is particularly difficult, and indeed, many authors have stated that the K_2CO_3-catalyzed alkylation does not proceed beyond disubstitution even with an excess of reactants (see for example refs 14b and 17). However, Reinhoudt and Ungaro have observed the occurrence of trisubstitution in methylation of calix[4]arenes when more than 1 equiv of K_2CO_3 is used.[9c] The low reactivity of 1,3-dialkoxycalix[4]arenes toward further alkylation has been attributed to the preferred conformation of these compounds (see ref 9a and 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*, 4165–4176).

2:1. Again, these latter compounds tend to accumulate, not only because of the low stability of the monoions that can be derived from them, but also because of the increased crowding, finally giving heptabenzyl ether **7**.

The data above indicate that the relative stability of anionic intermediates is a major controlling factor for the regioselectivity of the reaction. Many intermediate compounds that appear in the reaction scheme are not seen at the sensitivity level of TLC analysis. This means that either they are not formed in appreciable amount or they undergo a faster subsequent alkylation. The presence of $\mathbf{3}_{1,3,5}$ in amounts higher than those of $\mathbf{3}_{1,3,6}$ indicates that 1,3- and 1,5-disubstitution are preferred to 1,4-disubstitution (Figure 2). Furthermore, the higher yields of $\mathbf{2}_{1,3}$ can be explained by its preferential formation or by assuming an alkylation rate through step c slower than that of the alkylation of $\mathbf{2}_{1,5}$ through step c′ (Figure 2). However, to assess the relative weight of thermodynamic versus kinetic factors, a detailed kinetic study is required.

Formation of $\mathbf{3}_{1,2,4}$ is more difficult to explain, since it implies a passage through less stable anions of type **B** (Figure 1) at the level of either dialkylation (if the triether is formed via 1,2-disubstitution, followed by alkylation at position 4) or trialkylation (if the triether is formed from 1,3- or 1,4-disubstituted compounds). Since we have no evidence for the formation of 1,2-disubstituted calix[8]arene, the latter hypothesis appears to be more plausible. A similar unexpected proximal substitution has been observed by Janssen et al.[12b] and by Otsuka et al.[26] in the weak base-catalyzed methylation of *p-tert*-butylcalix[6]arene and has been related to the weaker circular hydrogen bonding of *p-tert*-butylcalix[6]arene responsible for a less pronounced difference in the acidity between adjacent or alternate phenolic hydroxyls.[12b] In addition to this explanation, we suggest that either temporary conformational preferences of intermediates or the conformational mobility of calix[8]arenes could also play a role in the hydrogen-bonding stabilization of the anions in the case at hand.

The alternate alkylation mechanism here investigated for calix[8]arenes appears to be of general validity for calix[*n*]arenes. It was first observed for calix[4]arenes,[9] and recent results from this laboratory indicate that it also applies to the alkylation of calix[6]arenes, provided that a suitable weak base is used.[13b]

Conclusions

The course of the reaction between *p-tert*-butylcalix[8]arene and *p*-methylbenzyl bromide in the presence of CsF has been investigated as a model to understand the mechanism of the formation of the 1,3,5,7-tetrasubstituted derivatives. Starting from *p-tert*-butylcalix[8]arene, we carried out a sequence of separate monalkylation steps leading to the isolation and structural characterization of several partially benzylated calix[8]arenes, ranging from mono- to heptaalkylated compounds. Successively, these compounds have been used as reference samples for a semiquantitative analysis of the product composition during the reaction in the conditions usually adopted for preparative purpose. It was thus possible to obtain evidence that the main pathway goes from the monobenzyl derivative to the 1,3-disubstituted compound which is rapidly converted into the 1,3,5-trisubstituted compound. This in turn gives rise to the 1,3,5,7-tetraether, which accumulates in the reaction mixture, since its conversion into the 1,2,3,5,7-pentaether is slow. Further alkylation to the hexasubstituted derivatives having free OH groups at positions 1,3 or 1,5 is followed by the formation of the heptaalkylated derivative. Isolation of small amounts of the 1,2,4-trisubstituted derivative indicates that a secondary pathway is also operating.

