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ORIGINAL RESEARCH

Comparative X-ray structural study of laterally mono-ethyl substituted 5,11,17,23-tetra-*tert*-butyl-25,26,27,28-tetramethoxycalix[4]arene and its non-substituted parent compound including guest free and solvated forms. Chemical straightening of guest channels

Conrad Fischer · Guisheng Lin · Petra Bombicz · Wilhelm Seichter · Edwin Weber

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Abstract Three solvate crystal structures of the laterally ethyl substituted tetra-*tert*-butyltetramethoxycalix[4]arene **1** [(**1**·THF (**1a**), **1**·$CHCl_3$ (**1b**) and **1**·CH_2Cl_2 (**1c**)] are compared to the corresponding solvent-free structure (**1**) using single crystal X-ray structure determination, isostructurality and molecular isometricity calculations. To study the effect of the lateral substitution, the laterally non-substituted host with the guest THF (**2a**) is also included to the comparison. The calixarene molecules in the different structures all adopt the *partial cone* conformation with different affection of the respective guest molecules, always being positioned interstitially. Depending on the lateral substitution and the size of the included guests, the molecular conformation of the calix[4]arene shows small differences relating to the alignment of the arene units. The channels disposable of the solvent guest molecules in the crystal structures straighten as the effect of lateral substitution of the host calix[4]arene. The orthorhombic crystal structures of **1a–c** are isostructural irrespective of the included solvent molecules, while **1** and **2a** crystallise in the same monoclinic space group.

Keywords Calix[4]arene · Inclusion compounds · Single crystal X-ray analysis · Isostructurality calculations · Crystal engineering

C. Fischer · G. Lin · W. Seichter · E. Weber (✉)
Institut für Organische Chemie, TU Bergakademie Freiberg, Leipziger Str. 29, 09596 Freiberg, Sachsen, Germany
e-mail: edwin.weber@chemie.tu-freiberg.de

P. Bombicz
Institute of Structural Chemistry, Chemical Research Center, Hungarian Academy of Sciences, P.O. Box 17, 1525 Budapest, Hungary

Introduction

Since decades, calixarenes act as attractive building units for supramolecular systems as they can be obtained easily and offer a huge range of possible modifications [1]. They consist of a hydrophobic cavity capable of binding small molecules and a hydrophilic lower rim, which after adequate functionalization is suitable for the complexation of ionic guest molecules. These facts result in a broad variety of applications in the field of ion sensing and reversible guest inclusion as well as for objects of biomimetics [2]. Another reactive site, giving rise to lateral substitution, involves the bridging methylene units which, however, has much less been taken into consideration for making calixarenes useful [3–6]. Even studies of the inclusion properties of simple laterally monosubstituted calix[4]arenes in the solid state are rather rare [7–9] although we recently reported the conformational behaviour of such monoalkyl substituted calix[4]arenes [10] and of a carboxy functionalized analogue [11] both in crystalline state and in solution. Here, we describe crystal structures of the unsolvated laterally ethyl substituted tetra-*tert*-butyltetramethoxycalix[4]arene **1** and its solvated inclusion compounds with tetrahydrofuran (THF) (**1a**) and dichloromethane (**1c**), and comparatively discuss these structures including also the known structures of the inclusion complexes of **1** with chloroform (**1b**) [10] and of the basic laterally non-substituted parent calixarene **2** with THF (**2a**) [12] (Fig. 1). A detailed study of structure and molecular similarity by means of isostructural and molecular isometricity calculations [13, 14] is performed in order to make the conclusions with regard to solvent and lateral substitution effects sound.

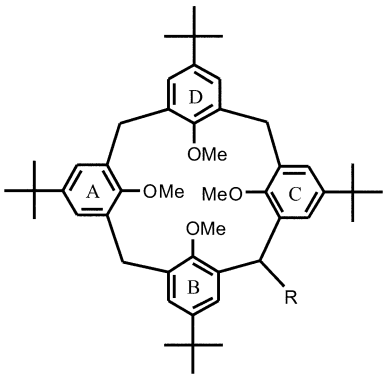

Fig. 1 Chemical structures of the compounds studied in this article with denotation of the aromatic rings

Experimental

The title calixarene, 2-ethyl-tetra-*tert*-butyltetramethoxycalix[4]arene (**1**), was prepared as described in our recent article [10] and following the references therein.

