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Unusual Intramolecular Bridging Reaction in Thiacalix[4]arene Series

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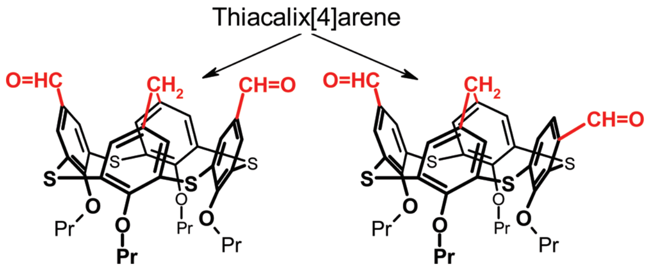
ABSTRACT



Thiacalix[4]arene immobilized in the *cone* conformation undergoes a direct formylation reaction giving unusual products in high yields. The Duff reaction (urotropine/TFA) leads to unprecedented intramolecularly bridged compounds possessing two formyl groups on the opposite *para-* or *para-/meta-*positions. The comparison with the corresponding classical calix[4]arene analogues indicates an amazingly different reactivity of the thiacalix[4]arene system.

Since their first appearance in 1997, thiacalix[4]arenes[1] have received considerable attention from the supramolecular community. Incorporation of four sulfur atoms instead of the common methylene bridges imparts many novel features to the thiacalix[4]arene derivatives[2] when compared to the classical analogues. Thiacalix[4]arenes exhibit substantially enhanced complexation capacities for transition metals,[3] considerably different conformational behaviors/preferences,[4] and novel types of chemistry[5] (e.g., oxidation of sulfur bridges) to mention at least some of their novel functions. All these features make them very promising candidates for the role of host molecules and/or building blocks with many potential applications in supramolecular chemistry.

On the other hand, despite more than a decade of research on thiacalixarenes, our knowledge of their chemistry is still rather fragmented. Consequently, the broader application of

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thiacalixarenes in supramolecular chemistry is limited by the absence of general derivatization methods that are otherwise well established for classical methylene analogues.

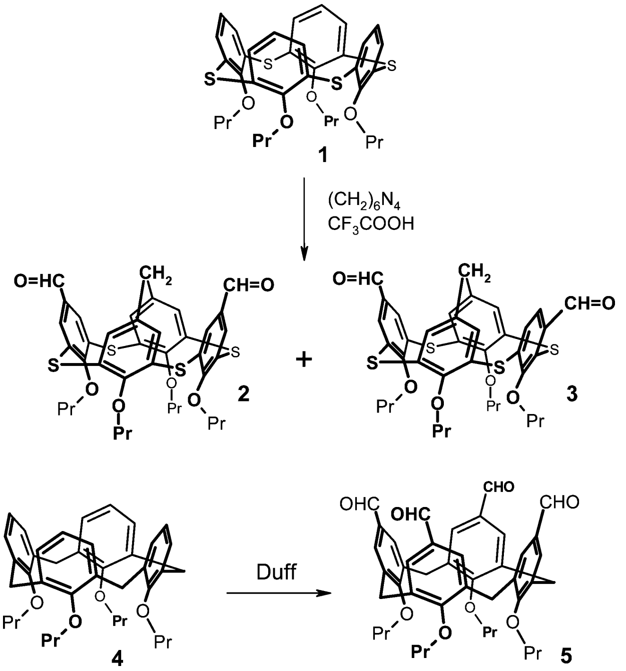
Although direct electrophilic substitution represents the most common upper-rim derivatization method for the classical series, the same reactions are scarcely used for thiacalixarenes. Most electrophilic reactions carried out so far (nitration, bromination) have been based either on the lower-rim unsubstituted parent thiacalix[4]arenes[6] or on partly substituted derivatives.[7] The weak point of this approach is that the products are not immobilized in specific conformations; hence, subsequent shaping of the molecule (alkylation/acylation on the lower rim) is needed. Unfortunately, these reactions frequently lead to unwanted conformers, and in fact, no upper-rim substituted derivative of thiacalix[4]arene immobilized in the *cone* conformation has been reported so far.

