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Synthesis and conformational behaviour of lower-rim tetraacetylated thiacalix[4]arenes

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Abstract

The acylation of thiacalix[4]arenes with AcCl or Ac_2O gave the corresponding lower-rim tetraacetoxy derivatives. In contrast to classical calix[4]arenes, tetraacetylated thiacalix[4]arenes are conformationally mobile in solution and represent a thermodynamic equilibrium of three different conformers at room temperature. As proven by a dynamic ^1H NMR study, conformational preferences of acetylated thiacalix[4]arenes considerably depend on the upper-rim substitution. Hence, *t*-Bu thiacalixarene prefers *1,3-alternate* and *1,2-alternate* conformations (43% and 38%, respectively), while the upper-rim unsubstituted compound adopts preferably the *partial cone* conformation (70%).

Thiacalixarenes **1** and **2**—heterocyclic members of a classical calixarene[1] family—have attracted considerable interest since their first appearance[2] in 1997. It was obvious from the beginning that these compounds represent very interesting host molecules with many possible applications in supramolecular chemistry. The introduction of four sulfur bridges imparts many novel features to thiacalix[4]arenes compared with the chemistry of classical calix[4]arenes possessing typical methylene bridges. Thus, thiacalixarenes exhibit significantly enhanced complexation abilities towards transition metals, substantially different chemistry, and broader derivatisation latitude,[3] as examples of their novel functions. Despite almost a decade of research on thiacalixarenes, information about their conformational dynamic behaviour and conformational preferences[4] is still rather fragmentary and incomplete, which hampers further utilisation of thiacalixarenes. Hence, a deeper understanding of their dynamic behaviour could make these compounds very useful building blocks for the design of novel receptors.

Modification of lower-rim –OH groups is the most common way how to immobilise calixarene molecules in a specific conformation,[1] and to shape the three-dimensional structures of their cavities. While alkylation[5] of thiacalix[4]arenes is already well understood and frequently used, the acylation of thiacalixarene is rare, and to the best of our knowledge, only a few examples[6] of a thiacalixarene acylation have been published. Consequently, during our ongoing research on thiacalixarene derivatisation, we have carried out a systematic study on lower-rim acylation of thiacalixarenes using acyl chlorides or anhydrides, a process which could be used for shaping thiacalixarene molecules.

It is known from the chemistry of classical calixarenes that lower-rim tetraacetoxy derivatives[7] of calix[4]arenes can be obtained in various conformations, which are stable under typical conditions, and can be purified and isolated. We wondered if the same holds true for the corresponding thiacalix[4]arene derivatives. In this Letter, we report a simple synthesis of 25,26,27,28-tetraacetoxythiacalix[4]-arenes and the dynamic conformational behaviour of these compounds, which substantially differs depending on the upper-rim substitution.

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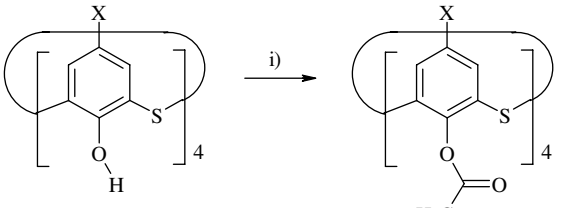


