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An integrated approach to the study of the recognition of guests containing CH_3 and CH_2 acidic groups by differently rigidified cone *p-tert*-butylcalix[4]arene derivatives†

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The efficiency and selectivity of calix[4]arenes, having different rigidities, in recognizing CH_3X and CH_2XY guests in apolar media have been investigated by ^{1}H NMR spectroscopy. 1,3-Dipropoxy-*p-tert*-butylcalix[4]arene (**1**) turns out to be less selective than the comparatively more rigid biscrown-3-*p-tert*-butylcalix[4]arene (**2**). To obtain further information on these recognition processes, both calorimetric and structural studies have been performed in solution and in the solid state, respectively. The calorimetric study shows that the inclusion process is enthalpically driven and entropically unfavoured in all cases. The favourable enthalpic contribution mainly results from specific host–guest CH–π interactions. Methyl substituted guests show a less unfavourable entropic contribution. Solid state structural determinations of the complexes help in explaining these results.

Introduction

Molecular recognition phenomena play a key role in several biological processes where a natural host, thanks to the particular chemical and structural information stored in its structure, is able to selectively recognise a complementary substrate (guest). Several studies have been carried out over the last couple of decades to disclose the nature and role played by host–guest intermolecular weak forces that drive these processes. In this context, remarkable achievements have been obtained in several instances by studying the molecular recognition processes that take place between specifically designed artificial receptors and simple (charged or neutral) guests. Nevertheless, basic and systematic studies carried out using different and complementary techniques able to provide a deeper understanding of the relative magnitude of the different forces (factors) that drive these processes are still lacking, especially in those cases where the energy gain associated with complex formation is of few kJ per mole.

Calixarenes,[1] thanks to the arrangement of their aromatic rings, possess an electron rich cavity, that is suitable for the inclusion of neutral guests of complementary size. Although the complexation of neutral guests by water soluble calixarenes is well documented,[2] a systematic study of the factors influencing the stability of calixarene complexes with neutral organic molecules in apolar media has been undertaken only recently. Arduini *et al.* have synthesized several calix[4]arenes, rigidified in a cone conformation by short ethereal bridges, which differ in their cavity width.[3] ^{1}H NMR titrations in organic media have demonstrated that these macrocycles are able to bind several neutral organic guests bearing acidic methyl residues and that the rigidity of the ligand skeleton is an essential prerequisite for their efficiency.[3b] Arena *et al.* have carried out a detailed study of the inclusion of acetonitrile and nitromethane into some of these calix[4]arenes in CCl_4.[4] The thermodynamic parameters (ΔH° and ΔS°) indicate that the investigated receptors form complexes of comparable stability with acetonitrile and nitromethane, thus suggesting that the different guest acidity is not the only factor affecting the extent of binding.

Stibor *et al.* performed a ^{1}H NMR study of the complexation of a series of neutral chloro, nitriles and nitro compounds with *p-tert*-butylcalix[4]arene derivatives, partially functionalised at the lower rim, in apolar solvents.[5] The lack of correlation between the electron effect of the substituent at the lower rim of the host and the complex stability, led them to suggest that the binding properties are mainly controlled by the calix rigidity and by the ligand geometry. Arduini *et al.* have investigated the inclusion of a series of CH_2XY guests of different acidity using partially alkylated *p-tert*-butylcalix[4]arene derivatives.[6] This study indicates that the guest acidity cannot represent the sole factor responsible for the formation of the complexes. In fact, whereas, on one hand, a linear correlation between the extent of binding and the acidity of the CH_2XY guests has been found, on the other hand, a dependence from the polarizability of the X and Y groups has also been shown.

† Electronic supplementary information (ESI) available: experimental conditions used for calorimetric measurements. See http://www.rsc.org/suppdata/nj/b3/b308996g/

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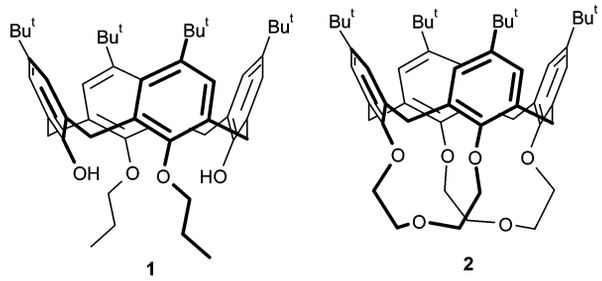

Fig. 1 Schematic representation of calix[4]arene derivatives **1** and **2**.

