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# Uncommon Regioselectivity in the Thiacalix[4]arene Series: Gross Formylation of the *Cone* Conformer

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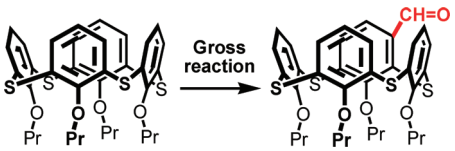


Thiacalix[4]arene immobilized in the *cone* conformation undergoes a direct Gross formylation reaction ($Cl_2CH$-O-$CH_3$/$SnCl_4$/$CH_2Cl_2$) to give the upper-rim formylated thiacalixarene. Albeit using excess of the formylation agent and various reaction temperatures, only one formyl group is introduced into the meta position of the thiacalixarene skeleton. The surprising regioselectivity indicates dramatically different reactivity of the thiacalix[4]arene system when compared with a classical calix[4]arene analogue, which yields exclusively para isomers. The introduction of functional groups into the meta position represents an exceptional substitution pattern in thiacalixarene chemistry, which imparts an interesting conformational behavior to these compounds. The systematic NMR study revealed that the *pinched cone*−*pinched cone* equilibrium is remarkably shifted toward one *pinched cone* structure depending on the substitution.

## Introduction

Thiacalix[4]arene emerged[1] as a new member of the calixarene[2] family in 1997, and since then has received considerable attention from the supramolecular community. The introduction of heteroatoms (sulfur) instead of common $-CH_2-$ bridges makes thiacalix[4]arenes very attractive molecules[3] with many uncommon properties as compared to the chemistry of "classical" calixarenes. Thus, the combination of a bigger cavity with the presence of heteroatoms results in considerably different conformational behavior/preferences.[4] Thiacalix[4]arenes exhibit significantly enhanced complexation abilities toward transition metals[5] (because of additional metal coordination by sulfur atoms), while the regio-/stereoselective oxidation of sulfur bridges (to sulfoxides or sulfones) represent novel types of chemistry unseen in classical calixarenes.[6]

Despite many interesting properties, the application of thiacalix[4]arenes as building blocks or molecular scaffolds in supramolecular chemistry, so typical for common calixarenes, is still rather restricted. The main reason for this is that the chemistry of these compounds is not well-understood, as

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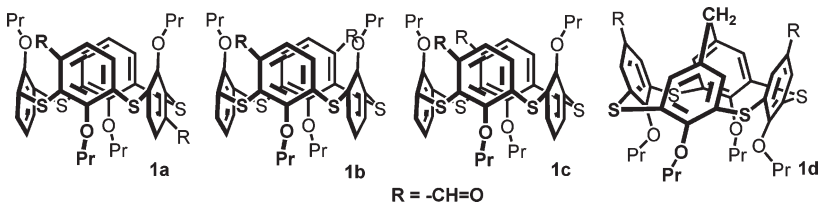


**FIGURE 1.** Selected derivatives obtained by the formylation of tetrapropoxy-substituted thiacalix[4]arene in the *1,3-alternate* (**1a**−**c**) and the *cone* (**1d**) conformation (Duff reaction).

documented by the lack of general derivatization methods which would enable regioselective and/or stereoselective substitution of the basic thiacalix[4]arene skeleton.[3] Hence, a deeper understanding of their chemical behavior could help us with the dissemination of thiacalixarenes in supramolecular chemistry applications.

The modification of the upper rim of thiacalixarenes would lead to novel derivatives enabling their further utilization in the design of more sophisticated molecules. While in classical calixarenes many functional groups can be introduced into the para position (relative to phenolic oxygen) by direct electrophilic substitution, only a few reactions have been employed in the thiacalixarene series so far. Direct substitutions (nitration, bromination, diazo-coupling) of lower rim unsubstituted[7] or partly substituted[8] thiacalix[4]arenes have been published. An obvious disadvantage of this approach is the necessity of a subsequent shaping of the molecule (alkylation/acylation on the lower rim) to ensure its immobilization in a specific conformation. Unfortunately, these reactions frequently lead to unexpected or unwanted conformers.[8a] This problem could be solved simply by the electrophilic substitution of conformationally immobilized thiacalix[4]arenes. This is the most common way for the derivatization of classical calixarenes, and until very recently, there was only one short communication[9] dealing with the electrophilic substitution of tetraalkylated thiacalixarenes.

