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Anion sensing 'venus flytrap' hosts: a modular approach

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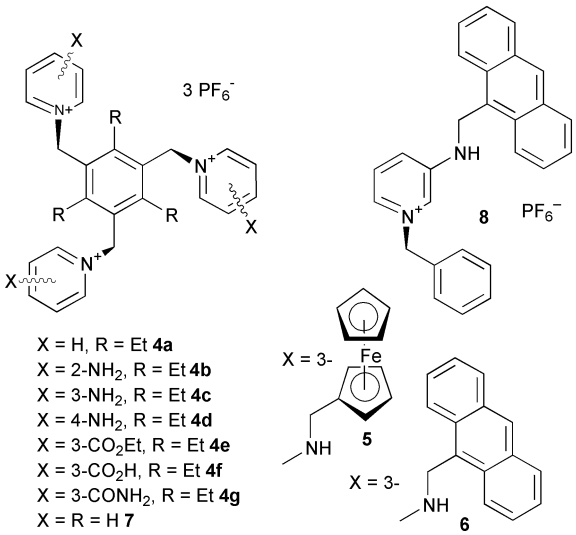
A series of podands based on three hydrogen bonding 'arms' have been prepared and their affinities for simple inorganic anions measured.

The design and synthesis of host molecules able to bind anionic guests in a fashion detectable to an observer electrochemically or *via* changes in fluorescence intensity is a topic of intense current interest.[1–6] Potential applications include the detection and remediation of environmentally relevant anions such as nitrate, phosphates, pertechnetate[7] and chromate[8] as well as monitoring biochemical levels of chloride. In general positively charged hosts offer scope for obtaining the largest binding constants, however, the non-directional electrostatic forces involved mean that these must be moderated by a preorganised host geometry and suitably placed directional binding sites. In this contribution we outline our initial work on a simple, modular approach to the construction of a very versatile range of cationic hosts for anions offering a great deal of scope for systematic studies of the correlation of host geometry, preorganisation and binding site placement on anion binding selectivity.



We have prepared a range of podands incorporating a hexasubstituted core, coupled with arms comprising a hydrogen bonding moiety as the primary binding site and cationic pyridinium group. A redox-active or fluorescent signalling unit was added in the cases of hosts **5** and **6**. This was achieved by reaction of substituted pyridyl 'arms' **1**–**3** with 1,3,5-tri(bromomethyl)triethylbenzene[9] to give hosts **4**–**6**, respectively, in good to excellent yields.†

Hosts **4**–**6** are expected to bind to anions in a chelating 'cone' conformation *via* the strong hydrogen donor functionalities on each arm and/or from weak interactions to the pyridinium *ortho* CH groups. The host geometry benefits from preorganisation into a binding 'cone' geometry by the steric preference for alternation around the hexasubstituted core.[10]

The X-ray crystal structure of host **6**·$(PF_6)_3$·MeOH·2MeCN‡ (Fig. 1) shows that the cationic host does adopt a cone conformation with alternation about the hexasubstituted core, the anthracenyl arms are splayed out, however, and the three NH groups do not converge. This arises from extensive intermolecular face-to-face π–π stacking and CH···pyridinium interactions in the solid state and is not consistent with the solution data, *vide infra*. The central cavity of the host is occupied by a PF_6 anion which interacts solely by multiple CH···F hydrogen bonds. Two of the three NH groups are also involved in hydrogen bonding to other PF_6^- anions while the final NH proton interacts with the only methanol molecule in the structure. This unusual, unsymmetrical arrangement suggests that the central binding pocket is the preferred anion binding site despite the lack of strong hydrogen bond donors.

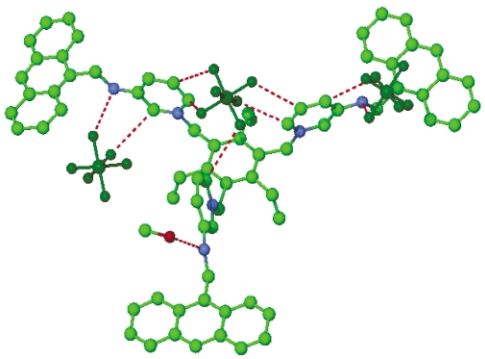


Fig. 1 X-Ray crystal structure of podand **6**·$(PF_6)_3$·MeOH·2MeCN showing cooperative anion binding of the central PF_6^- anion by weak hydrogen bonds.

