Calix[4]arenes with perfluorinated alcoholic functions at the upper rim: a new class of neutral anion receptors

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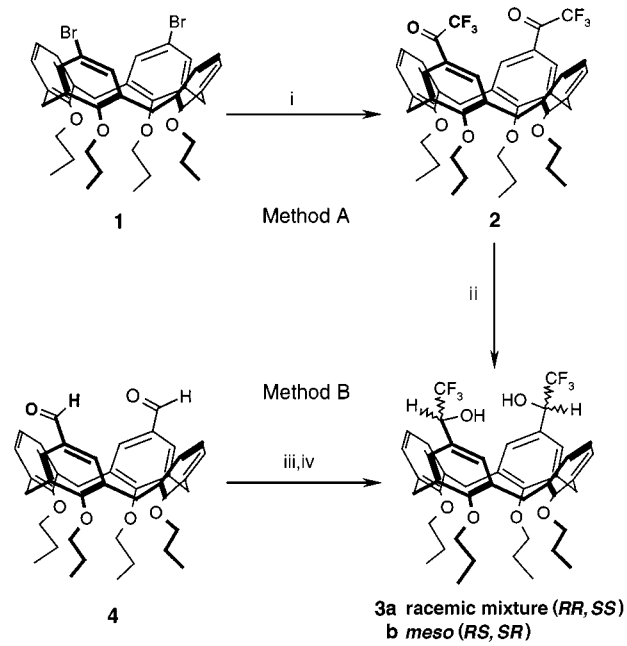
Two or four perfluorinated alcoholic functions were successfully introduced at the upper rim of calix[4]arenes, affording a new type of neutral receptor for anion recognition; preliminary binding studies indicate that the difunctionalized receptors 3a and 3b are selective for Y-shaped carboxylate ions over spherical anions which are, on the contrary, more efficiently bound by the tetraalcohol 6.

Compared with cation complexation, anion recognition represents a less explored area of research, in spite of the important role played by anionic species both in chemistry and biology. However, very recently interest in this field has grown and several new hosts which specifically recognize anions have been synthesized.[1] Most of the organic synthetic receptors for anions are charged species[2] or contain a metal center which directly coordinates to the anion[3] or increases the binding ability of other functional groups.[3] Nevertheless, neutral hosts which complex anions *via* hydrogen bonding are known.[4] So far mainly amides[5] and (thio)ureas[6] or a combination of the two[7] have been used as hydrogen bonding donor groups for the synthesis of electroneutral organic receptors. These groups have also been linked to calixarenes, at either the upper or lower rim, for the synthesis of selective anion receptors. It is well known that perfluoro alcohols are very good anion solvating agents,[8] and that they can affect the kinetics of chemical processes by specific anion solvation.[9] Moreover Pirkle *et al*. used chiral fluoro alcohols as chiral solvating agents and were able to determine the enantiomeric compositions of chiral Lewis bases.[10] Surprisingly, nobody has exploited so far the fluoro alcohol function as a binding site in the design of more complex receptors for anions and polar organic molecules.

We explored the possibility of introducing two or four fluoro alcohol functions at the upper rim of calix[4]arenes blocked in the cone conformation, and report here our successful synthetic results together with some preliminary anion binding properties of the new ligands synthesized.

The difunctionalized anion receptors **3a**,**b** are obtained by two different methods (Scheme 1). Method A exploits the known procedure reported in the literature for the synthesis of simple fluoro ketones.[11] The reaction of the dibromotetrapropoxycalix[4]arene **1**[6b] with Bu^{t}Li in dry THF gives the diketone **2** in 18% yield. The subsequent reduction of **2** with $NaBH_4$ in dry MeOH gives the fluorinated calix[4]arene dialcohol **3** as 1:1 mixture of **3a** (*RR, SS* racemic mixture) and **3b** (*RS, SR meso*). Better yields (85%) are obtained by Method B, reacting the tetrapropoxy calix[4]arene dialdehyde **4**[12] with trifluoromethyltrimethylsilane in the presence of a catalytic amount of TBAF.[13] The two diastereoisomers **3a** (racemic mixture) and **3b** (*meso*) can be separated by column chromatography (SiO_2, hexane–EtOAc 9:1) and their structure assigned by NMR analysis in $CDCl_3$.† The racemic mixture **3a** and the *meso* compound **3b** are easily distinguished by the multiplicity of the signals of the unsubstituted aromatic nuclei; **3a** presents a C_2 axis and gives three doublets of doublets, while **3b** has a symmetry plane and generates two doublets and two triplets.

