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Functionalization of the Methylene Bridges of the Calix[6]arene Scaffold

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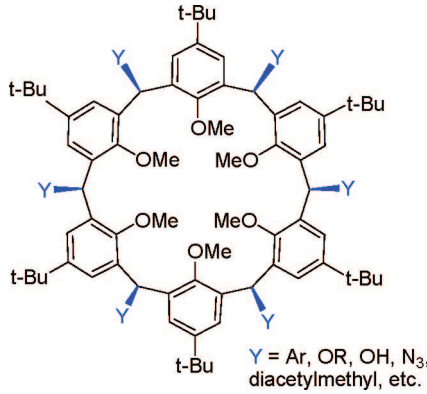

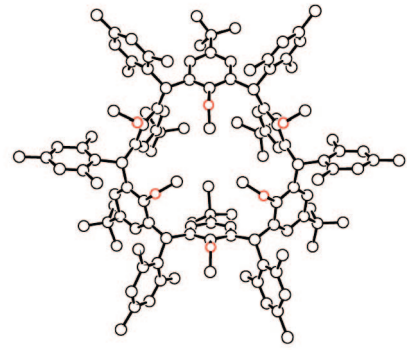

The bromine atoms of the hexabromo calixarene derivative **3** were replaced by other groups under S_N1 conditions, allowing the facile synthesis of calix[6]arene derivatives incorporating identical functionalities at all bridges. Heating at reflux a mixture of **3** and the appropriate alcohol incorporated primary and secondary alkoxy substituents. Hydride abstraction was observed when the reaction with EtOH and *i*-PrOH was conducted in hexafluoroisopropanol (HFIP). Solvolysis of **3** in TFE in the presence of strong nucleophiles (such as N_3^- and aniline) afforded the corresponding hexaazido and hexaanilino derivatives. Hydroxyl groups were incorporated into the calix[6]arene scaffold via acetolysis of **3**, followed by $LiAlH_4$ reduction of the hexaacetate derivative obtained. Friedel−Crafts alkylations in the absence of Lewis acids were conducted by heating at reflux a mixture of **3**, HFIP, and a substituted benzene derivative (e.g, *m*-xylene, *p*-methyl anisole, mesitylene). The calix[6]arene bridges were alkylated by heating at reflux a mixture of **3** and 2,4-pentanedione in TFE or HFIP. In all cases the reaction proceeded with high diastereoselectivity, and the major isomer isolated was assigned to the rc_5 (i.e., *all-cis*) form. NMR spectroscopy indicates that the conformation adopted by the macrocycle possesses 3-fold symmetry (a "pinched cone") that is rigid in the laboratory time scale in the mesityl-substituted derivative.

Introduction

Although numerous synthetic methods have been developed for the modification of the aromatic rings of the calixarene scaffold,[1] a versatile method for the introduction of substituents at *all* of the methylene groups has remained an elusive goal.[2] Calix[6]arenes functionalized at one or two bridges have been synthesized by the fragment condensation method,[3] by a spirodienone route,[4] by an homologous anionic *ortho*-Fries rearrangement,[5] and via alkylation of a monolithiated tetramethoxy *p-tert*-butylcalix[4]arene.[6,7] Calix[4]arenes substituted

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(2) For recent studies of aza[1_4]metacyclophanes substituted at the nitrogen bridges see: (a) Ishibashi, K.; Tsue, H.; Tokita, S.; Matsui, K.; Takahashi, H.; Tamura, R. *Org. Lett.* **2006**, *8*, 5991. (b) Tsue, H.; Ishibashi, K.; Takahashi, H.; Tamura, R. *Org. Lett.* **2005**, *7*, 2165. (c) Zhang, E.-X.; Wang, D.-X.; Zheng, Q.-Y.; Wang, M.-X. *Org. Lett.* **2008**, *10*, 2565. (d) Vale, M.; Pink, M.; Rajca, S.; Rajca, A. *J. Org. Chem.* **2008**, *73*, 27. (e) Ito, A.; Inoue, S.; Hirao, Y.; Furukawa, K.; Kato, T.; Tanaka, K. *Chem. Commun.* **2008**, 3242.

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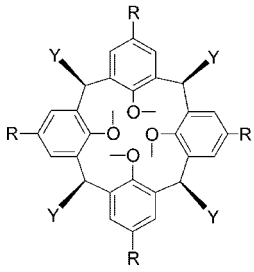
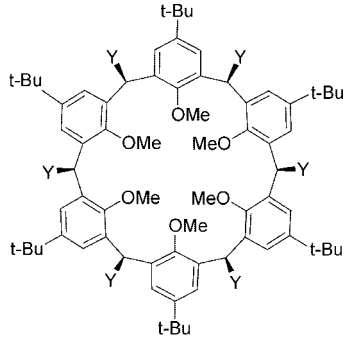
by phenyl groups at all of the bridges have been prepared via addition of PhLi to a ketocalix[4]arene derivative followed by ionic hydrogenation of the tetraalcohol product.[8] The methylene groups of calix[6]arene derivatives have been oxidized to carbonyl groups[9] and have been monobrominated,[10] but no general synthetic procedure has been reported for the preparation of calix[6]arenes with all methylene bridges monosubstituted. We have recently reported that the tetrabromocalix[4]arene derivatives **1a** and **1b** are useful intermediates for the preparation of methylene-functionalized calix[4]arenes. C−O, C−N, and even C−C bonds can be readily formed at the four bridges under mild solvolytic conditions.[11] Here we describe the application of this synthetic route to the large-ring calix[6]arene scaffold.



1a R = H, Y = Br
1b R = *t*-Bu, Y = Br
1c R = *t*-Bu, Y = OMe



2 Y = H
3 Y = Br

Results and Discussion

Configurational Stereoisomerism in Methylene-Functionalized Calix[6]arenes. A calix[6]arene derivative monofunctionalized at each methylene bridge possesses six stereocenters, and several configurational isomers are possible. Under a time scale of rapid rotation around the Ar−C bonds, the macrocyclic ring of the calixarene can be depicted schematically by a planar hexagon, with each corner representing a monosubstituted bridge. Eight diastereomeric forms are possible for a calix[6]arene derivative monosubstituted at all bridges by an identical substituent. These forms arise from the possible relative dispositions (*cis* or *trans*) of the substituents at the bridges (Figure 1). The eight diastereomeric forms of a substituted calix[6]arene are analogous to those present in the classical case of a 1,2,3,4,5,6-hexasubstituted cyclohexane (e.g., the inositols).[12] The different forms can be designated by describing the *cis* (*c*) or *trans* (*t*) disposition of the substituents relative to the reference (*r*) substituent. For simplicity, a series of *n* substituents on adjacent bridges in a *cis* or *trans* disposition relative to the reference substituents are designated as c_n and t_n, respectively.

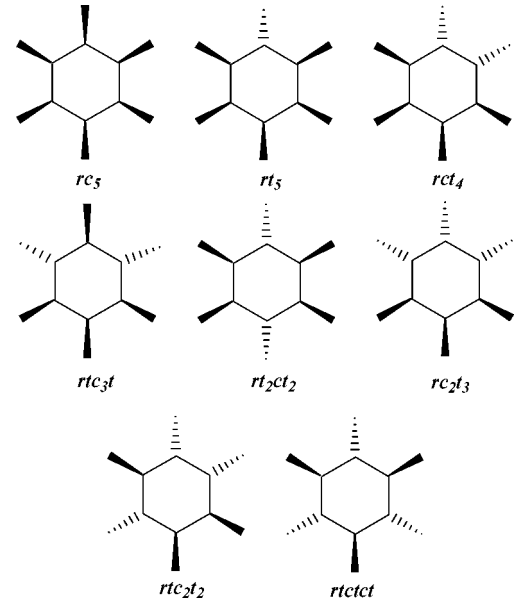


FIGURE 1. Stereoisomers arising from the different *cis* or *trans* disposition of identical substituents on the six bridges of a calix[6]arene. The calixarene macrocycle is schematically represented as a hexagon.

Although each descriptor unambiguously characterizes each isomer, in some cases several descriptors are possible for a given structure, depending on the identity of the substituent chosen as reference and whether a clockwise or counterclockwise sequencing order is used. In Figure 1, we chose arbitrarily the more "compact" descriptor (e.g., rt_5 and rtc_3t, instead of rc_4t and rc_2tct, respectively). Under a time scale of rapid internal rotations, only the rtc_2t_2 form (which is stereochemically analogous to the "*chiro*" isomer of inositol)[12] is chiral, while the rest are achiral. Clearly, the monofunctionalization of the six methylene bridges of a calix[6]arene in stereoselective fashion is more challenging than the corresponding transformation of a calix[4]arene due to the larger number of possible diastereomeric products (eight for a substituted calix[6]arene vs four for a calix[4]arene).

