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Synthesis and Conformational Studies on Hexa-*O*-alkyl p-Unsubstituted Calix[6]arenes

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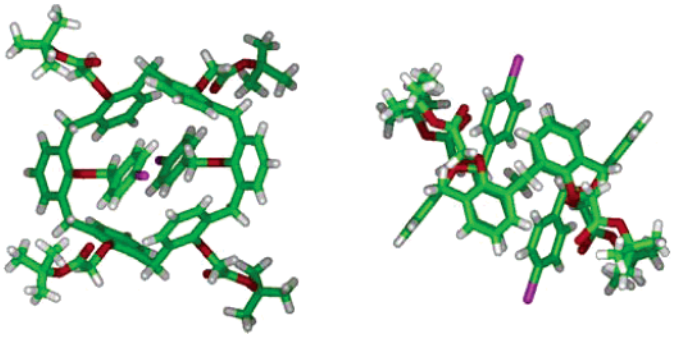

In this article we describe the selective *O*-benzylation of para-unsubstituted calix[6]arene **1** in rings 1 and 4 (**2a**−**c**) and the subsequent alkylation of phenol groups with α-haloesters (methyl esters **3a**, **3c**, and **3e**; *tert*-butyl esters **3b**, **3d**, and **3f**) to determine the effect of these groups on their conformational behavior. 2D NMR studies at 188 K reveal that compounds **2a**−**c**, **3b**, **3d**, and **3f** are less flexible, showing a 1,2,3-alternate conformation. The same conformation has been observed in the solid state.

Introduction

Calixarenes constitute useful platforms to anchor functional groups for molecular recognition, catalysis, and capsule formation through self-assembly.[1] However, to fully benefit from these capabilities the flexibility of these macrocycles should be restrained or "frozen" into the cavity-shaped *cone* conformation.[2] While this is easily achieved in cyclic tetramers by simply attaching alkyl groups larger than ethyl to the phenol OHs at the narrow rim,[3] conformational restriction by O-alkylation has proven more difficult for larger cyclic oligomers, although several conformationally restricted O-functionalized *p-tert*-butylcalix[6]arenes have been reported. For instance, mono-O-benzylation causes a slow inversion of the ring, due to the simultaneous presence of the substituent and the hydrogen-bonded network arising from the remaining five OH groups which prevents rotation of the ring from either side.[4] This is also observed for 1,4-di- and 1,2,4,5-tetra-*O*-benzyl derivatives.[5] Another strategy to restrict *cone*−*cone* inversion is based on bridging several phenol rings by suitable linkers.[6]

p-Unsubstituted calix[6]arenes are far more flexible than their *p-tert*-butyl homologues. This is clearly ob-

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(1) (a) Pochini, A.; Ungaro, R. In *Comprehensive Supramolecular Chemistry*; Atwood, J. L., Davis, J. E. D., MacNicol, D. D., Vögtle, F., Eds.; Pergamon Press: New York, 1996; Vol. 2. (b) de Namor, A. F. D.; Cleverly, R. M.; Zapata-Ormachea, M. L. *Chem. Rev*. **1998**, *98*, 2495−2525. (c) Hof, F.; Craig, S. L.; Nuckllos, C.; Rebek, J., Jr. *Angew. Chem., Int. Ed.* **2002**, *41*, 1488−1508. (d) Rudkevich, D. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 558−571.

(2) (a) Böhmer, V. *Angew. Chem., Int. Ed. Engl*. **1995**, *34*, 713−745. (b) Gutsche, C. D. *Calixarenes Revisited*; The Royal Society of Chemistry: Cambridge, U.K., 1998. (c) Sansone, F.; Segura, M.; Ungaro, R. In *Calixarenes 2001*; Asfari, Z., Böhmer, V., Harrowfield, J., Vicens, J., Eds.; Kluwer Academic Publishers: Dordrecht, The Netherlands, 2001; pp 496−512.

(3) Shinkai, S. *Tetrahedron* **1993**, *49*, 8933−8968.

(4) Magrans, J. O.; Rincón, A. M.; Cuevas, F.; López-Prados, J.; Nieto, P. M.; Pons, M.; Prados, P.; de Mendoza, J. *J. Org. Chem*. **1998**, *63*, 1079−1085.

(5) (a) Kanamathareddy, S.; Gutsche, C. D. *J. Org. Chem*. **1992**, *57*, 3160−3166. (b) Numbers 1−6 refer to the corresponding phenol positions.

(6) Chen, Y.; Gong, S. *J. Inclusion Phenom. Macrocyclic Chem.* **2003**, *45*, 165−184 and references therein.

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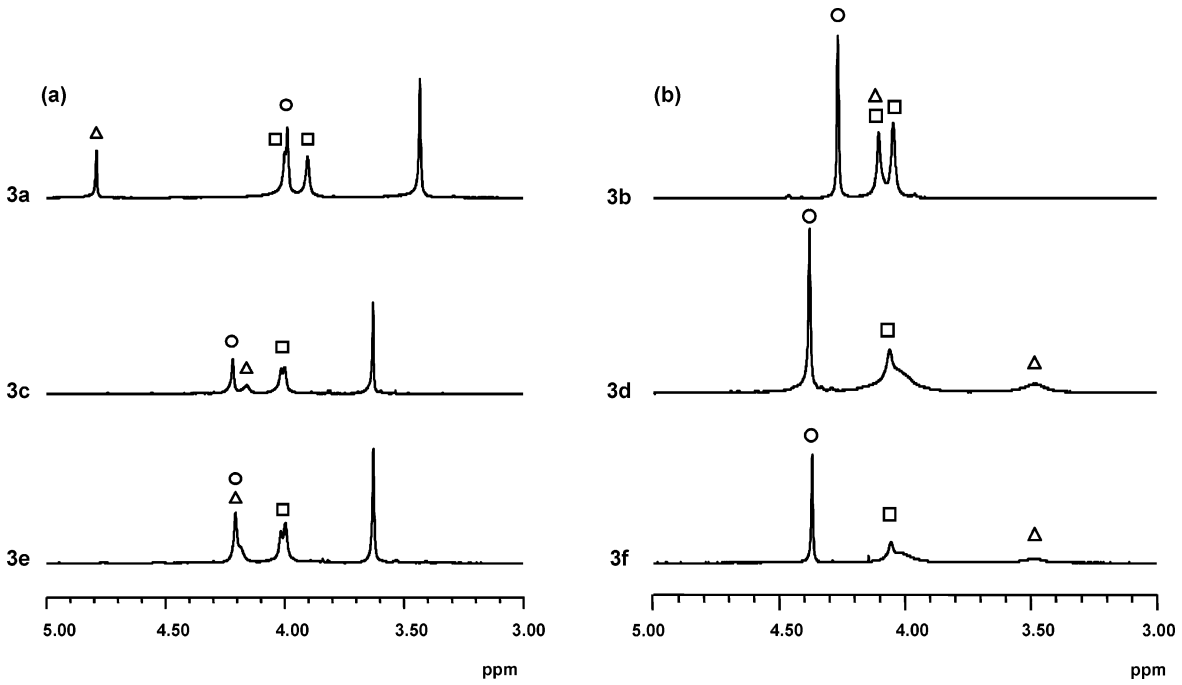


