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Nitration of thiacalix[4]arene derivatives

Pavel Lhoták,[a,*] Jiri Svoboda, Jr.,[a] Ivan Stibor[a] and Jan Sykora[b]

[a]*Department of Organic Chemistry, Institute of Chemical Technology, Technická 5, 166 28 Prague 6, Czech Republic*
[b]*Institute of Chemical Process Fundamentals, Czech Academy of Sciences, Rozvojova 135, 165 02 Prague 6, Czech Republic*

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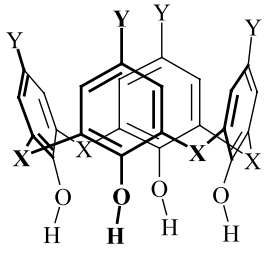
Abstract—A direct nitration of the upper rim of thiacalix[4]arenes is not possible due to the undesirable oxidation of the sulphur atoms during the nitration step leading to very complicated reaction mixtures. On the other hand, thiacalix[4]arene derivatives can be at first transformed intentionally to the highest oxidation state—sulfones, and subsequently *ipso*-nitrated using 100% HNO_3 in CF_3COOH. This procedure gives smoothly mono- or dinitro-derivatives in acceptable yields which opens the way for further derivatisation of the upper rim of thiacalixarenes.

Thiacalix[4]arene **1**,[1] bearing four sulphur atoms instead of the usual CH_2 bridging groups, represents a new member of the calix[n]arene family.[2,3] As demonstrated very recently, thiacalixarene derivatives exhibit many novel properties and uncommon chemical behaviour when compared with the chemistry of 'classical' calixarenes. The oxidations of sulphur bridges to the corresponding sulfoxide[4] **3a** or sulfone[5] **3b** derivatives—reactions unknown in the chemistry of 'classical' calixarenes have been described. Similarly, the 'amination' of the thiacalixarene lower rim[6] and the formation of intramolecular lactone derivatives[7] should also be mentioned. These novel features, together with substantially different conformational preferences[8] and unusual complexation abilities,[9] make thiacalixarenes good candidates for the role of building blocks and molecular scaffolds.



1, X = S, Y = Bu^t
2, X = S, Y = H
3a, X = SO
3b, X = SO_2

While the chemistry of classical calixarenes is very well established and developed,[2] the wider application of thiacalixarenes in supramolecular chemistry requires new knowledge dealing with the general and/or regioselective derivatisation of these compounds. During our on-going research on the electrophilic substitution of thiacalix[4]arene, we came to the conclusion that the chemical behaviour of this new system is very different from that of calix[4]arene. Thus, starting from 25,26,27,28-tetraalkoxythiacalix[4]arenes, all our attempts at the direct halogenation, nitration, Friedel–Crafts acylation or formylation of the upper rim, using procedures well-known from classical calixarene chemistry, have failed. Only very recently it was found that **2** reacts smoothly with diazonium salts to form tetrasubstituted azo derivatives that can be subsequently reduced to give upper rim amino-substituted thiacalixarene derivatives.[10] Another example of upper rim transformation is the bromination of the 25,27-dialkoxy-derivative of thiacalix[4]arene **2** leading to the corresponding dibromo or tetrabromo derivatives,[11] and *ipso*-sulfonation of **1** with concentrated sulphuric acid to give a water-soluble tetrasulfonated derivative in high yield.[12]

In this paper we report the first example of direct nitration of the thiacalix[4]arene upper rim by reaction with 100% HNO_3 in trifluoroacetic acid. This reaction enables the introduction of one or two nitro groups into thiacalixarene which opens the way for subsequent derivatisation of the upper rim.

