Modular assembly of a preorganised, ditopic receptor for dicarboxylates

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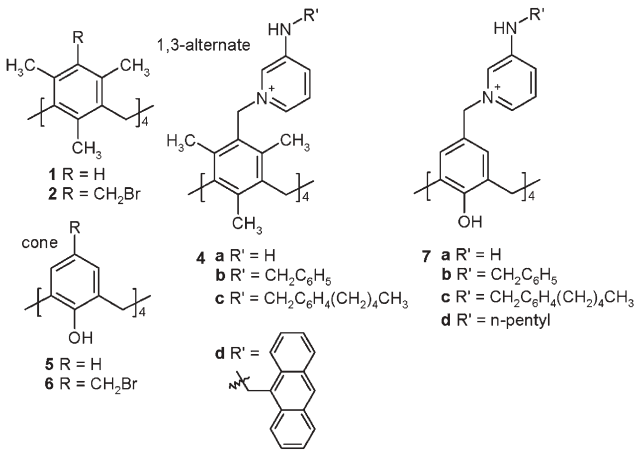
Received (in Columbia, MO, USA) 8th September 2005, Accepted 20th October 2005
First published as an Advance Article on the web 17th November 2005
DOI: 10.1039/b512779c

Two types of calix[4]arene derived hosts for anions with, respectively, 1,3-alternate and cone conformations have been prepared; the 1,3-alternate system binds dicarboxylate anions in a ditopic manner while the cone compounds are deprotonated by carboxylates.

There is considerable current interest in anion binding[1–4] and transport[5,6] and the field is likely to redouble in importance with the award of the 2003 Nobel Prize in Chemistry to MacKinnon in part for his work on Cl^- channels.[7] In addition to the well-studied Cl^-, there are a number of other biological anions that warrant particular attention from a monitoring and biomimetic standpoint, particularly HCO_3^-, phosphates and di- and tricarboxylates.[8,9] In this study we report preliminary data on the selective shape-recognition of linear dicarboxylates using our simple modular approach.[10–13] We have previously reported the preparation of a series of hosts for Cl^- in particular by appending three 'arm modules' comprising an aminopyridinium binding group with or without redox or fluorescent reporter groups to a 'core' based on triethylbenzene.[10,12] The triethylbenzene core is small and relatively flexible and as a result the tripodal binding pocket of three NH and three CH donors distorts to form a trigonal prismatic array of XH···Cl^- bonds on interaction with Cl^- in an induced fit binding process.[10] In the present work we show that the triethylbenzene core can be replaced by a much larger calixarene unit exhibiting less flexibility, with consequent alteration of complexation properties.

Calixarenes have proved to be very versatile as scaffolds in supramolecular chemistry.[14] Calixarene-derived anion binding hosts have been previously reported, although the majority rely on lower rim functionalisation[15–18] or are organometallic derivatives.[19–23] The mesityl, hydrocarbon calix[4]arene **1** is readily prepared in one step from α′-chloroisodurene.[24] It is locked into a 1,3-alternate conformation of the aryl rings and has been used as a scaffold for organometallic units[25] and, as a nitrile or pyridyl derivative, as a ligand in the formation of coordination arrays.[26,27] Reaction of **1** with paraformaldehyde in the presence of Zn–HBr results in facile bromomethylation of the aryl rings to give **2** (characterised spectroscopically, by elemental analysis and X-ray crystallography). Reaction of **2** with 3-aminopyridine (**3a**), *N*-benzylaminopyridine (**3b**), *N*-4-n-pentylbenzylaminopyridine



(**3c**) and *N*-anthracenylmethylaminopyridine (**3d**) results in the formation of hosts **4a–d** as the bromide salts in good yields. Metathesis with NH_4PF_6 cleanly gives the corresponding hexafluorophosphate salts. Analogous bromomethylation of calix[4]arene **5** to give **6** was achieved in a single step in a similar fashion to **1** in 95% yield in a slightly modified version of the literature procedure.[28] Reaction of **6** with **3a–c** and *N*-n-pentylaminopyridine (**3e**) followed by metathesis gave the hydoxy hosts **7a–d** again in good yield. These straightforward syntheses using two new core moieties of different conformation (1,3-alternate or cone) highlights the modularity of our approach giving ready access to a range of substituted host species. In general the large size and highly charged nature of compounds **4** and **7** meant that the compounds proved rather insoluble in common solvents, particularly on addition of anions. As a result binding studies have focused on the most soluble pentylbenzyl species **4c** and **7c** and the pentyl compound **7d**.