Based on these results, the prerequisites, that determine the ability of cone conformers of calix[4]arenes to form endo-cavity inclusion complexes in apolar media, are: *i.* the presence in the guests molecule of acidic "activated" CH_3 or CH_2 groups and *ii.* the reduction of the conformational flexibility of the receptor. Specific CH–π(aromatic) interactions[7] represent the main driving force for the formation of these complexes, as indicated by solution studies in apolar media and shown by structure data in the solid state. The analysis of the solid state structure of these calix[4]arene host–guest complexes indicate that, whereas CH_3X guests are bound preferentially by hosts having an aromatic cavity with a C_{4v} symmetry, CH_2XY guests are bound in a complementary manner by calix[4]arene receptors, that can assume a flattened cone structure having a C_{2v} symmetry.[8]

However no comparison of the selectivity of the recognition process in apolar solvents, using the two different approaches to the rigidification of the calixarene *cone* conformer, have been reported in the literature so far. In fact, whereas 1,3-dialkoxycalix[4]arene derivatives have been widely studied as receptors of several neutral species, biscrown-3-calix[4]arene derivatives have been employed as hosts only for CH_3X guests.

In this paper we report a study of the binding of *p-tert*-butylcalix[4]arene *cone* conformers rigidified through different approaches. The comparatively more versatile‡ and more flexible 1,3-dipropoxy-*p-tert*-butylcalix[4]arene (**1**) and the more rigid biscrown-3-*p-tert*-butylcalix[4]arene (**2**) were selected as hosts (Fig. 1) for CH_3X and CH_2XY neutral guest molecules, to have information on the relative weight of host rigidity and guest complementarity in the recognition process. In previous studies it was demonstrated that, for guests bearing the methylene moiety, the binding process depends also upon the polarizability of the X and Y substituents; these studies also showed that the presence of CH_3, Cl or CN groups did not markedly affect polarizability.[6] Based on these findings, $ClCH_2CN$, CH_3CH_2CN and CH_2Cl_2 were chosen as guests, to keep the polarizability of X and Y groups constant.

The systematic study of the energetics of the inclusion of CH_3X and CH_2XY guests into the π-donor cavity of calix[4]-arene derivatives was carried out using ^{1}H NMR spectroscopy in CCl_4 and direct calorimetry. In fact, the determination of ΔH° and ΔS° contributions, which reveal information that are not expressed in the ΔG° term,[9] may provide a better understanding of the forces involved in the inclusion processes and may help in explaining the different stability of the adducts formed. Further information was obtained by comparing the solid state structures of the adducts formed by hosts **1** and **2** with acetonitrile and chloroacetonitrile.

‡ 1,3-Disubstituited calix[4]arene derivatives represent a versatile class of synthetic receptors. In fact, this class of compounds makes it easy to realise active components of new artificial sensors for small organic molecules based on calix[4]arene compounds having 1,3-dialkoxy substituents functionalised with groups that allow the anchoring of the host onto sensor surfaces.

Results and discussion

NMR binding studies

In order to compare the impact of the different rigidification of hosts **1** and **2** on the formation of the adducts, the binding constant of biscrown-3-*p-tert*-butylcalix[4]arene (**2**) with $ClCH_2CN$ and CH_3CH_2CN were measured under the same experimental conditions used for host **1** (see Table 1).[3,6] These two guests were chosen as suitable CH_2XY type guests because of the similar polarizability of their X and Y groups.[6] The spectroscopic titrations proved the formation of 1 : 1 inclusion complexes in all cases.

Moreover, the upfield shifts of the acidic CH protons indicated that each guest is included *via* its methylene moiety, thanks to CH–π interactions with the π-donor aromatic rings of the calixarene. The binding constant values were obtained by refining proton upfield shifts using a non-linear least-squares fitting procedures.[10] On this base, considering CH_3CN, and $ClCH_2CN$ as referring molecules of the two classes of guests, the relative binding constants in CCl_4 were 150 and 102 M^{-1} respectively for host (**1**) and 320 and 25 for host (**2**). As expected the less flexible host **2** turns out to be a more efficient and selective host for CH_3X guests. On the contrary, the more flexible derivative **1** is able to recognise both classes of guests and shows a lesser selectivity for CH_2XY guests.

