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Thiacalixarenes : Synthesis and Structural Analysis of Thiacalix[4]arene and of *p-tert*-Butylthiacalix[4]arene

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Abstract: The synthesis of tetrathiacalix[4]arene was achieved by the detertiobutylation of *p-tert*-butyl-tetrathiacalix[4]arene. X-ray diffraction studies revealed that in the solid state whereas *p-tert*-butyl-tetrathiacalix[4]arene forms inclusion complexes with solvent molecules, tetrathiacalix[4]arene undergoes self-inclusion leading to trimeric units. The same behaviour in the crystalline phase was also demonstrated for calix[4]arene.

For some time now, we have embarked upon a programme dealing with the formation of molecular networks in the crystalline phase by self-assembly.[1] In our approach, using inclusion processes to direct the formation of molecular a-networks in the solid state, we have been engaged in a systematic search for suitable building blocks possessing both a pre-organised cavity and chemical functionalities allowing their inter-connection. Cyclic polyphenols named calixarenes[2] (compound **1**) form an interesting class of molecules. They have been used for the design of a variety of receptor molecules or as pre-organised backbones displaying a wide range of properties.[2] In the context of the formation of molecular networks, we have extensively employed calix[4]arene derivatives in cone conformation for the design of hollow molecular modules.[1]

The increasing interest in the development of calixarenes is certainly due to their versatility in terms of structural modification. For example, dealing with calix[4]arene derivatives, the modification of both the upper and lower rims as well as partial or complete replacement of oxygen atoms by other elements has been thoroughly investigated.[3] In particular, the synthesis[4-6] and binding ability of di- and tetra-mercapto-calix[4]arenes towards mercury have been reported.[5,6]

In our search for hollow molecular modules based on the fusion of two calix[4]arene units, by varying the bulkiness of the R substituent at the upper rim, we have demonstrated that the dimension of both interconnected cavities may be finely controlled.[7] When analysing the structural features of calix[4]arene derivatives, another possibility consisting in replacing the connecting methylene groups by sulphur atoms may be the envisaged. In the present contribution we report the first synthesis of tetrathiacalix[4]arene **3** as well as structural analyses of the latter and, for comparison purposes, of calix[4]arene **4**. Although the synthesis of the parent compound **2** has been recently reported,[8] to our knowledge no structural data in the solid state are available for this compound and therefore its structural features in the solid state have been also studied.

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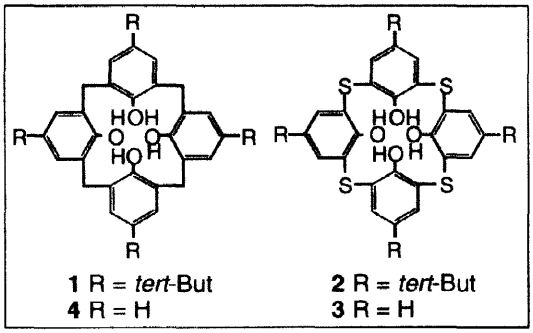

Adapting the procedure developed for the synthesis of calix[4]arene,[9] the tetrathiacalix[4]arene **3** was obtained by aluminium chloride de-*tert*-butylation of **2** in 51 % yield.[10] The inclusion ability of **2** towards small solvent molecules such as CH_2Cl_2, $CHCl_3$ and MeOH was investigated on monocrystals by X-ray diffraction methods. For both CH_2Cl_2 (Fig. 1a) and $CHCl_3$ (Fig. 1b) suitable crystals were obtained upon slow liquid-liquid diffusion of MeOH into a dichloromethane or chloroform solution of **2** respectively, whereas for the methanol inclusion complex, crystals were again grown by slow liquid-liquid diffusion of MeOH into a *p*-xylene solution of **2** (Fig. 1c). Although in all three cases X-ray data are available, in the present communication, we present only the solid state structure of the dichloromethane inclusion complex.[11]