In our previous work we have shown that the formylation of thiacalix[4]arene in the *1,3-alternate* conformation leads surprisingly to *meta*-substituted products.[8] In this paper, we report unusual regio- or chemoselectivity of formylation reactions carried out with the *cone* conformers. These reactions clearly indicate a remarkably different reactivity of the thiacalix[4]arene system compared to the classical calix[4]arene analogue.

Starting compound **1** was prepared from the corresponding dipropoxy derivative by a known procedure[9] (PrI/NaH, DMF), and its upper-rim substitution was carried out using the Duff procedure: reaction of the aromatic compound with hexamethylenetetramine (HMTA) in trifluoroacetic acid (TFA) (Scheme 1). These reaction conditions are well-known from classical calixarene chemistry where they are used in the preparation of *para*-substituted formyl calix[4]arenes.[10] Thus, tetraalkyloxy compounds can be smoothly transformed into tetraformyl derivatives as documented by the transformation of compound **4** to derivative **5** in 87%.[11]

The Duff formylation was carried out by reacting thiacalix[4]arene **1** with an excess of urotropin in refluxing CF_3COOH overnight. Analysis of the crude reaction mixture showed the presence of two products in an approximately 3:1 ratio which were separated using preparative TLC on silica gel plates. The main product **2** (isolated in 51% yield) possesses a rather simple ^1H NMR spectrum, reflecting the high symmetry of this compound (Figure 1).

Scheme 1. Regioselectivity of Duff Formylation in Thiacalix[4]arene vs Classical Calix[4]arene Series



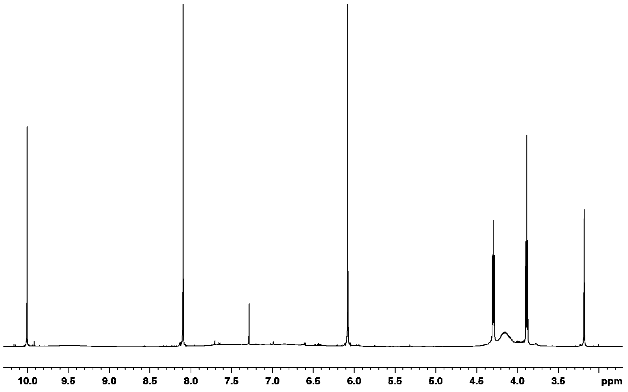


Figure 1. ^1H NMR spectrum of compound **2** ($CDCl_3$, 298 K, 600 MHz).

The presence of just two singlets (8.07 and 6.06 ppm) in the aromatic part of the spectrum indicates that only *para*-substituted aromatic rings are present. The reasonable difference in their chemical shifts (2.0 ppm) is known as a typical feature of the so-called *pinched cone* conformation.[4c] The intensity of the singlet corresponding to the formyl groups (9.98 ppm) points to the fact that only two carbonyl

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groups are present. Also, the presence of two different triplets for the $-OCH_2-$ groups (4.27 and 3.86 ppm) is characteristic of calix[4]arene derivatives possessing two perpendicular symmetry plains. On the other hand, ESI$^+$ MS of **2** shows a signal at *m/z* = 732.171 corresponding to the molecular peak of the diformylated product having an additional $-CH_2-$ group. Based on these observations, we finally assigned the unexpected structure of derivative **2** with two distal formyl groups and two opposite aromatic units bridged intramolecularly by methylene group.

The final unambiguous structural evidence was obtained using X-ray crystallography, which proved that thiacalix[4]arene **2** adopts a *pinched cone* conformation enforced by the short (methylene) bridge (Figure 2). In this conformation, the two opposite phenolic units bearing formyl groups are pointing outward with an interplanar angle of approximately 128°. The remaining aromatic units are tilted toward each other inside the cavity with an interplanar angle of 70°.

