Rigid cone calix[4]arenes as π-donor systems: complexation of organic molecules and ammonium ions in organic media

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One step synthesis of calix[4]arene biscrowns, with a rigid cone structure and alkyl or phenyl groups at the 'upper rim', has been performed. The binding ability of these rigidified cone calix[4]arenes 1–4, 13 has been evaluated, in apolar organic media, towards neutral organic molecules and ammonium cation salts. Comparison with more flexible analogues 5, 6, 11 shows that only rigid *cone* calix[4]arenes are able to complex organic species. The association constants strongly depend on the type of substituents present at the upper rim. The X-ray crystal structure of the *endo* complex *p*-cyclohexyl-25,26-27,28-biscrown-3-calix[4]arene 3 with CH_3NO_2 has been resolved.

Introduction

A main goal of supramolecular chemistry is the use of specific non-covalent binding forces to obtain in a selective way stable host–guest complexes. Recently, specific interactions of guests with π-donor systems have received considerable attention[1] particularly with regard to biological processes.[2] These interactions have been demonstrated in model systems during studies on the complexation of quaternary ammonium ions with anionic cyclophanes containing electron-rich aromatic nuclei in water solution.[3]

Complexation studies of alkylammonium cation in aprotic organic solvents have also been performed with uncharged cyclophane hosts, thus obtaining data unaffected by charge–charge interactions and under conditions where no hydrophobic effect is operating.† Macrocyclic hosts bearing electron-rich aromatic nuclei such as 'assembled' cyclophanes,[5] calixarenes[6] and homoxacalixarenes[7] were used, generally obtaining low binding constants. As expected only with macropolycyclic cyclophanes, *e.g.* cryptophanes[3n] and capped calix[6]arenes[8] were higher stability constants observed.

Calix[4]arenes and other cavitands are also able to form inclusion complexes with neutral molecules in the solid state, where CH-π interactions seem to play an important role.[9] However, such complexes have not been observed so far in organic media, due to competing solvation and to the conformational mobility of the host. It is known that alkylation of the phenolic OH groups of calix[4]arenes (lower rim) can suppress the interconversion between the different conformers (*cone*, *partial cone*, 1,2-*alternate*, 1,3-*alternate*) if the O-substituents introduced are more bulky than an ethyl group. We[10] and others[11] have recently shown that *cone* tetraalkoxycalix[4]arenes are not completely blocked in solution but experience residual conformational mobility between two C_{2v} (flattened cone) structures‡ (see Fig. 1).

Thinking that this residual mobility could affect the molecular recognition properties of calix[4]arenes cavitands, we tackled the problem of further rigidifying these macrocycles by functionalisation at the lower rim.[10] We report in this paper full details of the synthetic results and of the molecular inclusion properties of the new rigidified hosts toward alkylammonium ions and organic molecules having acidic C–H groups.

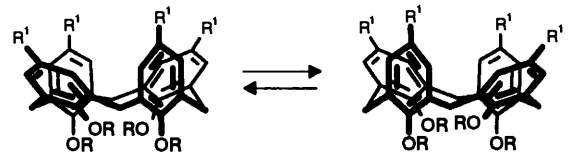


Fig. 1 Dynamic stereochemistry of tetraalkoxycalix[4]arenes in the *cone* conformation

Results and discussion

Rigidified calix[4]arene cone conformers

Examination of CPK molecular models showed that an attractive target for a very rigid and non distorted calix[4]arene cone derivative was the attachment of short diethyleneglycol bridges in proximal (25,26-27,28) positions at the lower rim.

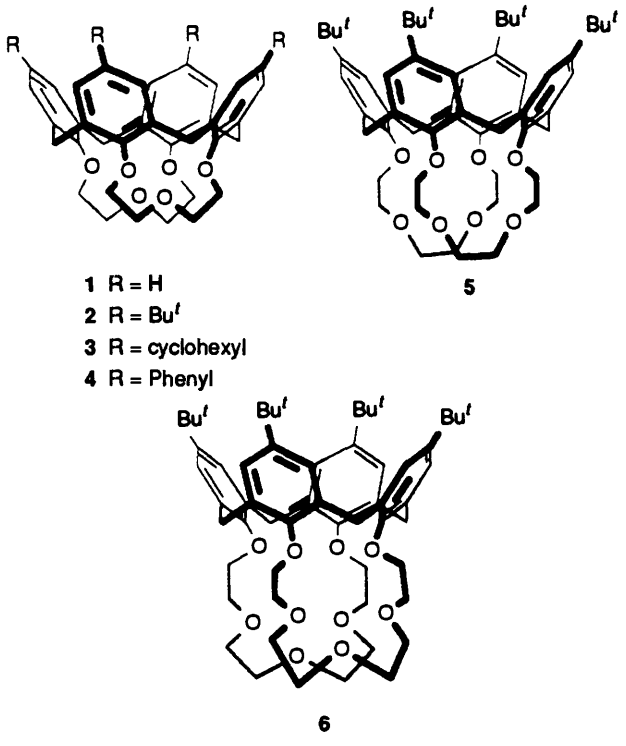
Some years ago we performed the selective proximal functionalisation of calix[4]arenes by a multi-step procedure starting from tetramethoxycalix[4]arene, with a sequence of selective demethylations and subsequent alkylations to give 25,26-27,28-*p*-*tert*-butylcalix[4]arene biscrown-5, **6**, in very low overall yield.[13] Subsequently this compound, which adopts a flattened cone conformation in the solid state[14] was obtained *via* a two-step synthesis in 16% overall yield, using NaH and tetraethyleneglycol di-*p*-toluenesulfonate in DMF for the first reaction,[15] then potassium *tert*-butoxide with the same di-*p*-toluenesulfonate in benzene for the second step.[16]

Through this improved procedure, the synthesis of *p*-*tert*-butylcalix[4]arenebiscrown-3, **2**, and biscrown-4, **5**, derivatives was attempted. Using sodium hydride with diethyleneglycol di-*p*-toluenesulfonate it was verified that the formation of the second crown bridge proceeds faster than for the first. So using *p*-*tert*-butylcalix[4]arene, **8**, and diethyleneglycol di-*p*-toluenesulfonate 1:2 molar ratio in the presence of an excess of sodium hydride in DMF the biscrown-3 ether **2** derivative was obtained in 30% yield.[10]

Improved purification procedures now give an increased

† Complexation studies of alkylammonium cation in aprotic organic solvent with charged cyclophanes have been reported.[4]

‡ In the solid state the C_{2v} flattened cone conformation is usually observed.[12]



yield (60%) of the isolated product **2**. Similarly *p-tert*-butylcalix[4]arenebiscrown-4, **5**, was obtained in 45% yield. Using the same procedure biscrown-3 derivatives **1** and **3** of other calix[4]arenes having hydrogen or cyclohexyl on the *para* position were also obtained (Scheme 1).