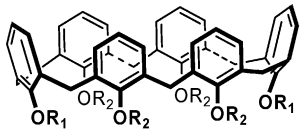
FIGURE 1. ^{1}H NMR spectra ($CDCl_3$, 298 K) of (a) compounds **3a**, **3c**, and **3e** (△ = O−CH_2−C_6H_4−R(*p*); □ = $ArCH_2Ar$; ○ = O−CH_2CO_2Me) and (b) compounds **3b**, **3d**, and **3f** (△ = O−CH_2−C_6H_4−R(*p*); □ = $ArCH_2Ar$; ○ = O−CH_2CO_2tBu).

served by ^{1}H NMR, where protons of methylene bridges linking the aryl rings ($ArCH_2Ar$) are observed as singlets.[7] The conformation can only be restrained by bridging.[8] To the best of our knowledge, only one example of an hexa-*O*-(diethoxyphosphoryloxy)calix[6]arene, which shows a partially rigid structure at −68 °C in d_6-acetone, has been reported so far.[9]

In this work, we describe the selective O-benzylation of p-unsubstituted calix[6]arene **1** at rings 1 and 4 (compounds **2a**−**c**) and the subsequent alkylation of the remaining phenols with α-haloesters of different steric hindrance (methyl esters **3a**, **3c**, and **3e**; *tert*-butyl esters **3b**, **3d**, and **3f**) to determine the effect of these groups on the restriction of the conformational equilibrium. Both 1D and 2D NMR spectroscopic methods were employed to determine the preferred conformations. X-ray diffraction structures for compounds **3a**, **3b**, and **3d** provided additional support to our studies in solution.

Results and Discussion

Synthesis. Di-O-alkylation of calix[6]arene **1** was performed under the conditions described for *p-tert*-butylcalix[6]arene,[5a] that is, $KOSiMe_3$ and the corresponding p-substituted benzyl derivative (6 mol equiv) in THF/DMF (9:1), to afford derivatives **2a**−**c** in 78−89% yields. Alkylation of the remaining phenol positions was achieved with potassium carbonate and the corresponding α-haloester,[7] giving rise to compounds **3a**−**f** in 73−80% yields.



1 R_1 = H; R_2 = H

2a R_1 = CH_2-C_6H_4-Me(*p*); R_2 = H

2b R_1 = CH_2-C_6H_4-Br(*p*); R_2 = H

2c R_1 = CH_2-C_6H_4-I(*p*); R_2 = H

3a R_1 = CH_2-C_6H_4-Me(*p*); R_2 = CH_2CO_2Me

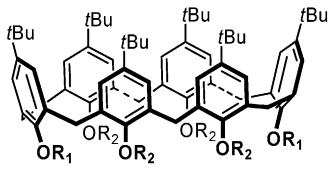
3b R_1 = CH_2-C_6H_4-Me(*p*); R_2 = CH_2CO_2tBu

3c R_1 = CH_2-C_6H_4-Br(*p*); R_2 = CH_2CO_2Me

3d R_1 = CH_2-C_6H_4-Br(*p*); R_2 = CH_2CO_2tBu

3e R_1 = CH_2-C_6H_4-I(*p*); R_2 = CH_2CO_2Me

3f R_1 = CH_2-C_6H_4-I(*p*); R_2 = CH_2CO_2tBu



4 R_1 = CH_2-C_6H_4-Me(*p*); R_2 = H

5a R_1 = CH_2-C_6H_4-Me(*p*); R_2 = CH_2CO_2Me

5b R_1 = CH_2-C_6H_4-Me(*p*); R_2 = CH_2CO_2tBu

Conformational Study. ^{1}H NMR spectra of compounds **2a**−**3f** in $CDCl_3$ at room temperature reveal a flexible structure for all of them. Methylene ($ArCH_2Ar$) calixarene protons are displayed as two singlets, accounting for a rapid interconversion of the macrocycle. Indeed,

(7) Nam, K. C.; Kang, S. O.; Lee, K. H.; Jeon, S.; Cho, H. J.; Chang, S.-K. *Bull. Korean Chem. Soc.* **1998**, *19*, 279−281.

(8) (a) Nam, K. C.; Choi, Y. J.; Kim, D. S.; Kim, J. M.; Chun, J. C. *J. Org. Chem.* **1997**, *62*, 6441−6443. (b) Ko, S. W.; Lee, S. H.; Park, K.-M.; Lee, S. S.; Nam, K. C. *Supramol. Chem.* **2003**, *15*, 117−125.

(9) Markovsky, L. N.; Kalchenko, V. I.; Vysotsky, M. A.; Pirozhenko, V. V.; Simonov, Y. A.; Dvorkin, A. A.; Iatsenko, A. V.; Lipkowski, J. *Supramol. Chem.* **1997**, *8*, 85−91.

TABLE 1. Comparative Study of the Methylene ($ArCH_2Ar$) ^{13}C NMR Data of Compounds 2a−3f and 5a

	chemical shifts (ppm)	
compound	$CDCl_3$ (293 K)	CD_2Cl_2 (188 K)
2a	31.5, 31.7	29.6, 30.8
2b	31.6, 31.8	29.5, 32.3
2c	31.6, 31.8	
3a	29.7, 31.0	30.0, 33.0
3b	30.8, 31.2	28.3, 30.2
3c	29.7, 30.6	28.1, 30.8
3d	29.7, 30.2	27.1, 30.8
3e	29.7, 30.6	
3f	29.7, 30.2	29.1, 31.6
5a[a]		30.0, 33.0

[a] Data for this compound were obtained at 248 K.

some differences in the chemical shifts are observed, depending on the substitution. For methyl esters **3a**, **3c**, and **3e**, methylene protons of benzyl substituents [O−CH_2−C_6H_4−R(*p*)] are increasingly shielded as the size of the para-substituent also increases. For example, it shifts from 4.79 ppm (*p*-tolylmethyl **3a**) to 4.15 and 4.20 ppm (*p*-bromo **3c** or *p*-iodobenzyl **3e**, respectively) (Figure 1a). Shielding is more pronounced in bulkier esters, such as **3b**, **3d**, and **3f**: 4.10 ppm for *p*-tolylmethyl derivative **3b** but 3.48 ppm for bromo and iodo derivatives **3d** and **3f**. Thus, *tert*-butyl esters induce a 0.7 ppm upfield shift with respect to the methyl ester analogues (Figure 1b).

