Selective perrhenate recognition in pure water by halogen bonding and hydrogen bonding alpha-cyclodextrin based receptors

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Alpha-cyclodextrin based anion receptors functionalised with pendant arms containing halogen and hydrogen bond donor motifs display selective association of perrhenate in aqueous media at neutral pH. NMR and ITC anion binding investigations reveal the halogen bonding receptor to be the superior host.

In spite of their numerous potential applications in the fields of biology, medicine and environmental science, examples of synthetic anion receptors that function in aqueous media are relatively rare. This is especially the case for pH independent host systems.¹ Primarily this is a consequence of the intrinsic properties anions possess, such as their pH dependence and high hydration energies. The preparation of water-soluble receptors however, also presents a significant synthetic challenge.²

The highly toxic and radioactive pertechnetate ($^{99}\text{TcO}_4^-$) anion has been highlighted as a particularly important target for selective recognition in aqueous environments.³ It is produced as a by-product of the nuclear fuel industry, and poses a significant environmental threat due to its long half-life, high water solubility and stability under aerobic conditions.^{4,5} Due to its radioactivity, direct study of this anion has been limited and the perrhenate anion (ReO_4^-), which has an identical geometry, similar size and hydration energy, has often been used as a surrogate.⁶ Additionally, $^{188}\text{ReO}_4^-$ is used for therapeutic applications in medicine and hence its selective recognition is also of significant importance.⁷ Only a handful of receptors capable of binding this oxoanion in pure water have been reported,^{8–11} with the majority of examples functioning in organic solvent systems.^{12–18} To the best of our knowledge, the most effective host known to date is Amendola's hexacationic azacryptand which binds perrhenate at low pH *via* a combination of hydrogen bonding and electrostatic

interactions.¹⁰ Furthermore, several groups have shown that hosts possessing a central hydrophobic cavity can form strong inclusion complexes with perrhenate.^{19–21} However, the selectivity trends of such receptors typically mirror the Hofmeister series.

Herein we report the preparation of two anion receptors containing either halogen bonding (XB) iodotriazole or hydrogen bonding (HB) prototriazole pyridinium donor motifs attached to diametrically opposed positions on the primary rim of an α -cyclodextrin (α -CD), a macrocyclic oligosaccharide that is known to complex inorganic anions within its central hydrophobic cavity.^{22–24} The hosts utilise inclusion complex formation and convergent XB/HB interactions in concert to provide selective recognition of perrhenate in neutral, aqueous media (**Figure 1**). Importantly the XB receptor is demonstrated to act as a more potent host than the HB analogue.

Figure 1: Schematic representation of the perrhenate binding mode of the XB and HB receptors (X = I or H).

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Scheme 1: Synthesis of XB and HB receptors **6** and **7**. ^a For X = I: $\text{Cu}(\text{MeCN})_4\text{PF}_6$, TBTA, THF; For X = H: $\text{Cu}(\text{MeCN})_4\text{PF}_6$, DIPEA, TBTA, CH_2Cl_2 .

The preparation of the target XB and HB receptors began with 6^{A,D}-dihydroxy-perbenzylated- α -CD **1** which was obtained through a regioselective de-*O*-benzylation of perbenzylated- α -CD.²⁵ Conversion of the CD's benzyl ether groups to methyl ether groups was then achieved, using an adapted four step procedure, to give a water-soluble diol precursor **2** (Scheme 1).^{26,27} Initial THP-protection of the two hydroxyl groups, was followed by debenzylation using palladium catalysed hydrogenolysis, methylation with methyl iodide and finally removal of the THP groups affording the desired diol **2** in a 43% yield over the four steps. Diol **2** was then converted to bis-azide **3** via a bis-mesylate intermediate.

