Methylation of *p-tert*-Butylcalix[8]arene. Products Obtained in the Presence of Strong Bases†

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Methylation of *p-tert*-butylcalix[8]arene with MeI in the presence of strong bases (NaH, BaO/Ba(OH)$_2$, or Cs_2CO_3) in THF has been investigated. Composition of the reaction mixtures differs remarkably from those obtained using weak bases and described in a preceding paper. Several previously unreported methylated products [two dimethoxy- (**2**$_{1,5}$ and **2**$_{1,4}$), a trimethoxy- (**3**$_{1,2,5}$), a tetramethoxy- (**4**$_{1,2,3,6}$), two pentamethoxy- (**5**$_{1,2,3}$ and **5**$_{1,2,4}$), and three hexamethoxy- (**6**$_{1,2}$, **6**$_{1,3}$, and **6**$_{1,4}$)] have been isolated. In many cases the substitution pattern was assigned unambiguously on the basis of spectroscopic evidence only, while in others chemical correlation with known compounds was required.

Introduction

Calixarenes[1] are a class of compounds of particular interest in supramolecular chemistry because of their inclusion properties toward cations,[2] anions,[3] and neutral molecules.[4] Their recognition ability can be enhanced and targeted by appropriate functionalization along the macrocycle.[2−4] Electrophilic substitution at the *para* positions (upper rim) and alkylation of phenolic hydroxyls (lower rim) are the simplest ways to introduce functional groups in these molecules.[1] Methylation of the OH groups has been largely investigated as the groundwork to define the regioselectivity under diverse conditions as well as a viable method to prepare partially substituted derivatives to be used as substrates in subsequent manipulations. In these studies all possible methylation products of *p-tert*-butylcalix[n]arenes (n = 4, 5, 6) except 1,2,3-trimethoxy-*p-tert*-butylcalix[5]arene were prepared.[5−7]

As regards the larger *p-tert*-butylcalix[8]arene (**C8**), in preceding papers[8] we reported the results obtained in the methylation promoted by weak bases (K_2CO_3 or CsF). Under those conditions a number of compounds partially methylated in alternate phenolic rings were obtained, some of them characterized by a very scarce solubility in organic solvents.[8c] They are formed through the so-called *alternate alkylation* route,[9] which is driven by the preferential formation of monoanions more stabilized by hydrogen bonding with neighboring OH groups. In addition, a concurrent secondary route leading to proximal substitution also occurs to some extent. Consequently, it was expected that in the presence of stronger bases, which are able to carry out less selective monodeprotonation or multiple deprotonation, products with different substitution patterns could be formed.[10] Considering the interest for methoxycalix[8]arenes with specific substitution patterns,[5−8] we have deemed useful

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(1) For comprehensive reviews on calixarenes see: Gutsche, C. D.; *Calixarenes*; Stoddart, J. F.; Ed.; Monographs in Supramolecular Chemistry; The Royal Society of Chemistry: Cambridge, 1989; Vol. 1. *Calixarenes, a Versatile Class of Macrocyclic Compounds*; Vicens, J.; Böhmer, V.; Eds.; Kluwer: Dordrecht, 1991. Böhmer, V. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 713. Ikeda, A.; Shinkai, S. *Chem. Rev.* **1997**, *97*, 1713.

(2) 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. Casnati, A.; Pochini, A.; Ungaro, R.; Ugozzoli, F.; Arnaud, F.; Fanni, S.; Schwing, M.-J.; Egberink, R. J. M.; de Jong, F.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1995**, *117*, 2767.

(3) Rudkevich, D. M.; Mercer-Chalmers, J. D.; Verboom, W.; Ungaro, R.; de Jong, F.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1995**, *117*, 6124 and references therein. Beer, P. D.; Gale, P. A.; Hesek, D. *Tetrahedron Lett.* **1995**, *36*, 767 and references therein.

(4) Timmerman, P.; Verboom, W.; van Veggel, F. C. J. M.; van Duynhoven, J. P. M.; Reinhoudt, D. N. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2345. Timmerman, P.; Brinks, E. A.; Verboom, W.; Reinhoudt, D. N. *J. Chem. Soc., Chem. Commun.* **1995**, 417.

(5) For the methylation of calix[4]arenes, see: Gutsche, C. D.; Dhawan, B.; Levine, J. A.; No, K. H.; Bauer, L. J. *Tetrahedron* **1983**, *39*, 409. Alfieri, C.; Dradi, E.; Pochini, A.; Ungaro, R. *Gazz. Chim. Ital.* **1989**, *119*, 335. 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. Groenen, L. C.; van Loon, J.-D.; Verboom, W.; Harkema, S.; Casnati, A.; Ungaro, R.; Pochini, A.; Ugozzoli, F.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1991**, *113*, 2385.

(6) For the methylation of calix[5]arenes, see Stewart, D. R.; Krawiec, M.; Kashyap, R. P.; Watson, W. H.; Gutsche, C. D. *J. Am. Chem. Soc.* **1995**, *117*, 586.

(7) For the methylation of calix[6]arenes, see: (a) Casnati, A.; Minari, P.; Pochini, A.; Ungaro, R. *J. Chem. Soc., Chem. Commun.* **1991**, 1413. (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. (c) Otsuka, H.; Araki, K.; Shinkai, S. *J. Org. Chem.* **1994**, *59*, 1542.

(8) Neri, P.; Battocolo, E.; Cunsolo, F.; Geraci, C.; Piattelli, M. *J. Org. Chem.* **1994**, *59*, 3880. (b) Cunsolo, F.; Consoli, G. M. L.; Piattelli, M.; Neri, P. *Tetrahedron Lett.* **1995**, *36*, 3751. (c) Consoli, G. M. L.; Cunsolo, F.; Neri, P. *Gazz. Chim. Ital.* **1996**, *126*, 791.

(9) Neri, P.; Geraci C.; Piattelli, M. *J. Org. Chem.* **1995**, *60*, 4126 and references therein.

(10) In fact, in the partial alkylation of calix[4]arenes the use of K_2CO_3 affords selectively 1,3-disubstituted derivatives[10a,b] and that of NaH the 1,2-regioisomers.[10c,d] (a) 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. (b) 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. (c) Bottino, F.; Giunta, L.; Pappalardo, S. *J. Org. Chem.* **1989**, *54*, 5407. (d) 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.

(11) To give an immediate insight into the substitution pattern of calix[8]arenes, in the present paper we used the same nomenclature system adopted in refs 7c and 8c. The bold-faced number indicates the number of substituents (i.e. methyl groups), while the subscript refers to their location. For shortness, in the case of penta- and hexasubstituted compounds the subscript refers to the unsubstituted aromatic rings. Thus, **6**$_{1,3}$ indicates a hexasubstituted derivative with the two unsubstituted rings in a 1,3 relative position.

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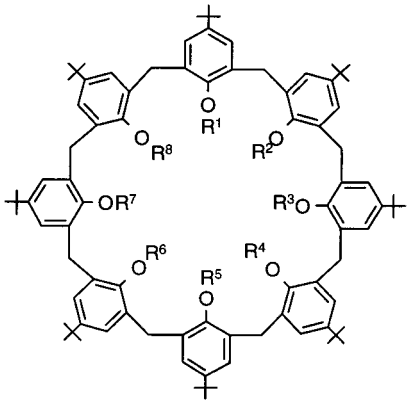
an investigation into the methylation of *p-tert*-butylcalix[8]arene in the presence of NaH, $BaO/Ba(OH)_2$, or Cs_2CO_3 and we report here the results obtained.