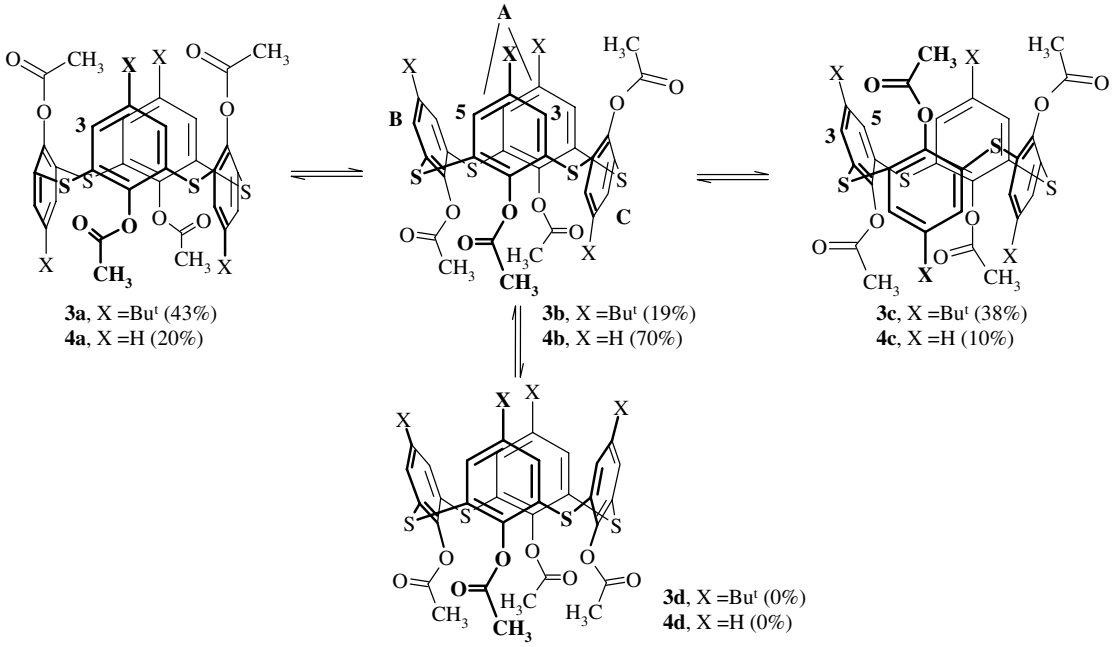
Scheme 1. Preparation of 25,26,27,28-tetraacetoxythiacalix[4]arenes, for reaction conditions and yields see Table 1.

Table 1
Tetraacetylation of thiacalix[4]arenes

Starting compd	Acylation agent	Conditions	Yield (%)
1	Ac_2O	AcONa/3 h reflux	84
1	AcCl	TEA/DCM/24 h rt	48
1	AcCl	TEA/DMAP/DCM/24 h rt	78
2	Ac_2O	AcONa/3 h reflux	75
2	AcCl	TEA/DCM/24 h rt	25
2	AcCl	TEA/DMAP/DCM/24 h rt	62

Tetraacetoxythiacalix[4]arenes **3** and **4** were prepared by several independent synthetic procedures (Scheme 1 and Table 1). Reaction of thiacalixarenes **1** and **2** with excess AcCl in the presence of triethylamine (TEA) gave the corresponding tetraesters **3** and **4** in low yields (48% and 25%, respectively). On the other hand, addition of a catalytic amount of 4-dimethylaminopyridine to the above reaction mixtures led to much better results (78% for **3**, 62% for **4**).[8] The highest yields were achieved by refluxing **1** or **2** in acetic anhydride in the presence of AcONa. Using these conditions, tetraesters **3** and **4** were obtained in 84% and 75% yields, respectively (see Table 1). Surprisingly, despite the different methods used, the same compounds **3** and **4** were isolated in all cases. As the splitting patterns of the ^{1}H NMR spectra of **3** and **4** were too complicated for single isomers, this indicated the presence of thermodynamic equilibrium between several conformers at room temperature. While this chemical exchange is slow on the ^{1}H NMR timescale (Scheme 2), the rate is too fast on the laboratory timescale and the corresponding conformers cannot be isolated.

The distribution of possible conformational isomers in equilibrium mixtures of compounds **3** and **4** was studied by means of NMR spectroscopy (^{1}H, ^{13}C, COSY, ^{1}H–^{13}C HMQC, ^{1}H–^{13}C HMBC, DPFGSE-NOE). The ^{1}H NMR spectra indicated that in both cases only three conformers were present in solution. For the detailed assignment of equilibrium conformers, derivative **3** bearing Bu^t on the upper-rim was used, as its spectrum was free of any overlap (Fig. 1g). The spectral symmetry indicated the presence of *partial cone* (Fig. 1c and d) and *1,2-alternate* (Fig. 1e and f) conformations, while the remaining isomer with the highest symmetry corresponded either to the *cone* or to the *1,3-alternate* conformation (Fig. 1a and b). To determine the structures unambiguously NOE experiments were used. Due to the slow molecular motion of compound **3** we encountered a negative NOE regime (molecular weight >900), and thus, NOE enhancements of spatially close signals had the same sign as that of the inverted resonance. The *1,3-alternate* conformation was proven by NOE contacts of methyl group with aromatic H-3 protons



Scheme 2. Distribution of the corresponding conformers in compounds **3** and **4** (^{1}H NMR 300 MHz, $CDCl_3$, 298 K) and the numbering used in discussion.

