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Partially O-Alkylated Thiacalix[4]arenes: Synthesis, Molecular and Crystal Structures, Conformational Behavior

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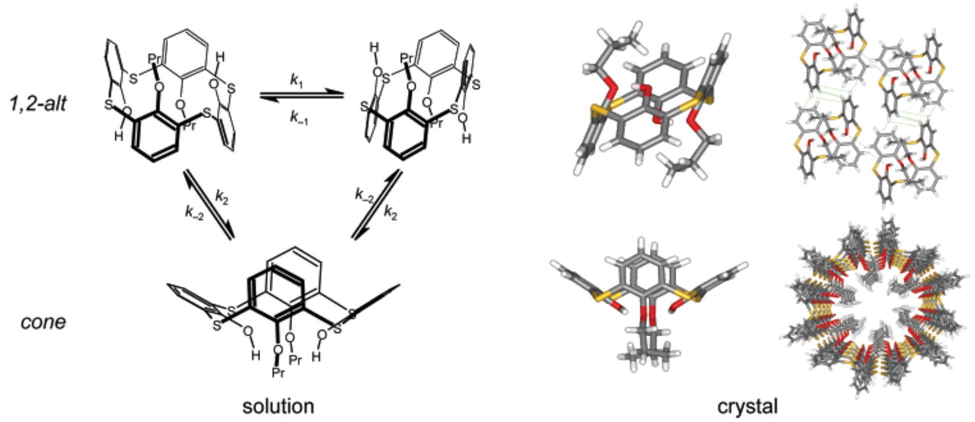

NMR spectroscopy, X-ray diffraction analysis, and quantum chemical calculations were used for conformational behavior study of partially alkylated thiacalix[4]arenes bearing methyl (**1**), ethyl (**2**), or propyl (**3**) groups at the lower rim. The conformational properties are governed by two basic effects: (i) stabilization by intramolecular hydrogen bonds, and (ii) sterical requirements of the alkoxy groups at the lower rim. While the monosubstituted derivatives **1a** and **3a** adopt the cone conformation in solution, distally disubstituted compounds **1b**, **1′b**, **2b**, **2′b**, **3b**, and **3′b** exhibit several interesting conformational features. They prefer pinched cone conformation in solution, and, except for **3′b**, they form also 1,2-alternate conformation, which is flexible and undergoes rather fast transition between two identical structures. The crystal structures of the compounds **1b**, **2b**, **2′b**, and **3b** revealed yet quite rare 1,2-alternate conformation forming molecular channels held together by $\pi-\pi$ interactions. Different channels—with hexagonal symmetry, 0.26 nm wide—are formed in the crystal structure of the pinched cone conformation of **3b**. An uncommon hydrogen bonding pattern was found in dimethoxy and dipropoxy derivatives **1′b** and **3′b** that adopt distorted cone conformations in crystal. Trialkoxy-substituted compounds **1c** and **3c** adopt the partial cone conformation in solution. A higher mobility of methyl derivative **1c** enables also existence of the cone conformer.

Introduction

Thiacalix[4]arenes[1] represent a very promising group of macrocyclic compounds with many applications in supramolecular chemistry. The presence of four sulfur atoms instead of methylene bridges imposes many novel interesting features on the thiacalixarenes[2,3] if compared with the classical calixarenes.[4,5] Among others, the introduction of sulfur atoms into the

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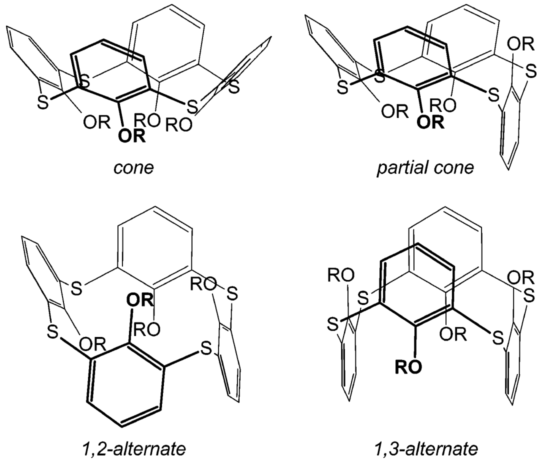

FIGURE 1. Four basic conformations of thiacalix[4]arenes.

calixarene skeleton induces considerable changes in its conformational behavior. As the cavity of thiacalix[4]arene is larger, the conformational preferences of the thia derivatives are different both in solid state and in solution when compared with the methylene-bridged ones.

Thiacalix[4]arenes and their derivatives can generally exist in four different conformational isomers:[6] cone, partial cone, 1,3-alternate, and 1,2-alternate (Figure 1). The nonsubstituted thiacalix[4]arene (R = H) adopts the cone conformation stabilized by a circular array of intramolecular hydrogen bonds.[1,7] Tetramethyl (R = Me) and tetraethyl (R = Et) ethers are conformationally flexible due to the absence of any hydrogen bond at ambient temperature. Both methoxy and ethoxy groups are small enough to allow rotation of aromatic rings via "the lower rim through annulus" pathway.[8] Thus, at room temperature, the tetramethyl ether exhibits time-averaged signals in the ^{1}H NMR spectrum caused by the fast chemical exchange of several conformers,[9] while in the case of the tetraethyl ether, an equilibrium between all four conformers under the slow exchange conditions has been observed.[6] Introduction of bulkier groups (R = Pr) to the lower rim of the cavity blocks these interconversions and enables formation of separable geometrical isomers at ambient temperature.[10]

Interesting properties are exhibited by partially O-alkylated calix[4]arenes. Considerable attention was paid to partially O-methylated[11−13] and partially O-propylated calix[4]arenes.[14] In both series, hydrogen bonding and sterical hindrance reduce the conformational mobility, and thus, mono-, di-, and trisubstituted methyl and propyl ethers adopt cone conformations both in solution and in the solid state. In the case of the tripropoxy compound, the partial cone conformation was also identified.

Despite the fact that the chemistry of thiacalixarenes has made substantial progress since their first appearance in 1997,[6,9,10,15−19] the general conformational behavior of simple derivatives is still not sufficiently well-known and/or understood. A deeper understanding of the relations between the thiacalixarene structure and their stereodynamic properties would be very useful in a design of novel receptors. Hence, in this paper, we focus on a detailed investigation of conformational behavior of partially alkylated (methyl−*n*-propyl) thiacalix[4]arenes (Figure 2). A number of NMR experiments was used (COSY, HMQC, HMBC, NOE) to achieve the conformational assignment in solution. Furthermore, single-crystal X-ray diffraction was used to study the conformational preferences in the solid state. The above results were supported by quantum chemical calculations carried out on the density functional theory (DFT) level.

