α-C=O provides access to the cavity in acyl calix[4]arenes: A comparative study of crystal structures†

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The structures of partially self-included forms of *para*-alkanoyl calix[4]arenes, with different lengths of acyl chain (C4–C16), were compared using X-ray diffraction data. The carbonyl group in the calix[4]arenes fixes the position of the two first carbon atoms in the plane of the phenyl ring and effectively expands the cavity. The accessibility of the cavity to small molecules strongly depends on the length of alkanoyl arm. For short arms (C4–C8), the host–host van der Waals interactions are not strong enough and enable easy access by potential guests to the cavity. Long alkanoyl arms compensate the directing effect of the carbonyl group and close the cavity to potential guests. A comparison of *para*-alkanoyl calix[4]arene with *para*-alkyl examples allows one to estimate the chain lengths that will enable easy inclusion of potential guests. It was found that the former should be *ca.* 1.5 times longer than the length of the rigid calixarene fragment.

Introduction

Understanding the structural factors responsible for the inclusion propensity of calix[4]arenes has become one of the main challenges in supramolecular chemistry.[1–3] Strong interactions, such as hydrogen bonding, metal coordination or predefined covalent bonding, can facilitate the generation of various structural motifs with rigid shapes and designed properties. However, the non-covalent interactions involved in inclusion complexes[4–9] are relatively weak, and this has limited the predictability of design for solid-state structures,[10] based on host–guest chemistry. Although the cone conformations of calix[4]arenes can be controlled *via* intramolecular hydrogen bonding,[1–3] their packing motifs, as well as inclusion ability, are diverse and hardly predictable.

The chemical modification of the lower or upper rims in calixarenes,[11] for application in molecular recognition,[12] membrane transport,[13] or in ion channel formation,[14] gives an additional contribution to the diversity of structures. However, in some cases, when systematic changes to the substituents become achievable, the thorough analysis of structural motifs can make it possible to predict and access desired structures. In particular, Friedel–Crafts acylation[15] enables easy access to amphiphilic *para*-alkanoyl calix[*n*]arenes with different lengths of alkanoyl chain. Their ability to complex small molecules is retained, and they are able to self-organize into solid lipid nanoparticles (SLN) in water.[16,17]

As many calixarenes are unsubstituted at the lower rim,[1–12] *para*-alkanoyl compounds have a preferred cone conformation and, hence, the cavity is potentially accessible to guest molecules. Depending on the size and polarity of guests, as well as on the crystallization conditions, three general types of inclusion complex structures can be distinguished.[17–23] In the first,[18,19,23] the calix[4]arene cavity, like a bowl, contains a foreign guest and is capped by a similar bowl above, usually including stabilization of the complex by hydrogen bonding of the OH groups of the upper bowl with an appropriate group of the guest. This structure can be called an open-container or head-to-tail complex and it is typical of *para*-hexanoyl calix[4]arene with such guests as DMSO, DMF, nitrobenzene,[18] hydroxylamine TEMPO-H,[19] as well as for some other calixarenes.[1–12,22–24] The second type is a nanocapsular complex,[4–8,20,21,23,25] which is also known for other "calix" type molecules, both in solution and in the solid state.[24,25] The complex is formed when calixarene molecules are arranged in tail-to-tail pairs, providing a hydrophobic cavity that can entrap a variety of molecules of relatively low polarity and of an appropriate size.[23] In this case, the guest serves as a stabilizing factor, preventing the penetration of alkanoyl arms deep into the cavity and, hence, allowing one to avoid the formation of the third type of complex. The latter can be termed a partially self-included or interdigitated complex, where the role of the guest is played by another molecule of calixarene, which provides chain fragments for entrapment by the first molecule, and *vice versa*.[17,18,26,27]

In previous publications[17–23] we have described and analysed all of these types of inclusion complexes of amphiphilic calixarenes, with a main focus on the first two types.[23] Despite the fact that nanocapsular complexes seem to be the most interesting structures, with a variety of potential applications, understanding the formation of interdigitated complexes, which one would expect to be the most thermodynamically

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† The HTML version of this article has been enhanced with colour images.

