A chlorophobic pocket in the *p-tert*-butylcalix[4]arene cavity: a test site for molecular recognition investigated by ^{13}C CP MAS NMR and X-ray crystallography†

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Five-membered aliphatic guests $X(CH_2)_3Y$ (X, Y = Me, OH, Cl, Br) adopt equilibrium positions in the asymmetric *p-tert*-butylcalix[4]arene cavity formed in the solid state and reveal a marked aversion of the host pocket for halogen end-groups.

Weak interactions are expected to play an important role in the construction of complex materials *via* self-assembly processes.[1] Although there are many studies of interactions involving H-bonding or π-stacking, there appear to be few methods where the relative importance of other weak interactions can be gauged in an unambiguous way.[2] Here we report on the use of the deep pocket in solid *p-tert*-butylcalix[4]arene host–guest materials as a site for testing relative interaction strengths, a concept also explored for guests in channel clathrates.

Recently we have reported the preparation and structural characterization of *p-tert*-butylcalix[4]arene (*t*-BC) compounds with aliphatic guests.[3] One example is the compound with pentane where the diffraction studies show that the guest molecule is inserted along the four-fold symmetry axis of the calix in the all-*trans* conformation with one methyl group deeply inserted in the calix cavity. It is therefore quite interesting that the ^{13}C NMR spectrum of the solid shows the presence of a single methyl resonance with a chemical shift close to where it is expected for pentane in solution (**1**, Table 1) rather than resonances for inequivalent methyls with one resonance shifted upfield by *ca.* 5 ppm owing to ring current effects from the four proximate aromatic rings of the calix.[4,5] The conclusion is that the pentane molecule can invert itself in the cavity on an NMR timescale. This process probably involves low concentrations of transient *gauche* isomers invisible in the diffraction experiment. The important conclusion is that linear molecules with an equivalent length of up to five carbon atoms are free to take up equilibrium orientations and conformations inside the calix cavity. This differs from monosubstituted and *para*-disubstituted aromatic guests in *t*-BC,[5,6] where the orientation of the guest is locked in during crystallization. The strongly asymmetric calix cavity therefore offers the unique possibility of using the deep pocket as a test site for molecular recognition for molecules of the type $X(CH_2)_3Y$ (Table 1). A somewhat similar strategy has been followed in the pursuit of end group interaction energies for guests in channel clathrates.[12]

Table 1 45.3 MHz ^{13}C CP MAS NMR chemical shifts for the guest in *p-tert*-butylcalix[4]arene·guest compounds **1**–**5**; Δδ refers to the difference in the guest carbon chemical shift between $CDCl_3$ solution and the host

Guest			Carbon chemical shifts			
$X(CH_2)_3Y$	X	Y	Carbon	δ(calix)[a]	δ(solution)	Δδ
1	CH_3	CH_3	CH_3	12.3	13.7	−1.4
			C^2	15.9	15.9	0.0
			C^3	—[b]	34.6	—[b]
2	CH_3	Cl	CH_3	8.7	13.0	−4.3
			C^3	23.5	23.0	+0.5
			C^2	35.6	34.7	+0.9
			C^1	45.0	44.3	+0.7
3	CH_3	Br	CH_3	9.0	13.0	−4.0
			C^3	22.3	21.2	+1.1
			C^2	—[b]	33.0	—[b]
			C^1	36.0	34.7	+1.3
4	Cl	Cl	C^2	29.0	34.4	−4.4
			C^1	40.4	41.1	−0.7
5	CH_3	OH	CH_3	12.2	13.6	−1.4
			C^2	—[b]	35.0	—[b]
			C^3	18.4	19.1	−0.7
			C^1	59.1	61.4	−1.7

[a] Solid-state NMR spectra were obtained on a Bruker CXP-180 spectrometer under cross-polarization and magic angle spinning conditions. Probe: Bruker 7 mm; number of acquisitions 200–500; recycle time 4 s; 90° pulse 3.5 μs; contact time 3–5 ms; 4 K data points acquired and zero-filled to 16 K before processing; spectral width = 20 kHz; ν = 3.5 kHz. [b] The guest resonance in the solid is hidden under host resonances.