The preferential formation of the above-discussed products of partial alkylation indicates that, when the alternate alkylation route is operating, the relative stability of the intermediate monoanions is affected not only by the number of stabilizing hydrogen bonds but also by other factors. These could be related either to the conformational preference of the intermediate monoanions or to the conformational mobility of this large macrocycle, since both could affect the effectiveness of H bond stabilization.

In the course of the present study, we have found that direct alkylations of *p-tert*-butylcalix[8]arene under suitable conditions lead to the isolation in 25–50% yields of mono(*p*-methylbenzyl)calix[8]arene **1**, 1,3-bis(*p*-methylbenzyl)calix[8]arene $\mathbf{2}_{1,3}$, 1,3,5,7-tetrakis(*p*-methylbenzyl)-calix[8]arene $\mathbf{4}_{1,3,5,7}$, 1,2,3,5,7-pentakis(*p*-methylbenzyl)-calix[8]arene $\mathbf{5}_{1,3,5}$, and heptakis(*p*-methylbenzyl)calix[8]-arene **7**, whereas other partially substituted calix[8]arenes were obtained in lower yields. These derivatives are potentially useful for the construction of new hosts for medium-sized molecules as well as being substrates for structure–activity studies on the nature of intermolecular interactions in the 1:1 complex of C_{60} and *p-tert*-butylcalix[8]arene.[4,31]

Experimental Section

General Comments. Melting points are uncorrected. NMR spectra were taken on a Bruker AC-250 spectrometer operating at 250.13 (^{1}H) and 62.9 (^{13}C) MHz, using Me_4Si as internal standard. Long-range HETCOR experiments were performed using a standard pulse sequence with polarization transfer delays optimized for $J_{C,H}$ = 10 Hz. Elemental analyses were obtained from the Institute of Pharmaceutical Chemistry of the University of Catania. Column chromatography was performed using silica gel (Kieselgel 60, 63–200 μm, Merck). Preparative TLC (PTLC) was carried out using silica gel plates (Kieselgel 60 F_{254}, 1 mm, 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 (**C8**) was prepared by a literature procedure.[32]

Monoalkylation of C8 with *p*-Methylbenzyl Bromide and CsF. A solution of of *p-tert*-butylcalix[8]arene (**C8**) (3 g, 2.3 mmol) in THF/DMF (10:1 v/v, 260 mL) was stirred at 60 °C until a clear solution was obtained (20 min), CsF (0.42 g, 2.77 mmol) was added, and stirring under nitrogen was continued for an additional 20 min. A solution of *p*-methylbenzyl bromide (4.27 g, 23.1 mmol) in THF (6 mL) was added, and the resulting mixture was refluxed for 40 h. Evaporation of the solvents afforded a solid residue that was subjected to trituration with 0.1 N HCl (100 mL), followed by washing with MeOH (50 mL). The remaining material was suspended in CH_2Cl_2/MeOH (1:1 v/v, 50 mL) and the suspension filtered. The filtrate was evaporated to dryness, and the residue was purified by column chromatography (CH_2Cl_2/*n*-hexane, 1:3 v/v as the eluent) to afford 5,11,17,23,29,35,41,47-octa-*tert*-butyl-49-[(4-methylbenzyl)oxy]calix[8]arene-50,51,52,53,54,55,56-heptol (**1**) (1.61 g, 49.7%): mp 361–362 °C; R_f 0.76 (CH_2Cl_2/

(31) The relevance of these studies has been recently highlighted (Constable, E. C. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2269–2271), and a first effort in this direction has appeared very recently (Suzuki, T.; Nakashima, K.; Shinkai, S. *Tetrahedron Lett.* **1995**, *36*, 249–252).

