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Proximal Regioselectivity of the *O*,*O*′-Dialkylation of Tetrahydroxyketocalix[4]arene

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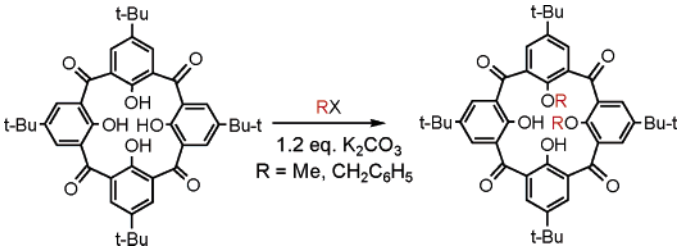
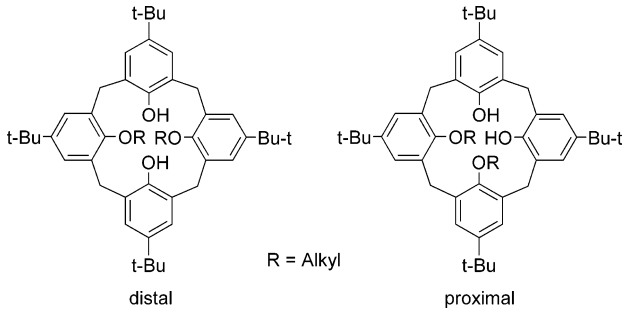


The only dialkylated products obtained in the reaction of tetrahydroxyketocalixarene **2a** with MeI/K_2CO_3 or $PhCH_2Br/K_2CO_3$ are the corresponding proximal (i.e., 1,2) *O*,*O*′-dialkyl ethers, in contrast to the parent tetrahydroxycalix[4]arene **1a** which affords the distal (1,3) dialkyl ether derivatives. Pairs of geminally alkylated phenoxy groups in the conformationally rigid dibenzylated and tetrabenzylated derivatives are oriented in an anti fashion. These results can be rationalized assuming that the *1,3-alternate* arrangement of the rings preferred by **2a** is adopted during all the intermediate stages of the alkylation. The NMR spectra (in $CDCl_3$) of the monomethyl, dimethyl, trimethyl, and tetramethyl ether derivatives of **2a** are in agreement with a *1,3-alternate* conformation.

Introduction

The alkylation of the hydroxyl groups of *p-tert*-butylcalix[4]arene (**1a**) under basic conditions and the conformation of its methyl ether derivatives have been the subject of several studies.[1] Dialkylation (e.g., dimethylation) using a weak base usually affords the distally dialkylated product rather than the proximally disubstituted derivative (Scheme 1).[2] Proximally dialkylated derivatives may be synthesized using a protection−deprotection method (e.g., via O,O′-bridging of two proximal groups followed by derivatization of the free phenolic hydroxyl groups and removal of the protecting group)[3] or via didealkylation of a tetraalkyl ether derivative.[4] The preparation of proximal diether derivatives by direct alkylation of **1a** has been achieved by the use of a strong base prior the alkylation step.[5,6]

SCHEME 1



The conformation of *p-tert*-butylcalix[4]arene (**1a**) is usually discussed in terms of four basic forms: *cone*,

(1) For reviews on calixarenes, see: (a) Gutsche, C. D. *Aldrichim. Acta* **1995**, *28*, 1. (b) Gutsche, C. D. *Calixarenes Revisited*; Royal Society of Chemistry: Cambridge, 1998. (c) Böhmer, V. In *The Chemistry of Phenols*; Rappoport, Z., Ed.; Wiley: Chichester, 2003; Chapter 19.

(2) See, for example: (a) 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. (b) No, K.; Hong, M. *J. Chem. Soc., Chem. Commun*. **1990**, 572. (c) Ungaro, R.; Pochini, A.; Andreetti, G. D. *J. Inclusion Phenom.* **1984**, *2*, 199. (d) Iwamoto, K.; Fujimoto, K.; Matsuda, T.; Shinkai, S. *Tetrahedron Lett.* **1990**, *31*, 7169 and **1991**, *32*, 830 (corrigendum). (e) Gutsche, C. D.; Dhawan, B.; Levine, J. A.; No, K. H.; Bauer, L. J. *Tetrahedron* **1983**, *39*, 403.

