Conformational behaviour and first crystal structures of a calix[4]arene featuring a laterally positioned carboxylic acid function in unsolvated and solvent-complexed forms†

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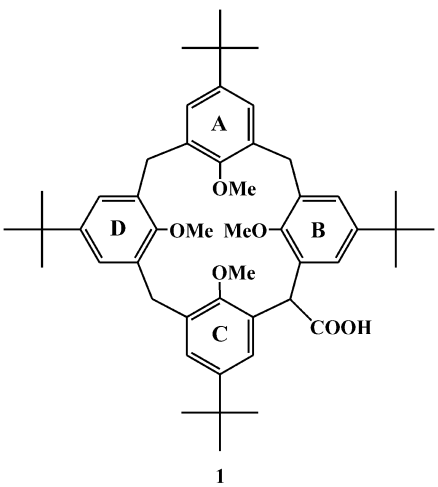
A detailed conformational analysis of a rarely investigated type of compound, a laterally monosubstituted calix[4]arene (**1**, which has a carboxylic acid function in the lateral position), is reported. 2D solution NMR techniques at various temperatures and in different solvents have been used, showing interesting aggregation behaviour for the different conformers. The first illustrations of crystal structures of this compound type are given, including the unsolvated carboxylic calix[4]arene and two mixed solvent complexes containing EtOH–H_2O and EtOH–THF, respectively. Isostructurality calculations have been carried out, allowing detailed comparison of the investigated structures, and an unusual conformational chirality isomerism of the calixarene molecule is demonstrated.

Introduction

Modification of the upper and the lower rim of the prototype calix[4]arene has been performed using a vast number of different substituents and functional groups.[1] This has given rise to an enormous range of individual structures of calix[4]-arene derivatives, some of which feature a very complex construction.[2] Many of them have been studied in detail with reference to their conformational behaviour,[3] inclusion properties[4] and more specific features, such as optical sensing.[5] On the other hand, derivatives of calix[4]arenes possessing modified methylene units on the backbone of the central ring are far less developed[6,7] (except for the thia-[8] and homo-calix[4]arenes,[9] which have complete replacement of the methylene bridges). In particular, examples of compounds that have only one of the methylene groups modified by hydrogen substitution are very rare.[10] Yet, this kind of lateral monosubstitution may open prospects for the design of new host structures, functional units and supramolecular aggregates based on calix[4]arene.[2] Another point of interest is the conformational behaviour of the calix[4]arene framework dependent on the lateral substitution.[10c,d]

In this paper, we describe in detail the conformational behaviour of a laterally monosubstituted calix[4]arene **1** (Scheme 1) featuring a carboxylic acid function on one of the methylene bridges, *i.e.* possessing a laterally attached carboxylic group. Analysis was performed in solution using 2D NMR techniques at various temperatures and in different



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1a: **1**·EtOH·H_2O (1:1:1)

1b: **1**·EtOH·THF (1:1:1)

Scheme 1 The compounds studied in this paper.

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† Electronic supplementary information (ESI) available: Complete ^1H and ^{14}C NMR data of **1** in $CDCl_3$ and TCl-d_2 at 269 and 295 K, respectively (Tables S1–S4); selected conformational parameters of the calixarene molecules (Table S5) and geometric parameters of the noncovalent interactions in the crystal structures (Table S6). Complete ^1H NMR spectra of **1** in TCl-d_2 (Fig. S1) at 269 and 295 K; DOSY spectra of **1** in $CDCl_3$ at 269 K (Fig. S2) and TCl-d_2 at 295 K (Fig. S3); denotation of **1** used for X-ray interpretation (Fig. S4); crystal packing diagrams of **1** and **1b** (Fig. S5 and S6); isostructural packing diagram of **1a** and **1b** (Fig. S7); superimposed conformations of the calixarene molecules in **1**, **1a**, **1b**, and the parent calixarene (Fig. S8 and S9). CCDC reference numbers CCDC-722388, CCDC-722389 and CCDC-722390. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b904489b

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solvents. We also provide the first illustration of a crystal structure of this compound class, reporting on the crystal structures of two mixed-guest inclusion compounds of **1** formed with EtOH–H_2O (**1a**) and EtOH–THF (**1b**). Moreover, isostructurality calculations[11] were carried out, allowing a detailed comparison of the investigated crystal structures, and pointing to an unusual conformational chirality isomerism in these structures.

Results and discussion

Compound preparation

The calixarene **1** was synthesized from the parent tetra-*tert*-butylcalix[4]arene[12] by permethylation[13,14] and carboxylation reactions following described protocols.[10a] The inclusion compounds **1a** and **1b** were obtained by recrystallization of **1** from the corresponding solvent mixtures.

NMR structural study in solution

Remarkably, tetramethoxytetra-*tert*-butylcalix[4]arenes substituted at one of the methylene bridging groups have only rarely been investigated by NMR spectroscopy in solution.[10c,d] In contrast with the unsubstituted parent calix[4]arene,[15] which adopts mainly a *partial cone* (*paco*) conformation in $CDCl_3$, compound **1** was previously found to form a pure *cone* structure in a 2:1 mixture of chloroform and acetonitrile. However, this measurement involved the presence of sodium ions, which would certainly have an effect on the conformation.[10] Consequently, the present conformational NMR study was performed free of sodium ions, *i.e.* without the interference of cation coordination, using solutions of **1** in $CDCl_3$ or 1,1,2,2-tetrachloroethane-d_2 (TCl-d_2). Under these circumstances, a complicated pattern of signals in the NMR spectra is displayed at various temperatures, indicating the existence of different conformers.[16] (Fig. 1 and Fig. S1†). This stimulated us to perform detailed 2D NMR studies using COSY, ^1H–^{13}C-correlated HSQC and HMBC as well as NOESY and ROESY methods, leading to a complete determination of conformational structures of **1** with full ^1H and ^{13}C signal assignment (Tables S1–S4†) and their distribution in solutions of $CDCl_3$ and TCl-d_2 at room temperature and below (Scheme 2 and Table 1). Starting from the methine proton H-1 at the substitution centre, the numbering of all positions in the different conformers is illustrated in Scheme 3.