(32) Munch, J. H.; Gutsche, C. D. *Org. Synth.* **1989**, *68*, 243–246.

cyclohexane, 1:1); ^{1}H-NMR ($CDCl_3$, 320 K) δ 1.20, 1.21, 1.22, 1.25, 1.27 (s, 18 H, 18 H, 18 H, 9 H, 9 H), 2.32 (s, 3 H), 3.74, 3.81, 3.94, 3.99 (s, 4 H each), 4.67 (s, 2 H), 7.07–7.31 (overlapped, 16 H), 7.37 and 7.57 (AB, J = 7.5 Hz, 4 H), 8.93, 8.99, 9.18 (bs, 2 H each), 9.47 (s, 1 H); ^{13}C-NMR ($CDCl_3$, 320 K) δ 21.5, 31.5 (q), 32.5, 32.8 (t), 34.0, 34.4 (s), 77.4 (t), 125.3, 125.6, 125.9, 126.8, 129.2, 129.6 (d), 127.0, 127.8, 127.9, 128.1, 128.3, 128.8, 133.0, 133.7, 138.8, 143.2, 144.2, 144.6, 144.8, 146.8, 146.9, 147.1, 147.4, 148.3, 148.7, 150.6 (s). Anal. Calcd for $C_{96}H_{120}O_8$: C, 82.24; H, 8.63. Found: C, 82.16; H, 8.56.

Monoalkylation of 1. A solution of **1** (1.2 g, 0.85 mmol) in THF/DMF (10:1 v/v, 100 mL) was stirred at 60 °C until a clear solution was obtained (20 min), CsF (0.15 g, 1.02 mmol) was added, and stirring under nitrogen was continued for an additional 20 min. A solution of *p*-methylbenzyl bromide (1.58 g, 8.5 mmol) in THF (8 mL) was then added, and the reaction mixture was refluxed for 24 h. After evaporation of the solvents, the residue was taken up in CH_2Cl_2 and washed with 0.1 N HCl (50 mL). The organic phase was dried (Na_2SO_4), and the solvent was evaporated to give a residue that was purified by column chromatography by eluting with CH_2Cl_2/cyclohexane (2:3 v/v) to afford fractions A–C.

Fraction A gave 5,11,17,23,29,35,41,47-octa-*tert*-butyl-49,51-bis[(4-methylbenzyl)oxy]calix[8]arene-50,52,53,54,55,56-hexol (**2**$_{1,3}$) (283 mg, 22%): mp 202–204 °C; R_f 0.63 (CH_2Cl_2/cyclohexane, 1:1 v/v); ^{1}H-NMR ($CDCl_3$, 335 K) δ 1.09, 1.10, 1.20, 1.21, 1.24 (s, 9 H, 9 H, 18 H, 18 H, 18 H), 2.30 (s, 6 H), 3.78, 3.82, 3.90, 3.97 (s, 4 H each), 4.80 (s, 4 H), 6.87–7.45 (overlapped, 24 H), 8.10–8.90 (overlapped, 6 H); ^{13}C-NMR ($CDCl_3$, 320 K) δ 21.3, 31.3, 31.5 (q), 32.2, 32.4 (t), 34.0, 34.3 (s), 77.7 (t), 124.4, 125.3, 125.5, 125.6, 125.8, 126.3, 126.8, 129.1, 129.6 (d), 128.0, 128.01, 128.6, 132.2, 132.7, 133.3, 138.7, 143.3, 144.2, 144.4, 146.9, 147.2, 148.0, 149.3, 150.9 (s). Anal. Calcd for $C_{104}H_{128}O_8$: C, 82.94; H, 8.56. Found: C, 82.68; H, 8.39.