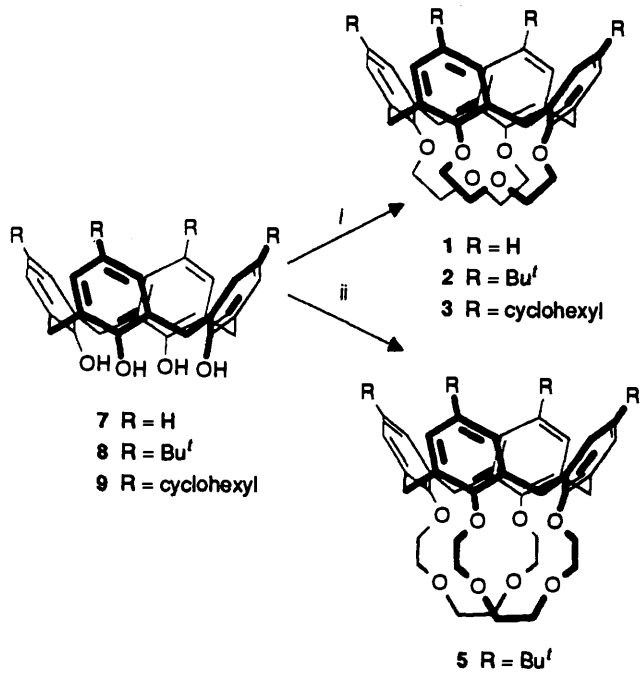
Compound **1** was also obtained by complete de-*tert*-butylation of **2**, evidencing the chemical stability of the bridging units. The bis-crown-3 derivative of *p*-phenyl calix[4]arene **4** was obtained by iodination and subsequent phenylation[17] of the unsubstituted biscrown ether **1** (Scheme 2).

The ^{1}H NMR spectra of the *p-tert*-butyl biscrowns **2**, **5** and **6** are strongly dependent on the length of the crown units. In fact, the 8 aromatic protons give a singlet at δ 6.78 ppm for biscrown-5, **6**, while for compounds biscrown-4, **5**, and -3, **2**, they show two distinct doublets at δ = 6.82 and 6.85, and δ = 6.90 and 6.94 ppm, respectively. Also, the calix[4]arene methylene protons are influenced by the dimensions of the two crowns; thus while the chemical shift of the two doublets experienced by the 4 equatorial protons are quite invariant, the two doublets of the 4 axial protons resonate downfield as the ether bridge length decreases. So, axial proton doublets for biscrown-5, -4 and -3 are at δ = 4.33 and 4.51, δ = 4.31 and 4.82 and δ = 4.46 and 5.04, respectively.

Complexation of ammonium ions

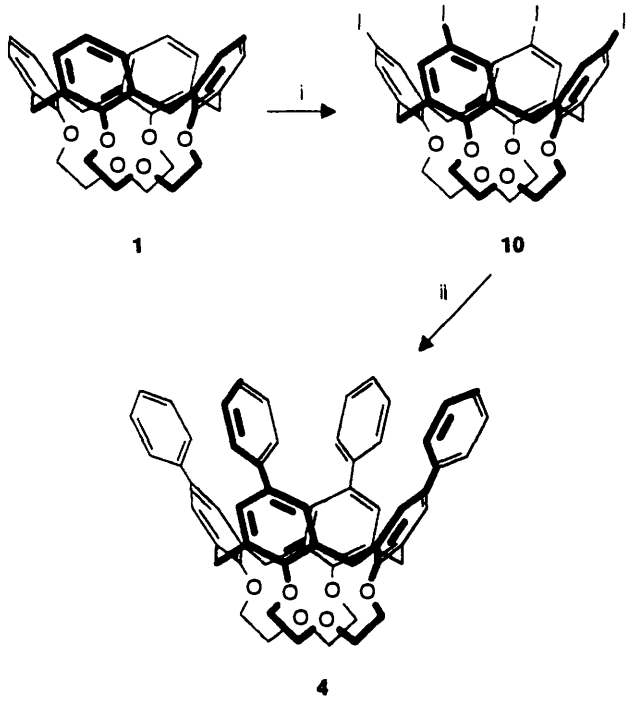
We first studied charged species such as ammonium ions, using *p*-toluenesulfonate as counterion because it allows most salts to be sufficiently soluble in $CDCl_3$ in order to perform NMR studies. The stability constants reported in Table 1 were established by non-linear least-squares analysis of the ^{1}H NMR titration data[18] using a 5×10^{-3} mol dm^{-3} ammonium salt concentration (see Experimental section). In the case of the methylammonium cation, titration experiments were also performed using the 18-crown-6 under the same conditions used for calixarene hosts.

Only the unsubstituted calix[4]arene-biscrown-3 derivative **1** is able to complex ammonium ions, with a clear preference for the methylammonium cation. Evidently steric reasons prevent the guests from entering the apolar cavity of the *tert*-butyl- and cyclohexyl-substituted calix[4]arenes-biscrown-3, **2** and **3**, respectively, having substituents in the *para* position.



i) NaH, $(TsOCH_2CH_2)_2O$, T = 80 °C
ii) NaH, $TsO(CH_2CH_2O)_2CH_2CH_2OTs$, DMF, T = 80 °C

Scheme 1



i) CF_3COOAg, I_2, CH_2Cl_2, reflux
ii) $Ni[P(Ph)_3]_4$, $ZnCl_2$, PhLi, THF, rt

Scheme 2

As expected, 18-crown-6 forms stronger complexes with methylammonium cation compared with rigid calix[4]arene **1**, but the binding mode is completely different in the two cases. In fact, upon addition of the guest to a $CDCl_3$ solution of the two hosts an upfield shift of the methyl protons is observed in the case of the calixarene host **1** (see Fig. 2), whereas for 18-crown-6 this signal moves downfield upon complexation as observed with other crown ethers[19] (see Table 2). A further insight into the structure of these two complexes can be obtained on the basis of ^{1}H NMR data of the *p*-toluenesulfonate counterion.