Examination of the ^{13}C NMR spectra of the guest inclusions with 1-chlorobutane and 1-bromobutane indicates that in this case the methyl resonances show the expected high field shifts for methyl groups inserted deeply inside the cavity (Table 1). This implies that the halogens are excluded from the cavity. A single-crystal X-ray diffraction study of the 1-chlorobutane compound confirms that this is indeed the case (Fig. 1).‡ The alkyl chain is inserted in the pocket, with the chlorine outside the cavity and situated just off the calixarene four-fold axis. The depth of penetration is limited by the unusual conformation of the chain which places C^2 and C^3 in close contact with the calix walls. We can exclude the influence of Cl···Cl interactions on the guest orientation,[2,7] as the Cl atoms are at least 6 Å apart. Although the X-ray structure is not of as high a quality as the

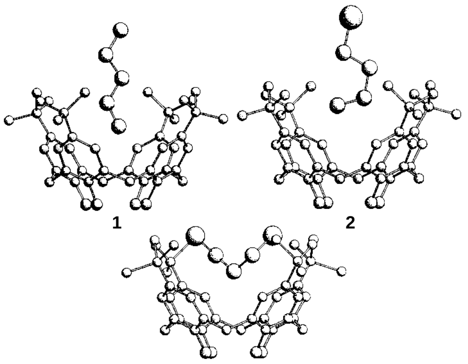

Fig. 1 Geometry of *p-tert*-butylcalix[4]arene inclusion compounds with pentane (**1**), 1-chlorobutane (**2**) and 1,3-dichloropropane (**4**). Only one of four symmetry-related guests is shown for **1** and **2**. For **4**, there is a second independent guest orientation, giving eight positions in all.

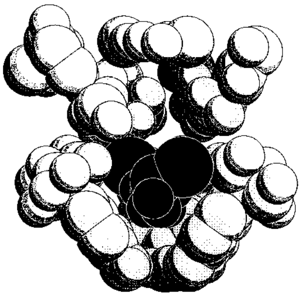

Fig. 2 A cutaway view of the highly anisotropic *p-tert*-butylcalix[4]arene cavity, showing the location of the 1,3-dichloropropane guest (**4**). The chlorophobic pocket is at the bottom in the cleft between aromatic rings.

others, the orientation of the guest is certain. Placing the chain with Cl in the cavity decreases the quality of the refinement.

Examination of the crystal structure of the compound with 1,3-dichloropropane (Fig. 1) is even more instructive, as now both chlorine atoms are excluded in favour of penetration of the cavity by a methylene group. The guest molecule is disordered equally over two orientations not related by symmetry which are in turn disordered equally about the compound's fourfold symmetry axis. Well defined positions for all guest atoms can be found, thus yielding eight possible orientations for the 1,3-dichloropropane guest. The carbon chemical shifts show only two guest lines (Table 1), indicating that the observed guest conformations are able to interchange. Considerable mobility of the guests is confirmed by dipolar dephasing experiments,[8] which show that both the terminal and central methylenes are mobile on an NMR timescale. It is interesting to note that the central methylene resonance is shifted by *ca.* 4 ppm, consistent with considerable penetration of the deep pocket by this group as observed in the diffraction study. This is also illustrated in Fig. 2, which shows a cutaway view of the calixarene cavity and illustrates its highly anisotropic nature. For the structure in question, the upper part of the cavity is occupied by a water molecule for about half the cages in the structure.

Since the steric requirements for a chlorine atom and a methyl group are very similar, one must conclude that there are very specific electronic effects that cause the exclusion of the chlorine atom. It is clear that the approach presented here is able to distinguish quite small energy differences. For instance, for **2**, complete exclusion of Cl requires that the energy difference between Cl_{in} and Cl_{out} is at least *ca.* 4 *kT*, *ca.* 10 kJ mol^{-1}.