As we have shown in our previous paper,[10] the formylation of thiacalix[4]arenes in a *1,3-alternate* conformation led unexpectedly to the meta-substituted dialdehydes **1a**−**c**, which illustrates a dramatically different regioselectivity in the thiacalixarene series. In contrast, the same reaction (Duff conditions: urothropin/$CF_3COOH$)[11] carried out with the *cone* conformation yielded the unusual intramolecularly methylene-bridged derivatives, such as compound **1d** (see Figure 1). This indicates that the conformation of starting thiacalix[4]arene plays a crucial role in the chemo-/regioselectivity of the formylation process—the phenomenon not observed in the chemistry of classical calixarenes. In this paper we report on the formylation of the *cone* thiacalix[4]arene under the Gross conditions ($Cl_2CH$-O-$CH_3$/$SnCl_4$/$CH_2Cl_2$). This reaction leads exclusively to the meta-substituted monoformyl derivative that can be used as an inherently chiral building block for the design of more elaborated structures.

## Results and Discussion

**Synthesis.** It is known[12] that tetrapropoxythiacalix[4]arene **4** immobilized in the *cone* conformation is not accessible via direct peralkylation of starting thiacalix[4]arene **2**. Instead, the two-step dialkylation/dialkylation procedure can be used.[13] Utilizing this, compound **2** was alkylated with propyl iodide under phase-transfer-catalysis conditions ($NaOH/H_2O$−toluene/TBAB) to give dipropoxy derivative **3** in 48% yield. Subsequent alkylation with PrI/NaH/DMF system[13] led to the mixture of *cone* and *partial cone* conformers from which derivative **4** was isolated by column chromatography in 68% yield.

Gross formylation ($Cl_2CH$-O-$CH_3$ + $SnCl_4$) is well-known from the chemistry of classical calixarenes where it is frequently used for the regioselective upper rim formylation (*para* position) of starting tetraalkyl-substituted calix[4]arenes.[14] As the Duff conditions did not lead to the expected formyl substituted derivatives and yielded rather unexpected products,[11] we decided to apply the Gross conditions to the thiacalix[4]arene *cone* series to achieve the upper-rim formylation. Reaction of the starting thiacalixarene **4** with an excess of dichloromethyl methyl ether (36 equiv) was carried out in DCM at room temperature with use of $SnCl_4$ as a catalyst. We found this reaction to be highly regioselective, as only a single product was isolated by simple column chromatography on silica gel. The electrospray TOF

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**TABLE 1. Gross Formylation of 4 (36 equiv of $CHCl_2$-O-$CH_3$, $SnCl_4$, DCM)**

| run | reaction temp, °C | reaction time, h | yield of derivative **5**[a] |
|---|---|---|---|
| 1 | reflux | 0.5 | 60 |
| 2 | 20 | 0.5 | 60 |
| 3 | 0 | 0.5 | 66 |
| 4 | 0 | 1 | 57 |
| 5 | 0 | 7 | 49 |
| 6 | −78 | 7 | 18[b] |

[a] Isolated yields in %. [b] Starting compound isolated in 50% yield.

MS revealed the signals at *m*/*z* 693.24, 715.19, and 731.18 corresponding to the protonated molecular peak of monoformylated product $[M + H]^+$, together with the analogous species bearing sodium $[M + Na]^+$ or potassium $[M + K]^+$ cations. Interestingly, the same monoformylated product **5** was isolated irrespective of the reaction conditions. As can be seen from Table 1, the monoaldehyde **5** was also formed at reflux, which is in contrast to the formylation of the *1,3-alternate* conformer, where the chloromethyl derivative was obtained under otherwise identical conditions. Although the *1,3-alternate* conformer gave smoothly corresponding dialdehydes **1a**−**c**,[11] the *cone* conformer **4** did not yield more substituted derivatives. In all cases, the formylation of **4** always leads to the isolation of monoformyl-substituted compound **5** while the formation of dialdehydes was not observed (Table 1).

The structural assignment of compound **5** is not a trivial task as this compound exhibits very broad averaged signals at ambient temperature (see Figure 1 in the SI). This behavior of the *cone* conformers of tetraalkylated thiacalix[4]arenes is known[4b,15] as a consequence of an additional dynamic process ascribed to the *pinched cone*−*pinched cone* interconversion (Scheme 2). Therefore, compound **5** was studied at lower temperatures (208−253 K) where all resonances in $^1H$ and $^{13}C$ spectra were sufficiently narrow so that all necessary experiments for resonance assignment ($^1H-^1H$ COSY, $^1H-^{13}C$ HMQC) and NOE experiments for conformation analysis could be performed.