Since it has been shown that calixarenes bearing strong hydrogen bonding groups like (thio)urea[14] form in apolar solvents dimeric molecular capsules we have studied solvent



Scheme 1 *Reagents and conditions*: i, Bu^{t}Li, CF_3CO_2Et, THF, −80 °C; ii, $NaBH_4$, MeOH; iii, CF_3SiMe_3, TBAF, THF; iv, 4 M HCl.

effects on **3a** and **3b**. The independency upon diluition of NMR spectra in $CDCl_3$ and the osmometric determination of the molecular weight indicate that there are no *inter*molecular hydrogen bonds and that **3a**,**b** are monomeric in solution. However a significant conformational rearrangement is observed in the ^1H NMR spectra of the diastereomeric mixture passing from $CDCl_3$ to [$^2H_6$]DMSO: the hydrogens *ortho* to the trifluoromethyl alcohol give signals between δ 6.2 and 6.6 in $CDCl_3$, whereas they are shifted to between δ 7.1 and 7.3 in [$^2H_6$]DMSO. On the contrary the signals of the unsubstituted aromatic rings, which are between δ 6.8 and 7.1 in $CDCl_3$, shift to the region between δ 6.0 and 6.7 in [$^2H_6$]DMSO. This behaviour is due to two different pinched cone conformations adopted in $CDCl_3$ and in [$^2H_6$]DMSO (Fig. 1). In $CDCl_3$ the upfield shift of the aromatic hydrogens of the nuclei bearing the fluorinated alcohols indicates that an intramolecular hydrogen bond is present between the two OH groups which keeps these

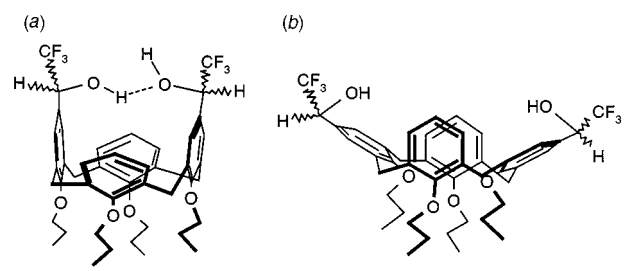
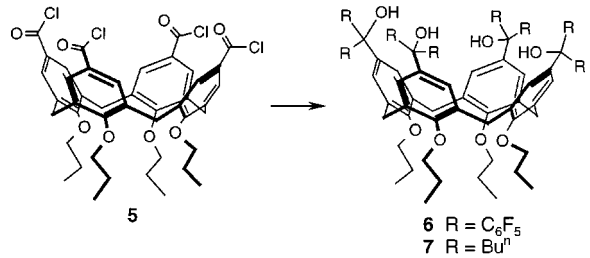


Fig. 1 The two pinched cone conformations adopted by **3a**,**b** in (*a*) $CDCl_3$ and (*b*) [$^2H_6$]DMSO.



Scheme 2 *Reagents and conditions*: i, RI, Li.

two functionalized aromatics in the shielding cone of the other two. On the contrary in [$^2H_6$]DMSO the intramolecular hydrogen bonding is prevented by solvation and the calixarene adopts a piched cone conformation where the unsubstituted aromatic rings are in the shielding cone of the other two.

We have also synthesized the calix[4]arene derivative **6** (Scheme 2), which bears four perfluorinated alcoholic functions at the upper rim, by reacting the tetraacyl chloride **5**[15] with C_6F_5I and lithium in dry Et_2O (yield 15%)† and, for comparison, compound **7** (yield 95%).†