It is not expected that dipole moments play a determining role in orienting the guest. This was checked by studying a *t*-BC compound with an *n*-butanol guest. It is clear from the NMR results that for this guest (**5**) there is little or no preference for either CH_3 or OH in the deep pocket (Table 1). The diffraction results indicate that the guest is located in the structure as a *gauche* conformer with the penetrating group on the axis (as in **2**). It makes no difference to the refinement whether OH or CH_3 is taken to be the penetrating group. Interactions involving acidic H such as O–H··π and alkyne C–H··π interactions have been duly studied.[2,9,10] More specifically, interactions between electron-rich calix[4]resorcarene hosts and CH-containing guests have been described in terms of a polarization-induced dipole interaction between a soft base (the host) and soft acid (the guest).[11] In the *n*-butanol case, the O–H··π interaction seems to be no stronger than the interaction of the aliphatic methyl group with the calix pocket. As well as being polarizable (*i.e.* soft) the *t*-BC cavity is also basic due to the electron-donating CH_2, Bu^t and OH substituents on the aromatic rings that form the deep pocket. While the OH group is more acidic than the CH_3 group, it is also less polarizable (*i.e.* harder) and the observed lack of specificity likely reflects a balance between the hard/soft and acid/base characteristics of the guest end groups. For the Cl-bearing groups in **2** and **4**, Cl is a hard base that does not show any attractive interaction with the soft and basic host, and thus gives rise to the observed orientations.

We note that the study of *t*-BC compounds with guests that have one more carbon atom per chain also are likely to give new insight, as preliminary X-ray diffraction evidence suggests that the hexane molecule forms a 2 : 1 compound with both ends inserted deeply in the *t*-BC pocket.

In conclusion, pentane-like linear guest molecules are free to take up equilibrium orientations and conformations inside the *p-tert*-butylcalix[4]arene cavity. The soft and basic *t*-BC pocket includes the guest deep in the cavity with the preference: $CH_3 \approx OH > CH_2 > Br, Cl$. It is hoped that modelling calculations should be able to provide significant new insight into the detailed nature of the interactions governing the guest orientations.

Notes and References

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‡ *Crystal data:* for **1**–**5**, space group *P*4/*n* ($Z = 2$). For **1** and **2**: Enraf Nonius CAD4 (Cu-Kα), $T = 150$ K, refinement against F_o. For **1**, $C_{44}H_{56}O_4\cdot C_5H_{12}$, $M = 721.08$, $a = 13.0230(19)$, $c = 12.6190(12)$ Å, $V = 2140.2$ $Å^3$, $D_c = 1.119$ g cm^{-3}, $\mu = 0.50$ mm^{-1}, $F(000) = 790.04$, 2154 reflections measured, 2045 unique, 1641 with $I > 2.5\sigma(I)$, $R = 0.048$, $R_w = 0.070$, residual density -0.200 to 0.190 e $Å^{-3}$. For **2**, $C_{44}H_{56}O_4\cdot C_4H_9Cl$, $M = 741.48$, $a = 13.0571(19)$, $c = 12.5986(15)$ Å, $V = 2144.4$ $Å^3$, $D_c = 1.148$ g cm^{-3}, $\mu = 1.09$ mm^{-1}, $T = 150$ K, $F(000) = 806.73$, 4048 reflections measured, 2046 unique, 1549 with $I > 2.5\sigma(I)$, $R = 0.090$, $R_w = 0.131$, residual density -0.84 to 1.37 e $Å^{-3}$. For **4** and **5**, Siemens SMART CCD, (Mo-Kα), $T = 273$ K, refined against F_o^2. For **4**: $C_{44}H_{56}O_4\cdot C_3H_6Cl_2$, $M = 761.87$, $a = 12.8869(12)$, $c = 13.1494(13)$ Å, $V = 2183.8$ $Å^3$, $D_c = 1.159$ g cm^{-3}, $\mu = 0.189$ mm^{-1}, $F(000) = 820$, 8398 reflections measured, 1591 unique, 1113 with $I > 2\sigma(I)$, $R = 0.039$, $R_w = 0.138$, residual density -0.106 to 0.126 e $Å^{-3}$. For **5**: $C_{44}H_{56}O_4\cdot C_4H_{10}O$, $M = 723.01$, tetragonal, space group *P*4/*n*, $a = 12.9590(3)$, $c = 13.1041(15)$ Å, $V = 2200.6$ $Å^3$, $D_c = 1.091$ g cm^{-3}, $\mu = 0.069$ mm^{-1}, $F(000) = 488$, 14494 reflections measured, 2845 unique, 1843 with $I > 2\sigma(I)$, $R = 0.099$, $R_w = 0.239$, residual density -0.215 to 0.366 e $Å^{-3}$. CCDC. 182/745.

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