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Unexpected behaviour of monospirothiacalix[4]arene under acidic conditions

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ABSTRACT

Treatment of the monospirodienone derivative of thiacalix[4]arene with various acidic agents (HCl and HBr) results in rearrangement of the thiacalixarene skeleton leading to the formation of a phenoxanthiin derivative in high yields (up to 80%). The structure of the unexpected product is confirmed using ^{1}H and ^{13}C NMR spectroscopy, and X-ray crystallography.

Calix[n]arenes are macrocyclic compounds frequently used in supramolecular chemistry as building blocks for the design and construction of various ligands and receptors. The popularity of these compounds stems, among others, from their simple preparation and easy derivatisation allowing the regioselective introduction of many functional groups into the basic macrocyclic skeleton.[1]

Chemical modifications of calix[4]arenes are usually based on lower rim (OH groups) alkylation/acylation leading to molecules with defined 3D-shapes (conformers), or on electrophilic substitution of the upper rim (aromatic part).[1] A rather unusual method for the substitution of the calixarene skeleton was reported in 1992 when the so-called spirodienone derivatives were described for the first time (Fig. 1).[2] These compounds, prepared by oxidation of the starting calixarenes, can serve as useful intermediates in the regioselective functionalisation of basic calixarene scaffolds[3] enabling the synthesis of otherwise inaccessible analogues. Thus, selective derivatisation of methylene bridges,[4] replacement of hydroxy groups by alkyl groups,[5] and introduction of *meta*-substituents on the upper rim[6] are examples.

Despite systematic research on thiacalix[4]arene[7] derivatisation, information on the chemistry of these compounds remains rather incomplete.[8] Potential applications of thiacalixarenes can be envisaged, however, the lack of general derivatisation methods still obstructs their utilisation in supramolecular chemistry. In order to develop novel alternative procedures for upper-rim modification in thiacalixarenes, we have applied the spirodienone route to thiacalix[4]arene **1**. In this Letter we report the unexpected results of our synthetic efforts which show that the behaviour of the thiacalix[4]arene system is substantially altered when compared with that of classical calix[4]arenes (see Scheme 1).

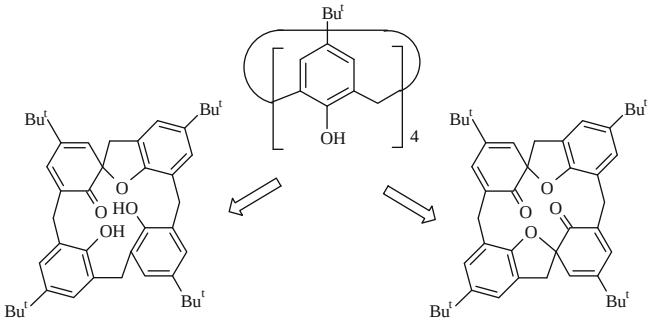
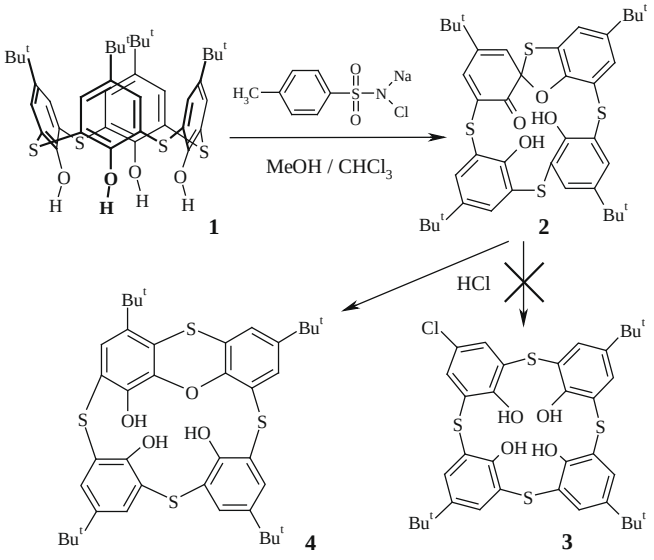


Figure 1. Mono- and bis(spirodienone) derivatives of calix[4]arene.