The 2D NMR experiments clearly show that two *partial cone* conformers, *paco-1* and *paco-2* are present, as well as the *1,2-alternate* and the *cone* conformations (Scheme 2), as indicated by the HSQC spectrum in the region of the OCH_3 groups (Fig. 2). This behaviour of **1** in solution is also supported by the detailed ROESY spectrum (Fig. 3a). Here, with exception of the *paco-1* isomer, we found strong positive ROE-correlations between the H-1 methine protons, always axially positioned, and the H-8 methoxy protons, indicating the vicinity of the latter with reference to the lower rim H-1 (Fig. 3b) and also the *syn*-orientation of the arene units next to the lateral substituent for the *paco-2*, *cone* and *1,2-alternate* conformers. Further characteristic interactions involving the aromatic protons and the protons of the OCH_3 or *tert*-butyl groups neighbouring a methylene bridge, marked in Fig. 3a and b and Scheme 2, suggest the orientation of the arene units on the

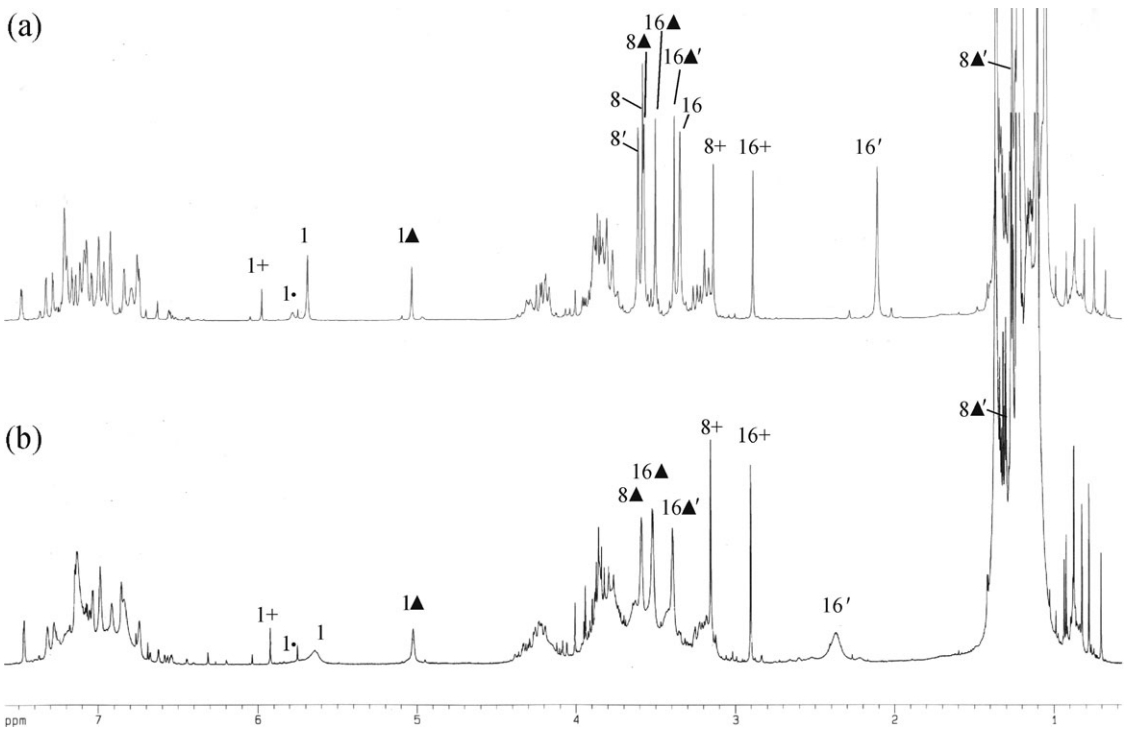
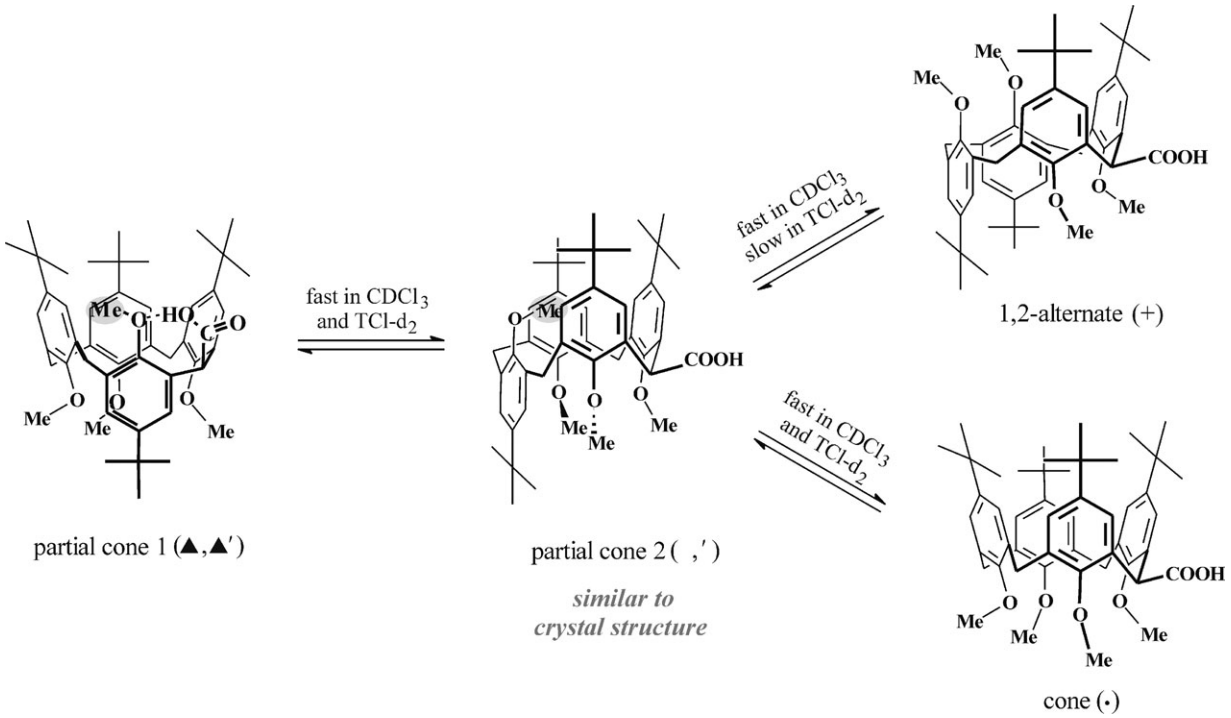


Fig. 1 ^1H spectrum of **1** in $CDCl_3$ at (a) 269 K and (b) 295 K showing the signals of the different conformers [*paco*-1 (▲/▲′), *paco-2* (, ′), *cone* (·) and 1,2-*alt* (+)].