Results

Synthesis. The obvious method for the preparation of partially alkylated thiacalixarenes is a direct alkylation of parent thiacalix[4]arenes with alkylation agents (alkyl iodides) using various molar ratios between the thiacalixarene and a base (K_2CO_3).[9] Thus, the alkylation of thiacalix[4]arene with excess of methyl or propyl iodide in the presence of K_2CO_3 (0.5 molar equiv) in refluxing acetone (2 days) led to the corresponding monoalkyl derivatives **1a** and **3a** in 11 and 15% yields, respectively. A similar method, using 1.5 molar equiv of K_2CO_3, was applied for the preparation of tripropoxy derivative **3c**, which was obtained in 23% yield. The general drawback of the above syntheses was the formation of complicated reaction mixtures that have to be purified using preparative TLC on silica gel. The alkylation of parent tetrahydroxy thiacalix[4]arene with an excess of alkylation agent and using 1.1 molar equiv of the base (K_2CO_3) gave smoothly the dialkylated derivatives **1b**, **1′b**, **2b**, **3b**, and **3′b**. These derivatives are accessible in acceptable yields (49−82%) using a simple precipitation technique ($CHCl_3$/MeOH). Surprisingly, in the case of diethoxy derivative **2′b**, the conformational outcome of the alkylation reaction was found to be dependent on the reaction workup. While the crude reaction mixture consists of substantially pure 1,2-alternate conformer (1,2-alternate/cone >12:1), the extraction of reaction mixture with chloroform and subsequent evaporation gives approximately a 3:1 mixture of 1,2-alternate and cone conformers. This indicates a slow conversion (in the time scale of hours) of the 1,2-alternate into the cone conformation in chloroform solution. The rate of this process was determined accurately by means of NMR (see below). As all our attempts on the direct trimethylation of thiacalix[4]arene with methyl iodide (1.5 molar

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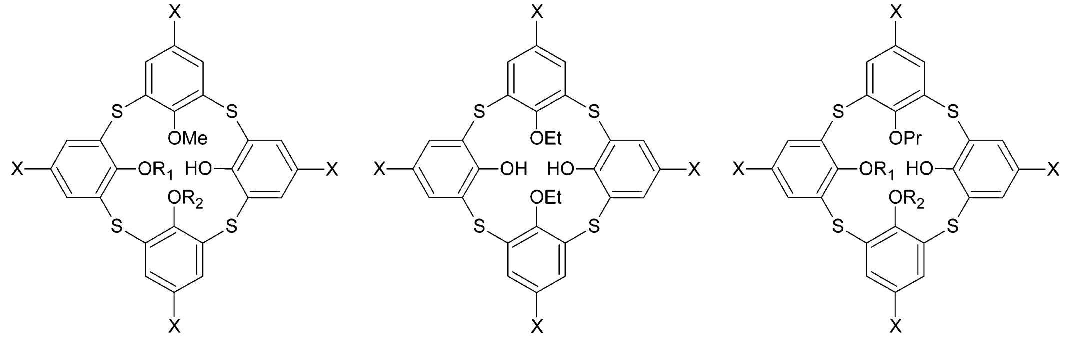
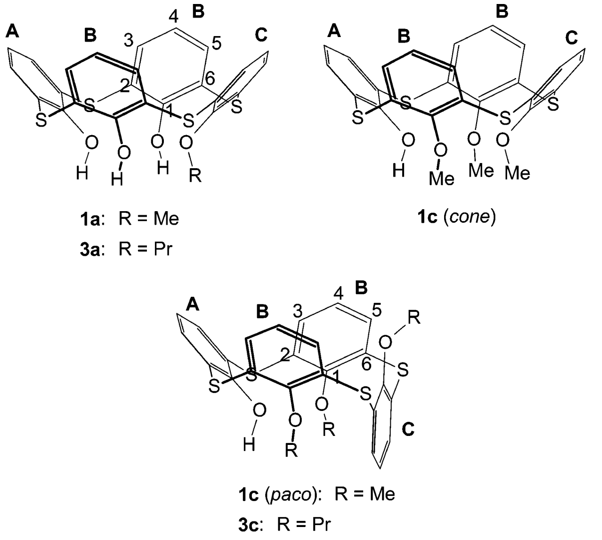


1a: X = H, $R_1 = R_2 = H$
1b: X = H, $R_1 = H$, $R_2 = Me$
1'b: X = *t*-Bu, $R_1 = H$, $R_2 = Me$
1c: X = H, $R_1 = R_2 = Me$

2b: X = H
2'b: X = *t*-Bu

3a: X = H, $R_1 = R_2 = H$
3b: X = H, $R_1 = H$, $R_2 = Pr$
3'b: X = *t*-Bu, $R_1 = H$, $R_2 = Pr$
3c: X = H, $R_1 = R_2 = Pr$

FIGURE 2. The partially O-alkylated thiacalix[4]arenes studied.



1a: R = Me
3a: R = Pr

1c (*cone*)

1c (*paco*): R = Me
3c: R = Pr

FIGURE 3. Numbering of mono- and trialkoxy thiacalix[4]arenes. General rules for the marking are: ring **A** always carries an OH group, rings **B** are the two adjacent ones to **A**.

equiv of K_2CO_3) failed, compound **1c** was prepared in 23% yield by the dealkylation reaction of 25,26,27,28-tetramethoxy derivative using trimethylsilyl bromide (3 molar equiv, CH_2Cl_2, 1 week reflux).

Conformational Assignment in Solution by NMR Spectroscopy. Monosubstituted Derivatives: The monomethyl derivative **1a** (X = H, R_1, R_2 = H) exists in a single conformation at the ambient temperature according to the ^1H NMR spectrum. It was assigned to the cone conformation by means of the 1D homonuclear NOE experiment revealing the direct dipole−dipole interaction between the *m*-protons (H-3 and H-5) of the pairs of adjacent aromatic rings **A**, **B** and **B**, **C** (Figure 3).[9] The resonances of H-3 and H-5 of the rings **B** were found to have accidentally the same chemical shift, although being chemically nonequivalent. This feature suggests that the molecule retains the geometry close to the 4-fold apparent symmetry of the nonsubstituted thiacalix[4]arene, in spite of the different substitution of the rings **A** and **C**.

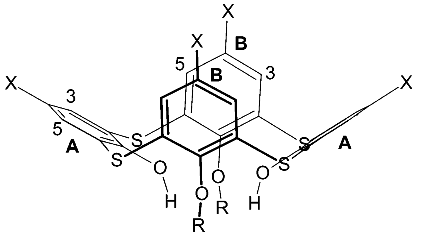
The spectral features of the propyl-substituted compound **3a** are similar to those of methyl derivative **1a**, and thus, its conformation was identified as the cone by the same method. The NOE buildup between the *m*-protons of the adjacent rings was also measured in a quantitative manner in order to determine distance between the interacting nuclei (for the results, see Table 1).

TABLE 1. Distance Calculations from the NOE Measurements for Compounds 2b, 3a, 3b, and 3c (For a Comparison, the Values Obtained from the DFT Calculations (B3LYP/6-311G) and from X-ray Crystallography are Also Displayed[a])**

		distance (Å)		
compound	interacting ^1H nuclei	NOE	DFT	crystal[c]
2b(cone)	H-3**A** ↔ H-3**B**	3.10	3.45[b] 3.06	
2b(inverting 1,2-alt)	H-3**A** ↔ H-5**B**	2.90	2.97[b]	2.90
3a(cone)	H-3**C** ↔ H-5**B**	2.87	3.31[b] 2.95	
	H-3**A** ↔ H-3**B**	3.03	3.23[b] 3.27[b]	
3b(cone)	H-3**A** ↔ H-3**B**	3.23	3.44[b] 3.07	3.44 3.40 3.32 3.25
3c(paco)	H-3**A** ↔ H-3**B**	3.15	3.47[b] 3.13	3.39[d] 3.17[d]

[a] When several different values of distances are reported as the results of the DFT calculations and of the X-ray structural analysis, they are related to deformation of the molecules from the ideal geometries (Figure 1) due to the lower rim hydrogen bonding. In solution, however, the fast switching of hydrogen bonds causes averaging of the parameters obtained by NMR. The standard error of distances obtained from the NOE spectra is estimated to 0.10 Å. [b] Connection of two adjacent rings by a hydrogen bond at the lower rim results in longer distance between the corresponding aromatic hydrogen atoms H-3 and H-5, respectively. [c] For this particular table, the X-ray crystal structures were refined with C−H bond length set to 1.085 Å in order to allow for a direct comparison with the NMR distances which are commonly somewhat larger than those obtained by the X-ray analysis. The value of 1.085 Å was also received from the DFT calculation. [d] Average distance in four nonequivalent molecules in the unit crystal cell.