Nitro-substituted calix[4]arenes represent typical intermediates in the preparation of amino-substituted derivatives (via reduction). As a result, nitration of the upper rim is a well-recognised reaction in calixarene chemistry that can be carried out either directly,[13] or via the *ipso*-substitution[14] procedure. During our nitra-

* Corresponding author. Tel.: +420-2-2435 4280; fax: +420-2-2435 4288; e-mail: lhotakp@vscht.cz

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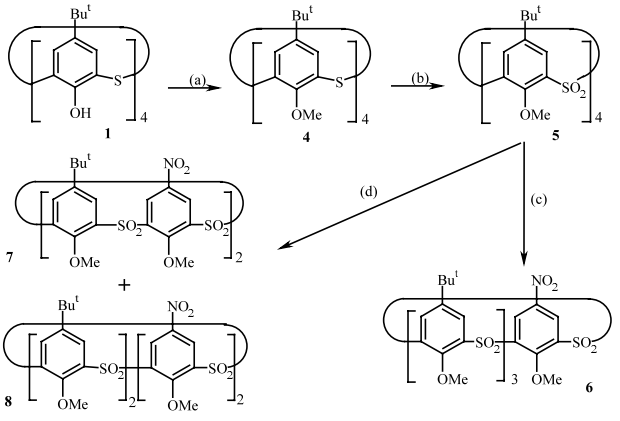
tion studies of thiacalixarenes we found that all the reaction conditions routinely used in 'classical' calixarene chemistry (conc. HNO_3 or 100% HNO_3 in CH_2Cl_2 or acetic acid, 100% HNO_3 in CF_3COOH, $NaNO_3$ in CF_3COOH) led to very complicated reaction mixtures where nitration is accompanied by concomitant oxidation of the sulphur bridges.[15] Consequently, nitro-substituted thiacalixarenes are still unavailable up to now.[16] On the other hand, the aforementioned nitration agents were used in some cases as excellent oxidising agents for the synthesis of tetraalkylated sulfones or sulfoxides.[15]

We realised, that to avoid nonspecific oxidation of thiacalixarenes during nitration, we could use as starting compound, derivatives having been already oxidised. *tert*-Butylthiacalix[4]arene **1** was used as the starting material and was tetraalkylated (Scheme 1) using MeI/K_2CO_3 in boiling acetone to form **4** in 95% yield. Subsequent oxidation with aqueous H_2O_2 (35%) in trifluoroacetic acid/$CHCl_3$ mixture gave the corresponding tetrasulfone **5**[17] in high yield (87%).

The nitration of **5** was attempted using 65% or 100% HNO_3 in glacial acetic acid. Unfortunately, reactions carried out either at room or elevated (80°C) temperatures did not lead to any products and only starting material was recovered from the reaction mixtures. On the other hand, the substitution of solvent for trifluoroacetic acid led to the appearance of a new spot on TLC after extended stirring of **5** with 100% HNO_3 at room temperature. We found best results were obtained at elevated temperature (80°C) using a large excess of nitrating agent (200 equiv.). Under these conditions, either one or two nitro groups could be selectively introduced into the upper rim of thiacalixarene derivatives depending on the reaction time. A shorter reaction time[18] (2 days stirring at 80°C) gave mononitro derivative **6** (45% yield) while 3.5 days stirring[19] led to the diametrically substituted dinitro derivative **7** (59%) accompanied by a small amount of proximal derivative **8** (2%). It is interesting that we were not able to isolate



Scheme 1. (a) MeI/ K_2CO_3, reflux, (95%); (b) H_2O_2/ $CF_3COOH/CHCl_3$, rt (87%), (c) 100% HNO_3/CF_3COOH, 80°C, 2 days (45%, **6**). (d) 100% HNO_3/CF_3COOH, 80°C, 3.5 days (59%, **7**).

any tetrasubstituted product under any conditions (higher excess of nitrating agent, longer reaction time). This indicates that the reactivity of the sulfone system towards *ipso* nitration is much lower in comparison with that of classical calix[4]arenes, where tetrasubstitution is the common result of the reaction carried out under milder conditions (65% HNO_3 in CH_2Cl_2/CH_3COOH at room temperature).[14] The electron-withdrawing effects of the two nitro groups make the subsequent nitration impossible and hence, under the conditions used, the dinitro derivative is the main product. Consequently, depending on the reaction time, we have quite a rare possibility of regioselective (mono-, di-) *ipso*-functionalisation of the thiacalixarene upper rim.