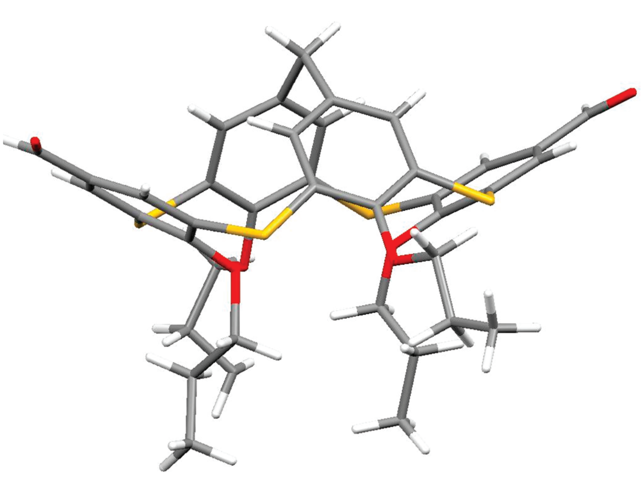

Figure 2. Crystallographic structure of compound **2**.

Although direct formylation represents a well-established and frequently used procedure for the upper rim substitution of classical calix[*n*]arenes, the formation of similar bridged structures has never been observed. Hence, this unexpected reaction is another illustrative example proving the dramatically different reactivity of the thiacalix[4]arene system compared to classical calix[4]arene analogues.[12] The formation of diarylmethanes upon reaction of various phenols with hexamethylene tetraamine (HMTA) is known in the literature, though the yields are usually low as they are formed only as byproducts.[13]

Repeated TLC chromatography on silica gel led to the isolation of pure byproduct **3** in 15% yield. The ^{1}H NMR spectrum of this compound showed a more complicated splitting pattern (Figure 3) than that of compound **2**. Again, the presence of the methylene bridge can be documented by singlet at 3.16 ppm. On the other hand, the presence of two different formyl groups (singlets at 10.59 a 9.98 ppm) indicated the lower symmetry of this molecule. Electrospray MS of derivative **3** revealed a peak at *m/z* = 732 corresponding to the same molecular weight as compound **2**. These findings could be ascribed to the bridged structure having one formyl group in *para*- and one formyl group in *meta*-positions.

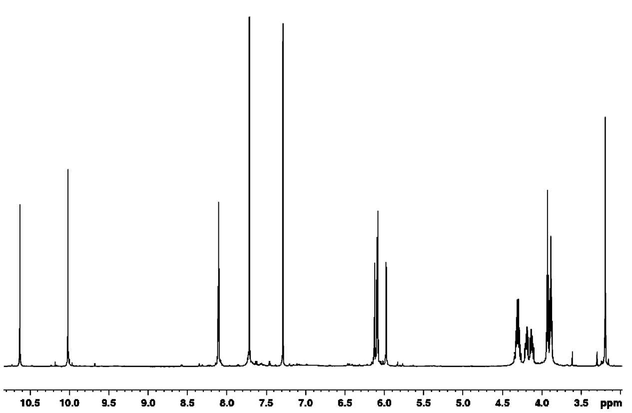

Figure 3. ^{1}H NMR spectrum of compound **3** ($CDCl_3$, 298 K, 600 MHz).

Unfortunately, even the ^{1}H NMR spectrum measured at higher frequency ($CDCl_3$, 600 MHz, see Figure 3) did not correspond with this assumption. Thus, the expected pair of doublets with an interaction constant around 7−8 Hz (typical value for aromatic *ortho* interactions), which should indicate possible *meta*-substitution of thiacalixarene skeleton, are missing as they coincidentally collapsed into the singlet at 8.10 ppm. As we did not succeed with growing of crystal suitable for the X-ray analysis, we decided to prepare the corresponding 2,4-dinitrophenyl hydrazone to invoke stronger differentiation of these signals.

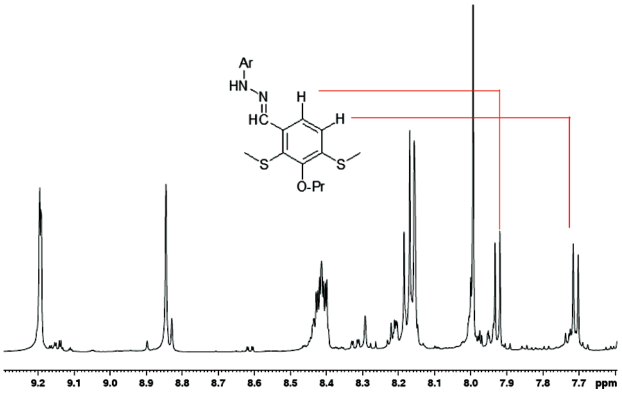

Figure 4. Partial ^{1}H NMR spectrum of compound **3a** ($CDCl_3$, 298 K, 600 MHz).