Trisubstituted Derivatives: The conformational behavior of trimethoxy thiacalix[4]arene derivative **1c** (X = H, $R_1 = R_2$ = Me) is more complex, and it had to be examined by the temperature-dependent ^1H NMR spectroscopy (Figure S1 in Supporting Information). The signals of **1c** were broadened by a conformational exchange at room temperature (298 K). The temperature-dependent measurements revealed that two conformers are present in approximately 5:4 ratio (203 K, in $CDCl_3$). Using 2D NOESY, it was possible to assign the major conformer of **1c** to the partial cone conformation **1c(paco)** with the methoxylated ring **C** inverted with respect to the remaining



1b: X = H, R = Me
1′b: X = *t*-Bu, R = Me
2b: X = H, R = Et
2′b: X = *t*-Bu, R = Et
3b: X = H, R = Pr
3′b: X = *t*-Bu, R = Pr

FIGURE 4. The pinched cone conformation of dialkoxy thiacalix[4]arenes and marking of the aromatic rings.

three (note that theoretically there are three distinguished atropisomeric forms of partial cone—the inverted ring could be either **A**, **B**, or **C**). The key NOE connectivities were found between the aromatic protons (H-3, H-5) of the adjacent aromatic rings **A** and **B** and between the ring **B** (H-5) and the methoxy group of the ring **C**. The transfer of magnetization was also detected between aromatic protons of the ring **C** and the methoxy groups of rings **B** (Figure 3). The minor conformation of **1c** was assigned to the cone conformation (**1c(cone)**) on the basis of NOE contacts between the *m*-protons of the adjacent aromatic rings.[9]

Tripropoxy thiacalix[4]arene **3c** adopts the partial cone conformation with the ring **C** bearing a propoxy group inverted with respect to the rings **A** and **B**, similar to trimethoxy derivative **1c**. The structure was documented by the NOEs between the *m*-protons (H-3) of the rings **A** and **B**, between the *m*-protons (H-5) of the ring **B**, and the propoxy group (H-1′) of the ring **C**, and between the *m*-protons of ring **C** and the propoxy group (H-1′) of the ring **B**. The distance between H-3 of the rings **A** and **B** was also determined by the quantitative measurement (3.15 Å, Table 1).

Distally Disubstituted Derivatives: Determination of the conformational behavior turned out to be most difficult for the distally disubstituted compounds since two crucial effects—the stabilization by formation of hydrogen bonds at the lower rim and the steric repulsions between hydrophobic groups bound at the lower rim—combine here in a subtle way.

The solution structures of dimethyl and diethyl derivatives **1b**, **1′b**, **2b**, and **2′b** have shown common features. In all cases, two interexchanging conformational isomers occur. The temperature-dependent ^{1}H NMR spectroscopy revealed the existence of chemical exchange between two conformers in the case of dimethoxy compound **1b**. The signals were broadened at room temperature ($CDCl_3$ solution), and the two present conformers could be identified only at decreased temperature (5.5:1 ratio at 213 K). Degeneracy of chemical shifts in the ^{1}H and ^{13}C spectra of the prevailing conformer at 213 K corresponds to the effective C_{2v} symmetry. The observed NOE contacts between the *m*-aromatic protons of the adjacent rings and also those between the substituents at the lower rim of the cavity (OH, OCH_3) prove that the major component is cone (**1b(cone)**) (Figure 4).[9] A considerable difference of the chemical shifts of the *m*-aromatic protons of the rings **A** (7.7 ppm) and **B** (7.1 ppm) is indicative for the pinched cone geometry,[6,17,20−22] where the rings **A** become more declined from the symmetry axis due to the lower rim hydrogen bonding, and conversely, the rings **B** become close to parallel. This geometry results in the shielding effect of the rings **A** (ring current shift) imposed on the nuclei of the rings **B**.

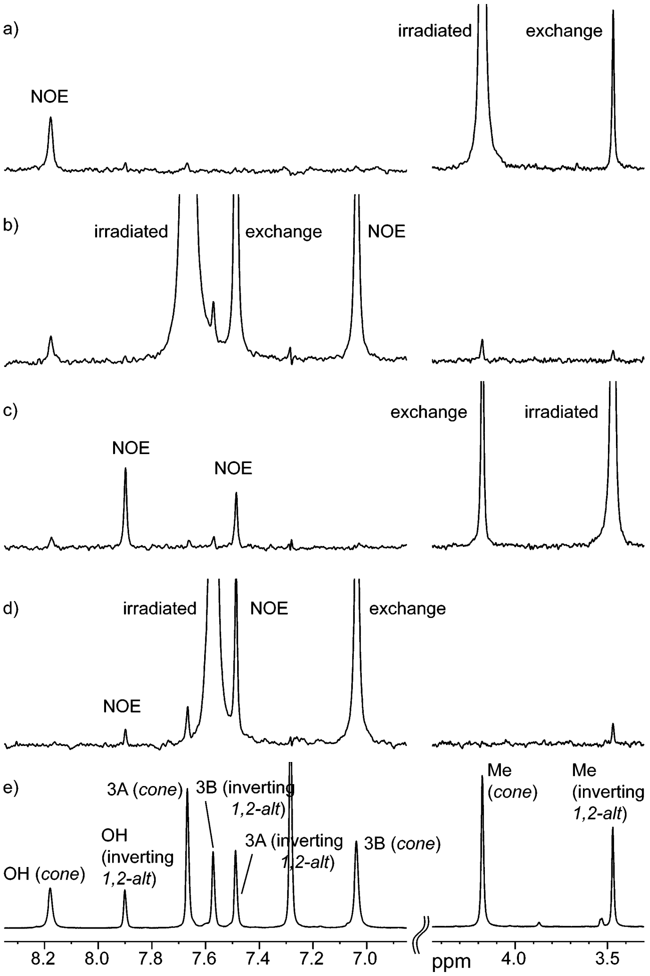


FIGURE 5. The DPFGSE-NOE spectrum of **1′b** with Me (**cone**) irradiated (a), DPFGSE-NOE spectrum with H-3**A** (**cone**) irradiated (b), DPFGSE-NOE spectrum with Me (**1,2-alt**) irradiated (c), DPFGSE-NOE spectrum with H-3**B** (**1,2-alt**) irradiated (d), and ^{1}H NMR spectrum of **1′b** ($CDCl_3$, 203 K) (e). For atom numbering, see Figures 4 (cone) and 7 (1,2-alt). For simplicity, the degenerated signals of H-3 and H-5 are marked as H-3 only.