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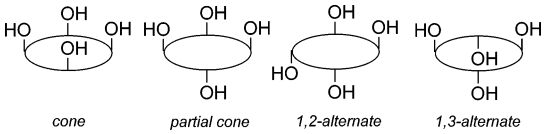
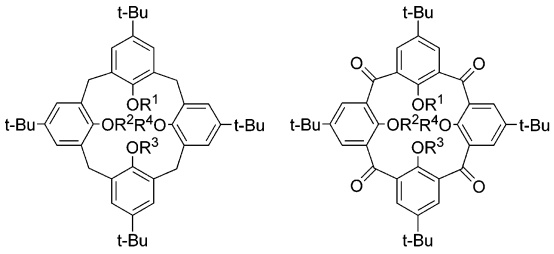


FIGURE 1. Schematic representation of the four ideal conformations of a tetrahydroxycalix[4]arene.

partial cone, *1,2-alternate*, and *1,3-alternate* (Figure 1). In $CDCl_3$, the *cone* form is the preferred conformation of **1a** and its monomethyl, dimethyl, and trimethyl ether derivatives (i.e., **1b**−**e**), whereas the tetramethyl ether derivative **1f** (lacking OH groups capable of forming intramolecular hydrogen bonds) exists in $CDCl_3$ solution as a conformational mixture where the partial *cone* form represents the major conformer.[7]



1a: $R^1 = R^2 = R^3 = R^4 = H$
1b: R^1 = Me, $R^2 = R^3 = R^4 = H$
1c: $R^1 = R^3$ = Me, $R^2 = R^4 = H$
1d: $R^1 = R^2$ = Me, $R^3 = R^4 = H$
1e: $R^1 = R^2 = R^3$ =Me, $R^4 = H$
1f: $R^1 = R^2 = R^3 = R^4$= Me

2a: $R^1 = R^2 = R^3 = R^4 = H$
2b: R^1 = Me, $R^2 = R^3 = R^4 = H$
2c: $R^1 = R^2$ = Me, $R^3 = R^4 = H$
2d: $R^1 = R^2 = R^3$ = Me, $R^4 = H$
2e: $R^1 = R^2 = R^3 = R^4$= Me
2f: $R^1 = R^2$ = Bz, $R^3 = R^4 = H$ *(anti)*
2g: $R^1 = R^2 = R^3 = R^4$= Bz (1,3-alternate form)

We have recently shown that, in contrast to **1a** that adopts a *cone* conformation, the preferred conformation of tetrahydroxyketocalixarene **2a**[8] is the *1,3-alternate*.[9] As shown by a study of tetrahydroxycalix[4]arene derivatives possessing both carbonyl and methylene bridges, a pair of geminal rings connected to a carbonyl group prefer an anti orientation, most likely since in that arrangement conjugation of the rings with the carbonyl group is maximized.[10] The goal of the present work was to determine whether the unique conformational preferences of **2a** affect the regioselectivity of the alkylation and influence the stereochemical outcome of the reaction and the preferred conformation of the methyl ether derivatives of the ketocalixarene.

Results and Discussion

Alkylation of 2a. The reactions chosen for the present study were methylation and benzylation of the phenolic oxygens of **2a** under weak basic conditions. Whereas the methyl ether derivatives are expected to be flexible at the laboratory time scale, the bulk of the benzyl ring should prevent the passage of an alkylated ring through the macrocyclic annulus, thus freezing on the laboratory time scale the resulting "up" or "down" orientation of a given benzylated ring.

Methylation of 2a. The dimethylation reaction of **2a** was conducted using reaction conditions (excess MeI, base, MeCN) similar to those reported for **1a** for the preparation of the distal dimethyl ether derivative **1c**[2e,7c] but using 1.2 equiv of K_2CO_3. According to the NMR analysis of the crude product, the reaction afforded a nearly 1:1 mixture of a dimethyl ether derivative and the monomethyl ether **2b**, which were separated by chromatography. Increasing the amount of base yielded the trimethyl and tetramethyl ether derivatives (**2d** and **2e**, respectively).