Thermodynamic studies

Although in the previous studies[6] the binding constants were determined either in CCl_4 or in $CDCl_3$, we only used CCl_4 in the calorimetric investigations. This solvent, in fact, cannot form hydrogen bonds with the reactants and is also too big to fit into the *p-tert*-butylcalix[4]arene cavity. It is not surprising that the log*K* values (Table 2) are larger than those determined in chloroform (a competing guest). The choice of CCl_4 was also dictated by the fast evaporation taking place when running the calorimetric experiment in chloroform, which hampered reproducible thermograms to be obtained (see experimental section).

Fig. 2 shows the total net heat (*i.e.* corrected for the dilution) for the reaction of CH_3CN with host **1** *vs.* the volume of titrant added. The guest/host ratio, at the end of the reaction (see ESI†), was set for each system in such a way as to reach saturation; only in this condition, *K* and ΔH° can be determined simultaneously. The results of the calorimetric study are reported in Table 2. The log*K* values determined calorimetrically are in excellent agreement, within the experimental error, with the figures obtained from ^{1}H NMR titrations (see Table 2). The ΔG° values indicate that the stability of the complexes with CH_2XY guests parallels their acidity ($ClCH_2CN$,[11] $pK_{a\text{-DMSO}} = 26$; CH_3CH_2CN,[11] $pK_{a\text{-DMSO}} = 31$; CH_2Cl_2,[11] $pK_{a\text{-DMSO}} = 35$), while the complex with CH_3CN is the most stable among the investigated adducts.

The dissection of the ΔG° values into the enthalpic and the entropic terms provides further insight into the forces driving the recognition processes and reveals some details that are not expressed by the log*K* values. The thermodynamic data (ΔH° and ΔS°) show that inclusion process is enthalpically

Table 1 Association constants (*K*) calculated for the complexation of CH_3CN, $ClCH_2CN$ and CH_3CH_2CN with hosts **1** and **2** in CCl_4[a]

Hosts	CH_3CN	$ClCH_2CN$	CH_3CH_2CN
1	150(30)[b]	102(5)[c]	30(2)[c]
2	320(10)[d]	25(5)[b]	[e]

[a] σ values are given in parentheses. [b] This work. [c] See ref. 6. [d] See ref. 4. [e] Negligible complexation.

Table 2 log$K$ values and thermodynamic parameters of complex formation of CH_3CN, $ClCH_2CN$, CH_3CH_2CN and CH_2Cl_2 with host **1**[a] and **2**[b] in CCl_4[c]

Complex	log$K$[d]	log$K$[e]	ΔG°/ kJ mol^{-1}	ΔH°/ kJ mol^{-1}	$T\Delta S^\circ$/ kJ mol^{-1}
1⊃CH_3CN	2.18	2.23(3)	−12.73	−35.2(6)	−22.5(7)
1⊃$ClCH_2CN$	2.01	1.95(4)	−11.13	−39.1(3)	−28.0(3)
1⊃CH_3CH_2CN	1.48	1.43(5)	−8.16	−27.7(4)	−19.6(4)
1⊃CH_2Cl_2	0.92	0.99(5)	−5.65	−23.1(4)	−17.5(3)
2⊃CH_3CN	2.5	2.39(5)	−13.64	−39.3	−25.4

[a] This work; [b] see ref. 4; [c] standard deviation values are given in parentheses; [d] log$K$ values determined *via* ^{1}H NMR; [e] log$K$ values determined by direct calorimetry.

driven for all systems, whilst the entropy of binding is unfavourable in all cases, as expected for the interaction of neutral partners in organic media. Table 2 shows that the binding efficiency of **1** is directly correlated with the enthalpic contribution. CH_3CN and $ClCH_2CN$ complexes, which have the largest binding constants, are also characterised by the largest enthalpic contributions.