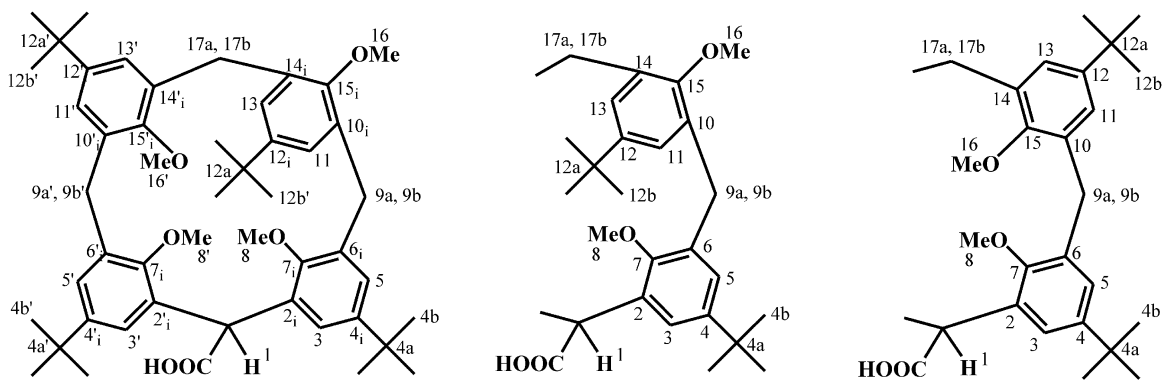
Scheme 2 Conformational transformations of **1** in solution.

Table 1 Distribution of the conformers of **1** in solutions of $CDCl_3$ or TCl-d_2 at various temperatures (mol%)

	$CDCl_3$		TCl-d_2	
Conformer	295 K	273 K	295 K	263 K
paco-1 (▲/▲′)	40	29	61	69
paco-2 (/′) / *cone* (·)	53[a]	48/14	32[a]	26[a]
1,2-alternate (+)	7	9	6	5

[a] Because of similar chemical shifts and the temperature-dependent signal broadening it is not possible to differentiate between the paco-2 and cone conformers under the assigned conditions.

central calixarene ring for each individual isomer. Following this, the *1,2-alternate* conformation can be assigned due to the H-16+/H-5+ crosspeaks as well as the relations H-12b+/H-8+ and H-4b+/H-16+. The *paco-2* conformer is clearly determined by the H-8′/H-11′ and H-16′/H-13 crosspeaks, and in addition by H-12b/H-5. The strongly shifted H-16′ proton of *paco-2* suggests that the related methoxy group also points inside the cavity, which is in accordance with the result of the X-ray structure (see below). On the other hand, we found for the designated *paco-1* isomer a conspicuously upfield-shifted methine proton at 5.02 ppm and a deshielded C-1 atom at 58.7 ppm. This suggests an isoclinal arrangement of the neighbouring arene units,[16] which was also confirmed by a respective ROESY spectrum of **1** performed in TCl-d_2 at 263 K. As shown in Table 1, the content of the *paco-1* isomer is particularly high under these conditions. Based on the strong correlations H-8▲/H-1▲ and H-1▲/H-3▲′, we observe two characteristic crosspeaks (H-16▲′/H-5▲′ and H-4b▲′/H-8▲)



Scheme 3 Numbering of atoms in molecule **1** for NMR examination.

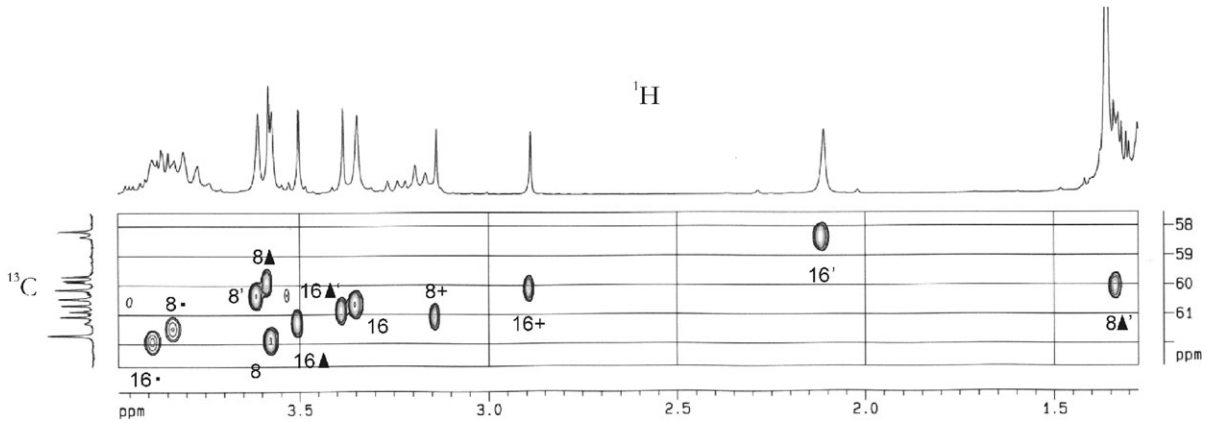


Fig. 2 HSQC spectrum of **1** in $CDCl_3$ at 265 K. Only the region of the OCH_3 groups is shown.