The ^{1}H NMR spectrum of the minor conformer of **1b** possesses the same level of degeneracy as the spectrum of the major cone (total of six resonances each). Its assignment was more problematic due to overlaps and due to the presence of chemical exchange peaks in the NOE spectra.

p-tert-Butyl-substituted derivative of dimethoxy thiacalix[4]arene (**1′b**) afforded better resolved and simplified spectra (Figure 5e), which enabled easier conformational assignment. The presence of two conformers (2:1 ratio) was observed at 203 K in $CDCl_3$, similarly to **1b**. Expectably, the major component of **1′b** was assigned by means of 1D DPFGSE-NOE

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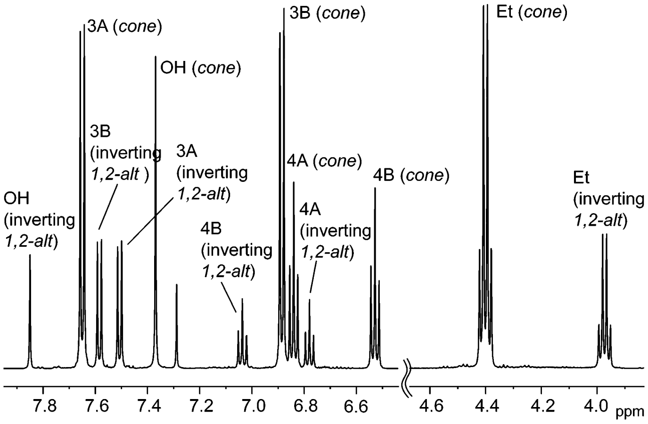


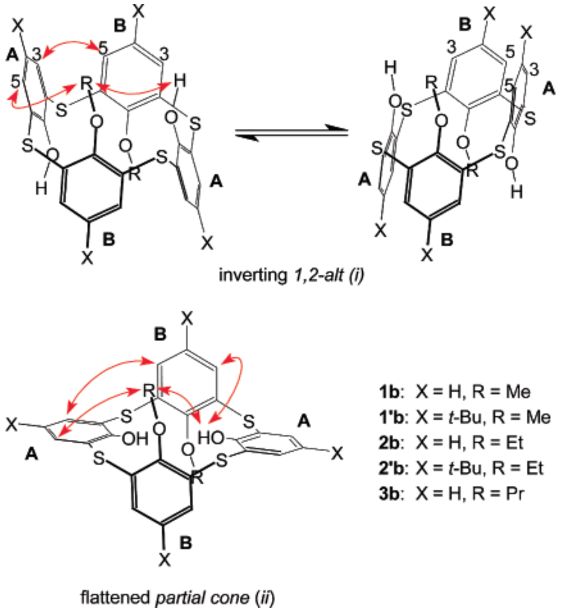
FIGURE 6. ^{1}H NMR spectrum of **2b** ($CDCl_3$, 298 K). For atom numbering, see Figures 4 (cone) and 7 (1,2-alt). For simplicity, the degenerated signals of H-3 and H-5 are marked as H-3 only.

and chemical shift analysis to the pinched cone conformation (**1′b(cone)**, Figures 4 and 5a,b). Despite the simplification of the spectra, the structural assignment of the minor component of **1′b** remained ambiguous. The enhancements of the *m*-aromatic proton H-3 (ring **A**) and of the OH proton (7.9 ppm) were detected after the selective excitation of the methoxy protons at 3.5 ppm (Figure 5c). The *m*-aromatic protons of the ring **B** (bearing the methoxy group) show NOE to the aromatic protons of the adjacent ring **A** (Figure 5d).

Also the distally disubstituted diethoxy thiacalix[4]arene **2b** showed a similar behavior. Due to the sterical hindrance of the ethoxy groups, the chemical exchange became slow at room temperature, and two conformers in 2:1 ratio were observed (Figure 6). The major one was assigned to the cone again.

The observed NOE contacts in all minor components of **1b**, **1′b**, and **2b** are thus consistent with the 1,2-alternate conformation. The profound degeneracy of chemical shifts, however, resembles more symmetrical cone or 1,3-alternate. This confusing feature has already been reported for the methylene-bridged distally disubstituted diethoxy-[23] and bis(diethoxyphosphoryloxy) *tert*-butyl calix[4]arenes.[24] There are two possible interpretations of such spectral patterns: (i) the fast chemical exchange between two identical 1,2-alternate conformers or (ii) a rigid flattened partial cone conformation, in which the two phenolic units lie in the plane of sulfur atoms (probably stabilized by hydrogen bonding), while the methoxylated rings are oriented perpendicular upward and downward with respect to this plane (Figure 7). The first option was recently documented to occur in *tert*-butyl calix[4]arene substituted by two bulky mesityl groups at distal methylene bridges.[25]

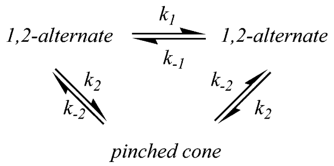
We also attempted to measure quantitatively the distances between H-3**A** ↔ H-5**B** in the minor species of **2b** by means of NOE. The derived distance should have enabled us to distinguish which of the two possible structures is correct. Unfortunately, the numbers of pairwise dipolar interactions in the two structures differ, and consequently, the interpretation of the NOE in terms of internuclear distance is ambiguous in this particular case. For a detailed description as well as a general discussion of the effect of chemical equivalence on the measured NOE and the derived distances, see the Supporting Information. The distance derived for 1,2-alternate is 2.90 Å (see also Table 1).



1b: X = H, R = Me
1′b: X = *t*-Bu, R = Me
2b: X = H, R = Et
2′b: X = *t*-Bu, R = Et
3b: X = H, R = Pr

FIGURE 7. Two possible interpretations of the conformational behavior of dialkoxy thiacalix[4]arene with indication of the observed NOE connectivities: two mutually exchanging 1,2-alternate conformers (i) and flattened partial cone geometry (ii). Aromatic hydrogen numbering used to describe NMR spectra of 1,2-alternate conformers (Figures 5 and 6) is also indicated. Chemical shifts of protons H-3 and H-5 are always averaged by fast chemical exchange.

SCHEME 1. Inversion between Two Identical 1,2-Alternate and Pinched Cone Conformation



The NMR experiments thus could not confirm unambiguously any of the two possibilities of the minor components' geometry. However, the quantum chemical calculations (vide infra) provided a substantially higher energy for the flattened partial cone compared to 1,2-alternate. The minor conformers of **1b**, **1′b**, and **2b** were thus assigned to 1,2-alternate undergoing inversion between two identical structures (we will call this conformation further as "inverting 1,2-alternate"). Therefore, within the distally disubstituted systems, two distinct conformational transitions exist. The inversion between two identical 1,2-alternates is much faster than the second motion leading to the pinched cone conformation ($k_1 = k_{-1} \gg k_2 \sim k_{-2}$, Scheme 1).

As mentioned in the Experimental Section, the NMR spectral pattern of the fresh isolated product **2′b** revealed only a single conformation identified as the inverting 1,2-alternate, while the pinched cone appeared after **2′b** was left at room temperature in chloroform solution. Kinetics of this equilibration (k_2 and k_{-2} in Scheme 1) was monitored using ^{1}H NMR (298 K, $CDCl_3$ solution) over the period of 22 h (Figure S7). The two rate constants were calculated as $k_2 = 1.73 \times 10^{-4}$ s^{-1} and $k_{-2} = 2.11 \times 10^{-4}$ s^{-1} (for details see, Supporting Information). The corresponding activation free energies of the interconversion ΔG_0* are 94.45 and 93.96 kJ·mol^{-1}, respectively. The difference as small as 0.49 kJ·mol^{-1} illustrates only little prevalence of the 1,2-alternate conformer in equilibrium (55:45).

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The synthesis of the dipropoxy compound **3b** afforded two products which do not interconvert into each other at room temperature, in contrast with other distally disubstituted compounds as described above. The main product (53% yield) was assigned to the pinched cone conformation by the NOE experiment. The distance between the protons H-3, H-5 of the adjacent rings **A** and **B** measured through the NOE was found to be 3.15 Å (Table 1). The spectral properties of the minor product (15% yield) are consistent with the fast exchange between two 1,2-alternate conformations again (Figure 7).