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[12] Methylene-bridged classical calix[4]arene was prepared in low yield (10%) by the cyclization of the corresponding mono(hydroxymethyl) derivative: Struck, O.; Van Duynhoven, J. P. M.; Verboom, W.; Harkema, S.; Reinhoudt, D. N. *Chem. Commun.* **1996**, 1517.

[13] See, e.g. : (a) Möhrle, H.; Trösten, K. *Arch. Pharm.* **1981**, *314*, 690. (b) Zinke, A.; Ziegler, E. *Ber.* **1944**, *77*, 264. (c) Hultzsch, K. *Ber.* **1949**, *82*, 16. (d) Gowan, J. E.; MacGiolla Riogh, S. P.; MacMahon, G. J.; O'Cleirigh, S.; Philbin, E. M.; Wheeler, T. S. *Tetrahedron* **1958**, *2*, 116.

The reaction of 2,4-dinitrophenyl hydrazine with **3** in ethanol (2 days reflux) gave the corresponding hydrazone **3a**, which was isolated by chromatography on silica gel in 78% yield. The splitting pattern of ^{1}H NMR spectrum of **3a** is considerably different from that of derivative **3**. As follows from Figure 4, both hydrogens on the *meta*-substituted aromatic ring are nicely split into a pair of doublets (7.71 and 7.93 ppm) with a typical *ortho*-interaction constant of 8.2 Hz.

To gain deeper insight into the mechanism of this reaction we have carried out the Duff reaction using shorter reaction times. Thus, the quenching of the reaction after 60 min gave rather complicated reaction mixture from which the monoformyl-substituted methylene-bridged compound **6** was isolated in 19% yield. Similarly, a shorter reaction time (30 min) enabled us to isolate the methylene-bridged derivative **7** in 9% yield (Figure 5). These findings indicate that the bridging reaction is very fast and the reaction sequence goes via bridged intermediate **7**. This compound is subsequently formylated in the *para* position to form compound **6**. Finally, in the last step of the sequence the remaining aromatic ring is attacked either in the *para* or the *meta* positions leading to isomers **2** or **3**, respectively.

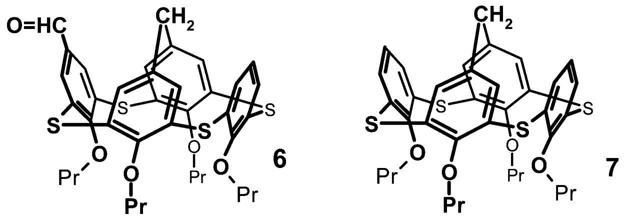

Figure 5. Intermediates isolated from the Duff reaction.

In conclusion, the results obtained from the Duff reaction of thiacalix[4]arene in the *cone* conformation are diametrically different from the same reaction carried out with the *1,3-alternate* thiacalix[4]arene analogue. As we have shown in our previous paper,[8] the formylation of *1,3-alternate* leads selectively to the formation of dialdehydes with formyl groups attached exclusively in the *meta* positions (*para* substitution was not observed at all). Our novel results obtained with the *cone* conformation indicate that the electronic effect of sulfur bridges is not the only factor governing the regioselectivity of electrophilic substitution in thiacalixarene series. Now it is obvious, that stereochemistry (conformation of the starting thiacalix[4]arene) represents another effect playing a crucial role in the process. To the best of our knowledge, similar connection between the conformation and the results of reaction (chemoselectivity, regioselectivity) has never been observed in classical calixarene chemistry.

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Supporting Information Available: Synthetic procedures, characterization of new compounds, and X-ray data of compound **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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