Preliminary binding studies using titration NMR experiments‡ reveal that both receptors are able to complex anions in $CDCl_3$. Difunctionalized receptors **3a** and **3b** show selectivity in the recognition of carboxylate over spherical anions with the racemic compound **3a** binding acetate anion (K_{ass} = 435 M^{-1}) more efficiently than the *meso* compound **3b** (K_{ass} = 200 M^{-1}). Also in the case of a chiral guest like the anion of *N*-lauroyl-L-phenylalanine we have observed a stronger association of the racemic compound **3a** (K_{ass} = 165 M^{-1}) with respect to the *meso* compound **3b** (K_{ass} = 40 M^{-1}), the latter probably giving rise to unfavorable steric interactions. On the other hand the tetrafunctionalized receptor **6** binds spherical anions such as bromide (K_{ass} = 480 M^{-1}) more efficiently than acetate anion (K_{ass} = 90 M^{-1}). Although these data may be negatively affected by the presence of intramolecular hydrogen bonding, a comparison with the data reported in the literature for the interactions between anions and other hydrogen bonding donor groups[5,16] seems to indicate that the strength of the interaction between the perfluorinated alcoholic functions and anions is smaller than that of the same anions with urea or sulfonamide groups, but comparable with carboxamides. The importance of the perfluorinated groups for anion binding is however indicated by the fact that compound **7** shows no interaction with either bromide and acetate anions under the same conditions.

We are currently working on the synthesis of more rigid calixarene receptors in order to avoid intramolecular hydrogen bonding.

