A water soluble, anion-binding zwitterionic capsule based on electrostatic interactions between self-complementary hemispheres[†]

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A water soluble anion receptor is reported that binds bromide in aqueous solution *via* $CH \cdots Br^-$ interactions in a dimeric capsule.

In the design of receptors for anionic guests¹⁻⁴ there is a tension between the selection of a cationic receptor or a neutral one. Cationic receptors exhibit strong ion-pairing interactions to anions, but target anion binding is in competition with the receptor's charge-balancing anion(s).⁵ Conversely, neutral anion receptors must also accommodate a cationic counterion and may exhibit intrinsically weaker binding.⁶ Competitive solvation effects are potentially highly significant in both cases depending on the medium. One interesting, but rarely deployed, compromise is the use of zwitterionic receptors. There have been a few effective examples of zwitterionic receptors based on macrobicyclic cage receptors reported by Schmidtchen's group.⁷⁻⁹ These results demonstrate that in general the anionic and cationic ends of the receptor must be well separated by a rigid linker to avoid self-inhibition by the host and consequently zwitterionic receptors are rare. We now report a simple tripodal zwitterion that forms a robust anionbinding capsule even in the absence of significant hydrogen bonding interactions. In contrast, a non-self-complementary control compound exhibits very little anion affinity.

Zwitterions 1 and 2 (Scheme 1) are readily prepared by reaction of either ethyl isonicotinate or ethyl nicotinate with 1,3,5-tribromomethyl-2,4,6-triethylbenzene¹⁰ followed by hydrolysis with sodium hydroxide in water to give the carboxylate of the corresponding ethyl ester derivatives.11 Compound 2 has the *meta* substitution pattern that has proved highly successful in anion binding aminopyridinium derivatives¹²⁻¹⁶ and the anion binding properties of this host in water were assessed by ¹H NMR spectroscopic titration. However, the highly competitive nature of the aqueous medium resulted in no chemical shift changes on titration with a range of both common and unusual anion salts, namely NaCl, NaI, MgATP, C₆H₃(COONa)₃ and K₃[Al(oxalate)₃]·H₂O. Similarly negative results were obtained in methanol and hence, in addition to the nature of the solvent, the proximity of the anionic carboxylates to the intended binding cavity and the lack of hydrogen bond donor functionality also mitigate against effective anion binding behaviour. Compound 2 was characterised by X-ray crystallography (Fig. 1)‡ as a nonahydrate.



Scheme 1 Zwitterionic receptors 1 and 2.



Fig. 1 X-Ray molecular structure of 2.9H₂O (ellipsoids 50%).

The structure confirms the zwitterionic nature of the molecule. The carboxylate groups adopt an 'out' conformation maximising the distance between them and presumably contributing to the water solubility of the molecule. The included water molecules form an infinite hydrogen bonded layer that links the carboxylate functionalities together. A notable feature is the bridging of two carboxylate groups on adjacent molecules by two water molecules to give an $R_4^4(12)$ motif,¹⁷ within a much more extensive network.

In the presence of excess HPF₆ it proved possible to isolate a monoprotonated form of **2**, which precipitated upon acidification of an aqueous solution of the receptor. The X-ray structure of **2**·HPF₆·2H₂O is shown in Fig. 2 and despite being isolated in the presence of excess acid contains only a single PF₆⁻ anion. The compound exists as an infinite 1D ribbon *via* CO₂⁻···HO₂C hydrogen bonds with the X-ray data suggesting that the acidic



Fig. 2 X-Ray crystal structure of 2·HPF₆·2H₂O (ellipsoids 50%).

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proton is shared almost equally between the two carboxylate groups in a fashion characteristic of a strong hydrogen bond.^{18–21} The O···O distance in this interaction is also very short at just 2.452(2) Å, comparable to the O···O separations found in oxonium ion species, for example.^{22,23} The carboxylate functionalities again adopt an 'out' conformation and are not directed towards the tripodal cavity. The PF₆⁻ anion is situated in between a pair of pyridinium groups engaging in anion– π interactions^{24–26} and does not take part in hydrogen bonding to the carboxylic acid group, nor to the pyridinium CH groups.¹²

The PF_6^- complex 2·HPF₆·2H₂O is insoluble in water but its anion affinity was assessed in DMSO- d_6 solution. Under these conditions the receptor does bind halides (NBu₄⁺ salts) with modest affinity. Chemical shift changes of *ca*. 0.8 ppm were observed in the case of chloride and binding constants for Cl⁻ and Br⁻ are log $K_{11} = 2.17(2)$ and 1.98(2), respectively.

In contrast to **2** which is readily isolated as a free zwitterion, difficult to protonate and exhibits very little anion affinity, the *para* isomer **1** proved to be extremely difficult to obtain in a guest-free form. The hydrolysis of the bromide salt of the precursor ester by NaOH results in the formation of NaBr as a byproduct, and it proved extremely difficult to obtain **1** free of NaBr despite repeated recrystallisation from water. The reason for this behaviour is immediately apparent in the X-ray crystal structure of the product (Fig. 3) which reveals a remarkable 2 : 1 host $: Br^-$ self-assembled capsular structure of formula Na[(1)₂Br]·13H₂O in which a bromide ion is completely enclosed by two zwitterions of **1** with the carboxylate groups of each zwitterion mutually interdigitated



Fig. 3 Two views of the $[(1)_2Br]^-$ anionic capsule in the X-ray structure of Na $[(1)_2Br]$ ·13H₂O. Bromide anion shown in space filling representation.

