# Conformational control by 'zipping-up' an anion-binding unimolecular capsule†

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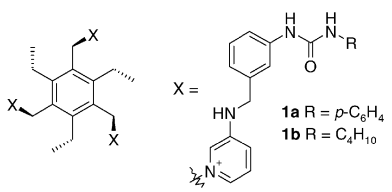
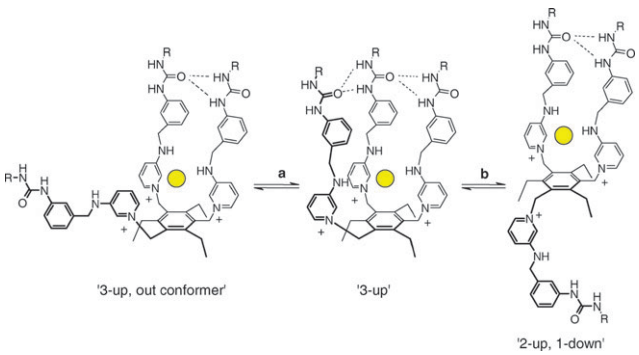
**A flexible capsule has been designed in which the anion-binding preorganisation is enhanced by a urea 'zipper'.**

The so-called 'pinwheel' trialkylbenzene-derived anion hosts have proved to be highly versatile tripodal receptors of enduring interest over the past decade.[1–8] The trialkylbenzene core provides some degree of preorganisation into a conical conformation with all three binding or sensing 'arms' co-aligned. However, in most cases the compounds remain highly flexible. This flexibility can be a very useful property since the system's conformational response to induced-fit anion binding can be applied in controlling sensor response by control of reporter group mutual proximity.[4,9–16] A few more rigid pinwheel-based cryptands have also been reported,[17,18] as well as other interesting rigid amide-based anion cryptands.[19] In seeking to control the conformational characteristics of these tripodal anion receptors, it is desirable to engineer compounds that are more preorganised than the very flexible tripods but still retain their ability to change conformation. One solution to this problem is to design compounds that are conformationally preorganised by supramolecular interactions that are remote from the binding site. We now report a pinwheel-based compound designed to reversibly close-up into a unimolecular capsule by remote hydrogen bonding, preorganising it for anion binding.




We have previously shown that conformationally flexible 3-aminopyridinium based tripodal hosts bind strongly to $Cl^-$.[14–16] Exchanging the secondary amine for the stronger hydrogen bond donor urea analogues results in significant changes to the compounds' conformational characteristics but it is clear that anion binding occurs *via* the charged pyridinium and lower urea NH group in the same way as the aminopyridinium hosts, rather than at the 'upper' urea NH groups that are further from the pyridinium moiety.[10] We therefore designed the extended compound **1** with two well-separated binding compartments, one comprising a trimeric 3-aminopyridinium pocket and the other involving the three remote urea groups. This tripodal 3-aminopyridinium pocket binds strongly to chloride as a result of charge assisted NH···$Cl^-$ and CH···$Cl^-$ hydrogen bonding, a binding mode that brings about a conformational change from the preferred '2-up, 1-down' conformer that predominates in the $PF_6^-$ salt.[14] The likely limiting conformational behaviour for the extended host **1** is shown in Scheme 1. We rationalized that in non-polar solvents the tendency of urea derivatives to self-associate[20–23] would favour the 3-up conformer by 'zipping' up the upper portion of the compound, thus preorganising the molecule for $Cl^-$ anion binding. In more polar media, urea self-association is less significant[22] and hence rearrangement to 'out' conformers and 'down' conformers would be more likely, resulting in less preorganisation.

Compounds **1a** and **1b** were prepared and fully characterized (see ESI for experimental details†). Compound **1a** proved insoluble in all solvents other than DMSO, however **1b** was soluble in a wide range of solvents and was metathesised to give the hexafluorophosphate salt. The chloride-binding ability of **1b**·$(PF_6)_3$ was examined by $^1$H NMR titration of the host with $NBu_4Cl$ in three solvents: acetone (in which urea···urea interactions are significant), acetonitrile and DMSO (where solvent competition will reduce the degree of urea···urea hydrogen bonding). In both acetone and acetonitrile, addition of less than one equivalent of chloride led to significant broadening of some parts of the spectrum consistent with slow exchange of free and bound chloride. Importantly,




**Scheme 1** The functional arms in the three-up conformer of 1 (centre) may rotate to (a) face away from the cavity to give an 'out' conformation or (b) move to the opposing side of the receptor to give a '2-up, 1-down' conformer.