as well as crosspeaks between the aromatic protons (H-11▲/H-5▲ and H-13▲/H-13▲′) leading to the proposed structure of the *paco-1* isomer.[17] Furthermore, it is very likely from the unusually upfield-shifted proton H-8▲′ (δ = 1.41 ppm!) that the corresponding methoxy group points into the cavity. Hence, an intramolecular H-bond involving the lateral COOH group can be formed as illustrated in Scheme 2, and the obvious difference between the corresponding shifts of *paco-1* with reference to the other three conformers (173.6 *vs.* 180.0 ppm for the carbonyl C-18 atom and 9.3 ppm *vs.* 12.0 ppm for the OH group; Tables S1 and S3†) is reasonable. Additional MM calculations of different possible conformational patterns of the present substitution type show that the four conformations discussed are stable and adopt similar ground-state energies.[18]

Because of the possible formation of hydrogen-bonded carboxylic dimers in the present rather apolar solvents, we measured diffusion-ordered (DOSY) 2D NMR spectra with bipolar gradients (Fig. 4, Fig. S2 and S3†). Using a solution of **1** in $CDCl_3$ at 265 K, the relevant section of the DOSY spectrum in Fig. 4 exhibits a clear separation between the methine H-1 signals of the *paco-2*, *1,2-alternate* and *cone* isomers of **1**, respectively, with slow molecular diffusion, while the signal H-1▲ for the *paco-1* isomer indicates a faster diffusion. Recently we have found that the *paco-1* isomer shows a similar high diffusion coefficient, being in the same level as the presumed monomeric conformers of a related compound featuring a laterally *n*-propyl substituted calixarene.[19] Therefore, we propose a monomeric structure for *paco-1* with an intramolecular H-bond, and more aggregated species with strong intermolecular H-bonds for the other conformers of **1** in solution.

Furthermore, in Fig. 3a, negative cross-peaks between different H-1 proton signals can be observed due to chemical exchange processes that occur in the form of a dynamic interconversion of different isomers. To extract the rate constants for the conformational chemical exchange (k_{chem}), the 2D-EXSY method[20] was used to calculate the free activation energies $\Delta G^{\#}$ (listed in Table 2 and illustrated in Scheme 2). As expected, the lower the temperature the lower is the chemical exchange. Moreover, the different conformers show variable rates in $CDCl_3$ and 1,1,2,2-tetrachloroethane-d_2 (TCl-d_2) solution. Interestingly, the activation energies range between 15.2 and 15.7 kcal mol^{-1} in $CDCl_3$ at 295 K, which is faster than reported values[21] for the *partial cone* interconversion of the non-carboxylic parent calixarene, amounting to approximately 13 kcal mol^{-1} under comparable conditions. Considering the higher polarity and smaller size of the $CDCl_3$ molecule, the reorientation of the arene unit in $CDCl_3$ is faster than in TCl-d_2. Hence, TCl-d_2 promotes the formation of *paco-1* and reduces the tendency for conformational change.

X-ray structural study

In order to gain knowledge of the conformational species frozen in the solid state, an X-ray crystal structure of the calixarene **1** was determined. In addition, we studied the crystal structures of two ternary (or mixed) inclusion compounds of **1** formed with EtOH–H_2O or EtOH–THF, both in stoichiometric ratios host:guest-1:guest-2 of 1 : 1 : 1, that is **1a** (**1**·EtOH·H_2O) and **1b** (**1**·EtOH·THF) (Scheme 1). A common-atom labelling diagram for the calixarene framework is given in Fig. S4†. Crystallographic data and selected refinement parameters of the structures are summarized in Table 3. Perspective views of the molecular structures are shown in Fig. 5 and 6, while illustrations of the crystal packings are given with Fig. S5 and S6†. In general, the conformation of the calixarene framework can be described by a set of interplanar angles which defines the inclination of the aromatic rings A–D with respect to the mean plane given by the methylene atoms C(7), C(14), C(21) and C(28). These data are included in Table S5†. Hydrogen bond parameters are listed in Table S6†. In these crystal structures, the calixarene skeleton itself is highly ordered, whereas some of the *tert*-butyl substituents in **1** and **1a** are disordered over two positions.

(a) Crystal structure of 1. Crystallization of the calixarene **1** from methanol yields solvent-free crystals of the monoclinic space group $P2_1/n$ with one molecule in the asymmetric unit. As illustrated in Fig. 5, the calixarene adopts a slightly distorted *partial cone* conformation in which the aromatic rings B and D are at an interplanar angle of 19.8(1)° to one another, but oriented in opposite directions. The dihedral angle between the opposite arene rings A/C is 99.9(1)°. The carboxy group, which is located in the energetically favourable