X-ray structure determination

Single crystals of **1**, **1a** and **1c** suitable for X-ray diffraction were obtained by slow evaporation of solutions of the calixarene **1** in acetonitrile/MeOH (1:1), THF/MeOH/Et_2O (1:2:2) and CH_2Cl_2/ethanol (1:1), respectively. The diffraction data were collected on a Bruker APEX II diffractometer with MoK_α radiation ($\lambda = 0.71073$ Å) using ω- and φ-scans. Reflections were collected for background, Lorentz and polarization effects. Preliminary structure models were derived by application of direct methods and were refined by full-matrix least squares calculation based on F^2 for all reflections [15]. All hydrogen atoms were included in the models in calculated positions and were refined as constrained to bonding atoms. Crystal data and details of the structure determination and refinement can be found in Table 1.

Isostructural and isometricity calculations

The cell similarity index (π) has been calculated as $\pi = [(a + b + c)/(a' + b' + c') - 1]$, where a, b, c, and a', b', c' are the orthogonalized lattice parameters of the compared crystals [14]. In the event of great similarity of the two unit cells, the value of π is close to zero [16]. For the calculation of the isostructurality index [I(s)], the distance differences between the crystal coordinates of identical non-H atoms within the same section of the related structures were used [14], taking into account both the differences in the geometry of the molecules and the positional differences caused by rotation and translation. The molecular isometricity calculations [I(m)]were carried out by least-squares fitting of the positions occupied by the identical heavy atoms of the two related molecules [13].

Results and discussion

While the solvent-free laterally ethyl substituted tetra-*tert*-butyltetramethoxy-calix[4]arene **1** (Fig. 1) shows the monoclinic $P2_1/n$ space group, its three solvate structures with THF (**1a**), $CHCl_3$ (**1b**) [10] and CH_2Cl_2 (**1c**) (Fig. 2) crystallise in the same orthorhombic space group $Pca2_1$. The THF solvated laterally non-substituted tetra-*tert*-butyltetramethoxycalix[4]arene **2a** [12] has the same space group as the laterally substituted calixarene **1** in unsolvated form. The calixarene inclusion structure **2a** differs from all the other presented structures involving **1** in Z′. There are two crystallographically independent host and guest molecules in the asymmetric unit of **2a** (their **2a1/2a2** conformations are rather different; the calculated molecular isometricity index I_m [13, 14] for the 40 non-hydrogen atoms of the calix[4]arene frame without the *tert*-butyl substituents is 92.54%), while only one host–guest pair is present in **1** and **1a–c**. Thus, only the crystals **1a–c** are isostructural. Both cell similarity (π) and isostructurality (I_s) indices [13, 14] calculated for 54 non-hydrogen atoms of the ethyl substituted host molecule in its inclusion crystals **1a–c** (Table 2) are high. The cell itself and the host conformation and placement in the cell are somewhat closer in the THF (**1a**) and CH_2Cl_2 (**1c**) inclusion structures compared to the $CHCl_3$ containing solvate (**1b**).

In a more detailed examination, similar to the laterally unsubstituted calix[4]arene **2a** [12], due to the absence of any intramolecular hydrogen bonding at the lower rim, the framework of the ethyl derivative **1** adopts a *partial cone* conformation, which has already been calculated to be the lowest energy conformer [10]. The calice exhibits a nearly coplanar arrangement of the aromatic units A and C, whereas the rings B and D enclose an angle of 49.7° (Table 3). The calixarene conformation of **1** can also be characterized by the angle of the arene rings with reference to the plane determined by the bridging methylene units (Table 3). In accordance with the lateral unsubstituted calixarene **2** [17], all methoxy groups point out of the cavity and therefore maintain no intramolecular interactions. In comparison with **2a**, the solvent-free lateral ethyl pendant **1** shows a similar molecular conformation, represented by high molecular isometricity indices I_m [13, 14] of 95.07% for **1/2a1** and 97.45% for **1/2a2** (Fig. 3a).

