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Solvent-Dependent Pseudopolymorphism of Tripyridoxycalix[4]arene: *cone* versus *partial-cone* Conformation

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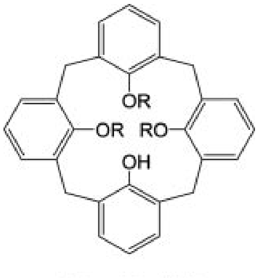
The preferred conformation of the tripyridoxycalixarene **1** in the crystalline state strongly depends on the applied solvents: The interaction with the clathrated solvent molecules influences the equilibrium between intra- and intermolecular hydrogen bonds and therefore the conformation of **1**. The *paco*-**1** molecules form methanol-containing channels; *cone*-**1** crystallizes as a clathrate with ethyl acetate fixed in the lattice voids. The conformations and their interconversion were studied by X-ray crystal structure analysis and DSC measurements.

Calixarenes are the most frequently used macrocycles to study supramolecular interactions,[1] e.g. for enzyme mimics,[2] host–guest interactions[3] or self assembly in the solid state.[4] The *p*-*tert*-butylcalix[4]arene reveals a fascinating and well-investigated polymorphism in the crystalline state, as determined by X-ray diffraction analysis, DSC or TGA, and solid-state ^{13}C NMR spectroscopy.[5] Even the absorption of versatile gases such as O_2, N_2, CO_2, or methane into the lattice voids of crystals of *p*-*tert*-butylcalix[4]arene were observed.[6] However, descriptions of other polymorph and pseudopolymorph calix[4]arenes are rare.[5,7]

As part of our ongoing studies on pyridoxycalixarenes as potential building blocks for supramolecular aggregates formed by metal-induced self assembly,[8] we discovered a preferred *cone* or *partial cone* (*paco*) conformation of tripyridoxycalix[4]arene (**1**) in the crystalline state, which is dependent on the applied solvent (Scheme 1).



1 (R = 2-Pyridyl)

Scheme 1. Structure of calixarene **1**.

X-ray diffraction quality single crystals of *cone*-**1** were obtained by the slow cooling of a saturated, boiling ethyl acetate solution. The calixarene molecules crystallize in the monoclinic space group $P2_1/n$ and contain four molecules of **1** and two disordered solvent molecules in the unit cell. The solvent molecules are fixed in the lattice voids. The pyridyl moieties are all almost orthogonal to the macrocyclic phenol units, whereas the nitrogen atoms are in the *exo* position. This is in common with the crystal structures of the other homologous pyridoxycalixarenes,[8,9] and can be explained by a repulsion of the pyridine nitrogen lone pair. Compound **1** adopts a *pinched cone* conformation, which is stabilized by just one intramolecular hydrogen bond of the unsubstituted hydroxy group to one proximal pyridoxy moiety [d(O···O) = 2.77(1) Å]. Two calixarene molecules face one another in an offset dimeric arrangement of the cavities (Figure 1a and b), with an intermolecularly almost coplanar orientation of the two phenol units. The distance between the two coplanar aromatic rings is 3.25(2) Å, which is in the typical range of π–π stacking.[10]

By slow dilution of a saturated dichloromethane solution of **1** with methanol, **1** crystallizes in the tetragonal space group $P\bar{4}2_1c$ with a *partial cone* conformation of the molecules (Figure 2a): the hydroxy group is in an *anti* position to the pyridyl substituents. The *paco*-**1** molecules build channels along the crystallographic *c* axis (Figure 2b)[8,11] that contain methanol molecules fixed by weak intermolecular hydrogen bonds to the hydroxy groups of **1** [$d(O_{Calix}\cdots O_{MeOH}) \approx 3.18$ Å]. The inner diameter of the channels is roughly 5.4 Å.

