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Conformational Flexibility of a Novel Tetraethylether of Thiacalix[4]arene. A Comparison with the "Classical" Methylene-Bridged Compounds

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Abstract: Conformational analysis of a novel tetraethylether of thiacalix[4]arene by means of NMR spectroscopy is presented. Equilibrium between three dominant conformers *paco*, *1,3-alt* and *cone* exists in $CDCl_3$ solution at room temperature. Observed chemical exchange between conformers indicates higher internal flexibility of the title compound in comparison with similar methylene bridged analogues of tetraethylethers of calix[4]arene and p-*tert*-butylcalix[4]arene. The *cone* conformer experiences additional internal motions. © 1998 Elsevier Science Ltd. All rights reserved.

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Calix[n]arenes are a class of molecules with pronounced binding affinity to various ligands which depends on the type of substituents on the upper and lower rims. A large number of substituted calix[n]arenes have already been synthesized with the aim of modifying these binding properties.[1-6] Substitution of the original methylene bridges between the aromatic rings in calix[4]arene by sulfur has recently been introduced.[6-8] These thioethers offer promising alternatives to the original design of this class of molecules leading to dramatic changes of their dynamic and complexation properties.

Calix[4]arenes can, in general, adopt four limiting conformations as demonstrated in Fig. 1. In the literature there are several studies of the conformational behaviour of calix[4]arenes. However, interpretation of the experimental results among different authors rather diverge.[9]

Straightforward conformational studies of the tetraethylethers of calix[4]arene and p-*tert*-

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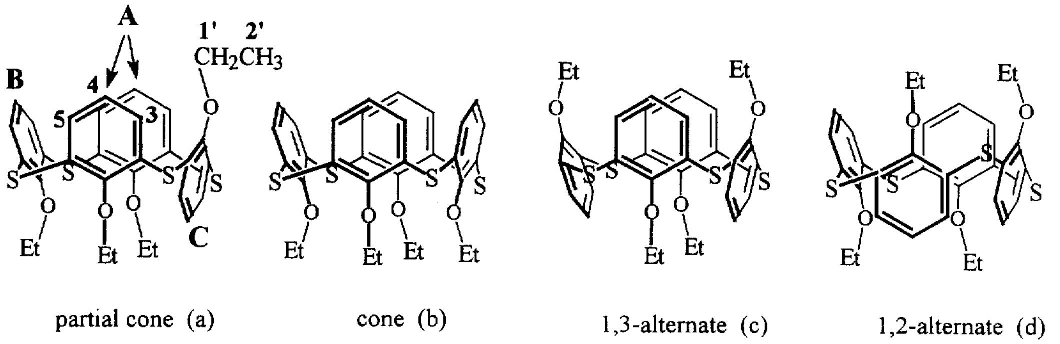

Figure 1: Limiting conformations of tetraethylether of thiacalix[4]arene (I): *partial cone* (*paco*) (a), *cone* (b), *1,3-alternate* (*1,3-alt*) (c) and *1,2-alternate* (*1,2-alt*) (d). Individual substituted rings of paco (a) are indexed as A, B, C and atom numbering within each ring is indicated (e.g. *paco*-A3).

butylcalix[4]arene (**II**, **III**, respectively)[10,11] and of related molecules[12,13] utilizing both experimental (NMR) and computational approaches have been published. It was established that the relative abundance of various conformers depends on the size of the inversion barriers of a single aryl ring. Therefore, the *partial cone* conformation (*paco*) represents an intermediate stage between the remaining three conformations. For the *cone* conformation a model of dynamic equilibrium between two "*pinched cone*" conformers was proposed on the basis of theoretical calculations. The *cone* conformer with the C_4 symmetrical geometry is a saddle point rather than a stable conformation.[13]

In this paper we present a conformational analysis of the recently synthesized[8] tetraethylether of 2,8,14,20-tetrathiacalix[4]arene (**I**) by means of NMR spectroscopy, and a comparison with the similar parent molecules containing methylene bridges. The modification of the parent calix[4]arenes by substitution of the methylene bridges by sulphur was presumed to lead to an enlargement of the calixarene cavity due to the longer C-S bond (0.177 nm)[8] in comparison with the C-C bond (0.154 nm).[14] Increasing the size of the cavity should yield increased conformational mobility, which might modify the binding capacity of the whole molecule.

The ^{1}H NMR spectrum of **I** (see Fig. 2) indicates that all possible conformers are present in solution. ^{1}H and ^{13}C resonances of single conformers were assigned by means of conventional one- and two-dimensional NMR experiments.[15] While the assignment of the *partial cone* and *1,3-alternate* (*1,3-alt*) was unambiguous, the *cone* conformer was identified indirectly. Broad aromatic signals at δ 6.64 and 7.0 ppm were shown to belong to the *cone* conformation since after increasing the temperature to 120 °C, the aromatic signals became sharper, and displayed a characteristic multiplet pattern. Moreover, the species exhibited only two aromatic resonances and one response of the ethyl group demonstrating the effective C_4 symmetry of the molecule. Broadening of the *cone* resonances at ambient temperature indicates additional conformational exchange with a free energy barrier only slightly lower than for a