The relative binding affinity of compounds **4**–**6** (PF_6^- salts) for a representative anion, Br^-, were assessed by ^1H NMR titration. Binding constants are shown in Table 1. The unsubstituted tris(pyridinium) species **4a** gives K_{11} = 850 M^{-1} for Br^- which represents the effect of cooperative electrostatic and CH···Br^- interactions. Removal of the preorganisation imparted by the ethyl functionalities (host **7**) reduced the binding to 17 M^{-1}, corresponding to a preorganisation contribution of *ca.* 10 kJ mol^{-1} for **4a** and implying a

Table 1 Binding constants (K_{11}) determined by ^1H NMR titration for the interaction of the new hosts with various anions.[a]

	Host K_1/M^{-1}						
Anion	**4a**	**4c**	**4e**	**5**	**6**	**7**	**8**
Cl^-	—	—	—	17 380	5370	—	
Br^-	850	13800	838	2950	486	17	~0
I^-	—	—	—	1860	355	—	—
NO_3^-	—	467	—	1410	617	—	7
$CH_3CO_3^-$	—	10500	—	3680	49000	—	7
ReO_4^-	—	—	—	4	4	—	—

[a] Anions as *n*-Bu_4N^+ salts in MeCN-d_3, host NH, *o*-pyridyl protons and CH_2 groups fit simultaneously with HypNMR 2000. Errors in K_{11} are < 10%.

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significant degree of cooperativity between the three arms in binding the first anion. The tris(ester) **4e** displayed almost identical behaviour to **4a**.

The tris(3-aminopyridinium) host **4c** proved to be an extremely effective host for bromide. Large ^{1}H NMR shifts were observed for the NH protons and the pyridyl CH singlet suggesting a sixfold envelopment of the anion by three NH and three pyridyl CH hydrogen bonds. Comparative data for the 3- and 4-aminopyridine derivatives **4c** and **4d** proved difficult to obtain because of the insolubility of **4d**. In mixed acetonitrile–DMSO (50% v/v) **4c** bound chloride extremely strongly (K_{11} *ca.* 82 000 M^{-1}). The analogous figure for **4d** in that solvent was *ca.* 3000 M^{-1} although solubility constraints rendered this measurement imprecise. Host **4c** also proved an effective host for acetate, while nitrate was bound much less strongly despite its similar geometry. It is likely that neither nitrate nor acetate fit the cavity very well and hence do not bind *via* a triple chelate mode. Enhanced acetate binding is likely to arise from the stronger basicity of acetate and the formation of a double hydrogen bonded interaction with a single NH_2 group.

The tris(ferrocenyl) complex **5** also exhibits a 3-aminopyridine derived binding geometry and, as for **4c** the binding constants for halides are high, although the bulky ferrocenyl substituents clearly depress the affinity. This trend is continued in **6** where the larger size of the three anthracene moieties further depresses intra-cavity halide binding. This is a consequence of steric crowding when all three arms enfold the halide guest. Titration results with Cl^-, Br^- and I^- confirm that **5** is extremely effective at binding chloride, in particular. Complexation-induced chemical shift changes ($\Delta\delta$) were up to 1.59 ppm for the NH protons. Most changes were almost complete upon addition of one equivalent of anion and the relative $\Delta\delta$ values for the various nuclei suggest that binding occurs first at the central cavity, *via* the sixfold array of CH···X^- and NH···X^- hydrogen bonds. The selectivity trend $Cl^- > Br^- > I^-$ is consistent with the anions′ relative degree of negative charge density (basicity) and size. While halide binding is depressed for **6** it appears to occur *via* the same mechanism.

The proposed geometry of the host–anion interaction for **5** with halides is supported by molecular mechanics calculations which show chloride bound within the molecular cavity in a sixfold array of weak and strong hydrogen bonds to NH and pyridyl CH protons (consistent with observed NMR changes). The interaction energy proved to be significantly greater for Cl^- than for PF_6^-. Calculations indicate that the cone conformer is favoured over the 'partial cone' conformer with one ferrocenyl group on the opposite side of the molecule to the other two, Fig. 2.