The structures of the novel nitro compounds were confirmed by ^1H NMR analysis. Thus, compound **7** possesses two singlets in the aromatic region (δ 8.33 and 9.12 ppm), two singlets due to the methoxy groups (δ 4.04 and 4.09 ppm) and one signal due to the *tert*-butyl groups (δ 1.37 ppm) thus showing highest symmetry of all three nitro derivatives, which is typical for diametrically disubstituted calixarenes. In contrast, due to the lower symmetry, proximal derivative **8** exhibits four signals in the aromatic region (δ 8.18, 8.25, 9.00, 9.06) with typical *meta*-coupling constants ($J=2.6$ and 3.1 Hz) together with singlets at δ 1.27 ppm (*tert*-butyl groups) and δ 4.19 and 4.30 ppm (methoxy groups).

Because of the absence of CH_2 bridges, the signals which are used for assignment in classical calix[4]arene chemistry, the conformational analysis of thiacalix[4]arene derivatives is not a simple task.[20] The above splitting pattern of **7** indicates three possible explanations: (i) the molecule adopts an *1,3-alternate* conformation, (ii) it prefers a *cone* conformation in $CDCl_3$ solution, (iii) the observed signals are in fact time-averaged signals of a dynamic system where phenyl units are quickly moving through the macrocyclic ring. To distinguish among the above-mentioned possibilities, a one-dimensional DPFGSE-NOE experiment was carried out. The NOE coupling (Fig. 1) observed between methoxy groups and the corresponding aromatic signals (4.04↔9.12 and 4.09↔8.33 ppm) ruled out the cone conformation, where such interactions are impossible. The above findings are in accordance with (i) or (iii), nevertheless, for time averaged signals (iii) one should observe an NOE coupling between the neighbouring methoxy groups, however, this was not the case. Furthermore, the dynamic ^1H NMR spectrum of dinitro derivative **7** did not exhibit any substantial changes up to −90°C (400 MHz, CD_2Cl_2), which fully corresponds to the *1,3-alternate* conformation being immobilised on the NMR time scale.

The final evidence for the conformational preferences of **7** was demonstrated by the single-crystal X-ray diffraction analysis[21] (suitable monocrystals were obtained by slow evaporation of an EtOAc solution). The molecule adopts a *1,3-alternate* conformation with two

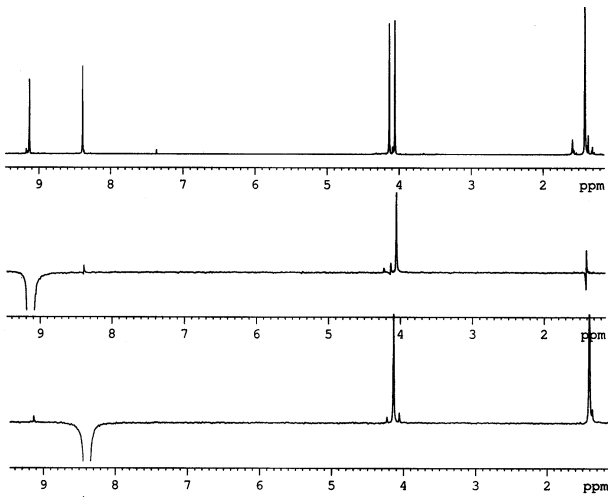


Figure 1. DPFGSE–NOE experiments (400 MHz, $CDCl_3$, 298 K): (a) ^1H NMR of **7**; (b) singlet at δ 9.12 ppm irradiated, (c) singlet at δ 8.33 ppm irradiated.

nitro and two *tert*-butyl groups pointing to the opposite sides of the macrocycle (Fig. 2). The average distances between two adjacent and two opposite sulphur atoms are approximately 5.53 and 7.84 Å, respectively, while the typical distances between corresponding CH_2 groups in calix[4]arene *1,3-alternate* are 5.0 and 7.1 Å. This demonstrates the bigger cavity of thiacalix[4]arenes in comparison to classical calix[4]arenes.