Scheme 1. Application of the spirodienone route in thiacalixarenes.

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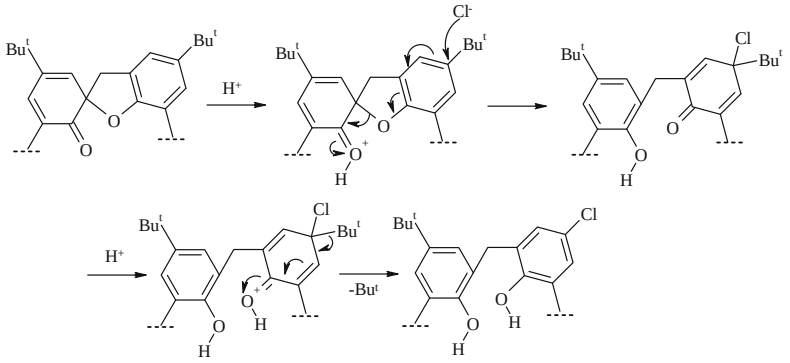


Scheme 2. Reaction of the spirodienone with HCl (classical calixarene).

The preparation of monospirodienone thiacalix[4]arene **2** was accomplished according to a known procedure.[9] The reaction of thiacalixarene **1** with chloramine-T in $CHCl_3$–MeOH mixture at 0 °C gave the corresponding spiro compound **2** in 60% yield. It is known that the analogous derivative of classical calix[4]arene reacts with HCl to yield a 5-chloro-substituted derivative. The reaction pathway is depicted in Scheme 2 and involves protonation of the spirodienone moiety followed by *ipso*-substitution of the *tert*-butyl group. The resulting chloro-substituted calix[4]arene was isolated in 60% yield.[10]

Reaction of spiro derivative **2** with concd aq HCl in acetonitrile at reflux smoothly gave one new compound which was easily isolated by crystallisation.[11] Surprisingly, this compound did not contain a chlorine atom (according to MS) and the ^{1}H NMR spectrum in $CDCl_3$ showed the presence of four inequivalent *tert*-butyl groups (1.43, 1.32, 1.16 and 1.15 ppm). On the other hand, the presence of only seven signals in the aromatic region of the spectrum (3×2 doublets with typical *meta* coupling $\approx$ 2.3–2.6 Hz and one singlet at 7.38 ppm) indicated a *meta*-substitution pattern on one of the aromatic rings (Fig. 2). As the nature of the substituent remained unclear, a similar reaction of **2** with aq HBr was carried out, again yielding an identical product. To eliminate the possible addition of water we also carried out the reaction with gaseous HCl under strictly anhydrous conditions. Not surprisingly, the same product was again isolated (see Table 1). The MS in all cases showed a molecular peak at $m/z = 717$ corresponding with the mass of the starting compound **2**, while IR analysis revealed the absence of a carbonyl group. Consequently, a logical explanation

Table 1
The formation of **4** under various reaction conditions

Acid	Conditions	Yield
Concd aq HCl	MeCN, reflux, 1.5 h	76
Concd aq HBr	MeCN, reflux, 1.5 h	82
Gaseous HCl	MeCN, reflux, 1.5 h	80
Gaseous HCl	MeOH, reflux, 1.5 h	30[a]
TFA	Toluene, MeOH, 80 °C/2 d	10[b]
p-TSA	Toluene, MeOH, 110 °C/2 d	11[b]

[a] Unreacted starting compound **2** (62%) isolated.
[b] Heated until complete disappearance of starting compound **2**.

should imply rearrangement of the starting dienone skeleton, such as in compound **4** which corresponds to all the structural features observed by spectroscopic methods. This type of reaction has never been observed with classical calixarenes[12] indicating substantial differences in the reactivity of both systems. A suggested mechanism is depicted in Scheme 3 and involves protonation of the carbonyl group followed by opening of the spiro-moiety. While in the classical calixarene series it is always the C–O bond which is cleaved, in the case of thiacalixarene the C–S bond seems to be the weakest point of the spiro-fragment. Sulfur can then attack the neighbouring position on the aromatic ring to form a more stable six-membered phenoxanthiin ring.