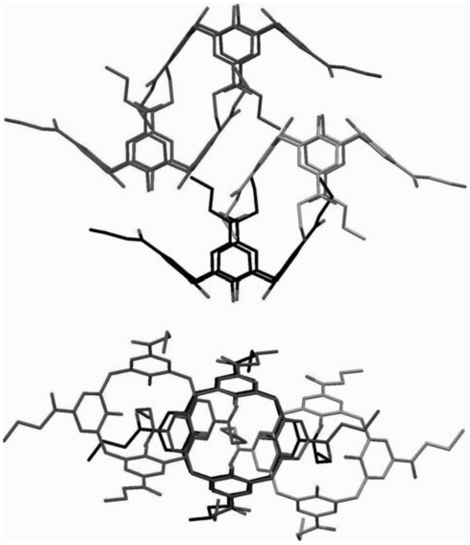


Fig. 1 Interdigitated structure of *para*-butanoyl calix[4]arene.

stable in the absence of guests, can shed light on general entrapping and complexation trends within the amphiphilic calixarene family, and on their ability to form stable SLNs for transportation purposes.

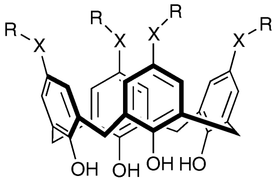
Here we report a comparative study and analysis of interdigitated forms in a series of *para*-alkanoyl calix[4]arenes with alkanoyl chain lengths increasing from *n*-butanoyl (C4) to *n*-hexadecanoyl (C16), as well as the interdigitated structures of *para*-*n*-butyl and *para*-*n*-hexyl calix[4]arene (Fig. 1). The structures of the calixarenes and the abbreviations used are shown in Scheme 1.

Methods and materials

para-Alkanoyl calix[4]arenes were synthesized according to the procedure previously described.[15b] The *para*-*n*-butyl and *para*-*n*-hexyl calix[4]arene were prepared by the reduction of alkanoyl calix[4]arenes with triethylsilane in trifluoroacetic acid.[15a] Solvents and reagents were purchased from Aldrich and used as supplied.

Crystals were obtained from solutions of 50–300 mg of calixarene in 5–10 ml of ethanol by slow cooling or slow evaporation at room temperature.

Single crystal X-ray diffraction data were collected in the ω-scan mode on Bruker Smart CCD and Bruker Kappa APEX2 diffractometers using graphite-monochromatized Mo-Kα radiation (λ = 0.71073 Å). The structures were solved by direct methods and refined by full-matrix least-squares on F^2 using the SHELXTL suite of programs.[28] Positions of disordered atoms were found directly from the maps of residual electron densities. The distances and angles for the disordered chains were fixed, and the site occupancies were refined for the different parts with the same thermal parameters for the same atoms in the various fragments. At the end of the refinement, all site occupancies were fixed and hydrogen atoms were placed in calculated positions. The summary of XRD data and the corresponding CCDC numbers are given in Table 1. The crystal structures of three polymorphs of **C8OH** have been published[17,29] and the crystals of **C12OH–C16OH** calixarenes were not suitable for single crystal XRD experiments.



CnOH: X = CO; R = $C_{n-1}H_{2n-1}$
rCnOH: X = CH_2; R = $C_{n-1}H_{2n-1}$

Scheme 1 *para*-Alkanoyl and *para*-alkyl calix[4]arenes.

The powder XRD (pXRD) data were collected on a Scintag X2 diffractometer using Cu-radiation (λ = 1.54078 Å) in the 2θ range from 3 to 30°. The unit cell parameters were estimated using the Crystal Cracker program.[30]

Results

n-Butanoyl and *n*-butyl calix[4]arenes (C4OH and rC4OH)

The interdigitated form of **C4OH** crystallizes in a triclinic crystal system, space group *P*-1, with an asymmetric unit containing one molecule of **C4OH**. No disorder was found. There are three main sources of stabilization of the structure. One of the four acyl chains (Fig. 1) of one molecule is deeply inserted into the cavity of another, providing a CH/π interaction between the terminal methyl group and the π-system of the four aromatic rings of the calixarene. In addition, the complex is stabilized by hydrogen bonds between the carbonyl group of one calixarene and the phenolic hydroxyl group of another, with an Ar–O···O=C distance of *ca.* 3.0 Å. The third distinct feature is the π–π interaction between two phenyl rings of neighbouring calixarenes (the shortest distance between two carbon atoms is 3.7 Å). The system of four calixarene molecules shown in Fig. 2 resembles a capsular structure, with two large guests whose role is played by two other calixarenes. Of course, the assignments of host and guest calixarenes are arbitrary.