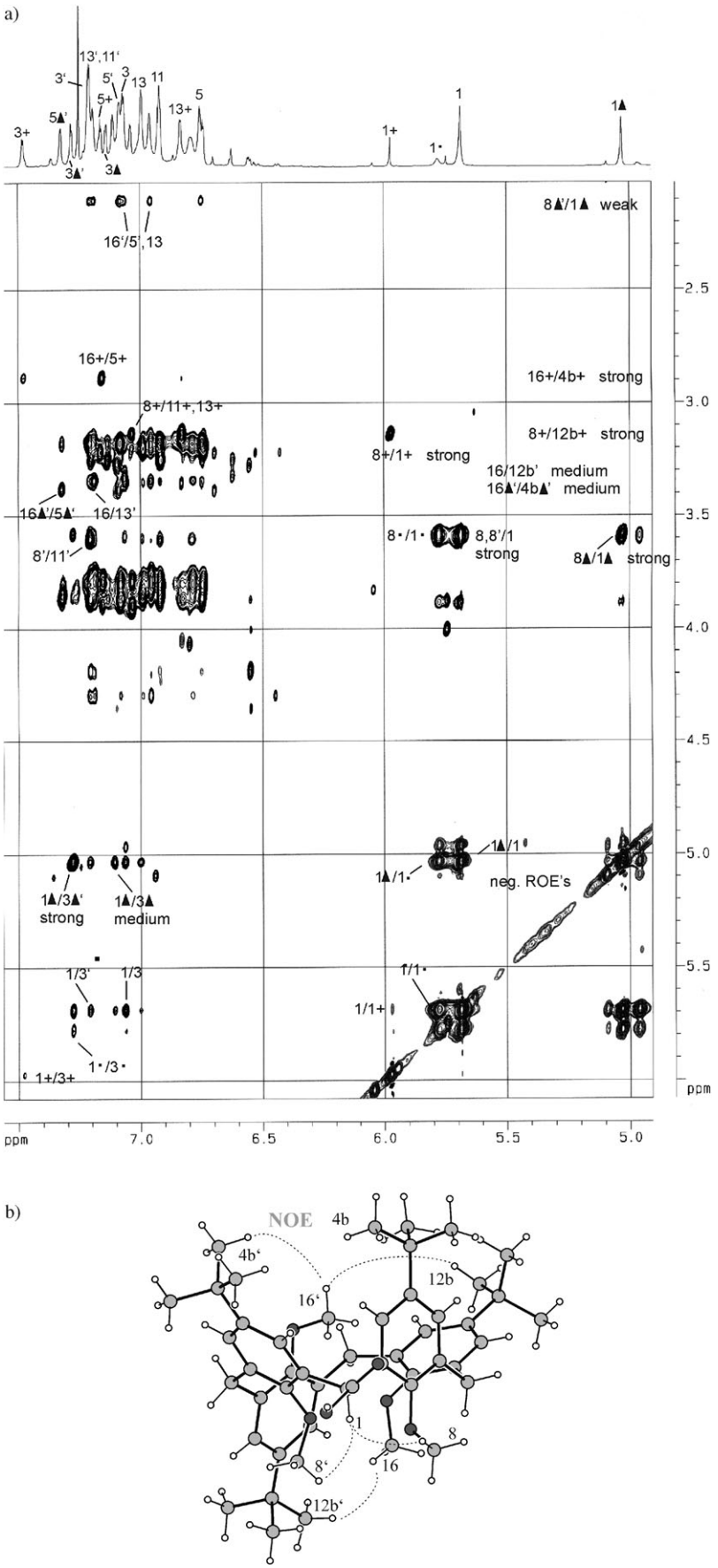


Fig. 3 (a) Detail of the ROESY spectrum of **1** in $CDCl_3$ at 265 K. (b) Molecular structure of **1** with NOE interactions detected by ROESY experiments.

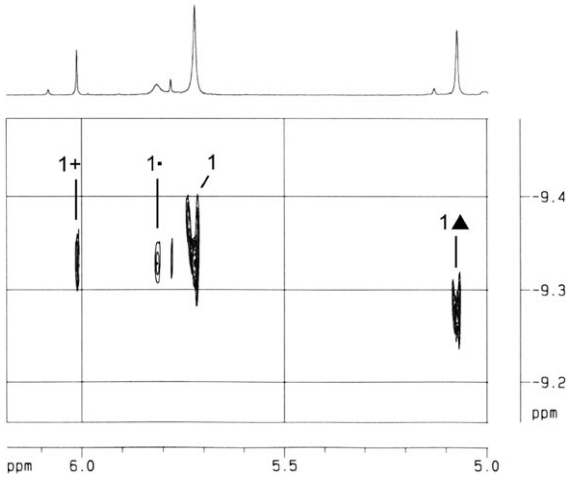


Fig. 4 Detail of the DOSY spectrum of **1** in $CDCl_3$ at 265 K.

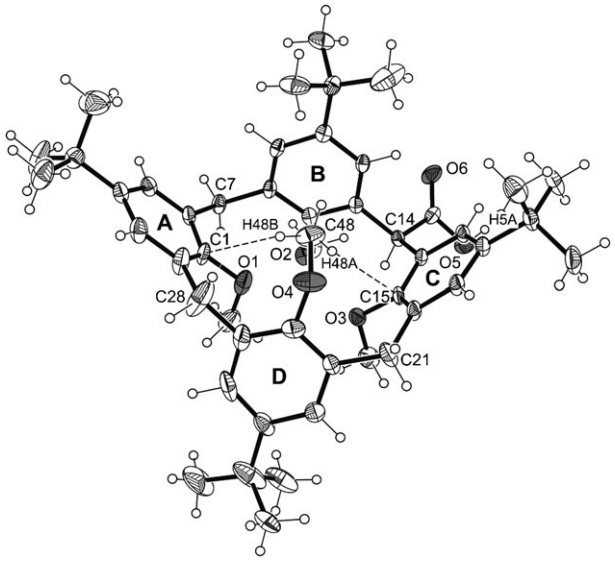


Fig. 5 Perspective view of the calix[4]arene **1** including the atom numbering of relevant atoms. Thermal ellipsoids are drawn at the 40% probability level. Broken lines represent C–H···π hydrogen bond type contacts.

equatorial position, is rotated in an angle of 42.9(3)° with respect to the mean plane given by the methylene carbon atoms. An interesting feature of the molecular structure is that, similar to the *paco-2* conformer detected in solution, the lower-rim substituent of the down-oriented ring D is inserted into the cavity, which allows relatively strong C–H···π interactions[22] between its methyl hydrogens and the π-electron systems of the aromatic rings A and C. In order to achieve reasonable hydrogen bond geometries, individual carbon atoms instead of ring centroids are chosen as acceptor positions [H(48A)···$C(15)_{ring\,C}$ 2.52 Å; H(48B)···$C(1)_{ring\,A}$ 2.58 Å].

The packing behaviour of **1** (Fig. S5†) is dominated by two strong hydrogen bonds involving the carboxylic functions of two neighbouring calixarene molecules to yield a common carboxylic dimer [O(5)–H(5A)···O(6) 1.82 Å, 166.4°]. These dimers are stacked in the direction of the crystallographic *a*-axis. Steric shielding of the aromatic units caused by their bulky upper-rim substituents and outward-oriented methoxy substituents prevents effective intermolecular arene–arene interactions, so that the crystal structure is primarily stabilized by van der Waals forces.