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

Compound	**1**	**1a**	**1c**
Empirical formula	$C_{50}H_{68}O_4$	$C_{54}H_{76}O_5$	$C_{51}H_{70}Cl_2O_4$
Formula weight (g/mol)	733.04	805.15	817.97
Crystal system	Monoclinic	Orthorhombic	Orthorhombic
Space group	$P2_1/n$	$Pca2_1$	$Pca2_1$
a(Å)	14.1735(7)	23.9039(7)	23.9285(6)
b(Å)	14.2566(6)	16.7362(5)	16.7150(4)
c(Å)	22.2241(10)	12.6603(3)	12.6920(4)
α(°)	90.00	90.00	90.00
β(°)	93.9420(10)	90.00	90.00
γ(°)	90.00	90.00	90.00
V(Å^3)	4480.1(4)	5064.9(2)	5076.4(2)
Z/Z'	4/1	4/1	4/1
F(000)	1,600	1,760	1,768
D_c (mg m^{-3})	1.087	1.056	1.070
μ (mm^{-1})	0.067	0.066	0.167
Data collection			
Temperature(K)	133(2)	96(2)	100(2)
No. of collected reflections	90,696	29,541	35,690
Within the θ limit (°)	1.65–28.40	1.22–28.35	1.22–25.60
Index ranges $\pm h$, $\pm k$, $\pm l$	−18/18, −19/19, −29/29	−31/26, −22/18, −12/16	−27/29, −20/18, −7/15
No. of unique reflections	11,236	6,601	5,006
R_{int}	0.0652	0.0772	0.1098
Weighting expression, w[a]	$[\sigma^2(F_o^2) + (0.0795P)^2 + 2.4643P]^{-1}$	$[\sigma^2(F_o^2) + (0.1070P)^2 + 2.0188P]^{-1}$	$[\sigma^2(F_o^2) + (0.1561P)^2 + 3.1769P]^{-1}$
No. of refined parameters	504	526	531
No. of F values used $[I > 2\sigma(I)]$	8,901	5,356	3,763
Final R indices			
R (= $\Sigma\|\Delta F\|/\Sigma\|F_0\|$)	0.0478	0.0574	0.0741
wR on F^2	0.1550	0.1783	0.2485
S (=Goodness of fit on F^2)	1.020	1.038	1.113
Final $\Delta\rho_{max}/\Delta\rho_{min}$ (e Å^{-3})	0.000	0.000	0.000

Corresponding data for **1b** [10] and **2a** [12]

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

In contrast, the molecular geometry of the calixarene host in the three solvates **1a–c** is marginally affected by the enclosed solvent molecules, which are always located interstitially in the vicinity of the aromatic ring C neighbouring the lateral ethyl substituent. Obviously, as a result of the C–H···π interactions [18] with the aromatic ring C (Table 4), the clathrate-like included solvent molecules in the complexes of **1** lead to a slight flattening of the calice in comparison to the guest free structure **1**. The opposing arene units A and C in all three solvates of **1** differ slightly from coplanarity (8.1–8.9°, Table 3), but the rings B and D enclose a perspicuously lower angle of 42.8–43.8° compared to the solvent-free calixarene **1**. The calixarene host molecular conformation is assisted by two weak C–H···O intramolecular secondary interactions [19] (C7–H7···O1 and C14–H14···O3) in all **1**, **1a–c** and **2a** structures, reducing the flexibility of the calixarene moiety where the arene units are placed upwards. The calculated molecular isometricity indices I_m [13, 14] prove the high molecular conformational similarity of the calix[4]arene hosts (Fig. 3b): **1a/1b** 98.99%, **1a/1c** 99.44% and **1b/1c** 99.47% calculated for all 54 non-hydrogen atoms. This value I_m of 97.98% for **1/1a** is getting lower comparing the calix[4]-arene hosts' 54 non-hydrogen atoms as a result of guest inclusion into the crystal. As a subsidiary effect of the lateral ethyl substituent, the molecular similarity decreases