Unequivocal proof of the structure of compound **4** was obtained from single crystal X-ray diffraction analysis (suitable monocrystals were grown by slow evaporation of a CH_2Cl_2 solution).[13]

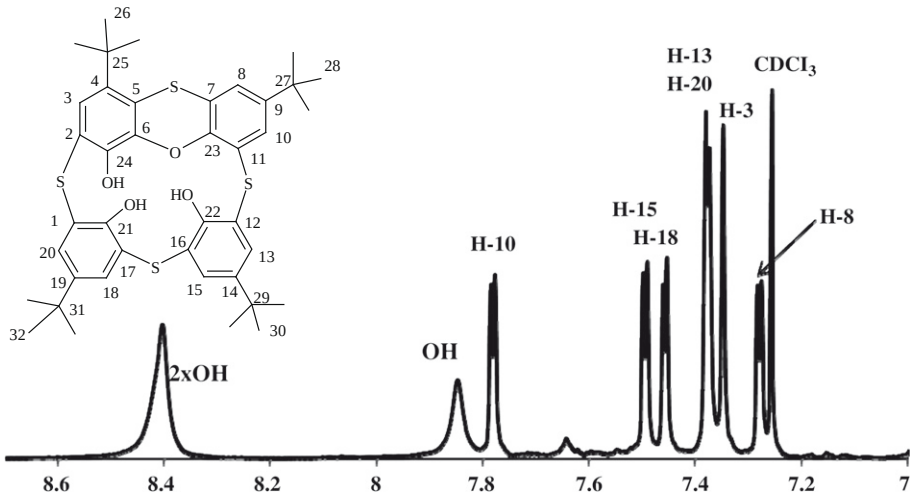
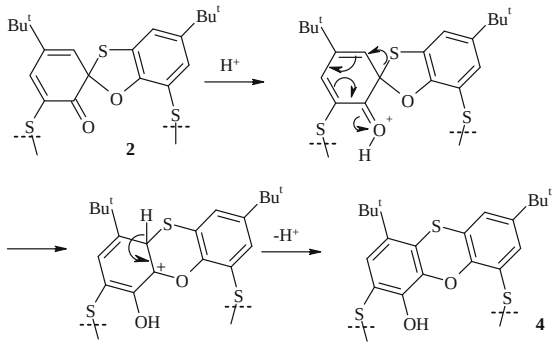


Figure 2.



Scheme 3. Suggested mechanism for phenoxanthiin formation from **2**.

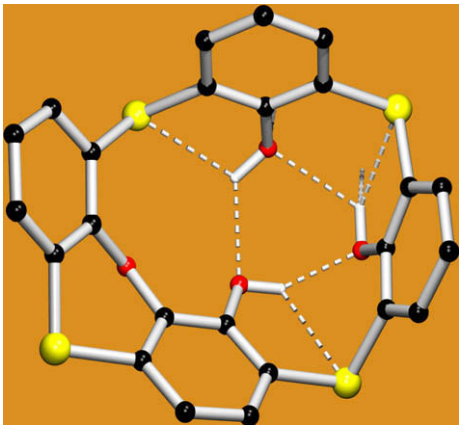


Figure 3. X-ray structure of **4** showing an array of intramolecular hydrogen bonds, the Bu^t groups and the remaining hydrogens are omitted for clarity.