Quantum Chemistry Calculations. The density functional theory calculations using the Gaussian03 program[26] were carried out to provide a common basis for experimental results and to allow certain generalizations (see the Discussion and Tables 1 and S1). The heats of formation were calculated for compounds occurring in two conformations (**1b**, **1′b**, **2b**, **2′b**, **3b**, and **1c**). In the dialkylated compounds, the cone is enthalpically favored over 1,2-alternate by 5−7 kJ·mol^{-1}. In **1c**, a small enthalpic preference of cone over paco (0.6 kJ·mol^{-1}) was found (Table S2). Besides that, the calculations facilitated assignments of the inverting 1,2-alternate species in solutions of the distally disubstituted compounds.

The B3LYP hybrid functional with the 6-311G** basis set is a level of theory sufficient to provide molecular geometries as well as a good qualitative insight into the conformational behavior of such systems.[17,19,27] Two possible structures of the minor component of **2b** were subjected to the geometry optimization. The structure of the 1,2-alternate conformer was found to be stabilized by two hydrogen bonds formed between the OH groups and the neighboring ether oxygen atoms. The calculated interaction distances between the oxygen atoms are about 2.93 Å (with O−HO distances being about 2.00 Å; for details, see Figure 8). The structure assumed as the second structural option (flattened partial cone conformation; see Figure 7) was found to lack such intramolecular stabilization by hydrogen bonding. The calculated distances between the opposite oxygens of the hydroxyl groups are 2.89 Å (with O−HO distances being about 2.55 Å), but the geometry of this system makes formation of the hydrogen bonds impossible (see Figure 8). Moreover, geometry of the sulfur bridges in this model is a source of substantial internal strain in the thiacalix[4]arene macrocycle. As a result, this structure is disfavored by 58.88 kJ·mol^{-1} when compared to the 1,2-alternate structure and is characterized by an imaginary vibration frequency (−76 cm^{-1}). The flattened partial cone conformation thus represents a transition state on the inversion pathway connecting the two stable 1,2-alternate structures.

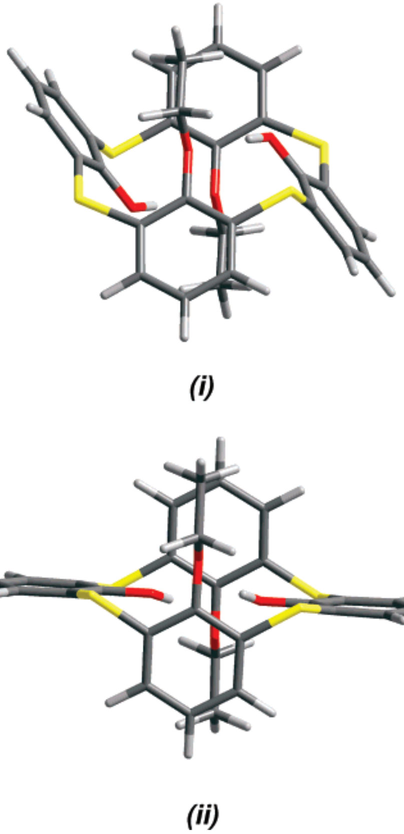

FIGURE 8. The DFT calculated geometry (B3LYP/6-311G**) of compound **2b**: the 1,2-alternate conformer (i) and flattened partial cone (ii).

Crystal Structures of the Dialkylated Derivatives 1b, 1′b, 2b, 2′b, 3b, and 3′b. A single-crystal X-ray diffraction structure analysis has demonstrated very interesting conformational preferences of the dimethoxy derivative **1b**.[9,28] This compound adopts the 1,2-alternate conformation, rather unusual within the thiacalix[4]arene family. The 1,2-alternate conformation is centro-symmetrical with the opposite inverted aromatic rings being parallel (Figure 9). Four sulfur atoms are placed in the corners of a rhombus with shorter and longer diagonals being 7.46 and 8.22 Å, respectively, and the distance between two proximal sulfur atoms being approximately 5.55 Å (compare with 5.13 Å, a typical distance between corresponding CH_2 groups in calix[4]arene in 1,2-alternate conformation). Both diethoxy **2b** and dipropoxy **3b(1,2-alt)** derivatives were found to exhibit almost identical arrangement in the solid state (Figure 9). The structures are stabilized by the intramolecular CH−π interaction between the hydrogen attached to the second carbon of the alkoxy group and the neighboring inverted aromatic ring **A**. The distances between the interacting species are about 2.80 and 2.85 Å in **2b** and **3b(1,2-alt)**, respectively. The molecules **1b**, **2b**, and **3b(1,2-alt)** form infinite channels that are held together by several noncovalent interactions (Figures S2 and S3). For the details of the crystal packing, please see the Supporting Information.

Additionally, **3b** adopts also the cone conformation in the solid state (**3b(cone)**), as well as in solution. The hydroxyl hydrogen atoms create common cyclic arrangement of hydrogen bonds at the thiacalixarene lower rim, and **3b** adopts in this structure C_2 symmetry. The molecule is widely open (pinched)

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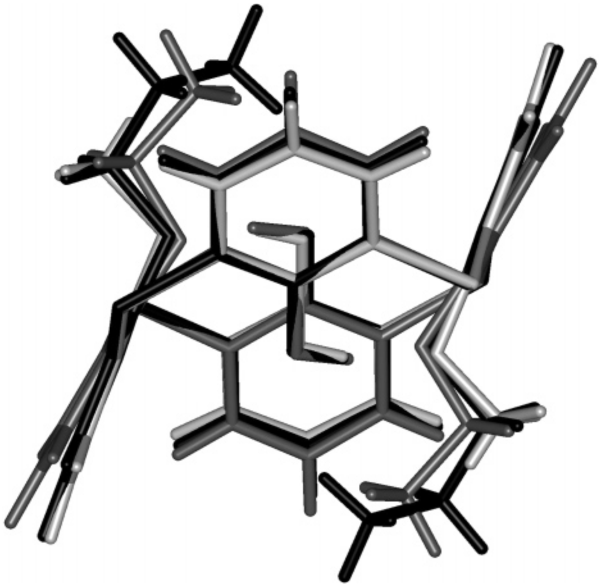

FIGURE 9. Comparison of the crystal structures of **1b** (light gray), **2b** (dark gray), and **3b(1,2-alt)** (black).

at the ring **A** sides, allowing inclusion of the aromatic unit **B** of another molecule into the cavity (Figure 10a). The molecules interact via strong $\pi-\pi$ stacking of parallel rings **B** (the interplanar distance is 3.51 Å), which is supported by two CH$-\pi$ interactions of H-3 and H-5 of ring **B** with the declined ring **A** (the distances of about 2.98 Å). A complex array of CH$-\pi$ and $\pi-\pi$ intermolecular interactions leads to the formation of tubular assemblies with star-like structures in the molecular packing. The propoxy groups point toward the center of the tubes and form a completely different kind of hydrophobic hexagonal channels (Figure 10b) along the *z*-crystallographic axis. Six-fold symmetry causes each channel to be surrounded by six other channels. On the basis of van der Waals atomic radii, the inner diameter of the channel is 2.6 Å, which may allow inclusion or, perhaps, even storage of small atoms or molecules such as helium or hydrogen.