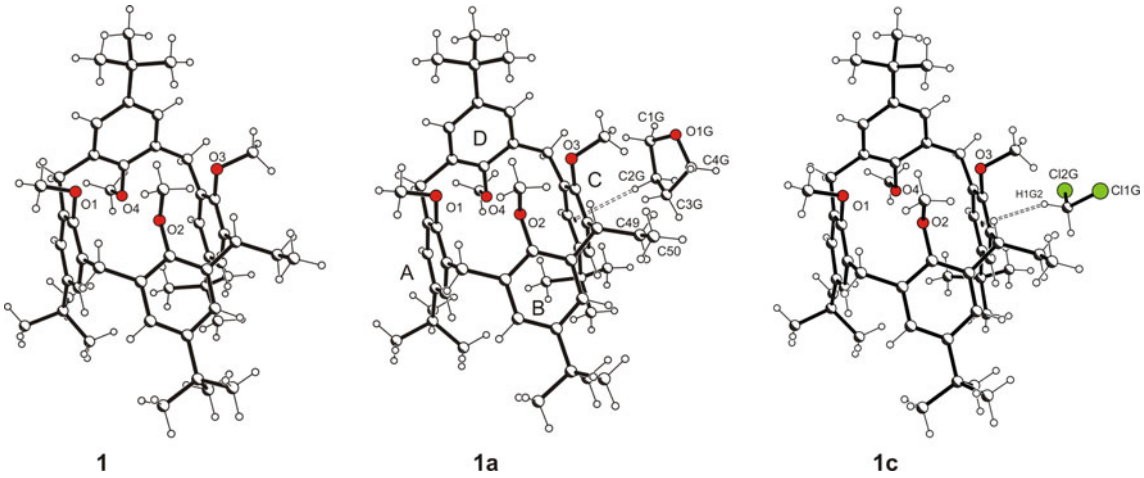

Fig. 2 Molecular structures of **1**, **1a** and **1c**. Heteroatoms are *shaded*

Table 2 Cell similarity index (π) and isostructurality index (I_s) calculated for 54 non-hydrogen atoms of the ethyl substituted tetra-*tert*-butyltetramethoxycalix[4]arene **1** in its solvates **1a–c**

Compounds	π	I_s (%)
1a/1b	0.00250	92.18
1a/1c	0.00066	96.88
1b/1c	0.00185	93.96

compared to the unsubstituted parent compound **2a** (Fig. 3a). Considering the two crystallographically different host molecules in the asymmetric unit of **2a**, the molecular isometricity indices (I_m) calculated for the host framework excluding the lateral ethyl substituent and the *tert*-butyl groups are 94.99% for **1a/2a1** and 95.68% for **1a/2a2**.

Owing to the absence of strong hydrogen donor sites and the non-polar nature of the calixarene host, the packing arrangement of all **1**, **1a–c** and **2a** structures is controlled by weak intermolecular C–H···π-interactions (Table 4) and van der Waals forces, meanwhile no π···π interactions [20] at all are observed. In detail, in the guest free structure **1**, a weak C–H···π-interaction is observed involving a *tert*-butyl group and the aromatic ring C of a neighbouring calixarene molecule [C(49)–H(49A)···*centroid*(C) 3.7164(4)]. A typical interaction between one methoxy group and an aromatic unit of the neighbouring calixarene molecule [C(33)–H(33C)···*centroid*(B) 3.475(4) Å (**1a**); C(33)–H(33A)···*centroid*(B) 3.4855 Å (**1b**); C(43)–H(43C)···*centroid*(B) 3.4874(4) Å (**1c**)] occurs in each of the three solvate structures **1a–c**.

As a further point of interest, we focused on the mode of molecular packing in each of the calixarene inclusions. For this reason, the potential solvent accessible area in the presence and absence of the solvent molecules, as well as

Table 3 Selected conformational parameters of the calixarene molecule in the compounds studied

Compound	**1**	**1a**	**1b** [10]	**1c**	**2a** [12]
Interplanar angles (°)[a]					
mpla[b]/A	87.7	82.9	83.7	88.9	88.7/86.4
mpla/B	37.9	44.1	43.7	44.2	34.3/37.4
mpla/C	88.4	88.8	87.4	83.0	83.5/85.5
mpla/D	87.5	87.9	86.5	87.1	89.9/84.7
A/C	3.9(1)	8.3(1)	8.9(2)	8.0(1)	7.8(1)/8.1(1)
B/D	49.7(1)	43.8(1)	42.8(2)	43.0(1)	55.7(1)/47.3(1)
KPI-index (%) [21]	64.1	62.5	61.7	60.9	63.2
Potential solvent accessible area per unit cell[c] [21] (Å^3/%)	–	179.4/3.5	113.1/2.2	381.5/7.5	153.2/1.6
Potential solvent accessible area per unit cell[d] [21] (Å^3/%)	122.3/2.7	913.9/18.0	957.9/18.8	933.7/18.4	1337.9/13.9