In contrast to **C4OH**, the main source of stabilization of **rC4OH** (Fig. 2) seems to be a CH/π interaction between an α-CH_2 group of a butyl arm of one molecule with the π-system of another calixarene. This makes the structure similar to that of *para*-ethyl calixarene (**rC2OH**) described in ref. 31. Considering the enhanced acidity of the α-CH_2 as a favourable factor for CH/π bonding,[32] both **rC4OH** and **rC2OH** interdigitated forms benefit from such interactions. However, the longer alkyl arm of **rC4OH** can better fold over the cavity of the second molecule, and the entire complex may gain additional stabilization due to additional van der Waals interactions. Finally, the π–π stacking between two neighbouring phenyl rings of calixarenes (shortest distance between two carbon atoms is 3.6 Å) contributes to the total stability of **rC4OH** and **rC2OH** complexes. All four butyl arms are highly disordered, reflecting the significant flexibility of the **rC4OH** structure. The calixarene molecules are in a pinched cone conformation and some disorder in the phenyl rings is also present.

Table 1 Crystal data and structure refinements of *para*-alkanoyl and *para*-alkyl calix[4]arenes[a]

	C4OH	**rC4OH**	**C6OH**	**C6OH · EtOH**	**rC6OH**	**C8OH-α**	**C10OH**
CCDC	632667	632663	632665	632666	632664	632669	632668
Formula	$C_{44}H_{48}O_8$	$C_{44}H_{56}O_4$	$C_{52}H_{64}O_8$	$C_{54}H_{70}O_9$	$C_{52}H_{72}O_4$	$C_{60}H_{80}O_8$	$C_{68}H_{96}O_8$
Formula weight	704.82	648.89	817.03	863.10	761.10	929.24	1041.45
Crystal system	Triclinic	Triclinic	Triclinic	Triclinic	Triclinic	Monoclinic	Monoclinic
Space group	*P*-1	*P*-1	*P*-1	*P*-1	*P*-1	$P2_1/n$	$P2_1/n$
a/Å	9.0322(7)	10.3228(4)	11.611(3)	12.053(3)	11.086(2)	21.762(1)	11.630(2)
b/Å	13.664(1)	11.9213(4)	17.372(4)	12.441(3)	14.413(2)	15.6647(8)	15.163(3)
c/Å	15.266(1)	15.8916(6)	33.165(7)	16.015(3)	14.802(2)	32.832(2)	33.741(6)
α/°	86.472(1)	71.948(2)	88.536(3)	91.504(3)	78.182(2)	90	90
β/°	76.962(1)	88.950(2)	88.251(4)	99.841(3)	74.463(2)	107.905(3)	99.117(3)
γ/°	86.250(1)	74.630(2)	87.077(4)	95.036(3)	88.892(2)	90	90
V/Å^3	1829.4(2)	1788.5(1)	6676(2)	2355.0(8)	2228.8(5)	10 650(1)	5875.1(17)
Z	2	2	6	2	2	8	4
Density/g cm^{-3}	1.280	1.205	1.219	1.217	1.134	1.159	1.177
T/K	125(2)	125(2)	125(2)	125(2)	125(2)	100(2)	125(2)
$\mu_{\text{Mo-K}\alpha}$/mm^{-1}	0.087	0.075	0.081	0.081	0.069	0.075	0.075
Measured/independent reflections	23054/10102	67314/17177	83305/36683	28400/12854	28230/12547	160632/21484	30096/5480
R_{int}	0.0151	0.0411	0.0457	0.0361	0.0291	0.1461	0.1214
$R1$ ($I > 2\sigma(I)$)	0.0436	0.0696	0.0685	0.0742	0.0465	0.0839	0.1234
w$R2$ ($I > 2\sigma(I)$)	0.1211	0.1891	0.1869	0.2076	0.1263	0.2006	0.2780

[a] For crystallographic data in CIF or other electronic format see DOI: 10.1039/b700308k

n-Hexanoyl and *n*-hexyl calix[4]arenes (C6OH, C6OH · EtOH, and rC6OH)

The interdigitated form of **C6OH** crystallizes in the triclinic crystal system and *P*-1 space group. The asymmetric unit contains 3 molecules of **C6OH**. Fig. 3 shows how the arms of calixarene molecules are included in the cavity of a neighbouring calixarene. The upper calixarene cavity can be considered as a host that entraps one alkanoyl arm from the second calixarene (left) by means of CH_2/π and CH_3/π interactions with the terminal ethyl fragment of the guest. The third (bottom) and fourth (right) calixarenes also provide one alkanoyl arm each for the host, but the stabilization here is only due to weak van der Waals interactions between corresponding fragments. It is clear that the extended C6-alkanoyl arm (in comparison to C4) can provide a larger number of CH_n/CH_n contacts and hence can make the van der Waals interactions more effective at stabilizing the complex. The inclusion of alkanoyl arms is similar to that for the **C6OH · MeOH** complex described in ref. 18, despite the different unit cell parameters (Table 2).