The reaction of **3** with two equivalents of either 3-(iodoethynyl)pyridine or 3-ethynylpyridine under CuAAC conditions gave bis-iodotriazole and bis-prototriazole derivatives **4** and **5**, respectively, in good yields. The pyridine units of both compounds were methylated using methyl iodide, which was followed by anion exchange using a nitrate-loaded Amberlite[®] column, to give the target water-soluble XB and HB receptors **6** and **7**. Nitrate was chosen as the counter-anion for the hosts due to the weakness of the inclusion complex it forms with α -CD ($K_a \sim 2 \text{ M}^{-1}$)²³, along with its non-coordinating nature in aqueous media.^{8,28}

Preliminary investigations into the anion binding properties of the XB and HB receptors were conducted using ¹H NMR spectroscopic titration experiments performed in pure D₂O, with the protons of the two hosts monitored upon addition of chloride, bromide, iodide, sulfate, perchlorate and perrhenate, as their sodium salts. Significant downfield perturbations of the H5^{C,F} CD protons were observed in the titrations with iodide, perchlorate and perrhenate for both receptors (Figure 2). As these protons are directed towards the inner cavity of

the CD, at the opening of the primary rim, the observed shifts provide strong evidence that these anions are at least partially included within the CD. In contrast, no shift of the same resonance occurred in titrations with chloride, bromide and sulfate, suggesting very weak or no inclusion of these anions.

In addition, pyridinium protons *b* (see Figure 2 for labels) underwent downfield shifts in the titration of the XB host **6** with perchlorate and perrhenate, whilst the triazole protons of the HB receptor **7** underwent a similar change in titrations with iodide and perrhenate. This implies that the XB/HB donor groups of the respective receptors also contribute to anion association in these cases.

Figure 2: Truncated ¹H NMR spectra of XB receptor **6** before (bottom) and after (top) addition of 120 equivalents of NaReO_4 (D₂O, 298 K, 500 MHz).

WinEQNMR2 analysis²⁹ of the titration data determined 1:1 stoichiometric association constants (**Table 1**). Importantly, both receptors display selectivity towards perrhenate, with the XB receptor perrhenate association constant value at least an order of magnitude greater than those calculated with iodide and perchlorate. As the hydration energy of perrhenate is the largest of the three binding anions (**Table 1**),^{6,30} and lies between the energies of chloride and bromide, which are not bound by either host, it is unlikely that the observed selectivity is the result of the hydrophobic effect. This suggests that perrhenate forms stronger interactions with the XB/HB donor groups of the hosts than the other anions. Perrhenate has the largest radius of the six anions investigated,³¹ which may enable the oxoanion to maximise its interactions with XB iodotriazole or HB triazole donor groups and C-H pyridinium donors, as evidenced by the observed proton shifts in the ¹H NMR titration experiments discussed above.

It is also noteworthy that the XB receptor forms a significantly stronger association with perrhenate in comparison to the HB host analogue. This result is in agreement with previous observations that XB is a potent and commonly superior binding interaction to HB to exploit for anion recognition in aqueous media^{8,28}. To the best of our knowledge, XB receptor **6** is the most effective host currently known for perrhenate recognition in neutral water.

Table 1: Anion association constants (K_a/M^{-1}) of XB **6** and HB **7** with various anions in pure D₂O, along with the hydration energies of these anions.

Anion	6 K_a (M^{-1}) ^a	7 K_a (M^{-1}) ^a	ΔG_{hyd} (kJ/mol)
Cl ⁻	<i>b</i>	<i>b</i>	-340 ³⁰
Br ⁻	<i>b</i>	<i>b</i>	-315 ³⁰
I ⁻	18	27	-275 ³⁰
SO ₄ ²⁻	<i>b</i>	<i>b</i>	-1295 ³⁰
ClO ₄ ⁻	27	36	-205 ³⁰
ReO ₄ ⁻	950	170	-330 ⁶

^a Obtained through a ¹H NMR titration (D₂O, 298 K, 500 MHz) monitoring ⁵H⁵C⁶F protons. Data was fitted using the WinEQNMR2 software package. Estimated errors within 10%. ^b Change in chemical shift too small to accurately determine K_a indicating very weak or no binding.