The crystallographic study revealed an "uncommon" hydrogen bonding pattern in dialkoxy derivatives **1′b** and **3′b** bearing *p*-*tert*-butyl groups. These thiacalixarenes adopt a distorted cone conformation where both free hydroxyls interact with the same OCH_3 group (Figure 11). The alkylated rings are nearly parallel, and they are tilted to the same direction. The alkoxy groups are also oriented in the same direction. This arrangement leads to the structure with approximate C_s overall symmetry. Furthermore, a search in the Cambridge Structure Database (CSD version 5.27, November 2005) has revealed that five out of the total number of six structures of distally disubstituted *p*-*tert*-butylthiacalix[4]arene adopt a similar conformation.[29−33]

This fact indicates a general behavior of the distally dialkylated cone conformers substituted with *tert*-butyl in the *para*

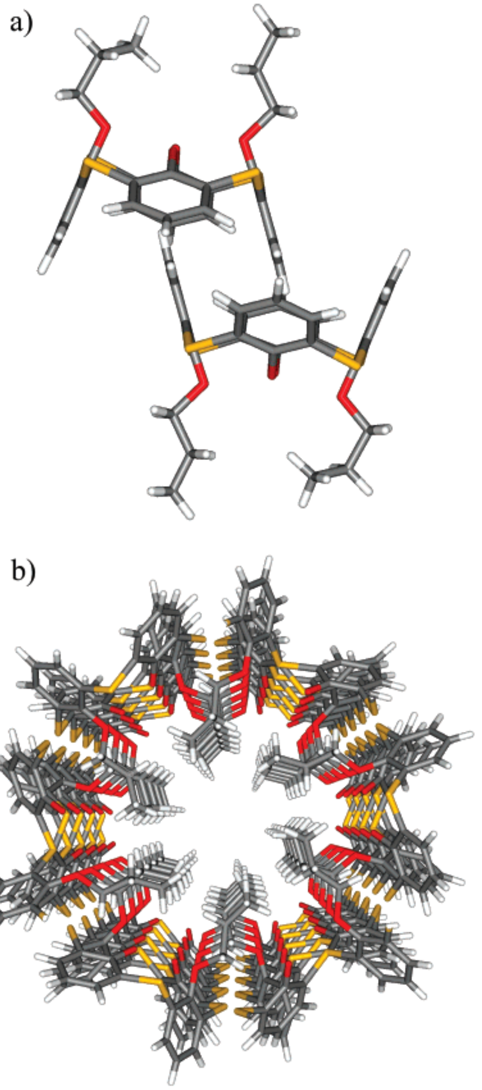

FIGURE 10. Molecular packing in the crystal structure **3b(cone)**: $\pi-\pi$ interactions (a) and star-like hexagonal hydrophobic channel along the crystal *z*-axis (b). The disorder of the propoxy groups was omitted for clarity.

position at the upper rim. It is another example of different properties of the thiacalixarene derivative family compared to the classical calix[4]arenes, in which the two OH groups at the lower rim always interact with different neighboring alkoxy substituents, retaining usually overall C_2 symmetry.[34] The second distinct difference is a solvent molecule frequently trapped in the cavity of methylene-bridged derivatives.[19]

Details of the crystal packing of **1′b**, **2′b**, and **3′b** can be found in the Supporting Information.

Discussion

The results obtained by several methods are summarized here for each of the groups: mono-, di-, and trialkylated compounds. Table 2 provides a concise overview of the conformations observed in solution and in crystal. Initially, only methyl- (**1**) and propyl (**3**)-substituted compounds were synthesized and characterized because it was expected that the first group would

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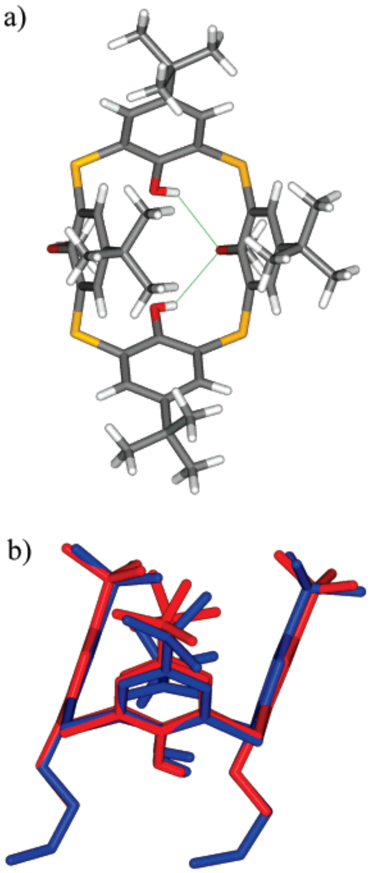

FIGURE 11. A single molecule of **1′b** showing approximate C_s symmetry (a), comparison of the crystal structures of **1′b** (red) and **3′b** (blue); hydrogen atoms and the disorder of the *tert*-butyl group were omitted for the clarity (b).

TABLE 2. Overview of Conformers Determined in Solution and in Crystal (The Major Conformation in Solution Is Always on Top)

	methyl (**1**)		ethyl (**2**)		propyl (**3**)	
	solution	crystal	solution	crystal	solution	crystal
mono (**a**)	cone	*a*	*b*	*b*	cone	*a*
di (**b**)	cone 1,2-alt	1,2-alt	cone 1,2-alt	1,2-alt	cone 1,2-alt	cone 1,2-alt
di (′**b**)	cone 1,2-alt	cone	1,2-alt cone	1,2-alt	cone	cone
tri (**c**)	paco cone	*a*	*b*	*b*	paco	paco

[a] No crystals obtained. [b] Compound was not synthesized.

be conformationally flexible in solution while the latter should be quite restricted at ambient temperature. This hypothesis was found to be true. Therefore, the ethoxy thiacalix[4]arenes were prepared as distally disubstituted derivatives only (**2b**, **2′b**) in order to achieve an intermediate chemical exchange regime allowing easier experimental characterization of 1,2-alternate conformation and its internal flexibility (1,2-alternate−“inverted” 1,2-alternate transition). The syntheses and conformational properties of monoethoxy and triethoxy derivatives were expected to be very comparable to the other monoalkylated and trialkylated compounds, respectively, and they have not been prepared. A majority of the studied compounds can adopt two conformations in solution, but they crystallize in a single thermodynamically favored geometry only. The only exception is the dipropylated compound **3b** occurring in both conformations also in crystals due to the sterical hindrance of the cone−1,2-alt transition.

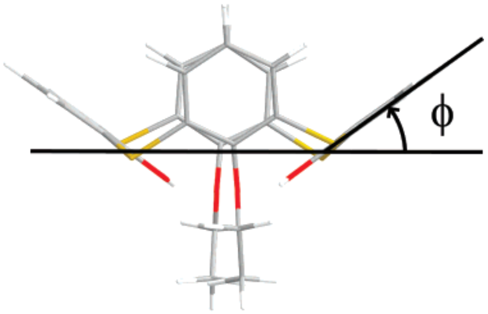

FIGURE 12. Definition of the angle ϕ included by the aromatic ring from the mean plane of the sulfur atoms. In cone and 1,2-alt, it adopts values of 0−180°. In the case of the inverted ring **C** of the partial cone conformation, the ϕ angle has a negative sign.

In order to compare results of the B3LYP/6-311G** calculation with crystal structures for different thiacalix[4]arene derivatives and their observed conformations, we utilize the declination angle ϕ included by a particular aromatic unit with respect to the plane of four sulfur atoms of thiacalix[4]arene (for a pictorial definition, see Figure 12). In the case that the sulfur atoms do not lie in a single plane, we take the plane representing the best fit of their positions.

All angles ϕ for the molecular structures determined by the ab initio calculation and the X-ray crystallography are collected in Table S1. The table allows comparison of thiacalix[4]arene cavity geometries in various ways, such as their dependence on the size of a substituent, number of substituents, conformation type, etc. Even though there are several crystal geometries unavailable (no crystals obtained, or some crystal conformations are thermodynamically disfavored), the results of DFT calculations allow tracking of the geometrical properties in the whole set of thiacalix[4]arene structures.