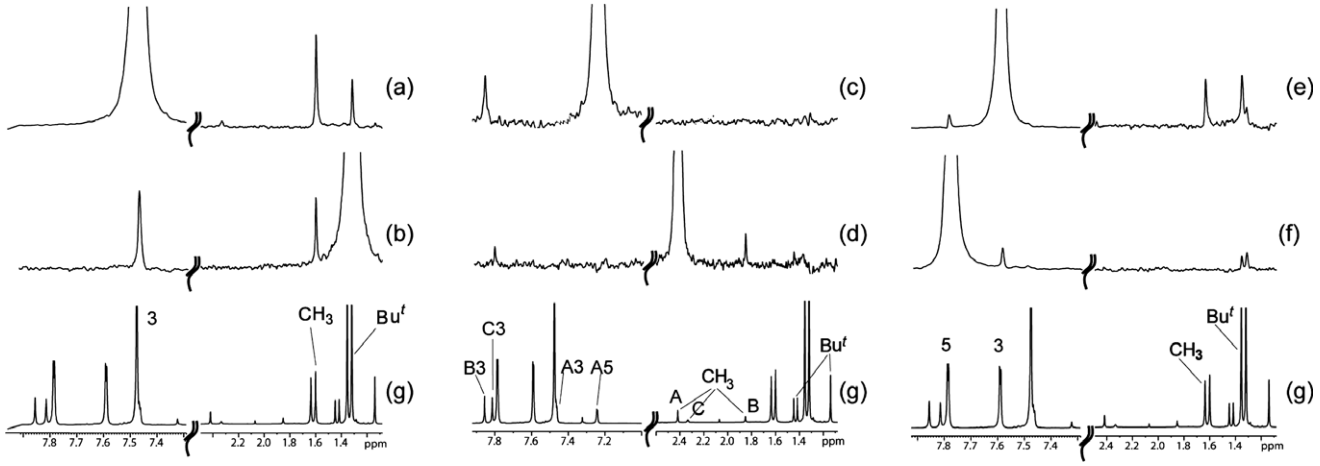


Fig. 1. The DPFGSE-NOE[9] spectra of **3** (CD_2Cl_2, 298 K), *1,3-alternate*, H-3 irradiated (a); *1,3-alternate*, Bu^t irradiated (b); *partial cone*, H-A5 irradiated (c); *partial cone*, methyl-A irradiated (d); *1,2-alternate*, H-3 irradiated (e); *1,2-alternate*, H-5 irradiated (f); and partial ^{1}H NMR spectrum (g).

and Bu^t (Fig. 1a and b), which clearly excluded the possible *cone* conformation. In the case of the C_2 symmetrical *1,2-alternate* conformer, the methyl group exhibited an NOE contact with the aromatic proton H-3, but not with H-5 (Fig. 1e and f). The *partial cone* conformation was characterised by NOEs between aromatic protons H-A5 and H-B3, and between H-C3 and the methyl of the acetyl group (Fig. 1c and d). Thus, in the equilibrium mixture of **3** the *1,3-alternate* (43%) and *1,2-alternate* (38%) strongly prevail over the *partial cone* (19%). As compound **4** (X = H) revealed the same spectral pattern, the assignment of conformers was analogous (Fig. 2). To our surprise, however, the upper-rim substitution seems to have a considerable effect on the conformer distribution. If compared with derivative **3**, compound **4** bearing only hydrogen atoms at the *p*-positions possesses a completely different distribution with a dominating *partial cone* (70%) conformer, while the percentage of *1,3-alternate* (20%) and *1,2-alternate* (10%) was much lower. Interestingly, the *cone* conformer (Scheme 2) was not observed in equilibria at all under the experimental conditions.

To gain a deeper insight into the conformational preferences of thiacalixarene tetraacetates, single crystals of **4** suitable for X-ray analysis were obtained by slow evaporation from a chloroform solution.[10] It was found that the asymmetric unit consists of one molecule of thiacalixarene **4** adopting a *partial cone* conformation and one molecule of solvent ($CHCl_3$). The crystal packing leads to a structural motif where one molecule of $CHCl_3$ is always surrounded by four thiacalixarene molecules and vice versa. The chloroform molecule is bound via hydrogen bonding to the carbonyl group of the inverted phenyl ring of the *partial cone* conformation (H···O=C distance = 2.60 Å). Additional close contacts between Cl and the oxygen of the carbonyl group (3.21 Å) and hydrogen bonding interactions between Cl and the *m*-/*p*-hydrogens of **4** (≈2.9 Å) were also observed in the crystal packing.