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however, the characteristic urea NH resonances at 5.97 and 7.92 ppm are neither broadened nor significantly shifted on initial exposure to $Cl^-$. In contrast, the pyridinium CH resonance at 8.08 ppm broadens immediately and shifts significantly ($\Delta\delta$ = 0.80 ppm at one equivalent $Cl^-$) suggesting that $Cl^-$ binding occurs as expected at the pyridinium/amine site, not the urea groups. Similarly the secondary amine NH resonance shifts from 6.38 ppm to 8.27 ppm ($\Delta\delta$ = 1.89 ppm) upon addition of one equivalent of chloride, although it is broadened into the baseline until 0.7 equivalents of anion has been added. In analogous 3-aminopyridinium compounds lacking the urea functionality we have observed slow exchange of free and bound chloride below room temperature.[14] The presence of the urea groups appears to slow the equilibrium still further, consistent with an increased rigidity of the host. After addition of 1 equivalent of the anion the spectrum becomes sharper with little further change in the chemical shift of the pyridinium CH resonance, however both of the urea NH resonances immediately begin to change chemical shift significantly and continue to do so up to 1.6 equivalents at which point precipitation occurs in both solvents (Fig. 1). We postulate that following intra-cavity binding of the first equivalent of anion, anion binding at the free urea residue causes aggregation and ultimately leads to precipitation. With the limited data available, a good fit was obtained for a 1 : 2 host : anion model with $K_{11} = 10^4\ M^{-1}$ and $K_{12} = 10^2\ M^{-1}$. This value of $K_{11}$ is comparable to those observed for unsubstituted 3-aminopyridinium hosts.[14] The sharpening of the pyridinium CH resonance upon addition of one equivalent of anion suggests that the anion has a role in 'locking in' the 3-up conformation, working synergically with the intramolecular urea hydrogen bonding. Similar results are observed on titration with $Br^-$ although the broadening is less significant and the magnitude of chemical shift change is smaller.

Titration of **1b** in DMSO does not result in precipitation. Binding is depressed with the maximum $\Delta\delta$ being *ca.* 0.5 ppm even after addition of five equivalents of chloride. The titration plot is a shallow curve, indicative of weak binding. The essentially linear dependence on anion concentration up to 5 equivalents contrasts to related compounds binding chloride in DMSO[10] and suggests that multiple anions are binding, with both aminopyridinium and urea binding sites on different arms acting independently. While the urea carbonyl is a relatively poor hydrogen bond acceptor, chloride is a strong enough acceptor to compete with the polar solvent.[24]

At room temperature, in acetone solution, the $^1$H NMR spectrum of **1b**·$(PF_6)_3$ exhibits time-averaged $C_{3v}$ symmetry in both the presence and absence of chloride. We examined the temperature dependence of the spectrum from 290 K to 180 K in the presence of 0.8 equivalents of $Cl^-$. The two resonances assigned to the urea NH protons shift markedly with temperature, consistent with increasing residence time in a more enthalpically favoured conformation involving changes in these hydrogen bonding groups as temperature decreases (Fig. 2).

One alternative possibility to the formation of single molecule capsules of the type shown in Scheme 1 is dimerisation *via* the urea groups to form a capsule with six-urea groups in a hydrogen bonded belt.[20,22] We sought evidence from ESI-MS and NMR dilution to rule out this possibility. The ESI-MS spectra of the pure salts **1b**·$(X)_3$ (X = Br or $PF_6$) both show high intensity peaks corresponding to $[\mathbf{1b} - X]^+$, $[\mathbf{1b} - 2X]^{2+}$ and $[\mathbf{1b} - 3X]^{3+}$ but no evidence for the formation of dimers. Addition of one equivalent of tetrabutylammonium fluoride, chloride, bromide or iodide to solutions of **1b**·$(PF_6)_3$ and examination of the ESI-MS spectra gave peaks corresponding