Results and Discussion

Methylation of C8 in the Presence of NaH or $BaO/Ba(OH)_2$. Initially we investigated the methylation of *p-tert*-butylcalix[8]arene **C8** in the presence of strong bases using excess (16 equiv) NaH, one of the most typical bases for *O*-alkylation of calixarenes. Under this condition, in the presence of amounts of MeI ranging from 4 to 10 equiv, octamethyl derivative **8**[11] was always obtained besides unreacted **C8**. When NaH was replaced by $BaO/Ba(OH)_2$, very similar results were attained. Partial methylation was instead achieved using 8 equiv of NaH and 8 equiv of MeI, leading to the isolation of 1,5-dimethoxycalix[8]arene $\mathbf{2}_{1,5}$[11] in 15% yield.



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	Me	H	H	H	H	H	H	H
$\mathbf{2}_{1,3}$	Me	H	Me	H	H	H	H	H
$\mathbf{2}_{1,4}$	Me	H	H	Me	H	H	H	H
$\mathbf{2}_{1,5}$	Me	H	H	H	Me	H	H	H
$\mathbf{3}_{1,2,4}$	Me	Me	H	Me	H	H	H	H
$\mathbf{3}_{1,2,5}$	Me	Me	H	H	Me	H	H	H
$\mathbf{4}_{1,2,3,6}$	Me	Me	Me	H	H	Me	H	H
$\mathbf{4}_{1,2,3,4}$	Me	Me	Me	Me	H	H	H	H
$\mathbf{5}_{1,2,3}$	H	H	H	Me	Me	Me	Me	Me
$\mathbf{5}_{1,2,4}$	H	H	Me	H	Me	Me	Me	Me
$\mathbf{6}_{1,2}$	H	H	Me	Me	Me	Me	Me	Me
$\mathbf{6}_{1,3}$	H	Me	H	Me	Me	Me	Me	Me
$\mathbf{6}_{1,4}$	H	Me	Me	H	Me	Me	Me	Me
7	Me	Me	Me	Me	Me	Me	Me	H
8	Me	Me	Me	Me	Me	Me	Me	Me
11	H	Et	Et	H	Et	Et	Et	Et
$\mathbf{Et2}_{1,4}$	Me	Et	Et	Me	Et	Et	Et	Et

As observed in a previous work,[8] methoxycalix[8]arenes are conformationally mobile because the small OMe groups can easily pass through the annulus. However, this motion is hindered by intramolecular H-bonds, and hence heating of the sample is sometimes required to have sharp signals in the NMR spectra. In the case of $\mathbf{2}_{1,5}$ the type of disubstitution was evidenced by the presence in its ^{1}H NMR spectrum, acquired at 330 K, of three resonances for *t*-Bu groups (1.21, 1.31, and 1.33 ppm, 1:2:1 intensity ratio), two 1:1 singlets for the $ArCH_2$-Ar (3.91 and 4.04 ppm) and one singlet for OMe groups (3.75 ppm), indicative of a calix[8]arene structure possessing two orthogonal 2-fold symmetry elements.

Table 1. Isolated Yields of Products in the Methylation of *p-tert*-Butylcalix[8]arene with Cs_2CO_3 as Base

compd	yield (%)	compd	yield (%)
$\mathbf{2}_{1,4}$	8	$\mathbf{2}_{1,5}$	5
$\mathbf{3}_{1,2,5}$	15	$\mathbf{4}_{1,2,3,6}$	11
$\mathbf{4}_{1,2,3,4}$	8	$\mathbf{5}_{1,2,3}$	13
$\mathbf{6}_{1,2}$	4	**7**	5
8	18		

Besides $\mathbf{2}_{1,5}$ a second product was isolated in 7% yield, which was identified as an asymmetrical trimethoxy derivative by the presence of seven resonances for *t*-Bu groups and three distinct singlets for methoxyls in its ^{1}H NMR spectrum. Its asymmetry was supported by the presence in the 140−155 ppm region of the ^{13}C NMR spectrum of twelve lines,[12] out of the expected 16, for aromatic quaternary carbons bearing oxygen or *t*-Bu groups. Since of the two possible asymmetrically trisubstituted derivatives $\mathbf{3}_{1,2,4}$ and $\mathbf{3}_{1,2,5}$ the former was known, we could assign the latter structure to the compound in hand.

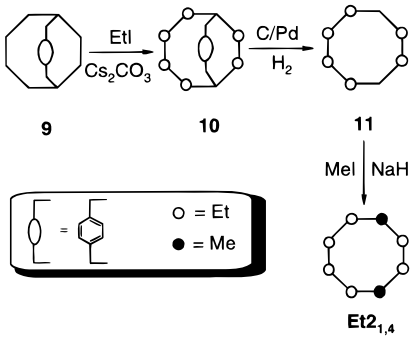
Methylation of C8 in the Presence of Cs_2CO_3. Cesium carbonate behaves as a base stronger than other alkaline carbonates, probably due to the formation of looser ion pairs.[13] Therefore, it was expected that in its presence the reaction would follow a course different from the *alternate alkylation* to give rise to partially methylated calix[8]arenes with unprecedented substitution patterns. Indeed, the mixture obtained by methylation in the presence of Cs_2CO_3 was significantly more soluble in dichloromethane than the analogous mixtures formed in the presence of K_2CO_3 or CsF,[8c] thus giving support to our supposition. In fact, column chromatography of this reaction mixture afforded several partial methyl ethers ranging from di- to octasubstituted calix[8]arenes (Table 1).

Two dimethyl ethers were isolated, one of which was identified as $\mathbf{2}_{1,5}$ while the second one was assigned structure $\mathbf{2}_{1,4}$ on the basis of chemical correlation, since attempts to demonstrate the substitution pattern by 2D NMR spectroscopy proved unsatisfactory. To this end a

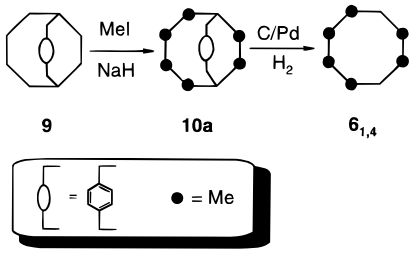
(12) The 28 partially substituted calix[8]arenes can be grouped as follows, in accordance with the number and type of symmetry elements: (a) asymmetrical [16], (b) one symmetry element bisecting opposite aromatic rings (Ar−Ar symmetry) [10], (c) one symmetry element bisecting opposite $ArCH_2Ar$ groups (CH_2-CH_2 symmetry) [8], (d) two orthogonal Ar−Ar elements of symmetry [6], (e) two orthogonal CH_2-CH_2 elements of symmetry [4], and (f) one C_4 axis of symmetry [4]. Assuming free conformational mobility of the macrocycle, the number of the expected NMR resonances for aromatic quaternary carbons bearing oxygen or *t*-Bu groups in the region 140−155 ppm, identical within each group, is indicated in brackets. See also Figure 1 in Neri, P.; Consoli, G. M. L.; Cunsolo, F.; Geraci, C.; Piattelli, M. *New J. Chem.* **1996**, *20*, 433.

(13) Dijkstra, G.; Hruizinga, W. H.; Kellogg, R. M. *J. Org. Chem.* **1987**, *52*, 4230. Iwamoto, K.; Araki, K.; Shinkai, S.; *Tetrahedron* **1991**, *47*, 4325. Shinkai, S. *Tetrahedron* **1993**, *49*, 8933 and references therein.

Scheme 1



Scheme 2



reference compound having two methoxyls certainly placed at 1,4-positions was prepared from the 1,4-(*p*-xylylene)-bridged calix[8]arene **9**, reported by Shinkai.[14] This compound was subjected to exhaustive ethylation to give **10** (Scheme 1), which was hydrogenated (H_2, Pd/C) in order to remove the bridge to yield **11**. Methylation of this last at the 1,4-positions yielded the mixed methyl ethyl ether $\mathbf{Et2}_{1,4}$. On the other hand, $\mathbf{2}_{1,4}$ was subjected to exhaustive ethylation (EtI, Cs_2CO_3) to give a compound indistinguishable from $\mathbf{Et2}_{1,4}$.

