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Uncommon Regioselectivity in Thiacalix[4]arene Formylation

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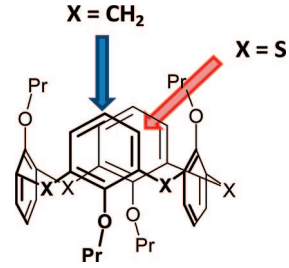
Received March 19, 2009



To reveal the alternative ways for upper-rim thiacalixarene derivatization, the formylation reactions (Gross and/or Duff conditions) of the corresponding tetrapropoxythiacalix[4]arene immobilized in the *1,3-alternate* conformation were systematically studied. Surprisingly, albeit using an excess of the formylation agent, only two formyl groups were introduced exclusively into the meta positions of thiacalixarene skeleton. Unexpected regioselectivity of these reactions opens the door for a unique substitution pattern in thiacalixarene chemistry. The formation of meta-substituted aldehydes is another illustration showing remarkably different reactivity of the thiacalix[4]arene system compared with that of a classical calyx[4]arene analogue.

Introduction

The chemistry of calix[*n*]arenes[1] represents one of the main supporting stones of modern supramolecular chemistry. In contrast to other frequently used macrocyclic compounds, such as crown ethers, cyclodextrines, porphyrins, and/or fullerenes, calixarenes possess a very attractive advantage—easy derivatization—which makes their role almost irreplaceable. Especially in the case of calix[4]arene there are many well-established methods leading to regioselective and/or stereoselective substitution of basic skeleton, thus offering almost unlimited possibility for the design of new receptors, ligands, self-assembled systems, etc. A deliberate substitution of either lower or upper rims results in massive applications of calix[4]arenes as molecular scaffolds and building blocks in the design and synthesis of more sophisticated molecules and supramolecular systems.[2]

Thiacalixarenes,[3] heterocyclic members of the calixarene family, have attracted considerable attention since their first appearance in 1997. The presence of four sulfur bridges imparts the molecules many novel properties if compared with classical calixarenes. Thus, thiacalix[4]arenes possess remarkably better complexation ability toward metal cations (because of S···metal interactions), unusual conformational preferences, or different dynamic behavior. Sulfur bridges can be regio-/stereoselectively oxidized to sulfone or sufoxide groups[4] bringing some novel structural features virtually impossible in classical calixarene chemistry. On the other hand, despite one decade of research, the chemistry of thiacalixarenes is still rather fragmentary and

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(1) For books on calixarenes, see: (a) Asfari, Z., Böhmer, V.; Harrowfield, J.; Vicens, J., Eds. *Calixarenes 2001*; Kluwer Academic Publishers: Dordrecht, The Netherlands, 2001. (b) Mandolini, L.; Ungaro, R. Eds.; *Calixarenes in Action*; Imperial College Press: London, UK, 2000. (c) Gutsche, C. D. *Calixarenes revisited: Monographs in Supramolecular Chemistry*; Stoddart, J. F., Ed.; The Royal Society of Chemistry: Cambridge, UK, 1998; Vol. 6.