To further assess the contribution of the appended XB/HB donor groups towards perrhenate association, an additional ¹H NMR titration experiment was performed to determine the stability of the inclusion complex formed between native (unfunctionalised) α -CD and sodium perrhenate. A 1:1 stoichiometric association constant of $96(\pm 2) \text{ M}^{-1}$ was calculated⁵⁵ from the titration data. This implies that the HB donor groups of receptor **7** play only a modest contribution to perrhenate binding with the inclusion of the anion within the CD cavity providing the main driving force for recognition. Interestingly, iodide and perchlorate association constant values of both receptors are of a similar magnitude to those reported for the binding of these anions to native α -CD ($K_a = 19 \text{ M}^{-1}$ and $K_a = 46 \text{ M}^{-1}$),²³ again suggesting that the appended XB/HB pyridinium motifs do not contribute significantly towards the association of these anions with either host. The

higher association constant of perrhenate with native α -CD is most likely due to its better size match with the central cavity of the macrocycle ($174 \text{ \AA}^3$, for native α -CD).³² Perrhenate has a significantly larger volume than perchlorate and iodide ($65 \text{ \AA}^3$, $55 \text{ \AA}^3$ and $35 \text{ \AA}^3$, respectively)³³ which means its packing coefficient is closest to the value of 0.55, suggested by Rebek as the optimal value for formation of the strongest inclusion complex.³⁴

Isothermal titration calorimetry (ITC) experiments were undertaken to determine the thermodynamic parameters for perrhenate binding with both receptors (**Figure 3**, **Table 2**§§§).

Figure 3: (top) Raw ITC data for the sequential addition of NaReO₄ to **6** (H₂O, 298 K); (bottom) integrated heat plot obtained from titration.

Table 2: Association constants and thermodynamic parameters determined using isothermal titration calorimetry for **6** and **7** with NaReO₄.

	6	7
K_a (M^{-1})	650(± 10)	290(± 100)
ΔG° (kJ/mol)	-16.1	-14.0
ΔH° (kJ/mol)	-54.0(± 0.4)	-21.9(8.5)
$-\Delta S^\circ$ (kJ/mol)	37.9	7.8

^a titration performed in unbuffered H₂O at 298 K

The K_a values are comparable with those determined from the ¹H NMR titration experiments with the XB host **6** shown to bind the oxoanion more strongly than the HB receptor **7**. In both cases association was found to be enthalpically driven and entropically disfavoured. The large, favourable enthalpic contribution observed with **6** indicates the receptor's iodotriazole motifs are forming strong XB interactions with the perrhenate anion. The data is in agreement with previously reported thermodynamic investigations of anion binding by XB

hosts in water, which were found to be enthalpically favoured and opposed by entropy.^{8,28}

In summary, two novel XB and HB alpha-cyclodextrin based receptors have been shown to selectively bind perrhenate over a range of other monoanionic species in water. NMR titration experiments suggest the binding mode of these receptors is unique with the oxoanion included within the central cavity of the CD whilst also forming XB/HB interactions with its pendant arms. Importantly, the XB host displayed a significantly higher affinity for the perrhenate anion than the HB analogue, which is enthalpically driven. This observation adds to the growing evidence that halogen bonding is proving to be an effective non-covalent interaction to exploit for the recognition of anions in water.

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Notes and references

§ Using a simple acyclic bis-iodotriazolium receptor we recently demonstrated XB to be a superior non-covalent interaction than HB for the recognition of perrhenate in water.⁸

§§ Obtained through a ¹H NMR titration (D₂O, 298 K, 500 MHz) monitoring ¹H₅ protons. Data was fitted using the WinEQNMR2 software package.

§§§ The heat outputs observed for each addition to HB receptor **7** were small (see ESI), making the errors associated with the fitting process large. The calculated values for this receptor are therefore only rough estimates.

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