[a] Aromatic rings: ring A: C(1)···C(6); ring B: C(8)···C(13); ring C: C(15)···C(20); ring D: C(22)···C(27)

[b] Best plane through atoms C(7), C(14), C(21), and C(28)

[c] Calculated in the presence of the guest

[d] Calculated in the absence of the guest

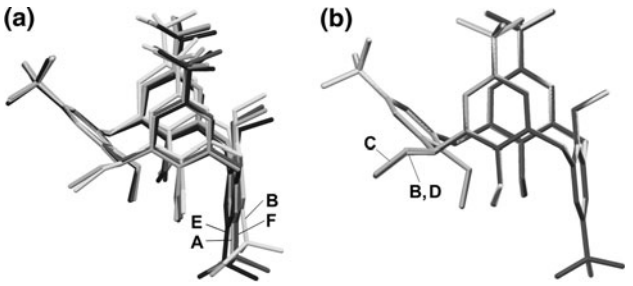

Fig. 3 Overlay of the host calix[4]arene molecules. The upward arene group opposite to the downward oriented one of each host are fitted in the figures only to visually enhance the geometrical differences. Assignment: **1** (A), **1a** (B), **1b** (C), **1c** (D), **2a1** (E), and **2a2** (F). **a** Hosts from the structures **1**, **1a**, **2a1**, and **2a2**. **b** Hosts from the structures **1a**, **1b**, and **1c**

the Kitaigorodskii Packing Index (KPI) [21] are calculated for all reported structures (Table 3). For comparison, the expected volume for a hydrogen bonded water molecule is around 40 $Å^3$, and for a small molecule like toluene it may range between 100 and 300 $Å^3$. The ethyl substituted calix[4]arene **1** can be well packed even without a solvent molecule having a packing coefficient average value of 64.1% and a small residual potential solvent accessible area of 2.7% as distinct voids in the crystal structure (Fig. 4a). A rather small inter-layer distance of about 7.77 Å between the nearest calixarene aromatic core centroids prevents any inclusion of solvent molecules. In a completely different manner, the guest solvent molecules in all **1a–c** and **2a** structures are located in channels. In the case of the calix[4]arene host **2a** featuring no lateral substituent, the serpentine like channels are running along the crystallographic *b* direction in the space group $P2_1/c$ (Fig. 4b). Absence of lateral substitution and inclusion of THF in the crystal structure as in **2a** result in a moderate well packing, giving rise to a packing coefficient of 63.2% and a small solvent accessible void of 1.6% additional to the THF. As an effect of the lateral substitution of the host, the channels are straightened in the crystals of **1a–c** and are running in the crystallographic *c* direction in the space group $Pca2_1$ (Fig. 5). The lateral substitution of the host decreases the packing ability of the inclusion crystals. The extra potential solvent accessible void in the presence of guest molecules increases (2.2–7.5%) in comparison to the laterally unsubstituted solvate **2a** (1.6%), while the packing coefficient decreases (Table 3). However, the total room available for guest molecules in the host structure is approximately the same, around 18% in all inclusion compounds **1a–c**, while it is smaller (13.9%) in the case of **2a**. The intermolecular distances between the nearest calixarene aromatic core centroids of 13.51 Å (**1b**) and 13.40 Å (**1c**) meet the

Table 4 Parameters of possible hydrogen-bond type interactions of the compounds studied

Atoms involved[a]	Symmetry	Distance/Å		Angle/°
		D···A	H···A	D–H···A
1				
C(49)–H(49A)···*centroid*(C)	$-x, -y, 1-z$	3.7164(4)	2.86	146
1a				
C(3G)–H(3G2)···*centroid*(C)	x, y, z	3.657(9)	2.72	159
C(33)–H(33C)···*centroid*(B)	$1-x, 1-y, -1/2+z$	3.475(4)	2.61	147
C(43)–H(43B)···*centroid*(D)	$1/2-x, y, 1/2+z$	3.864(4)	2.99	149
1b				
C(1G)–H(1G2)···*centroid*(C)	x, y, z	3.8855(10)	2.90	170
C(33)–H(33A)···*centroid*(B)	$-x, 1-y, 1/2+z$	3.4855(10)	2.62	147
C(1GA)–H(1GA)···*centroid*(C)	x, y, z	3.5692(10)	2.63	157
1c				
C(1G)–H(1G2)···*centroid*(C)	x, y, z	3.4564(2)	2.55	152
C(33)–H(33C)···*centroid*(B)	$1-x, 1-y, -1/2+z$	3.4874(4)	2.63	147
2a				
C(14A)–H(14D)···*centroid*(A)	$2-x, -1/2+y, 1/2-z$	3.8170(4)	2.93	144
C(43)–H(43A)···*centroid*(C')[b]	x, y, z	3.4256(2)	2.64	137
C(48)–H(48A)···*centroid*(A')[b]	$1-x, 1/2+y, 1/2-z$	3.5863(4)	2.82	136
C(48)–H(48D)···*centroid*(B')[b]	$1-x, 1/2+y, 1/2-z$	3.5798(4)	2.84	133