Compound **4c**·4Br^- crystallised from CH_2Cl_2 solution during synthesis as a very large, pale greenish block measuring some 4 × 4 × 5 cm. The crystals proved to be multiple, extremely weakly diffracting and readily desolvated. With significant effort a data set was obtained to low resolution which yielded an isotropic model sufficient to show the structure of the molecule along with salient features of the Br^- anion binding.† The n-pentyl chains and a molecule of dichloromethane solvent were completely disordered and could not be located reliably on the difference Fourier map. Their contribution to the diffraction along with disordered CH_2Cl_2 molecules was handled using the Platon SQUEEZE protocol.[29] Despite the low precision of the crystal structure (Fig. 1), the key features are clear. The calixarene core adopts the expected 1,3-alternate conformation. The four pyridinium arms are all splayed

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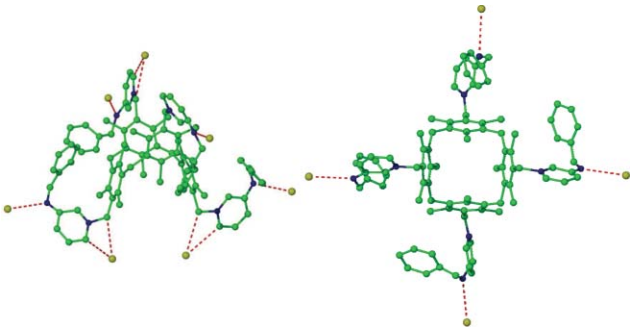

Fig. 1 X-Ray crystal structure of the pentylbenzyl species **4c**·4Br$^-$ showing the splayed conformation of the pyridinium arms, each interacting with a single Br$^-$ anion. The n-pentyl chains are disordered and were not located experimentally.

outwards and bent back from the calixarene with each acting independently and interacting separately and in a unidentate fashion with a Br$^-$ anion. Br$^-$ binding is *via* NH···Br$^-$ or longer CH···Br$^-$ interactions as seen in related triethylbenzene based systems.[10] The calixarenes are arranged in pairs about a cavity that contains two CH_2Cl_2 solvent molecules, two bromide anions and the unresolved alkyl chains of the host (Fig. 2). It is noteworthy that the environment around the methylene unit linking the pyridinium nitrogen atoms to the calixarene core is significantly sterically hindered as a result of the presence of the –CH_3 substituents and might result in hindered rotation as observed previously in related systems.[10]

The X-ray crystal structure of **4c**·4Br$^-$ poses the question of the degree of anion binding cooperativity between the independent anion binding arms in solution. Host **4c**·4PF_6 was titrated with NBu_4Br^- in MeCN solution at room temperature. The resulting titration curves (fit for four independent resonances) proved consistent with weak 1 : 2 Br$^-$ binding. Binding constants are given in Table 1.

Similar results were obtained for other single charged anions such as Cl$^-$ and from titration of the bromide salt with PF_6^-. This

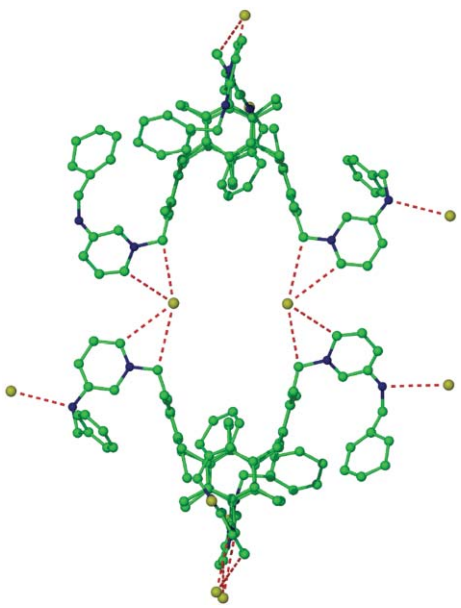

Fig. 2 Intermolecular pocket in **4c**·4Br$^-$ containing two bromide anions and a disordered solvent molecule (not shown).