The ability to accommodate more than one guest is also retained for another interdigitated form of **C6OH**, which was isolated from a solution of **C6OH** in EtOH in the presence of 4-cyano-2,2,6,6-tetramethylpiperidine-*N*-oxyl (free radical 4-cyano-TEMPO).[33] The unit cell of the complex consists of two molecules of **C6OH** and two molecules of ethanol. The molecules in the complex are not disordered. Ethanol is not included deep in the calixarene pocket (shown in Fig. 4 by a ball-and-stick notation); its stabilization is provided by

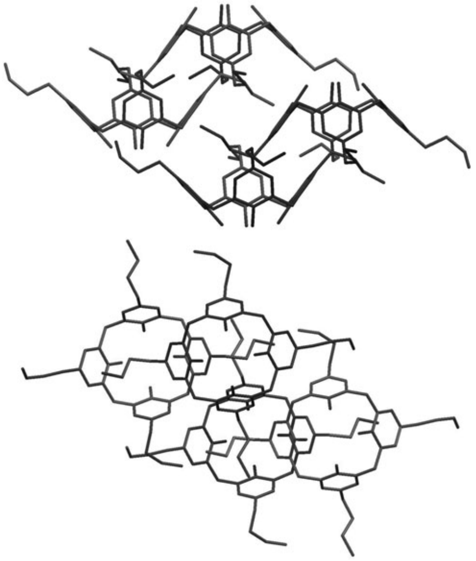


Fig. 2 Interdigitated structure of *para*-butyl calix[4]arene.

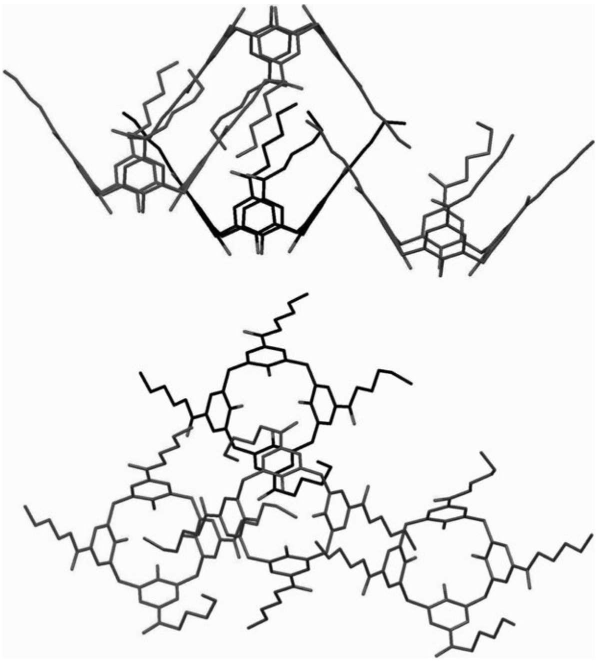


Fig. 3 Interdigitated structure of *para*-hexanoyl calix[4]arene **C6OH**.

Table 2 Unit cell parameters for interdigitated forms of *para*-alkanoyl and *para*-alkyl calix[4]arenes

Calixarene	Space group	a/Å	b/Å	c/Å	α/°	β/°	γ/°
rC2OH[a]	**$P2_1/c$**	**12.44**	**12.32**	**19.87**	**90**	**100.3**	**90**
C4OH	P-1	9.03	13.66	15.27	86.5	76.9	86.2
rC4OH	**P-1**	**10.32**	**11.92**	**15.89**	**71.9**	**89.0**	**74.6**
C6OH	P-1	11.61	17.37	33.16	88.5	88.3	87.1
C6OH · EtOH	P-1	12.05	12.44	16.01	91.5	99.8	95.0
C6OH · MeOH[b]	P-1	11.62	13.10	15.41	105.2	90.2	91.8
rC6OH	**P-1**	**11.09**	**14.41**	**14.80**	**78.2**	**74.5**	**88.9**
C8OH[c]	$P2_1/c$	11.59	15.69	**29.49**[f]	90	96.4	90
C8OH[d]	P-1	12.21	15.25	**15.19**	77.0	89.7	82.1
C8OH-α	$P2_1/n$	21.76	15.66	32.83	90	107.9	90
C10OH	$P2_1/n$	11.63	15.16	**33.74**[f]	90	99.1	90
C12OH[e]	(P-1)	11.7	15.5	**19.2**	78	88	83
C14OH[e]	(P-1)	12.2	16.0	**21.7**	78	93	78
C16OH[e]	(P-1)	11.6	16.8	**23.6**	78	93	85