Hexabromo Calix[6]arene Derivative 3. The calixarene **3** was prepared by reaction of the corresponding hexamethoxy derivative **2** with NBS under irradiation using a minor modification of the reported literature procedure.[10] The NMR spectrum of **3** displays a simple pattern (one singlet each for the *t*-Bu, methoxy, methine, and aromatic protons) indicating a highly symmetric molecule. The NMR pattern could correspond to either rc_5 or *rctctct* configuration patterns. However, by analogy with **1a** and **1b**, which according to the X-ray crystallography possess the *rccc* configuration,[11a,13] we tentatively ascribe to **3** the rc_5 configuration.

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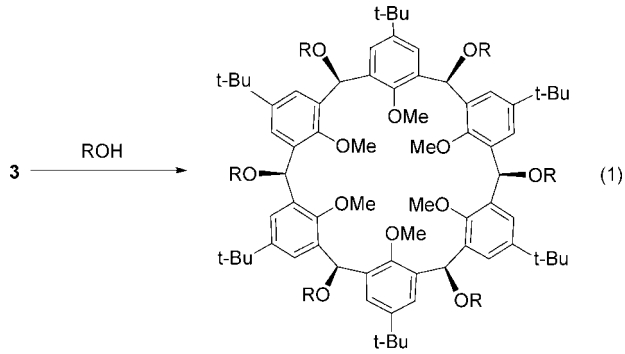
Reaction of 3 with Alcohols. Preparation of Hexaalkoxy Derivatives. Heating at reflux a solution of **3** in primary (MeOH, EtOH, 1-PrOH, 1-*n*-BuOH, 1-*i*-BuOH) or secondary alcohols (*i*-PrOH, cyclopentanol, cyclohexanol) afforded in good yields a single major hexaalkoxy product (**4a**−**g**, eq 1). By analogy to **1b**, we assume that these reactions take place via a S_N1 mechanism involving heterolytic stepwise cleavage of the C−Br bonds followed by reaction of the resulting benzhydryl-type cation with the solvent. The reaction conditions for the solvolysis of **3** are milder than those used for achieving a similar transformation in the tetrabromo derivative **1b** (an ionizing solvent such as 2,2,2-trifluoroethanol (TFE) or hexafluoroisopropanol (HFIP) or higher temperatures are required). No reaction was observed for the bulky *t*-BuOH. Reflux of **3** in TFE afforded the corresponding hexakis(trifluoroethoxy) derivative **4i**.



4a R = Me (43%) **4f** R = 1-*i*-Bu (44%)
4b R = Et (37%) **4g** R = *c*-C_5H_9 (37%)
4c R = 1-Pr (45%) **4h** R = *c*-C_6H_{11} (40%)
4d R = 2-Pr (60%) **4i** R = CH_2CF_3 (52%)
4e R = 1-*n*-Bu (53%) **4j** R = $CH(CF_3)_2$ (21%)
4k R = CH_2CH_2OH (3%)

Two alcohols required modified reaction conditions. Calixarene **3** is insoluble in HFIP, and only starting material was obtained after reflux for 3 h in the fluorinated alcohol. The hexakis(hexafluoropropoxy) derivative **4j** was obtained when the reaction was conducted in the presence of a base (i.e., 10% v/v lutidine in HFIP). It seems likely that the role of the lutidine is to increase the solubility of **3** in the reaction medium and to generate hexafluoroisopropoxide, which is a better nucleophile than HFIP. Solvolysis of **3** in ethylene glycol afforded a mixture of products, but using a 3:1 mixture of the glycol and TFE yielded **4k** in low yield.[14] In all cases a single major hexasubstituted isomer was obtained, which on the basis of its high symmetry is ascribed to the *rc*$_5$ form. X-ray crystallography corroborated the *rc*$_5$ configuration of **4a** (Figure 2). The macrocycle adopts a "pinched cone" conformation (see below).[15]

The possibility of selectively cleaving the lower rim methoxy groups in the presence of the alkoxy substituents on the bridges was briefly examined. We chose the hexaisopropoxy derivative **4d** as substrate since we expected that the bulky isopropyl groups should hinder the approach of the cleavage reagent to the ether groups at the bridges, thus resulting in preferential O-Me cleavage. However, treatment of **4d** with BBr_3/CH_2Cl_2 afforded the hexabromo derivative **3** as the major reaction

(14) A higher proportion of TFE yielded products (according to NMR spectroscopy) containing bridges substituted by both 2-hydroxyethoxy and trifluoroethoxy groups.

(15) Unfortunately, the structure could only be refined to a relatively high *R* factor ($R = 0.1339$).

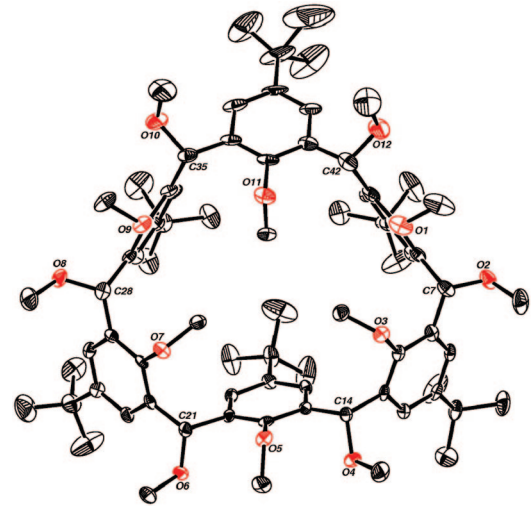


FIGURE 2. Crystal structure of **4a**.

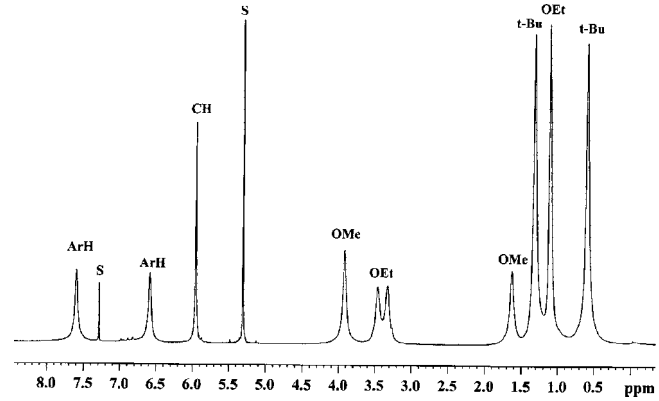
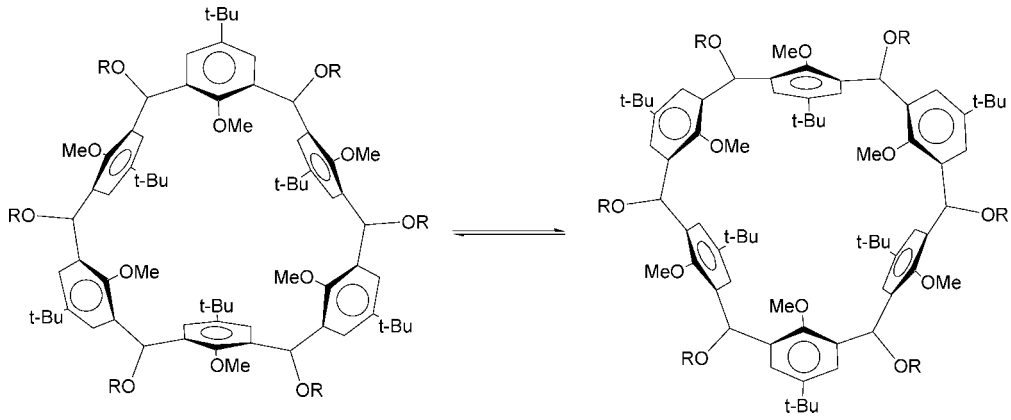


FIGURE 3. ^{1}H NMR spectrum (500 MHz, CD_2Cl_2) of **4b** at 170 K. Two methylene signals are observed for the OCH_2 groups (3.48 and 3.31 ppm). As a result of broadening effects, the ethoxy groups signals display no measurable coupling.

product. The calix-OPr^i bonds are apparently the more labile ether bonds in the molecule. For the methylene-functionalized calix[4]arenes we have observed previously that in some cases the ether bonds to the calix scaffold can be quite labile. Specifically, attempted recrystallization of the *rccc* form of a tetramethoxy derivative of calix[4]arene (**1c**) resulted in a mixture of the *rccc*, *rcct*, and *rctt* forms indicating that isomerization took place, most likely proceeding via heterolytic cleavage of the C-OMe bonds.[11b]