The $^1H$ NMR spectrum of derivative **5** acquired at 253 K exhibited a typical feature of the *pinched cone*−*pinched cone* equilibrium: the number of resonances was doubled (see Figure 2 in the SI). This phenomenon is obvious in the aromatic part of the spectrum (6.0−7.8 ppm), and in particular, in the aldehydic proton region where two different resonances for the formyl group can be found at 10.07 and 10.65 ppm. Surprisingly, $^1H$ NMR analysis of the aromatic system bearing the formyl group showed the absence of singlets characteristic for the para-substituted systems. On the other hand, two doublets with a coupling constant of 8.2 Hz determined unambiguously the introduction of the formyl group into the meta position (relative to phenolic oxygen). The remaining unsubstituted aromatic rings exhibited the expected spectral pattern consisting of two doublets and one doublet of doublets (pseudotriplets) (see Figure 2 in SI).

The unusual meta regioselectivity in thiacalixarene formylation opens new perspectives in supramolecular chemistry as this unique substitution pattern is so far rare[16] in classical calixarenes. Direct introduction of the formyl group into the meta position of the *cone* conformer leads to inherently chiral thiacalixarenes which could be used as valuable building blocks or chiral molecular scaffolds. To show the usefulness of this synthetic approach we have carried out several simple transformations of the formyl group (see Scheme 1). Thus, compound **5** was quantitatively reduced to the hydroxymethyl derivative **6** with use of $NaBH_4$ or it was transformed into the methyl-substituted thiacalixarene **7** (89% yield) by the $Et_3SiH$/TFA system. Finally, compound **5** was transformed into the cyano derivative **8** in 70% yield via the formation of oxime and subsequent dehydration with $Ac_2O$. All these reactions confirmed normal reactivity of *m*-formyl group.

The phenomenon of the *pinched cone*−*pinched cone* interconversion (Scheme 2) has been studied so far only on symmetrical compounds. As a result, the 1:1 ratio of the corresponding pinched conformers was always observed. On the other hand, the dynamic NMR study of novel meta-substituted compounds **5**−**8** revealed that this equilibrium is shifted toward one of the nonsymmetrical *pinched cone* conformations. To determine the structure of the prevailing *pinched cone* of derivative **5**, characteristic chemical shifts in the aromatic region and NOE experiments were used (see Figure 3 in the SI). The significant upfield shift of the signals belonging to the ring bearing formyl group **A** and the opposite ring **C** indicates that rings **A** and **C** face each other in the cavity. On the other hand, the remaining rings **B1** and **B2** are oriented outside the cavity. This was documented also by distinct NOE contact between the protons in the para positions of rings **A** and **C** (see Figure 3c in the SI). The above preferred conformation was further supported by NOE connectivities between protons **C**-5−**B1**-3 and **A**-5−**B2**-5 (see Figure 3a,b in the SI). A very similar spectral pattern as well as the key NOE contacts of the major conformer were observed for the meta-substituted cyano derivative **8** at 208 K. This indicates that ring **A** (bearing the cyano group) and the opposite ring **C** are facing each other in the cavity analogously to compound **5**.

The major conformer of the meta-substituted hydroxymethyl and methyl derivatives **6** and **7**, respectively, exhibited a completely different spectral pattern in the aromatic region as compared with those of compounds **5** and **8**. Accordingly, the protons of the rings **B1** and **B2** are shifted to lower chemical shift values, which indicates parallel vertical arrangements of these rings. Unfortunately, the NOE contacts of protons in the para positions of rings **B1** and **B2** could not be observed due to their overlaps.

In our opinion, it is rather unexpected that the introduction of a functional group into the meta position of the thiacalix[4]arene cavity causes the different conformational preferences depending on the nature of the substituent. The formyl and cyano groups in compounds **5** or **8**, respectively, shifted the equilibrium toward the *pinched cone* conformation with the meta substituents at the vertical rings. Conversely, the hydroxymethyl and methyl groups in the case of compounds **6** and **7**, respectively, led to the prevailing conformers having the meta substituents at the rings facing out of the cavity. This indicates that the phenomenon is not