Table 1 Binding constants in MeCN-d_3 for new hosts with various anions[a]

	Host K/M^{-1}					
	4c		**7c**[e]		**7d**[e]	
Anion	K_{11}	K_{12}	K_{11}	K_{12}	K_{11}	K_{12}
Cl$^-$	1780	355	6309	724	3980	23
Br$^-$	646	467	24 550	1990	53 470	5610
NO_3^-	3090	302	51 290	912	12 440	513
$CH_3CO_2^-$	9550	9332	—	—	—	—
Malonate^{2-}	58 800[b]	83[b]	—	—	—	—
	2720[c]	15[c]				
Succinate^{2-}	2690[c]	37[c]	—	—	—	—
Citrate^{3-}	4370[c]	52[c]	—	—	—	—
$Re_2Cl_8^{2-}$	148	~0	—	—	—	—
PF_6^-[d]	35	32	—	—	—	—

[a] Anions added as $N^nBu_4^+$ salts, host concentration 0.5–1.5 mM depending on solubility. [b] In MeCN-d_3 : DMSO-d_6 60 : 40. [c] In DMSO-d_6 at 60 °C. [d] With **4c**·4Br$^-$. [e] Deprotonation by carboxylate anions.

1 : 2 stoichiometry is consistent with related species with the smaller triethylbenzene core in which significant inter-arm cooperativity was observed on halide binding. In contrast to the results with halide anions, **4c**·4PF_6^- binds carboxylate dianions extremely strongly in both acetonitrile and DMSO solution, again in a 1 : 2 host : guest ratio with some selectivity for citrate. Binding constants in DMSO are lower than those in acetonitrile consistent with the more competitive nature of the former solvent. The stoichiometry was confirmed by a Job plot (Fig. 3b), suggesting ditopic behaviour in which anions are chelated by pairs of pyridinium arms, as in Fig 3a. While this 1 : 2 model bis(chelate) is at odds with the X-ray crystal structure, the effective concentration of anions in the sold state is very high and it is not surprising that these flexible species can rearrange in solution.

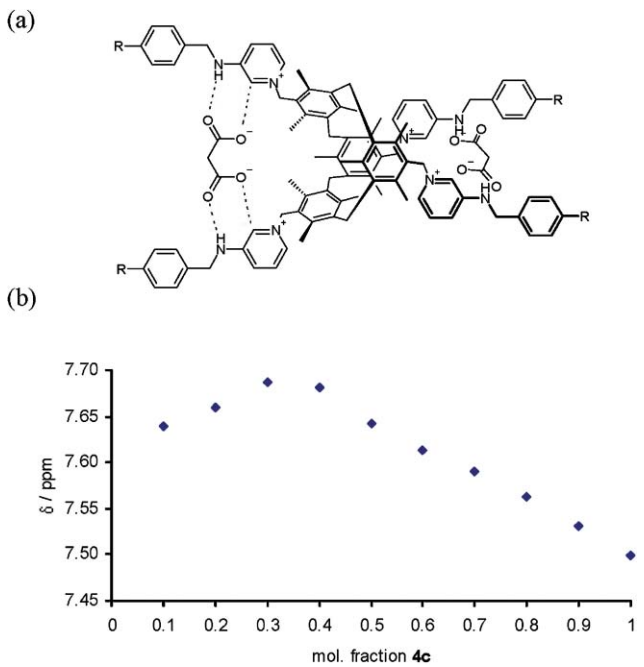

Fig. 3 (a) Model for 1 : 2 ditopic anion binding; (b) Job plot for **4c** with malonate showing the 1 : 2 host : guest ratio. Similar plots were observed for halides.

