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Perturbing the Hofmeister series: a steroid-based anion receptor with preorganised quaternary ammonium and H-bond donor groups

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Preorganised urea groups moderate the anion-exchange properties of cationic receptor 2, favouring halide extraction and promoting anion transport through a bulk liquid membrane.

Anion recognition has become a major theme of supramolecular chemistry.[1] Synthetic anion receptors serve as models for their biological counterparts, and have potential for sensing, separations and biological/medical applications (for example, the treatment of cystic fibrosis).[2] Anionophore design has been based on various strategies involving Lewis acidic metal centres, neutral H-bond donor groups, cationic H-bond donors and/or quaternary cationic centres.[1] However one straightforward option seems remarkably under-exploited. Quaternary ammonium salts are well established as phase transfer agents, transporting anions into non-polar media according to their lipophilicities (as expressed in the classical Hofmeister series).[3] By adding H-bond donors it should be possible to create "smart" phase transfer agents, showing selectivities which depart from the Hofmeister pattern and which can be controlled through preorganisation of the donor hydrogens.[4]

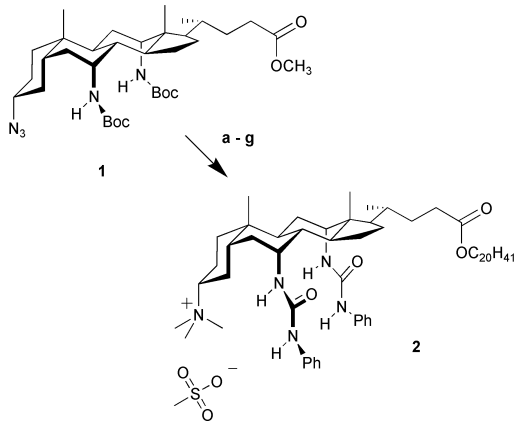
The steroid-based "cholapod"[5a] architecture provides a means to explore such possibilities. We have previously shown that electroneutral cholapods can bind anions with exceptionally high affinities in non-polar media.[5] We now describe a cationic, quaternary ammonium cholapod **2**, with distinctive "non-Hofmeister" ion-exchange properties.

Cholapod **2** was designed with particular reference to chloride as substrate. The urea and quaternary ammonium groups create a concave surface lined with CH and NH groups. Extreme selectivities were not expected due to the open binding site. However, modelling suggested that **2**, in an unstrained conformation, could bind to a spherical anion through 4 NH···X^- contacts of *ca.* 2.5 Å and at least one $N^+CH\cdots X^-$ contact of *ca.* 3 Å, quite favourable for X = Cl.[6]

2·$MeSO_3^-$ was prepared from azide **1**[7] as shown in Scheme 1. Its recognition properties were explored through ion exchange experiments in which an anion X^- and $EtSO_3^-$, both dissolved in water, were allowed to compete for the cationic receptor dissolved in $CHCl_3$. The equilibrium constant for this process was used as a measure of the receptor's ability to attract X^- across the phase boundary, with ethanesulfonate acting as a reference substrate (chosen because of its ^{1}H NMR signature).† Briefly, the cationic cholapod was dissolved in $CHCl_3$ and stirred rapidly with an aqueous phase containing the test substrate NaX and $NaEtSO_3$ (both in large excess). The $MeSO_3^-$ was lost to the aqueous phase (confirmed by NMR; see below), setting up the equilibrium represented in eqn. (1).

$$\mathbf{2}\cdot EtSO_3^- \text{ (org)} + X^- \text{ (aq)} \rightleftarrows \mathbf{2}\cdot X^- \text{ (org)} + EtSO_3^- \text{ (aq)} \quad (1)$$

The phases were separated, the organic phase was evaporated, and the contents analysed by NMR. The ratio of ethanesulfonate to receptor was measured by integration, used to infer the ratio of $X^-/EtSO_3^-$ in the organic phase, and thus to calculate *K* for eqn. (1). In most cases several experiments were performed at a range of substrate concentrations. Values for *K* were self-consistent, validating the simple ion-exchange model. Loss of receptor to the aqueous phase was minimal, and control experiments confirmed the absence of background $NaEtSO_3$ extraction.



Scheme 1 *Reagents and conditions*: (a) NaOH, MeOH/THF/H_2O; (b) i. Cs_2CO_3, MeOH; ii. $C_{20}H_{41}Br$, NaI, DMF, 47 °C; (c) trifluoroacetic acid/DCM (1 : 2); (d) phenyl isocyanate, DMAP, triethylamine, THF, 50 °C; (e) i. Me_3P, THF; ii. H_2O; (f) MeI, K_2HPO_4, MeCN; (g) CH_3SO_3Ag, THF/H_2O.

To provide a comparison, the same series of experiments was repeated with tetraoctylammonium (TOA) methanesulfonate. The results for both cations are listed in Table 1. The *K* values for TOA provide a measure of lipophilicity, generally in agreement with expectations.[1,3] However, for cholapod **2**, significant deviations are observed. The cholapod shows particular affinity for halides, favouring bromide over the more lipophilic nitrate and iodide over all other anions tested. Also revealing are the ratios K_2/K_{TOA}, which quantitate selectivity after taking account of lipophilicity. The values span a wide range, covering three orders of magnitude. The effect of the H-bond donors is best appreciated by normalising the ratios to that for PF_6^-, the anion least affected by their presence (Table 1, right hand column). In general the values increase with hydrophilicity, but it is notable that they peak at Cl^-.