In each molecule of **1**, the pyridyl units are almost orthogonal to the connected phenol units and are fixed in an all-*syn* manner; however, in comparison to the crystal structure of *cone*-**1**, only two pyridyl rings are *exo* oriented. The nitrogen atom of the pyridyl ring in the σ_v plane is in the *endo* position and is slightly oriented towards the bottom of the calixarene molecule. The average distance between each of these pyridyl 3-H atoms and the centre of the

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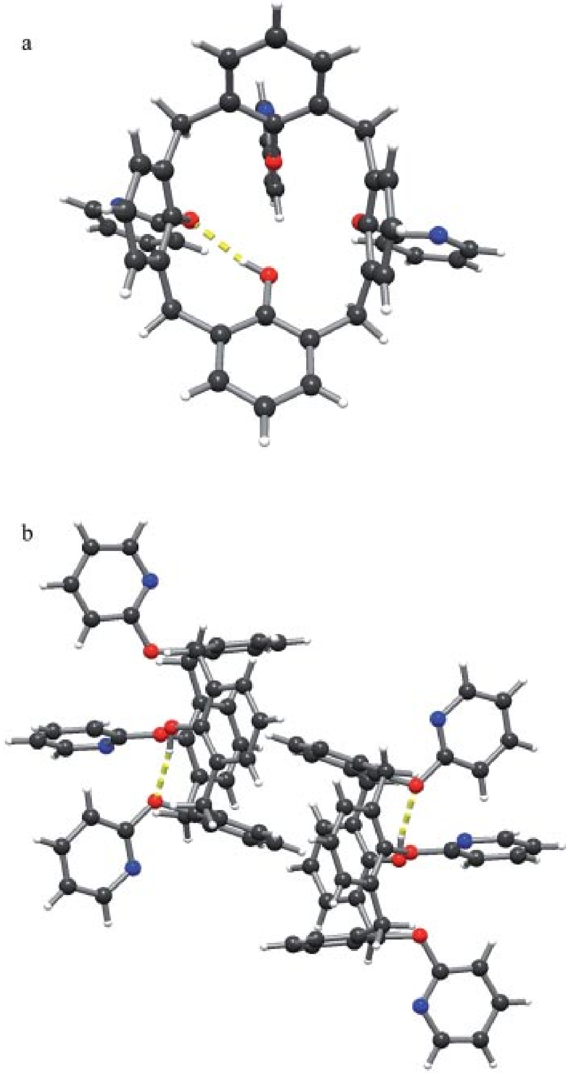

Figure 1. a: Crystal structure of *cone*-**1**. View from the upper rim into the cavity. b: Section of the crystal structure of *cone*-**1**, showing the dimeric unit in an offset arrangement.

pyridyl ring in the σ_v plane is approximately 3.5 Å, which can be regarded as a hint for intramolecular CH–π interactions.[10] The two cofacial aromatic units of the macrocyclic ring are almost parallel [dihedral angle = 4.0(8)°]. It is worth mentioning that the dihedral angle between the unsubstituted phenol ring and one of the pyridyl rings out of the σ_v plane is 3.9(8)°. However, this orientation may be induced by undirected forces of π–π stacking.[10]

Most interestingly, even in the presence of a zinc(II) or copper(I) salt, *paco*-**1** exclusively crystallizes from dichloromethane/methanol – no transition metal ion is incorporated.

Both crystal systems were investigated by DSC measurements (Figure 3). The crystals were collected by vacuum filtration and dried for 20 min in the vacuum stream of the pump at room temperature. The DSC trace of *cone*-**1** (trace b in Figure 3) shows two endothermic peaks, a small broad one at 174 °C and a sharp one at 307 °C (onset temperatures). The peak at 174 °C is caused by loss of the clathrated ethyl acetate molecules. At 307 °C, the crystals begin to melt. At higher temperatures (386 °C), the compound starts to decompose. Indeed, no peak at 174 °C was observed in the DSC trace of a sample of crystals treated in a Kugelrohr oven at 250 °C/0.8 mbar for 4 h (trace c in Figure 3) prior to use.