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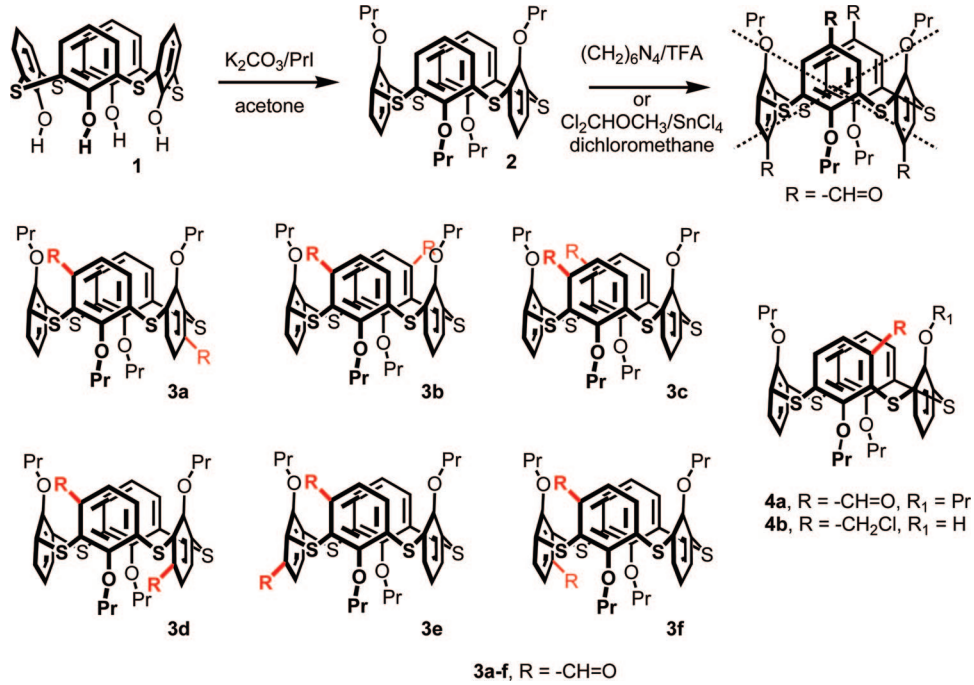
10.1021/jo9005574 CCC: $40.75
Published on Web 05/28/2009

SCHEME 1. Formylation of Thiacalix[4]arene



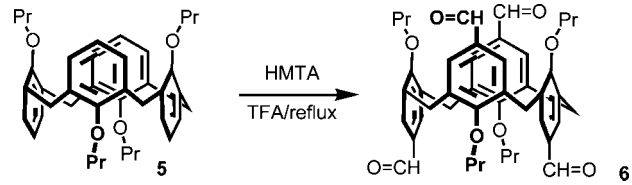
underdeveloped. Although many potential applications can be envisaged, the lack of suitable derivatization methods considerably hampers the utilization of thiacalixarenes in supramolecular chemistry. Hence, the deeper understanding of their chemical behavior could make these compounds very useful building blocks for the design of novel receptors.

Electrophilic aromatic substitution represents a straightforward way to the upper-rim derivatization of calix[4]arenes. Starting from preorganized conformation (usually tetraalkylated compounds) various functional groups (Br, NO_2, SO_3H, C(=O)R, CH=O, etc.) can be introduced directly into the para position of calixarene skeleton. While these reactions are well-known and frequently used in classical calixarene chemistry,[1] surprisingly, there is only one short communication[5] dealing with the electrophilic substitution of tetraalkylated thiacalix[4]arenes that describes the unexpected formation of meta-substituted trialkylated product **4b**. As formyl-substituted calix[4]arenes were proven as very useful intermediates in the synthesis of more complex calixarene-based structures, the direct formylation of upper rim was chosen as the model reaction for electrophilic substitution of thiacalix[4]arenes.

Results and Discussion

Synthesis. Starting thiacalix[4]arene **1** was alkylated according to a published procedure[6] with propyl iodide in the presence of K_2CO_3 in refluxing acetone. Under these conditions, the corresponding tetrapropoxy derivative **2** immobilized[7] in the *1,3-alternate* conformation was obtained in 71% yield. The formylation of this compound was carried out by using several different formylation procedures: (i) Vilsmeier−Haack reaction (DMF + $POCl_3$), (ii) Duff reaction (hexamethylenetetramine (HMTA) + trifluoroacetic acid (TFA)), and (iii) Gross reaction (Cl_2CHOCH_3 + $SnCl_4$).

SCHEME 2. Formylation of Classical Calix[4]arene



Vilsmeer−Haack[8] reaction of compound **2** (Scheme 1) was carried out under several reaction conditions. After the formation of active formylation agent (DMF + $POCl_3$), the reaction was carried out either at ambient (20 °C) or at elevated (70 °C) temperatures. Unfortunately, in both cases only unreacted starting thiacalixarene **2** remained after the workup. For comparison, the same reaction conditions were applied to classical calix[4]arene analogue **5**, again unsuccessfully.