The ^1H NMR spectrum (in $CDCl_3$) of the dimethyl ether derivative displayed, in addition to two singlets for the *t*-Bu and a singlet for the MeO groups, four doublets for the aromatic protons. This pattern is consistent with proximal disubstitution of the phenolic oxygens (i.e., **2c**). The reactivity of **2a** is therefore in marked contrast to that of the parent **1a** which under similar reaction conditions yields the distally disubstituted derivative **1c**. Disregarding some minor temperature-dependent changes in the chemical shifts, no major changes were observed in the ^1H NMR spectra of **2b** and **2c** in $CDCl_3$ upon lowering the temperature to 215 K. Precluding an unusually low rotational barrier for the compounds, the NMR data indicate that in each case only a single conformation is significantly populated.

Notably, in all the methyl ether derivatives, the MeO groups resonated at a relatively high field (δ 3.11−2.94 ppm) indicating that these groups are located within the shielding region of the neighboring aryl groups. This suggests that the anti arrangement of pairs of geminal rings connected to a carbonyl is preferred over the syn (cf., Scheme 2).

Further support for a conformation with an anti arrangement of pairs of geminal rings was provided by NOESY spectra. Compound **2b** displayed NOE cross-peaks between the OH signal integrating for two protons (corresponding to the hydroxyl attached to the rings adjacent to the methylated ring) and two aromatic signals located on different rings (methylated and non methylated). The NOESY spectrum of **2c** displayed NOE cross-peaks between the methoxy signal and a pair of aromatic

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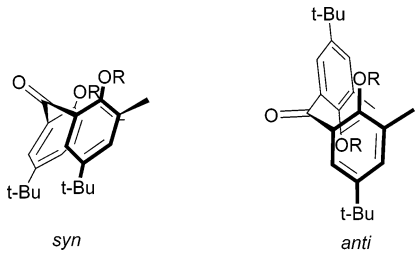
SCHEME 2



protons located on different rings. Similar NOE interactions were observed also for **2d**. These NOE interactions indicate an anti disposition of geminal rings since in this arrangement the methoxy or hydroxy protons are in a spatial proximity to aromatic protons of a neighboring ring. The relative high-field resonance of the OH groups of **2b** and **2d** (δ 5.60 and 5.33 ppm) which is reminiscent of the chemical shift observed for **2a** (δ 5.98 ppm)[9] indicates the absence of intramolecular hydrogen bonds. On the basis of the NOE interactions observed, the chemical shifts of the OH groups in **2b**−**d**, and the shielding of the methoxy signals, we ascribe to **2b**−**e** a *1,3-alternate* conformation, which is also the favored conformation of tetrahydroxy derivative **2a**. In contrast to the case of **1b**−**e**, all the methyl ethers **2b**−**e** adopt the same conformation as the parent **2a**. Apparently, since the *1,3-alternate* conformation of **2a** is not stabilized by hydrogen bonds between adjacent OH groups, methylation does not change the intrinsic conformational preference of the tetraoxocalixarene scaffold for the *1,3-alternate* form.

Benzylation of 2a. Reaction of **2a** with 4 equiv of benzyl bromide and excess K_2CO_3 in refluxing acetone (conditions reported to afford the 1,3-dibenzyloxy derivative of **1a**)[3d] afforded exclusively the tetrasubstituted derivative **2g**. This is probably the result of the increased acidity of the phenolic OH groups in the bis(*O*-benzylated) derivative of **2a** as compared to the corresponding compound derived from **1a**.[11] The reaction was therefore conducted using the reaction conditions utilized for the preparation of the dimethyl ether derivative **2c** yielding, as judged by ^{1}H NMR spectroscopy, a ca. 3:2:1 mixture of the dibenzyl ether derivative of **2a** (main product), the tribenzyl ether, and the monobenzyl ether. The isolation of the dibenzyloxy derivative proved to be somewhat challenging, since the compound cocrystallizes with the tribenzyloxy derivative and both compounds possess identical chromatographic R_f values in silica gel in all the solvents examined. However, addition of Et_3N to the eluent resulted in a complete chromatographic separation of the two compounds.[12] The spot of the dibenzyloxy derivative in the preparative TLC plate had a R_f value near zero and was yellow, suggesting that deprotonation occurred due to the presence of the base in the eluting mixture.[13]