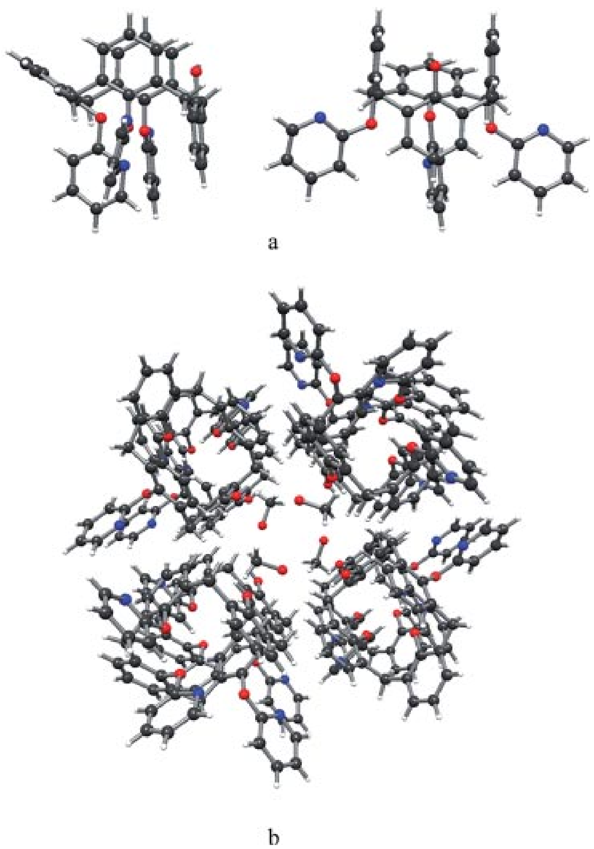

Figure 2. a: Crystal structure of *paco*-**1** from two different points of view. b: Packing of *paco*-**1**, forming methanol-containing channels along the crystallographic *c*-axis.

The DSC trace of the *paco*-**1** crystals (trace a in Figure 3) reveals the loss of methanol, which is indicated by a small, very broad endothermic peak at 162 °C. At 295 °C, a sharp endothermic peak is observed, followed directly by an exothermic peak at roughly 300 °C and another endothermic peak at 309 °C, similar to the peak observed for the *cone*-**1** sample mentioned above. This can be explained by the melting of the *paco*-**1** crystals at 295 °C, followed by conversion of the *paco* to the *cone* conformation at 300 °C, and finally melting of the *cone* compound at 309 °C. The enthalpy for the intramolecular conformational ring inversion is estimated to be $\Delta H \approx -13$ kJ/mol. This is in the expected range which correlates with the collected X-ray data and the differences in the O–H stretching bands in the IR spectra (*paco*-**1**: 3530 cm^{-1}; *cone*-**1**: 3442 cm^{-1}).[12] Again, decomposition was observed at higher temperatures (394 °C). In comparison, the DSC trace of a well-dried sample of *paco*-**1** crystals is very similar to that of the dried sample of *cone*-**1** crystals: only one endothermic peak at 309 °C was observed, which indicates that during the 4 h of drying in the