Both **5** and particularly **6**, also proved to be good hosts for acetate despite the fact that acetate is too bulky to fit within the cone cavity. Indeed, complex **6** proved to be highly selective for acetate, giving a binding constant of *ca.* 49 000 M^{-1}, comparable to that recently observed for a rigidly preorganised system.[11] Complexation induced chemical shifts ($\Delta\delta$) were as much as 3.07 ppm for the NH protons. This remarkably strong binding is accompanied by interesting sigmoidal behaviour for the *ortho* pyridyl singlet during the titration. Little change is observed during the addition of the first equivalent of anion. The chemical shift change then increases markedly before tailing off again after addition of three equivalents of anion. In contrast, for halide binding, this proton behaves in a similar way to the NH protons. This is interpreted as resulting from the involvement of the alternative partial cone conformer in the acetate binding process. Thus the first acetate anion interacts with two NH protons, on two of the three arms. The second anion binds to both the NH and pyridyl CH protons of the remaining arm on the opposite side of the molecule. The extremely strong binding is explained by the fact that this conformation does not involve unfavourable anthracene–anthracene steric interactions but does benefit from chelation of the first anion by two NH groups. In **5**, where steric interactions are less important, this acetate-selective conformation is less significant.

The importance of chelate effects in all of the hosts studied is highlighted by the model compound **8** which displays essentially no intrinsic affinity for bromide and only very weak binding of acetate and nitrate (K_{11} = 7 M^{-1} in acetonitrile-d_3).

The electrochemistry and photochemistry of hosts **5** and **6** is under extensive investigation. Preliminary results suggest relatively poor coupling between the binding and signalling moieties. However, the observed selectivity sequence is in good agreement with that obtained by NMR and supports the model of effective, chelate anion binding.

In conclusion a simple, modular approach has been described to a series of effective three-arm anion hosts displaying a marked anion chelate effect and well-defined structural selectivity. This flexible synthetic approach means that a wide range of hosts of varying structure may be readily prepared in high yield. Reporter groups may also be conveniently appended.

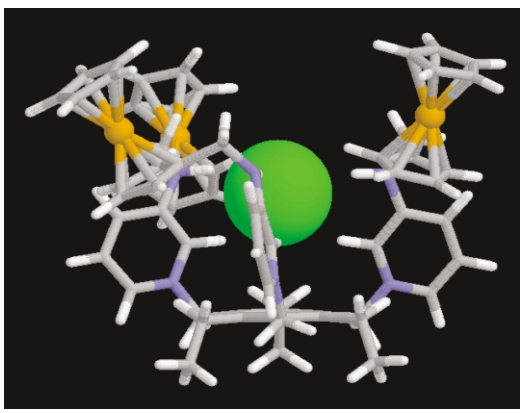

Fig. 2 Model of the cation in **5** showing a bound Cl^- anion enveloped in a sixfold array of CH···Cl^- and NH···Cl^- hydrogen bonds (calculated NH···Cl distances 2.56, 2.65 and 2.87 Å). The existence of these interactions is confirmed by NMR and the X-ray structure of **6**.

Notes and references

† All new compounds were characterised by ^{1}H NMR, FAB-MS and elemental analysis. Binding studies were pursued by ^{1}H NMR titrations using HypNMR 2000.

‡ Crystal data for **6**·$(PF_6)_3$·MeOH·2MeCN: $C_{80}H_{77}F_{18}N_8OP_3$, M = 1601.41, triclinic, space group $P\bar{1}$, a = 9.890(2) , b = 17.600(4), c = 22.450(5) Å, α = 104.40(3), β = 97.60(3), γ = 91.30(3)°. U = 3745.4(13) Å^3, Z = 2, μ = 0.177 mm^{-1}, T = 120 K, Reflections measured: 17 493, unique data: 10 301, parameters: 984, R_1 [$F^2 > 2\sigma(F^2)$] 0.1881, wR_2 (all data) 0.3269. The overall precision of the structure is poor, however the location of the anions and overall molecular conformation are unambiguous. CCDC reference number 174751. See http://www.rsc.org/suppdata/cc/b1/b110576k/ for crystallographic data in CIF or other electronic format.

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