The conformational flexibility of host **4c** was probed by variable temperature ^{1}H NMR spectroscopy. Cooling **4c**·4PF_6^- to 203 K in acetone-d_6 solution resulted in broadening and splitting of many resonances. The spectra are too complicated to assign with confidence but it is possible this fluxionality is linked to restricted rotation of the pyridinium group about the mesityl ring, and indeed the fluxionality is absent for the core calixarene **1**. Repeating the VT NMR spectroscopic work in the presence of 0.4 and 0.8 equivalents of malonate and chloride again resulted in splitting of the resonances on cooling below 220 K. Previous work suggests that fluxionality can be linked to slow anion exchange. In this case the anion has a marked influence on the appearance of the spectra but it is not possible to deconvolute anion exchange and host conformational fluxionality.

For the hydroxyl calix[4]arene species **7c** and **7d** significant binding was observed for halides in contrast to **4c**, with selectivity for Br^- over Cl^- in both cases. This represents a reverse in the selectivity observed for the tripodal analogues[10] and may be linked to the larger cavity of the calixarenes. Rather high affinity for nitrate was noted for both **7c** and **7d** again consistent with an improved fit of the larger anion within the larger cavity. On titration with acetate and dicarboxylates, there was little change in the chemical shift of the NH resonances until after one equivalent of acetate, or 0.5 equivalents of the dicarboxylates had been added, at which point binding commenced (Fig. 4). We interpret this behaviour as deprotonation of one calixarene OH proton by these relatively basic anions. Related behaviour has been observed for deprotonation of F^- by Gale *et al.* in a series of pyrrole clefts,[30] and remarked upon for $H_2PO_4^-$ by Beer *et al.*[15] This enhanced acidity presumably arises from the stabilisation of the phenolate anion by the pyridinium moiety. Indeed, over time elimination was observed accompanied by the formation of free **3c** and **3d** consistent with the good leaving group character of the pyridinium group. The acidity of **7d** was probed by potentiometric titration with tetrabutylammonium acetate in 90% DMSO–water solution (following rigorous calibration of the pH electrode in DMSO–water mixtures and taking adequate precautions to eliminate CO_2 interference). The resulting titration curve gave a good fit to a single deprotonation process with pK_a 4.4(5), consistent with the NMR results.

In conclusion, new routes have been developed to allow ready incorporation of calixarene-based cores within a simple, modular anion binding system. Cores can be chosen in two preorganised conformations and the much larger hosts exhibit very different selectivity to analogous triethyl-benzene based tripodal receptors with affinity for dicarboxylate binding by the ditopic **4c**.

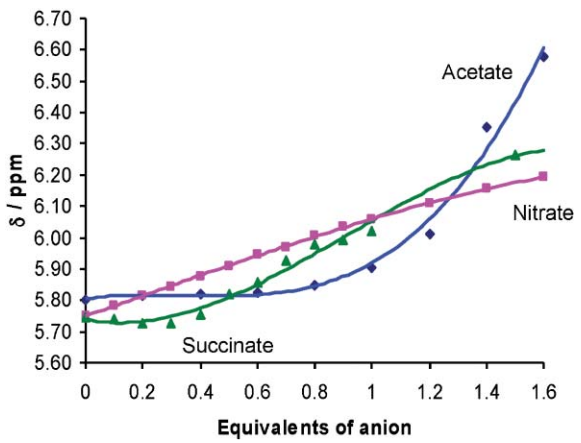

Fig. 4 ^{1}H NMR titration curves for **7d** in the presence of NO_3^- (squares), $CH_3CO_2^-$ (diamonds) and succinate^{2-} (triangles).

Notes and references

† Crystal data for **4c**·4Br^-·2CH_2Cl_2: $C_{114}H_{144}Br_4Cl_4N_8$, M = 2087.81, monoclinic, space group $C2/m$ (No. 12), a = 30.829(6), b = 31.707(6), c = 17.422(4) Å, β = 124.057(3)°, V = 14109(5) Å^3, Z = 4, Dc = 0.983 g cm^{-3}, $F000$ = 4368, KappaCCD, MoKα radiation, λ = 0.71073 Å, T = 123(2) K, 2θmax = 45.0°, 15169 reflections collected, 6939 unique (Rint = 0.1866). Final GooF = 1.120, $R1$ = 0.1783, w$R2$ = 0.4079, R indices based on 2534 reflections with $I > 2\sigma(I)$ (refinement on F^2), 240 parameters, 52 restraints. Lp and absorption corrections applied, μ = 1.255 mm^{-1}. CCDC 283688. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b512779c

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