The ^{1}H NMR spectrum of the dibenzylated derivative displayed in C_6D_6 one pair of doublets for the methylene groups,[14] indicating proximal disubstitution of the ketocalixarene skeleton (i.e., **2f**).[15] In principle both syn and anti atropisomers (cf. Scheme 2) are possible for this derivative. On the basis of the relatively high field of the chemical shifts of the ortho aromatic protons of the benzyl groups (δ 6.20 ppm) (indicating proximity to the shielding region of a neighboring aryl ring), we ascribe to this compound an anti stereochemistry.

The tetrasubstituted derivative **2g** displayed a simple signal pattern in the ^{1}H NMR spectrum (e.g., a single singlet for the methylene protons) in agreement with a *cone* or *1,3-alternate* disposition of the rings. However, since as in the case of **2f**, the ortho protons of the benzyl groups of **2g** displayed chemical shifts indicating shielding, (δ 6.60 ppm) the disposition of the rings is ascribed as all-anti (i.e., *1,3-alternate*).

Proximal vs Distal Regioselectivity of the Alkylation Reaction. The regioselectivity of the dialkylation of **1a** in the presence of a weak base is commonly rationalized by the preferred deprotonation site of the intermediate monoalkylated derivative.[5] Monodeprotonation of the OH group at a distal position (i.e., opposite to the alkylated ring) generates a phenolate that can be stabilized by two hydrogen bonds with the two adjacent rings (Figure 2). In contrast, deprotonation at a ring proximal to the alkylated ring generates a phenolate, which at most may be stabilized by a single hydrogen bond interaction with a proximal ring.[16] Since the distal phenolate is more stable than the proximal one, the major product of the dialkylation is the distal diether derivative.[17]

In the case of **2a**, if the preferred *1,3-alternate* conformation is adopted by the phenolate derived from the monoalkylated derivatives, there should be no increased stabilization of the distal over the proximal phenolate (Figure 2) since neither form should be preferentially stabilized by hydrogen bonds. It seems likely that the proximal product is formed preferentially, since the population of the proximal phenolate is statistically favored by a factor of 2 compared to the unique distal phenolate, and since, due to the orientation of the rings, alkylation at a distal ring is more sterically hindered.

Conclusions

In contrast to the parent **1a**, dialkylation of the ketocalixarene **2a** yields the proximal (i.e., 1,2) disubstituted derivative.

(11) A similar formation of the tetrabenzylated derivative has been observed for the *p*-cyanomethyl analogue of **1a** (Sharma, S. K.; Alam, I.; Gutsche, C. D. *Synthesis* **1994**, 813).

(12) The addition of Et_3N was suggested to us by Dr. Artem Melman.

(13) As noticed in the present study, the colorless ketocalixarene **2a** and some of its derivatives (e.g., **2f**) become yellow upon deprotonation. In contrast to other chromoionophores derived from **1a**, in **2a** and its derivatives the whole macrocycle ring can be viewed as the chromophore. For a review on chromo- and fluroionophores derived from calixarenes, see: Ludwig, R. In *Calixarenes 2001*; Asfari, Z., Böhmer, V., Harrowfield, J., Vicens, J., Eds.; Kluwer Academic Publishers: Dordrecht, 2001.

(14) The protons are accidentally isochronous in $CDCl_3$.

(15) A derivative *O*-benzylated at two distal positions should display a singlet for these protons, irrespective of the syn or anti disposition of the rings.

(16) Hydrogen bonding involving pairs of rigs located at distal positions is usually not observed in calix[4]arenes, due to the relative large distance separating the rings.