[a] Ref. 31. [b] Ref. 18. [c] Ref. 17. [d] Ref. 29. [e] pXRD estimations. [f] These species can be compared with other interdigitated structures by dividing the parameter c of the unit cell by 2.

hydrogen bonding with the neighbouring C=O group, with Et–O···O=C distances of 2.9 Å. Two carbonyl groups are oriented towards the hydroxyl group of ethanol, which resembles the inclusion complex of **C6OH** with 1-hydroxy-2,2,6,6-tetramethylpiperidine (TEMPO-H) published recently.[19,34] Since some space in the pocket has been occupied by EtOH, the cavity of the "host" calixarene (very top molecule in Fig. 4) accommodates only two alkanoyl chains, arising from two different molecules. One chain is included deep in the cavity (grey) and the other (black) has about the same settlement "rights" as ethanol but, of course, without hydrogen bond stabilization.

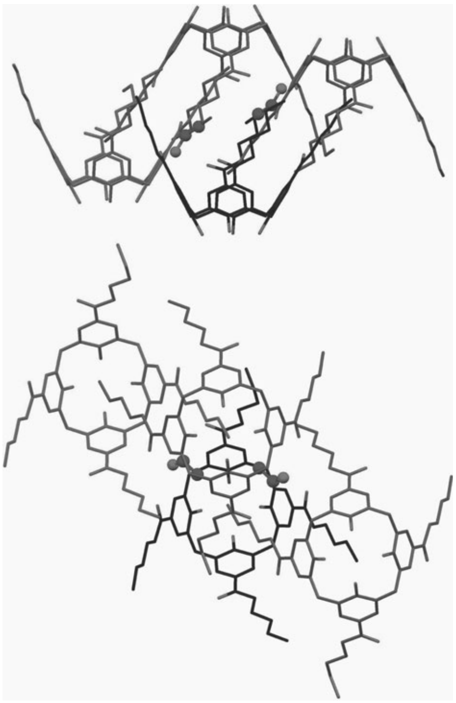


Fig. 4 Interdigitated structure of *para*-hexanoyl calix[4]arene with ethanol (shown in a ball-and-stick notation) **C6OH · EtOH**.

The removal of C=O groups in **C6OH** (*i.e.*, reduction to *para*-hexyl calix[4]arene **rC6OH**) dramatically changes the accessibility of the cavity for potential guests. The interdigitated form of **rC6OH** crystallizes in the triclinic crystal system, space group P-1, with an asymmetric unit containing one molecule of **rC6OH**. Every two molecules build a dimer, which is stabilized by the inclusion of one alkyl arm into the cavity of the other molecule (Fig. 5). No disorder of the alkyl chains is observed. The shortest distance between two carbon atoms in the "host" and "guest" alkyl chains is *ca.* 3.9 Å. The layers in the crystalline lattice are stabilized by π–π interactions between phenyl rings of neighbouring calixarenes.

In contrast to **rC4OH**, the main interaction responsible for directing the structural motif is not an α-CH_2/π but a terminal-CH_3/π interaction. Presumably, the number of van der Waals contacts in such long alkyl arms is sufficient to provide better stability to the dimer, eliminating the need for the more acidic CH group (like α-CH_2) required for interacting with the π-systems of the calixarene's four phenyl rings. The hydrogen bond link between the C=O group of one calixarene and the OH group of a second (see **C4OH**, Fig. 2) is absent in **C6OH** complexes due to the inappropriate length of the alkyl arms.

n-Octanoyl calix[4]arene (C8OH)

Two polymorphs ($P2_1/n$ and P-1) of the interdigitated dense form of **C8OH** have been described in ref. 17 and ref. 29, respectively. In both cases, the structural motif is directed by the inclusion of one acyl arm in the calixarene cavity (Fig. 6), and is generally similar to the **rC6OH** structure (Fig. 5). One can also see some similarity with **C6OH** and **C6OH · EtOH** (Fig. 3 and Fig. 4). One arm in **C8OH** bends into the cavity, replacing either an alkanoyl arm of another molecule (going from **C6OH** to **C8OH**) or ethanol (going from **C6OH · EtOH** to **C8OH**).

