Contra-Hofmeister anion extraction by cyclosteroidal receptors†

Adam L. Sisson, John P. Clare and Anthony P. Davis*

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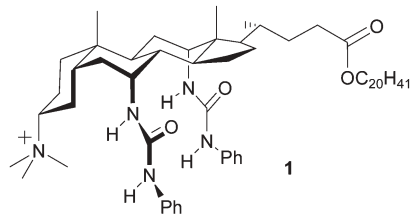
Steroid-based receptors with enclosed binding sites, formed from quaternary ammonium and macrocyclic bis-urea units, can substantially override the Hofmeister series in anion phase transfer experiments.

The transfer of anions from aqueous to organic phases is governed primarily by hydrophobicity, as reflected in the Hofmeister series.[1] Large, charge-diffuse anions are poorly solvated by water and relatively easily extracted, while small, charge-dense anions are well hydrated and difficult to extract. The effect is a powerful one; intrinsic extractabilities vary over 6 orders of magnitude between the lipophilic PF_6^- and the hydrophilic AcO^- (see below). Selective "contra-Hofmeister" anion extraction is an important goal of supramolecular chemistry, relevant to anion separations[2] and sensing,[3] and to the prospects for biological activity through anion transport across cell membranes.[4] In principle, it can be achieved by employing arrays of H-bond donors which effectively replace the hydration shells for particular anions.[5] In practice, attenuation of the Hofmeister effect can be achieved with simple, readily accessible anion receptors,[6] but major reordering remains a challenge.[7]



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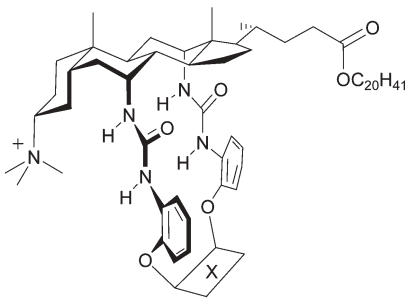
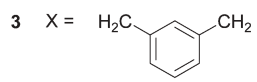


2 X = $(CH_2)_3$

3 X = 

School of Chemistry, University of Bristol, Cantock's Close, Bristol, UK BS8 1TS. E-mail: Anthony.Davis@bristol.ac.uk; Fax: +44 1179 298611; Tel: +44 1179 546334

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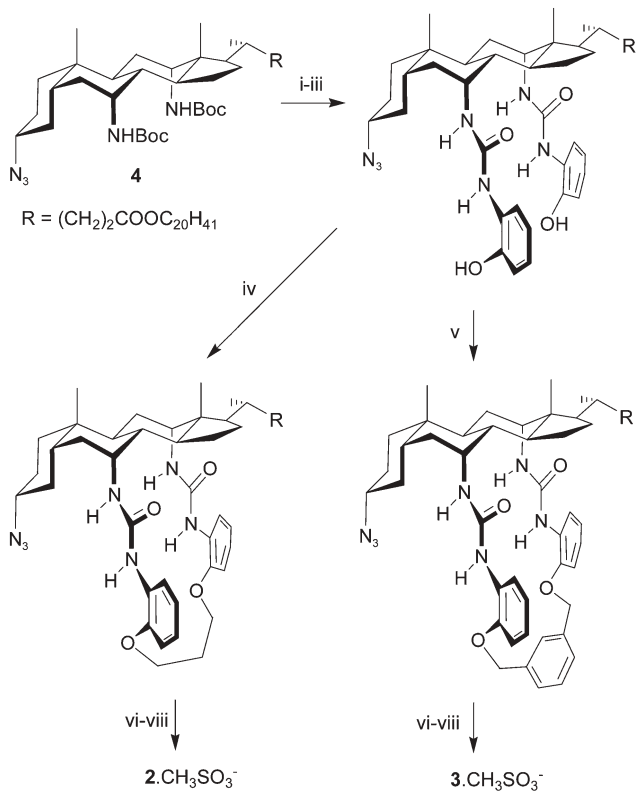
We have been exploring steroid-based architectures for anion recognition,[8] with particular emphasis on the transport of chloride ions across cell membranes.[9] Recently we described the cationic "cholapod"[10] **1**, designed as a chloride-selective extractant and transporter.[11] In anion exchange experiments, receptor **1** showed some bias towards chloride when compared with tetraoctylammonium (TOA) cation. However, in absolute terms, there were few deviations from Hofmeister ordering. We now report a new type of receptor, represented by **2** and **3**, in which the binding site is constrained both by the steroidal framework and by cyclisation. Xylyl-bridged "cholaphane"[10] **3**, in particular, realises strongly shape-selective, contra-Hofmeister anion extraction.