Low-Temperature NMR Studies of 4b and 4d. The ^{1}H NMR spectrum of the alkoxy derivatives displayed at room temperature a broad signal for the lower-rim methoxy groups. The hexaethoxy and hexaisopropoxy ether derivatives (**4b** and **4d**, respectively) were chosen for low-temperature NMR studies. Upon lowering the temperature of samples of **4b** (500 MHz, CD_2Cl_2) the broad signals decoalesced, and at 170.1 K (slow exchange conditions on the NMR time scale) the *t*-Bu, aromatic, and methoxy groups each appeared as a pair of signals (Figure 3). Notably, a large separation was present between the two methoxy signals (ca. 2.3 ppm). One methoxy signal resonates at an unusual high field for a methoxy group (1.61 ppm), indicating that one type of methoxy group is located in the shielding region of a neighboring aryl group. Two signals were

SCHEME 1

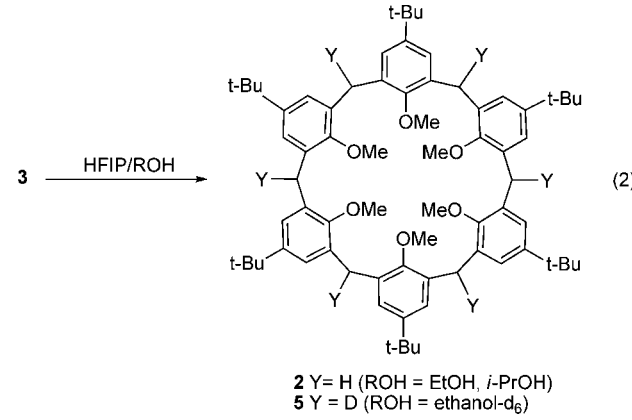


observed for the methylene protons of the ethoxy groups.[16] This pattern suggests that in the conformation adopted, the six substituted bridges are equivalent, but no mirror planes bisecting a pair of opposite bridges are present. On the basis of the 3-fold symmetry indicated by the NMR data and the shielding of only one type of methoxy groups, we propose that in solution the molecule adopts a "pinched cone" conformation of C_3v symmetry, which can be viewed as generated from a 3-fold distortion of the ideal cone conformation of C_6v symmetry. In this conformation the six bridges are symmetry equivalent, but the rings at positions 1, 3, and 5 are less twisted than the rings at the 2, 4 and 6 positions (cf. Scheme 1). The methoxy signal at 1.61 ppm is assigned to the methoxy groups of the less twisted rings that are pointing "in" (toward the cavity) and are shielded by the neighboring aryl rings, while the methoxy signal at 3.91 ppm is ascribed to the methoxy groups that are pointing "out".

From the chemical shift difference of groups under slow exchange conditions in CD_2Cl_2 at 500 MHz ($\Delta\nu$ = 513.5, 86.0, and 1150.5 Hz for the aromatic, methylene, and methoxy groups), and their coalescence temperatures (206.0, 191.3, and 215.0 K, respectively), a rotational barrier of 9.0 ± 0.1 kcal mol^{-1} was calculated for **4b** by means of the Gutowsky−Holm[17] and Eyring equations. This rotational process is ascribed to a pinched cone/pinched cone interconversion, a process that exchanges the two types of rings in the macrocycle (Scheme 1).

The low-temperature ^{1}H NMR spectrum of the hexaisopropoxy derivative **4d** displayed two signals for the isopropyl methyl groups (δ 1.30 and 1.20 ppm at 168 K). The coalescence data for **4d** ($\Delta\nu$ = 420 and 1100 Hz and T_c= 185.2 and 198.0 K, for the aromatic and methoxy groups, respectively) afforded a lower barrier (8.2 ± 0.2 kcal mol^{-1}) than the one found for **4b**. Thus, in the case of the alkoxy substituents, increasing the bulk of the alkoxy groups reduces the rotational barrier, most likely due to preferential steric destabilization of the ground state.

Hydride Capture by Carbocation Intermediates. In an attempt to introduce chiral groups on the calix[6]arene bridges, calixarene **3** was reacted with *R*-(−)-2-butanol. The reaction was conducted using a ca. 20:1 (v/v) mixture of HFIP and the chiral alcohol. Surprisingly, the only product obtained was the unsubstituted derivative **2**. The reaction was examined using mixtures of HFIP with different alcohols. Reaction with HFIP/MeOH or HFIP/ethylene glycol afforded a mixture of reduced products containing methylene and CH-OR bridges, whereas in the case of the HFIP/TFE only starting material was recovered after 2 h reflux. Full reduction of the bridges was obtained in the reaction of **3** with HFIP/ethanol and HFIP/isopropanol mixtures (eq 2). The formation of **2** can be viewed as resulting from hydride transfer between the alcohol molecules and the carbocationic intermediates. Since no reduced product was obtained in the reaction of **3** with pure TFE, EtOH or HFIP (eq 1), it seems likely that a mixture of both HFIP and the nonfluorinated solvents is required.



To determine the source of the hydride transferred to the bridges of the calixarene, we conducted the reaction in a mixture of HFIP and ethanol-d_6. If the source of the hydride is the HFIP, no labeling should be present in the final product, whereas if the source is a C-D bond of the ethanol molecules, the final product should incorporate a single deuterium atom on each bridge.[18] ^{1}H NMR analysis of the product indicated that compound **5** was formed, possessing a deuterium atom in each bridge (Figure 4). This demonstrates that the source of the atom transferred to the carbocationic intermediates is the ethanol molecules and not the fluorinated alcohol present in excess.

(16) As a result of broadening effects, no coupling is observed for the signals of the diastereotopic methylene and the methyl moieties of the ethoxy groups.
(17) Gutowsky, H. S.; Holm, C. H. *J. Chem. Phys.* **1956**, *25*, 1228.
(18) Upon mixing the two solvents, there is a fast exchange between the OD group of the ethanol-d_6 and the OH group of the HFIP molecules. For the ca. 20:1 mixture used, the labeling of the OH groups of both the ethanol and HFIP molecules should be about 5%. If the source of the hydrogen transferred is the hydroxyl group of either the ethanol or HFIP molecules (a mechanism not involving hydride transfer), disregarding solvent isotope effects, it could be expected that only a small percent of deuterium should be incorporated at the bridges.

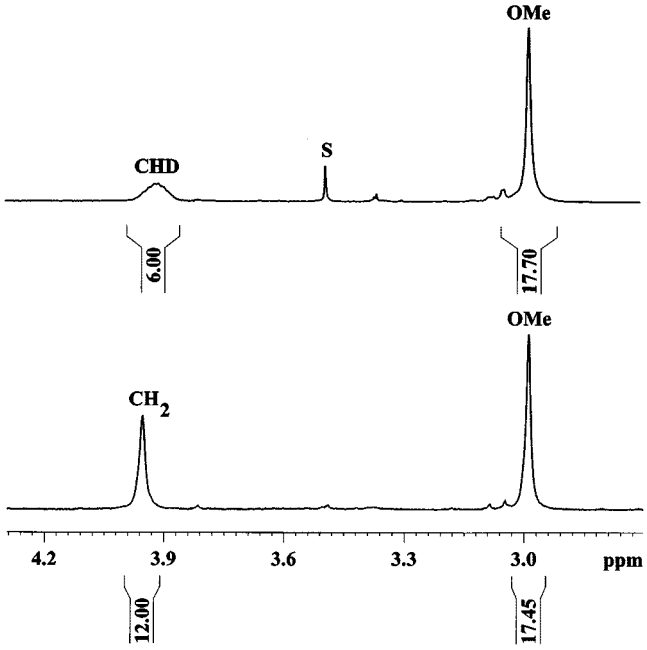
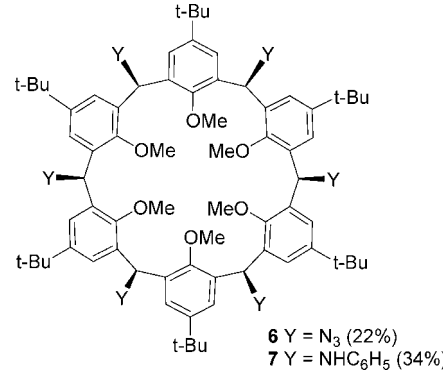


FIGURE 4. ^{1}H NMR spectrum ($CDCl_3$) of the methoxy and methylene groups of **2** (bottom) and **5** (top). The broadening of the CHD signal is due to unresolved H-D coupling.