Table 1 Association constants for 1 : 1 complexation of host **1** with different ammonium salts in $CDCl_3$

Guest	K (dm^3 mol^{-1}, 300 K)	δ(free guest)	δ(complex)(calc.)
CH_3NH_3OTs[a]	220 ± 60	2.41	2.1 ± 0.5
$(CH_3)_4NOTs$	33 ± 10	3.35	0.6 ± 0.8
$(CH_3)_4NCl$[a]	80 ± 25	3.54	1.6 ± 0.5
$(CH_3)_4NO_2CCH_3$	247 ± 3	3.46	0.3 ± 0.5

[a] Monomethylammonium *p*-toluenesulfonate and tetramethylammonium chloride are only partially soluble in $CDCl_3$ (see Experimental section).

Table 2 Comparison of the calculated chemical shifts (in ppm) of methylammonium-*p*-toluenesulfonate (OTs) and picrate (Pic) in different complexes measured in $CDCl_3$

	$CH_3NH_3^+$	Anion
CH_3NH_3OTs	2.41	2.37, 7.18, 7.75
1·CH_3NH_3OTs	2.1	2.36, 7.18, 7.75
18C6·CH_3NH_3OTs	2.6	2.32, 7.11, 7.83
18C6·CH_3NH_3Pic[a]	2.6	8.81

[a] The free salt is insoluble in $CDCl_3$.

In fact, with 18-crown-6 the *p*-toluenesulfonate counterion changes chemical shift on complexation suggesting that the ion-pair is broken. Indeed the similarity between the chemical shifts of the picrate and *p*-toluene sulfonate complexes (Table 2) is further evidence that the ion-pair is broken. So the methylammonium is complexed, probably as a ligand separated ion-pair (LSIP), ligated at the NH_3^+ group as has been previously observed with the picrate.[20] With the rigid calix[4]arene **1** the *p*-toluenesulfonate counterion, however, does not change chemical shift on complexation and the ammonium salt is still probably complexed as a tight ion-pair. This clearly indicates that, in the case of rigid calix[4]arene **1** the methyl group of the cation penetrates inside the π-donor cavity of the host, whereas the ammonium part is preferentially complexed by 18-crown-6.[20]

In the free methylammonium ion the NH_3^+ group is more acidic than the CH_3 group and so, in principle, the NH_3^+ group might be expected to be preferentially complexed when the counterion is separated, as in the case of 18-crown-6. However, this is certainly not possible because of the ion-pairing with the *p*-toluenesulfonate counterion, which has already been shown to be very strong on this particular ion-pair, studied in *tert*-butyl alcohol.[21] Since the ion-pairing is evidently very tight, and the complexation observed with calix[4]arene-biscrown-3, **1**, is presumably not sufficiently powerful to break such an ion-pair, the methyl group is complexed into the cavity, with the ion-pair still significantly intact. In a ligand-separated ion pair (LSIP) a shift would be expected in the *p*-toluenesulfonate counterion which has not been observed. (However, all three of these types of ion-pair complexes have previously been seen in UV studies of pyridino-crown ethers with a substituted ammonium picrate; moreover using Orange 2, a sulfonate, as counterion the ion-pair appeared more stable than with picrate.)[22]

As far as the selectivity of the complexation is concerned, the comparison of methylammonium and tetramethylammonium *p*-toluenesulfonate (see Table 1) exhibited a low but significant preference for the less hindered methylammonium ion-pair. To further study the influence of the counterion on the complexation, a range of titrations were performed using calix[4]arene biscrown-3, **1**, with tetramethylammonium *p*-toluenesulfonate, chloride and acetate. Only the tetramethylammonium salts were studied because, in $CDCl_3$, for methylammonium the chloride is insoluble and the acetate is a non-ionised 'salt'. In all three cases the chemical shift for the tetramethylammonium salt in the complex was moved upfield compared with the free salt. These results showed

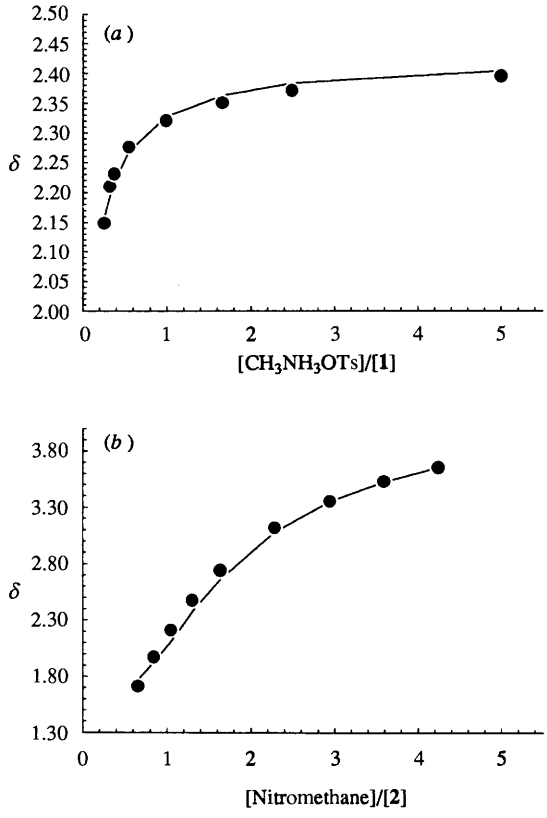


Fig. 2 ^1H NMR titrations of (*a*) methylammonium *p*-toluenesulfonate with host **1** in $CDCl_3$ at 300 K ([CH_3NH_3OTs] = 5.0 × 10^{-3} mol dm^{-3}) and (*b*) host **2** with nitromethane in CCl_4 at 300 K ([**2**] = 3.0 × 10^{-2} mol dm^{-3})

the tetramethylammonium *p*-toluenesulfonate to be the most weakly complexed and the acetate to be the most strongly complexed. This suggests that tightening the ion-pair weakens the complexation, which is in accordance with the minor acidity and the high steric requirements of the tight methylammonium *p*-toluenesulfonate ion-pair.