A very small number of crystals with a different shape were found in the precipitate of **C8OH** (**C8OH-α**). Refinement of

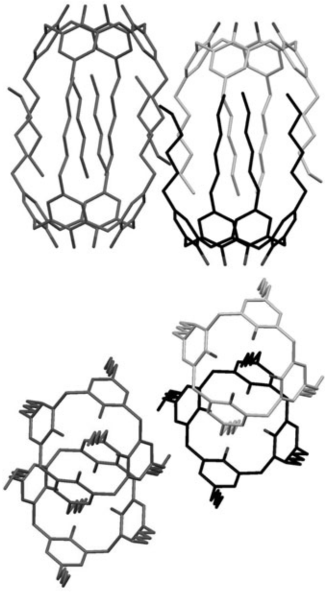


Fig. 5 Interdigitated structure of *para*-hexyl calix[4]arene **rC6OH**.

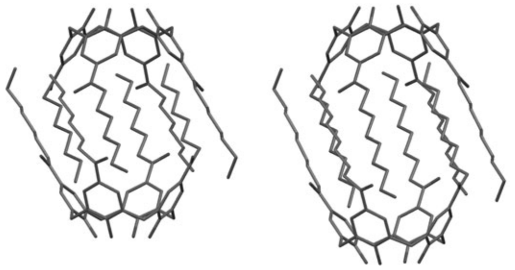


Fig. 6 Comparison of interdigitated structures **C8OH** (left) and **C10OH** (right).

XRD data taken on a suitable crystal revealed another interdigitated structure (Fig. 7), which proved to be generally similar to that of **rC4OH** (Fig. 3). The structural motif in **C8OH-α** appears to be directed, as in **rC4OH**, by a CH/π interaction of an α-CH_2 group of an octanoyl arm of one molecule with the π-system of another calixarene. In addition, the π–π stacking between neighbouring C═O groups and phenyl rings of the calixarene (shortest distance between two carbon atoms is 3.6 Å) make a further contribution, and van der Waals interactions between the rest of arms provides the "last brick" in the entire composition.

n-Decanoyl calix[4]arene (C10OH) and higher calixarenes

The interdigitated form of **C10OH** ($P2_1/n$) (Fig. 6) looks very similar to **C8OH** described in ref. 17 and ref. 29.

We were unable to obtain samples of higher calixarenes **C12OH–C16OH** suitable for single crystal XRD analysis. A probable crystal structure was derived by comparison of their pXRD patterns with those of **C4OH–C8OH**. Fig. 8 shows that the main trend in the pXRD patterns[36] with increasing arm length corresponds to a gradual elongation of mainly one dimension of the unit cell (parameter *c*, Table 2). Therefore, one can confidently predict that the type of inclusion for higher alkanoyl calixarenes should be similar to those for **C8OH–C10OH**.

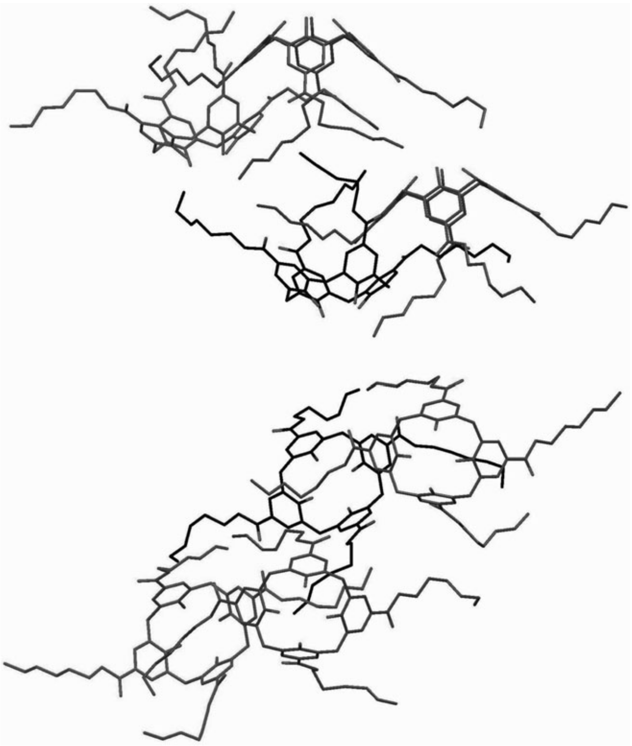


Fig. 7 Interdigitated structure of *para*-octanoyl calix[4]arene **C8OH-α**.