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Notes and references

† All new compounds were characterized by ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectroscopy, CI mass spectrometry, IR spectroscopy and melting point. *Selected data* for **3a** (*RR*, *SS* racemic mixture): mp 99–102 °C; δ_H($CDCl_3$) 0.93 (t, 6H, *J* 7.4, $OCH_2CH_2CH_3$), 1.06 (t, 6H, *J* 7.5, $OCH_2CH_2CH_3$), 1.86–2.01 (m, 8H, $OCH_2CH_2CH_3$), 3.16 (d, 2H, *J* 13.3, $ArCH_{eq}Ar$), 3.18 (d, 2H, *J* 13.3, $ArCH_{eq}Ar$), 3.74 (t, 4H, *J* 7.1, $OCH_2CH_2CH_3$), 3.99 (t, 4H, *J* 7.6, $OCH_2CH_2CH_3$), 4.42 [q, 2H, *J* 6.6, $ArCH(OH)CF_3$], 4.45 (d, 2H, *J* 13.3, $ArCH_{ax}Ar$), 4.46 (d, 2H, *J* 13.3, $ArCH_{ax}Ar$), 6.31 (d, 2H, *J* 2.0, ArH), 6.58 (d, 2H, *J* 2.0, ArH), 6.81 (dd, 2H, *J* 7.4, ArH), 6.93 (dd, 2H, *J* 7.4, *J* 2.0, ArH) and 6.95 (dd, 2H, *J* 7.4, 2.0, ArH); δ_C($CDCl_3$) 9.7, 10.3 (q, $OCH_2CH_2CH_3$), 22.7, 23.1 (t, $OCH_2CH_2CH_3$), 30.6, 30.7 (t, $ArCH_2Ar$), 72.2 [qd, *J* 30, $ArCH(OH)CF_3$], 76.3, 76.9 (t, $OCH_2CH_2CH_3$), 122.1 (s, Ar *para*), 123.9 (q, *J* 275, CF_3), 125.1 (d, ArH *para*), 128.0, 128.4, 128.7 (d, Ar *meta*), 133.7, 134.4, 135.6 (s, ArH *ortho*) and 156.7, 156.8 (s, Ar *ipso*); *m/z* (CI) 789 (90, M), 771 (100, M − H_2O) and 751 (80, M − $2H_2O$). For **3b** (*RS*, *SR meso*): mp 105–107 °C; δ_C($CDCl_3$) 0.92 (t, 6H, *J* 7.3, $OCH_2CH_2CH_3$), 1.07 (t, 6H, *J* 7.3, $OCH_2CH_2CH_3$), 1.84–2.01 (m, 8H, $OCH_2CH_2CH_3$), 3.15 (d, 2H, *J* 13.3, $ArCH_{eq}Ar$), 3.19 (d, 2H, *J* 13.3, $ArCH_{eq}Ar$), 3.73 (t, 4H, *J* 7.0, $OCH_2CH_2CH_3$), 4.00 (t, 4H, *J* 8.7, $OCH_2CH_2CH_3$), 4.43 [q, 2H, *J* 6.6, $ArCH(OH)CF_3$], 4.46 (d, 4H, *J* 13.3, $ArCH_{ax}Ar$), 6.22 (d, 2H, *J* 2.0, ArH), 6.55 (d, 2H, *J* 2.0, ArH), 6.84 (t, 1H, *J* 7.2, ArH), 6.85 (t, 1H, *J* 7.2, ArH), 6.98 (d, 2H, *J* 7.2, ArH) and 7.1 (d, 2H, *J* 7.2, ArH); δ_C($CDCl_3$) 9.8, 10.5 (q, $OCH_2CH_2CH_3$), 22.8, 23.3 (t, $OCH_2CH_2CH_3$), 30.7, 30.9 (t, $ArCH_2Ar$), 72.2 [qd, *J* 33, $ArCH(OH)CF_3$], 76.4, 77.1 (t, $OCH_2CH_2CH_3$), 122.1, 122.2 (s, Ar *para*), 123.9 (q, *J* 285, CF_3), 125.1 (d, ArH *para*), 127.6, 128.7, 128.9 (d, Ar *meta*), 133.6, 134.2, 135.9 (s, ArH *ortho*) and 156.7, 157.0, 157.2 (s, Ar *ipso*); *m/z* (CI) 789 (100, M), 771 (95, M − H_2O) and 751 (65, M − $2H_2O$). For **6**: Yield 15%; mp 168–170 °C; δ_H($CDCl_3$) 1.02 (t, 12H, *J* 7.5, $OCH_2CH_2CH_3$), 1.92–1.99 (m, 8H, $OCH_2CH_2CH_3$), 3.15 (d, 4H, *J* 13.0, $ArCH_{eq}Ar$), 3.90 (br s, 4H, OH), 3.95 (t, 8H, *J* 7.6, $OCH_2CH_2CH_3$), 4.52 (d, 4H, *J* 13.0, $ArCH_{ax}Ar$) and 6.64 (s, 8H, ArH); δ_C($CDCl_3$) 10.1 (q, $OCH_2CH_2CH_3$), 22.9 (t, $OCH_2CH_2CH_3$), 31.3 (t, $ArCH_2Ar$), 77.8 (t, $OCH_2CH_2CH_3$), 118.0 (s, Ph *ipso*), 126.1 (d, Ar *meta*), 134.4 (s, Ar *ortho*), 135.9 (s, Ar *para*), 137.6 (d, J_{CF} 241, Ph *meta*), 141.0 (d, J_{CF} 240, Ph *para*), 144.6 (d, J_{CF} 241, Ph *ortho*) and 156.9 (s, Ar *ipso*); *m/z* (CI) 2040 (50, M) and 2022 (100, M − H_2O). For **7**: Yield 95%; mp 103–104 °C; δ_H($CDCl_3$) 0.85 (t, 24H, *J* 7.2, $CH_2CH_2CH_2CH_3$), 0.98 (t, 12H, *J* 7.4, $OCH_2CH_2CH_3$), 1.20–1.24 (m, 16H, $CH_2CH_2CH_2CH_3$), 1.53–1.64 (m, 16H, $CH_2CH_2CH_2CH_3$), 1.86-2.0 (m, 16H, $CH_2CH_2CH_2CH_3$), 1.94 (m, 8H, *J* 7.4, $OCH_2CH_2CH_3$), 3.13 (d, 4H, *J* 12.8, $ArCH_{eq}Ar$), 3.85 (t, 8H, *J* 6.9, $OCH_2CH_2CH_3$), 4.44 (d, 4H, *J* 12.8, $ArCH_{ax}Ar$) and 6.73 (s, 8H, ArH); δ_C($CDCl_3$) 10.2 (q, $OCH_2CH_2CH_3$), 14.0 (q, $CH_2CH_2CH_2CH_3$), 23.1 (t, $OCH_2CH_2CH_3$), 25.8 (t, $CH_2CH_2CH_2CH_3$), 31.4 (t, $ArCH_2Ar$), 39.7 (t, $CH_2CH_2CH_2CH_3$), 75.5 (t, $OCH_2CH_2CH_3$), 76.5 (t, *C*OH), 125.0 (s, Ar *meta*), 134.0 (d, Ar *para*), 140.7 (s, Ar *ortho*) and 154.9 (s, Ar *ipso*); *m/z* (CI) 1090 (100, M − $4H_2O$+H).

‡ Association constants (K_{ass}) were determined by ^{1}H NMR titration experiments in $CDCl_3$; stock solutions of host and guest in $CDCl_3$ at different concentrations were prepared and mixed together in the NMR tube in various molar ratios. ^{1}H NMR spectra were recorded at 300 K and the chemical shift of some protons were plotted *versus* guest concentration. Non-linear regression analyses allowed the determination of K_{ass} (accuracy ±10%).

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