For the CH_2XY guests, *i.e.* for $ClCH_2CN$, CH_3CH_2CN and CH_2Cl_2 complexes, the stabilities are linearly correlated with the acidity of CH_2 groups ($ClCH_2CN$,[11] $pK_{a\text{-DMSO}} = 26$; CH_3CH_2CN,[11] $pK_{a\text{-DMSO}} = 31$; CH_2Cl_2,[11] $pK_{a\text{-DMSO}} = 35$). A higher acidity of the aliphatic moieties results also in a larger ΔH° of binding for the corresponding adduct and, ultimately, in a larger ΔG°. This indicate that CH–π interactions, that are maximized in the presence of acid methylene residues, are the forces principally responsible for the formation of this class of complexes in organic media. The entropic term is significantly negative for all the systems investigated (see Table 2), due to reduction of degrees of freedom resulting from complex formation. As shown previously, *p-tert*-butyl functionalities widen and deepen the typical calix cavity, thus increasing the interaction points. This, leads on the one hand to a more favourable enthalpic contribution, but on the other causes a more pronounced stiffening of the host–guest system. In line with this reasoning, the more negative ΔS° values are obtained for the systems presenting the higher enthalpic stabilization, as the complexes formed with CH_3CN and $ClCH_2CN$. The CH_3CN complex is the most stable among the systems investigated in this study. For the sake of comparison, in Table 2 we have also reported the thermodynamic parameters for the inclusion of CH_3CN in host **2**. The inclusion of CH_3CN into this more preorganized and rigid host is more stabilized (ΔG°: −13.64 *vs.* −12.73 kJ mol^{-1}) than the inclusion in host **1**. The residual mobility of host **1** worsens the efficiency of the receptor; the rigid host **2**, blocked in the *cone* conformation (a C_{4v} symmetry), can have a larger number of interactions with CH_3X guests and turns out to be more efficient in their recognition. This extra-stabilization mainly derives from a more favourable enthalpic contribution and it seems that the different rigidification approach used in the two receptors is not reflected by the corresponding variation of the entropic contribution. However, differently from what is observed for CH_2XY guests, for CH_3CN the binding constant is not straightforwardly correlated either with the guest acidity (CH_3CN,[12] $pK_{a\text{-DMSO}} = 31.3$; $ClCH_2CN$,[11] $pK_{a\text{-DMSO}} = 26$) or with the enthalpic contribution.

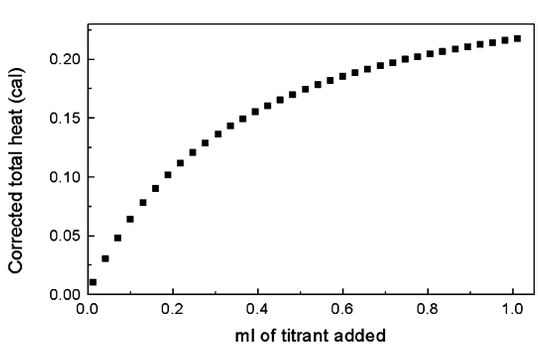

Fig. 2 Calorimetric run for the titration of 25 ml of 1,3-dipropoxy-*p-tert*-butylcalix[4]arene (**1**) (0.00144 mol dm^{-3}) with CH_3CN (0.53203 mol dm^{-3}) in CCl_4.

As previously hypothesized by Arduini *et al.*,[6] the larger binding constant value observed for CH_3CN, and more generally for CH_3X complexes, is the result of the incorporation of the guest methyl group that, upon inclusion into the cavity of **1**, still maintains its rotational freedom along its C–C or C–X bond. This implies a smaller loss of mobility in the formation of the [**1**⊃CH_3–X] if compared to the complexation of the more mobile CH_2XY guests. The thermodynamic parameters (ΔH and ΔS) support this hypothesis. In fact, if we compare CH_3CN and $ClCH_2CN$ complexes with ligand **1**, which are those described by the larger log$K$ values, we can notice that the higher stability of the [**1**⊃CH_3CN] complex does not result from a more favourable enthalpic term, but from a less unfavourable entropic contribution. This also indicates that the acidity of CH groups is not the sole factor affecting the extent of binding of CH_3X guests. Moreover the different geometry of the complexes and the difference in the host–guest contact do not allow a direct comparison of the interactions present in the complexes with CH_3–X and CH_2XY guests, respectively.

Solid state structural studies

Further information on the recognition processes of CH_3CN and $ClCH_2CN$ guests were obtained by comparing the solid state structures of their complexes with hosts **1** and **2**.

The solid state complexes of host **1** with acetonitrile and host **2** with acetonitrile and chloroacetonitrile were prepared. Their structures were determined by X-ray diffractometric methods and compared with those previously resolved for host **1** and chloroacetonitrile.[6] The molecular structures of the four complexes are shown in Fig. 3. These structures were analysed to understand the nature and the strength of the host–guest interactions. In this analysis we have taken advantage of the use of appropriate geometrical descriptors,[8] in order to have a rational base to describe the host geometries and the orientations of the guests inside the host cavities (see Fig. 4). The calculated values are reported in Table 3.