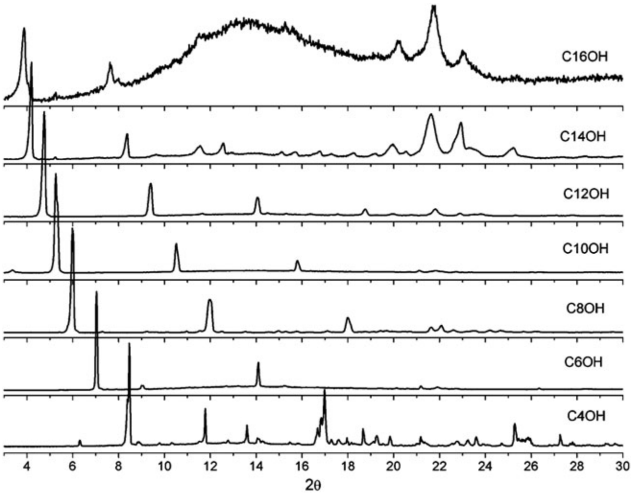


Fig. 8 Powder XRD diagrams of interdigitated structures of **C4OH** to **C16OH**.

Discussion

As mentioned above, the calixarene molecules studied here consist of three parts: (i) 4 OH groups—which are mainly responsible for the stabilization of the cone conformation, (ii) 4 phenyl rings—a rigid fragment, which is responsible for the cavity shape and (iii) alkyl or acyl arms—flexible parts, which can give additional stabilization to the guest, allowing or restricting access to the cavity.

The essential part of the molecule is the carbonyl group, which belongs to the flexible fragment but, in fact, serves as an extension of the cavity. One can see from Fig. 9 that the C═O group affects the space between the acyl arms: the cavity of *para*-hexyl calix[4]arene is less open and therefore is expected to be less accessible to guests than the cavity of **C6OH**. Due to conjugation, the carbonyl groups fix the positions of the first two carbon atoms of each chain in the plane with the corresponding phenyl ring and interrupts the expected host–guest CH_2/CH_2 interactions between the arms. Thus, the calixarene molecule needs longer chains to eliminate the effect of the "expanded" cavity. This can easily be seen by

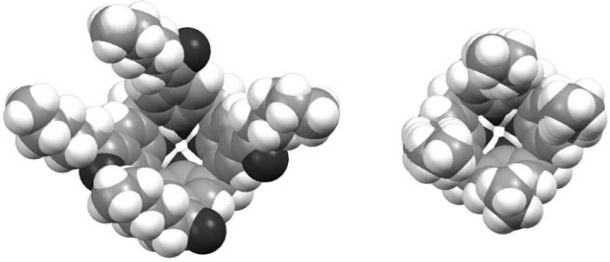


Fig. 9 Top view to the cavity of **C6OH** (left) and **rC6OH** (right).

comparing the alkanoyl calixarenes with their alkyl counterparts: a smaller cavity of alkyl calixarenes requires a $\geq$ C6 alkyl chain length to provide a good interaction with the guest arm and, hence, to protect the cavity from access by a foreign molecule, but the expanded cavity of alkanoyl calixarenes already requires a $\geq$ C7 (C=O is not counted) chain length to compensate for the effect of expansion. The similarity of the structures of **rC6OH** and **C8OH** generally confirms that this compensation occurs at a chain length of *ca.* $>2CH_2$ per 1 carbon atom (*i.e.*, C=O) inserted into rigid part of the molecule. This is also in general agreement with the observation that the structures of **rC4OH** and **C8OH-α** are similar, *i.e.* there is still some residual flexibility in **C8OH**,[29] which completely disappears for a chain length of C10.

A quantitative estimate of the appropriate chain length can be made, as depicted in Fig. 10. The length of the rigid part (R) in alkyl calixarenes can be considered as the distance between C-1 and C-4 in the benzene ring ($R \approx 2.8$ Å). In alkanoyl calixarenes, the parameter R is the distance between the C-1 and C(=O) atoms ($R \approx 4.3$ Å). The rest is the flexible part (F), provided that it is a fully extended *n*-alkyl chain. In this case, the F/R ratio can be an estimate of the "availability" of the cavity:

F/R = 2.1 (**C8OH**), 1.5 (**C6OH**), 0.9 (**C4OH**) and
F/R = 2.7 (**rC6OH**), 1.9 (**rC4OH**).