(17) This explanation is strictly correct if the rate of alkylation is faster that the mutual interconversion between the proximal and distal monodeprotonated forms (i.e., a "kinetic quenching"). However, it seems likely that the rate of interconversion between the two phenolate forms is faster than the alkylation reaction. In such case, the proximal/distal product distribution is not solely dictated by the relative stabilities of the reacting monodeprotonated forms, but also by the individual rates of alkylation (Curtin−Hammett principle). See: (a) Seeman, J. I. *Chem. Rev.* **1983**, *83*, 83. (b) Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994; p 652.

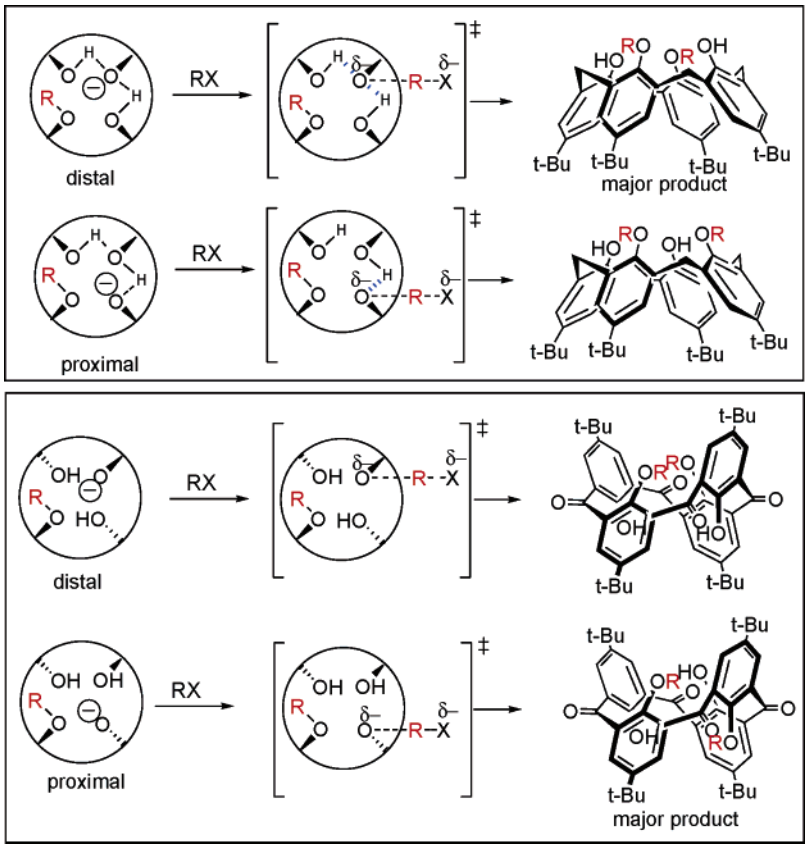


FIGURE 2. Differential reactivity of the phenolates derived from the monoalkyl ether derivatives of **1a** (top) and **2a** (bottom). In the case of **1a**, the charge on the distal phenolate in both the monodeprotonated form and in the transition state of the alkylation is stabilized by two hydrogen bonds while only a single bond is possible in the case of the proximal alkylation. Assuming an *1,3-alternate* arrangement in the corresponding phenolates of the ketocalixarene derivative and in the transition states of the alkylation, there is no preferential charge stabilization of the distal pathway since neither the proximal nor distal transition states are stabilized by hydrogen bonds. The proximal pathway is likely favored by statistical and steric effects.

Experimental Section

General Procedure for the Preparation of 2b−f. A mixture of calixarene **2a**[8−10] and the proper amount of K_2CO_3 was refluxed in acetonitrile for 30 min. The alkyl halide (MeI or benzyl bromide) was then added and the reflux continued. Chloroform was added and the mixture washed twice with aq HCl 1 N. After washing with water, phase separation, drying, and evaporation of the organic phase, the residue was recrystallized from the appropriate solvent, or in the case of **2a**,**2b** and **2f** chromatographed yielding the corresponding alkyl ether derivatives.