Duff reaction is well-known from classical calixarene chemistry where it serves for the synthesis of para-substituted formyl calix[4]arenes.[9] Thus, tetrapropoxy compound **5** was smoothly transformed into the corresponding tetraformyl derivative **6** in 76% yield (Scheme 2).[10]

The same reaction conditions (overnight reflux of reactants), when applied to thiacalixarene **2**, led to rather complicated reaction mixtures. Surprisingly, the ^1H NMR analysis showed the absence of any singlets (characteristic for para-substituted derivatives) in the aromatic part of the spectra. On the other

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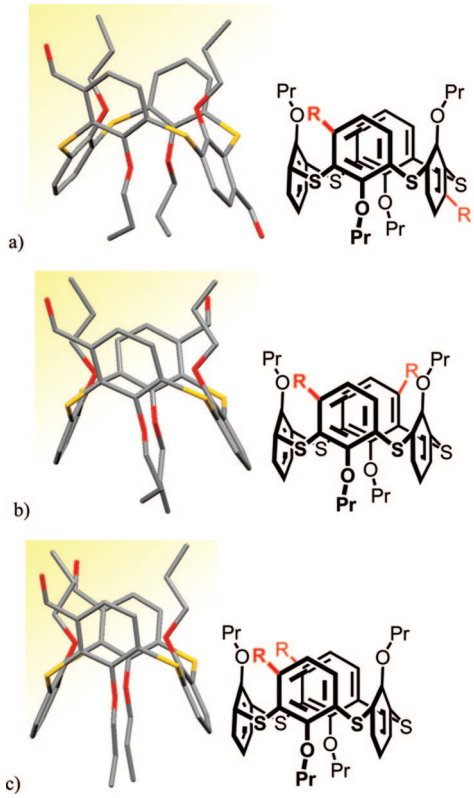

FIGURE 1. X-ray structures of compounds **3a**, **3b**, and **3c**. Hydrogen atoms were omitted for better clarity.

hand, the pair of doublets around 7.5 ppm with interaction constant $J = 8.2$ Hz (typical value for aromatic ortho interactions) indicated possible meta-substitution of thiacalixarene skeleton. The relative integral intensities of aromatic protons area and formyl groups (singlet at 10.7 ppm) indicated that only two formyls have entered the upper rim of thiacalixarene.

While column chromatography on silica gel did not lead to the isolation of pure products, using alumina (PE:DCM = 3:2) led finally to the successful separation of three regioisomers **3a**, **3b**, and **3c** in 11%, 13%, and 15% yields, respectively. Electrospray MS revealed in all cases the same signal *m/z* 743 corresponding to the molecular peak of diformylated product with Na^+ cation [M + Na^+].

Theoretically, up to six different disubstituted regioisomers **3a**−**f** could be formed. Unfortunately, the assignment of ^{1}H NMR spectra of the isolated products was impossible as all spectra were almost identical having the same splitting pattern and/or chemical shifts (see Figure 1 in the SI). Hence, the final unambiguous structural evidence was obtained by using X-ray crystallography, which proved thiacalix[4]arene in a *1,3-alternate* conformation bearing two formyl groups on the opposite sites (compound **3a**) or at the same site (compounds **3b** and **3c**) of the skeleton (Figure 1).