Comparison of the F/R parameters for these calixarenes reveals that there should be some similarity between the inclusion propensities of **C8OH** and **rC4OH**, and this was observed experimentally (structures **C8OH-α** and **rC4OH**), though with **C8OH-α** as a minor fraction. In addition, a F/R ratio around 1.5 seems to reflect the most appropriate cavity for access, and this has been observed for **C6OH**, where various complexes and structures have been isolated.[18–21,23] Larger F/R values (>2) correspond to an interdigitated (dimeric) form (similar to **C8OH** and higher, and **rC6OH** and higher) as the thermodynamically preferred structure, which can hardly be changed by an appropriate guest. If $F/R < {\sim}1.5$, the cavity of the calixarene is easily available to a guest, but no capsular complexes can be formed because of an insufficient number of CH_2 groups, which are required for its stabilization. In addition, the guests can easily leave such a cavity if only weak van der Waals and CH/π interactions are available to stabilize the complex.

Similar rules can be derived for other structures such as resorcinarenes and pyrogallolarenes,[37] calix[*n*]arenes bridged at the lower rim, *etc*., but the F/R parameter may be different in these cases. Of course, this approach is a very simplified one and may be valid only for linear alkyl, alkanoyl and similar calixarenes in cone conformations. The approach does not account for possible specific interactions (like hydrogen bonds) between guests or between host and guest. For example, a similar closure of the calix[4]arene cavity has been recently observed in the case of *para*-sulfonatomethyl calix[4]arene, as compared to *para*-sulfonatocalix[4]arene,[38] but such a closure occurs here due to hydrogen bonds involving sulfonato groups.

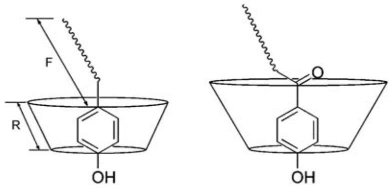


Fig. 10 Rigid and flexible parts of calix[4]arene molecules.

In general, this approach may be considered as a complementary example to the generalized topological analysis based on hydrophilic-to-hydrophobic volume ratios in organic crystals developed by Lee *et al.*[39,40] and others.[41] However, such an analysis, employing a "top-to-bottom" philosophy,[40] requires a clearer distinction to be made between the hydrophobic and hydrophilic parts of the molecule, if one follows the examples showed in ref. 39 and ref. 40. Our calixarenes are amphiphilic by their nature, but the hydrophilic component of the molecule is rather smaller than that considered in ref. 39. On the other hand, if one assigns the calixarene rim as a partly hydrophilic fragment (or, better, less hydrophobic), the topology of packing, *e.g.*, of **C4OH** *vs.* **C10OH**, would follow the predictions derived from Lee's[39,40] analysis, such as perforated layers *vs.* layers, respectively. In this case, the C=O group can be considered as an expansion of the hydrophilic (instead of rigid) part of the molecule, and the differences in packing between C*n*OH and rC*n*OH can (at least, qualitatively) be explained in terms of Lee's method. However, the goal of our analysis was to predict the inclusion propensity of the calixarene cavity rather than the packing motifs.

Motivated by this goal, a possible expansion of the cavity of calix[4]arenes, *e.g.*, by building up *para*-alkylphenyl substituents[42] or funnelene structures,[43] can be discussed. In this case, the cavity would allow the complexation of very large molecules, up to peptides, steroids, *etc*. A simple calculation of the alkyl chain needed for the simplest 4-(4-alkylphenyl) calixarene gives a F value of *ca.* 11 Å, *i.e.* a linear, *ca.* octyl, chain. However, other factors may begin to play an important role for such a structure; for example, large empty spaces in the cavity walls due to divergence of substituents or deviations from planarity for the corresponding substituents.

Conclusion

This is, to the best of our knowledge, the first systematic and detailed analysis of the ability of calixarenes to partially self-include and accommodate guests. The approach is based on a comparison of the crystal structures of interdigitated complexes of *para*-alkanoyl and *para*-alkyl calix[4]arenes. Although not all factors were taken into account and more sophisticated geometrical approaches can be used, this relatively simple consideration allows one to predict the types of structure able to entrap guests of different sizes: from simple gas molecules to biologically interesting species. This consideration is more structure oriented than crystal oriented, *i.e.* we discussed the calixarenes in terms of their ability to interdigitate (or include guest molecules) instead of their ability to form one or other kind of crystal lattice. Based on this methodology, the prediction of inclusion propensities of calixarenes, aiming to utilize these compounds for the storage and delivery of interesting substrates, can be done with a significant degree of success.

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