Preparation of 5,11,17,23-Tetra-*tert*-butyl-2,8,14,20-tetraoxo-25-methoxy-26,27,28-trihydroxycalix[4]arene (2b) and 5,11,17,23-Tetra-*tert*-butyl-2,8,14,20-tetraoxo-25,26-dihydroxy-27,28-dimethoxycalix[4]arene (2c). The reaction was conducted using 0.2 g of **2a** (0.28 mmol), 0.024 g of K_2CO_3 (0.17 mmol), 10 mL of MeCN, and 0.5 mL of MeI. After 3 h reflux, ^{1}H NMR analysis of the crude product indicated that a ca. 1:1 mixture of **2b** and **2c** was obtained. The mixture was separated by column chromatography (SiO_2, eluent: CH_2Cl_2) yielding 26 mg **2b** (mp 320 °C dec) and 28 mg **2c** (mp 360 °C dec).

2b: ^{1}H NMR (400.133 MHz, $CDCl_3$, rt) δ 7.98 (d, J = 2.6 Hz, 2H), 7.94 (s, 2H), 7.92 (s, 2H), 7.91 (d, J = 2.7 Hz, 2H), 5.71 (s, 2H), 5.60 (s, 1H), 3.11 (s, 3H), 1.37 (s, 9H), 1.36 (s, 27H); ^{13}C NMR (100.6 MHz, $CDCl_3$, rt) δ 192.0, 191.0, 155.1, 152.3, 151.7, 150.1, 146.3, 145.0, 133.7, 132.8, 132.6, 132.3, 132.1, 128.8, 128.1, 127.3, 64.1, 35.1, 34.7, 34.6, 31.2, 31.2 ppm; MS *m/z* 719.4 (MH^+).

2c: ^{1}H NMR (400.133 MHz, $CDCl_3$, rt) δ 7.98 (d, J = 2.6 Hz, 2H), 7.96 (d, J = 2.6 Hz, 2H), 7.92 (d, J = 2.6 Hz, 2H), 7.91 (d, J = 2.6 Hz, 2H), 5.33 (s, 2H), 3.06 (s, 6H), 1.38 (s, 18H), 1.36 (s, 18H) ppm; ^{13}C NMR (100.6 MHz, $CDCl_3$, rt) δ 193.4, 192.6, 191.9, 155.5, 152.2, 149.1, 145.5, 133.9, 133.5, 131.9, 131.8, 131.7, 129.6, 129.5, 63.9, 34.9, 34.6, 31.23, 31.18 ppm; MS *m/z* 733.4 (MH^+).

5,11,17,23-Tetra-*tert*-butyl-2,8,14,20-tetraoxo-25-hydroxy-26,27,28-trimethoxycalix[4]arene (2d). A 250 mg (0.35 mmol) portion of **2a** was reacted according to the general procedure using 0.05 g of K_2CO_3 (0.36 mmol), 1 mL of MeI, and 10 mL of acetonitrile. After 1 h of reflux, an additional 1 mL of MeI was added and the mixture refluxed overnight. After recrystallization from $CHCl_3$/MeOH, 140 mg (53%) of **2d** was obtained: mp 310 °C dec; ^{1}H NMR (300.133 MHz, $CDCl_3$, rt) δ 7.98 (s, 2H) 7.95 (s, 2H), 7.92 (d, J = 2.6 Hz, 2H), 7.89 (d, J = 2.6 Hz, 2H), 4.98 (s, 1H), 3.06 (s, 6H), 2.97 (s, 3H), 1.38 (s, 9H), 1.37 (s, 9H), 1.36 (s, 18H) ppm; ^{13}C NMR (100.6 MHz, $CDCl_3$, rt) δ 194.0, 193.6 (C=O), 155.9, 155.8, 152.7, 148.2, 148.1, 146.0, 134.2, 133.7, 133.2, 132.4, 131.4, 131.2, 131.1, 130.9, 63.5, 63.4, 34.8, 34.7, 34.5, 31.22, 31.17 ppm; CI MS (+DCI) *m/z* 747.3 (MH^+).