Hydride transfer reactions from alcohols to carbocations under acidic conditions are known.[19] However, the formation of **2** in the solvolysis of **3** in the mixtures HFIP/EtOH and HFIP/*i*-PrOH was unexpected, since only the hexaalkoxy derivatives were formed in the reaction with the neat aliphatic alcohols. The formation of **2** can be rationalized if initially an ether bond is formed between the aliphatic alcohol and the calix carbocation, but in the highly ionizing and acidic solvent HFIP this bond undergoes a reversible heterolytic cleavage, regenerating the carbocation. The competing hydride transfer reaction, although slower than the ether formation reaction, is irreversible, and eventually all of the bridges are reduced (Figure 5). To test this hypothesis, a solution of the hexaisopropoxy derivative **4d** was heated at reflux for 2 h in a HFIP/*i*-PrOH mixture (reaction conditions identical to those used in the reaction of **3**). Examination of the crude product indicated complete conversion to **2**, indicating that indeed the ether bonds of **4d** are cleaved under the experimental conditions. In the case of the reaction of **3** with the neat aliphatic alcohols, most likely the lower ionizing power and lower acidity of the alcohol (as compared to HFIP) are sufficient for inducing the dissociation of the C−Br bonds but not sufficient for the heterolytic cleavage of the C−O bonds at the bridges, and therefore the reaction does not proceed beyond the hexalkoxy stage. The aliphatic alcohols EtOH and *i*-PrOH are better hydride transfer reagents than HFIP, since hydride transfer from the latter would result in protonated hexafluoroacetone, in which the positive charge in the protonated carbonyl group is destabilized by the two electron-withdrawing CF_3 groups. The reaction conditions can be used for other systems generating relative stable carbocations as shown by heating at reflux a solution of trityl chloride in a HFIP/*i*-PrOH mixture, which afforded triphenylmethane.

Reaction with N-Nucleophiles: Azide and Aniline. We also examined the reaction of **3** with N-nucleophiles, specifically azide and aniline. The incorporation of azido groups into the calix scaffold is of interest since they may enable a large number of chemical modifications, e.g., via 1,3-dipolar cycloaddition to alkynes (click chemistry).[20] The reaction of aniline, if proceeding via C−N bond formation will result in calixarene derivatives incorporating basic functionalities at the bridges.[21]

The reaction with azide was conducted by heating at reflux a mixture of **3**, NaN_3, and TFE. 18-Crown-6 was added to the mixture to increase the solubility of the azide salt in the solvent. NMR and MS analysis of the product obtained after recrystallization from $CHCl_3$/MeOH indicated the formation of the hexaazido derivative **6** (rc_5 isomer, ca. 95% pure).[22]



Reaction of **3** with aniline was conducted in TFE. ^{1}H NMR analysis indicated that C−N bond formation took place, as evidenced by a pattern characteristic of a monosubstituted phenyl ring.

Hexaacetoxy and Hexahydroxy Derivatives. Incorporation of hydroxy groups on the bridges was achieved by a two-step process, involving acetolysis of **3**, followed by $LiAlH_4$ reduction of the hexaacetoxy derivative **8** (eq 3). Hexahydroxycalix[6]arene **9** displayed a doublet for the OH protons ($\delta = 5.50$, $J = 6$ Hz) in the ^{1}H NMR spectrum in DMSO-d_6.

Friedel−Crafts Reactions. Solvolytic Friedel−Crafts alkylation reactions in the absence of a Lewis acid were recently reported by Mayr and co-workers.[23] We have shown that these types of reactions can be conducted on the tetrabromocalixarenes **1a** and **1b** using TFE/butylene oxide (for 2-methylfuran) or HFIP (for *m*-xylene) as solvents. Notably, the product obtained in the reaction of **1a** with *m*-xylene was partially demethylated.[11b] Apparently, the HBr released in the solvolytic reaction is capable of cleaving the lower rim O-Me bonds. The Friedel−Crafts reaction failed when the reaction was attempted with the crowded mesitylene as the aromatic substrate.

We found that the solvolytic Friedel−Crafts reaction of calixarene **3** proceeds readily with aryl rings substituted by electron-donating groups. To avoid the formation of mixture of products arising from substitution at different positions of the ring (e.g., *ortho* and *para* to the electron-donating substituent), only aromatic rings expected to preferentially undergo monosubstitution at a single position were used. In contrast to

(19) Bartlett, P. D.; McCollum, J. D. *J. Am. Chem. Soc.* **1956**, *78*, 1441. See also: Lu, Y.; Qu, F.; Moore, B.; Endicott, D.; Kuester, W. *J. Org. Chem.* **2008**, *73*, 4763.

(20) For an example of the utilization of the 1,3-dipolar cycloaddition of azides for the preparation of water soluble calixarenes, see: Ryu, E.-H.; Zhao, Y. *Org. Lett.* **2005**, *7*, 1035.

(21) For a calix[4]arene substituted at two bridges by dimethylamino groups, see: Simaan, S.; Biali, S. E. *Org. Lett.* **2005**, *7*, 1817.

(22) The minor product formed is probably a pentaazido mono(trifluoroethoxy) calix[6]arene derivative as evidenced by the small quartet at ca. 3.95 ppm characteristic of the protons of a trifluoroethoxy group.

(23) Hofmann, M.; Hampel, N.; Kanzian, T.; Mayr, H. *Angew Chem. Int. Ed.* **2004**, *43*, 5402.

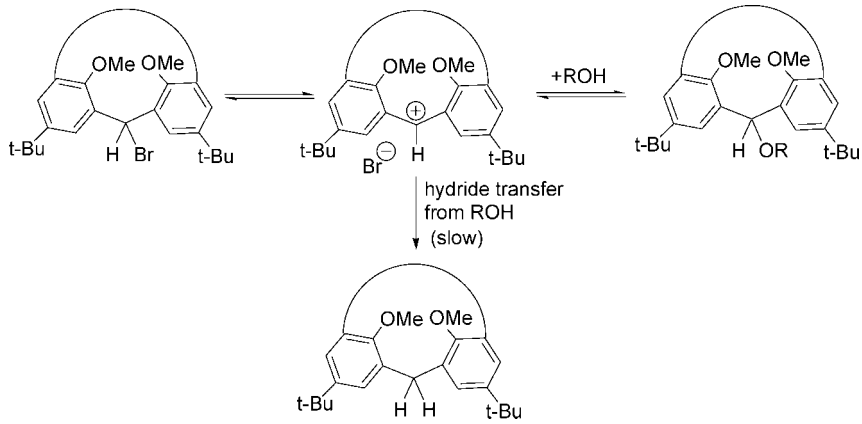
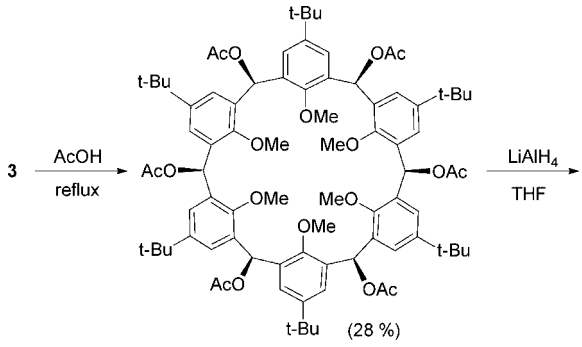


FIGURE 5. Hydride transfer versus capture by the nonfluorinated alcohol (ROH) in the solvolysis of **3** in a HFIP/ROH mixture.



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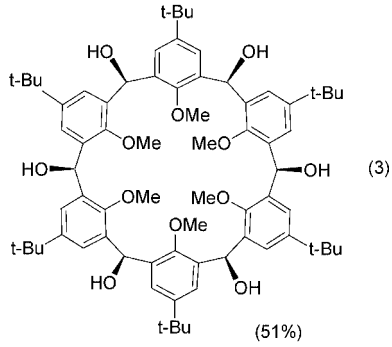
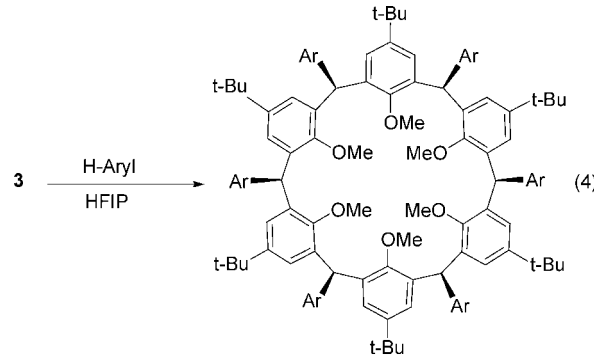


(3)

9



(4)

10 Ar = 2,4-$Me_2C_6H_3$(67%)
11 Ar = 2,5-$Me_2C_6H_3$ (78%)
12 Ar = 2,3,4,5-Me_4C_6H (57%)
13 Ar = 2-OMe,4-MeC_6H_3 (59%)
14 Ar = 2,4,6-$Me_3C_6H_2$ (66%)

the reaction of **1a** and **1b**, no demethylation was observed under the reaction conditions, and the single major product was the hexaaryl-substituted derivatives **10**−**13** (eq 4). Moreover, even the crowded mesitylene reacted readily, affording the hexamesityl derivative **14**. Since HFIP is relatively expensive, we examined also the reaction in the presence of a cosolvent. We found that the reaction proceeds readily even if a 4:1 mixture of chloroform and HFIP is used instead of pure HFIP.