[a] *Centroid* means the centre of gravity of the corresponding aromatic ring as specified in Table 3

[b] Apostrophe(') labels ring *centroids* of a second calixarene molecule in the asymmetric unit

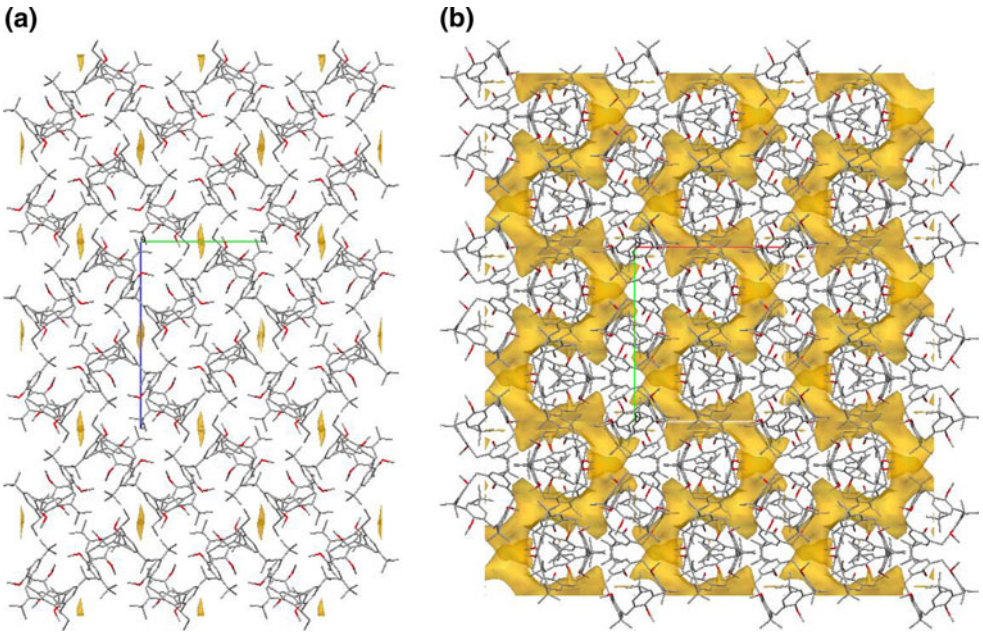

Fig. 4 **a** Packing arrangement of **1** viewed along the crystallographic *a* direction. There are small voids among the semi-rigid calix[4]arene molecules. **b** Solvent channels in the crystal structure of **2a**. The serpentine like channels are in the crystallographic *b* direction, space group $P2_1/c$