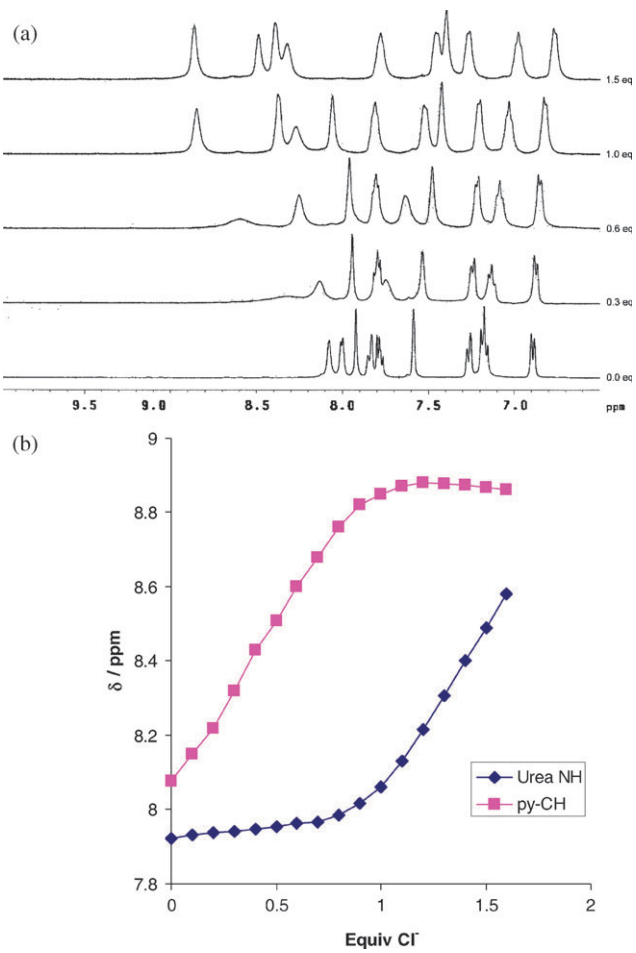


**Fig. 1** (a) NMR titration of **1b**·$(PF_6)_3$ with $NBu_4{}^+Cl^-$ in acetone-$d_6$, (b) plots of the pyridinium CH and urea NH resonances.

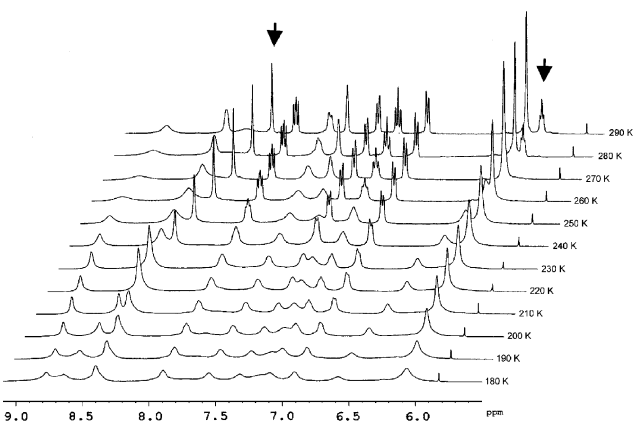


**Fig. 2** VT $^1$H NMR spectra of **1b**·$(PF_6)_3$ with 0.8 equivalents of $NBu_4{}^+Cl^-$ in acetone-$d_6$. Urea NH resonances are marked by arrows.

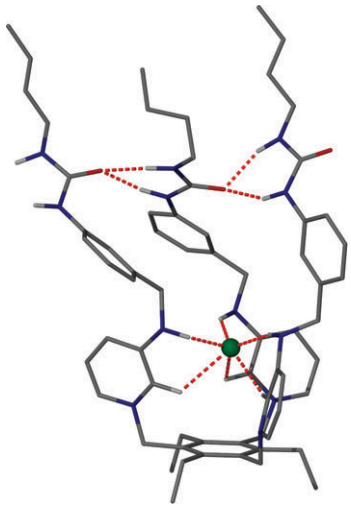

**Fig. 3** DFT model of **1b**·$Cl^-$ showing the urea tape 'zipper' motif.

to the expected $m/z$ for $[\mathbf{1b} + X - 2PF_6]^+$ and $[\mathbf{1b} + X - 3PF_6]^{2+}$ (X = Cl, Br, I) except in the case of $F^-$ which gives only $[\mathbf{1b} + F - 2PF_6]^+$. No peaks assignable to dimeric capsules were observed. These experiments show that the hosts bind well to halides but remain as monomers. In confirmation, the $^1$H NMR spectra of **1b**·$(PF_6)_3$ both alone and in the presence of one equivalent of $Cl^-$ proved invariant with concentration in acetone-$d_6$.

We carried out a DFT optimization for **1b**·$Cl^-$, using B3LYP and a mixed basis within the Gaussian 03 program.[25] The basis consisted of 6-311++G* on chloride, 6-31+G* on oxygen and nitrogen, 4-31G on carbon and hydrogen. The hydrogen atoms involved in possible hydrogen-bonding regions were further augmented with a diffuse set of *s* and *p* functions.[10] The DFT model of the 3-up conformer of **1b**·Cl is shown in Fig. 3. The model reproduces the expected trigonal prismatic hydrogen bonded arrangement around the $Cl^-$ ion comprising three NH···$Cl^-$ and three pyridinium CH···$Cl^-$ interactions, consistent with previous crystallographic and NMR spectroscopic results in related compounds, and shows that this anion binding mode is compatible with the proposed urea tape 'zipper' motif.

In conclusion we have shown that in relatively non-polar solvents, intramolecular hydrogen bonding between remote functional groups can increase the preorganisation of an anion-binding unimolecular capsule. This work suggests new strategies for conformational control and increasing preorganisation in flexible anion hosts.

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