In the 500 MHz ^{1}H NMR spectra of the calixarenes **10**−**12** and **14** at room temperature, each of the *t*-Bu, aromatic and methoxy groups appeared as a pair of signals. In all cases the aryl rings at the bridges displayed a single set of signals. The ^{1}H NMR spectrum of calixarene **13** in $CDCl_3$ displayed at room temperature sharp signals for the aryl rings at the bridges, but broad signals for the lower rim methoxy groups, *t*-Bu, and aromatic protons of the calix[6]arene skeleton, suggesting that this calixarene is the more flexible in the series **10**−**14**. Upon lowering the temperature of a sample of **13**, a pattern similar to that found for the other calixarenes indicating 3-fold symmetry was observed.[24]

The NMR pattern under slow exchange conditions (on the NMR time scale) of the macrocyclic rings of **10**−**14** indicating 3-fold symmetry suggests that the calix[6]arenes functionalized at the bridges by aryl groups adopt also pinched cone conformations of 3-fold symmetry.[25]

Rotational Barriers of Arylated Calixarenes. The rotational barriers of calixarenes **10**, **11**, and **13** were determined by dynamic NMR. From the coalescence of the *t*-Bu and aromatic protons of **10** (k_c = 136.6 and 261.0 s^{-1} and T_c = 413.0 and 427.0 K), a barrier of 20.5 ± 0.1 kcal mol^{-1} was calculated by means of the Eyring equation. For the *p*-xylyl derivative **11**, a barrier of 20.4 kcal mol^{-1} was determined from the coalescence of the *t*-Bu groups. Calixarene **13** is significantly more flexible, and from the coalescence data of the calix aromatic protons and lower rim methoxy groups, a barrier of 14.1 ± 0.2 kcal mol^{-1} was determined. The lower barrier of **13** suggests that the barrier height is a function of the bulk of the substituent

(24) Notably, in the low temperature NMR spectrum of **13** in CD_2Cl_2 (278 K) both lower rim methoxy groups resonated at a relatively low field (4.26 and 4.08 ppm) compared to the other hexaaryl derivatives. This suggests that the conformation adopted by **13** in that solvent is somewhat different. It may be possible that in CD_2Cl_2 all of the lower rim methoxy groups are oriented in an "out" fashion (i.e., pointing away from the cavity) and/or the twist angles of the rings is different.

(25) X-ray crystallography of **14** (see Supporting Information) indicates that the configuration of the substituents is rc_5 and that the macrocycle adopts a "pinched cone" conformation. Unfortunately, the structure could only be refined to a relatively high *R* factor, but we believe the major structural features mentioned above are trustworthy.

located *ortho* to the bond connecting the aryl substituent with the calix macrocycle. The dynamic process is ascribed to a pinched cone/pinched cone interconversion (cf. Scheme 1).

Notably, separate signals were observed in the room temperature ^{1}H NMR spectrum of **14** for both the *ortho* methyl groups and the aromatic protons of the mesityl groups. This indicates that, at least for **14**, both the internal rotations of the macrocyclic ring and the rotations of the aryl substituents at the bridges are slow at room temperature on the NMR time scale. Heating a sample of **14** in $C_6D_5NO_2$ up to 458 K did not result in any appreciable broadening of the signals. From the chemical shift difference between the *t*-Bu signals at 458 K (8 Hz at 500 MHz) and assuming that the coalescence of the signals is at least 460 K, a lower limit of 24.6 kcal mol^{-1} was estimated for the pinched cone-pinched cone interconversion of **14**. The rotational barrier of **14** could be measured by EXSY. From the relative integration of the cross peaks between the methoxy signals in an EXSY spectrum at 452.4 K, a rotational barrier of 27.8 kcal mol^{-1} was determined.[26] The hexamesityl derivative **14** can be viewed as conformationally rigid at room temperature in the laboratory time scale. Clearly, the introduction of bulky aryl group at the bridges increases the rigidity of the pinched cone conformation. This approach may be used when a reduction in the flexibility (preorganization) of the calix[6]arene scaffold is desirable.[27]

Alkylation of Calixarene Bridges. Although $C_{(sp3)}$-$C_{(aryl)}$ rings can be readily introduced at the bridges via the solvolytic Friedel−Crafts reaction, it was not clear at first whether alkyl substituents can be attached to the bridges by an analogous route using a substituent possessing a double bond (i.e., a process involving formation of $C_{(sp3)}$−$C_{(sp3)}$ bonds). Carbonyl compounds in equilibrium with a relatively highly populated enol form were selected as nucleophiles, since reaction of the intermediate carbocation with the enol form of the carbonyl was expected to occur readily. The Lewis acid catalyzed alkylation of benzhydryl cations with compounds possessing active methylenes has been reported in the literature.[28] Since the solvolytic Friedel−Crafts reaction in the absence of Lewis acid work efficiently for **3**, we attempted the reaction with active methylene compounds under similar reaction conditions (i.e., TFE or HFIP as solvents without the introduction of an additional Lewis acid).

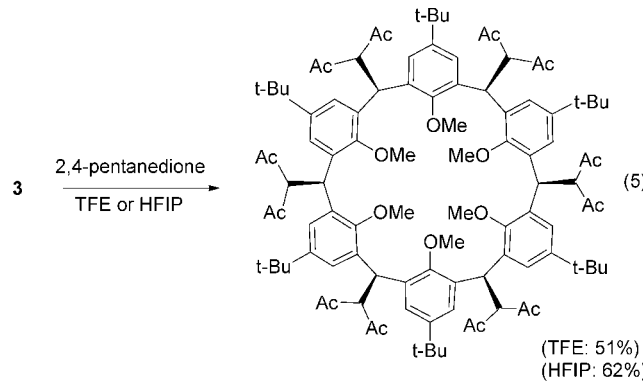
Initial experiments were conducted by heating at reflux a solution of **3** and ethyl acetoacetate in HFIP or TFE. Since a complex mixture of products was obtained, the reaction was repeated in neat ethyl acetoacetate. Unexpectedly, the product consisted of the hexaethoxy derivative **4b**. It seems likely that under the reaction conditions there is a partial hydrolysis of the ethyl acetoacetate and the EtOH formed successfully competes with the enolic form of the ethyl acetoacetate in the reaction with the carbocation intermediate. No reaction was observed when the hexaisopropoxy derivative **4d** was heated in neat ethyl acetoacetate.

TABLE 1. Summary of Reactions Involving the Replacement of All Bromine Atoms of 3

nucleophilic reagent	solvent	product
MeOH	MeOH	**4a**
EtOH	EtOH	**4b**
1-PrOH	1-PrOH	**4c**
2-PrOH	2-PrOH	**4d**
1-*n*-BuOH	1-*n*-BuOH	**4e**
1-*i*-BuOH	1-*i*-BuOH	**4f**
cyclopentanol	cyclopentanol	**4g**
cyclohexanol	cyclohexanol	**4h**
TFE	TFE	**4i**
HFIP	HFIP[a]	**4j**
ethylene glycol	3:1 ethylene glycol/TFE	**4k**
	20:1 HFIP/ethanol-d_6	**5**
NaN_3	TFE	**6**
aniline	TFE	**7**
acetic acid	acetic acid	**8** (**9**)[b]
m-xylene	4:1 $CHCl_3$/HFIP	**10**
p-xylene	4:1 $CHCl_3$/HFIP	**11**
1,2,3,4-tetramethylbenzene	4:1 $CHCl_3$/HFIP	**12**
p-methylanisole	4:1 $CHCl_3$/HFIP	**13**
mesitylene	4:1 $CHCl_3$/HFIP	**14**
acetylacetone	TFE or HFIP	**15**

[a] In the presence of 10% lutidine. [b] Hexahydroxy calixarene **9** was obtained after $LiAlH_4$ reduction of the hexaacetoxy calix[6]arene **8**.

To avoid the formation of alkoxy products, the reaction was conducted with 2,4-pentanedione, which is highly enolic, but in contrast to ethyl acetoacetate does not undergo hydrolysis. The reaction proceeded in either HFIP or TFE, affording the hexaalkylated calixarene **15** (eq 5).[29] No signals corresponding to the enol form of the diacetylmethyl substituents were detected in both $CDCl_3$ and DMSO-d_6.



(5)

Conclusions

Calix[6]arenes derivatives monosubstituted at all bridges can be prepared by reaction under S_N1 conditions of the hexabromo calixarene derivative **3** with the appropriate nucleophile. The reaction proceeds with a wide array of nucleophiles (alcohols, azide ion, aniline, benzene derivatives) and even with acetylacetone (Table 1). The reaction in general is cleaner than the one for the tetrabromo derivatives **1a** and **1b**, with fewer side reactions (no demethylation was observed in the solvolytic Friedel−Crafts reactions). In all cases a single major product

(26) We thank Dr. Roy Hoffman (Hebrew University) for conducting this experiment.