The above results seem to indicate that bulk *O*-benzyl p-substituents and bulky esters cause a substantial degree of congestion at the calixarene narrow rim, forcing the benzyl methylene groups to get inside the cavity, which explains the unusual NMR shielding. On the other hand, ^{13}C NMR spectra and HMQC experiments for **2a**−**3f** showed two signals around 30 ppm for the methylene carbons ($ArCH_2Ar$), which accounts for an equilibrium between two *cone* conformations (Table 1).[10]

Above room temperature ($C_2D_2Cl_4$, 393 K), all ^1H NMR signals are sharp for **3a** and **3d**. Methylene ($ArCH_2Ar$) protons appear as two singlets, and benzyl (OCH_2Ar) protons of **3a** do not show any significant shift with respect to the spectrum at room temperature. On the contrary, the OCH_2Ar protons of compound **3d** are deshielded by 0.5 ppm (δ = 4.03 ppm) with respect to room tempera-

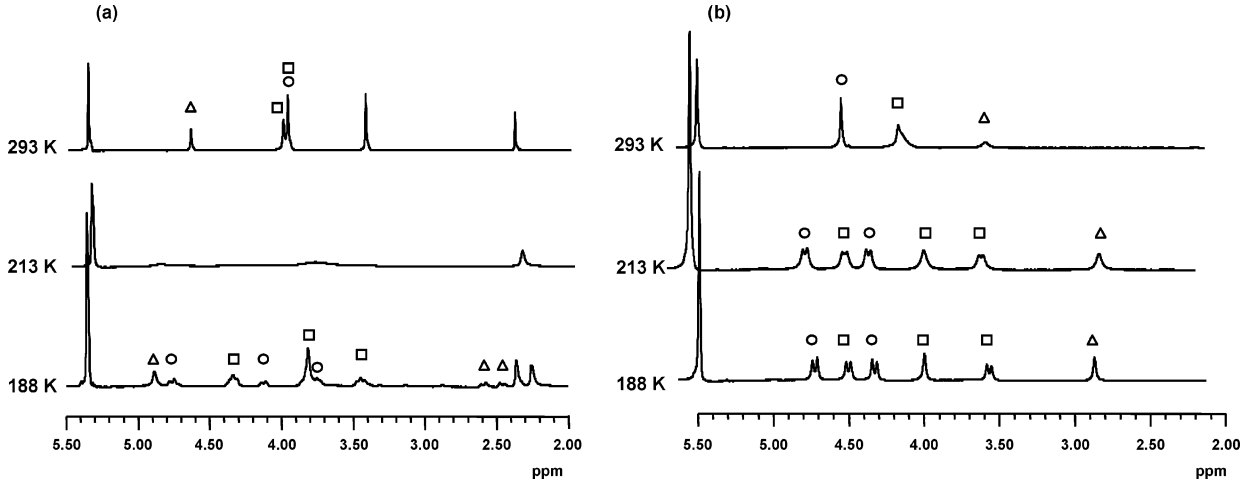


FIGURE 2. ^1H NMR spectra (CD_2Cl_2) of (a) compound **3a** (△ = O−CH_2−C_6H_4−R(*p*); □ = $ArCH_2Ar$; ○ = O−CH_2CO_2Me) and (b) compound **3d** (△ = O−CH_2−C_6H_4−R(*p*); □ = $ArCH_2Ar$; ○ = O−CH_2CO_2tBu).

TABLE 2. ^1H NMR Data[a] (CD_2Cl_2, 188 K) of Compounds 2a,b, 3a−d, 3f, and 5a

	chemical shifts (ppm)					
compound	ArH[b]	$ArCH_2Ar$	CH_2CO_2R	OCH_2Ar	CO_2Me	CO_2tBu
2a	para (2)	3.82−3.49 (AB)		4.99		
	meta (3)	3.46 (s)				
2b	para (2)	3.61−3.84 (AB)		4.85		
	meta (3)	3.53 (s)				
3a	para (3)	4.32−3.43 (o)[c]	4.76−4.32	4.89	3.82	
	meta (5)	4.12−3.43	2.68−2.45		2.26	
		3.81−3.75 (*)[c]				
3b	para (2)	4.33−3.43 (AB)	4.62−4.15	2.86		1.51
	meta (3)	3.85 (s)				
3c	para (2)	4.32−3.39 (AB)	4.69−4.36	2.67	2.25	
	meta (3)	3.77 (s)				
3d	para (2)	4.32−3.42 (AB)	4.58−4.15	2.64		1.48
	meta (3)	3.79 (s)				
3f	para (2)	4.33−3.43 (AB)	4.60−4.18	2.77		1.51
	meta (3)	3.84 (s)				
5a	meta (6)	4.57−3.52 (o)	4.50−4.36	4.89	3.83	
		4.57−3.38	3.92−3.45		2.19	
		3.95−3.87 (*)				

[a] Protons were assigned by COSY and HMQC experiments. [b] Number of signals in parentheses. [c] Exchangeable protons in the ROESY experiment (see text).

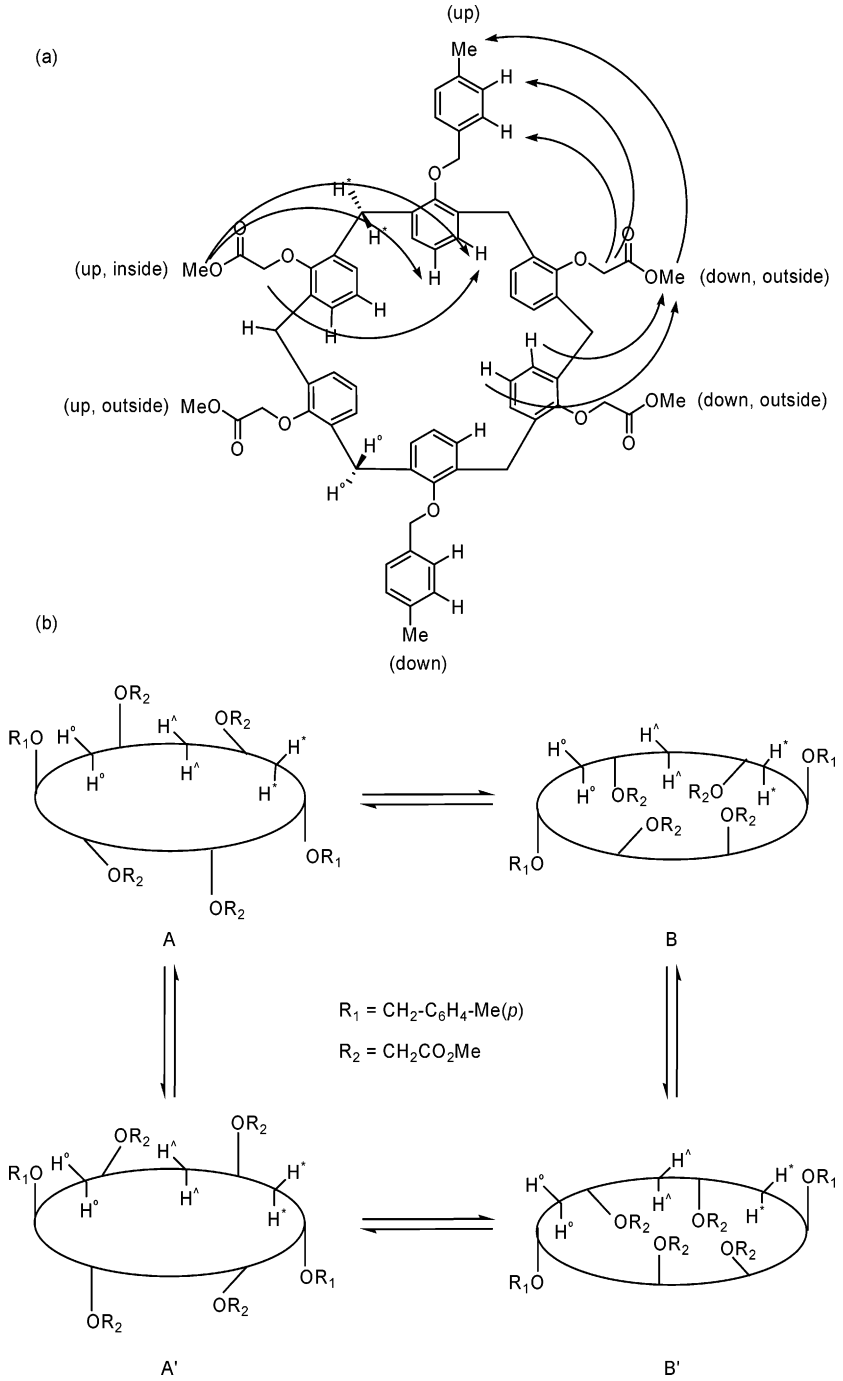


FIGURE 3. (a) Most significant ROE contacts in compound **3a**. (b) Schematic representation of the equilibrium between several 1,2,3-alternate conformations (A/A′ and B/B′) of compound **3a**.