The known[8a] tetramethoxy compound $\mathbf{4}_{1,2,3,4}$ and trimethoxy derivative $\mathbf{3}_{1,2,5}$ were isolated in 8% and 15% yield, respectively. A further tetramethoxy derivative, $\mathbf{4}_{1,2,3,6}$, was also isolated (11%), possessing a 2-fold symmetry element bisecting opposite aromatic rings (Ar−Ar symmetry), as evidenced by the presence in its ^{1}H NMR spectrum of five resonances for *t*-Bu groups at 1.17, 1.18, 1.20, 1.22, and 1.28 ppm (2:1:2:1:2). Only two tetramethoxycalix[8]arenes with this symmetry are possible, namely 1,2,4,5- and 1,2,3,6-tetramethoxycalix[8]arene. The choice could be easily made on account of the presence in the ^{1}H NMR spectrum of the isolate of three methoxyl signals at 3.60, 3.75, and 3.82 ppm in a 1:1:2 intensity ratio and three methoxyl resonances at 60.9, 61.7, and 62.1 ppm in its ^{13}C NMR spectrum.

From the more polar chromatographic fractions, four compounds were isolated, two of which were identified as the known[8c] heptamethoxy- and octamethoxycalix[8]arenes, **7** and **8,** while the others were assigned structure $\mathbf{5}_{1,2,3}$ and $\mathbf{6}_{1,2}$ on the basis of the following considerations. ^{1}H NMR data for $\mathbf{6}_{1,2}$ (four 18 H *t*-Bu signals at 1.12, 1.13, 1.18, and 1.25 ppm as well as three 6 H methoxyl singlets at 3.44, 3.47, and 3.58 ppm) clearly evidenced the presence of a symmetry axis bisecting opposite $ArCH_2$-Ar groups (CH_2−CH_2 symmetry), compatible with a 1,2- or 1,4-substitution pattern. To discriminate between them we decided to prepare a sample of hexamethoxycalix[8]arene $\mathbf{6}_{1,4}$ of certain structure by an indirect route.

(14) Ikeda, A.; Akao, K.; Harada, T.; Shinkai, S. *Tetrahedron Lett.* **1996**, *37*, 1621.

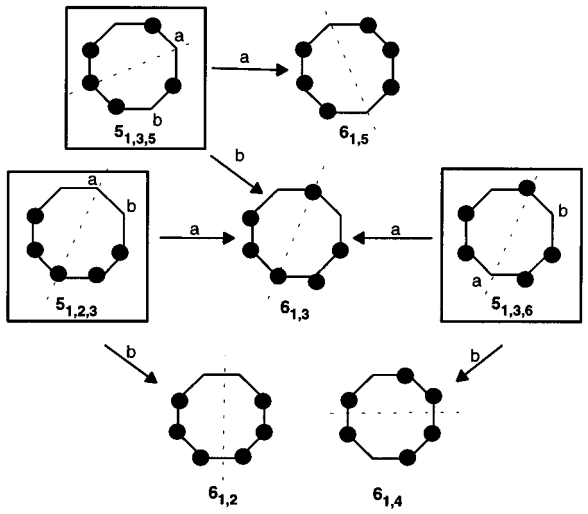


Figure 1. Possible monomethylation products of the three pentamethoxycalix[8]arene regioisomers possessing Ar−Ar symmetry, $\mathbf{5}_{1,3,5}$, $\mathbf{5}_{1,2,3}$, and $\mathbf{5}_{1,3,6}$.

Therefore, 1,4-(*p*-xylylene)-bridged calix[8]arene **9**[14] was subjected to exhaustive methylation to give **10a**, which by catalytic hydrogenation with Pd/C and H_2 (Scheme 2) yielded hexamethoxycalix[8]arene $\mathbf{6}_{1,4}$. Its NMR spectra and chromatographic behavior were different from those of the hexamethoxy compound obtained by direct methylation. Hence, this latter could be assigned confidently the only possible alternative structure, namely $\mathbf{6}_{1,2}$.

Pentamethoxy derivative $\mathbf{5}_{1,2,3}$, in accordance with the presence of five *t*-Bu signals (1.11, 1.14, 1.16, 1.23, and 1.24 ppm) in its ^{1}H NMR spectrum, possesses Ar−Ar symmetry compatible with two other regioisomers, $\mathbf{5}_{1,3,5}$ and $\mathbf{5}_{1,3,6}$. Attribution of the substitution pattern was based on the nature of the product of monomethylation. In fact, as shown in Figure 1, monomethylation of each of the three regioisomers can afford only two hexamethoxy compounds, one ($\mathbf{6}_{1,3}$) common to all and the second characteristic of the specific starting compound ($\mathbf{6}_{1,5}$ from $\mathbf{5}_{1,3,5}$, $\mathbf{6}_{1,2}$ from $\mathbf{5}_{1,2,3}$, and $\mathbf{6}_{1,4}$ from $\mathbf{5}_{1,3,6}$). Monomethylation of the pentamethoxy derivative in hand gave a mixture of $\mathbf{6}_{1,2}$ and $\mathbf{6}_{1,3}$, thus demonstrating the $\mathbf{5}_{1,2,3}$ structure (hexamethoxy derivative $\mathbf{6}_{1,3}$ was readily identified from the presence in its ^{1}H NMR spectrum of five *t*-Bu resonances and four methoxyl singlets at 3.35, 3.54, 3.57, and 3.67 ppm, 2:1:1:2).

It is worth mentioning here an experiment of monomethylation of the known $\mathbf{4}_{1,2,3,4}$, which led to the hitherto undescribed pentamethoxy derivative $\mathbf{5}_{1,2,4}$. Besides this compound, hexamethoxy derivatives $\mathbf{6}_{1,4}$ and $\mathbf{6}_{1,3}$ were obtained, possibly derived through the intermediate formation of $\mathbf{5}_{1,2,3}$ (Figure 2). The asymmetrical substitution pattern in $\mathbf{5}_{1,2,4}$ was evidenced by the presence of five methoxyl resonances (3.43, 3.54, 3.65, 3.67, and 3.70 ppm) and six *t*-Bu singlets (1.11, 1.15, 1.18, 1.20, 1.21, and 1.26 ppm), whereas the substitution pattern was assigned because only this asymmetrical isomer can be obtained by monomethylation of $\mathbf{4}_{1,2,3,4}$ (Figure 2).

Comparative Features of Methoxycalix[8]arenes. OH Chemical Shifts. The availability of several methoxycalix[8]arenes allows comparison of some of their properties. An interesting spectral feature of partially methylated calix[8]arenes is the dependence of the chemical shift value of hydroxyl groups from the substitution pattern. In fact, in the smaller members of calix-

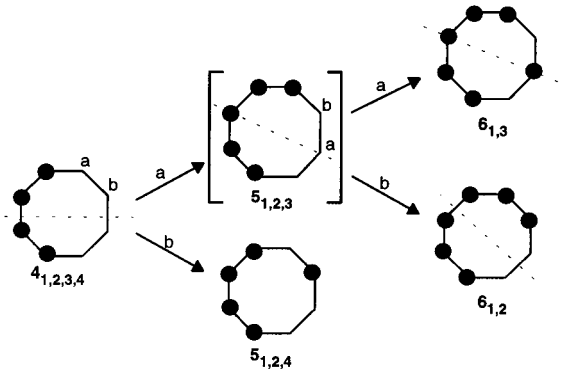


Figure 2. Products formed by methylation of tetramethoxycalix[8]arene $\mathbf{4}_{1,2,3,4}$.