Fraction B afforded 5,11,17,23,29,35,41,47-octa-*tert*-butyl-49,52-bis[(4-methylbenzyl)oxy]calix[8]arene-50,51,53,54,55,56-hexol (**2**$_{1,4}$) (207 mg, 16%): mp 143–145 °C; R_f 0.54 (CH_2Cl_2/cyclohexane, 1:1 v/v); ^{1}H-NMR (C_6D_6, 307 K) δ 1.04, 1.09, 1.10, 1.12 (s, 18 H each), 1.99 (s, 6 H), 3.59 (s, 4 H), 3.59, 3.65, 3.71, 3.86, 3.96 (s, 4 H, 2 H, 2 H, 4 H, 4 H), 4.83 (s, 4 H), 6.99–7.12 (overlapped, 24 H), 7.11 and 7.42 (AB, J = 7.6 Hz, 8 H), 8.71, 9.31, 9.41 (s, 2 H each); ^{13}C-NMR (C_6D_6, 307 K) δ 21.4, 31.5, 31.8 (q), 32.0, 32.8, 32.9 (t), 34.0, 34.1, 34.4 (s), 78.3 (t), 125.3, 125.9, 126.0, 126.2, 126.6, 127.2, 128.4, 129.6, 130.1 (d), 127.6, 128.0, 133.4, 135.6, 134.0, 138.9, 142.9, 143.2, 144.0, 148.2, 149.5, 149.7, 151.1 (s). Anal. Calcd for $C_{104}H_{128}O_8$: C, 82.94; H, 8.57. Found: C, 82.87; H, 8.42.

Fraction C provided 5,11,17,23,29,35,41,47-octa-*tert*-butyl-49,53-bis[(4-methylbenzyl)oxy]calix[8]arene-50,51,52,54,55,56-hexol (**2**$_{1,5}$) (181 mg, 14%): mp 175–177 °C; R_f 0.47 (CH_2Cl_2/cyclohexane, 1:1 v/v); ^{1}H-NMR ($CDCl_3$, 308 K) δ 1.13, 1.15, 1.16 (s, 36 H, 18 H, 18 H), 2.15 (s, 6 H), 3.61, 3.93 (s, 8 H each), 4.73 (s, 4 H), 6.89–7.11 (overlapped, 16 H), 7.22 and 7.34 (AB, J = 7.8 Hz, 8 H), 8.41, 8.51 (s, 2 H, 4 H); ^{13}C-NMR ($CDCl_3$, 308 K) δ 21.3, 31.5, 31.9 (q), 33.9, 34.2 (t), 33.9, 34.3 (s), 77.8 (t), 125.1, 125.3, 125.5, 126.6, 128.8, 129.7 (d), 127.1, 127.5, 132.5, 132.8, 138.8, 142.7, 143.4, 147.8, 147.9, 148.6, 150.5 (s). Anal. Calcd for $C_{104}H_{128}O_8$: C, 82.94; H, 8.57. Found: C, 82.84; H, 8.46.

Monoalkylation of 2$_{1,5}$. A solution of **2**$_{1,5}$ (0.15 g, 0.099 mmol) in THF/DMF (10:1 v/v, 12 mL) was stirred at 60 °C until a clear solution was obtained (20 min), CsF (18 mg, 0.12 mmol) was added, and stirring under nitrogen was continued for an additional 20 min. A solution of *p*-methylbenzyl bromide (0.184 g, 0.995 mmol) in THF (1 mL) was added, and the resulting mixture was refluxed for 24 h. After evaporation of the solvents, the residue was taken up in CH_2Cl_2 and washed with 0.1 N HCl (50 mL). The organic phase was dried (Na_2SO_4), and the solvent was evaporated to give a residue that was subjected to PTLC (CH_2Cl_2/cyclohexane, 3:2 v/v) to yield 5,11,17,23,29,35,41,47-octa-*tert*-butyl-49,51,53-tris[(4-methylbenzyl)oxy]calix[8]arene-50,52,54,55,56-pentol (**3**$_{1,3,5}$) (66 mg, 41%): mp 163–165 °C; R_f 0.36 (CH_2Cl_2/cyclohexane, 1:1 v/v); ^{1}H-NMR (C_6D_6, 325 K) δ 1.07, 1.13, 1.22, 1.28, 1.30 (s, 9 H, 18 H, 9 H, 18 H, 18 H), 2.07, 2.08 (s, 6 H, 3 H), 3.81, 3.97, 4.00, 4.07 (s, 4 H each), 4.74, 4.80 (s, 2 H, 4 H), 6.90–7.33 (overlapped, 28 H); ^{13}C-NMR ($CDCl_3$, 310 K) δ 21.0, 21.1, 31.3, 31.6 (q), 32.1, 32.3 (t), 33.9, 34.2 (s), 77.2, 77.7 (t), 125.3, 125.6, 125.9, 126.0, 126.3, 126.7, 128.6, 128.9, 129.2, 129.3, 129.5 (d), 127.7, 127.9, 129.1, 129.3, 129.5, 130.5, 132.7, 133.0, 138.5, 142.1, 143.0, 143.6, 147.6, 149.1, 150.4, 151.0 (s). Anal. Calcd for $C_{112}H_{136}O_8$: C, 83.54; H, 8.51. Found: C, 83.44; H, 8.46.