ture. This indicates that, despite a rapid *cone*−*cone* inversion in both cases, the *tert*-butyl ester derivative has a different behavior than the methyl ester analogue **3a**.

At low temperatures (CD_2Cl_2), the distinct behavior of *tert*-butyl and methyl esters was again observed. Whereas derivatives **3a**, **3c**, and **3e** coalesced at 233 K, compounds **2a**−**c**, **3b**, **3d**, and **3f** did it at a slightly higher temperature, namely around 243 K. Below these coalescence temperatures, compounds **3a**, **3c**, and **3e** showed well-defined spectra only at 188 K, whereas signals for **2a**−**c**, **3b**, **3d**, and **3f** were sharp at 213 K or below this temperature (Figure 2).

Moreover, at 188 K, ^{1}H NMR spectra of compound **3a** are different from those of the other derivatives. Three AB systems are observed for the calixarene methylene bridges ($ArCH_2Ar$) in 1:1:1 ratio, as well as eight signals for the aromatic protons. Remarkably, signals corresponding to one of the CH_2CO_2Me chains are strongly shielded, a sign of inclusion of this leg into the cavity. On the contrary, *O*-CH_2Ar signals do not move. In the *tert*-butyl ester series (**3b**, **3d**, and **3f**), the calixarene $ArCH_2Ar$ signals appear as an AB system and a singlet (2:1 ratio) and only five signals for the aromatic protons are observed. On the other hand, the OCH_2CO_2R signals

are at their expected position and the benzyl methylenes (OCH_2Ar) are abnormally shielded, indicating their inclusion (Table 2). In the ^1H NMR spectra of methyl esters **3c** and **3e**, two conformations are observed, the majority one showing a signal pattern similar to that found for compounds **3b**, **3d**, and **3f**, while the minority one presents a signal pattern similar to that of **3a**. Finally, for compounds **2a**−**c**, benzyl protons do not shift significantly at room or at low temperature. These results indicate that compound **3a** is in a conformation displaying only one element of symmetry, whereas two symmetry elements are present in **2a**−**c** and **3b**−**f** (Table 2).

To have a better insight into the conformation of these p-unsubstituted calix[6]arenes, 2D NMR experiments (HMQC and ROESY) were performed at 188 K on compounds **2a**, **3a**, and **3f**. In the HMQC spectrum of **3a** three signals are visible for the calixarene methylene bridges, which correspond to the two AB systems in the ^1H NMR spectrum (see Table 1); two at ca. 30 ppm and the other at ca. 33 ppm. In compound **3f**, these carbon signals are present at ca. 30 ppm (which correlates with the AB system) and ca. 32 ppm (which correlates with the singlet). Compared to the spectra at room temperature, one carbon is not affected whereas the other is shifted downfield. Although the observed values (ca. 32 or 33 ppm) are away from the 37 ppm standard shift to confirm an anti arrangement of the bridged aromatic rings,[10] it has been reported (for calix[4]arenes) that large deviations from the usual 31 and 37 ppm values for "pure" syn or anti arrangements, respectively, may be interpreted either as a distorted conformation or as a fast equilibrium between syn and anti forms.[11]

A ROESY experiment on compound **3a** (188 K, CD_2Cl_2) revealed exchange peaks between similar protons, involving axial and equatorial protons of each AB system, but also between the protons of the system at 3.75−3.81 ppm and the protons of the one at 3.43−4.32 ppm. Considering the symmetry of the compound (inversion center) and the observed ROESY peaks (Figure 3a), we can conclude that an equilibrium between several 1,2,3-alternate conformations of lower symmetry operates as a result of the inclusion from the two opposite rings carrying ester groups that are more shielded and close to the AB system at 3.75−3.81 ppm (H* in Figure 3b). This accounts for the exchanges observed between H* and H° in the ROESY spectrum (Table 2) and the fact that the ^{13}C NMR chemical shift for one of the methylene carbons lies midway between syn and anti conformations (Table 1).

Compound **3f**, given its symmetry, could be either in a 1,2,3- or in a 1,4-alternate conformation. ROE contacts between H_3 and H_4 protons with the *tert*-butyl group of the ester and with the CH_2 of the benzyl group rule out the latter structure and indeed point to the symmetric 1,2,3-alternate conformation (Figure 4a).

Exchange between axial and equatorial positions of the AB system, as well as between OCH_2CO_2R protons, indicates exchange between the two identical 1,2,3-alternate conformations, even at 188 K (Figure 4b). The inversion occurs at the methylene carbon showing a singlet in the ^1H NMR (H*), as the result of the inclusion of the aromatic ring carrying a benzyl inside the cavity. This fact would justify the ^{13}C NMR midway position of the signal between anti and syn orientations.

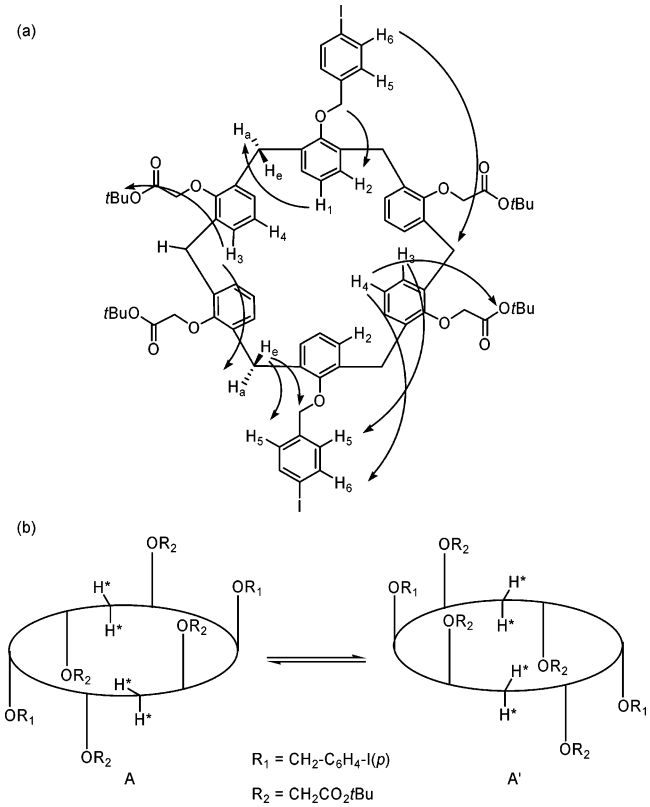


FIGURE 4. (a) Most significant ROE contacts in compound **3f**. (b) Schematic representation of the equilibrium between two identical 1,2,3-alternate conformations (A and A′) of compound **3f**.