Compound **4** adopts the *cone* conformation which is supported by an intramolecular circular array of hydrogen bonds between the three OH groups on the lower rim. The interatomic O···O distances (O1–O3 2.8569 (18), O2–O1 2.8935 (18) and O3–O2 2.7548 (18) Å) correspond well with hydrogen bonds of moderate strength.[14] This bonding motif is further strengthened by hydrogen bonding interactions between the bridging sulfur atoms and the hydrogens from the adjacent OH groups (S···H 2.52–2.57 Å; Fig. 3).

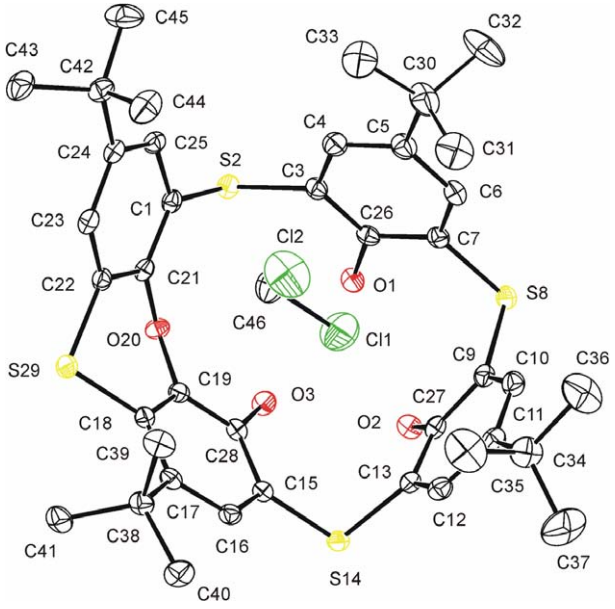


Figure 4. A view of derivative **4** showing the CH_2Cl_2 molecule within the cavity. Hydrogens and second positions of disordered atoms are omitted for clarity. Displacement ellipsoids are drawn at 50% probability level.

Compound **4** crystallises with two molecules of dichloromethane (crystallisation solvent). While one solvent molecule resides outside the cavity within the free space of the unit cell, the other solvent molecule is situated directly inside the thiacalix[4]arene cavity. Interestingly, one chlorine atom (Cl1) is located almost precisely above the centre of the phenolic unit (C9–C13, C27) with a distance of 3.31 Å from the aromatic plain (Fig. 4). This short distance indicates the presence of Cl···π interactions, recently recognised as being important noncovalent interactions in various biological[15] and/or artificial[16] systems.

In conclusion, we have shown that a spirodienone derivative of thiacalix[4]arene possesses remarkably different reactivities compared with common –CH_2– analogues. The unexpected acid-induced rearrangement of the spirodienone skeleton leads to a phenoxanthiin derivative, a structural motif not formed from classical calixarenes.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.08.105.