(27) For other approaches based on derivatizing the OH groups of a calix[6]arene with bulky groups or via bridging, see: (a) Grynszpan, F.; Aleksiuk, O.; Biali, S. E. *J. Chem. Soc., Chem. Commun.* **1993**, 13. (b) Araki, K.; Akao, K.; Otsuka, H.; Nakashima, K.; Inokuchi, F.; Shinkai, S. *Chem. Lett.* **1994**, 1251. (c) Otsuka, H.; Araki, K.; Shinkai, S. *J. Org. Chem.* **1994**, *59*, 1542. (d) Otsuka, H.; Araki, K.; Matsumoto, H.; Harada, T.; Shinkai, S. *J. Org. Chem.* **1995**, *60*, 4862. (e) Otsuka, H.; Shinkai, S. *J. Am. Chem. Soc.* **1996**, *118*, 4271. See also: (f) Janssen, R. G.; Verboom, W.; van Duynhoven, J. P. M.; van Velzen, E. J. J.; Reinhoudt, D. N. *Tetrahedron Lett.* **1994**, *35*, 6555. (g) Kraft, K.; Bohmer, V.; Vogt, W.; Ferguson, G.; Gallagher, J. F. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1221. (h) Chen, Y. Y.; Li, H. B. *New J. Chem.* **2001**, *25*, 340.

(28) (a) Bisaro, F.; Prestat, G.; Vitale, M.; Poli, G. *Synlett* **2002**, 1823. (b) Jana, U.; Biswas, S.; Maiti, S. *Tetrahedron Lett.* **2007**, *48*, 4066. (c) Sanz, R.; Miguel, D.; Martinez, A.; Alvarez-Gutierrez, J. M.; Rodriguez, F. *Org. Lett.* **2007**, *9*, 2027.

(29) This reaction was also attempted with the tetrabromocalixarene **1b**, but reaction in either TFE or HFIP afforded only a complex mixture.

was formed (assigned to the rc_5 form) that could be purified by simple recrystallization. Introduction of the substituents at the bridges rigidifies the calix[6]arene scaffold.

Experimental Section

2,8,14,20,26,32-Hexabromo-5,11,17,23,29,35-hexa-*tert*-butyl-37,38,39,40,41,42-hexamethoxy-calix[6]arene (3). A mixture of **2** (11.0 g, 10.4 mmol), NBS (13.6 g, 76.4 mmol), and CCl_4 (500 mL) was heated at reflux for 22 h while being irradiated with a spotlight (100 W). After the mixture cooled to room temperature, aqueous Na_2SO_3 was added. The organic phase was filtered, and the solid product was recrystallized from $CHCl_3$/MeOH yielding 7.2 g (54%) of **3** as a white solid. If after the addition of aqueous Na_2SO_3 there was no solid in the organic phase, it was washed twice with water, dried ($MgSO_4$) and evaporated. Recrystallization was carried out in $CHCl_3$/MeOH.

General Procedure for Preparation of the Hexaalkoxy Calix[6]arene Derivatives 4a−4i. If not stated otherwise, all of the reactions were conducted under an open atmosphere without any moisture protection. A mixture of **3** (0.10 g, 0.07 mmol) and 10 mL of the appropriate alcohol was heated at reflux for two h. After evaporation of the solvent, the residue was recrystallized from $CHCl_3$/MeOH.

5,11,17,23,29,35-Hexa-*tert*-butyl-2,8,14,20,26,32,37,38,39,40,41,42-dodecamethoxycalix[6]arene (4a). Yield 35 mg (43%). Mp 235−238 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.26 (s, 12H), 6.06 (s, 6H), 3.74 (s, 18H), 3.11 (br s, 18H), 1.09 (s, 54H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.5, 146.3, 133.4, 124.9, 73.2, 61.4, 57.3, 34.4, 31.3 ppm. HRMS (ESI) *m/z* 1259.7733 [(M + Na)$^+$, calcd for $C_{78}H_{108}NaO_{12}$, 1259.7738].

5,11,17,23,29,35-Hexa-*tert*-butyl-37,38,39,40,41,42-hexamethoxy-2,8,14,20,26,32-hexaethoxy-calix[6]arene (4b). Yield 32 mg (37%). Mp 242−244 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.25 (s, 12H), 6.14 (s, 6H), 3.52 (q, J = 6.8 Hz, 12H), 3.07 (br s, 18H), 1.21 (t, J = 6.8 Hz, 18H), 1.09 (s, 54H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.4, 146.0, 133.7, 125.1, 71.6, 64.9, 61.3, 34.3, 31.3, 15.6 ppm. HRMS (ESI) *m/z* 1343.8672 [(M + Na)$^+$, calcd for $C_{84}H_{120}NaO_{12}$, 1343.8677].

5,11,17,23,29,35-Hexa-*tert*-butyl-37,38,39,40,41,42-hexamethoxy-2,8,14,20,26,32-hexa-1-propoxycalix[6]arene (4c). Yield 41 mg (45%). Mp 303−305 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.25 (s, 12H), 6.12 (s, 6H), 3.43 (t, J = 6.0 Hz, 12H), 3.06 (br s, 18H), 1.60 (m, 12H), 1.08 (s, 54H), 0.93 (t, J = 7.6 Hz, 18H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.4, 145.9, 133.8, 125.1, 71.6, 71.2, 61.3, 34.4, 31.4, 23.4, 11.1 ppm. HRMS (ESI) *m/z* 1427.9611 [(M + Na)$^+$, calcd for $C_{90}H_{132}NaO_{12}$, 1427.9616].

5,11,17,23,29,35-Hexa-*tert*-butyl-37,38,39,40,41,42-hexamethoxy-2,8,14,20,26,32-hexa-2-propoxycalix[6]arene (4d). Yield 55 mg (60%). Mp 303 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.31 (s, 12H), 6.31 (s, 6H), 3.61 (s, J = 6.0 Hz, 6H), 3.14 (br s, 18H), 1.20 (d, J = 6.0 Hz, 36H), 1.09 (s, 54H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.2, 145.7, 134.0, 125.7, 69.5, 68.3, 61.8, 34.4, 31.3, 22.4 ppm. HRMS (ESI) *m/z* 1427.9611 [(M + Na)$^+$, calcd for $C_{90}H_{132}NaO_{12}$, 1427.9616].

5,11,17,23,29,35-Hexa-*tert*-butyl-37,38,39,40,41,42-hexamethoxy-2,8,14,20,26,32-hexa-1-*n*-butoxycalix[6]arene (4e). Yield 52 mg (53%). Mp 228 °C.^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.24 (s, 12H), 6.11 (s, 6H), 3.46 (t, J = 6.4 Hz, 12H), 3.06 (br s, 18H), 1.57 (m, 12H), 1.38 (m, 12H), 1.08 (s, 54H), 0.88 (t, J = 7.6 Hz, 18H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.4, 145.9, 133.8, 125.1, 71.6, 69.4, 61.3, 34.3, 32.3, 31.3, 19.7, 14.0 ppm. HRMS (ESI) *m/z* 1513.0584 [(M + Na)$^+$, calcd for $C_{96}H_{144}NaO_{12}$, 1513.0555].

5,11,17,23,29,35-Hexa-*tert*-butyl-37,38,39,40,41,42-hexamethoxy-2,8,14,20,26,32-hexa-1-*i*-butoxycalix[6]arene (4f). Yield 43 mg (44%). Mp 265 °C.^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.25 (s, 12H), 6.10 (s, 6H), 3.25 (d, J = 6.5 Hz, 6H), 3.06 (br s, 18H), 1.88 (m, 6H), 1.08 (s, 54H), 0.92 (d, J = 6.5 Hz, 36H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.4, 145.8, 133.8, 125.2, 76.4, 71.5, 61.2, 34.3, 31.3, 28.9, 19.8 ppm. HRMS (ESI) *m/z* 1513.0584 [(M + Na)$^+$, calcd for $C_{96}H_{144}NaO_{12}$, 1513.0555].

5,11,17,23,29,35-Hexa-*tert*-butyl-37,38,39,40,41,42-hexamethoxy-2,8,14,20,26,32-hexacyclopentyloxycalix[6]arene (4g). Yield 38 mg (37%), mp 319−321 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.28 (s, 12H), 6.21(s, 6H), 3.95 (m, 12H), 3.13 (br s, 18H), 1.59 (br m, 48H), 1.08 (s, 54H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz) δ 154.1, 145.6, 134.07, 125.8, 80.2, 69.9, 61.6, 34.4, 32.4, 31.4, 23.5 ppm. HRMS (ESI) *m/z* 1585.0584 [(M + Na)$^+$, calcd for $C_{102}H_{144}NaO_{12}$, 1585.0555].