To verify if this behavior was a consequence of the lack of a substituent in the para positions, we tried to prepare the *tert*-butyl analogues of compounds **3a** and **3f**, namely **5a** and **5b**. O-Alkylation of **4**[5a] with methyl α-bromoacetate, under the conditions described above, afforded **4a** in 90% yield. However, we were unable to prepare **5b** under the same and various other conditions, probably due to the steric hindrance of the alkylating agent.

Coalescence was observed at room temperature in the ^1H NMR spectrum of **5a** in CD_2Cl_2 for all signals but the OBn residue, although a pattern similar to compound **3a** resulted at 248 K (Tables 1 and 2). The ROESY spectrum at 248 K is also similar to **3a** (i.e., exchange between axial and equatorial protons AB calixarene systems; Figure 3). Therefore, we could conclude that the differences in the conformation of **3a** or **3f** are not due to the higher flexibility of the former, lacking bulky *tert*-butyl groups in para positions, but to the steric congestion created at the lower rim of the calixarene, depending on the size of the ester. The different behavior observed for **3a** with respect to the rest of the methyl esters (**3c** and **3e**), in which the benzyl group is located inside the cavity, could be attributed to electronic effects caused by the para substituent of the benzyl residue (Br or I).

(10) (a) For the ^{13}C NMR rule in calix[4]arenes, see: Jaime, C.; de Mendoza, J.; Prados, P.; Nieto, P. M.; Sánchez, C. *J. Org. Chem.* **1991**, *56*, 3372−3376. (b) Kanamathareddy, S.; Gutsche, C. D. *J. Org. Chem.* **1994**, *59*, 3871−3879.

(11) Magrans, J. O.; de Mendoza, J.; Pons, M.; Prados, P. *J. Org. Chem.* **1997**, *62*, 4518−4520.

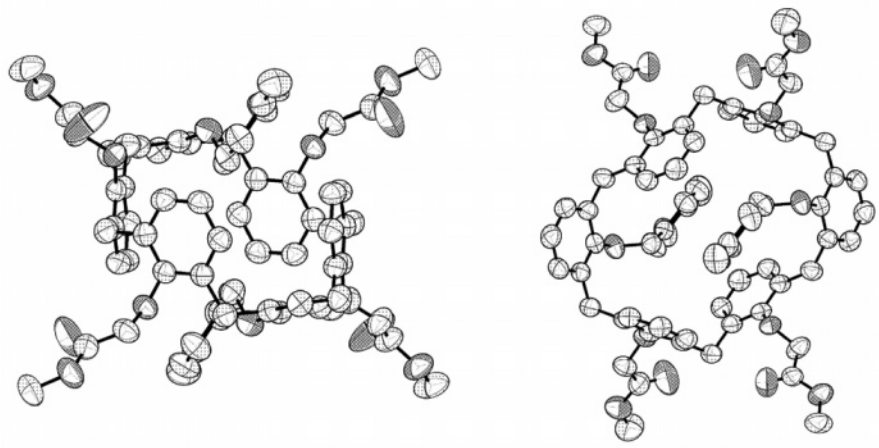


FIGURE 5. X-ray structure of compound **3a**. Hydrogen atoms have been omitted for clarity. Displacement ellipsoids are drawn at the 50% probability level.

X-ray crystal structures of *p-tert*-butylcalix[6]arenes have been reported under three different conformations: "pinched cone",[12a–d] "1,2,3-alternate",[12e] and "1,2,4,5-alternate".[13] Unfortunately, most of the scarce structures published for unsubstituted calix[6]arenes refer to metal complexes of their anions, displaying flattened cone[14] or 1,2,3-alternate conformations,[14a] bis-crowned derivatives in cone,[15] 1,2,3-[16] or 1,4-alternate conformations,[17] or a mono-O-substituted calix[6]arene in cone conformation.[18]

Single crystals of **3a**, **3b**, and **3d** were obtained from chloroform/methanol. Crystals of **3d** were of poorer quality than those of **3a** or **3b** due to difficulties in crystallization, which resulted in twinned crystals of low diffraction intensity. However, the goodness-of-fit on F^2 was 1.049, indicating a correct resolution, although the R values were slightly high probably due to the thermal vibration of the lateral chain involving the ester group.

In the solid state, compounds **3a**, **3b**, and **3d** display 1,2,3-alternate conformations in all cases, in agreement with our studies in solution at low temperature (Figure 5, see Supporting Information). The structures of the three compounds are very similar, with torsion angles for the rings accounting for a u,u,u,d,d,d conformation.[19] The only significant difference was the dihedral angle between the calixarene aromatic ring endowed with *O*-benzyl and the substituents themselves [151.3(2) for **3a**; −172.78(14) for **3b**; and −179.9(4) for **3d**].

Conclusions

The ^{1}H NMR studies performed at room temperature have shown a high conformational flexibility for all the calix[6]arenes synthesized. Nevertheless, at low temperatures, the 1,4-di-*O*-benzyl calix[6]arenes endowed with groups in para positions (methyl, bromo, or iodo) of the pending sidearms, and O-alkylated with α-haloesters in the remaining phenols (**3a**−**f**), possess less conformational mobility, showing a 1,2,3-alternate conformation both in the solid state and in solution. To the best of our knowledge, these constitute the first examples of this kind of calix[6]arenes where the conformational equilibrium has been partly restricted.

Experimental Section

General Procedure A. 1,4-Di-*O*-alkylation. To a solution of **1** (200 mg, 0.31 mmol) in anhydrous THF (90 mL) and DMF (10 mL) was added $KOMe_3Si$ (239 mg, 1.86 mmol), and the reaction was cooled to 0 °C for 15 min. A solution of the corresponding halide (1.86 mmol) in THF (10 mL) was added, and the mixture was stirred at room temperature for 4 h. The solvent was removed under reduced pressure, and the residue was triturated with 1 N HCl, affording a solid that was filtered. The crude product was purified by crystallization with $CHCl_3$/MeOH (3:1).

37,40-Bis[(4-methylbenzyl)oxy]-38,39,41,42-tetrahydroxycalix[6]arene (2a). This compound was prepared (227 mg, 87%) by general procedure A, from **1** and 4-methylbenzyl bromide (348 mg). mp 136−138 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.34 (s, 6H, CH_3), 3.80 (s, 4H, $ArCH_2Ar$), 3.95 (s, 8H, $ArCH_2Ar$), 5.02 (s, 4H, OCH_2Ar), 6.76 (t, J = 7.5 Hz, 4H, ArH), 6.99−7.06 (m, 18H, ArH), 7.26 (d, J = 7.9 Hz, 4H, ArH), 8.05 (s, 4H, OH); ^{13}C NMR (125 MHz, $CDCl_3$, DEPT) δ 21.3 (CH_3), 31.5, 31.7 ($ArCH_2Ar$), 77.6 (OCH_2Ar), 120.2, 125.7, 128.4, 128.7, 129.0, 129.2, 129.4 (ArCH), 127.0, 127.4, 132.4, 133.4, 138.4, 151.8, 152.6 (ArC); MALDI-TOF MS *m/z* 845.3 $[M + H]^+$, 867.3 $[M + Na]^+$, 889.3 $[M + K]^+$. Anal. Calcd for $C_{58}H_{52}O_6 \cdot 2CHCl_3$: C, 66.49; H, 5.02. Found: C, 66.09; H, 5.12.