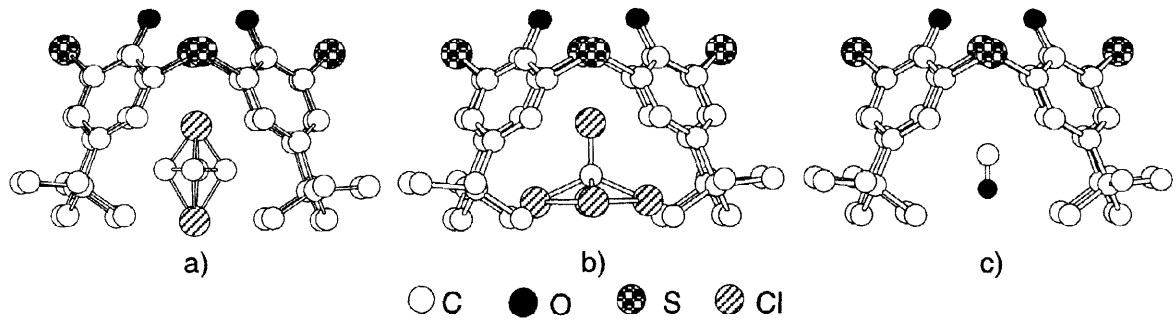

***Figure 1** : Lateral views of the crystal structures of the inclusion complexes formed by compound 2 with by CH_2Cl_2 (a), $CHCl_3$ (b), and MeOH (c). For clarity, H atoms are not presented. Both CH_2Cl_2 and $CHCl_3$ substrate as well as the p-tert-butyl groups of the receptor molecule were found to be disordered in the crystalline phase. Selected average bond distances : C-S 1.79 Å, C-O 1.34 Å.*

In all three cases, the following common structural features were observed : i) the thiacalix **2** adopts a cone conformation leading to inclusion complexes with all three guest molecules; ii) in all three cases, the substrate penetrates deeply into the cavity of the calix in cone conformation; iii) both CH_2Cl_2 and $CHCl_3$ substrates as well as the *p-tert*-butyl groups were found to be disordered in the crystalline phase; iv) the average distance between two adjacent oxygen atoms was 2.85 Å. Although one cannot exclude the stabilising role of the substrate included, the rather short distance between adjacent oxygen atoms for all three structures may be responsible for the existence of an intramolecular H-bonds array stabilising the cone conformation. In the case of **1** (average distance between two adjacent oxygen atoms of *ca* 2.70 Å), the same argument has been previously employed to justify the cone conformation at low temperature and in the solid state.[2]

In the case of dichloromethane inclusion complex with compound **2**, the crystals (tetragonal crystal system with P4/n as the space group) were formed, in a centrosymmetric mode, by alternate columns composed of inclusion complexes. (Fig. 2a). Interestingly, within each infinite column, the inclusion complexes were packed on the top of one another, leading thus to a distance of 3.31 Å between the chlorine atom of the substrate

pointing towards the exterior of the cavity and all four oxygen atoms belonging to the next thiacalix unit (Fig. 2b). For the other two cases, the same type of packing was observed.