In addition to the above-mentioned interactions, strong π–π intermolecular interactions between two coplanar phenyl rings of **4** were apparent. The rings are offset to one other which simplifies the formation of π–π interactions. The shortest distance between the rings was 3.32 Å while the molecules of **4** are oriented opposite to each other. This self-assembly motif is further strengthened by hydrogen bonding interactions between the carbonyl group and

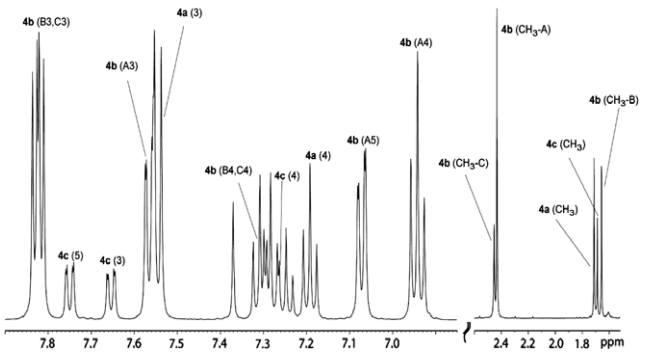


Fig. 2. ^{1}H NMR spectrum of **4** ($C_2D_2Cl_4$, 298 K).

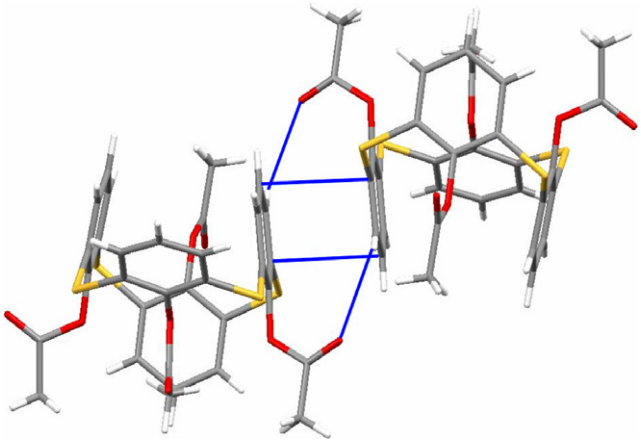


Fig. 3. Crystal packing of **4** with highlighted π–π and hydrogen bonding interactions.

hydrogens in the *meta* position (2.72 Å) of the opposite phenyl ring (Fig. 3).

In conclusion, we have shown that contrary to classical calix[4]arenes, lower-rim tetraacetoxy thiacalix[4]arenes are conformationally mobile in solution, and hence, cannot be used for immobilisation of the thiacalixarene skeleton. On the other hand, these compounds possess an interesting relationship between the upper-rim substitution (H vs Bu^t) and the conformational preferences in solution. The synthesis of higher tetraacyl derivatives which may be attractive starting materials in thiacalixarene chemistry is currently in progress.