The design of first-generation receptor **1** features a quaternary ammonium centre adjacent to axial urea groups. Rotational restrictions on the axial C–N bonds ensure that the NH groups are convergent, preorganised for anion binding. Modelling indicates that, in unstrained conformations, the binding site of **1** is nicely complementary to chloride. However, the urea appendages are



Scheme 1 i, TFA, DCM then $NaHCO_3$ aq.; ii, *o*-MeO(C_6H_4)NCO, Et_3N, DMAP, THF; iii, $BBr_3.SMe_2$, DCM; iv, $Br(CH_2)_3Br$, DBU, DMAP, DMF; v, α,α′-dibromo-*m*-xylene, DBU, DMF; vi, Me_3P, THF, then H_2O; vii, MeI, Na_2HPO_4, MeCN, THF; viii, $MeSO_3Ag$, THF, H_2O.

quite flexible and can distort to accommodate other anions. The macrocyclic units in **2** and **3** were designed to rigidify the binding site while restricting access by larger anions. Modelling suggested that the *m*-xylyl bridge in **3** would leave the NH groups essentially unmoved, retaining the preference for chloride. In contrast the shorter linker in **2** would pull the ureas inward and compress the binding site, favouring smaller anions.[12]

Cholaphanes **2** and **3** were prepared from cholic acid *via* intermediate **4**[13] as indicated in Scheme 1.[12] The new receptors were tested by setting up the exchange shown in eqn (1) (H = host, org = species dissolved in chloroform, aq = species dissolved in water), and measuring the associated equilibrium constant K (eqn (2)) as described previously for **1**.[11] Ethanesulfonate serves as a reference, chosen so that the position of the equilibrium may be determined by ^{1}H NMR integration.

$$H{\cdot}EtSO_3^-{}_{org} + X^-{}_{aq} \rightleftharpoons H{\cdot}X^-{}_{org} + EtSO_3^-{}_{aq} \quad (1)$$

$$K = \frac{[H \cdot X]_{org}[EtSO_3]^-{}_{aq}}{[H \cdot EtSO_3]_{org}[X]^-{}_{aq}} \quad (2)$$

The results are summarized in Table 1 and Fig. 1; also included are data for TOA and **1**. $K(EtSO_3^-) = 1$ for all receptors, by definition. To a first approximation, the results for TOA may be considered those for uncomplexed anions, defining the Hofmeister series. The anions are listed according to their position in this series. Comparing the trace for TOA (blue diamonds) with that for **1** (pink squares), it can be seen that the slope for **1** is shallower (Hofmeister attenuation), but that reordering effects are limited.

Table 1 Equilibrium constants K for receptor-mediated anion exchange as represented in eqn (1). Organic phase = $CHCl_3$

	TOA[a]	**1**[a]	**2**	**3**
AcO^-	0.012	0.047	2.6	1.1
$EtSO_3^-$	1	1	1	1
Cl^-	1.2	4.9	19	920
Br^-	22	24	19	3200
NO_3^-	31	6.0	68	250
I^-	1600	98	81	970
PF_6^-	7700	13	120	94

[a] Data from ref. 11.

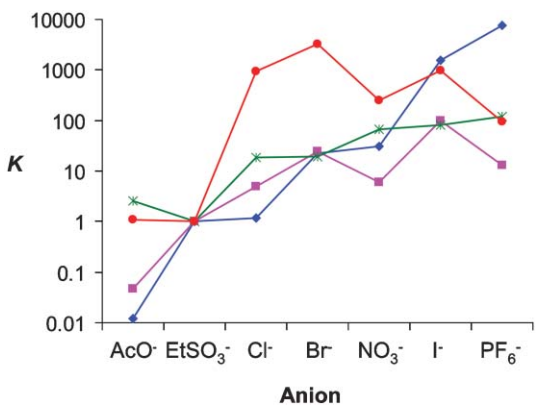


Fig. 1 Values of K from Table 1 represented graphically (logarithmic scale). Blue ♦ = TOA, purple ■ = **1**, green * = **2**, red ● = **3**. Anions are placed in order of increasing hydrophobicity (Hofmeister series).