(12) (a) Andreetti, G. D.; Calestani, G.; Ugozzoli, F.; Arduini, A.; Ghidini, E.; Pochini, A.; Ungaro, R. *J. Inclusion Phenom.* **1987**, *5*, 123−126. (b) Halit, M.; Oehler, D.; Perrin, M.; Thozet, A.; Perrin, R.; Vicens, J.; Bourakhouadar, M. *J. Inclusion Phenom.* **1988**, *6*, 613−623. (c) Andreetti, G. D.; Ugozzoli, F.; Casnati, A.; Ghidini, E.; Pochini, A.; Ungaro, R. *Gazz. Chem. Ital.* **1989**, *119*, 47−50. (d) Janssen, R. G.; Verboom, W.; Harkema, S.; van Hummel, G. J.; Reinhoudt, D. N.; Pochini, A.; Ungaro, R.; Prados, P.; de Mendoza, J. *J. Chem. Soc., Chem. Commun.* **1993**, 506−508. (e) Moran, J. K.; Georgiev, E. M.; Yordanov, A. T.; Mague, J. T.; Roundhill, D. M. *J. Org. Chem.* **1994**, *59*, 5990−5998.

(13) Neri, P.; Foti, M.; Ferguson, G.; Gallagher, J. F.; Kaitner, B.; Pons, M.; Molins, M. A.; Giunta, L.; Pappalardo, S. *J. Am. Chem. Soc.* **1992**, *114*, 7814−7821.

(14) (a) Murayama, K.; Aoki, K. *Inorg. Chim. Acta* **1998**, *281*, 36−42. (b) Hanna, T. A.; Liu, L. H.; Angeles-Boza, A. M.; Kou, X. D.; Gutsche, C. D.; Ejsmont, K.; Watson, W. H.; Zakharov, L. N.; Incarvito, C. D.; Reingold, A. L. *J. Am. Chem. Soc.* **2003**, *125*, 6228−6238.

(15) Blanda, M. T.; Farmer, D. B.; Brodbelt, J. S.; Goolsby, B. J. *J. Am. Chem. Soc.* **2000**, *122*, 1486−1491.

(16) Ko, S. W.; Yang, Y. S.; Mun, J. H.; Park, K.-M.; Lee, S. S.; Nam, K. C. *Bull. Korean Chem. Soc.* **2002**, *23*, 1379−1380.

(17) Ko, S. W.; Ryu, B. J.; Park, K.-M.; No, K. H.; Kim, J. S.; Nam, K. C. *Bull. Korean Chem. Soc.* **2004**, *25*, 957−958.

(18) Da Silva, E.; Memmi, L.; Coleman, A. W.; Rather, B.; Zaworotko, M. J. *J. Supramol. Chem.* **2001**, *1*, 135−138.

(19) Ugozzoli, F.; Andreetti, G. D. *J. Inclusion Phenom. Mol. Recognit. Chem.* **1992**, *13*, 337−348.

37,40-Bis[(4-bromobenzyl)oxy]-38,39,41,42-tetrahydroxycalix[6]arene (2b). This compound was prepared (269 mg, 89%) by general procedure A, from **1** and 4-bromobenzyl bromide (470 mg). mp 170−175 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.77 (s, 4H, $ArCH_2Ar$), 3.96 (s, 8H, $ArCH_2Ar$), 4.97 (s, 4H, OCH_2Ar), 6.76 (t, J = 7.5 Hz, 4H, ArH), 7.07 (d, J = 7.5 Hz, 4H, ArH), 7.08−7.11 (m, 10H, ArH), 7.23 (s, 4H, ArH), 7.31 (s, 4H, ArH), 8.14 (s, 4H, OH); ^{13}C NMR (125 MHz, $CDCl_3$, DEPT) δ 31.6, 31.8 ($ArCH_2Ar$), 76.5 (OCH_2Ar), 120.4, 126.0, 128.8, 129.2, 129.3, 129.4, 131.7 (ArCH), 122.5, 127.0, 127.4, 133.3, 134.3, 151.5, 152.5 (ArC); MALDI-TOF MS *m/z* 973.2 $[M + H]^+$, 995.2 $[M + Na]^+$, 1011.2 $[M + K]^+$. Anal. Calcd for $C_{56}H_{46}Br_2O_6$·3MeOH: C, 66.17; H, 5.46. Found: C, 66.05; H, 4.88.

37,40-Bis[(4-iodobenzyl)oxy]-38,39,41,42-tetrahydroxycalix[6]arene (2c). This compound was prepared (258 mg, 78%) by general procedure A, from **1** and 4-iodobenzyl bromide (552 mg). mp 190−193 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.78 (s, 4H, $ArCH_2Ar$), 3.97 (s, 8H, $ArCH_2Ar$), 4.97 (s, 4H, OCH_2Ar), 6.76 (t, J = 7.5 Hz, 4H, ArH), 7.09−7.11 (m, 18H, ArH), 7.44 (d, J = 8.1 Hz, 4H, ArH), 8.17 (s, 4H, OH); ^{13}C NMR (125 MHz, $CDCl_3$, DEPT) δ 31.6, 31.8 ($ArCH_2Ar$), 76.6 (OCH_2-Ar), 120.4, 126.1, 128.8, 129.3, 129.4, 129.5, 137.7 (ArCH), 94.3, 127.1, 127.5, 133.3, 135.0, 151.6, 152.4 (ArC); MALDI-TOF MS *m/z* 1069.1 $[M + H]^+$, 1091.1 $[M + Na]^+$. Anal. Calcd for $C_{56}H_{46}I_2O_6$·2MeOH: C, 61.49; H, 4.80. Found: C, 61.74; H, 4.29.

General Proceduce B. O-Alkylation with Alkyl Bromoacetate. A suspension of the corresponding calix[6]arene (0.11 mmol) and K_2CO_3 (0.66 mmol) in acetone (10 mL) was heated at 60 °C for 1 h. The alkyl bromoacetate (0.88 mmol) was added, and the mixture was refluxed for 6 days. The solvent was removed at reduced pressure, and the residue was partitioned between EtOAc and 1 N HCl. The organic layer was washed with H_2O, dried ($MgSO_4$), and evaporated to dryness. The residue was purified by precipitation with $CHCl_3$/MeOH (3:1).