Acknowledgement

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8. *Acylation of thiacalixarene*: Thiacalixarene **1** or **2** (200 mg) and sodium acetate (100 mg) were suspended in 10 ml of acetic anhydride, and the reaction mixture was refluxed for 2 h. After cooling to room temperature, the reaction mixture was poured into 30 ml of cold water and extracted with chloroform (3 × 20 ml). The organic layers were collected and washed successively with saturated aqueous Na_2CO_3 solution and diluted with HCl (10%). After drying with magnesium sulfate the solvent was removed under reduced pressure and the crude product was crystallised from $CHCl_3$–petroleum ether (1:1) mixture. *p-tert-Butyl-25,26,27,28-tetraacetoxythiacalix[4]arene* (**3**)—168 mg of white crystals (84% yield), mp: 282–284 °C, IR (KBr): 1773 cm^{-1}. EA calcd for $C_{48}H_{56}O_8S_4$, C, 68.84; H, 6.35; S, 14.42. Found C, 68.80; H, 6.41; N, 14.11. MS ESI+ *m/z* 911.21 $[M+Na]^+$ (100%). ^1H NMR ($C_2D_2Cl_4$, 500 MHz, 298 K) δ (ppm): *conformer* **3a**: 1.32 (s, 36H, Bu^t), 1.60 (s, 12H, –COCH_3), 7.48 (s, 8H, H-3-arom). *Conformer* **3b**: 1.14 (s, 18H, Bu^t-A), 1.42 (s, 9H, Bu^t-B), 1.45 (s, 9H, Bu^t-C), 1.85 (s, 3H, –COCH_3-B), 2.33 (s, 3H, –COCH_3–C), 2.42 (s, 6H, –COCH_3-A), 7.24 (d, 2H, $J = 2.3$ Hz, H-A5-arom), 7.46 (d, 2H, $J = 2.3$ Hz, H-A3-arom), 7.81 (s, 2H, H-C3-arom), 7.86 (s, 2H, H-B3-arom). *Conformer* **3c**: 1.35 (s, 36H, Bu^t), 1.64 (s, 12H, –COCH_3), 7.59 (d, 4H, $J = 2.0$ Hz, H-3-arom), 7.78 (d, 4H, $J = 2.0$ Hz, H-5-arom).
25,26,27,28-Tetraacetoxythiacalix[4]arene (**4**)—150 mg of white crystals (75% yield), mp: 335–337 °C, IR (KBr): 1776 cm^{-1}. EA calcd for $C_{32}H_{24}O_8S_4$, C, 57.82; H, 3.64; S, 19.25. Found C, 58.08; H, 3.51; N, 18.91. MS ESI+ *m/z* 686.95 $[M+Na]^+$ (100%). ^1H NMR (CD_2Cl_2, 500 MHz, 298 K) δ (ppm): *conformer* **4a**: 1.71 (s, 12H, –COCH_3), 7.19 (t, 4H, $J = 7.8$ Hz, H-4-arom), 7.54 (d, 8H, $J = 7.8$ Hz, H-3-arom). *Conformer* **4b**: 1.66 (s, 3H, –COCH_3-B), 2.43 (s, 6H, –COCH_3-A), 2.45 (s, 3H, –COCH_3–C), 6.94 (t, 2H, $J = 7.8$ Hz, H-A4-arom), 7.07 (dd, 2H, $J = 8.0$ and 1.4 Hz, H-A5-arom), 7.27–7.33 (2 × t, 2 × 1H, H-4B and H-4C-arom), 7.56 (dd, 2H, $J = 8.0$ and 1.4 Hz, H-A3-arom), 7.79–7.85 (2 × d, 2 × 2H, $J = 7.6$ Hz, H-3B and H-3C-arom). *Conformer* **4c**: 1.69 (s, 12H, –COCH_3),7.25 (t, 4H, $J = 7.8$ Hz, H-4-arom), 7.65 (dd, 4H, $J = 1.4$ and 7.8 Hz, H-3-arom), 7.75 (dd, 4H, $J = 1.4$ and 7.8 Hz, H-5-arom).
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10. *Crystallographic data for* **4b**·*CHCl*$_3$: $C_{33}H_{25}Cl_3O_8S_4$, $M = 784.18$ g mol^{-1}, monoclinic system, space group $P2_1/c$, $a = 14.3458(2)$ Å, $b = 14.8610(2)$ Å, $c = 16.8091(4)$ Å, $\beta = 101.7153(10)°$, $Z = 4$, $V = 3508.93(9)$ $Å^3$, $D_c = 1.26$ g cm^{-3}, μ(Mo-Kα) = 0.549 mm^{-1}, crystal dimensions of 0.20 × 0.40 × 0.50 mm. Data were collected at 150(2) K on a Nonius Kappa CCD diffractometer with graphite monochromated Mo-Kα radiation. The structure was solved by direct methods[11] using the CRYSTALS suite of programs[12] and anisotropically refined by full-matrix least-squares on F values to final $R = 0.0349$ and $R_w = 0.042$ using 6192 independent reflections ($\theta_{max} = 27.52°$) and 532 parameters. At the end of refinement, hydrogen atoms were placed in calculated positions. Crystallographic data for structure **4b**·$CHCl_3$ have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 668907. 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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