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Structure elucidation of phenoxathiin-based thiacalix[4]arene conformations using NOE and RDC data

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ABSTRACT

Phenoxathiin-based thiacalix[4]arene, obtained by the acid-catalysed rearrangement of the corresponding spirodienone derivative, was immobilized using the alkylation with chloroacetonitrile to yield three (out of four theoretically possible) stereoisomers. As the conformational outcome of the reaction could not be unambiguously assigned using standard NMR techniques, the method of Residual Dipolar Coupling constants (RDCs) was applied. The measuring of an anisotropic through-space dipole-dipole interactions in the lyotropic liquid crystalline alignment medium (PELG, poly-γ-ethyl-L-glutamate, and PBLG, poly-γ-benzyl-L-glutamate) enabled the assignment of the individual conformers. The usefulness of this approach was finally confirmed by the X-ray crystallography data.

1. Introduction

Thiacalix[n]arenes[1] represent an interesting family of macrocyclic oligophenols bearing four sulfur atoms instead of the common $-CH_2-$ bridges typical for classical calixarenes.[2] Over the last two decades, since their discovery[3] in 1997, the thiacalixarenes have demonstrated surprisingly different properties when compared with their classical analogues, as can be proven by the noticeably different conformational preferences or chemistry of these compounds.[1] Obviously, the presence of sulfur enables reactions which are impossible or virtually unknown in classical calixarene series, such as (chemo-, regio-, stereo-) selective oxidation[4] to sulfoxides and/or sulfones or the *S*-alkylation[5] to form the sulfonium ions.

Among these unusual reactions, the synthetic exploration of the so called spirodienone derivatives **2** (Fig. 1) must be mentioned. These compounds ($X{=}CH_2$) are well-known in calixarene chemistry[6] where they represent useful intermediates[7] in the preparation of some less common calixarene derivatives exhibiting substitution patterns hardly accessible using other synthetic methods. On the other hand, the monospirodienone derivative **2** ($X = S$), synthesized[8] from basic thiacalixarene **1**, showed very unusual behaviour never observed by its classical analogue. Reaction with hydrochloric acid provided the rearranged compound **3** (in an excellent 92% yield) that can be classified as phenoxathiin-based macrocycle.[9]

This compound, in fact, represents a new type of thiacalix[4]arene system possessing a rigidified cavity, which is, because of the non-symmetric nature of the bridges, inherently chiral. Hence, the further exploitation of this macrocycle as a building block in supramolecular chemistry applications could be of interest. In this paper we report on the structure elucidation of various conformers, obtained by the alkylation of the free phenolic functional groups with chloroacetonitrile, which was found to be a rather challenging task, and which was finally achieved using a combination of NMR methods and X-ray crystallography.

2. Results and discussion

The synthesis of the starting phenoxathiin-based macrocycle **3** was carried out as reported previously.[10c] Briefly, basic thiacalixarene **1** was oxidized by the sodium salt of *N*-chloro-*p*-

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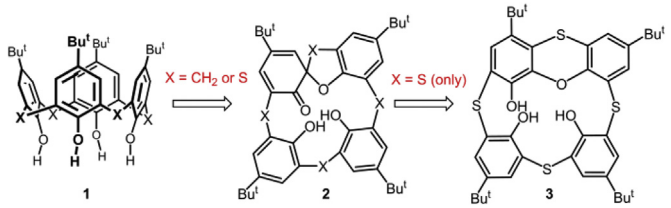
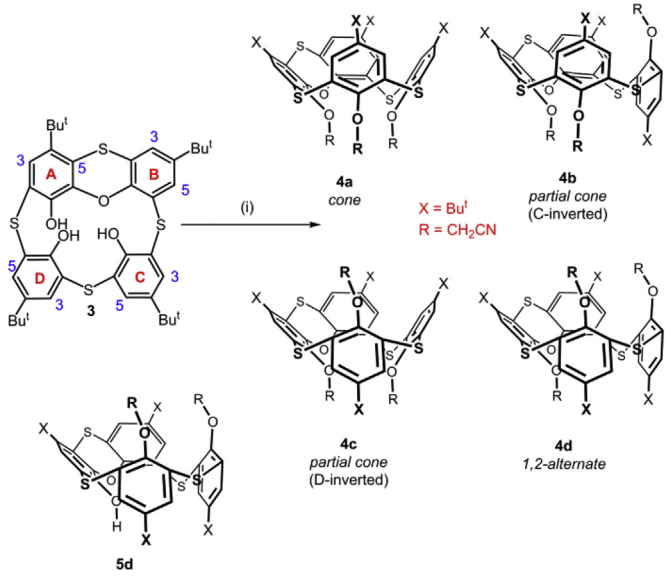


Fig. 1. The formation of phenoxathiin-based thiacalixarene.

toluenesulfonamide (chloramine-T) in MeOH-$CHCl_3$ at 0 °C for 90 min to provide the corresponding mono(spirodienone) compound **2** (X=S) in 70% yield. This compound was then reacted with conc. HCl(aq.) in MeCN at reflux to yield phenoxathiin derivative **3** in 92% yield. The alkylation of the phenolic OH groups was carried out using standard reaction conditions,[1] namely by refluxing compound **3** with chloroacetonitrile and K_2CO_3 as a base in MeCN. To enhance the reactivity of the alkylating agent a catalytic amount of NaI was added (Scheme 1). The crude reaction mixture contained four products that were isolated using iterative preparative TLC on silica gel. Thus, the three peralkylated conformers **4a**, **4c** and **4d** were obtained in 3%, 21% and 16% yield, respectively, accompanied by a small amount (4%) of dialkylated derivative **5d**.