37,40-Bis[(4-methylbenzyl)oxy]-38,39,41,42-tetrakis[(metoxycarbonylmethyl)oxy]calix[6]arene (3a). This compound was prepared (518 mg, 75%) by general procedure B, from **2a** (500 mg) and methyl bromoacetate (0.45 mL). mp 201−204 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.40 [s, 6H, Ar−CH_3(p)], 3.43 (s, 12H, OCH_3), 3.90 (s, 8H, OCH_2CO), 3.99 (s, 8H, $ArCH_2Ar$), 4.00 (s, 4H, $ArCH_2Ar$), 4.79 (s, 4H, OCH_2Ar), 6.77 (t, J = 7.2 Hz, 2H, ArH), 6.80 (t, J = 7.2 Hz, 4H, ArH), 6.92 (d, J = 7.2 Hz, 4H, ArH), 6.97 (d, J = 7.2 Hz, 4H, ArH), 7.01 (d, J = 7.2 Hz, 4H, ArH), 7.22 (d, J = 7.9 Hz, 4H, ArH), 7.33 (d, J = 7.9 Hz, 4H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$, DEPT) δ 21.3 [Ar-CH_3(p)], 29.7, 31.0 ($ArCH_2$-Ar), 51.7 (OCH_3), 69.5 (OCH_2CO), 74.8 (OCH_2Ar), 124.1, 124.3, 128.0, 128.9, 129.1, 129.3, 130.0 (ArCH), 133.6, 133.9, 134.2, 134.6, 137.5, 154.7, 154.9 (ArC), 169.4 (CO); MALDI-TOF MS *m/z* 1155.5 $[M + Na]^+$, 1171.4 $[M + K]^+$. Anal. Calcd for $C_{70}H_{68}O_{14}$: C, 74.19; H, 6.05. Found: C, 73.68; H, 6.35.

37,40-Bis[(4-methylbenzyl)oxy]-38,39,41,42-tetrakis-[(*tert*-butoxycarbonylmethyl)oxy]calix[6]arene (3b). This compound was prepared (550 mg, 73%) by general procedure B, from **2a** (500 mg) and *tert*-butyl bromoacetate (0.7 mL). mp 190−193 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.51 [s, 36H, $C(CH_3)_3$], 2.34 [s, 6H, Ar-CH_3(p)], 4.04 (s, 8H, $ArCH_2Ar$), 4.11 (s, 8H, $ArCH_2Ar$, OCH_2Ar), 4.26 (s, 8H, OCH_2CO), 6.52 (t, J = 7.5 Hz, 4H, ArH), 6.58 (d, J = 7.5 Hz, 4H, ArH), 6.75 (m, 4H, ArH), 6.83 (s, 2H, ArH), 6.95 (d, J = 7.5 Hz, 4H, ArH), 7.02 (d, J = 7.5 Hz, 4H, ArH), 7.08 (m, 4H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$, DEPT) δ 21.3 [Ar-CH_3(p)], 28.1 [C(CH_3)$_3$], 30.8, 31.2 ($ArCH_2Ar$), 70.7 (OCH_2CO), 74.2 (OCH_2Ar), 81.6 [C(CH_3)$_3$], 123.7, 124.4, 127.8, 128.2, 128.8, 129.5 (ArCH), 129.7, 133.7, 134.3, 134.8, 136.6, 154.7, 155.2 (ArC), 168.4 (CO); MALDI-TOF MS *m/z* 1323.7 $[M + Na]^+$, 1339.7 $[M + K]^+$. Anal. Calcd for $C_{82}H_{92}O_{14}$·1.5 $CHCl_3$·MeOH: C, 67.09; H, 6.50. Found: C, 66.58; H, 6.35.

37,40-Bis[(4-bromobenzyl)oxy]-38,39,41,42-tetrakis-[(methoxycarbonylmethyl)oxy]calix[6]arene (3c). This compound was prepared (555 mg, 80%) by general procedure B, from **2b** (500 mg) and methyl bromoacetate (0.4 mL). mp 203−205 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.62 (s, 12H, OCH_3), 3.99 (s, 12H, $ArCH_2Ar$), 4.15 (s, 4H, OCH_2Ar), 4.21 (s, 8H, OCH_2CO), 6.73 (t, J = 7.4 Hz, 4H, ArH), 6.81 (d, J = 7.4 Hz, 4H, ArH), 6.88 (t, J = 7.4 Hz, 2H, ArH), 7.01 (d, J = 7.2 Hz, 4H, ArH), 7.02 (d, J = 8.1 Hz, 4H, ArH), 7.10 (d, J = 7.4 Hz, 4H, ArH), 7.38 (d, J = 8.1 Hz, 4H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$, DEPT) δ 29.7, 30.6 ($ArCH_2Ar$), 51.9 (OCH_3), 69.7 (OCH_2CO), 73.5 (OCH_2Ar), 124.0, 124.6, 128.8, 129.5, 129.6, 129.8, 131.4 (ArCH), 121.4, 133.67, 133.76, 133.79, 136.5, 154.4, 154.7 (ArC), 169.5 (CO); MALDI-TOF MS *m/z* 1283.1 $[M + Na]^+$, 1299.1 $[M + K]^+$. Anal. Calcd for $C_{68}H_{62}Br_2O_{14}$·2MeOH: C, 63.35; H, 5.32. Found: C, 63.15; H, 5.51.

37,40-Bis[(4-bromobenzyl)oxy]-38,39,41,42-tetrakis[(*tert*-butoxycarbonylmethyl)oxy]calix[6]arene (3d). This compound was prepared (625 mg, 80%) by general procedure B, from **2b** (500 mg) and *tert*-butyl bromoacetate (0.65 mL). mp 210−213 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.55 [s, 36H, $C(CH_3)_3$], 3.48 (br s, 4H, OCH_2Ar), 4.06 (br s, 12H, $ArCH_2Ar$), 4.37 (s, 8H, OCH_2CO), 6.58 (br s, 8H, ArH), 6.71 (br m, 4H, ArH), 7.01 (br s, 6H, ArH), 7.21 (d, J = 8.0 Hz, 4H, ArH), 7.31 (br s, 4H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$, DEPT) δ 28.2 [C(CH_3)$_3$], 29.7, 30.2 ($ArCH_2Ar$), 70.9 (OCH_2CO), 73.0 (OCH_2-Ar), 81.9 [C(CH_3)$_3$], 123.7, 124.5, 127.6, 129.6, 129.8, 131.1 (ArCH), 121.0, 133.6, 133.7, 134.4, 136.5, 154.4, 154.7 (ArC), 168.2 (CO); MALDI-TOF MS *m/z* 1451.7 $[M + Na]^+$, 1467.7 $[M + K]^+$. Anal. Calcd for $C_{80}H_{86}Br_2O_{14}$·MeOH: C, 66.48; H, 6.20. Found: C, 65.86; H, 6.28.

37,40-Bis[(4-iodobenzyl)oxy]-38,39,41,42-tetrakis-[(methoxycarbonylmethyl)oxy]calix[6]arene (3e). This compound was prepared (94 mg, 78%) by general procedure B, from **2c** (100 mg) and methyl bromoacetate (0.07 mL). mp 208−211 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.62 (s, 12H, OCH_3), 3.99 (s, 12H, $ArCH_2Ar$), 4.20 (s, 12H, OCH_2Ar, OCH_2CO), 6.74 (t, J = 7.5 Hz, 4H, ArH), 6.81 (d, J = 7.3 Hz, 4H, ArH), 6.88 (m, 6H, ArH), 6.98 (d, J = 6.9 Hz, 4H, ArH), 7.09 (d, J = 6.9 Hz, 4H, ArH), 7.58 (d, J = 8.0 Hz, 4H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$, DEPT) δ 29.7, 30.6 ($ArCH_2Ar$), 51.9 (OCH_3), 69.7 (OCH_2CO), 73.6 (OCH_2Ar), 124.0, 124.6, 128.9, 129.6, 129.7, 137.3 (ArCH), 93.2, 133.7, 133.76, 133.78, 137.4, 154.7 (ArC), 169.5 (CO); MALDI-TOF MS *m/z* 1379.3 $[M + Na]^+$, 1395.3 $[M + K]^+$. Anal. Calcd for $C_{68}H_{62}I_2O_{14}$: C, 60.19; H, 4.61. Found: C, 60.57; H, 4.72.