Monoalkylation of 2$_{1,4}$. Diether **2**$_{1,4}$ (0.15 g, 0.099 mmol) was reacted under the same conditions as **2**$_{1,5}$ to give a crude product that was purified by PTLC (AcOEt/cyclohexane, 1:19 v/v) to give 5,11,17,23,29,35,41,47-octa-*tert*-butyl-49,51,54-tris[(4-methylbenzyl)oxy]calix[8]arene-50,52,53,55,56-pentol (**3**$_{1,3,6}$) (53 mg, 33%): mp 146–149 °C; R_f 0.33 (CH_2Cl_2/cyclohexane, 1:1 v/v); ^{1}H-NMR (C_6D_6, 340 K) δ 1.11, 1.17, 1.24, 1.26, 1.27 (s, 18 H, 9 H, 18 H, 18 H, 9 H), 2.11, 2.13 (s, 6 H, 3 H), 3.86, 3.96, 4.01, 4.02 (s, 4 H each), 4.77, 4.88 (s, 4 H, 2 H), 7.00–7.32 (overlapped, 28 H). Anal. Calcd for $C_{112}H_{136}O_8$: C, 83.54; H, 8.51. Found: C, 83.47; H, 8.44.

Monoalkylation of 2$_{1,3}$. Diether **2**$_{1,3}$ (0.15 g, 0.099 mmol) was reacted in the same conditions as **2**$_{1,5}$ to give a crude product that was purified by PTLC (AcOEt/cyclohexane, 1:19 v/v) to give compounds **3**$_{1,3,5}$ (37 mg, 23%) and **3**$_{1,3,6}$ (31 mg, 19%).

Monoalkylation of 4$_{1,3,5,7}$. A solution of **4**$_{1,3,5,7}$ (60 mg, 0.035 mmol) in THF/DMF (10:1 v/v, 6.6 mL) was reacted with CsF (6 mg, 0.042 mmol) and *p*-methylbenzyl bromide (65 mg, 0.35 mmol) for 9 h under reflux. Usual workup afforded a crude product that was subjected to PTLC (CH_2Cl_2/cyclohexane, 3:2 v/v) to give 5,11,17,23,29,35,41,47-octa-*tert*-butyl-49,50,51,53,55-pentakis[(4-methylbenzyl)oxy]calix[8]arene-52,54,56-triol (**5**$_{1,3,5}$) (30 mg, 48%): mp 136–140 °C; R_f 0.49 (CH_2Cl_2/cyclohexane, 1:1 v/v); ^{1}H-NMR ($CDCl_3$, 295 K) δ 0.85, 1.01, 1.12, 1.19, 1.22 (s, 9 H, 18 H, 18 H, 9 H, 18 H), 2.09, 2.26, 2.27 (s, 6 H, 3 H, 6 H), 3.82, 3.91, 4.15 (s, 8 H, 4 H, 4 H), 4.60, 4.76, 4.90 (s, 4 H, 2 H, 4 H), 6.72–7.31 (overlapped, 38 H), 7.66 (s, 1 H); ^{13}C-NMR ($CDCl_3$, 295 K) δ 21.0, 21.1, 21.2 (q), 29.7, 30.5, 32.0 (t), 31.2, 31.3, 31.6 (q), 33.9, 34.1 (s), 74.7, 76.0, 76.8 (t), 124.9, 125.0, 125.4, 125.5, 125.9, 126.4, 126.7, 127.6, 128.0, 128.2, 128.9, 129.0, 129.1, 129.2 (d), 127.0, 132.6, 132.7, 132.9, 134.1, 134.9, 137.3, 137.6, 137.8, 141.7, 141.8, 146.9, 147.1, 147.2, 150.7, 150.8, 151.3, 151.9, 152.4 (s). Anal. Calcd for $C_{128}H_{152}O_8$: C, 84.54; H, 8.42. Found: C, 84.38; H, 8.34.