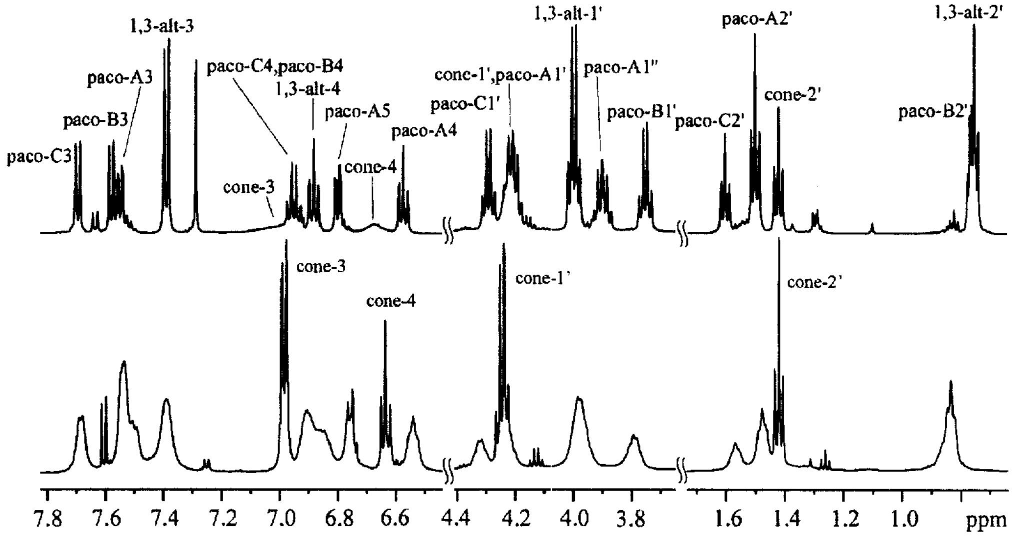

Figure 2: ^{1}H NMR spectrum of compound I acquired (a) in chloroform-d_1 at 30 °C, (b) in 1,1,2,2-tetrachloroethane-d_2 at 110 °C.[15]

single aryl ring inversion.[16] Minor signals at 7.60, 7.48, 6.73, 4.14 and 1.51 ppm probably belong to the *1,2-alternate* (*1,2-alt*) conformation. This assignment was also based on the expected number of NMR resonances corresponding to the C_2 group of symmetry.

It is worth mentioning the large differences in chemical shifts of the ^{1}H resonances of the corresponding groups. The most dramatic differences were observed for the methyl protons when the *1,3-alt* signal can be found at 0.72 ppm while the most downfield shifted resonance in this region (1.57 ppm) belongs to the methyl protons of the *paco*-C subunit (Fig. 2). The same difference in proton chemical shifts is discernible when the *paco*-C and B subunits are compared, and a similar trend, though less pronounced, can be followed when comparing the corresponding methylene resonances.

The large upfield shift of the *1,3-alternate* methyl is an effect of the adjacent aromatic rings (the ring current shift). Surprisingly, a similar shift is not observed for the *paco*-C subunit with the ring in a similar position as the rings in *1,3-alt* but for the *paco*-B subunit methyl group. This indicates that the *paco*-B ethoxy group points into the partial calix while the ethoxy groups of the subunits A and C are predominantly oriented out of the calix as supported by their downfield shifted methyl and methylene resonances. This conformation is in contrast to the observation of Gutsche *at al* who observed for the methylene-bridged calix[4]arenes **II** and **III** that the ethoxy group of the C subunits were oriented to the cavity.[10] The methyl and methylene resonances of the *cone* conformer when several ethoxy groups should point outside the calix due to steric reasons are rather deshielded as well. The ring current shift can also be observed for the aromatic resonances (compare the *paco*-A3 versus A5 resonances).

Besides the dipolar cross-relaxation between protons, the one-dimensional DPFGSE-NOE experiment[17] also revealed chemical exchange between the various conformations. It proves that the *paco* conformation is the central intermediate for the whole exchange pathway, which is described by the scheme:

$$\textit{1,3 alternate} \xleftrightarrow{K_{AP}} \textit{partial cone} \xleftrightarrow{K_{PC}} \textit{cone},$$

with relative abundance of the conformers 26:56:17, and the equilibrium constants $K_{AP} = 2.2$, $K_{PC} = 0.30$.

The equilibrium populations of the single conformers (*paco*/*1,2-alt*/*cone*/*1,3-alt*) of the thiaderivative **I** (56/traces/17/26 at 30 °C) can be compared with the parent compounds **II** and **III**, which occur only in the *paco* conformation at room temperature.[10,11] A conformational exchange of the analogue **III** takes place exclusively at elevated temperatures. An equilibrium was reached after heating for 12 hours to a temperature of 132°C yielding the ratio of 47/43/7/3 after cooling the system down to 25 °C.[11]

We conclude that all four conformers of the thia derivative calix[4]arene **I** have been found in solution. The equilibrium populations indicate different conformational preferences compared to the parent compounds. Chemical exchange observed between the individual conformers at ambient temperature confirms the higher flexibility of the sulphur-bridged scaffold. Bearing in mind the complexity of the problem, a more detailed study is in progress.

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[15] The spectra were acquired on Bruker Avance DRX 500 spectrometer. Assignment was accomplished by means of 2D ^{1}H COSY, 1D DPFGSE NOE (mixing time 2 s), 2D ^{1}H-^{13}C HMBC, 2D ^{1}H-^{13}C HMQC, 1D ^{1}H-^{13}C HSQC methods.

[16] Possible explanation might be an exchange between two C_2 symmetrical "*pinched cone*" conformers, however, with the transition barrier higher compared to the value calculated for the tetramethylether of p-*tert*-butylcalix[4]arene.[13] The reason may be an interaction of sulphur and/or the ethoxy group (e.g. via self-inclusion) with the aromatic system.

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