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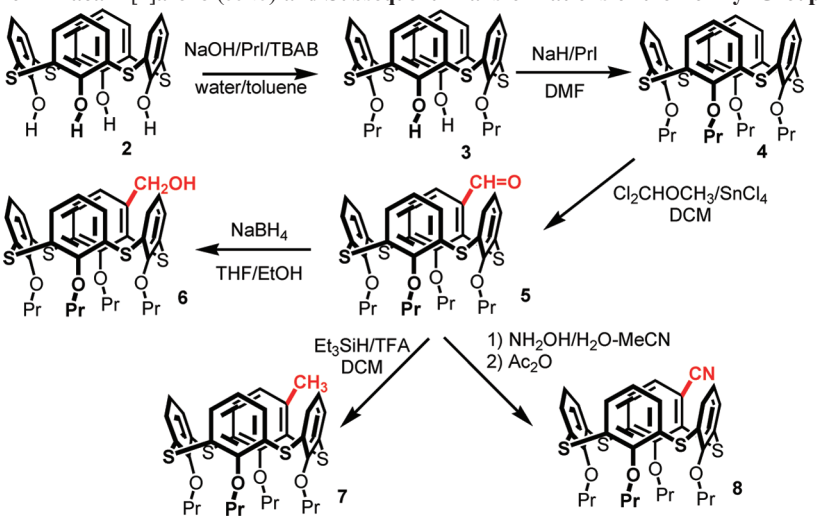
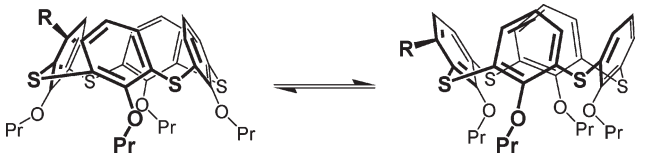
**SCHEME 1. Formylation of Thiacalix[4]arene (*cone*) and Subsequent Transformations of the Formyl Group**




**SCHEME 2. *Pinched Cone*−*Pinched Cone* Interconversion in Meta-Substituted Thiacalixarenes**



caused entirely by the steric hindrance of meta substituents, but rather that electronic effects play an important role here (compare electron withdrawing substituents in **5** and **8** with electron donating hydroxymethyl and methyl groups in **6** and **7**, respectively).

The identification of the minor conformers and their exact amount were problematic due to massive overlaps in $^1$H NMR spectra. Fortunately, well-separated resonances for the formyl hydrogens in derivative **5** (Figure 2, in the SI) enabled us to estimate the ratio of the two conformers (4:1). Similarly, the coalescence temperature of these two signals ($T_c \approx 320$ K) was used for the calculation of the activation free energy $\Delta G^*$ of this conformational equilibrium (56 kJ/mol).

To gain a deeper insight into the *pinched cone*−*pinched cone* equilibrium we have also studied this phenomenon in the solid state. While we failed to grow suitable monocrystals of aldehyde **5**, the corresponding crystals of its 2,4-dinitrophenylhydrazone derivative **5a** were obtained by slow evaporation of THF−DCM solution. The X-ray crystallography proved that thiacalix[4]arene **5a** adopts a *pinched cone* conformation with the meta substituent on the vertical rings, which is in line with our solution experiments (see Figure 28 in the SI). In this conformation, two opposite unsubstituted phenolic units are pointing outside with an interplanar angle of approximately 124°. The remaining aromatic units (including the meta-substituted ring) are tilted toward each other inside the cavity with an interplanar angle of 56°. The presence of meta substituents leads to the distortion of the basic thiacalix[4]arene skeleton. This is indicated by the nonplanar arrangement of the four sulfur bridges where the sulfur atom next to the hydrazone substituent is 0.84 Å above the plane defined by the remaining three sulfurs.

In conclusion, contrary to the classical calixarenes the Gross formylation of thiacalix[4]arene immobilized in the *cone* conformation leads selectively to the mono meta-substituted aldehyde. This unique regioselectivity opens a pathway to the inherently chiral meta-substituted thiacalixarenes, hitherto inaccessible by other methods. The systematic NMR study revealed that the *pinched cone*−*pinched cone* equilibrium of these derivatives is markedly influenced by the nature of the substituent in the meta position.