Dialkylation of 4$_{1,3,5,7}$. A mixture of **4**$_{1,3,5,7}$ (72 mg, 0.042 mmol) in THF/DMF (10:1 v/v, 8.6 mL), CsF (15 mg, 0.099 mmol), and *p*-methylbenzyl bromide (75 mg, 0.405 mmol) was reacted for 20 h as usual. PTLC (CH_2Cl_2/cyclohexane, 1:1 v/v) of the crude product gave four bands with R_f = 0.57 (A), 0.64 (B), 0.69 (C), and 0.72 (D). From band A, compound **5**$_{1,3,5}$ was recovered (23 mg, 30%), while bands C and D gave **7** (8 mg, 9%) and **8** (2 mg, 2%), respectively. Band B turned out to be a mixture of hexasubstituted derivatives which were separated by PTLC (AcOEt/cyclohexane, 1:19 v/v, two runs) to give **6**$_{1,3}$ and **6**$_{1,5}$.

5,11,17,23,29,35,41,47-Octa-*tert*-butyl-49,50,51,52,53,55-hexakis[(4-methylbenzyl)oxy]calix[8]arene-54,56-diol (6$_{1,3}$) (12 mg, 15%): mp 140–143 °C; R_f 0.33 (AcOEt/cyclohexane, 1:19 v/v); ^{1}H-NMR ($CDCl_3$, 334 K) δ 0.98, 0.99, 1.07, 1.11, 1.23 (s, 18 H, 18 H, 9 H, 9 H, 18 H), 2.08, 2.20, 2.24, 2.26 (s, 3 H, 6 H, 3 H, 6 H), 3.80, 3.88, 4.08, 4.12 (s, 4 H each), 4.55, 4.63, 4.71, 4.80 (s, 2 H, 4 H, 2 H, 4 H), 6.42 (s, 2 H), 6.78–7.26 (overlapped, 40 H); ^{13}C-NMR ($CDCl_3$, 295 K) δ 20.8, 21.0, 21.1 (q), 30.5, 30.6 (t), 31.1, 31.2, 31.3 (q), 33.9, 34.0 (s), 74.7, 74.9, 75.8, 76.5 (t), 124.9, 125.4, 125.9, 126.1, 126.2, 127.4, 127.6, 128.0, 128.6, 128.9, 129.1 (d), 125.7, 127.1, 128.3, 132.5, 132.6, 132.8, 132.9, 133.2, 133.3, 134.0, 134.7, 134.8, 137.0, 137.6, 141.7, 146.1, 146.3, 146.6, 146.9, 150.5, 151.6, 151.8, 152.8, 153.1 (s). Anal. Calcd for $C_{136}H_{160}O_8$: C, 84.96; H, 8.39. Found: C, 84.84, H, 8.25.