[*n*]arene family it has been demonstrated that this value moves to lower field upon formation of intramolecular hydrogen bonds.[15] The displacement increases with increasing the number of contiguous H-bonds, reaching its highest value (around 10 ppm) for the parent calixarenes with their typical "circular H-bond".[16] In partially substituted derivatives an OH group can be classified as "isolated", "singly-H-bonded", or "doubly-H-bonded", if it is flanked by none, one, or two hydroxyls, respectively, and its resonance moves to lower field in that order.[7c,15] Consequently, the δ of OH groups has been considered a useful probe for structure assignment of regioisomers of calix[5]arenes,[6,17] and we used it previously for structure assignment of $\mathbf{3}_{1,2,4}$ and $\mathbf{4}_{1,2,3,4}$.[8a] The availability of several methoxycalix[8]arenes makes it now possible to check the validity of this method in the calix[8]arene series.[18]

A "perfectly isolated" hydroxyl is found in heptamethoxycalix[8]arene **7**, resonating at 7.45 ppm (Figure 3). In hexamethoxy calix[8]arenes $\mathbf{6}_{1,4}$ and $\mathbf{6}_{1,3}$ the isolated OH groups resonate at 7.51 and 7.52 ppm, respectively. The signal for the singly-H-bonded OH in $\mathbf{6}_{1,2}$ appears at 8.14 ppm, clearly deshielded with respect to other cases, suggesting 8.0 ppm as the discriminating value between isolated and singly-H-bonded OH. Asymmetrical pentamethoxycalix[8]arene $\mathbf{5}_{1,2,4}$ offers an interesting testing case, since both kinds of OH are present within the same molecule. As expected the isolated OH resonates at 7.59 ppm, clearly separated from the singly-H-bonded hydroxyls at 8.17 and 8.43 ppm. The isomeric $\mathbf{5}_{1,2,3}$ affords the opportunity to put forward this analysis, since with three hydroxyls in succession it provides the simpler case of doubly-H-bonded (8.66 ppm) and two equivalent singly-H-bonded (8.45 ppm) hydroxyls. Four contiguous hydroxyls are present in $\mathbf{4}_{1,2,3,4}$, for which the effect of a "semicircular" H-bond is evidenced by the further increase of the downfield shift for doubly- (8.85 ppm) and singly-H-bonded (8.51 ppm) OH groups. Tetramethylcalix[8]arene $\mathbf{4}_{1,2,3,6}$ possesses two symmetry related couples of singly-H-bonded OH groups in a "broken" array, whose resonances consequently appear at slightly higher field (8.23 and 8.49 ppm). Asymmetrical trimethoxy compounds $\mathbf{3}_{1,2,4}$ and $\mathbf{3}_{1,2,5}$ offer additional arguments in support of the general rule and constitute an a posteriori verification since structure assignment of $\mathbf{3}_{1,2,4}$ was based, *inter alia*, on the chemical shift value of the OH groups. A clear distinction among isolated (7.67 ppm), singly- (8.86 and 8.74), and doubly-H-bonded hydroxyls (9.08 and 9.10 ppm) is observed for $\mathbf{3}_{1,2,4}$, while $\mathbf{3}_{1,2,5}$, lacking isolated hydroxyls, shows in the ^{1}H NMR spectrum only signals well above 8.0 ppm [8.24, 8.42, 8.61 (2 H), and 8.88 ppm]. The spectrum of dimethoxycalix[8]arenes $\mathbf{2}_{1,3}$ contains resonances for three different types of hydroxyls, namely 8.30 (isolated hydroxyl), 8.79 (singly-H-bonded OH groups), and 9.01 ppm (doubly-H-bonded hydroxyl). In this case, it seems that the δ value for the isolated OH is influenced by the tendency, due to the presence of a sequence of contiguous hydroxyls more extended than in the previously discussed compounds, to give a quasicircular hydrogen bond through some kind of "jumped" interaction. Finally, the other two dimethoxy derivatives $\mathbf{2}_{1,4}$ and $\mathbf{2}_{1,5}$ as well monomethoxycalix[8]arene, all lacking isolated OH groups, show signals for hydroxyls resonances in the deshielded area of their ^{1}H NMR spectra, coherently with the OH types, singly- or doubly-H-bonded.

Comparative Features of Methoxycalix[8]arenes. ^{13}C NMR Chemical Shifts. A second interesting point regards the chemical shift changes experienced by the aromatic carbons upon methylation. In a previous paper we noticed a downfield displacement of ^{13}C NMR resonances for quaternary carbons of the phenol rings following benzylation, and indeed this observation was used as a tool in signal assignment and in subsequent structure determination by 2D NMR.[9] In this case also the availability of several calix[8]arene methyl ethers makes it now possible to check the limits of this rule.

Considering first the oxygen-bearing carbons, we may observe the displacement from δ 146.6 in **C8** to δ 154.3 in octamethoxy derivative **8**. However, as shown in Figure 4, this difference is less marked if the two kinds of carbon are compared within the same molecule. In this case an average $\Delta\delta$ of 4.0 ppm is observed for all derivatives. A clear concomitant downfield trend is observed on passing from less to more alkylated derivatives, probably due to the reduced extent of intramolecular hydrogen-bonding. Analogous considerations apply to the *tert*-butyl-bearing carbons, which show an average $\Delta\delta$ of 3.8 ppm upon methylation of the relevant phenol ring. However, in this a case a partial overlap is observed between the region of hydroxyl-bearing carbons and the zone of *tert*-butyl-bearing carbons of methylated rings. This fact poses some difficulties in signal assignment without resorting to a complete 2D NMR study.

A clear downfield displacement is observed for bridgehead carbons ($C-CH_2$) upon methylation with an average $\Delta\delta$ of 5.5 ppm. Hence, they move from the region at 126−128 ppm, crowded by the C−H resonances, to an empty zone of the spectrum at 132−134 ppm. On the basis of the above consideration, the downfield shift rule is valid

(15) Araki, K.; Iwamoto, K.; Shinkai, S.; Matsuda, T. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 3480. Groenen, L.; Steinwender, E.; Lutz, B.; van der Maas, J.; Reinhoudt, D. N. *J. Chem. Soc., Perkin Trans. 2* **1992**, 1893.

(16) Gutsche, C. D. *Acc. Chem. Res.* **1983**, *16*, 161. Keller, S. W.; Schuster, G. M.; Tobiason, F. L. *Polym. Mater. Sci. Eng.* **1987**, *57*, 906.

(17) Kraft, D.; Arnecke, R.; Böhmer, V.; Vogt, W. *Tetrahedron* **1993**, *49*, 6019.

(18) For a similar comparison in the calix[4]arene series see ref 15, and for the calix[6]arene series, see ref 7c and Janssen, R. G.; Verboom, W.; Lutz, B. G.; van der Maas, J. H.; Maczka, M.; van Duynhoven, J. P. M.; Reinhoudt, D. N. *J. Chem. Soc., Perkin Trans. 2* **1996**, 1869.

(19) Recently we have applied this rule also to calix[8]crowns: Geraci, C.; Piattelli, M.; Neri, P. *Tetrahedron Lett.* **1996**, *37*, 3899.

(20) Kalinowski, H.-O.; Berger, S.; Braun, S.; *Carbon-13 NMR Spectroscopy*; John Wiley & Sons: Chichester, 1988; pp 311−331.