(b) Crystal structures of 1a and 1b. Crystallization of the calixarene **1** from aqueous ethanol–ethyl acetate or an ethanol–tetrahydrofuran mixture yields the inclusion complexes **1a** [**1**·EtOH·H_2O (1 : 1 : 1)] and **1b** [**1**·EtOH·THF (1 : 1 : 1)], respectively. Identical space groups ($Pca2_1$) as well as the similar cell parameters (Table 3) indicate that the crystal structures of **1a** and **1b** are isomorphous. Hence, a detailed characterization can be confined to the crystal structure of **1b**. Structural similarities are evident from Fig. 6a and 6b, which depict the asymmetric units of **1a** and **1b**.

Although in the inclusion structures **1a** and **1b** the calixarene molecules also exist in a *partial cone* geometry, the detailed conformational parameters differ from that shown in the unsolvated structure **1** (Table S5†). In the case of **1b**, the relatively strong intramolecular C–H···π interactions[22] formed between the methoxy substituent located inside the calixarene cavity and two flanking aromatic rings A and C seem to stabilize the molecular structure, which is obvious from the unusually short contact distances between methyl hydrogens and the centres of the arene rings [C(48)–H(48C)···centroid(A) 2.30 Å, 152°; C(48)–H(48A)···centroid(C) 2.29 Å, 153°]. The interplanar angle between the facing rings A/C is 23.5(2)°, while the pair of aromatic rings oriented in opposite directions (rings B and D) have an angle of 34.2(1)°. The carboxylic substituent is inclined at an angle of 77.1(3)° with respect to the reference plane of the calixarene. The ethanol guest molecule (GA) is associated in the expected manner to the carboxylic group of the host by a strong hydrogen bond with

Table 2 Rate constants k_{chem} and activation energies $\Delta G^{\#}$ of the conformers of **1**

	k_{chem} (s^{-1})				$\Delta G^{\#}$ (kcal mol^{-1})				
	$CDCl_3$		TCl-d_2		$CDCl_3$		TCl-d_2		
Conformer pair	295 K	273 K	295 K	265 K	295 K	273 K	295 K	260 K	Coalescence in TCl-d_2
paco-1/*paco-2*	14.4	8.0	18.6	1.8	15.7	14.8	15.5	14.9	16.4 (T_c = 363 K)
paco-2/*cone*	Fast	18.9	Fast	—	—	14.3	—	—	T_c > 363 K[a]
paco-2/*1,2-alternate*	34.9	0.6	5.9	—	15.2	16.2	16.2	—	T_c > 363 K[a]
paco-1/*cone*	Fast	7.1	Fast	—	—	14.9	—	—	T_c > 363 K[a]
paco-1/*1,2-alternate*	18.6	0.1	8.6	—	15.5	17.4	16.0	—	T_c > 363 K[a]

[a] The coalescence could not be determined exactly up to 363 K.

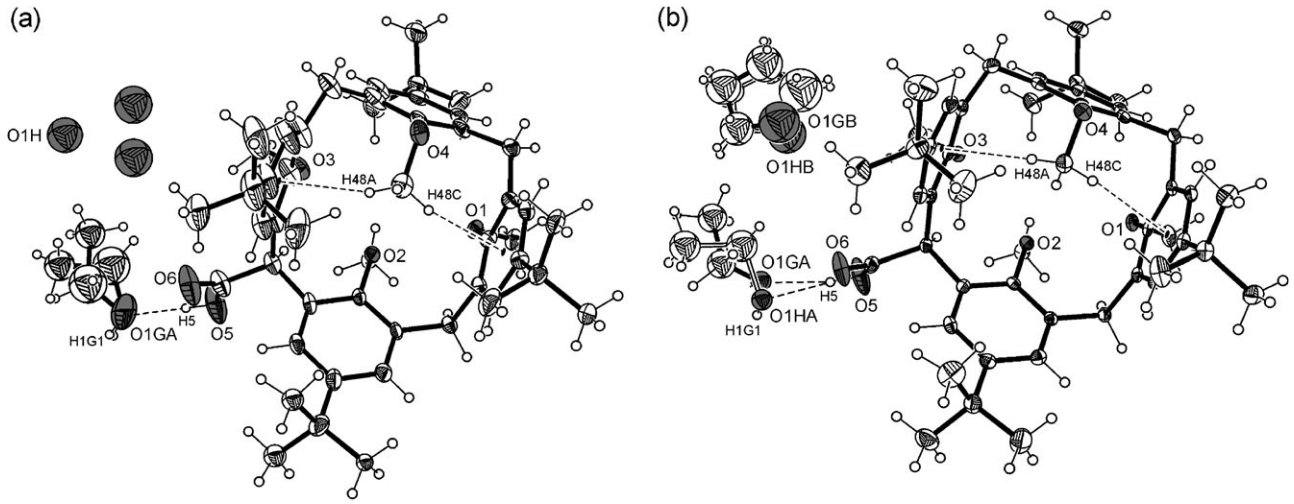


Fig. 6 Perspective views of the stoichiometric units of (a) **1a** [**1**·EtOH·H_2O (1 : 1 : 1)] and (b) **1b** [**1**·EtOH·THF (1 : 1 : 1)] including the atom numbering of relevant atoms. Thermal ellipsoids are drawn at the 40% probability level. Broken lines represent hydrogen bonding contacts.

Table 3 Crystal data and selected details of the data collection and refinement calculations of compounds **1**, **1a** and **1b**