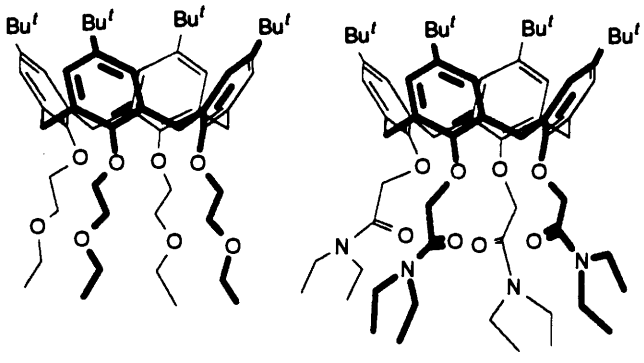
Complexation of neutral molecules containing acidic C–H groups

Complexation studies of nitromethane and malononitrile with *p-tert*-butylcalix[4]arene biscrown-3, **2**, were performed by ^1H NMR spectroscopy.[19,23] By adding variable amounts of the guest to a solution of the host in CCl_4 a significant upfield shift of the signal experienced by the CH protons of the guest can be observed (see Fig. 2). These shifts clearly show an interaction of the acidic protons of the guest with the electrons of the calixarene cavity. In fact, a possible interaction of these protons with the crown-ether region of these ditopic receptors should result in a downfield shift of these signals—as observed in other systems.[19] These experiments showed the formation of 1 : 1 complexes and provided quantitative information on the host–guest interactions (see Table 3). In order to gain further insight into the role of rigidity on the molecular recognition properties of calix[4]arene cavitands we studied the behaviour of the more mobile hosts tetrakis(2-ethoxyethoxy)-*p-tert*-butylcalix-[4]arene **11** and *p-tert*-butylcalix[4]arenebiscrown-5 **6**.

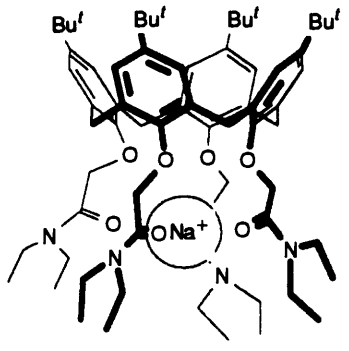
Table 3 Association constants, K ($dm^3\ mol^{-1}$), for 1 : 1 complexation with various guests at 300 K

Calix[4]arene	CH_3NO_2 $K_{1:1}$, $CDCl_3$	CH_3NO_2 $K_{1:1}$, CCl_4	$CH_2(CN)_2$ $K_{1:1}$, $CDCl_3$
1	5 ± 2	28 ± 7	17 ± 2
2	27 ± 4	230 ± 60	6 ± 2
3	36 ± 8	123 ± 25	23 ± 5
4	*c*	*a*	*b*
5	*b*	50 ± 10	*b*
6	*b*	*c*	*b*
11	*c*	*c*	*b*
12	*c*	*b*	*b*
13	34 ± 7	*b*	*b*

[a] Insoluble in CCl_4. [b] Not determined. [c] No significant variation of the chemical shift of the guest observed.



11 **12**



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With both hosts no variation of the chemical shifts of the nitromethane in CCl_4 was observed. On the contrary, with *p-tert*-butylcalix[4]arene-biscrown-4, **5**, complexation does occur but with a lower binding constant than with the more rigid biscrown-3 derivative **2** (see Table 3).

These results demonstrate the importance of rigidity in determining the complexation properties of the π-donor cavity of these cavitands.

Another interesting observation, which confirms the importance of rigidity and, consequently, of the reorganisation of cone conformers of calix[4]arenes in determining complexation ability, was obtained by comparison between *p-tert*-butylcalix[4]arene tetramide **12** and its sodium picrate complex **13** in the complexation of nitromethane in $CDCl_3$. The conformationally mobile host **12** does not show significant complexation of the guest whereas its sodium complex **13**, which is more rigid,[24] strongly interacts with the guest (see Table 3).

The effect of the substituents present on the upper rim of biscrown-3-calix[4]arenes on the complexing properties was also studied. Whereas the substitution of *tert*-butyl with hydrogen strongly reduces the binding ability of the host, the presence of a cyclohexyl group results in a small decrease in the binding constant for nitromethane (see Table 3). However, with the phenyl derivative **4** no significant variation in the chemical shifts of nitromethane was observed. The absence of host–guest interactions was also verified using ^{13}C NMR spectroscopy.[19d] Using the more polar $CDCl_3$ as solvent the binding constants are decreased as observed in other complexation processes involving hydrogen bonding.[19]

The better complexing properties of *p-tert*-butyl **2** and *p*-cyclohexyl derivative **3** are in agreement with the hypothesis that the extension of the cavity increases the interaction between the host and the guest. The interpretation of the results obtained with the *p*-phenyl derivative **4** is more difficult and can be tentatively explained assuming that the dihedral angle[25] between the phenyl group and the aryl group of the calix results in a partial occupation of the cavity which can inhibit the host–guest interaction. Malononitrile was also studied as a guest using, for solubility reasons, $CDCl_3$ as solvent. Using **1** as host, a larger association constant was observed in agreement with the higher acidity of this guest, compared with nitromethane.[26] Contrary to the results obtained with nitromethane, no significant change in the complexation constant with cyclohexyl derivative **3**, and a strong decrease with *p-tert*-butyl derivative **2** were observed with malononitrile. These results show that, although it is more acidic, the more sterically demanding malononitrile experiences steric hindrance with *tert*-butyl or cyclohexyl groups with a concomitant reduction in the binding constant. The three-dimensional nature of the binding site allows, through steric control, high shape selectivity to be achieved in the complexation process.