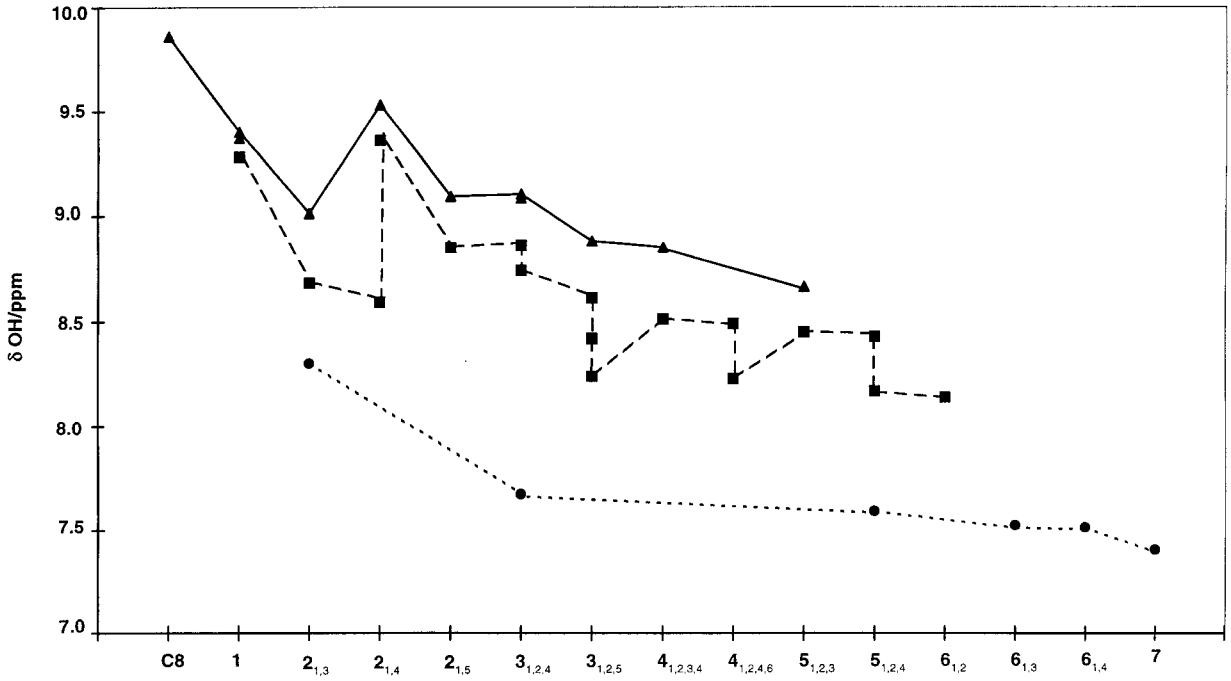


Figure 3. ^{1}H NMR chemical shift of OH groups ($CDCl_3$, 295 K) of methoxycalix[8]arenes. The lines connect δ values of hydroxyls belonging to the same class: (●) isolated, (■) singly-H-bonded, (▲) doubly-H-bonded (OH groups flanked by none, one, or two hydroxyls, respectively).

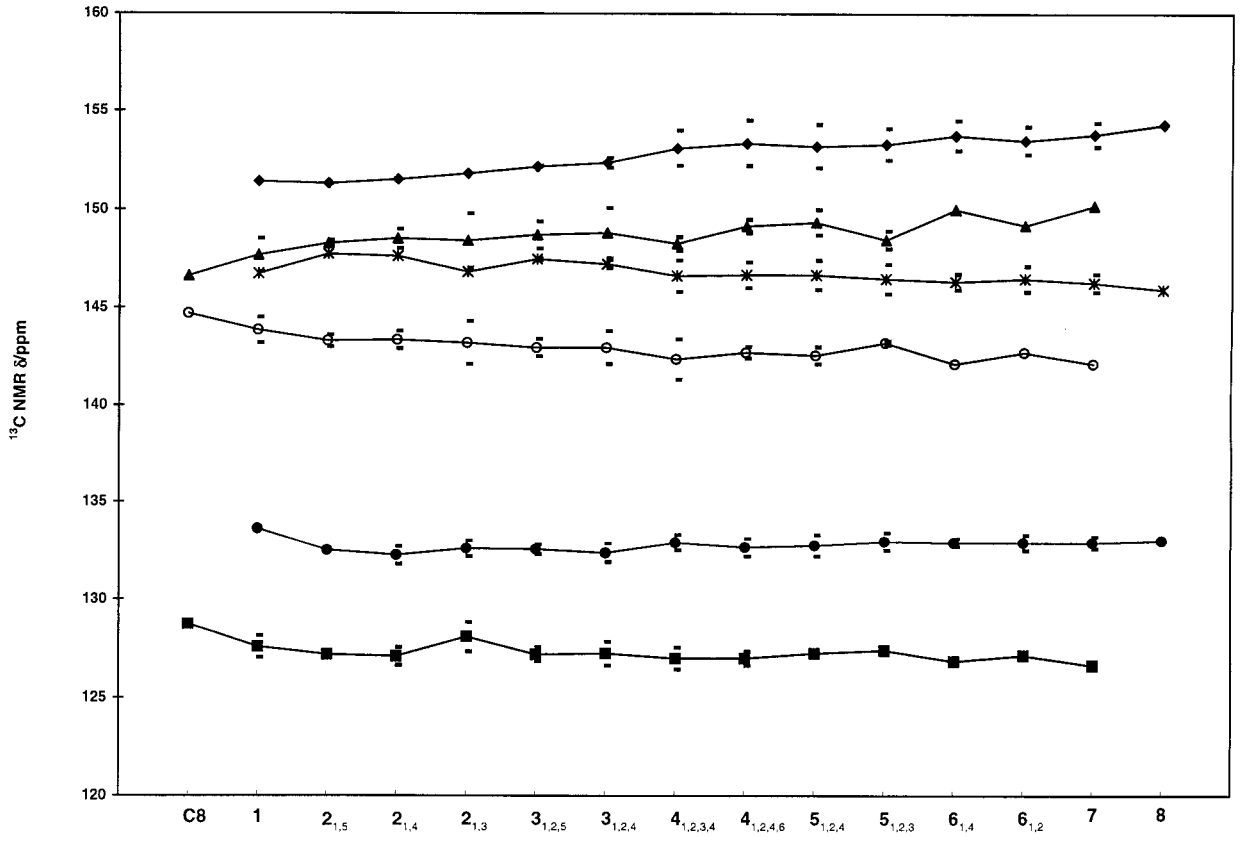


Figure 4. ^{13}C NMR chemical shift of quaternary aromatic carbons ($CDCl_3$, 295 K) of methoxycalix[8]arenes. The lines connect the average (or single) δ value of carbons belonging to the same class for each compound: (◆) *C*-OMe, (▲) *C*-OH, (*) *C*-Bu^t of ArOMe, (○) *C*-Bu^t of ArOH, (●) *C*-CH_2 of ArOMe, (■) *C*-CH_2 of ArOH.

in the entire range of partially methylated calix[8]arenes. Moreover, a perusal of literature data indicates its general validity in the alkylation of other calix[*n*]arenes. Consequently, this rule appears to be confidently applicable in ^{13}C NMR signal assignment and structural elucidation of any alkylated calixarene.[19] Finally, it is worth observing that calculation of $\Delta\delta$ using the additivity rule of substituent effects[20] in the case in hand

gives upfield values for $C-CH_2$ ($\Delta\delta = -1.6$) and $C-Bu^t$ ($\Delta\delta = -0.3$) in disagreement with the experimental ones. This can be ascribed to steric interactions and intramolecular hydrogen bonds.

Conclusions

Methylation of *p-tert*-butylcalix[8]arene with MeI in the presence of strong bases (NaH, BaO/$Ba(OH)_2$, or Cs_2CO_3) has been investigated to complement our previous study conducted in the presence of weak bases (CsF or K_2CO_3), which had evidenced the so-called *alternate alkylation* pathway. As was expected, products with different substitution patterns (and enhanced solubility) were formed in the presence of stronger bases, as the result of a probable multiple deprotonation or less selective monodeprotonation. Several previously unreported methylated products have been isolated and characterized: two dimethoxy (**2**$_{1,5}$ and **2**$_{1,4}$), a trimethoxy (**3**$_{1,2,5}$), a tetramethoxy (**4**$_{1,2,3,6}$), two pentamethoxy (**5**$_{1,2,3}$ and **5**$_{1,2,4}$), and three hexamethoxy derivatives (**6**$_{1,2}$, **6**$_{1,3}$, and **6**$_{1,4}$). Comparison of NMR spectral features of available methoxycalix[8]arenes confirms the validity of the use of OH chemical shift as a structural probe and highlights the utility of the downfield displacement upon alkylation of ^{13}C NMR resonances of aromatic rings of calixarenes.