The same conformational preferences in the solid state[22] were found in the case of mononitro derivative **6**. This molecule also prefers a *1,3-alternate* conformation with similar structural parameters as described for **7** (Fig. 3).

In conclusion, we have demonstrated that thiacalix[4]arene derivatives with oxidised sulphur bridges ($-SO_2-$) can be directly *ipso*-nitrated. Depending on the conditions, either mono- or di-nitro derivatives can be prepared in good yields, which opens the way for further chemical transformations of the upper rim of thiacalixarenes.

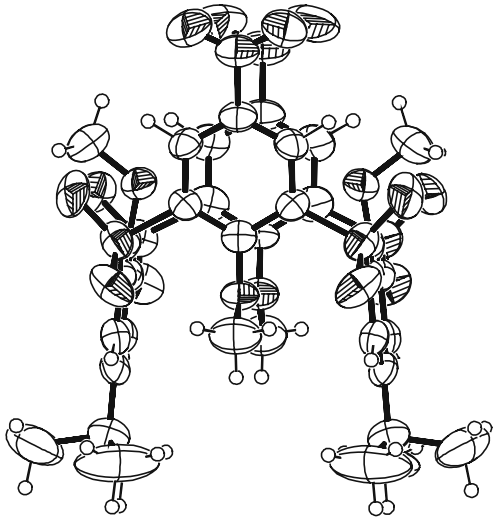


Figure 2. ORTEP drawing of **7**.

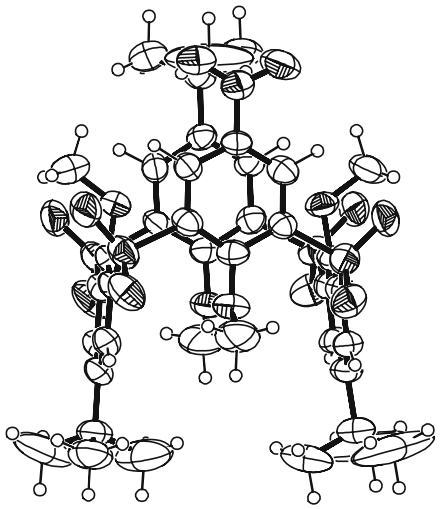


Figure 3. ORTEP drawing of **6**.