X-Ray studies

The X-ray crystal structure of the *p*-cyclohexylcalix[4]arene biscrown-3 1 : 1 nitromethane complex [see Figs. 3(*a*) and 3(*b*)] shows that the host exists in a distorted *cone* conformation.

The four *p*-cyclohexyl groups, which extend the intramolecular cavity at the upper rim, are all in the chair conformation. The dihedral angles δ formed by the least-squares planes through the phenolic rings and the molecular reference plane R[27] [A–R = 118.4(2), B–R = 117.4(2), C–R = 118.3(2) and D–R = 115.0(2)°] show that the *cone* is slightly irregular and more 'closed' than in the two fourfold symmetric *p-tert*-butylcalix[4]arene **1** : **1** toluene complex[28] and *p-tert*-butylcalix[4]arene 1 : 1 acetonitrile complex[29] which show dihedral angles R–Ph of 123.03(7) and 123.05(2)° respectively. More closed is the conformation of the *cone* in the *p-tert*-butylcalix[4]arene tetracarbonate 1 : 1 acetonitrile complex[30] which exhibits only one δ value of 114.6(1)°. The conformational parameters φ and χ[31] reported in Table 4, suggest a symbolic C1 + −, + −, + −, + − conformation. The comparison with those observed in the *p-tert*-butylcalix[4]arene 1 : 1 toluene complex [φ = 88.9(4), χ = −89.4(5)°] illustrates the strong conformational rearrangement of the macrocycle when the two crown-3 polyethereal chains block the calix[4]arene residual flexibility.

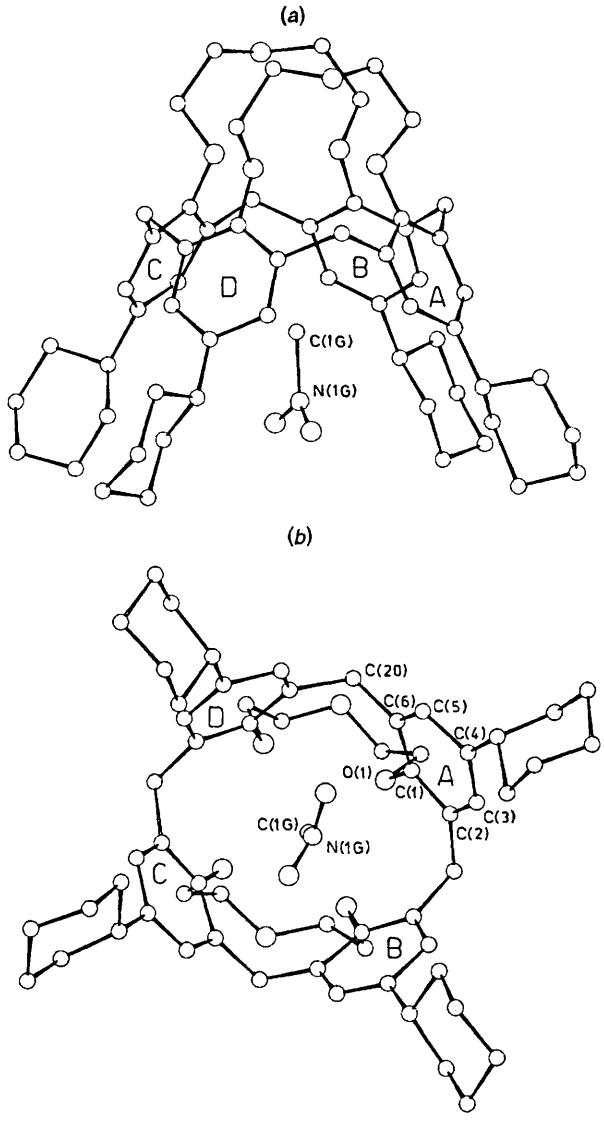

Fig. 3 (*a*) Side view of molecular structure for 1 : 1 complex of nitromethane with compound **3**. (*b*) View along the channel of the molecular structure for 1 : 1 complex of nitromethane with compound **3**.

Table 4 Conformational parameters (°) in the *p*-cyclohexylcalix[4]-arene biscrown-3 1 : 1 nitromethane complex

	φ	χ
A–B	78(1)	−79(1)
B–C	87(1)	−83(1)
C–D	78(1)	−76(1)
D–A	79(1)	−82(1)

In the solid state the nitromethane guest molecule lies inside the cavity and orients its N–CH_3 bond along the axis of the cone with CH_3 group faced on the aromatic nuclei of the host.

As far as the CH_3–π interaction is concerned, the crystal structure determination did not allow location of the atomic co-ordinates of the H atoms of the guest. However, some consideration can equally be drawn by comparing the intermolecular distances CH_3–C_{ph} between the C atom of the guest and those of the host aromatic nuclei§ and by comparison with the corresponding distances observed in the other calix[4]arene complexes (all possessing four-fold symmetry) with guests having a methyl group inside the intramolecular cavity such as the *p-tert*-butylcalix[4]arene 1 : 1 toluene,[28] *p-tert*-butylcalix[4]arene 1 : 1 acetonitrile[29] and *p-tert*-butylcalix-[4]arene tetracarbonate 1 : 1 acetonitrile[30] complexes. The crystal structure shows that the C_{Me} is closer to the two rings B [distance range: 3.82(2)–3.94(1) Å] and D [3.83(1)–3.94(1) Å]¶ rather than to the rings A [3.85(1)–4.07(1) Å] and C [3.88(1)–4.10(1) Å].‖ This asymmetry in the position of the guest C_{Me} group with respect to aromatic faces seems only a consequence of the asymmetry of the host *cone*. In any case the distances observed are all longer than the shortest C_{Me}–C_{ph} of 3.676(6) Å involving the CH_3 group of the guest in the *p-tert*-butylcalix[4]arene 1 : 1 toluene complex [3.676(6)–4.159(5) Å].[28]

On the other hand, since recent INS (Inelastic Neutron Scattering) experiments have clearly established that the methyl group of the toluene in the latter complex behaves as an almost free quantum rotor,[32] *i.e.* the rotational barrier provided by the host molecule is particularly small, it seems reasonable to expect in the solid state similar results for the methyl group of the nitromethane guest inside the biscrown-3 **3** derivative as well.