Interestingly, the variation of reaction conditions (excess of HMTA up to 36 equiv, longer reaction time) led virtually to the same reaction mixtures (disubstituted products) from which no tri- or tetrasubstituted derivatives could be isolated. Hence, contrary to classical calixarenes, Duff reaction is suitable for partial substitution (diformylation) of thiacalix[4]arene, where formyl groups are located exclusively in the meta-positions. This kind of substitution pattern has no precedence in calixarene

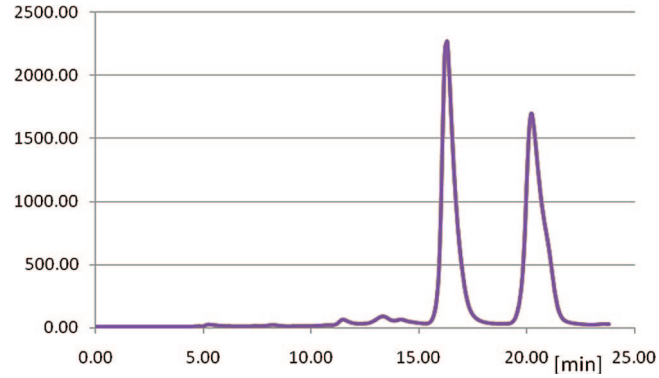

FIGURE 2. HPLC chromatogram of **3b** on (*R*,*R*)-Wheelk-O1 column (conditions: 0.5 mL/min CH_2Cl_2:heptane 1:4 v/v mixture, isocratic).

literature[11] opening thus new perspectives in thiacalixarene chemistry. For instance, simple meta-formylation of thiacalixarene gives us an opportunity for direct one-step synthesis of inherently chiral derivatives, as documented by compounds **3a** and **3b** with many potential applications in the design and synthesis of chiral receptors. The inherent chirality of novel thiacalixarene derivatives was demonstrated by using HPLC chromatography on a chiral column. As shown in Figure 2, compound **3b** gave an impressive baseline separation of enantiomers on the (*R*,*R*)-Wheelk-O1 column (Merck) with retention times of 16.3 and 20.2 min for the corresponding enantiomers.

Gross reaction is a well-established procedure in classical calixarene chemistry where it served for the upper-rim formylation.[12] Contrary to previous Duff reaction, this procedure was also successfully used for regioselective formylation of starting tetraalkyl-substituted calix[4]arenes.[13] In this context, we decided to apply the Gross reaction conditions in the thiacalix[4]arene series with the aim to enhance the regioselectivity of the upper-rim formylation.

Reaction of thiacalixarene **2** with an excess of dichloromethyl methyl ether (36 equivalents) was carried out in DCM with $SnCl_4$ as a catalyst. As we found, the Gross formylation of thiacalixarenes is highly regioselective and several different products can be isolated depending on the reaction conditions. Simple preliminary screening of reactivity indicated that product distribution is strictly dependent on the reaction temperature used—see Table 1.

Small-scale reaction carried out at −78 °C (run 7) led almost exclusively to diformylated isomer **3c** after long reaction time (24 h). Interestingly, besides the small amount of unreacted starting compound **2** no other possible regioisomers **3a**,**b**,**d**−**f** were detected in the crude reaction mixture (NMR analysis).

(11) Meta-substitution of calix[4]arenes was observed only in case where strong electron-donating substituent is present in the para-position. See e.g.: (a) Xu, Z.-X.; Zhang, C.; Zheng, Q.-Y.; Chen, C.-F.; Huang, Z.-T. *Org. Lett.* **2007**, *9*, 4447–4450. (b) Mascal, M.; Naven, R. T.; Warmuth, R. *Tetrahedron Lett.* **1995**, *36*, 9361–9363. (c) Verboom, W.; Bodewes, P. J.; van Essen, G.; Timmerman, P.; van Hummel, G. J.; Harkema, S.; Reinhoudt, D. N. *Tetrahedron* **1995**, *51*, 499–512.

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TABLE 1. Gross Formylation of 2 (36 equiv of $CHCl_2$-O-CH_3, $SnCl_4$, DCM)

run	reaction temp	reaction time	**2**	**3c**	4a[a]	4b[a]
1	reflux	30 min	0	0	0	100
2	20 °C	30 min	0	0	10	90
3	0 °C	30 min	0	0	50	50
4	0 °C	10 min	10	0	90	0
5	−78 °C	30 min	90	0	10	0
6	−78 °C	8 h	60[b]	30[b]	10[b]	0
7	−78 °C	24 h	10	90	0	0

[a] Relative ratios measured by the integration of the corresponding signals in ^{1}H NMR (300 MHz, $CDCl_3$, 298 K). [b] Substantial overlapping of signals.