Monoalkylated Compounds. All monoalkylated compounds adopt the cone conformation in solution. The distances between the protons of the adjacent rings in **3a** as determined from the NOE measurements (2.87 and 3.03 Å) are quite close to those calculated by the DFT (see Table 1). The two DFT calculated structures—**1a** and **3a**—are fairly similar. The lack of one hydrogen bond, as compared to the parent tetrahydroxy thiacalix[4]arene ($\phi = 51°$, C_4 symmetry), leads to a certain distortion of the structures displacing the sulfur atoms from the common plane. The substituted ring **A** becomes more declined (68−69°). On the other hand, the two adjacent rings **B** are somewhat closer to the plane of the sulfur atoms (declination angle = 40−47°), and the whole structure is thus slightly flattened (Table S1).

Trialkylated Compounds. Trialkylated compounds adopt a strongly flattened pinched cone and partial cone (with the ring **C** inverted) conformations. The ring **A** bearing hydroxyl is always involved in the conical part of the molecule (rings **B**−**A**−**B**) that adopts very similar geometries in both conformations. The ring **A** includes angle ϕ of 32−34°, and the rings **B** are nearly perpendicular (73−99°) to the sulfur atoms’ mean plane. Geometry and chemical equivalence of the rings **B** suggest that the hydrogen bond switches between the two adjacent ether oxygen acceptors (rings **B**) and thus hinders rotations of the three rings involved. The ring **C** adopts two possible orientations with respect to the rest of the molecule. It is interesting to note that dihedral angles describing its declination C-(2**B**)−S−C-(2**C**)−C-(3**C**) are almost exactly opposite for the two conformers (pinched cone and paco). In the case of trimethyl derivative **1c**, both of these conformations do mutually interconvert, and very similar populations (cone/paco 5:4) are in accord with a very small difference in the ab initio calculated enthalpies (Table S2). The tripropyl derivative **3c** was found only in the paco conformation at laboratory temperature. The measured distance of *m*-protons of the adjacent rings (3.15 Å) is in a very good agreement with distances obtained from the DFT calculations as well as from the X-ray crystal analysis (see Table 1).

Dialkylated Compounds. The dialkylated compounds occur in the two conformations that maximize the number of hydrogen bonds at the lower rim—cone and 1,2-alternate. The cone conformer is dominant in solution in the case of the compounds **1b**, **1′b**, **2b**, **3b**, and **3′b** and in crystals of **1′b**, **3b**, and **3′b** (Table 2), which is in agreement also with the ab initio calculated heats of formation (Table S2). The cone conformer is slightly exceeded by the 1,2-alternate in solution of **2′b**, however, which has to be ascribed to entropic effects.

As follows from the DFT calculations, the cone conformations of **1b**, **2b**, and **3b** are flattened (pinched), regardless of substitution at the lower rim. The unsubstituted OH rings **A** include an angle of 35−36°. The lower rim alkylated rings **B** decline by 77−78° from the mean plane of sulfur atoms. The values obtained from the X-ray crystal structure of **3b** are very similar: 31 and 36° for OH rings **A**, and 70 and 72° for the propylated rings **B**. In addition, the distances between *m*-protons of adjacent rings of **3b** obtained from NOE measurements and from X-ray diffraction are almost identical. These data well demonstrate very good overall agreement between the results of both experimental methods used and the DFT calculations.

The upper rim substituted compounds **1′b** and **3′b** have remarkably different geometries in the solid state as discussed above. The DFT calculation, however, provided ordinary geometries very close to the compounds **1b**−**3b**. Therefore, the distorted cone geometry with one ring pushed into the cavity has to be attributed to crystal packing.

According to the DFT calculations, the major conformation of **2′b** and the minor species of **1b**, **1′b**, **2b**, and **3b** in solution were assigned to the inverting 1,2-alternate. Finding this conformation in the crystals of **1b**, **2b**, and **2′b** is the additional evidence supporting this assignment. The declinations of all aromatic rings from the mean plane of sulfur atoms fall in the range of 49−66° in the crystal structures, which is in perfect agreement with the DFT calculations (53−62°) as well as with the NOE distance (2.90 Å) between the *m*-protons of the adjacent rings in **2b(1,2-alt)**. Therefore, the geometry of 1,2-alternate is generally largely invariant over the studied group of dialkylated compounds. However, their structure is not rigid in solution due to the conformational transition between two identical 1,2-alternate conformers (see Figure 7). This motion is analogical to the well-known transition cone−“inverted” cone that turns the tetrahydroxy calix[4]arenes “inside out”.[35]

Hydrogen Bonding. Different amount and strength of hydrogen bonding are the main factors determining the structural properties of the compounds in the studied series. The ^{1}H chemical shift of hydroxy groups in conjunction with the frequency of the stretching vibration in the infrared spectra can be used to monitor the strength of hydrogen bonding. While the chemical shifts differ substantially (6.91−8.74 ppm) among all the studied compounds, the vibrational frequencies occur in a narrow range of 3329−3389 cm^{-1} (with an exception of a band at 3436 cm^{-1} of **1b**). These values indicate generally weaker hydrogen bonding in the studied series than in calix[4]arene (10.2 ppm, 3150 cm^{-1} in CCl_4 solution).[13]

The ^{1}H chemical shift of the hydroxyl groups indicates the presence of the strongest hydrogen bond interactions in the molecules of monosubstituted compounds (8.63 ppm in **1a** and 8.74 ppm in **3a**). Only moderate hydrogen bonding is in **3c** (7.62 ppm). Interestingly, OH chemical shifts were found to be very different for the two conformers of **1c**. While the chemical shift of the major paco is as large as 8.40 ppm, the minor cone displays only 6.91 ppm. The shielding of the inverted ring **C** exerted on the hydroxyl group should lead to a decreased OH chemical shift in paco rather than increased as observed. Therefore, the hydrogen bond seems to be stronger in paco, even though the overall geometries of hydrogen bonding are very similar. The populations of the two conformers (5:4) may be related to the hydrogen bonds stabilities.

The OH chemical shift in the disubstituted derivatives can be rated as medium among the studied compounds (7.97 ppm in **1b(cone)**, 7.92 ppm in **1b(inverting 1,2-alt)**, 8.15 ppm in **1′b(cone)**, 7.87 ppm in **1′b(inverting 1,2-alt)**, 7.34 ppm in **2b(cone)**, 7.82 ppm in **2b(inverting 1,2-alt)**, 7.95 ppm in **2′b(inverting 1,2-alt)**, 7.65 ppm in **2′b**(**cone**), 7.43 ppm in **3b(cone)**, 7.85 ppm in **3b(inverting 1,2-alt)**, and 7.97 ppm in **3′b**). The shift is significantly decreased in the case of the cone conformers of **2b(cone)** and **3b(cone)**, suggesting that certain steric crowding of the lower rim may weaken the hydrogen bonds. This crowding may be avoided at the upper rim substituted **2′b(cone)** and **3′b** that may adopt the distorted cone geometry observed in crystals. Nevertheless, it is obvious that the effects influencing the stability of hydrogen bonding require a further investigation.

Comparison with the “Classical” Methylene-Bridged Calix[4]arenes. The monomethoxy *p-tert*-butyl calix[4]arene, the distally disubstituted dimethoxy *p-tert*-butyl calix[4]arene, and dimethoxy calix[4]arene were found only in the cone conformation, both in solution and in crystal.[13] The first compound was reported to adopt geometry of nearly 4-fold symmetry, while the latter two rather adopt the pinched cone conformation. Only the trimethoxy *p-tert*-butyl calix[4]arene is conformationally flexible in solution, although adopting predominantly the cone conformation as well. It also crystallizes forming the cone conformer. Thus, it is clear that the thiacalix[4]arene derivatives display remarkably higher flexibility in solution and conformational variability in the solid state.