Experimental Section

General Comments. NMR spectra were taken on a Bruker AC-250 spectrometer operating at 250.13 (^1H) and 62.9 (^{13}C) MHz, at 295 K in $CDCl_3$ unless otherwise stated. Column chromatography (CC) 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 THF was purchased from Aldrich. Petroleum ether (PE) refers to the fraction with bp 40−60 °C. Compounds **1**, **2**$_{1,3}$, **3**$_{1,2,4}$, **4**$_{1,2,3,4}$, **7**, and **8** were available from previous studies[8] whereas **C8**[21] and **9**[14] were prepared according to literature procedures.

Methylation of C8 in the Presence of NaH. A suspension of *p-tert*-butylcalix[8]arene (1 g, 0.76 mmol) in THF (100 mL) was refluxed under stirring until a clear solution was obtained (20 min). Then NaH (147 mg, 6.1 mmol) was added, and stirring was continued for additional 20 min. After addition of MeI (0.384 mL, 6.1 mmol), the reaction mixture was stirred under reflux for 5.5 h. Solvent was removed under vacuum to leave a residue which was suspended in 0.1 N HCl (30 mL). The insoluble material was collected by filtration, washed with MeOH (10 mL), and dried. The crude product was purified by column chromatography using as solvent hexane−CH_2Cl_2 mixtures starting from 1:1 vol/vol and increasing the polarity by 5% stepwise addition of CH_2Cl_2 to give **2**$_{1,5}$ and **3**$_{1,2,5}$.

5,11,17,23,29,35,41,47-Octa-*tert*-butyl-50,51,52,54,55,56-hexahydroxy-49,53-dimethoxycalix[8]arene (2$_{1,5}$) (154 mg, 15%): mp dec 240 °C; R_f 0.5 (PE/CH_2Cl_2, 35:65 v/v); ^1H NMR (C_6D_6, 330 K) δ 1.21, 1.31, 1.33 (s, 18 H, 18 H, 36 H), 3.75 (s, 6 H), 3.91, 4.04 (s, 8 H each), 7.15 (d, J = 2.2 Hz, 4 H), 7.23, 7.25 (s, 4 H each), 7.30 (d, J = 2.3 Hz, 4 H); ^{13}C NMR ($CDCl_3$, 295 K) δ 31.2 (t), 31.3, 31.4 (q), 31.9 (t), 33.9, 34.2 (s), 62.8 (q), 125.3, 125.6, 126.5 (d), 127.0, 127.3, 132.5, 142.9, 143.6, 147.7, 148.1, 148.4, 151.3 (s). Anal. Calcd for $C_{90}H_{116}O_8$: C, 81.53; H, 8.82. Found: C, 81.65; H, 8.80.

5,11,17,23,29,35,41,47-Octa-*tert*-butyl-49,50,51,52,55,56-pentahydroxy-53,54,57-trimethoxycalix[8]arene (3$_{1,2,5}$) (75 mg, 7%): mp dec 210 °C; R_f 0.5 (PE/CH_2Cl_2,1:3 v/v); ^1H NMR ($CDCl_3$, 295 K) δ 1.15, 1.17, 1.19, 1.23, 1.24, 1.26, 1.27 (s, 9 H, 9H, 9 H, 9 H, 9 H, 9 H,18 H), 3.81, 3.84 (s, 6 H, 3 H), 3.86, 3.87, 3.90, 3.96, 4.12 (s, 2 H, 2 H, 2 H, 6 H, 2 H), 6.94 (d, J = 2.2 Hz, 1 H), 6.99 (d, J = 2.5 Hz, 1 H), 7.0 (d, J = 3.2 Hz, 1 H), 7.03 (bs, 3 H), 7.09−7.13 (m, 10 H), 8.24, 8.42, 8.61, 8.88 (bs, 1 H, 1H, 2H, 1H); ^{13}C NMR ($CDCl_3$, 295 K) δ 29.6, 29.7, 30.9 (t), 31.0, 31.3, 31.5 (q), 32.0, 32.1 (t), 33.9, 34.2 (s), 61.9, 62.1 (q), 125.4, 125.7, 126.0, 126.6 (d), 126.8, 126.9, 127.1, 127.3, 127.4, 127.5, 132.3, 132.5, 132.6, 132.8, 142.5, 142.7, 142.9, 143.4, 147.4, 147.5, 148.0, 148.3, 148.9, 149.1, 149.4, 152.2 (s). Anal. Calcd for $C_{91}H_{118}O_8$: C, 81.57; H, 8.87. Found: C, 81.67; H, 8.80.

Methylation of C8 in the Presence of Cs_2CO_3. The reaction was carried out essentially as above, replacing NaH with Cs_2CO_3 (4.016 g, 12.16 mmol). The crude reaction product was subjected to CC using as solvent hexane−CH_2Cl_2 mixtures starting from 50 to 100% CH_2Cl_2, followed by Et_2O in CH_2Cl_2 from 1 to 10%. The obtained products with the relevant isolated yields are listed in Table 1.

5,11,17,23,29,35,41,47-Octa-*tert*-butyl-50,51,53,54,55,56-hexahydroxy-49,52-dimethoxycalix[8]arene (2$_{1,4}$): mp dec 200 °C; R_f 0.5 (PE/CH_2Cl_2, 45:55 v/v); ^1H NMR (C_6D_6, 350 K) 1.11, 1.20, 1.21, 1.22 (s, 18 H each), 3.72 (s, 6 H), 3.79, 3.80, 3.86, 3.87, 3.99 (s, 2 H, 4 H, 4 H, 2 H, 4 H), 7.06 (d, J = 2.3 Hz, 2 H), 7.13 (d, J = 2.5 Hz, 2 H), 7.15 (bs, 8 H), 7.18 (d, J = 2.2 Hz, 2 H), 7.21 (d, J = 2.4 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 295 K) δ 29.7 (t), 31.3, 31.5 (q), 32.4, 32.7 (t), 34.0, 34.3 (s), 62.9 (q), 124.8, 125.5, 125.7, 125.9, 126.8 (d), 126.6, 126.7, 127.0, 127.1, 127.3, 127.5, 131.8, 132.7, 142.9, 143.2, 143.8, 147.6, 148.0, 148.8, 149.0, 151.5 (s). Anal. Calcd for $C_{90}H_{116}O_8$: C, 81.53; H, 8.82. Found: C, 81.58; H, 8.90.

5,11,17,23,29,35,41,47-Octa-*tert*-butyl-49,50,54,55-tetrahydroxy-51,52,53,56-tetramethoxycalix[8]arene (4$_{1,2,3,6}$): mp 218−220 °C; R_f 0.4 (PE/CH_2Cl_2, 1:9 v/v); ^1H NMR ($CDCl_3$, 295 K) δ 1.17,1.18, 1.20, 1.22, 1.28 (s, 9 H, 18 H, 9 H, 18 H, 18 H), 3.60, 3.75, 3.82 (s, 3 H, 3 H, 6 H), 3.87, 3.90, 3.94, 4.09 (s, 4 H each), 6.94 (d, J = 2.3, 2 H), 6.97 (d, J = 2.4 Hz, 2 H), 7.00, 7.03 (s, 2 H each), 7.09 (d, J = 2.3 Hz, 2 H), 7.12 (d, J = 2.4 Hz, 2 H), 7.14 (d, J = 2.4 Hz, 2H), 7.16 (d, J = 2.2 Hz, 2 H), 8.23, 8.49 (s, 2 H each); ^{13}C NMR ($CDCl_3$, 295 K) δ 30.0, 30.8 (t), 31.3, 31.5 (q), 31.8, 32.1 (t), 33.9, 34.2 (s), 60.9, 61.7, 62.1 (q), 125.3, 125.7, 125.9, 126.0, 126.4 (d), 126.6, 126.7, 127.0, 127.3, 132.2, 132.4, 132.7, 133.1, 142.4, 143.0, 146.0, 147.1,147.3, 148.8, 149.5, 152.2, 152.6, 154.5 (s). Anal. Calcd for $C_{92}H_{120}O_8$: C, 81.61; H, 8.93. Found: C, 81.71; H, 8.90.