On this basis further experiments including INS on the nitromethane 1 : 1 biscrown-3 complex are planned in order to clarify the nature of the host–guest interactions.

Conclusions

In conclusion, these results indicate that the preorganisation of the aromatic π-system of the cavity of the cone conformer of calix[4]arenes determines the stability of their complexes with guest molecules possessing acidic C–H bonds. The host preorganisation has been obtained either through the introduction of short bridges at the lower rim or by complexation with cations which act co-operatively[33] to enhance the binding properties of the calix[4]arene cavity. The association constants of the resulting complexes with neutral molecules are of the same order of magnitude of those observed with crown ethers.[19] However, the three-dimensional nature of the calixarene apolar binding cavity is responsible for the shape selectivity observed. X-Ray studies confirm that in the solid state the nitromethane guest molecule lies inside the cavity and orientates its N–CH_3 bond along the axis of the *cone* with the CH_3 group faced on the aromatic nuclei of the host. On the contrary, a comparison of the association constants with methylammonium *p*-toluenesulfonate of calix[4]arene-biscrown-3, **1**, and 18-crown-6 shows a large difference in the numerical values. This result can be ascribed to the different binding mode, *i.e.*, *via* the $-NH_3^+$ moiety for 18-crown-6 and *via* the $-CH_3$ moiety of the tight ion-pair for this calix[4]arene derivative.

Experimental

General

All reactions were carried out under nitrogen, and all solvents were freshly distilled under nitrogen and stored over molecular sieves for at least 3 h prior to use (unless otherwise indicated) whereas all other reagents were reagent grade quality obtained from commercial supplies and used without further purification. NMR spectra were recorded on Bruker AC 100, AC 300 and AMX 400 instruments operating at 300, 400 MHz respectively for ^1H, and at 25, 75 MHz, respectively for ^{13}C. Chemical shifts (δ) are expressed in ppm from the internal reference tetramethylsilane. Mass spectra were determined in the CI mode (CH_4) using a Finnigan MAT SSQ 710. Melting points were measured with an Electrothermal Melting Point apparatus and are uncorrected. Analytical thin layer chromatography was

§ See Table SV of the supplementary materials.

¶ The distances are quite similar to those observed in the *p-tert*-butylcalix[4]arene tetracarbonate 1 : 1 acetonitrile complex [3.80(1)–3.904(8) Å].[30]

‖ The C_{Me} distances are comparable to those in the *p-tert*-butylcalix[4]arene 1 : 1 acetonitrile complex [3.776(4)–4.173(2) Å].[29]

performed on precoated silica gel plates (Merck, 60 F_{254}) and column chromatography was performed with silica gel (ICN, particle size 63–200 and ICN, particle size 32–63). Compounds **7**,[34] **8**,[35] **9**,[36] **11**[37] and **12**[24a] were synthesised according to literature procedures. Commercial sodium hydride (55% in oil) was washed with dry toluene and stored under nitrogen. Elemental analysis was performed at the Dipartimento Chimico Farmaceutico of the University of Parma. As verified also by other authors[38] the results with calixarenes are very often incorrect, nevertheless, the spectral data are in agreement with the structure of these new compounds.

General procedure for the synthesis of 25,26-27,28-biscrown-*n*-calix[4]arenes

The appropriate calix[4]arene (**7**, **8**, **9**), (5.0 mmol) was dissolved in DMF (500 cm^3) and the resulting mixture was purged from oxygen with three vacuum-nitrogen cycles. NaH (0.60 g, 25.0 mmol) was then added and after 10 min the appropriate glycol di-*P*-toluenesulfonate (12.5 mmol) dissolved in DMF (50 cm^3) was added. The reaction mixture was then stirred at 50 °C for 4 h and the excess of NaH eliminated by addition of a minimal quantity of methanol (**CAUTION**!), evaporated to dryness and the residue taken up with a solution of HCl (10% w/v, **CAUTION**!) and extracted with ethyl acetate. The organic layer was separated and washed twice with water, and the solvent evaporated *in vacuo* to dryness.

25,26-27,28-Biscrown-3-calix[4]arene 1.** The residue was purified by flash chromatography (60:40 hexane-ethyl acetate) affording 1.7 g (60% yield) of **1** as a white solid, mp 265–268 °C (Found: C, 75.51; H, 7.15. $C_{36}H_{36}O_6$ requires C, 76.57; H, 6.43%).

5,11,17,23-Tetrakis(1,1-dimethylethyl)-25,26-27,28-biscrown-3-calix[4]arene 2.** The residue was treated with CCl_4 and the precipitate formed removed by filtration, the organic solution evaporated *in vacuo* to dryness and the residue triturated with CH_3CN and recovered by filtration to give 1.9 g (60% yield) of **2** as a white solid, mp 273–275 °C (Found: C, 76.80; H, 9.25. $C_{52}H_{68}O_6$ requires C, 79.15; H, 8.69%).

5,11,17,23-Tetracyclohexyl-25,26-27,28-biscrown-3-calix-[4]arene 3. The residue was purified by flash chromatography (80:20 hexane-ethyl acetate) affording 2.2 g (50% yield) of **3** as a white solid: mp 238–240 °C (Found: C, 80.67; H, 9.38. $C_{60}H_{76}O_6$ requires C, 80.68; H, 8.58%). δ_H(300 MHz, $CDCl_3$) 1.15–1.39 (22 H, m, C*H* cyclohexyl, axial), 1.67–1.77 (18 H, m, C*H* cyclohexyl, equatorial), 2.24 (4 H, bt, ArC*H* cyclohexyl), 3.10 and 3.16 (4 H, 2d, *J* 12.0 and 12.3, ArCH_2Ar equatorial), 3.87–3.94 and 4.18–4.31 (16 H, 2m, ArOCH_2CH_2O–), 4.44 and 4.99 (4 H, 2d, *J* 12.3 and 12.0, ArCH_2Ar axial), 6.74 and 6.76 (8 H, 2d, *J* 1.8, Ar-*H*); δ_C(75 MHz, $CDCl_3$) 26.3, 26.9, 34.5, 34.6 (t, CH_2 cyclohexyl), 29.9, 30.9 (t, ArCH_2Ar), 43.6 (d, *C*H cyclohexyl), 74.2, 75.8 (t, –OCH_2–), 126.0, 127.1, 134.7, 135.0, 142.1, 153.0 (Ar); *m*/*z* 893 (MH^+, 40%), 811 (100).