Groenen et al.[13] noticed that the cone−inverted cone interconversion is hindered in the case of the partially O-alkylated methylene-bridged compounds, although it is rather easy for both tetrahydroxycalix[4]arene and tetramethoxycalix[4]arene. It was explained by a cooperative effect of remaining hydrogen bonds (upon substitution) that stabilizes the lower rim geometry and by steric requirements of alkyl group bound at the substituted ring.[11] In the case of methylene bridged calixarenes, interconversion is observable thanks to the presence of diastereotopic protons of methylene bridges which display chemical exchange broadening. Unfortunately, this movement is in principle “invisible” for NMR of thiacalix[4]arenes, and thus the cone−inverted cone interconversion could not be observed in the systems studied in this work.

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The complete set of the various propyl-substituted calix[4]arenes was synthesized by Iwamoto et al.[14] The propyl group was found to be too bulky to allow rotation of the propoxylated aromatic ring through the annulus of calix[4]arene. Most of the prepared compounds were in the cone conformation when obtained by a single-step synthesis. However, the tripropoxy species were prepared both as the cone and the partial cone using the template effect of alkaline metal ions. Obviously, their conformational preferences are similar to our compound **1c**. The remaining geometrical isomers had to be prepared by means of protection−deprotection method. The authors noticed that geometry of the synthesized distally disubstituted species is the "flattened partial cone". Most probably, they in fact prepared analogues of our **1b**, **1′b**, **2b**, **2′b**, and **3b** species adopting the inverting 1,2-alternate conformation.

Conclusions

The newly synthesized lower rim partially alkylated thiacalix[4]arenes possess interesting conformational behavior both in solution and in the solid state, as determined by NMR spectroscopy, X-ray crystallography, and quantum chemical calculations (Tables 1, 2, S1, and S2).

The distally disubstituted compounds (**1b**, **1′b**, **2b**, **2′b**, **3b**, **3′b**) most often prefer the pinched cone geometry in solution. However, with the exception of **3′b**, they are flexible enough to form also the 1,2-alternate conformer, which undergoes an additional transition (fast in the time scale of ^{1}H chemical shift) between two identical structures, as documented by ^{1}H NMR spectra and DFT calculations. The cone is only slightly exceeded by 1,2-alternate in the solution equilibrium mixture of **2′b**.

The solid-state structures of the dimethoxy and diethoxy derivatives **1b**, **2b**, and **2′b** showed 1,2-alternate conformations stabilized by two hydrogen bonds between the alkoxy and hydroxy groups of the adjacent aromatic rings. The 1,2-alternate molecules form a novel type of molecular channels held by $\pi-\pi$ interactions. However, dipropoxy derivative **3b** prefers the C_{2v} symmetrical pinched cone conformation in the solid state. Interestingly, the CH−π and $\pi-\pi$ interactions in the crystal of **3b** led to the formation of hexagonal hydrophobic channels that seem to be large enough to accommodate small atoms or molecules. The crystallographic study revealed also yet uncommon hydrogen bonding pattern in dimethoxy and dipropoxy derivatives **1′b** and **3′b** which adopt the distorted cone conformation.

Among the monosubstituted compounds, both methyl **1a** and propyl **3a** derivatives adopt a cone conformation in solution, which is stabilized by hydrogen bonds formed by three hydroxy groups. The tripropoxy thiacalix[4]arene **3c** adopts the partial cone conformation. The trimethyl derivative **1c** is conformationally flexible at room temperature, and it can also form the cone conformer. The two conformers interexchange by rotation of the methylated ring, which is opposite to the hydroxylated one, and which cannot be involved in hydrogen bonding.

Thus, partially O-alkylated thiacalix[4]arenes have been found to offer a great variety of well-defined structural templates applicable in supramolecular chemistry, and some applications may take advantage of the limited amount of their structural flexibility.

Experimental Section

Typical Procedure for the Preparation of Partially Alkylated Thiacalix[4]arenes. 25,27-Dimethoxy-*p-tert*-butylthiacalix[4]arene (1′b) Cone and 1,2-Alternate: The mixture of *p-tert*-butylthiacalix[4]arene (500 mg, 0.69 mmol), potassium carbonate (95 mg, 0.693 mmol), and methyl iodide (1970 mg, 13.8 mmol) was stirred under reflux in 30 mL of acetone for 5 days. The acetone was removed under reduced pressure, and the residue was treated with diluted hydrochloric acid and extracted with chloroform. The organic layer was washed with water, dried over $MgSO_4$, and evaporated to yield crude product. The precipitation from a $CHCl_3$/methanol mixture gave pure derivative **1b′** (80%) as white crystals: mp 239−242 °C; IR ($CHCl_3$) ν_{max} (cm^{-1}) 3391 (OH); 2966 (Bu^t). Anal. Calcd for $C_{42}H_{52}O_4S_4$: C, 67.34; H, 7.00; S, 17.12. Found: C, 67.51; H, 6.98; S, 16.98.

1′b(cone): ^{1}H NMR (500.1 MHz, $CDCl_3$, 203 K) δ 0.78 and 1.27 (36 H, s, *t*-Bu A and B), 4.15 (6H, s, CH_3), 7.01 (4H, s, 3,5-H arom. B), 7.64 (4H, s, 3,5-H arom. A), 8.15 (2H, s, OH); ^{13}C NMR (125.8 MHz) δ 30.47 (*t*-Bu), 31.27 (*t*-Bu), 33.95 ($C(CH_3)_3$), 34.12 ($C(CH_3)_3$), 64.57 (CH_3), 120.77 (2,6-C arom. A), 127.80 (2, 6-C arom. B), 133.12 (3,5-C arom. B), 134.37 (3,5-C arom. A), 147.82 (4-C arom.), 147.95 (4-C arom.), 155.29 (1-C arom.), 156.73 (1-C arom.).

1′b(1,2-alternate): ^{1}H NMR (500.1 MHz, $CDCl_3$, 203 K) δ 1.24 and 1.29 (36 H, s, *t*-Bu A and B), 3.44 (6H, s, CH_3), 7.46 (4H, s, 3,5-H arom. A), 7.54 (4H, s, 3,5-H arom. B), 7.87 (2H, s, OH); ^{13}C NMR (125.8 MHz) δ 30.95 (*t*-Bu), 31.13 (*t*-Bu), 34.03 ($C(CH_3)_3$), 34.56 ($C(CH_3)_3$), 60.25 (CH_3), 118.25 (2,6-C arom. A), 127.28 (2,6-C arom. B), 130.22 (3,5-C arom. A), 130.99 (3,5-C arom. B), 142.21 (2 × 4-C arom.), 154.99 (1-C arom.), 155.15 (1-C arom.).

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Supporting Information Available: ^{1}H NMR spectrum of **1c** at 298 and 203 K, crystal packing of **1b**, **2b**, **3b(1,2-alt)**, **1′b**, **2′b**, and **3′b**, kinetic and distance measurements, Table S1 displaying all ring declination angles ϕ of aromatic rings determined by DFT calculations and X-ray crystallography, Table S2 displaying the differences between calculated heats of formation of conformers present in equilibrium mixtures, X-ray crystallographic data for **1′b**, **2b**, **2′b**, **3b**, **3′b**, and **3c**, experimental details of DFT calculations, experimental procedures, full characterization, ^{1}H and ^{13}C NMR spectra of all new compounds, and CIF files for the X-ray structural analysis of corresponding compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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