Compound	**1**	**1a**	**1b**
Empirical formula	$C_{49}H_{64}O_6$	$C_{49}H_{64}O_6{\cdot}C_2H_5OH{\cdot}H_2O$	$C_{49}H_{64}O_6{\cdot}C_2H_5OH{\cdot}C_4H_8O$
Formula weight	749.00	813.09	867.17
Crystal system	Monoclinic	Orthorhombic	Orthorhombic
Space group	$P2_1/n$	$Pca2_1$	$Pca2_1$
a/Å	10.0674(8)	23.887(5)	23.9696(6)
b/Å	13.3559(9)	17.151(3)	17.1752(5)
c/Å	33.067(2)	12.429(3)	12.4147(3)
α/°	90.0	90.0	90.0
β/°	98.054(2)	90.0	90.0
γ/°	90.0	90.0	90.0
V/Å^3	4402.3(6)	5092.1(18)	5110.9(2)
Z	4	4	4
F(000)	1624	1768	1888
D_c/g cm^{-3}	1.130	1.061	1.127
μ/mm^{-1})	0.073	0.070	0.074
Data collection			
T/K	173(2)	93(2)	93(2)
No. of collected reflections	23 568	38 796	58 087
θ-range/°	1.2–21.6	1.5–25.1	1.2–27.1
Index ranges $\pm h$, $\pm k$, $\pm l$	−10/10, −13/13, −31/34	−28/28, −20/20, −14/13	−30/30, −22/21, −15/15
No. of unique reflections	5085	4759	5898
R_{int}	0.0643	0.0592	0.0472
Refinement calculations: full-matrix least- squares on all F^2 values			
Weighting expression w^a	$[\sigma^2(F_o^2) + (0.0850P)^2 + 0.0000P)^{-1}$	$[\sigma^2(F_o^2) + (0.1633P)^2 + 3.0043P)^{-1}$	$[\sigma^2(F_o^2) + (0.0833P)^2 + 1.1865P)^{-1}$
No. of refined parameters	538	562	578
No. of F values used [$I>2\sigma(I)$]	3062	3725	5183
Final R-indices			
R (= $\Sigma\|\Delta F\|/\Sigma\|F_o\|$)	0.0604	0.0791	0.0566
wR on F^2	0.1613	0.2411	0.1619
S (= Goodness of fit on F^2)	1.027	1.054	1.044
Final $\Delta\rho_{max}/\Delta\rho_{min}$/e Å^{-3}	0.44/−0.35	0.55/−0.46	0.53/−0.49

[a] $P = (F_o^2 + 2F_c^2)/3$.

the carboxyl hydrogen acting as a donor site [O(5)–H(5)···O(1GA) 1.73 Å, 169°], whereas the OH hydrogen of the alcohol is connected to the methoxy oxygen of another calixarene molecule [O(1GA)–H(1G1)···O(4) 1.91 Å, 150°]. Consequently, hydrogen-bonded molecular chains extending along the c-axis and with an alternating order of calixarene and alcohol molecules are the basic supramolecular aggregates of the crystal structure (Fig. S6†). Molecules of adjacent strands are displaced by half a translation unit. The non-centrosymmetry of the crystal structure implies that the polar molecular strands have a unique running direction, giving rise to a polar character of the crystal. A view of the crystal packing in the a-direction reveals that the THF molecules, as the second guest species, are accommodated on sites

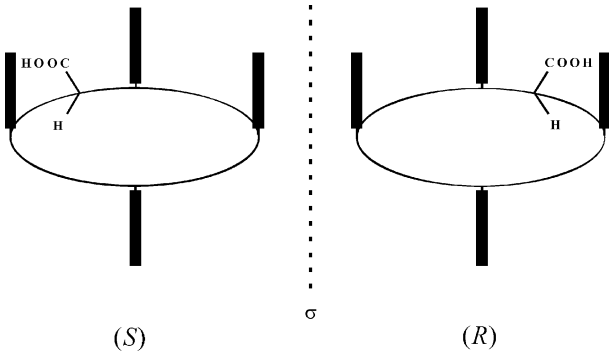


Fig. 7 Scheme illustrating the molecular conformation and the resultant enantioisomerism of **1** in the present structures.

between the molecular strands. The fact that these latter guest molecules are fixed by the steric barrier of the host lattice rather than non-covalent bonding may explain the molecular disorder and relatively large displacement parameters.

The conformation of the calixarene molecule in **1a** is highly similar to that of **1b**. Hence the presence of a water molecule instead of THF neither affects the semirigid calixarene molecular structure nor influences the packing behaviour of the calixarene and alcohol molecules. However, the lack of any steric fit of the water molecule, which is located between the supramolecular strands, induces an even higher degree of molecular disorder.

(c) A special steric feature. An interesting finding relating to the conformation of the calixarene in the three structures is as follows. In a supposed *cone* conformation, the benzylic carbon atom carrying the carboxy group features a prochiral centre. However, in the present case of the *partial cone* conformation it becomes a centre of chirality due to the asymmetric geometry of the calixarene. This rather uncommon mode of stereoisomerism is not easy to handle. However, in order to determine the absolute configurations of the respective enantiomers, the systematic of rules described by Prelog[23] and Mata[24] provide a possible answer to the problem (Fig. 7). According to these rules, the proximate arene groups can assume a *cis* or *trans* configuration. For example, starting from the chirality center, this leads for the (*S*)-enantiomer to a clockwise *seqcis-seqtrans* or *unlike* order and an anti-clockwise *seqtrans-seqtrans* or *like* configuration for the (*S*)-enantiomer starting from the chirality center. The descriptor of the absolute configuration follows from the priority of the substituents of the stereogenic center: (1) COOH, (2) like, (3) unlike. Corresponding to the space groups of the crystals, the calixarene molecules are connected by a glide plane symmetry, resulting in racemic crystals.

(d) Isostructurality calculations. The cell similarity (π), the isostructurality [$I(s)$] as well as the molecular isometricity indices [$I(m)$] were estimated for the compounds **1**, **1a** and **1b**.[11,25,26]

As mentioned before, the crystal structures of **1a** and **1b** are isostructural (Fig. S7†). The calculated cell similarity index is 0.00173. The isostructurality index for the calixarene molecules (homostructurality) in **1a** and **1b** is 88.5%. Besides the increase of the unit cell (Table 3), we find a change in the space group from $P2_1/n$ for **1** to $Pca2_1$ for **1a** and **1b** by the solvent uptake. A remaining total potential solvent-accessible area[27] of 100.0 Å^3 (2.3% per unit cell volume) was calculated for **1** (*cf.* a hydrogen-bonded H_2O molecule occupies $\approx$40 Å^3, and a small molecule such as toluene requires 100–300 Å^3).

The molecular similarity index for the solvate structures in comparison with the solvent-free **1** was calculated without the possibly rotating terminal methyl groups of the *tert*-butyl moieties (43 atoms) to be 80.89 for **1a** and 81.21 for **1b**. While a high conformational similarity of **1** is observed in the solvent complexes, the conformation of the unsolvated calixarene **1** is significantly different (Fig. S8a, S9a, S9b†). This is best demonstrated by the different distances between the methoxy oxygen atom of the rotated aryl moiety and the plane determined by the other three methoxy oxygen atoms, as well as the angle between the rotated phenyl group and the same plane (Table S5†).