37,40-Bis[(4-iodobenzyl)oxy]-38,39,41,42-tetrakis[(*tert*-butoxycarbonylmethyl)oxy] calix[6]arene (3f). This compound was prepared (104 mg, 76%) by general procedure B, from **2c** (100 mg) and *tert*-butyl bromoacetate (0.11 mL). mp 189−194 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.55 [s, 36H, $C(CH_3)_3$], 3.49 (br s, 4H, OCH_2Ar), 4.06 (br s, 12H, $ArCH_2Ar$), 4.37 (s, 8H, OCH_2CO), 6.59 (br s, 12H, ArH), 6.95−7.10 (br m, 6H, ArH), 7.31−7.39 (m, 8H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$, DEPT) δ 28.2 [C(CH_3)$_3$], 29.7, 30.2 ($ArCH_2Ar$), 70.9 (OCH_2CO), 73.2 (OCH_2Ar), 81.9 [C(CH_3)$_3$], 123.7, 124.6, 127.6, 129.8, 130.6, 137.1 (ArCH), 92.9, 133.59, 133.63, 134.4, 154.4, 154.7 (ArC), 168.2 (CO); MALDI-TOF MS *m/z* 1547.1 $[M + Na]^+$, 1563.1 $[M + K]^+$. Anal. Calcd for $C_{80}H_{86}I_2O_{14}$: C, 62.99; H, 5.68. Found: C, 63.15; H, 5.51.

5,11,17,23,29,35-Hexa-*tert*-butyl-37,40-bis[(4-methylbenzyl)oxy]-38,39,41,42-tetrakis[(methoxy carbonylmethyl)oxy]calix[6]arene (5a). This compound was prepared (115 mg, 90%) by general procedure B, from **4** (100 mg) and methyl bromoacetate (0.07 mL). mp 200−202 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.20 [s, 18H, $C(CH_3)_3$], 1.61 [s, 36H, $C(CH_3)_3$], 2.40 [s, 6H, Ar-CH_3(p)], 3.46−3.54 (br s, 12H, OCH_3), 3.82−4.15 (br s, 12H, $ArCH_2Ar$), 4.38−4.68 (br s, 8H, OCH_2CO), 4.92 (s, 4H, OCH_2Ar), 7.03−7.20 (br s, 8H, ArH), 7.23 (d, J = 7.8 Hz, 4H, ArH), 7.38 (s, 4H, ArH), 7.53 (d, J = 7.8 Hz, 4H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$, DEPT) δ 21.2 [Ar-CH_3(p)], 31.3 [C(CH_3)$_3$], 30.1, 31.4 ($ArCH_2Ar$), 51.7 (OCH_3), 70.1 (OCH_2CO),

75.1 (OCH_2Ar), 80.7 [$C(CH_3)_3$], 128.5, 128.9, 129.1, 129.3 (ArCH), 127.9, 133.9, 133.1, 134.5, 137.8, 146.0, 146.5, 152.7 (ArC), 169.5 (CO); MALDI-TOF MS *m/z* 1492.7 $[M + Na]^+$, 1508.7 $[M + K]^+$. Anal. Calcd for $C_{94}H_{116}O_{14}$: C, 76.81; H, 7.95. Found: C, 77.10; H, 8.15.

Crystallographic Studies of Compounds 3a, 3b, and 3d. The samples were mounted on a glass fiber and transferred to a Bruker SMART[20] 6K CCD area-detector three-circle diffractometer with a Rigaku rotating anode (Cu Kα radiation, λ = 1.54178 Å) generator equipped with Goebel mirrors at settings of 50 kV and 100 mA. X-ray data were collected at 296 K, with a combination of six runs at different φ and 2θ angles, 3600 frames. The data were collected using 0.3° wide ω scans (10 s/frame at $2\theta = 40°$ and 20 s/frame at $2\theta = 100°$ for compound **3a**, 3 s/frame at $2\theta = 40°$, and 10 s/frame at $2\theta = 100°$ for compound **3b**, and 30 s/frame at $2\theta = 40°$ and 100 s/frame at $2\theta = 100°$ for compound **3d**) with a crystal-to-detector distance of 4.0 cm. The substantial redundancy in data allows empirical absorption corrections (SADABS)[21] to be applied using multiple measurements of symmetry-equivalent reflections. The raw intensity data frames were integrated with the SAINT[22] program, which also applied corrections for Lorentz and polarization effects. Crystallographic details for each compound are reported in Table S1 (see Supporting Information).

The software package SHELXTL[23] version 6.10 was used for space group determination, structure solution, and refinement. The space group determination was based on a check of the Laue symmetry and systematic absences and was confirmed using the structure solution. The structure was solved by direct methods (SHELXS-97),[24] completed with difference Fourier syntheses, and refined with full-matrix least-squares using SHELXL-97[25] minimizing $\omega(F_o^2 - F_c^2)^2$. Weighted R factors (R_w) and all goodness of fit S are based on F^2; conventional R factors (R) are based on F. All non-hydrogen atoms were refined with anisotropic displacement parameters. All scattering factors and anomalous dispersions factors are contained in the SHELXTL 6.10 program library.

Crystallographic data for the structural analyses of **3a**, **3b**, and **3d** have been deposited within the Cambridge Crystallographic Data Centre (CCDC) as 285296, 285297, and 285298, respectively. Copies of this information may be obtained from The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. (Fax: +44 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk) or http//www.ccdc.cam.ac.uk.

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Supporting Information Available: General methods; X-ray crystallographic data of compounds **3a**, **3b**, and **3d**; VT-^{1}H NMR spectra (298−188 K) of compounds **2a**, **3a**−**f**, and **5a**; VT-^{1}H NMR spectra (403−298 K) of compounds **3a** and **3d**; HMQC spectra of compounds **2a**,**b**, **3a**−**d**, **3f**, and **5a**; ROESY spectra of compounds **3a**, **3f**, and **5a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) *SMART* v 5.625, Area-Detector Software Package; Bruker AXS: Madison, WI, 1997−2001.

(21) Sheldrick, G. M. *SADABS: A Program for Empirical Absorption Correction*, version 2.03; University of Göttingen: Göttingen, Germany, 1997−2001.

(22) *SAINT+ NT: SAX Area-Detector Integration Program*, version 6.04; Bruker AXS: Madison, WI, 1997−2001.

(23) *SHELXTL: Structure Determination Package*, version 6.10; Bruker AXS: Madison, WI, 2000.

(24) Sheldrick, G. M. *Acta Crystallogr., Sect. A* **1990**, *46*, 467−473.

(25) Sheldrick, G. M. *SHELXL-97: Program for Crystal Structure Refinement*; University of Göttingen: Göttingen, Germany, 1997.