5,11,17,23-Tetrakis(1,1-dimethylethyl)-25,26-27,28-biscrown-4-calix[4]arene (5). The residue was purified by chromatography (PriOH:THF:NH_4OH = 100:80:5) affording 2.0 g (45% yield) of **5** as a white solid: mp 249–251 °C (Found: C, 76.60; H, 9.93. $C_{56}H_{76}O_8$ requires C, 76.68; H 8.73%). δ_H(400 MHz, $CDCl_3$) 1.04 [36 H, s, –C(CH_3)$_3$], 3.06 and 3.13 (4 H, 2d, *J* 12.4 and 12.5, ArCH_2Ar equatorial), 3.74–3.90 (16 H, m, –CH_2OCH_2–), and 4.20–4.30 (12 H, m, ArOCH_2CH_2O– and ArCH_2Ar axial), 4.76 (2 H, d, *J* 12.4 ArCH_2Ar axial), 6.75 and 6.79 (8 H, 2d, *J* 2.4, Ar-*H*); δ_C(25 MHz, $CDCl_3$) 29.7(t, ArCH_2Ar), 31.5 [(q, C(CH_3)$_3$]), 33.8 [(s, *C*(CH_3)$_3$]), 70.4, 71.0, 73.3 (t, –OCH_2–), 125.0, 125.1, 133.6, 134.2, 144.6, 153.3 (Ar); *m*/*z* 877 (MH^+, 40%).

25,26-27,28-Biscrown-3-calix[4]arene 1, method b. To a solution of **2** (1.0 g, 1.3 mmol) dissolved in a mixture of toluene not distilled (30 cm^3) and dichloromethane (1.5 cm^3), was added $AlCl_3$ (1.0 g, 7.5 mmol). The heterogeneous mixture was vigorously stirred at room temperature for 3 h, and then poured into a beaker of crushed ice (50 cm^3, **CAUTION**!). The organic phase was separated and washed twice with water, dried over Na_2SO_4 and the solvent evaporated *in vacuo* to dryness. Purification of the residue afforded 0.64 g (90% yield) of **1** as a white solid.

5,11,17,23-Tetraiodo-25,26-27,28-biscrown-3-calix[4]arene 10. To a suspension of CF_3COOAg (2.0 g, 9.0 mmol) in refluxing dichloromethane (300 cm^3) were added compound **1** (1.0 g, 1.8 mmol) and iodine (2.3 g, 9.0 mmol). The heterogeneous mixture was refluxed with stirring for 2 h, then the yellow precipitate formed during the reaction was removed by filtration. The organic solution was washed with a solution of $Na_2S_2O_5$ (10% w/v) and twice with water, dried over Na_2SO_4, and the solvent was evaporated *in vacuo* to dryness. Recrystallization from chloroform afforded 1.2 g (62% yield) of **10** as a white solid: mp > 350 °C (Found: C, 67.23; H, 4.75. $C_{36}H_{32}I_4O_6$ requires C, 40.48; H, 3.02%). δ_H(400 MHz, $CDCl_3$) 3.10 and 3.16 (4 H, 2d, *J* 12.0, ArCH_2Ar equatorial), 3.74–3.79 and 4.15–4.26 (16 H, 2m, ArOCH_2CH_2O–), 4.30 and 4.89 (4 H, 2d, *J* 12.0, ArCH_2Ar axial), 7.31 and 7.33 (8 H, 2d, *J* 2.0, Ar-*H*); δ_C(25 MHz, [$^2H_5$]-Py) 29.2, 30.5 (t, ArCH_2Ar), 74.5, 77.1 (t, –OCH_2–), 88.6, 123.8, 135.6, 137.6, 138.2, 138.8, 150.0 (Ar); *m*/*z* 1068 (M^-, 100%).

5,11,17,23-Tetraphenyl-25,26-27,28-biscrown-3-calix-[4]arene 4. Phenyllithium (3 cm^3 of 2 mol dm^{-3} solution in hexane) was diluted with diethyl ether (25 cm^3) and anhydrous $ZnCl_2$ (0.82 g, 6.0 mmol) dissolved in THF (5 cm^3) was added at room temperature and the mixture stirred for 10 min. To the resulting white heterogeneous mixture, Ni[$P(C_6H_5)_3$]$_4$ (2 cm^3 of 0.2 mol dm^{-3} solution in THF) was added and once the mixture became dark brown and homogeneous, compound **10** (0.3 g, 0.28 mmol), dissolved in THF (5 cm^3), was added. The reaction mixture was stirred at room temperature for 2 h, then the solvent was evaporated *in vacuo* to dryness and the residue taken up with a solution of HCl (10% w/v) and extracted with dichloromethane. The organic layer was separated, washed with water, dried over Na_2SO_4 and the solvent was evaporated *in vacuo* to dryness. Purification of the residue by column chromatography (chloroform as eluent, **CAUTION**!) afforded 0.12 g (50% yield) of **4** as a white solid: mp 334–336 °C (Found: C, 82.12; H, 7.52. $C_{60}H_{52}O_6$ requires C, 82.92; H 6.03%). δ_H(400 MHz, $CDCl_3$) 3.41 and 3.45 (4 H, 2d, *J* 12.4 and 12.0, ArCH_2Ar equatorial), 3.98–4.21 and 4.33–4.44 (16 H, 2m, ArOCH_2CH_2O–), 4.65 and 5.20 (4 H, 2d, *J* 12.0 and 12.4, ArCH_2Ar axial), 7.27–7.43 (28 H, m, Ar-*H*); δ_C(25 MHz, $CDCl_3$) 30.4, 31.2 (t, ArCH_2Ar), 74.8, 78.4 (t, –OCH_2–), 126.6, 127.0, 127.1, 128.1, 128.5, 135.6, 135.7, 136.7, 141.2, 155.1 (Ar); *m*/*z* 869 (MH^+, 100%).