The molecular structure of **1** has also been compared with the corresponding parent tetramethoxycalix[4]arene without the carboxylic acid substituent (Fig. S8b, S9c, S9d†), CCDC reference code KEVXUE.[28] This latter compound involves two crystallographically independent molecules in the asymmetric unit. The molecular isometricity was calculated to be 74.59 for **1**/KEVXUE1 and 74.86 for **1**/KEVXUE2 (40 heavy atoms; excluding the carboxylic moiety and the methyl groups of the *tert*-butyl units). The conformations of the two crystallographically independent molecules in KEVXUE are rather similar (98.07). Unlike the conformations in **1a** and **1b**, the methoxy group of the down-oriented arene moiety points outward, and the cone conformation of the calixarene is even more open.

Conclusion

A detailed structural study including the conformational behaviour of the tetramethoxytetra-*tert*-butylcalix[4]arene **1** featuring a laterally attached carboxylic function has been performed both in solution and in the crystalline state. In $CDCl_3$ or 1,1,2,2-tetrachloroethane-d_2 solution, the calixarene **1** undergoes a fast interconversion of arene units with relatively low activation energies of about 15.2–17.4 kcal mol^{-1} at room temperature, dependent on the solvent. These are higher values than mentioned in the literature for the non-carboxylic parent calixarene. Due to the steric crowding by the *tert*-butyl groups on the upper rim, the formation of less symmetrical *partial cone* conformers is favoured, whereas the more symmetric *cone* and *1,2-alternate* conformations are less populated. The existence of a special monomeric *partial cone* conformation (*paco-1*) with an intramolecular hydrogen bond in apolar solvents is proved using the DOSY NMR technique as well as MM calculations, while the *paco-2*, *1,2-alternate* and *cone* conformers of **1** give rise to aggregated species.

In the crystalline state, **1** adopts a similar conformation to the *paco-2* conformer in solution, with the methoxy group of the down-oriented aromatic ring pointing into the cavity of the calixarene molecule both in the unsolvated compound and the solvent complexes (**1a** and **1b**), although the individual conformations of the calixarene in **1** and the complexes differ rather significantly, as substantiated by a molecular similarity calculation. The solvents are thus not accommodated in the

calixarene cavity but are located outside. The carboxylic dimer formation, typical of the unsolvated packing structure, changes to hydrogen-bonded strands in the solvent complexes, showing an alternating order of calixarene and alcohol molecules, while the second species of guest solvent molecules, THF or water, are on interstitial sites between the strands. It is worth noting that the non-carboxylic parent compound of **1** also crystallizes in a *partial cone* conformation,[28–30] but here the methoxy groups of the down-oriented aromatic rings point out of the cavity, giving an opportunity for the *endo* inclusion of solvent molecules.[31]

Hence, the introduction of a laterally positioned carboxylic acid function clearly influences the conformational behaviour of the corresponding parent calixarene molecule, with potential relevance for both the crystal-engineering[32] and inclusion properties of calixarenes.[1,3,4] Analogously functionalized calixarenes are also promising in the realm of immobilized devices[33] and organized nanoarchitectures.[2,34] Therefore, the present findings may stimulate more detailed studies of this particular class of laterally substituted calix[4]-arenes, especially if two or more carboxylic groups are attached in a lateral position. Investigations in this direction are ongoing in our group.

Experimental

General methods

^{1}H, ^{13}C and 2D NMR spectra were recorded on a Bruker DRX 500 MHz spectrometer. The chemical shifts are expressed in ppm with respect to TMS as an internal standard (δ = 0 ppm), and coupling constants are reported in Hz. The 2D DOSY experiments were performed using the pulse programme *ledbpgp2s* with 16 steps and a gradient strength P30 = 4400 μs.

Preparation of compounds

The title calixarene **1**[35] was synthesized from 5,11,17,23-tetra-*tert*-butyl-25,26,27,28-tetrahydroxycalix[4]arene[12] according to the literature. Crystals of unsolvated **1**, suitable for X-ray diffraction, were obtained by slow evaporation of a solution in MeOH. The inclusion compounds **1a** and **1b** were obtained by recrystallization of **1** from EtOH–ethyl acetate (1:1) and EtOH–THF (1:1), respectively.

X-Ray crystallography

The crystal data and experimental parameters of **1**, **1a** and **1b** are summarized in Table 3.† Single crystals of the compounds, suitable for X-ray diffraction study, were obtained by recrystallization from the solvents used for their synthesis. The intensity data were collected on a Kappa APEX II diffractometer (Bruker-AXS) with graphite-monochromated CuKα radiation (λ = 0.71073 Å) using ω- and φ-scans. Reflections were corrected for background, Lorentz and polarization effects. Preliminary structure models were derived by application of direct methods[36] and were refined by full-matrix least-squares calculation based on F^2 for all reflections.[37] An empirical absorption correction based on multiple scans was applied by using the SADABS program.[38] With the exception of the disordered solvent molecules (water in **1a**, THF in **1b**) all non-hydrogen atoms were refined anisotropically. All hydrogen atoms were included in the models in calculated positions and were refined as being constrained to bonding atoms. In case of the inclusion structures, the disordered *tert*-butyl group and the water molecule in **1a**, as well as the tetrahydrofuran in **1b**, proved difficult to model and therefore were only refined isotropically. In the course of the refinement procedure, the bond lengths of the disordered parts of the *tert*-butyl groups in **1** and **1a**, the alcoholic component in **1a** and **1b**, and the THF molecule in **1b** were constrained to target values of 1.54(1) Å for C–C, 1.48(1) Å for C–O and 0.84(1) Å for O–H bonds. Because of the weak diffraction power of the crystals of the unsolvated calixarene, only a poor data set could be obtained, resulting in a resolution of Θ = 21.62° and a data-to-parameter ratio of 5.8. Nevertheless, we succeeded in refining the crystal structure to an acceptable level, as reflected by the reasonable standard of uncertainty in the geometrical parameters.

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