5,11,17,23,29,35-Hexa-*tert*-butyl-37,38,39,40,41,42-hexamethoxy-2,8,14,20,26,32-hexacyclohexyloxycalix[6]arene (4h). After evaporation of the solvent, the crude product was dissolved in 50 mL of chloroform and washed twice with water, and the organic phase was dried with $MgSO_4$. Recrystallization from $CHCl_3$/MeOH yielded 43 mg (40%) of the hexacyclohexyloxy derivative. Mp 315−317 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.34 (s, 12H), 6.33 (s, 6H), 3.26 (m, 6H), 3.18 (s, 18H), 1.97 (m, 12H), 1.70 (m, 12H), 1.53 (m, 12H), 1.32 (m, 12H), 1.06 (m, 12H), 1.08 (s, 54H) ppm. ^{13}C NMR (HRMS (ESI) *m/z* 1669.1523 [(M + Na)$^+$, calcd for $C_{108}H_{156}NaO_{12}$, 1669.1494].

5,11,17,23,29,35-Hexa-*tert*-butyl-37,38,39,40,41,42-hexamethoxy-2,8,14,20,26,32-hexakis(2,2,2-trifluoroethoxy)calix[6]arene (4i). The reaction was carried out as described in the general procedure, but the mixture was heated at reflux for 4 h. Recrystallization from $CHCl_3$/MeOH yielded 56 mg (52%). Mp 325−328 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.31 (s, 12H), 6.26 (s, 6H), 3.83 (q, J = 7.6 Hz, 12H), 3.08 (br s, 18H), 1.10 (s, 54H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz) δ 154.6, 147.1, 132.1, 128.9, 125.4 (q, J = 278.8 Hz), 72.3, 66.6 (q, J = 30.0 Hz), 61.7, 34.5, 31.2 ppm. ^{19}F NMR ($CDCl_3$, 376 MHz) δ −73.67 ppm. HRMS (ESI) *m/z* 1667.6976 [(M + Na)$^+$, calcd for $C_{84}H_{102}F_{18}NaO_{12}$, 1667.6981].

5,11,17,23,29,35-Hexa-*tert*-butyl-37,38,39,40,41,42-hexamethoxy-2,8,14,20,26,32-hexakis-(1,1,1,3,3,3-hexafluoro-2-propoxy)calix[6]-arene (4j). A mixture of **3** (0.10 g, 0.07 mmol), 10 mL of HFIP, and 1 mL lutidine was heated at reflux for 2 h. After evaporation of the solvent, the residue was recrystallized from $CHCl_3$/MeOH yielding 28 mg (21%) of **4j**. Mp 187 °C (dec).^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.51 (s, 12H), 6.52 (s, 6H), 4.25 (h, J = 5.6 Hz, 6H), 3.53 (s, 18H), 1.14 (s, 54H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz) δ 153.6, 148.4, 131.0, 127.5, 121.6 ((CF_3)$_2$), 72.7, 72.4(*C*H(CF_3)$_2$), 61.8, 34.8, 31.2 ppm.[30] ^{19}F NMR ($CDCl_3$, 470 MHz) δ −74.11 (d, J = 5.6 Hz) ppm. HRMS (ESI) *m/z* 2075.6219 [(M + Na)$^+$, calcd for $C_{90}H_{96}F_{36}NaO_{12}$, 2075.6224].

5,11,17,23,29,35-Hexa-*tert*-butyl-37,38,39,40,41,42-hexamethoxy-2,8,14,20,26,32-hexakis(2-hydroxyethoxy)-calix[6]arene (4k). A mixture of **3** (0.50 g, 0.33 mmol), 15 mL of TFE, and 45 mL of ethylene glycol was heated at reflux for 18 h. After evaporation of the TFE, the crude product was dissolved in 50 mL chloroform and washed twice with water, and the organic phase was dried ($MgSO_4$). Recrystallization from $CHCl_3$/MeOH yielded 15 mg (3%) of **4k**. Mp 350 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.28 (s, 12H), 6.18 (s, 6H), 3.75 (t, J = 4.5 Hz, 12H), 3.61 (t, J = 5.0 Hz, 12H), 3.13 (br s, 18H), 1.09 (s, 54H) ppm.^{13}C NMR ($CDCl_3$, 125 MHz) δ 154.1, 146.6, 133.4, 126.3, 71.8, 70.8, 62.0, 61.4, 34.4, 31.2 ppm. HRMS (ESI) *m/z* 1439.8367 [(M + Na)$^+$, calcd for $C_{84}H_{120}NaO_{18}$, 1439.8372].

5,11,17,23,29,35-Hexa-*tert*-butyl-37,38,39,40,41,42-hexamethoxy-2,8,14,20,26,32-hexadeuterio-calix[6]arene (5). A mixture of **3** (0.10 g, 0.07 mmol), 10 mL of HFIP, and 0.5 mL ethanol-d_6 was heated at reflux for 2 h. After evaporation of the solvent, the residue was recrystallized thrice from $CHCl_3$/MeOH yielding 36 mg (52%) of **5**, mp 218 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.01 (s, 12H), 3.91 (br s, 6H), 2.99 (s, 18H), 1.14 (s, 54H) ppm. ^{13}C NMR ($CDCl_3$,

(30) The signals for the OCH(CF_3)$_2$ group were detected in a ^{19}F decoupled ^{13}C NMR spectrum.

125 MHz) δ 154.0, 145.7, 133.4, 126.0, 60.0, 34.1, 31.4 ppm. HRMS (ESI) *m/z* 1085.7476 [(M + Na)$^+$, calcd for $C_{72}H_{90}D_6NaO_6$, 1085.7475].

5,11,17,23,29,35-Hexa-*tert*-butyl-37,38,39,40,41,42-hexamethoxy-2,8,14,20,26,32-hexaazido-calix[6]arene (6). A mixture of **3** (0.10 g, 0.07 mmol), sodium azide (0.20 g, 3.08 mmol), 18-crown-6 (0.81 g, 3.08 mmol), and 10 mL of TFE was heated at reflux for 18 h. After evaporation of the solvent, the residue was dissolved in 30 mL of chloroform and washed twice with 1 M aqueous HCl. Three recrystallizations from $CHCl_3$/MeOH yielded 18 mg (22%) of **6** 95% pure. Mp 182−185 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.30 (s, 12H), 6.42 (s, 6H), 3.33 (s, 18H), 1.10 (s, 54H) ppm.^{13}C NMR ($CDCl_3$, 125 MHz) δ 152.9, 147.3, 132.2, 125.8, 61.7, 56.1, 34.5, 31.2 ppm. HRMS (ESI) *m/z* 1325.7183 [(M + Na)$^+$, calcd for $C_{72}H_{90}N_{18}NaO_6$, 1325.7188].

5,11,17,23,29,35-Hexa-*tert*-butyl-37,38,39,40,41,42-hexamethoxy-2,8,14,20,26,32-hexaanilino-calix[6]arene (7). A mixture of **3** (0.20 g, 0.07 mmol), aniline (0.25 g, 2.74 mmol), and 30 mL of TFE was heated at reflux for two h. Chloroform was added, and the organic phase was washed twice with water. After drying ($MgSO_4$) and evaporation of the solvent, the residue was recrystallized from $CHCl_3$/MeOH yielding 36 mg (34%) of the hexaanilino derivative **7**. Mp 383 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.28 (s, 12H), 7.08 (t, J = 8.0 Hz, 12H), 6.64 (t, J = 7.5 Hz, 6H), 6.54 (d, J = 7.0 Hz, 12H), 6.47 (d, J = 6.0 Hz, 6H), 4.08 (d, J = 5.5 Hz, 6H), 3.14 (br s, 18H), 1.04 (s, 54H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.7, 146.7, 146.5, 135.0, 129.0, 124.7, 117.5, 113.3, 61.5, 49.3, 34.3, 31.2 ppm. HRMS (ESI) *m/z* 1603.9767 [(M)$^+$, calcd for $C_{108}H_{126}N_6O_6$, 1603.9738].

5,11,17,23,29,35-Hexa-*tert*-butyl-37,38,39,40,41,42-hexamethoxy-2,8,14,20,26,32-hexaacetoxy-calix[6]arene (8). Calixarene **3** (1.5 g, 0.98 mmol) and 200 mL of acetic acid were heated at reflux for 18 h. After cooling, the acetic acid was evaporated, and the residue was recrystallized from $CHCl_3$/MeOH to yield 0.38 g of the hexaacetoxy derivative **8** (28%). Mp 392 °C (dec). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.52 (s, 6H), 7.26 (s, 12H), 3.66 (s, 18H), 2.08 (s, 18H), 1.12 (s, 54H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.5, 153.5, 146.6, 132.8, 125.3, 66.3, 61.7, 34.4, 31.3, 20.9 ppm. HRMS (ESI) *m/z* 1427.7424 [(M + Na)$^+$, calcd for $C_{84}H_{108}NaO_{18}$, 1427.7433].