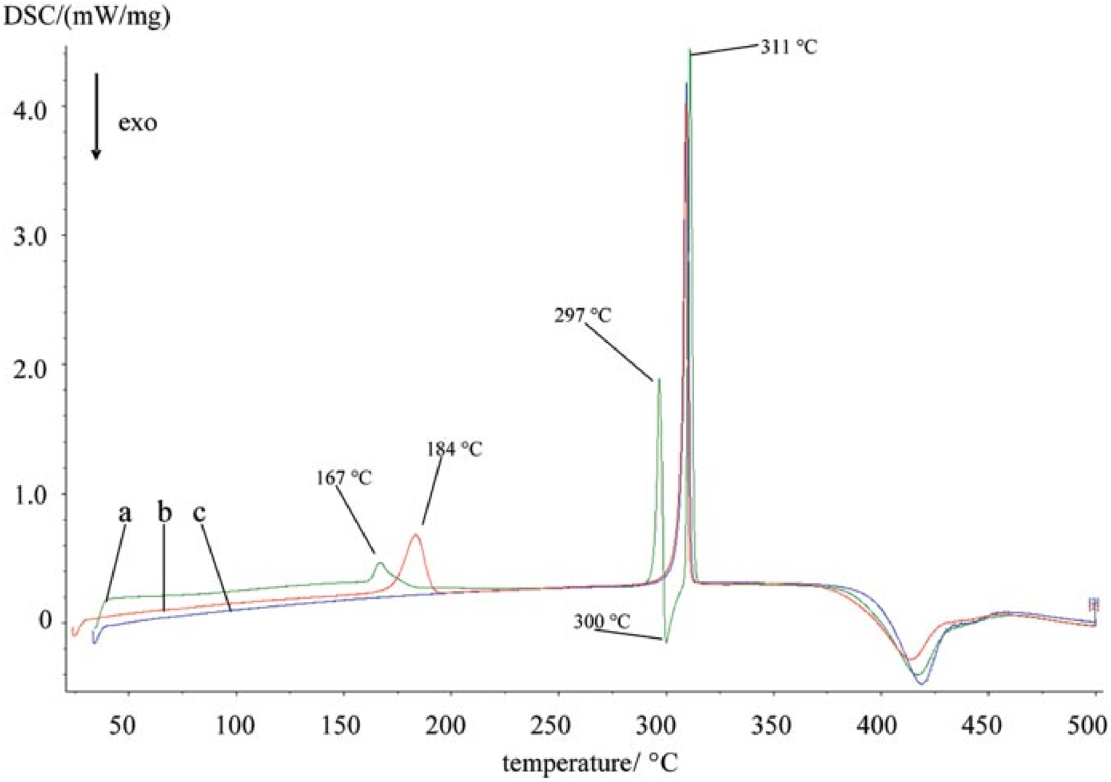

Figure 3. DSC traces of calixarene **1**. Trace a: *paco*-**1** crystals from dichloromethane/methanol; trace b: sample of *cone*-**1** crystals from ethyl acetate; trace c: well-dried sample of *cone*-**1** crystals.

Kugelrohr oven (250 °C/0.8 mbar), the clathrated methanol is removed. Thus, the *paco* conformation becomes thermodynamically unstable, such that the molecules convert into the more stable *cone* conformation and melt at 309 °C. Another DSC experiment reveals that *paco*-**1** is thermodynamically metastable without the clathrated methanol molecules: The DSC sample was first heated to 210 °C (10 K/min) and kept at this temperature for 15 min. The loss of methanol was observed in the DSC trace at 162 °C. The sample was slowly cooled to 100 °C (2 K/min) and subsequently heated to 330 °C (10 K/min). No peak at 162 °C was observed, which indicates that methanol was already removed. At 295 °C, the previously described triad of peaks could be detected once more.

In conclusion, the tripyridoxycalixarene **1** shows an exceptional solvent-dependent conformational isomerism by the thermodynamic competition between weak intra- and intermolecular forces. In contrast to the structures of crystals of the homologous pyridoxycalixarenes grown under the same conditions (dichloromethane/methanol), tripyridoxycalixarene **1** is the only compound that favors the *paco* conformation in the solid state.[8,9]

Experimental Section

IR spectra were measured with a Bruker Equinox 55 (KBr, $\tilde{\nu}$ in cm^{-1}). Calixarene **1** was synthesized according to literature.[8] DSC measurements were performed with a Netzsch DSC 204 Phoenix and a TASC 414/4 controller. The scanning rates were 10 K·min^{-1} for all samples; given are the onset temperatures. Data for both structures were collected with an Xcalibur2 [Oxford diffractometer (Cu-K_α radiation)]. Both structures were solved by direct methods and refined by full-matrix least squares using SHELXTL-97.[13] All non-hydrogen atoms were refined using anisotropic thermal parameters. CCDC-279773 (*cone*-**1**) and -279774 (*paco*-**1**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Crystal data for *cone*-**1**: T = 103(2) K, $C_{43}H_{33}N_3O_4\cdot\frac{1}{2}C_4H_8O_2$, M = 699.78, monoclinic space group $P2_1/n$, a = 12.4118(18), b = 11.8887(18), c = 24.054(3) Å, β = 96.628(11)°, V = 3525.7(9) Å^3, Z = 4, $D_{\text{calcd.}}$ = 1.318 g/cm^3, μ = 0.693 mm^{-1}, $4.15° < \Theta < 65.6°$, reflections collected/unique: 31358/5946 [R(int) = 0.0960], data/restrains/parameters: 5946/0/471, GOF = 0.982, final R [$I > 2\sigma(I)$]: R_1 = 0.0583, wR_2 (all data) = 0.1655, residual density: 0.843/–0.675 e·A^{-3}. The high residual density is due to the disordered solvent molecules, which could not be modelled with satisfaction. Crystal data for *paco*-**1**: T = 103(2) K, $C_{43}H_{33}N_3O_4\cdot CH_3OH$, M = 687.77, tetragonal space group $P\bar{4}2_1c$, $a = b$ = 26.240(3) Å, c = 10.3749(16) Å, V = 7143.7(16) Å^3, Z = 8, $D_{\text{calcd.}}$ = 1.279 g/cm^3, μ = 0.674 mm^{-1}, $4.58° < \Theta < 65.77°$, reflections collected/unique: 65412/3390 [R(int) = 0.0951], data/restrains/parameters: 3390/0/475, GOF = 1.114, final R [$I > 2\sigma(I)$]: R_1 = 0.0671, wR_2 (all data) = 0.1605, residual density: 0.475/–0.376 e·A^{-3}. Twin refinement.

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