The structure refined for **1** ⊂ CH_3CN (see Fig. 3a) shows that the shape of this complex is mainly determined by two strong intramolecular hydrogen bonds which link the OH of one unfunctionalised phenolic ring to the phenolic oxygen of the adjacent functionalised rings [D···A distances: 2.768(2) and 2.748(2) Å; D–H···A angles: 176(2) and 172(3)°]. This is significantly different from what found for the corresponding chloroacetonitrile complex, where the analogous hydrogen bonds are stronger [D···A distances: 2.712(2) and 2.675(2) Å; D–H···A angles: 171(3) and 169(2)°].

However it is noteworthy that the host is not completely rigid since a little change in the geometrical parameters of the two (although strong) intramolecular hydrogen bonds (obtainable with little expense in enthalpy) can induce a significant conformational change at the upper-rim. Consequently, the host can change the symmetry of its aromatic cavity for a better steric match of the guest. The δ_{1-4} values reported in Table 3 show that the host cavity turns into an almost flattened partial cone C_{2v}-like or into a C_{4v}-like symmetry to better fit CH_2ClCN (C_{2v} symmetry) or the cylinder-like CH_3CN guest, respectively.

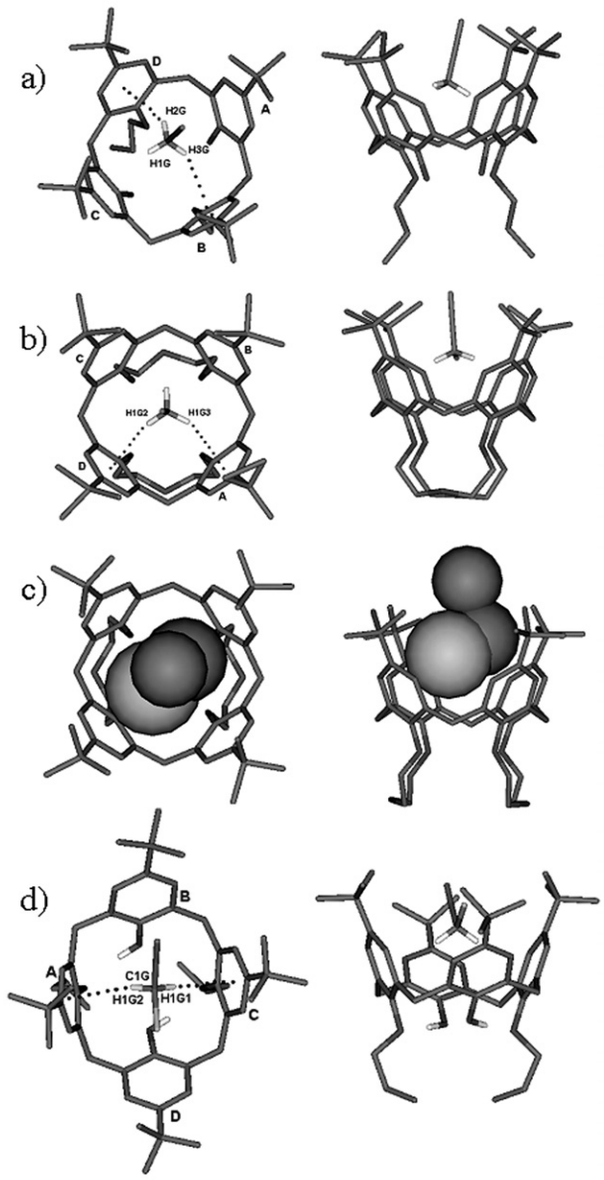

Fig. 3 Top and side views of the X-ray solid state inclusion complexes of a) **1**⊃CH_3CN, b) **2**⊃CH_3CN, c) **2**⊃$ClCH_2CN$ and d) **1**⊃$ClCH_2CN$.[6]