The constitutions of the alkylated compounds were confirmed by a combination of MS and NMR techniques. Thus, the HRMS ESI^+ analysis of **4a** showed signals at $m/z = 835.26$, 858.25 and 874.22, in agreement with the expected $[M+H]^+$ (835.26004), $[M+Na]^+$ (858.24981), and $[M+K]^+$ (874.22375) cations for the trialkylated products, respectively. Similarly, the presence of only two alkyl chains was proven for compound **5d** (819.24 $[M+Na]^+$).

Generally, the structure assignment of the conformations in the classical calixarene series relies on the characteristic splitting patterns and chemical shifts of the CH_2 bridging units. From this point of view, structure elucidation of thiacalixarenes usually represents a much more challenging task due to the substitution of methylene bridges by sulfur atoms. To determine the spatial structure of the alkylated compounds, a 1D-DPFGSE-NOE[11] experiment was employed. Thus, the *cone* conformation of **4a** was assigned on the bases of NOE contacts between the aromatic protons A3-D5, D3-C5



Scheme 1. Reagents and conditions: (i) $ClCH_2CN/K_2CO_3$/NaI (cat.), MeCN, reflux, 7 days (3%, **4a**; 21%, **4c;** 16%, **4d;** 4%, **5d**). The numbering of basic skeleton for the NMR spectra shown in blue.

and C3-B5 (Fig. S1 in Supplementary Material). The *partial cone* conformation with inverted ring D **4c** was determined by the NOE contacts observed between aromatic protons C3-B5 and between the methylene protons of the CH_2CN residue of ring D and aromatic protons C5 and A3 (Fig. S2). Finally, the NOE contacts between aromatic protons C5-D3, between aromatic protons A3 and the methylene protons of the CH_2CN residue of ring D and between aromatic protons B5 and the methylene protons of the CH_2CN residue of ring C unambiguously established the *1,2-alternate* conformation of dialkylated compound **5d** (Fig. S3). Unfortunately, the NOE experiment was unsuccessful in elucidation the spatial structure of **4d** due to overlaps in aromatic region, which did not make selective excitation possible. Therefore, we utilized the method of measuring residual dipolar coupling constants (RDCs).

The RDC methodology has recently been used for a number of applications in the field of small organic molecules,[12] including calix and thiacalix[4]arene derivatives.[10] The method is based on measuring the dipole-dipole interaction of partly aligned samples. As this interaction depends on the distance of the coupled nuclei and their orientation within the external magnetic field, the RDCs include detailed spatial information, and, in contrast to NOE, provide "long range" information. The anisotropic interaction, which is averaged to zero in a solution due to fast molecular tumbling, is observable and contributes an additional splitting to the scalar (J) interaction.

Partly aligned samples of **4d** were prepared using LLC based alignment media, poly-γ-benzyl-L-glutamate (PBLG) and poly-γ-ethyl-L-glutamate (PELG).[13,14]

The RDCs were calculated using scalar coupling constants (measured in $CDCl_3$) and the total coupling constants (measured in aligned samples) according to the equation ${}^1T_{C\text{-}H} = 2{}^1D_{C\text{-}H} + {}^1J_{C\text{-}H}$ (where ${}^1T_{C\text{-}H}$ is the one-bond heteronuclear coupling constant (total splitting) elucidated from coupled ^{13}C NMR or CLIP-HSQC[15] spectra of anisotropic solution, ${}^1D_{C\text{-}H}$ is the one-bond heteronuclear residual dipolar coupling constant, and ${}^1J_{C\text{-}H}$ represents the one-bond heteronuclear scalar coupling constant elucidated from coupled ^{13}C NMR or CLIP-HSQC spectra of an isotropic solution). For the fitting procedures in program PALES[16] (Prediction of ALignmEnt from Structure) or MSPIN[17] input structures (structural proposals) were generated by *ab initio* calculation (RB3LYP/6-31G* level in Gaussian03).[18]

The fitting results for compound **4d** in both alignment media PELG and PBLG for all four structural proposals (*cone*, *1,2-alternate*, *partial cone* (C-inverted) and *partial cone* (D-inverted)) are summarized in Fig. 2 and Table S2. The comparison of the experimentally observed and back calculated RDCs for the *1,2-alternate* conformer provided excellent correlation, while the fitting procedures for the *cone*, *C-partial cone* and *D-partial cone* displayed wide differences between the experimental data and the back calculated data (Fig. 2). Both alignment media PELG and PBLG provided similar fitting results (Table S2), which confirmed our previous observations concerning the general applicability of both commercially available alignment media.[10]

Final proof of the structure of compound **4d** was obtained by single crystal X-ray analysis. The compound clearly adopted the *1,2-alternate* conformation (triclinic, space group $P\text{-}1$) which was, when compared with common thiacalixarene derivatives, highly distorted due to the presence of the phenoxathiin moiety (Fig. 3). Similarly, the *partial cone* conformation of **4c** with the D-ring inverted (monoclinic, space group $P2_1/c$) was unambiguously confirmed by single crystal X-ray analysis (see Fig. S4.).

The most interesting motif was found in the crystal packing of **4d**. Two molecules formed a dimer held together by four hydrogen bonding interactions between the C-H bonds at the *meta* positions of the phenolic rings and the nitrogen atoms from CN moieties