5,11,17,23,29,35,41,47-Octa-*tert*-butyl-49,50,51-trihydroxy-52,53,54,55,56-pentamethoxycalix[8]arene (5$_{1,2,3}$): mp dec 270 °C; R_f 0.5 (CH_2Cl_2); ^1H NMR ($CDCl_3$, 295 K) δ 1.11, 1.15, 1.17, 1.24 (s, 9 H, 18 H, 18 H, 27 H), 3.49, 3.62 (s, 9 H, 6 H), 3.84, 3.86, 4.02, 4.05 (s, 4 H each), 6.90 (d, J = 2.0 Hz, 2 H), 6.94 (s, 2 H), 7.02 (d, J = 2.0 Hz, 2 H), 7.06 (bs, 6 H), 7.10 (d, J = 2.1 Hz, 2 H), 7.13 (bs, 2 H), 8.45, 8.66 (bs, 2 H, 1 H); ^{13}C NMR ($CDCl_3$, 295 K) δ 29.6, 30.1, 30.7 (t), 31.3, 31.5 (q), 32.0 (t), 33.9, 34.1, 34.3 (s), 60.6, 61.6 (q), 125.5, 125.7, 126.3, 126.5, 126.7 (d), 127.3, 127.4, 132.5, 132.7, 132.9, 133.2, 133.4, 143.1, 145.7, 145.9, 147.2, 148.0, 148.9, 152.4, 154.1 (s). Anal. Calcd for $C_{93}H_{122}O_8$: C, 81.65; H, 8.99. Found: C, 81.75; H, 8.90.

5,11,17,23,29,35,41,47-Octa-*tert*-butyl-49,50-dihydroxy-51,52,53,54,55,56-hexamethoxycalix[8]arene (6$_{1,2}$): mp 248−250 °C; R_f 0.4 (Et_2O/CH_2Cl_2, 3:97 v/v); ^1H NMR ($CDCl_3$, 295 K) δ 1.12, 1.13, 1.18, 1.25 (s, 18 H each), 3.44, 3.47, 3.58 (s, 6 H each), 3.85, 3.87, 4.02, 4.05, 4.07 (s, 2H, 4 H, 4 H, 4 H, 2 H), 6.88 (d, J = 2.1 Hz, 2 H), 6.94 (d, J = 2.2 Hz, 2 H), 7.03 (bs, 10 H), 7.11 (d, J = 2.0 Hz, 2 H), 8.14 (s, 2 H); ^{13}C NMR ($CDCl_3$, 295 K) δ 29.7, 30.0, 30.5, 30.6 (t), 31.3, 31.5 (q), 33.9, 34.2 (s), 60.4, 60.5, 61.5 (q), 125.5, 125.7, 125.9, 126.1, 126.6, 126.7 (d), 127.1, 132.5, 132.7, 133.0, 133.2, 133.3, 142.7, 145.8, 145.9, 147.1, 149.2, 152.8, 154.2 (s). Anal. Calcd for $C_{94}H_{124}O_8$: C, 81.69; H, 9.04. Found: C, 81.78; H, 9. 01.

Preparation of 1,4-Bridged Hexaethoxycalix[8]arene 10. 1,4-Xylylene-bridged calix[8]arene **9** (100 mg, 0.07 mmol) was dissolved in acetone (10 mL), and then Cs_2CO_3 (420 mg, 1.28 mmol) and EtI (0.1 mL, 1.28 mmol) were added. The mixture was refluxed under strirring for 30 h. Usual workup afforded a crude product that was subjected to CC (Et_2O/CH_2-

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

Cl_2, 7−10% v/v) to give 5,11,17,23,29,35,41,47-octa-*tert*-butyl-50,51,53,54,55,56-hexaethoxy-49,52-(*p*-xylylendioxy)calix[8]-arene (**10**) (86 mg, 76%): ^{1}H NMR (C_6D_6, 355 K) δ 1.06−1.42 (m, 18 H), 1.11, 1.23, 1.24, 1.38 (s, 18 H each), 3.45 (q, J = 6.7 Hz, 4 H), 3.57 (q, J = 7.0 Hz, 4 H), 3.68 (q, J = 6.9 Hz, 4 H), 4.19, 4.24 (bs, 8 H each), 6.46 (s, 4H), 6.96 (d, J = 2.2 Hz, 2 H), 7.03 (d, J = 2.3 Hz, 2 H), 7,07 (d, J = 2.3 Hz, 2 H), 7,15−7,17 (m, 6 H), 7,29 (d, J = 2.3 Hz, 2 H), 7.32 and 7.36 (AB, J = 2.4 Hz, 4 H), 7.43 (d, J = 2.4 Hz, 2 H). Anal. Calcd for $C_{108}H_{150}O_8$: C, 82.29; H, 9.59. Found: C, 82.05; H, 9.80.

Preparation of Hexaethoxycalix[8]arene 11. Pd/C was added to a solution of hexaethoxy 1,4-xylylene-bridged calix-[8]arene **10** (86 mg) in CH_2Cl_2 (5 mL). The suspension was stirred under H_2 for 15 h and then filtered. The filtrate was evaporated to dryness to give 5,11,17,23,29,35,41,47-octa-*tert*-butyl-49,52-dihydroxy-50,51,53,54,55,56-hexaethoxycalix[8]-arene (**11**) (57 mg, 71%): ^{1}H NMR ($CDCl_3$, 295 K) δ 0.82−1.34 (m, 18 H), 1.02, 1.12, 1.14, 1.18 (s, 18 H each), 3.44 (q, J = 6.9 Hz, 4 H), 3.60 (q, J = 7.1 Hz, 4 H), 3.82 (q, J = 6.8 Hz, 4 H), 3.86, 3.91, 3.95, 3.99, 4.01 (bs, 4 H, 4H, 2H, 2H, 4H), 6.89 (bs, 4H), 6.93 (d, J = 2.4 Hz, 2 H), 6.94 (d, J = 2.4 Hz, 2 H), 7.00 (d, J = 2.3 Hz, 4 H), 7.01 (d, J = 2.3 Hz, 2 H), 7.04 (d, J = 2.4 Hz, 2 H), 7.58 (s, 2 H). Anal. Calcd for $C_{100}H_{142}O_8$: C, 81.58; H, 9.72. Found: C, 81.50; H, 9.78.

Chemical Correlation of $2_{1,4}$ with 11. A solution of dimethoxycalix[8]arene $\mathbf{2}_{1,4}$ (20 mg, 0.015 mmol) in anhydrous THF (5 mL) was refluxed under stirring, and then NaH (12 mg, 0.48 mmol) and excess EtI (38 μL, 0.48 mmol) were added. Refluxing under stirring was continued for 36 h. Usual workup led to 5,11,17,23,29,35,41,47-octa-*tert*-butyl-49,52-dimethoxy-50,51,53,54,55,56-hexaethoxycalix[8]arene ($\mathbf{Et2}_{1,4}$) (19 mg, 85%): ^{1}H NMR (C_6D_6, 355 K) δ 1.05−1.16 (m, 18 H), 1.13, 1.14, 1.16 (s, 18 H, 36 H, 18 H), 3.40 (s, 6 H), 3.57 (q, J = 7.0 Hz, 12 H), 4.19, 4.24 (bs, 6 H, 10 H), 7.08 (bs, 4H), 7.15 (bs, 12 H); ^{13}C NMR ($CDCl_3$, 355 K) δ 15.5 (q), 30.2 (t), 31.3 (q), 60.3 (q), 68.5 (t), 125.6, 125.8 (d), 133.0, 145.6, 145.8, 153.5, 154.4 (s). Anal. Calcd for $C_{102}H_{146}O_8$: C, 81.66; H, 9.81. Found: C, 81.75; H, 9.75.