The same reaction carried out at 0 °C gave after 10 min stirring (run 4) only one product—monoformylated derivative **4a** (again with ca. 10% of unreacted **2**). Longer reaction time (30 min at 0 °C, run 3) yielded an equimolar mixture of monoformyl **4a** and monochloromethyl derivative **4b**. The formation of this unexpected product was already reported by French authors,[5] who isolated **4b** in 68% yield using Gross reaction conditions ($CHCl_3$, 40 °C, $TiCl_4$). The comparison of runs 1−3 (Table 1) clearly shows that the relative proportion of **4b** in the crude reaction mixture increased with increasing temperature reaching finally 100% abundance at DCM reflux. This indicates that monoformyl derivative **4a** is the kinetic product that is subsequently transformed into chloromethyl derivative **4b** under thermodynamic control of the reaction. The corresponding mechanism for removing one propyl group during this transformation (**4a** → **4b**) remains currently unclear. It should be stressed again that under any experimental conditions used throughout our study we never observed the formation of any para-formylated products.

On the basis of these preliminary results, the same reactions were carried out on a bigger scale to show synthetic usefulness of Gross formylation in the thiacalixarene series. Consequently, monoformyl derivative **4a** was obtained in 71% yield after the reaction mixture was stirred at 0 °C. Simple change of the reaction temperature (−78 °C) then led to the isolation of diformyl isomer **3c** in 56% (yields after column chromatography on silica gel). While diformyl product **3c** is an achiral molecule, monoformyl thiacalixarene **4a** represents an inherently chiral building block with many potential applications in the synthesis of more elaborated supramolecular systems based on thiacalix[4]arenes.

The surprising regioselectivity of formylation led us to the attempt at a quantum-chemical prediction of electrophilic substitution in thiacalix[4]arene *1,3-alternate* series. Generally, the common approach is based on the assumption (Hammond postulate) that the free energies of the transition state (TS) and the corresponding intermediate (sigma complex) are close to each other, as the geometry of both structures is very similar. Because of the extensiveness and complexity of a given thiacalix[4]arene system, initially, the simplest possible species (H^+ proton) was selected as the electrophilic agent in aromatic substitution. Several quantum-chemical models[14] have been tested by using this simplification: A (AM1), B (PM6), C (HF/6-31G**//HF/6-31G**), D (B3LYP/6-311+G(d, p)//HF/6-31G**), and E (MP2/6-31G**//HF/6-31G**). As is obvious from Table 2 (Supporting Information), while the application of semiempirical methods or HF/6-31G** basis set (A, B) gave chaotic results, the satisfactory predictions in agreement with our experimental observations (*m*-H-substitution) were obtained by the last three models C−E. These calculations indicated that depending on the method used the meta substitution is preferred over the corresponding para position by 5.3−10.1 kcal·mol^{-1}.

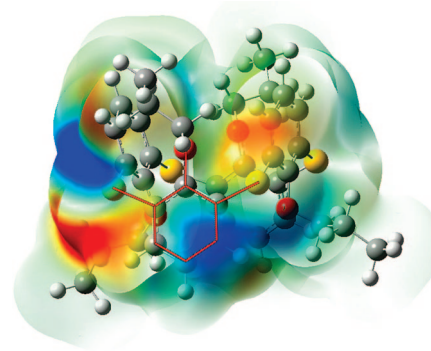

FIGURE 3. HOMO orbital of tetrapropoxythiacalix[4]arene **2**. The place of electrophilic attack (meta position) on the front aromatic ring (highlighted in red for better clarity) is shown in blue (the second blue area in the left part corresponds to the free nonbonding electrons at one of the sulfur atoms).