5,11,17,23,29,35-Hexa-*tert*-butyl-37,38,39,40,41,42-hexamethoxy-2,8,14,20,26,32-hexahydroxy-calix[6]arene (9). To an ice-cold solution of **8** (0.36 g, 0.27 mmol) in 50 mL of dry THF was added $LiAlH_4$ (0.11 g, 2.89 mmol) under an inert atmosphere, and the mixture was stirred for 30 min. Ethyl acetate was added to quench the excess of $LiAlH_4$, and the solution was washed with water, and then with 1 M aq HCl. After drying ($MgSO_4$) the organic phase was filtered and evaporated. Recrystallization from $CHCl_3$/MeOH yielded 0.15 g of **9** (51%). Mp 348 °C (dec). ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.24 (s, 12H), 6.32 (d, J = 6.0 Hz, 6H), 5.51 (d, J = 6.0 Hz, 6H), 3.01 (br s, 18H), 1.05 (s, 54H) ppm. ^{13}C NMR (CD_3OD, 125 MHz) δ 152.4, 145.4, 135.6, 124.2, 63.0, 60.8, 33.6, 30.1 ppm. HRMS (ESI) *m/z* 1175.6794 [(M + Na)$^+$, calcd for $C_{72}H_{96}NaO_{12}$, 1175.6799].

General Procedure for the Preparation of the Hexaaryl Derivatives 10−14. A mixture of **3** (0.10 g, 0.07 mmol), 2 mL of HFIP, 8 mL chloroform, and 1 mL of the appropriate reagent was heated at reflux for 2 h. After evaporation of the solvent, the residue was recrystallized from $CHCl_3$/MeOH.

5,11,17,23,29,35-Hexa-*tert*-butyl-37,38,39,40,41,42-hexamethoxy-2,8,14,20,26,32-hexakis(2,4-dimethylphenyl)calix[6]arene (10). Yield 74 mg (67%). Mp 385 °C (dec). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.97 (s, 6H), 6.81 (m, 12H), 6.78 (s, 6H), 6.73 (d, J = 8.2 Hz, 6H), 6.37 (s, 6H), 2.84 (s, 9H), 2.45 (s, 9H), 2.20 (s, 18H), 2.06 (s, 18H), 1.04 (s, 27H), 0.92 (s, 27H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz, 233 K) δ 153.3, 153.1, 145.1, 144.9, 140.8, 136.2, 136.1, 135.0, 134.6, 131.0, 128.1, 126.0, 125.9, 125.6, 60.7, 59.7, 39.5, 34.3, 34.2, 31.4, 31.3, 21.1, 19.7 ppm. MALDI MS, *m/z* 1705.0 (M + Na)$^+$.

5,11,17,23,29,35-Hexa-*tert*-butyl-37,38,39,40,41,42-hexamethoxy-2,8,14,20,26,32-hexakis(2,5-dimethylphenyl)calix[6]arene (11). Yield 86 mg (78%). Mp 383 °C (dec). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.96 (s, 6H), 6.89 (d, J = 7.5 Hz, 6H), 6.80 (d, J = 8.5 Hz, 6H), 6.76 (s, 6H), 6.59 (s, 6H), 6.38 (s, 6H), 2.88 (s, 9H), 2.50 (s, 9H), 2.15 (s, 18H), 2.02 (s, 18H), 1.05 (s, 27H), 0.95 (s, 27H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz,) δ 153.6, 153.2, 145.4, 145.1, 143.8, 136.4, 135.2, 134.1, 133.6, 130.0, 129.2, 126.3, 126.0, 125.9, 60.5, 60.0, 40.4, 34.2, 31.3, 21.2, 18.8 ppm. HRMS (ESI) *m/z* 1682.0991 (M+, calcd for $C_{120}H_{144}NaO_6$, 1682.0962).

5,11,17,23,29,35-Hexa-*tert*-butyl-37,38,39,40,41,42-hexamethoxy-2,8,14,20,26,32-hexakis(2,3,4,5-tetramethylphenyl)calix[6]arene (12). A reaction was carried out as described in the general procedure. After evaporation of the solvent, the residue was recrystallized from C_6H_6/MeOH yielding 69 mg (57%) of **12**. Mp 376 °C (dec). ^{1}H NMR (C_6D_6, 400 MHz) δ 7.46 (s, 6H), 7.34 (s, 6H), 7.03 (s, 6H), 6.82 (s, 6H), 3.17 (s, 9H), 2.92 (s, 9H), 2.39 (s, 18H), 2.21 (s, 18H), 2.01 (s, 18H), 1.98 (s, 18H), 1.26 (s, 27H), 1.11 (s, 27H) ppm. ^{13}C NMR (C_6D_6, 125 MHz) δ 154.0, 153.8, 145.4, 145.1, 141.5, 137.6, 136.7, 135.2, 132.7, 132.3, 132.2, 128.5, 126.4, 60.5, 60.1, 41.2, 34.5, 34.2, 31.6, 31.3, 21.0, 16.2, 15.8, 15.6 ppm. MALDI MS, *m/z* 1875.5 (M + Na)$^+$.

5,11,17,23,29,35-Hexa-*tert*-butyl-37,38,39,40,41,42-hexamethoxy-2,8,14,20,26,32-hexakis-(2-methoxy-4-methylphenyl)calix[6]arene (13). Yield 68 mg (59%). Mp 390 °C (dec). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.86 (d, J_o = 8.4 Hz, J_m = 2.0 Hz, 6H), 6.82 (br s, 12H), 6.62 (d, J_o = 8.8 Hz, 6H), 6.55 (s, 6H), 6.51 (s, 6H), 3.48 (s, 18H), 2.13 (s, 18H), 0.99 (br s, 54H) ppm.^{13}C NMR ($CDCl_3$, 125 MHz, 238K) δ 155.0, 153.3, 152.9, 144.9, 144.2, 136.2, 134.0, 130.1, 128.5, 127.0, 125.7, 124.7, 111.0, 60.4, 60.0, 56.1, 34.2, 34.2, 31.5, 31.3, 21.1 ppm. HRMS (ESI) *m/z* 1801.0584 [(M + Na)$^+$, calcd for $C_{120}H_{144}NaO_{12}$, 1801.0555].

5,11,17,23,29,35-Hexa-*tert*-butyl-37,38,39,40,41,42-hexamethoxy-2,8,14,20,26,32-hexamesityl-calix[6]arene (14). Yield 75 mg (66%). Mp 405 °C (dec). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.12 (s, 6H), 7.07 (s, 6H), 6.69 (s, 6H), 6.59 (s, 6H), 6.47 (s, 6H), 2.58 (s, 9H), 2.21 (s, 18H), 2.18 (s, 9H), 2.13 (s, 18H), 2.08 (s, 18H), 1.15 (s, 27H), 0.91 (s, 27H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.7, 152.7, 145.9, 143.3, 138.6, 138.0, 137.3, 135.9, 135.4, 134.9, 131.0, 129.5, 127.9, 126.2, 60.4, 60.3, 40.7, 34.3, 34.0, 31.4, 27.3, 21.0, 20.6 ppm. HRMS (ESI) *m/z* 1789.1828 [(M + Na)$^+$, calcd for $C_{126}H_{156}NaO_6$, 1789.1799].

5,11,17,23,29,35-Hexa-*tert*-butyl-37,38,39,40,41,42-hexamethoxy-2,8,14,20,26,32-hexakis-(2,4-pentanedione-3-yl)calix[6]arene (15). A mixture of **3** (0.10 g, 0.07 mmol), 1 mL of 2,4-pentanedione, and 10 mL of TFE was heated at reflux for 2 h. After evaporation of the solvents, the residue was recrystallized from $CHCl_3$/MeOH yielding 55 mg (51%) of **15**. When HFIP was used instead of TFE as a solvent the yield of **15** was 67 mg (62%). Mp 260−262 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.19 (s, 12H), 5.51 (d, J = 12.0 Hz, 6H), 4.39 (d, J = 11.6 Hz, 6H), 4.10 (s, 18H), 2.02 (s, 36H), 1.14 (s, 54H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 202.8, 152.7, 146.3, 133.8, 124.7, 77.6, 60.6, 36.7, 34.4, 31.0, 29.8 ppm. HRMS (ESI) *m/z* 1668.9318 [(M + Na)$^+$, calcd for $C_{102}H_{132}NaO_{18}$, 1668.9311].

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of **4a−k** and **5−15** and molecular structures of **4a** and **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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