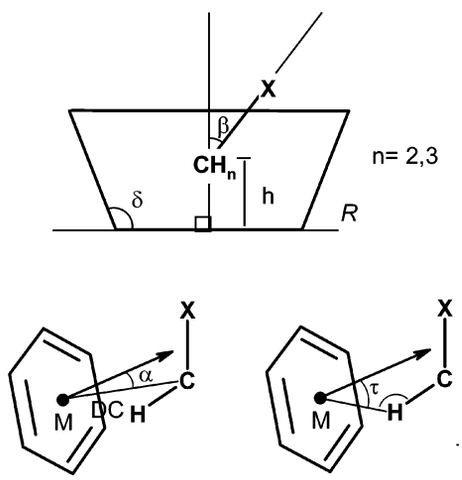

Fig. 4 Geometrical descriptors for solid state host–guest complexes.[8]

Unlike **1**, the more rigid biscrown-3-*p*-*tert*-butylcalix[4]arene **2** lacks this ability. In fact, in the two CH_2ClCN and CH_3CN complexes, the host cavity remains in an almost C_{4v} symmetry and is unaffected by the guest shape.

Therefore the aromatic cavity can host CH_3CN by including its methyl group, but it is not flexible enough to host CH_2ClCN by including its CH_2 group. As a consequence the latter guest enters in the cavity by inserting its chlorine atom and this geometry weakens the CH–π intermolecular host–guest attractive interaction in the solid state.

Both hosts **1** and **2** show a *pseudo* C_4 symmetry in the two complexes with acetonitrile (see δ angles in Table 3); the more mobile **1** is slightly more symmetrical than host **2**. In both complexes, the methyl group is included into the aromatic cavity of the hosts; however, the methyl group of the guest is not perfectly perpendicular to the plane defined by the methylene groups of the calixarene (see β angle in Table 3 and Fig. 4) and the deviation from the perpendicularity is greater in the complex with host **1**. Moreover, the geometrical descriptors for the CH_3CN complex with **1** and **2** show that in the former adduct the host skeleton is more open and consequently the guest molecule is more deeply buried in the cavity. In fact, the distance h of the C_{Methyl} from the weighted least-squares plane through the four bridging methyl groups of the calix[4]arene are 2.699(2) and 2.814(6) Å, respectively.

Host–guest attractive interactions in acetonitrile complexes. The crystal structure analysis of the **1**⊃CH_3CN and **2**⊃CH_3CN complexes makes it possible to compare host–guest interactions in these two complexes. In both the cases, the guest is linked to the host *via* a couple of weak intermolecular CH–π interactions whose geometrical parameters are summarized in Table 4.

The four equilibrium distances $C_{Guest}\cdots M$ (M = ring centroid) indicate that the guests are stabilized by CH–π interactions. Tzuzuki *et al.* reported the most accurate calculation of the magnitude of the CH–π interactions obtained so far for the methane–benzene synthon.[13] They found an equilibrium distance of 3.8 Å and the binding energy was 1.45 kcal mol^{-1}. For the more "acidic" CH in CH_3Cl interacting with benzene, the equilibrium distance decreases to 3.6 Å and the binding energy goes up to 3.0 kcal mol^{-1}, but the energy profile is large around the minimum so that considerably attraction still exists up to 3.8 Å.[7b]

In the two acetonitrile complexes here reported all the four $C_{Guest}\cdots M$ are close to 3.6 rather than to 3.8 Å and the angles C–H···M and τ (see Fig. 4) indicate that in both complexes the $C–H_{Methyl}$ bond is almost aligned to the normal to the ring (through its centroid) as expected for an ideal CH–π interaction geometry.

Host–guest attractive interactions in chloroacetonitrile complexes. In a previous study,[6] we reported the structure of **1**⊃$ClCH_2CN$. All the calculated geometrical parameters indicate that the CH–π interactions are the strongest ones among the series; in fact, the H···M and C···M distances and the C–H···M angle are the shortest and the greatest, respectively, among the series of complexes investigated.

In the **2**⊃CH_2ClCN complex, the aromatic cavity is occupied by the chlorine atom and the guest is disordered. This structure suggests that dispersive interactions are involved in the stabilization of this complex and this would explain the low binding constant observed in apolar solvents.