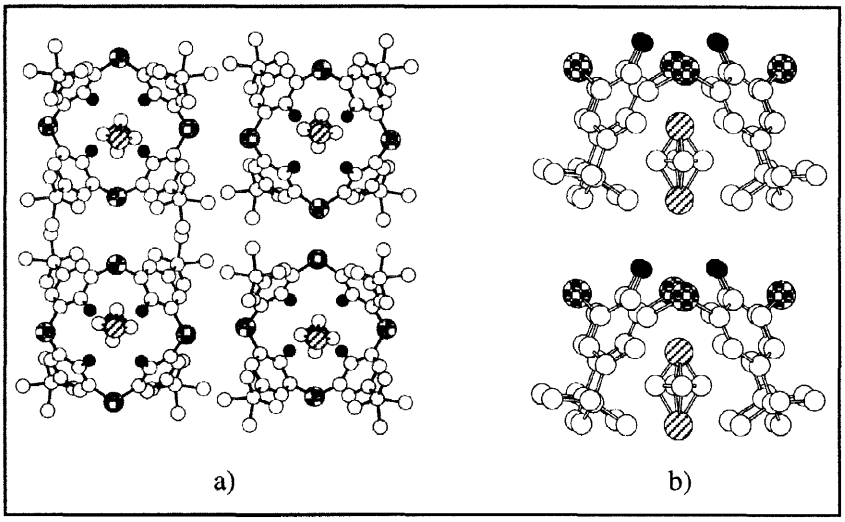

Figure 2 : Portions of the structure of the inclusion complex formed by compound 2 with CH_2Cl_2. The top view (a) shows the alternate packing of columns composed of the inclusion complexes. The lateral view (b) shows the packing of complexes within the same column. For clarity, H atoms are not presented.

The solid state structure of **3** was also investigated by X-ray analysis.[12] Suitable monocrystals were obtained upon slow liquid-liquid diffusion of hexane into a chloroform solution of **3**. The study revealed the following features (Fig. 3a): i) **3** crystallised in the hexagonal crystal system with $P6_3/m$ as the space group and the unit cell contained both **3** and two water molecules which were not localised within the cavity of the host molecule; ii) **3** adopts a cone conformation; iii) as in the above mentioned case, the average distance between two adjacent oxygen atoms of 2.64 Å may again be responsible for the formation of intramolecular H-bonded array.

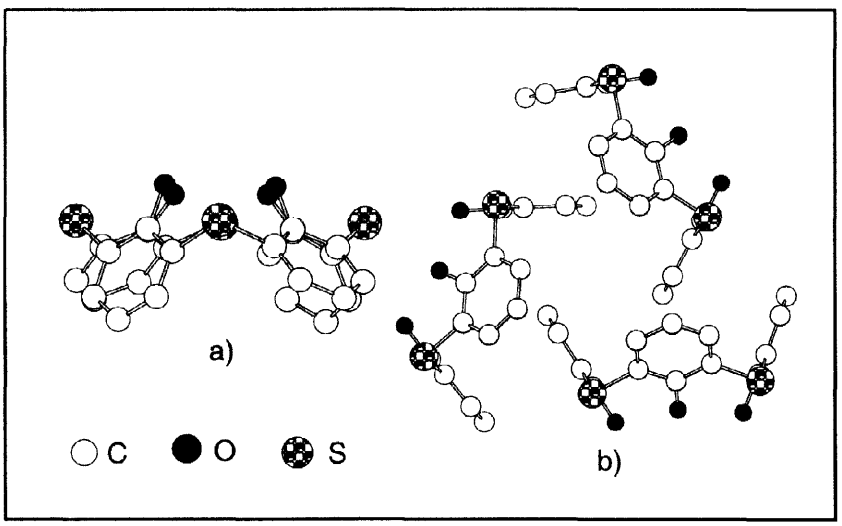

Figure 3 : Crystal structure of the compound 3: a) lateral view of the molecular unit, b) lateral view of the trimeric inclusion complex. For clarity, water molecules and H atoms are not presented. Selected bond distances : C-S 1.77 Å, C-O 1.37 Å.

Surprisingly, **3** forms, by self-inclusion, trimeric units stabilised by edge-to-face interactions between aromatic moieties(Fig. 3b). In order to further confirm this particular arrangement, suitable monocrystals of **4** were grown from CH_2Cl_2 solution and studied by X-ray diffraction. Although the structure was solved (hexagonal crystal system with $P6_3/m$ as the space group), the data will not be reported here. The study revealed that ,although in the lattice CH_2Cl_2 molecules were present, none of them was localised within the cavity of the calix adopting also a cone conformation. Interestingly, again in this case the formation of a similar trimeric

inclusion complex was observed. This observation in the solid state is not unprecedented. Indeed, the same behaviour has been previously observed for the calix[4]arene-acetone clathrates.[13]

These two aspects may be rationalised in the following manner. In the case of *p-tert*-butylcalix [4] derivatives **1** and **2**, due to the presence of bulky groups at the upper rim, self-inclusion seems to be unfavourable. Consequently, both compounds may form inclusion complexes with appropriate substrates. In marked contrast, in the case of both compounds **3** and **4**, since the formation of self-inclusion complexes may not be excluded for steric reasons, both compounds may form trimeric complexes by self-inclusion.