5,11,17,23,29,35,41,47-Octa-*tert*-butyl-49,50,51,53,54,55-hexakis[(4-methylbenzyl)oxy]calix[8]arene-52,56-diol (6$_{1,5}$) (6 mg, 7%): mp 124–126 °C; R_f 0.35 (AcOEt/cyclohexane, 1:19 v/v); ^{1}H-NMR ($CDCl_3$, 295 K) δ 0.95, 1.03, 1.22 (s, 36 H, 18 H, 18 H), 2.12, 2.20 (s, 6 H, 12 H), 3.86, 4.00 (s, 8 H each), 4.41, 4.64 (s, 4 H, 8 H), 6.84–7.26 (overlapped, 42 H); ^{13}C-NMR ($CDCl_3$, 295 K) δ 21.1, 21.2 (q), 29.7, 30.4 (t), 31.3, 31.6 (q),

33.8, 34.1 (s), 74.8, 75.3 (t), 125.3, 125.6, 125.8, 126.3, 127.3, 128.0, 128.9, 129.0 (d), 132.7, 132.9, 134.1, 134.6, 136.7, 137.4, 141.9, 146.1, 146.5, 150.8, 151.9, 153.4 (s). Anal. Calcd for $C_{136}H_{160}O_8$: C, 84.96; H, 8.39. Found: C, 84.78; H, 8.27.

5,11,17,23,29,35,41,47-Octa-*tert*-butyl-49,50,51,52,53,54,55-heptakis[(4-methylbenzyl)oxy]calix[8]aren-56-ol (7). A solution of **C8** (0.5 g, 0.385 mmol) in THF/DMF (10:1 v/v, 44 mL) was refluxed with *p*-methylbenzyl bromide (2.28 g, 12.32 mmol) and CsF (1.87 g, 12.31 mmol) for 20 h. Column chromatography (CH_2Cl_2/cyclohexane, 9:11 v/v) of the residue afforded compound **8** (202 mg, 25%) and compound **7** (296 mg, 38%): mp 142–144 °C; ^{1}H-NMR ($CDCl_3$, 295 K) δ 0.92, 0.93, 1.00, 1.05, 1.17 (s, 9 H, 18 H, 18 H, 18 H, 9 H), 2.12, 2.16, 2.23 (s, 6 H, 3 H, 12 H), 3.84, 4.05, 4.12 (s, 4 H, 4 H, 8 H), 4.53, 4.58, 4.60, 4.70 (s, 4 H, 2 H, 4 H, 4 H), 6.72–7.26 (overlapped, 45 H); ^{13}C-NMR ($CDCl_3$, 295 K) δ 20.7, 21.0, 21.1 (q), 29.7, 30.2, 30.5 (t), 31.3, 31.5 (q), 33.9, 34.0, 34.1 (s), 74.7, 75.6 (t), 125.2, 125.7, 126.0, 126.2, 126.3, 126.5, 126.6, 127.6, 127.9, 128.9 (d), 127.8, 132.6, 133.0, 133.1, 133.2, 133.6, 134.6, 134.7, 134.9, 137.0, 137.01, 137.4, 141.8, 146.0, 146.03, 146.2, 146.5, 150.5, 152.3, 152.6, 152.7, 152.9 (s). Anal. Calcd for $C_{144}H_{168}O_8$: C, 85.33; H, 8.35. Found: C, 85.24; H, 8.26.

Preparation of 5,11,17,23,29,35,41,47-Octa-*tert*-butyl-49,50,51,52,53,54,55,56-octakis[(4-methylbenzyl)oxy]calix[8]arene (8). Compound **C8** (0.5 g, 0.385 mmol) in THF/DMF (10:1 v/v, 44 mL) was reacted with *p*-methylbenzyl bromide (2.28 g, 12.32 mmol) and NaH (0.3 g, 12.5 mmol) in the standard conditions for 70 h. The final treatment with HCl was followed by washing with MeOH to give compound **8** (0.64 g, 78%): mp 252–255 °C; ^{1}H-NMR ($CDCl_3$, 323 K) δ 1.01 (s, 72 H), 2.08 (s, 24 H), 4.09 (s, 16 H), 4.60 (s, 16 H), 6.80 and 7.06 (AB, J = 7.5 Hz, 32 H), 7.05 (s, 16 H); ^{13}C-NMR ($CDCl_3$, 295 K) δ 20.8 (q), 30.0 (t), 31.3 (q), 34.0 (s), 74.7 (t), 126.0, 127.8, 128.8 (d), 133.2, 134.5, 136.9, 145.9, 152.7 (s). Anal. Calcd for $C_{152}H_{176}O_8$: C, 85.67; H, 8.32. Found: C, 85.52; H, 8.23.