Conclusions

This multidisciplinary approach to the study of the recognition of guests containing CH_3 and CH_2 acidic groups by differently rigidified cone conformers of *p*-*tert*-butylcalix[4]arene provides

Table 3 Geometrical descriptors for solid state inclusion complexes (see text)[8]

Complex	δ_1 [°]	δ_2 [°]	δ_3 [°]	δ_4 [°]	β [°]	h [Å]	DC$_1$[Å]	DC$_2$[Å]	DC$_3$[Å]	DC$_4$[Å]	α_1 [°]	α_2 [°]	α_3 [°]	α_4 [°]
1⊂CH_3CN	116.53(4)	117.54(4)	116.33(4)	117.41(4)	16.44(7)	2.699(2)	3.535(3)	3.713(3)	3.545(3)	3.699(3)	3.77(5)	5.46(5)	4.49(5)	4.80(5)
2⊂CH_3CN	113.9(1)	115.1(1)	118.0(1)	114.6(1)	5.9(2)	2.814(6)	3.681(8)	3.655(6)	3.656(7)	3.632(8)	1.4(1)	1.2(1)	1.7(1)	1.1(1)
2⊂$ClCH_2CN$	115.5(2)	118.0(1)	117.4(1)	116.1(2)	5.9(2)[a]	[b]	[b]	[b]	[b]	[b]	[b]	[b]	[b]	[b]
1⊂$ClCH_2CN$	110.3(2)	138.2(2)	109.7(2)	135.3(2)	48.5(4)	2.857(2)	3.548(3)	3.934(3)	3.552(3)	4.103(3)	6.06(5)	15.81(5)	6.24(6)	19.04(5)

[a] Calculated from CN. [b] Disordered guest : distances h calculated from Cl atom are 2.843(9), 2.426(7) and 2.462(7) Å.

new interesting information on these processes. In particular the rigidity of host **2** and the different complexes with the two types of guests can be easily explained on the basis of the different structures of the complexes. The thermodynamic data evidenced that these processes are enthalpically driven but that it is the entropy difference that favours the recognition of CH_3X guests. CH–π interaction, evidenced by solid state studies, explain the enthalpic data and in particular the better efficiency of host **2** in the recognition process of acetonitrile.

Experimental

Acetonitrile, dichloromethane and NaCl (Merck, >99.5%) chloroacetonitrile, propionitrile and 18-crown-6 (Aldrich, 99%) were commercial products and were used without any further purification. Carbon tetrachloride and methanol (>99.8%) were purchased from Carlo Erba. Calix[4]arene derivatives (**1**)[14] and (**2**)[3b] were synthesized analogously to the procedures previously described.

NMR experiments

^{1}H NMR titration experiments were performed adding increasing amounts of a $0.5–1.0 \times 10^{-1}$ M stock solution of the guest to a $0.5–1.0 \times 10^{-2}$ M stock solution of the host in CCl_4(C_6D_6 as external standard), by monitoring the guest chemical shift variation. All the NMR spectra showed time-averaged signals for the free and complexed species and, having verified a 1 : 1 stoichiometry for the host–guest association by means of continuous variation methods,[15] the stability constants (K) for the complex formation were calculated using methods that have been previously described based on the non-linear fitting of the experimental data.[10]

Calorimetric measurements

The calorimetric titrations were performed at 25.000 ± 0.001 °C in CCl_4, using a Tronac 450 (Utah, USA) isoperibolic calorimeter. This calorimeter measures the temperature changes, following the addition of titrant, through a precision thermistor, which generates a voltage output; this output is converted into a heat quantity by a precision heater. This instrument was equipped with a 25 ml Dewar cell, although this dramatically increased the amount of calix[4]arene needed for each titration, since fast evaporation phenomena were observed employing the 4 ml Dewar.[4] Otherwise, regular and reproducible baselines of the thermograms were obtained with the 25 ml Dewar cell, with a marked positive slope. Usually a 0.5–1.5 mol dm^{-3} solution of the guest (CH_3CN, $ClCH_2CN$, CH_3CH_2CN or CH_2Cl_2) was added to a $1.2–1.5 \times 10^{-3}$ mol dm^{-3} solution of host **1**, recording 30–40 points for each of the 4–6 independent titrations, maintaining the guest–host molar ratios at the end of the titration in the range of 15.2–27.0 (see ESI†). Blank experiments were carried out before each titration, in order to correct the experimental data for all non chemical energy contributions, such as the heat of dilution and heat of friction effects, resulting from the addition of the titrant to the titrate solution in the calorimetric vessel. The calorimeter was calibrated electrically (twice for each single run, before and after the titration) to check for accuracy and reproducibility. The calorimeter was calibrated chemically too, by titrating a solution of 18-crown-6 in methanol with a methanolic solution of NaCl. The $\Delta H°$ and log$K$ values were in good agreement with the literature values.[16] The experimental data were treated by using a modified version of the computer program EQDH,[17] able to perform a simultaneous refinement of log$K$ and $\Delta H°$ values.