such that each carboxylate functionality is sandwiched in between two pyridinium groups of the opposite zwitterion. The entire assembly exhibits crystallographic threefold symmetry in space group R3 with one third of the capsule unique. A Na⁺ cation and solvent water are disordered on the outside of the capsule. The bromide anion is held entirely by CH···Br⁻ hydrogen bonding interactions to the pyridinium CH group in a fashion that we have shown previously is an effective anion binding mode.¹²

A loosely related, neutral tripodal receptor has been shown to form a dimeric capsule containing two F^- ions and six water molecules recently, but this system is based on strong hydrogen bonding interactions.²⁷ While there have been a few reports of electrostatically self-assembled capsules that exist in solution, they remain extremely rare.^{28–32} The advantage, however, is that electrostatics offer the possibility of selfassembly in highly competitive media such as water, whereas hydrogen bonding interactions are generally overwhelmed by solvation.

The stability and existence of the anionic capsule $[(1)_2Br]^$ in solution were probed by negative ion ESI mass spectrometry which showed a peak at m/z 1213 corresponding to the anion $[(1)_2Br]^-$ with a calculated isotopic distribution consistent with the proposed formulation. The capsule proved to be sufficiently soluble in D₂O to obtain an ¹H NMR spectrum which showed sharp resonances consistent with a single, threefold symmetric species. Attempts were made to remove the NaBr by treating the capsule with AgPF₆ in water. Following removal of the precipitated AgBr the ¹H NMR spectrum was re-recorded and showed a small but significant change in the chemical shift of the host resonances, particularly those assigned to the CH protons ortho to the pyridinium groups. However, it proved impossible to prepare a sample that was completely free of bromide and hence quantitative NMR measurements were not attempted.

In conclusion we have prepared a water soluble zwitterionic receptor (1) that exhibits strong affinity for bromide anion due to its unique ability to form a capsular complex. The non-capsule-forming analogue (2) does not bind anions in water or other polar solvents. Both the electrostatically driven self-assembly mode and the use of 'soft' CH…anion interactions to give effective binding in water are surprising features of the system and suggest a new strategy towards anion templated capsules in highly competitive media.

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Notes and references

‡ Crystal data for **2**·9H₂O: C₃₃H₅₁N₃O₁₅, *M* = 729.77, 0.30 × 0.25 × 0.15 mm, triclinic, space group *P*I (No. 2), *a* = 10.5704(15), *b* = 17.283(2), *c* = 19.733(3) Å, *α* = 82.800(3)°, *β* = 89.161(3)°, *γ* = 80.989(3)°, *V* = 3532.4(9) Å³, *Z* = 4, *D*_c = 1.372 g cm⁻³, *F*₀₀₀ = 1560, MoKα radiation, *λ* = 0.71073 Å, *T* = 120(2) K, 2*θ*_{max} = 46.7°, 31 569 reflections collected, 10 199 unique (*R*_{int} = 0.0398). Final *GooF* = 1.019, *R*₁ = 0.0616, *wR*₂ = 0.1500, *R* indices based on 7995 reflections with *I* > 2*σ*(*I*) (refinement on *F*²), 947 parameters, 0 restraints. Lp and absorption corrections applied, *μ* = 0.108 mm⁻¹. Crystal data for **2**·HPF₆·2H₂O: C₃₃H₃₈F₆N₃O₈P, *M* = 749.63, colourless block, 0.40 × 0.20 × 0.08 mm, triclinic, space group *P*I (No. 2), *a* = 11.9455(4), *b* = 12.1050(5), *c* = 12.7773(5) Å, *α* = 77.5830(10)°, *β* = 67.744(2)°, *γ* = 88.694(2)°, *V* = 1666.44(11) Å³, *Z* = 2, *D*_c = 1.494 g cm⁻³, *F*₀₀₀ = 780, MoKα radiation, *λ* = 0.71073 Å, *T* = 120(2) K, 2*θ*_{max} = 55.0°, 21.557 reflections collected, 7660 unique

 $(R_{\rm int} = 0.0358)$. Final GooF = 1.049, $R_1 = 0.0497$, $wR_2 = 0.1289$, R indices based on 5886 reflections with $I > 2\sigma(I)$ (refinement on F^2), 480 parameters, 6 restraints. Lp and absorption corrections applied, $\mu = 0.173 \text{ mm}^{-1}$. Crystal data for Na[(1)₂Br]·13H₂O: C_{66} H₉₂BrN₆NaO₂₅, M = 1472.36, colourless cube, $0.13 \times 0.12 \times 0.12$ mm, trigonal, space group R3 (No. 146), a = b = 17.636(3), c = 20.817(4) Å, V = 5607.2(16) Å³, Z = 3, $D_c = 1.308$ g cm⁻³, $F_{000} = 2328$, SMART 6000, MoK α radiation, $\lambda = 0.71073$ Å, T = 120(2) K, $2\theta_{\rm max} = 55.0^{\circ}$, 18976 reflections collected, 5532 unique ($R_{\rm int} = 0.0484$). Final GooF = 1.004, $R_1 = 0.0506$, $wR_2 = 0.1246$, R indices based on 4283 reflections with $I > 2\sigma(I)$ (refinement on F^2), 343 parameters, 91 restraints. Lp and absorption corrections applied, $\mu = 0.635$ mm⁻¹. Absolute structure parameter = 0.517(16); racemic twin.

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