Nitrate and hexafluorophosphate are repositioned between chloride and bromide, but otherwise the order remains the same. In contrast, the xylyl-bridged receptor **3** (red dots) shows strongly contra-Hofmeister preferences. The order of extractabilties mutates to $Br^- > I^- \approx Cl^- > NO_3^- > PF_6^- > AcO^- \approx EtSO_3^-$. The most hydrophobic anion PF_6^- is thus moved below all but the highly hydrophilic acetate and ethanesulfonate, while the spherical halide anions are gathered at the top of the series. The smaller macrocycle **2** (green stars) shows less dramatic selectivity, but is also quite different to **1**. In this case acetate is promoted over ethanesulfonate, while chloride is raised equal to bromide.

The values in Table 1 and Fig. 1 result from two competing effects, anion binding by the receptors and solvation differences between chloroform and water. Assuming that binding to TOA is negligible, the figures for K_{TOA} reflect solvation only. The intrinsic binding preferences of **1–3** may therefore be obtained by dividing K_{TOA} into $K_{receptor}$. It is also helpful to renormalize to PF_6^-, the least strongly-bound anion. The results are shown in Table 2 and Fig. 2. This treatment of the data highlights the intrinsic selectivity of **3** for chloride, especially over larger anions such as $EtSO_3^-$, I^- and PF_6^-. Indeed, modelling[14] of **3**·Cl^- shows that the chloride fits neatly into an enclosed binding site which shows little sign of strain (Fig. 3); on removal of the anion and reminimisation, only minor changes are observed.[12] Receptor **2**, by contrast, is revealed as selective for acetate. The smaller binding site shows lower affinity for chloride, but gives greater Cl^-/Br^- selectivity.

In conclusion, the cationic cholaphanes **2** and **3** possess novel structures characterized by enclosed binding sites, preorganised H-bond donors and rigidly positioned cationic centres. Both

Table 2 Intrinsic substrate preferences, as represented by $K_{receptor}/K_{TOA}$, normalized to PF_6^-.[a] Data taken from Table 1

	TOA	**1**	**2**	**3**
AcO^-	1	2300	14000	7500
$EtSO_3^-$	1	590	65	81
Cl^-	1	2500	1000	66000
Br^-	1	640	56	12000
NO_3^-	1	110	140	670
I^-	1	37	3.4	52
PF_6^-	1	1	1	1

[a] For each receptor+anion combination, K (eqn (1)) is divided by the corresponding figure for TOA+anion. For each receptor, all ratios are then divided by that for PF_6^-. All values involving TOA and PF_6^- are therefore 1 by definition.

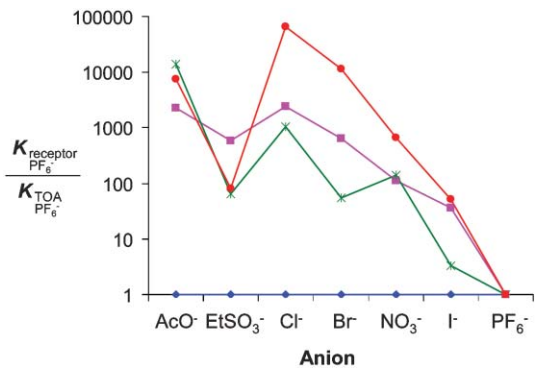


Fig. 2 Values from Table 2 represented graphically (logarithmic scale). ♦ = TOA, ■ = **1**, * = **2**, ● = **3**.

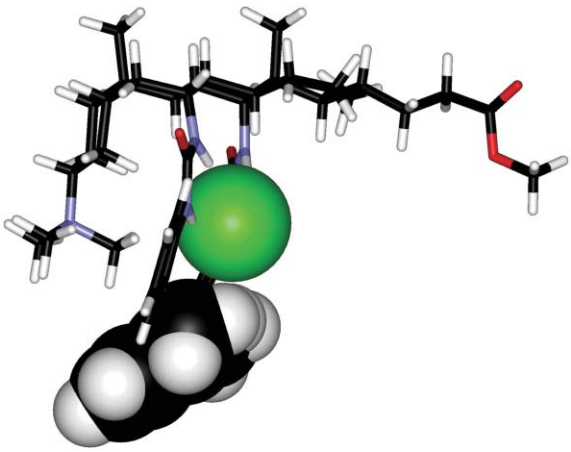


Fig. 3 Structure of **3**·Cl^- as predicted by modelling,[14,12] with the chloride anion and *m*-xylyl bridge shown as CPK surfaces.

behave as "smart phase transfer agents",[11] showing clear, structure-dependent preferences in anion extraction. Receptor **3** favors halides, overcoming Hofmeister bias to a remarkable extent. This selectivity bodes well for applications in biology and medicine, where the promotion of chloride transport is relevant to potential treatments for conditions caused by absent or malfunctioning chloride channels, notably cystic fibrosis.[4]

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