A solution of **11** (57 mg, 0.04 mmol) was treated with MeI (40 μL, 0.64 mmol) under the above conditions to give a product that had physical properties indistinguishable from those of $\mathbf{Et2}_{1,4}$ (54 mg, 90%).

Synthesis of of Hexamethoxy 1,4-Bridged Calix[8]-arene 10a. Cs_2CO_3 (420 mg, 1.28 mmol) and MeI (80 μL, 1.28 mmol) were added to a solution of 1,4-xylylene-bridged calix-[8]arene **9** (100 mg, 0.07 mmol) in acetone (10 mL). The mixture was maintained under reflux and strirring for 30 h. Usual workup led to 5,11,17,23,29,35,41,47-octa-*tert*-butyl-50,51,53,54,55,56-hexamethoxy-49,52-(*p*-xylylendioxy)calix[8]-arene (**10a**) (86 mg, 76%): ^{1}H NMR ($CDCl_3$, 295 K) δ 1.25, 1.31, 1.35, 1.44 (s, 18 H each), 3.24 (bs, 6 H), 3.85−4.20 (bm, 28 H), 4.68 (bs, 4 H), 6.88 (d, J = 2.4 Hz, 2 H), 6.92 (bs, 2 H), 6.99 (s, 4 H) 7.16−7.21 (bm, 6 H), 7.29 (d, J = 2.4 Hz, 2 H), 7.38 (d, J = 2.3 Hz, 2 H), 7.49 (d, J = 2.3 Hz, 2 H).

Hydrogenolysis of 10a To Give $6_{1,4}$. Pd/C was added to a solution of hexamethoxy 1,4-bridged calix[8]arene **10** (98 mg, 0.06 mmol) in CH_2Cl_2 (5 mL). The suspension was stirred under H_2 for 15 h and then filtered. The filtrate was evaporated to dryness to give 5,11,17,23,29,35,41,47-octa-*tert*-butyl-49,52-dihydroxy-50,51,53,54,55,56-hexamethoxycalix[8]-arene ($\mathbf{6}_{1,4}$) (68 mg, 75%): mp dec 245 °C; R_f 0.42 (Et_2O/CH_2Cl_2, 3:97); ^{1}H NMR ($CDCl_3$, 295 K) δ 1.07, 1.12, 1.20 (s, 18 H, 36 H, 18 H), 3.39, 3.51, 3.62 (s, 6 H each), 3.88, 3.90, 3.95, 4.01 (s, 4 H, 4 H, 2 H, 6 H), 6.89 (d, J = 2.4 Hz, 2 H), 6.91 (d, J = 2.2 Hz, 2 H), 6.93 (bs, 6 H), 6.96 (d, J = 2.2 Hz, 2 H), 7.0 (d, J = 2.0 Hz, 2 H), 7.03 (d, J = 2.1 Hz, 2 H), 7.51 (s, 2 H); ^{13}C NMR ($CDCl_3$, 295 K) δ 29.7, 30.1, 30.4 (t), 31.3, 31.5 (q), 33.9, 34.1 (s), 60.5, 61.2, 61.3 (q), 125.2, 125.4, 125.9 (d), 126.7, 126.9, 132.7, 132.9, 133.1, 142.1, 145.9, 146.7, 150.0, 150.5 153.0 (s). Anal. Calcd for $C_{94}H_{124}O_8$: C, 81.69; H, 9.04. Found: C, 81.67; H, 9.08.

Monomethylation of $5_{1,2,3}$. Pentamethoxycalix[8]arene $\mathbf{5}_{1,2,3}$ (45 mg, 0.03 mmol) in anhydrous THF (10 mL) was refluxed under stirring for 20 min, K_2CO_3 (2.7 mg, 0.02 mmol) was added, and, after 10 min, MeI (120 μL, 1.94 mmol) was added. The reaction mixture was refluxed under stirring for 42 h. The organic solvent was removed under vacuum to leave a residue which was suspended in 0.1 N HCl (20 mL). The insoluble material was collected by filtration, dried, and subjected to PTLC (Et_2O/CH_2Cl_2, 3:97) to give hexamethoxycalix-[8]arene $\mathbf{6}_{1,2}$ (2 mg, 5%) and 5,11,17,23,29,35,41,47-octa-*tert*-butyl-49,51-dihydroxy-50,52,53,54,55,56-hexamethoxycalix[8]-arene ($\mathbf{6}_{1,3}$) (4 mg, 9%): R_f 0.43 (Et_2O/CH_2Cl_2, 3:97); ^{1}H NMR ($CDCl_3$, 295 K) δ 1.06, 1.11, 1.12, 1.13, 1.20 (s, 9 H, 18 H, 9 H, 18 H, 18 H), 3.35, 3.54, 3.57, 3.67 (s, 6 H, 3 H, 3 H, 6 H), 3.88, 4.03 (bs, 8 H each), 6.88 (d, J = 2.4 Hz, 2 H), 6.89 (bs, 2 H), 6.90 (d, J = 2.2 Hz, 2 H), 6.98 (bs, 6 H), 7.02 (d, J = 2.0 Hz, 2 H), 7.04 (d, J = 2.2 Hz, 2 H), 7.52 (bs, 2 H). Anal. Calcd for $C_{94}H_{124}O_8$: C, 81.69; H, 9.04. Found: C, 81.75; H, 8.98.

Methylation of $4_{1,2,3,4}$. Tetramethoxycalix[8]arene $\mathbf{4}_{1,2,3,4}$ (32 mg, 0.02 mmol) in anydrous THF (5 mL) was refluxed under stirring, K_2CO_3 (2 mg, 0.01 mmol) was added, and, after 10 min, MeI (100 μL, 1.6 mmol) was added. The reaction mixture was refluxed under stirring for 42 h. The organic solvent was removed under vacuum to leave a residue which was suspended in 0.1 N HCl (10 mL). The insoluble material was collected by filtration, dried, and subjected to PTLC (Et_2O/CH_2Cl_2, 2:98) to give hexamethoxycalix[8]arenes $\mathbf{6}_{1,4}$ (4 mg), $\mathbf{6}_{1,3}$ (3 mg), and 5,11,17,23,29,35,41,47-octa-*tert*-butyl-49,50,-52-trihydroxy-51,53,54,55,56-pentamethoxycalix[8]arene ($\mathbf{5}_{1,2,4}$) (9 mg, 26%): mp dec 265 °C; R_f 0.45 (CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 295 K) δ 1.11, 1.15, 1.18, 1.20, 1.21, 1.26 (s, 27 H, 9 H, 9 H, 9 H, 9 H, 9 H), 3.43, 3.54, 3.65, 3.67, 3.70 (s, 3 H each), 3.84, 3.86, 3.89, 4.03 (s, 2H, 2 H, 6 H, 6 H), 6.90 (bs, 2 H), 6.94 (d, J = 2.3 Hz, 2 H), 6.96 (d, J = 2.4 Hz, 2 H), 6.97 (bs, 2 H), 7.01 (bs, 2 H), 7.04 (bs, 2 H), 7.08 (d, J = 2.2 Hz, 2 H), 7.13 (d, J = 2.3 Hz, 2 H), 7.59, 8.17 (bs, 1 H, 2 H); ^{13}C NMR ($CDCl_3$, 295 K) δ 29.7, 30.2, 30.5, 30.8 (t), 31.3, 31.5 (q), 31.9 (t), 33.9, 34.1 (s), 60.6, 60.7, 61.6, 61.7, 61.8 (q), 125.1, 125.4, 125.8, 126.1, 126.5, 126.9 (d), 127.1, 127.3, 132.2, 132.4, 132.7, 132.9, 133.2, 133.3, 142.1, 142.4, 143.0, 145.9, 147.0, 148.7, 149.5, 150.0, 152.5, 152.6, 154.3 (s). Anal. Calcd for $C_{93}H_{122}O_8$: C, 81.65; H, 8.99. Found: C, 81.70; H, 8.90.

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