In conclusion, the synthesis of tetrathiacalix[4]arene **3** was achieved. A solid state structural analysis revealed that compound **3** forms by self-inclusion trimers in the crystalline phase. The same behaviour was demonstrated for calix[4]arene **4**. Since no structural data in the solid state for the parent compound **2** were reported, its binding ability towards small solvent molecules such as CH_2Cl_2, $CHCl_3$ and MeOH was established by X-ray analysis which revealed the formation of inclusion complexes in all three cases. The formation of hollow molecular modules by double fusion of compounds **2** and **3** is under current investigation.

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10 To a solution of **2** (1 g, 1.4 mmol) in dry toluene (30 ml), phenol (1.32 g, 14.0 mmol) and $AlCl_3$ (7.41 g, 55.6 mmol) were added and the mixture refluxed for 7 days before it was allowed to cool to rt. The dark solution thus obtained was poured into HCl solution (100 ml, 0.2N). The organic layer was separated and the aqueous phase was further extracted with CH_2Cl_2 (2x50 ml). The organic layers were combined, dried ($MgSO_4$) and evaporated to dryness leaving a black oil. The treatment of the latter with hexane gave a precipitate which was isolated and crystallised from a $CHCl_3$/hex. mixture affording the pure compound **3** in 51 % yield (353 mg) as a white solid. M.p. 298-300 °C; ^1H ($CDCl_3$, 200 MHz, 25 °C): d(ppm): 6.75 (t, J=7.7 Hz, 4H, Ar.), 7.61 (d, J=7.7 Hz, 8H, Ar.), 9.45 (s, 4H, OH); ^{13}C ($CDCl_3$, 75 MHz, 25 °C): d(ppm): 120.4, 121.56, 139.12, 157.83 (Ar). FAB^+ (*meta*-nitrobenzylalcohol matrix) m/z 495.9 (M^+); IR (KBr) 3277, 1438 cm^{-1}. Found: C 55.43, H 3.30; calc. for $C_{24}H_{16}O_4S_4$-0.25 $CHCl_3$: C 55.32, H 3.11.

11. *X-ray data for* **2**-CH_2Cl_2 : $C_{40}H_{48}O_4S_4.CH_2Cl_2$, M = 806.02, tetragonal, $a = b$ = 15.704(3), c = 8.604(2) Å, U = 2121(1) $Å^3$, space group P 4/n, Z = 2, Dc = 1.26 gcm^{-3}, m(Mo-Ka) = 0.378 cm^{-1}. Crystal dimensions 0.30x0.30x0.30 mm. Data were measured at 294K on a Enraf-Nonius CAD4 diffractometer with graphite monochromated Mo-Ka radiation. The structure was solved by direct methods using OpenMoleN 2.2 and refined anisotropically using absorption corrected data to give R = 0.091, Rw = 0.108 for 848 independent observed reflections [$|F_o| > 3s(|F_o|$]. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.

12. *X-ray data for* **3** : $3(C_{24}H_{16}O_4S_4).2H_2O$, M = 1525.98, hexagonal, $a = b$ = 14.908(2), c = 18.268(2) Å, U = 3516(1) $Å^3$, space group P 63/m, Z = 2, Dc = 1.44 gcm^{-3}, m(Mo-Ka) = 0.420 cm^{-1}. Crystal dimensions 0.40x0.35x0.35 mm. Data were measured at 294K on a MACH3 Nonius diffractometer with graphite monochromated Mo-Ka radiation. The structure was solved by direct methods using OpenMoleN 2.2 and refined anisotropically using absorption corrected data to give R = 0.080, Rw = 0.105 for 1056 independent observed reflections [$|F_o| > 3s(|F_o|$]. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.

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