Acknowledgements

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18. **Preparation of mononitro-derivative 6**: Tetramethoxy-tetrasulfone **5** (1.00 g, 1.10 mmol) was dissolved in 10 mL of trifluoroacetic acid, then 100% nitric acid (10 mL, 236 mmol) was added and the reaction mixture was stirred under reflux for 45 h. The mixture was neutralised with a saturated aqueous solution of $NaHCO_3$, the organic layer was separated and the aqueous layer was extracted three times with $CHCl_3$. The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The solid residue was purified by column chromatography on silica gel using petroleum ether:AcOEt = 7:1 mixture as eluent to yield 533 mg of product **6** (45% yield). Mp: 306°C (decomp.). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.28 (s, 9H, Bu^t), 1.35 (s, 18H, Bu^t), 4.06 (s, 3H, -OCH_3), 4.13 (s, 6H, -OCH_3), 4.17 (s, 3H, -OCH_3), 8.21 (d, J = 2.5 Hz, 2H, H-arom.), 8.23 (s, 2H, H-arom.), 8.29 (d, J = 2.5 Hz, 2H, H-arom.), 9.05 (s, 2H, H-arom.). EA calcd for $C_{40}H_{47}NO_{14}S_4$: C, 53.74; H, 5.30; N, 1.57; S, 14.35; Found: C, 54.09; H, 5.11; N, 1.31; S, 13.96. FAB MS m/z 894.0 $[M]^+$.
19. **Preparation of dinitro-derivative 7**: Tetrasulfone **5** (3.65 g, 4.04 mmol) was dissolved in 36.5 mL of CF_3COOH and 100% nitric acid (36.5 mL, 863 mmol) was added to the solution. The reaction mixture was stirred at 80°C for 84 h after which the mixture was neutralised with a saturated aqueous solution of $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted with $CHCl_3$. The combined organic layers were dried over $MgSO_4$. The solution was evaporated to dryness and the residue was triturated with 20 mL of $CHCl_3$. The suspension formed was filtered off and dried at 85°C in an oven to yield 2.11 g of **7** (59% yield). The filtrate was evaporated and purified using radial thin layer (2 mm plate) chromatography (Chromatotron, Harrison Research, CA, USA) using a mixture of petroleum ether/AcOEt = 20:1 as eluent to yield 100 mg of proximal derivative **8** (3% yield). Compound **7**: mp: 313°C (decomp.). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.37 (s, 18H, Bu^t), 4.04 (s, 6H, O-CH_3), 4.09 (s, 6H, O-CH_3), 8.33 (s, 4H, H-arom.), 9.12 (s, 4H, H-arom.). FAB MS m/z 883.7 $[M]^+$.
Compound **8**: mp: 302–303°C. ^{1}H NMR ($CDCl_3$): δ 1.27 (s, 18H, Bu^t), 4.19 (s, 6H, O–CH_3), 4.30 (s, 6H, O–CH_3), 8.18 (d, 2H, J = 2.6 Hz, H-arom.), 8.25 (d, 2H, J = 2.6 Hz, H-arom.), 9.00 (d, 2H, J = 3.0 Hz, H-arom.), 9.06 (d, 2H, J = 3.0 Hz, H-arom.). FAB MS m/z 881.7 $[M]^+$.
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21. X-Ray data for **6**: $C_{40}H_{47}O_{14}N_1S_4 \cdot 1/3C_6H_6 \cdot 1/2CHCl_3$, M = 964.07 g/mol, orthorhombic system, space group $P2_1c$, a = 13.627(1), b = 17.301(1), c = 22.305(1) Å, β = 104.90(1) Z = 4, V = 5081.5(6) Å^3, D_{calcd} = 1.26 g cm^{-3}, μ(Cu Kα) = 2.95 mm^{-1}, crystal dimensions of 0.3×0.3×0.6 mm. Data were measured at 293 K on an Enraf–Nonius CAD4 diffractometer with graphite monochromated Cu Kα radiation. The structure was solved by direct methods.[23] The whole structure was refined by full matrix least-squares on F values[24] to final R = 0.0997 and R_w = 0.0694 using 4543 independent reflections (θ_{max} = 60°). Hydrogen atoms were located from expected geometry and were not refined. Benzene solvent molecule was localised from the difference Fourier map. Carbon atoms in the solvent molecules (both benzene and chloroform) were refined only isotropically and hydrogen atoms were not included. Additionally, carbon atoms of the benzene solvent were restrained in two disordered positions with partial occupancy 0.15. The chloroform molecule was refined with the occupancy 0.5.
22. X-Ray data for **7**: $C_{36}H_{38}O_{16}N_2S_4 \cdot C_4H_8O_2$, M = 955.04 g/mol, orthorhombic system, space group $Pcmn$, a = 13.142(1), b = 18.085(1), c = 19.767(1) Å, Z = 4, V = 4698(1) Å^3, D_{calcd} = 1.35 g cm^{-3}, μ(Cu Kα) = 2.46 mm^{-1}, crystal dimensions of 0.1×0.1×0.3 mm. Data were measured at 293 K on an Enraf–Nonius CAD4 diffractometer with graphite-monochromated Cu Kα radiation. The structure was solved by direct methods.[23] The whole structure was refined by full matrix least-squares on F values[24] to final R = 0.1008 and R_w = 0.0848 using 2117 independent reflections (θ_{max} = 60°). Hydrogen atoms were located from the expected geometry and were not refined. Atoms of the solvent molecule (ethyl acetate) were refined only isotropically and hydrogen atoms were not included both due to the disorder of the solvent into four positions. Crystallo-

graphic data for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 185281 and 185282. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0) 1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

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