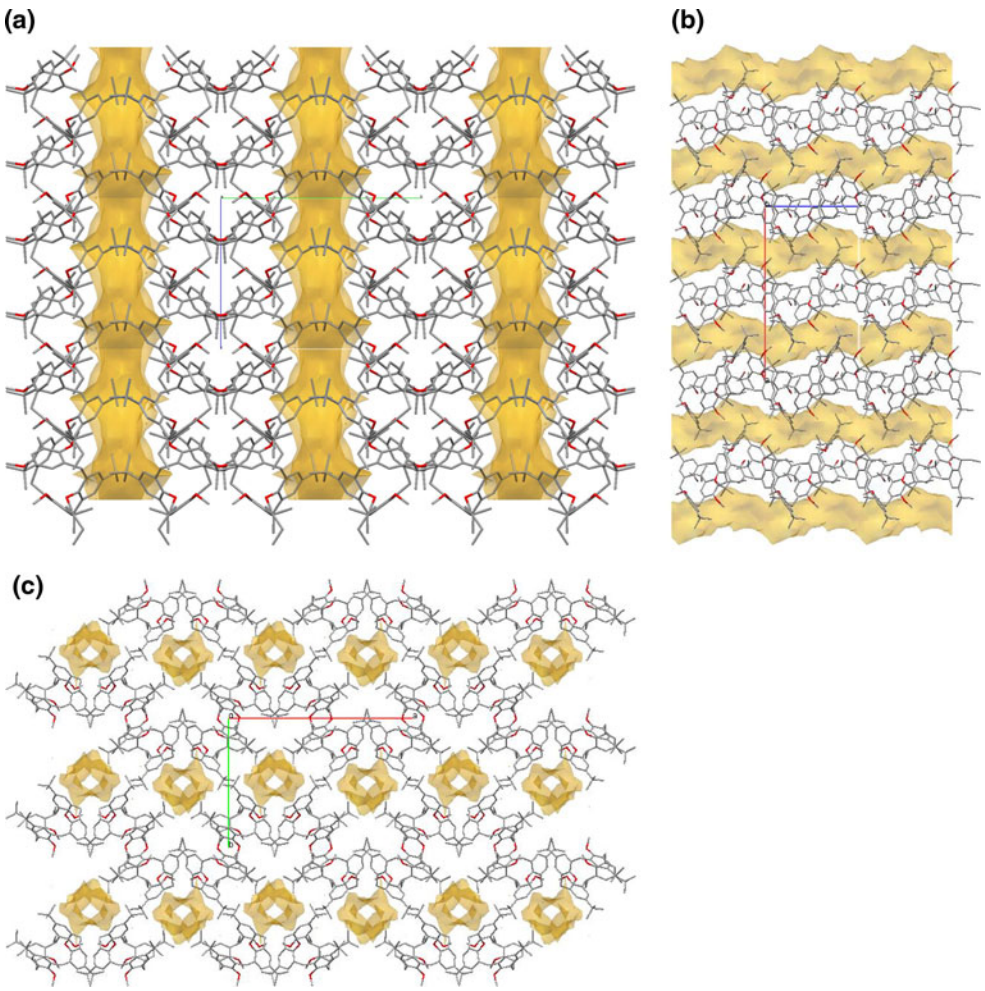

Fig. 5 Straightened solvent channels in the crystal structure of **1a** viewed along the crystallographic *a*, *b* and *c* direction (**a**), (**b**) and (**c**), respectively. Crystals of **1a–c** are isostructural, space group $Pca2_1$

requirements for a close packing arrangement [21], which is also reflected by the KPI packing indexes of 61.7(**1b**) and 60.9 (**1c**), respectively.

Conclusion

In comparison with the parent lateral unsubstituted tetramethoxycalix[4]arene inclusion structure **2a**, the introduction of a lateral ethyl substituent scarcely affects the molecular conformation of the calixarene framework, as indicated by similar conformational parameters in **1a**–**c**. Due to the non-polar nature of the calixarene core, the intramoleular interactions within the different structures are highly limited to differently strong C–H$\cdots\pi$ contacts [18]. However, the inclusion of solvent molecules of different size and polarity causes a greater change of the packing behaviour. Primarily, the presence of solvent molecules induces the formation of the higher symmetrical orthorhombic crystal structures **1a**–**c**, being isostructural irrespective of the included guest molecule. Besides, the lateral attachment of one ethyl group leads to a staggered arrangement of calixarene molecules along the crystallographic *b*-axis. As a consequence, the serpentine like channels observed in the laterally unsubstituted calixarene structure **2a** are straightened to linear channels running along the crystallographic *c* direction. This fact seems to be an interesting crystal engineering aspect [22], as the channel geometry of a calixarene lattice can be straightened by the effect of a simple lateral monosubstitution to the host molecule. Moreover, it is shown that the introduction of a lateral substituent may expand the total room available for guest molecule inclusion by nearly 30%, being another promising fact for crystal inclusion chemistry (For examples in regard to reversible guest exchange of calix[4]arenes, see: ref. [23]).

Supplementary data

CCDC-804619 (**1**), CCDC-804620 (**1a**) and CCDC-804621 (**1c**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/data_request/cif (or from the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0) 1223-336033; e-mail: deposit@ccdc.cam.ac.uk).

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