NMR and X-ray crystallography confirmed the role of the NH groups as H-bond donors. The methyl ester analogue of

Table 1 Ion exchange constants *K* for cholapod **2** and tetraoctylammonium (TOA) with a series of sodium salts

Anion[a]	$K_{cholapod\ 2}$	K_{TOA}	K_2/K_{TOA}	K_2/K_{TOA} normalised to ratio for PF_6^-
AcO^-	0.047	0.0125	3.8	2200
$EtSO_3^-$	*1*	*1*	*1*	*590*
Cl^-	4.9	1.17	4.2	2500
Br^-	24	22	1.1	650
NO_3^-	6.0	31	0.19	114
I^-	98	1600	0.062	37
ClO_4^-	13.4	3100	0.0044	2.6
PF_6^-	12.9	7700	0.0017	1.0

[a] Anions listed in order of decreasing hydrophilicity.

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2·$MeSO_3^-$ was prepared by following Scheme 1 with the omission of steps a and b, and crystallised from ethyl acetate. The crystal structure (Fig. 1)‡ reveals the methanesulfonate counterion in a well-defined binding site, held by 4 NH···O hydrogen bonds and making close contact with one N^+CH. ^1H NMR spectra ($CDCl_3$) were obtained of **2** paired with all eight anions from Table 1. For all NH protons, the chemical shifts increased broadly in line with counterion hydrophilicity, suggesting that all act as H-bond donors throughout the series of complexes.

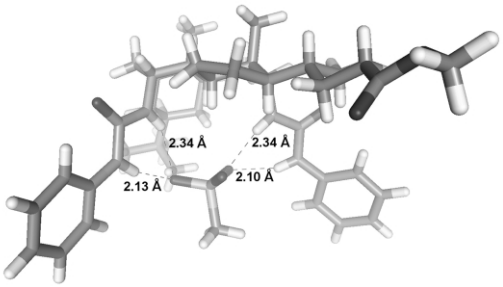

Fig. 1 X-Ray crystal structure of the methyl ester analogue of **2**·$MeSO_3^-$, showing NH···O hydrogen bonding distances.

The ability of cholapod **2** to facilitate anion transport through a bulk liquid membrane was also investigated.[8] A U-tube apparatus[9] was employed containing a source phase (NaX aq., 0.5 M) and a receiving phase (sodium picrate aq., 0.035 M) separated by a chloroform solution of carrier (0.24 mM). Standard temperature (28 °C) and stirring rate were maintained. The appearance of picrate anion in the source phase was followed by UV-visible absorbance and taken to quantify picrate/X^- antiport through the stirred chloroform layer. The cholapod was compared with two simple quaternary ammonium carriers, tetraoctylammonium and cetyltrimethylammonium. A typical set of results, for X = Cl, is shown in Fig. 2. Transport due to the control cations was very slow, while **2** was more effective by ~2 orders of magnitude. The rate was relatively constant throughout the experiment despite picrate depletion in the receiving phase, suggesting that phase transfer across the source phase boundary was the rate determining step.

The anion-dependence of transport rate was also investigated. Resultant flux rates are shown in Table 2. The variation is small[10] and not easily rationalised but it is interesting that, again, the values peak at chloride.

In conclusion, we present a new architecture for anion recognition, in which quaternary ammonium and H-bond donor groups are preorganised to create a well-defined three-dimensional binding site. In anion exchange experiments, receptor **2** has been shown to promote the extraction of polar anions, countering the bias imposed by anion hydrophilicity,

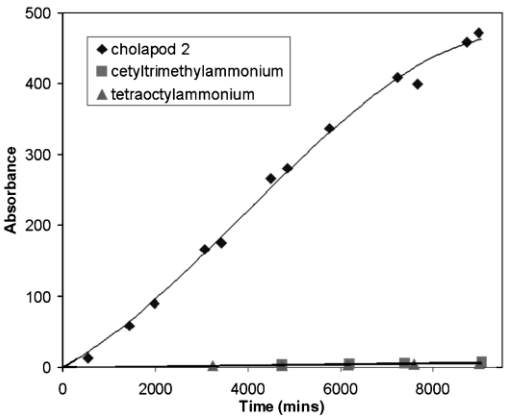

Fig. 2 Plots depicting picrate/chloride antiport for cholapod **2** and control transporters. At the end of the experiment, **2** has transported ~90% of available picrate.

Table 2 Steady state flux rates (10^{-6} mol m^{-2} s^{-1}) of picrate/anion[a] antiport facilitated by cholapod **2**

I^-	NO_3^-	Br^-	Cl^-	AcO^-
0.87	0.98	1.02	1.28	0.29

[a] Anions placed in order of hydrophilicity, increasing from left to right.

and moreover to specifically favour halides over oxoanions of comparable lipophilicity. The receptor is also capable of anion transport across a non-polar barrier, raising the possibility of similar effects in biological membranes.[11] Further elaboration, especially to create a more enclosed binding site, is likely to lead to greater selectivity and will be the focus of future work.

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Notes and references

† Methanesulfonate might seem a more obvious choice, given that it is already present in **2**·$MeSO_3^-$. However spectra containing **2** and $MeSO_3^-$ proved difficult to integrate accurately.

‡ Crystal data: $C_{43}H_{65}N_5O_7S$, M = 796.06, orthorhombic, a = 15.084(6), b = 15.853(4), c = 18.043(6) Å, U = 4315(2) Å^3, T = 173 K, space group $P2_12_12_1$ (no. 19), Z = 4, μ(Mo-Kα) = 0.13 mm^{-1}, R_{int} = 5.3% (for 45967 data), wR_2 = 9.0% (for all 9916 unique data), R_1 = 3.9% [for 7287 data with $I > 2\sigma(I)$]. Flack parameter: −0.03(6). CCDC 210645. See http://www.rsc.org/suppdata/cc/b3/b305261c/ for crystallographic data in CIF or other electronic format.

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