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11. *Acidic rearrangement of spiro-compound* **2**: Spirodienone **2** (100 mg, 0.14 mmol) was suspended in a mixture of acetonitrile (200 ml) and concd aqueous HBr (5 ml), and the reaction mixture was heated at reflux for 1.5 h. After cooling to room temperature, the reaction mixture was concentrated to approx. one half volume using a rotary evaporator. Trituration with $CHCl_3$ gave a white powder (product of acetonitrile self-condensation) which was removed by filtration. The mother liquor was evaporated to dryness and the crude product was crystallised from MeCN:$CHCl_3$ (3:1 v/v) to give 82 mg (82%) of compound **4** as white crystals. Mp: 123–126 °C (MeCN–$CHCl_3$), IR (KBr): 1773 cm^{-1}. EA calcd for $C_{40}H_{46}O_4S_4$, C, 66.82; H, 6.45; S, 17.84. Found C, 66.58; H, 6.39; S, 17.61%. MS ESI− *m/z* 717.37 $[M-H]^+$ (100%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): 8.40 (br s, 2H, OH), 7.85 (br s, 1H, OH), 7.78 (d, 1H, Ar-H10, *J* = 2.4 Hz), 7.49 (d, 1H, Ar-H15, *J* = 2.6 Hz), 7.46 (d, 1H, Ar-H18, *J* = 2.4 Hz), 7.38 (d, 2H, Ar-H13,20, *J* = 2.3 Hz), 7.38 (s, 1H, Ar-H3), 7.28 (d, 1H, Ar-H8, *J* = 2.3 Hz), 1.43 (s, 9H, Bu^t-H26), 1.32 (s, 9H, Bu^t-H28), 1.16 (s, 9H, Bu^t-H32), 1.15 (s, 9H, Bu^t-H30). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm): 154.81 (C22), 153.65 (C21), 151.48 (C23), 148.60 (C9), 145.26 (C14), 144.79 (C5/24), 143.93 (C19), 142.20 (C5/24), 138.87 (C4), 136.21 (C15), 135.77 (C13), 135.23 (C10), 133.54 (C18), 131.60 (C20),

127.81 (C3), 126.35 (C8), 124.15 (C2), 123.91 (C17), 123.50 (C11), 123.36 (C7), 122.19 (C16), 120.97 (C12), 120.42 (C1), 120.22 (C6), 36.11 (C25), 34.95 (C27), 34.48 (C29/31), 31.89 (C28), 31.77 (C30/32), 30.82 (C30/32), 30.29 (C26).

12. Treatment of the monospirodienone derived from calix[6]arene with MeOH/H^+ gave a xanthene derivative. This compound was formed by formal dehydration of two neighbouring hydroxy groups: Aleksiuk, O.; Cohen, S.; Biali, S. E. *J. Am. Chem. Soc.* **1995**, *117*, 9645.
13. Crystallographic data for **4**·$2CH_2Cl_2$: $C_{40}H_{46}O_4S_4{\cdot}2CH_2Cl_2$, M_r = 888.86, triclinic system, space group P-1(No2), a = 12.8448(2) Å, b = 13.23190(10) Å, c = 14.3631(2) Å, α = 98.0288(7)°, β = 90.7382(6)°, γ = 114.1555(6)°, Z = 2, V = 2198.94(5) Å^3, D_x = 1.342 g cm^{-3}, μ(Mo-Kα) = 0.50 mm^{-1}, colourless crystal of dimensions 0.40 × 0.40 × 0.40 mm. Data were collected at 150(2) K on a Nonius Kappa CCD diffractometer with graphite monochromated MoKα radiation. An absorption was neglected (μ = 0.50 mm^{-1}); a total of 67374 measured reflections (θ_{max} = 27.5°), from which 10118 were unique (R_{int} = 0.027) and 9040 observed according to the $I > 2\sigma(I)$ criterion.
The structure was solved by direct methods[17] and refined by full matrix least squares based on F^2 (SHELXL97).[18] The hydrogen atoms of the –OH moieties were found on the difference Fourier map, others were calculated into idealised positions, all hydrogens were constrained during refinement (riding model) with assigned temperature factors either H_{iso}(H) = 1.2 U_{eq}(pivot atom) or H_{iso}(H) = 1.5 U_{eq}(pivot atom) for the methyl moiety. Atoms of one *tert*-butyl moiety were refined as disordered into two positions with occupation factors 0.8:0.2. The refinement converged (Δ/σ_{max} = 0.004) to R = 0.043 for observed reflections and $wR(F^2)$ = 0.110, GOF = 1.02 for 508 parameters and all 10118 reflections. The final difference map displayed no peaks of chemical significance ($\Delta\rho_{max}$ = 1.09, $\Delta\rho_{min}$ −0.98 e Å^{-3}). Crystallographic data have been deposited at the Cambridge Crystallographic Data Centre as CCDC registration number 734277.
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