## Experimental Section

**4-Formyl-25,26,27,28-tetrapropoxythiacalix[4]arene (*cone*) 5.** Thiacalix[4]arene **4** (200 mg, 0.30 mmol) was dissolved in dry dichloromethane (20 mL). The solution was cooled to 0 °C, and the 1,1-dichloromethyl methyl ether (0.98 mL, 10.8 mmol) and tin(IV) chloride (1.27 mL, 10.8 mmol) were added under a nitrogen atmosphere. The reaction mixture was stirred for 30 min at 0 °C, then quenched by aqueous 1 M HCl. The crude reaction mixture was extracted with dichloromethane, then the organic phase was washed with water, dried over $MgSO_4$, and evaporated to dryness. Crude product was purified by column chromatography on silica gel (hexane/dichloromethane 3:2) to yield 122 mg (59%) of the title compound as a yellow solid, mp 199−203 °C (ethyl acetate). IR (KBr) $\nu$ (cm$^{-1}$) 1689 (CHO). Major conformer: $^1$H NMR ($CD_2Cl_2$, 500 MHz, 253 K) $\delta$ 10.07 (s, 1H, CH=O), 7.72 (d, 1H, $J$ = 7.6 Hz, H−$B_2$-3), 7.63 (d, 1H, $J$ = 7.6 Hz, H−$B_2$-5), 7.58 (d, 1H, $J$ = 7.8 Hz, H−$B_1$-5), 7.49 (d, 1H, $J$ = 7.8 Hz, H−$B_1$-3), 7.08 (t, 1H, $J$ = 7.6 Hz, H−$B_2$-4), 6.99 (t, 1H, $J$ = 7.8 Hz, H−$B_1$-4), 6.88 (d, $J$ = 8.2 Hz, H−A-4), 6.46 (d, 1H, $J$ = 6.8 Hz, H−C-3), 6.41 (t, 1H, $J$ = 6.8 Hz, H−C-4), 6.16 (d, 1H, $J$ = 8.2 Hz, H−A-5), 6.10 (d, 1H, $J$ = 6.8 Hz, H−C-5), 4.15 − 4.35 (m, 4H, $OCH_2$), 3.67−3.83 (m, 4H, $OCH_2$), 1.65−1.95 (m, 8H, $OCH_2CH_2CH_3$), 1.05−1.15 (m, 6H, $OCH_2CH_2CH_3$), 0.75−0.90 (m, 6H, $OCH_2CH_2CH_3$). $^{13}$C NMR ($CD_2Cl_2$, 125 MHz, 253 K) $\delta$ 190.5 (1C, CH=O), 161.8, 160.09, 157.6, 157.5 (4C, C-1), 137.6, 137.1, 136.0, 134.2, 132.5, 130.5, 130.4, 125.3, 124.7, 122.93, 122.90 (11C, CH-3, CH-5), 140.6, 134.1, 133.6, 132.6, 131.5, 130.9, 130.6 (9C, C-2, C-6, C-A-3, 2 resonances are overlapped), 78.5, 78.3, 76.9, 75.1 (4C, $OCH_2$), 23.50, 23.47, 23.0, 22.6 (4C, $OCH_2CH_2CH_3$), 10.7 (4C, $OCH_2CH_2CH_3$). Minor conformer: $^1$H NMR ($CD_2Cl_2$, 500 MHz, 253 K) $\delta$ 10.64 (s, 1H, CH=O), 6.23 (d, 1H, $B_2$-5), other resonances are overlapped by major conformer. $^{13}$C NMR (125 MHz, $CD_2Cl_2$, 253 K) $\delta$ 192.4 (1C, CH=O), 161.7,

161.4 (4C, C-1), 136.8, 136.7, 135.2, 132.2, 132.0, 131.8, 131.1, 124.9, 124.8, 122.5, 121.5 (11C, CH-3, CH-5, CH A-4), 139.9, 138.2, 136.9, 133.0, 132.9, 131.9, 131.6, 129.8 (9C, C-2, C-6, C-A-3, 1 resonance is overlapped), 78.41, 78.42, 76.6, 75.9 (4C, $OCH_2$), 23.2, 22.9 (4C, $OCH_2CH_2CH_3$, 2 resonances are overlapped), 10.0, 9.8 (4C, $OCH_2CH_2CH_3$, 2 resonances are overlapped). ESI+ TOF MS *m*/*z* calcd for ($C_{37}H_{40}O_5S_4$) 692.18, found 693.24 [$M^+$ + H], 715.19 [$M^+$ + Na]. Anal. Calcd for $C_{37}H_{40}O_5S_4$: C, 64.13; H, 5.82; S, 18.51. Found: C, 63.97; H, 5.72; S, 18.31.

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**Supporting Information Available:** Synthesis and characterization of all new compounds **5**−**8**, and the copies of $^1H$, $^{13}C$ NMR, $^1H-^1H$ COSY, $^1H-^{13}C$ HMQC spectra, IR spectra, and MS spectra. This material is available free of charge via the Internet at http://pubs.acs.org.