Time Course Dependence of the Concentration of Partial Derivatives. A suspension of **C8** (0.5 g, 0.385 mmol) in THF/DMF (10:1 v/v, 44 mL) was refluxed under stirring until a clear solution was obtained (20 min), CsF (0.93 g, 6.122 mmol) was added, and stirring under nitrogen was continued for an additional 20 min. A solution of *p*-methylbenzyl bromide (0.57 g, 3.081 mmol) in THF (3 mL) was then added, and stirring under reflux was maintained. Aliquots of the reaction mixture were withdrawn at 30 min intervals and concentrated under vacuum, and the residue was washed with 0.1 N HCl, followed by MeOH. The crude product was analyzed by TLC (CH_2Cl_2/cyclohexane, 9:11 v/v) in comparison with reference samples. For preparative purposes, six separate experiments were run and stopped at 2, 3, 7, 13, 23, and 32 h, respectively. The residue obtained was subjected to PTLC (CH_2Cl_2/cyclohexane, 9:11 v/v) in order to identify the products by spectral methods and to estimate their relative abundance. The results are reported in Figure 9. PTLC of the reaction quenched after 7 h gave, in addition to $\mathbf{2}_{1,3}$, $\mathbf{3}_{1,3,5}$, $\mathbf{4}_{1,3,5,7}$, $\mathbf{5}_{1,3,5}$ and a mixture of hexasubstituted $\mathbf{6}_{1,3}$ and $\mathbf{6}_{1,5}$, the triether 5,11,17,23,29,35,41,47-octa-*tert*-butyl-49,50,52-tris[(4-methylbenzyl)oxy]calix[8]arene-51,53,54,55,56-pentol ($\mathbf{3}_{1,2,4}$) (31 mg, 10%): mp 154–159 °C; R_f 0.63 (CH_2Cl_2/cyclohexane, 1:1 v/v); ^{1}H-NMR ($CDCl_3$, 295 K) δ 1.00, 1.08, 1.15, 1.22, 1.23 (s, 9 H, 9 H, 9 H, 9 H, 36 H), 2.25, 2.26, 2.29 (s, 3 H each), 3.79, 3.84, 3.86, 3.89, 3.92, 4.18 (s, 4 H, 4 H, 2 H, 2 H, 2 H, 2 H), 4.78, 4.82, 4.96 (s, 2 H each), 6.76–7.42 (overlapped, 28 H), 7.47, 8.70, 8.77, 9.04 (s, 1 H, 1 H, 1 H, 2 H); ^{13}C-NMR ($CDCl_3$, 295 K) δ 21.2, 21.3 (q), 29.7, 30.5, 30.9, 32.0, 32.2, 32.4 (t), 31.1, 31.3, 31.5 (q), 33.9, 34.1, 34.2 (s), 76.3, 76.6, 76.7 (t), 124.3, 125.1, 125.2, 125.5, 125.8, 126.4, 126.6, 126.8, 127.2, 127.4, 127.9, 128.0, 128.5, 128.7, 129.0, 129.2, 129.4, 129.6, 129.7, 129.8 (d), 127.6, 127.7, 132.1, 132.4, 132.49, 132.5, 132.9, 133.0, 132.2, 132.3, 133.7, 137.8, 138.2, 141.9, 142.8, 143.3, 143.7, 143.8, 147.0, 147.2, 147.24, 147.4, 147.5, 147.9, 148.4, 149.3, 150.4, 151.0, 151.4 (s). Anal. Calcd for $C_{112}H_{136}O_8$: C, 83.54; H, 8.51. Found: C, 83.42; H, 8.45.

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