5,11,17,23-Tetra-*tert*-butyl-2,8,14,20-tetraoxo-25,26,27,-28-tetramethoxycalix[4]arene (2e). A 0.5 g portion of **2a** (0.7 mmol) and 0.5 g K_2CO_3 (3.6 mmol) in 20 mL of acetonitrile and 2 mL of MeI were reacted according to the general procedure. An additional 1 mL of MeI was added after 1 h of reflux, and the mixture was refluxed for 4 h, yielding 0.51 g (0.67 mmol, 95%) of essentially pure **2e**: mp 380 °C dec; ^{1}H NMR (300.133 MHz, $CDCl_3$, rt) δ 7.84 (s, 8H), 2.94 (s, 12H), 1.36 (s, 36H) ppm; ^{13}C NMR (100.6 MHz, $CDCl_3$, rt) δ 195.7, 157.4, 146.7, 133.9, 130.1, 62.8, 34.6, 31.2 ppm; CI MS (+DCI) *m/z* 761.2 (MH^+).

5,11,17,23-Tetra-*tert*-butyl-2,8,14,20-tetraoxo-25,26-dibenzyloxy-27,28-dihydroxycalix[4]arene (2f). A 0.5 g portion of **2a** (0.71 mmol) and 0.06 g of K_2CO_3 (0.43 mmol) in 30 mL of acetone and 0.7 mL of benzyl bromide were reacted according to the general procedure, and the mixture was refluxed for 3 h. A 260 mg portion of the crude product (consisting of a ca. 3:2:1 mixture of **2f**, and the tri- and monobenzyloxy derivatives) was purified by column chromatography (silica, CH_2Cl_2). The ^{1}H NMR of the first eluted fraction (120 mg), although consisting of a single spot by TLC, indicated a 2:1 mixture of **2f** and the tribenzyloxy derivative. Pure **2f** was obtained by preparative TLC separation of 80 mg of the mixture (silica, eluent: 8:1:1 hexane/EtOAc/Et_3N). Extraction with chloroform of the yellow spot (of R_f nearly 0) with $CHCl_3$ afforded 45 mg of pure **2f** as its triethylammonium salt. Treatment of a chloroform solution of the salt with dilute HCl, phase separation, and evaporation of the organic phase afforded 19 mg of pure **2f**: mp 284 °C; ^{1}H NMR (400.133 MHz, $CDCl_3$, rt) δ 7.86 (m, 8H, COAr-H), 7.05 (t, J = 7.4 Hz, 2H), 6.94 (t, J = 7.3 Hz, 4H), 6.24 (d, J = 7.2 Hz, 4H), 5.18 (br, 2H), 4.34 (s, 4H), 1.28 (s, 18H), 1.24 (s, 18H); ^{13}C NMR (100.6 MHz, $CDCl_3$, rt) δ 194.1, 192.6, 191.4, 154.1, 152.8, 149.2, 144.9, 128.9, 128.7, 128.2, 128.1, 127.2, 80.0, 34.8, 34.4, 31.15, 31.11 ppm; MS *m/z* 907.5 ($M + Na^+$).

5,11,17,23-Tetra-*tert*-butyl-2,8,14,20-tetraoxo-25,26,27,-28-tetrabenzyloxycalix[4]arene (2g). A mixture of 1 g of **2a** (1.42 mmol), 2.13 g of K_2CO_3 (15.4 mmol), and 0.74 mL (6.16 mmol) of benzyl bromide in 30 mL of acetone was refluxed for 3 h. After workup as described in the general procedure, the residue was recrystallized from $CHCl_3$/MeOH yielding 1 g (66%) of **2g**: mp 290 °C; ^{1}H NMR (300.133 MHz, $CDCl_3$, rt) δ 7.50 (s, 8H), 7.19 (m, 12H), 6.61 (d, J = 7.1 Hz, 2H), 4.35 (s, 8H), 1.09 (s, 36H) ppm; ^{13}C NMR (100.6 MHz, $CDCl_3$, rt) δ 196.5, 154.5, 146.9, 135.4, 135.1, 130.0, 128.1, 128.0, 127.7, 78.9, 34.3, 30.9 ppm; MS *m/z* 1111.7 ($M + K^+$).

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Supporting Information Available: ^{1}H NMR spectra of compounds **2b**−**g**. This material is available free of charge via the Internet at http://pubs.acs.org.

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