Besides the simplest model of electrophilic species (H^+), the quantum-chemical prediction of regioselectivity was also carried out by using the CH_3-O-$(CHCl)^+$ cation, which is the proposed electrophile in a Gross reaction. Again, the simpler models AM1 and PM6[15] gave only ambiguous results. Even the implicit evolvement of the solvent effect (CH_2Cl_2) at the PCM-HF/6-31G** level did not give better results. The application of the HF/6-31G**//HF/6-31G** model led to the false prediction where meta attacks (both inside and outside the thiacalixarene cavity) of electrophile are disfavored if compared with the para substitution (13.1 kcal·mol^{-1} for endoattack, 14.5 kcal·mol^{-1} for exoattack). On the other hand, the calculations with the DFT method B3LYP/6-311+G(d, p)//HF/6-31G** (method D) gave again the results in agreement with experiments. As these calculations were extremely time-consuming a similar prediction for CH_3-O-$(CHCl)^+$ cation was not done with the method E. Figure 3 shows the visualization of the HOMO orbital of tetrapropoxy derivative **2** demonstrating the highest electron density in the meta position of the basic skeleton.

Conclusion

The formation of meta-substituted derivatives can serve as a nice illustration of remarkably different reactivity of thiacalix[4]arenes if compared with classical calix[4]arene analogues. The unexpected meta regioselectivity opens the door for so far inaccessible substitution patterns in calixarene chemistry al-

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lowing the design and synthesis of novel building blocks and receptors with many potential applications in supramolecular chemistry.

Experimental Section

Duff Reaction: General Procedure for Synthesis of Derivatives 3a, 3b, and 3c. Thiacalixarene **2** (300 mg, 0.451 mmol) and hexamethylenetetramine (2.27 g, 16.2 mmol) were dissolved in TFA (30 mL) and the solution was refluxed under a nitrogen atmosphere overnight. After cooling to room temperature water (30 mL) was added and the reaction mixture was stirred for 1 h. A mixture was then extracted with dichloromethane (3 × 30 mL) and the organic layer was washed with water (3 × 30 mL), dried over $MgSO_4$, and evaporated on vacuum evaporator to dryness to yield a mixture of isomers **3a**, **3b**, and **3c**. The corresponding products were obtained by column chromatography on alumina with petroleum ether: dichloromethane mixture (3:2) as an eluent.

4,12-Diformyl-25,26,27,28-tetrapropoxythiacalix[4]arene (1,3-alternate) (3a): yield 11%; mp 221−222 °C; IR (KBr) 1683 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, 25 °C) δ 10.73 (s, 2H), 7.57 (d, ^3J = 8.2 Hz, 2H), 7.45−7.36 (m, 6H), 6.88 (t, ^3J = 7.6 Hz, 2H), 3.98−3.83 (m, 6H), 3.67−3.61 (m, 2H), 1.13−0.83 (br m, 8H), 0.66−0.58 ppm (m, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C) δ 190.9, 160.5, 159.2, 136.0, 135.1, 133.2, 132.6, 131.8, 130.7, 128.8, 128.3, 123.5, 123.4, 71.5, 70.8, 29.6, 22.9, 22.3, 10.0, 9.9 ppm; ESI-MS *m/z* calcd for ($C_{38}H_{40}O_6S_4$) 720.171, found 743.143 [M + Na^+]. Anal. Calcd for $C_{38}H_{40}O_6S_4$: C, 63.30; H, 5.59; S, 17.79. Found: C, 63.36; H, 6.13; S, 17.52.

Acknowledgment. This research was partly supported by the Czech Science Foundation (grants 104/07/1242 and 203/09/0691) and by the Research Centre LC06070 of the Ministry of Education, Youth and Sports of the Czech Republic.

Supporting Information Available: Synthesis and characterization of all new compounds **3a**−**c** and **4a**; the copies of ^1H and ^{13}C NMR spectra, IR spectra, and MS spectra; X-ray structures of compounds **3a**, **3b**, and **3c**; tables of atomic coordinates, absolute, and relative energies from theoretical calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

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