Complexation studies††

General. Tetramethylammonium chloride and acetate were commercial samples from Fluka AG, and were dried and used without further purification. The ammonium *p*-toluenesulfonates are known compounds[21,39] and are simple to prepare. $CDCl_3$ was dried over 3 Å molecular sieves before use.

Methods for NMR titrations. *Ammonium salts.* A solution, or dispersion,‡‡ of a substituted ammonium salt (5.00 ± 0.05 × 10^{-3} mol dm^{-3}) in $CDCl_3$ was titrated with a solution

** For the spectral data of the known compounds **1** and **2** see reference 10.

†† For the experimental procedures for the complexation of neutral molecules see references 19*a*,*b*.

‡‡ Monomethylammonium *p*-toluenesulfonate and tetramethylammonium chloride are only partially soluble at this concentration and so were dispersed using ultrasound. On addition of a complexon, solubilisation was observed and the data points after this process of solubilisation were used for the calculation of the stability constants.

Table 5 Experimental data for the X-ray diffraction studies

Formula	$C_{60}H_{72}O_6 \cdot CH_3NO_2$
Symmetry	triclinic
space group	$P\bar{1}$
Cell parameters at 295 K[a]	
a/Å	22.574(6)
b/Å	11.019(4)
c/Å	11.071(3)
α/°	116.93(2)
β/°	86.29(2)
γ/°	83.27(2)
V/Å^3	2738(2)
Z	2
D_{calc}/g cm^{-3}	1.153
$F(000)$	1024
Mol wt.	950.26
Linear abs. coeff./cm^{-1}	5.945
Diffractometer	Siemens AED
Radiation	CuKα (1.541 78 Å)
2θ Range/°	6–140
Unique data	10 385($\pm h, \pm k, \pm l$)
Unique data with $I \geqslant 2\sigma(I)$	4136
Agreement between equivalent obsd. reflcns.	0.037
No. of variables	453
Max Δ/σ on last cycle	0.07
$R = \Sigma\|\Delta F\|/\Sigma\|F_o\|$	0.095
$R_w = \Sigma_w^{\frac{1}{2}}\|\Delta F\|/\Sigma_w^{\frac{1}{2}}\|F_o\|$	0.095
GOF = $[\Sigma_w^{\frac{1}{2}}\|\Delta F\|^2/(NO\text{-}NV)]^{\frac{1}{2}}$	2.008
Max. in final ΔF Fourier map/e Å^{-3}	0.309

[a] Unit cell parameters were obtained by least-squares analysis of the setting angles of 30 carefully centred reflections found in a random search on the reciprocal space.

of the relevant calixarene (*ca.* 0.5–1.0 mol dm^{-3}) in $CDCl_3$, and a ^{1}H NMR spectrum was acquired (300 MHz, 300 K) after each incremental addition. The total dilution throughout the titration was limited to 5% of total volume with blank dilution experiments (in the absence of calixarene) showing negligible changes in the signals of the salt on dilution. The analytical concentration (allowing for dilution) of the calixarene after each addition was calculated by integration of the NMR signals of guest and host. The titrations were repeated at least twice and so the quoted results are values averaged over different titrations. At 300 K fast exchange between complexed and free guest was observed, giving a single signal averaged between the two forms, the chemical shift of which varies with the ratio between host and guest. Non-linear regression analysis[18] of the induced shifts on the MeN signal of the ammonium salt facilitated calculation of the chemical shift for the complex and of the apparent stability constants for association of the ammonium salt with the calixarene, always assuming a 1:1 preferred stoichiometry for the complex formed.

X-Ray crystallography

Compound **3** was crystallised from a nitromethane solution at room temperature. A colourless prismatic single crystal of *ca.* 0.2 × 0.3 × 0.4 mm suitable for X-ray analysis was mounted on a glass rod without protection from the air.

The crystal data and the most relevant experimental details of the X-ray diffraction measurements and crystal structure analysis are reported in Table 5. All the intensities were calculated by profile analysis according to the Lehmann and Larsen method[40] and corrected for Lorentz and polarisation effects. No absorption correction was applied. One standard reflection collected every 100 showed no significant fluctuations. The structure was solved by direct methods using SIR92[41] which revealed all the non-H atoms of the host but not the guest. The structure was completed, first by successive Fourier ΔF and then refined by full matrix-least squares methods using the SHELX76 computer program.[42] Isotropic atomic displacement parameters were assigned to the carbon and oxygen atoms of the calix[4]arene moiety; whereas for the carbon and oxygen atoms of the crown chains and of the cyclohexyl groups anisotropic displacement parameters were assumed. The isotropic displacement parameters of the atoms of the guest nitromethane molecule, which showed enormous thermal motion, were blocked in the last stage of the structure refinement.

The H atoms were located in their calculated position with the geometrical constraint C–H 1.0 Å and refined 'riding' on their C atoms with a common temperature factor.

The atomic scattering factors of the non-H atoms were taken from Cromer and Waber,[43] the values of $\Delta F'$ and $\Delta F''$ were those of Cromer.[44] The geometrical calculations were obtained by PARST.[45] The fractional atomic coordinates of the non-H atoms (Table SI), list of the atomic displacement parameters for the non-H atoms (Table SII), list of the fractional atomic coordinates of the H atoms (Table SIII), a full list of the bond distances and angles (Table SIV) and a list of interatomic distances (Å) between the guest methyl C atoms and the C atoms of the phenyl rings in the *p*-cyclohexyl calix[4]arene biscrown-3 1:1 nitromethane complex (Table SV) have been deposited at the Cambridge Crystallographic Data Centre (CCDC).[5] The list of the observed and calculated structure factors are available from F. U. on request.§§

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§§ *Supplementary material:* see 'Instructions for Authors' in the January issue, 1996. Any request to the CCDC for this material should quote the full literature citation and the reference number 188/1.

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