Table 4 Geometrical parameters for CH–π interactions[a]

	C–H···M[b]	H···M/Å	C–H···M/°	C···M/Å	τ/°[c]
1 ⊂ CH_3CN	C–H3G···B	2.90(5)	142(4)	3.713(3)	14.5(8)
	C–H2G···D	2.87(5)	149(4)	3.669(3)	3.1(9)
2 ⊂ CH_3CN	C–H1G3···A	2.79(1)	153(1)	3.681(8)	7.3(1)
	C–H1G···C	2.70(1)	164(1)	3.656(7)	15.7(1)
1 ⊂ $ClCH_2CN$	C–H1G2···A	2.624(2)	161.4(2)	3.548(3)	4.61(4)
	C–H1G1···C	2.669(2)	167.6(2)	3.552(2)	2.98(5)

[a] See Figs. 3a and 3d for ring and guest tags. [b] M is the ring centroid. [c] τ is the angle formed by H···M line and the normal to the ring (→), see Fig. 4.

X-ray data collection, structure solution, and refinement

Crystal data end experimental detail for the three structures are collected in Table 5. The raw frame data of **2**⊃$ClCH_2CN$ were processed using SAINT[18] and SADABS[19] to yield the reflection data file.

The three structures were solved by direct methods with SIR92[20] and refined with SHELXL-97.[21] In the structure of **2**⊃CH_3CN the *tert*-butyl groups were affected by severe static disorder. In **2**⊃$ClCH_2CN$ the guest showed severe static disorder with the C and Cl atoms of the terminal CH_2Cl group statistically distributed over two and tree different positions respectively. Molecular geometries were analysed with PARST97.[22],§

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§ CCDC reference numbers 215593 (**2**⊃CH_3CN), 215594 (**2**⊃$ClCH_2CN$), 215595 (**1**⊃CH_3CN). See http://www.rsc.org/suppdata/nj/b3/b308996g/ for crystallographic data in .cif or other electronic format.

Table 5 X-Ray data and structural refinement details for **1**⊃CH_3CN, **2**⊃CH_3CN, and **2**⊃$ClCH_2CN$ inclusion compounds

Compound	**1**⊃CH_3CN	**2**⊃CH_3CN	**2**⊃$ClCH_2CN$
Molecular formula	$C_{52}H_{71}NO_4$	$C_{54}H_{71}NO_6$	$C_{54}H_{70}ClNO_6$
Formula weight	774.137	830.158	864.603
Crystal system	Monoclinic	Triclinic	Monoclinic
Space group	$P2_1/a$	$P\bar{1}$	$P2_1$
a [Å]	19.892(5)	12.064(5)	11.237(5)
b [Å]	19.296(5)	19.817(5)	19.743(5)
c [Å]	12.102(5)	11.242(5)	12.286(5)
α [°]	90	90.27(2)	90
β [°]	90.69(2)	114.16(2)	113.69(2)
γ [°]	90	88.53(2)	90
V [Å^3]	4645(3)	2451(2)	2496(2)
Z	4	2	2
ρ (calcd.) [g cm^{-3}]	1.107	1.125	1.150
$F(000)$	1688	900	932
T [K]	173	298	298
λ [Å]	1.54178	1.54178	0.71069
μ [mm^{-1}]	5.262	5.628	1.248
Reflections collected	9340	9264	26 879
Independent refections	8620	9264	10 604
R_{int}	0.013	0.000	0.025
Observed reflections[a]	7380	1957	5717
Data/parameters/ restraints	551/0	549/0	578/9
Goodness-of-fit on F^2 [b]	1.472	0.832	1.116
R_1	0.0505	0.0765	0.0977
wR_2	0.1818	0.1980	0.3275
Largest diff. peak and hole [e Å^{-3}]	0.57, −0.36	0.46, −0.23	0.70, −0.81

[a] $F_0 \geq 4\sigma(F_0)$. [b] $R_1 = \Sigma \parallel F_0| - | F_c \parallel / \Sigma |F_0|$, $wR_2 = [\Sigma\, w(F_0^2 - F_c^2)^2 / \Sigma w\, F_0^4]^{1/2}$. Goodness-of-fit $= [\Sigma\, w(F_0^2 - F_c^2)^2/(n-p)]^{1/2}$, where n is the number of reflections and p the number of parameters.

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