

A pyrrole-containing cleft-type halogen bonding receptor for oxoanion recognition and sensing in aqueous solvent media

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The synthesis and anion binding properties of a novel pyrrole-containing dicationic halogen bonding (XB) motif is described. When incorporated into an acyclic cleft-type receptor, rare selectivity for tetrahedral oxoanions (H_2PO_4^- and SO_4^{2-}) over halides is observed in aqueous solvent media.

Oxoanions are an abundant class of anions which play crucial roles in biology and the environment. For instance, while phosphates and sulfates are essential intermediates in biological metabolism, excess quantities are toxic^{1–3} and contribute significantly to environmental pollution.^{4,5} However, they are highly-challenging targets for selective binding and sensing with abiotic receptors owing to their considerable free energies of hydration⁶, pH sensitivity and geometry-dependence. Despite these difficulties, recent years have witnessed considerable advances in receptor development for oxoanion binding,⁷ utilising strategies such as convergent hydrogen bonding (HB) interactions^{8–10} and strong oxoanion-metal coordination^{11–14} to outcompete the extensive anion hydration. While halogen bonding (XB), the non-covalent attractive interaction between an electron-deficient halogen atom and a Lewis base,^{15,16} has been applied in anion recognition^{17–19} and often shown to outperform structurally-analogous HB host molecules, few examples of XB receptors are known to bind and sense oxoanions selectively over halides,^{17,20–23} especially in protic media.^{24,25} This may be a consequence of the XB donor groups' inherent hydrophobicities and proclivity towards binding 'softer' anions (e.g. I^-).²⁶

To address this deficiency, we designed a novel anion recognition motif comprising of a central pyrrole unit 2,5-disubstituted with potent XB-donor iodotriazolium units in an acyclic cleft-type receptor **1.XB** (Figure 1). The strong HB donor capability of the pyrrole NH group was envisaged to enhance

anion recognition, as evident from its effectiveness for anion binding in a range of anion receptors^{27,28} which include natural²⁹ and artificial anion transporters,^{30,31} macrocycles such as calixpyrroles and their strapped analogues,³² as well as porphyrins^{33,34} and their expanded counterparts smaragdyrins³⁵ and sapphyrins.^{36,37} Furthermore, the use of pyrrole as a spacer motif between the iodotriazoliums also results in a wider XB bite angle compared to that achievable with six-membered aromatic functionalities such as benzene²³ or pyridine,³⁸ geometrically favouring coordination of larger oxoanions. Indeed, we demonstrate herein that receptor **1.XB** is capable of strongly and selectively binding tetrahedral oxoanions such as dihydrogen phosphate and sulfate in competitive solvent media containing up to 10 % water, with augmented anion affinities compared to its HB receptor analogue **1.HB**. In addition, importantly, this preferential oxoanion binding over halides is accompanied by an enhanced UV-visible sensing response.

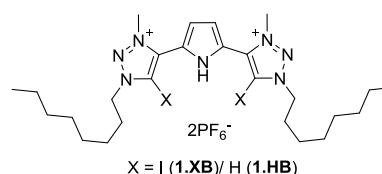
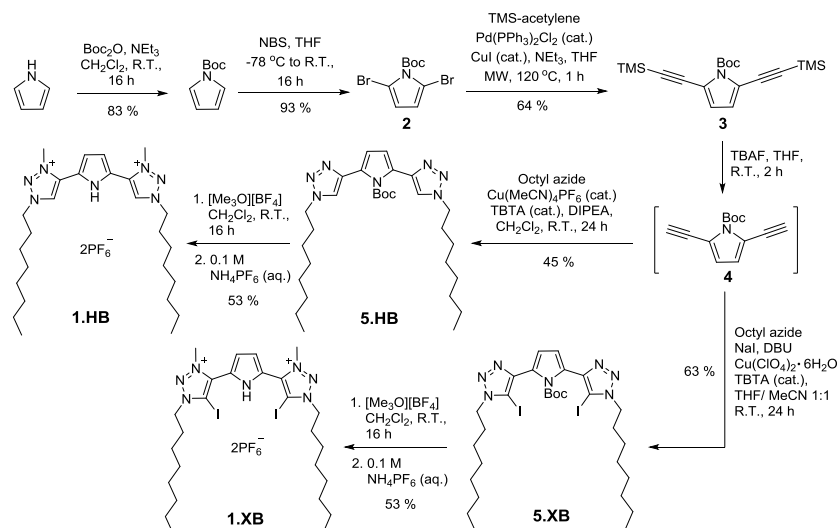


Figure 1. Design of acyclic cleft-type pyrrole-containing receptors **1.XB** and **1.HB**.

The multi-step synthesis of receptors **1.XB** and **1.HB** is summarised in Scheme 1. Initial NBoc-protection of pyrrole facilitated exclusive regioselective dibromination at the 2,5-positions using N-bromosuccinimide (NBS) to form intermediate **2**.³⁹ Microwave-assisted Sonogashira coupling of **2** with trimethylsilyl (TMS)-acetylene afforded the corresponding protected bis-alkyne **3**. While **3** was stable under ambient conditions, deprotection of its TMS groups resulted in rapid darkening of the product, possibly due to the propensity of the electron-rich pyrrole aromatic system

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Scheme 1. Synthesis of target receptors **1.XB** and **1.HB** starting from pyrrole. TBTA = Tris[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]amine.

towards aerobic oxidation. Hence, TMS-deprotection of **3** using TBAF.3H₂O under an inert N₂ atmosphere yielded bis-alkyne intermediate **4** which was reacted directly with *n*-octyl azide without isolation under copper(I)-catalysed azide-alkyne cycloaddition (CuAAC) reaction conditions to afford neutral receptor precursors **5.XB** and **5.HB** in yields of 45 % and 63 % respectively. **5.XB** and **5.HB** were then reacted with trimethyloxonium tetrafluoroborate (3.0 eqv.) for simultaneous bis-(iodo)triazole methylation and deprotection of the *N*Boc-group. Anion exchange to the non-coordinating PF₆[−] salts afforded the target receptors **1.XB** and **1.HB**, which were characterised by ¹H, ¹³C, ¹⁹F and ³¹P NMR spectroscopy as well as high-resolution ESI mass spectrometry (see Supporting Information).

The anion binding properties of receptors **1.XB** and **1.HB** were initially probed by preliminary ¹H NMR titration experiments performed in CDCl₃/CD₃OD/D₂O 45:45:10 v/v/v with tetrabutylammonium (TBA) chloride. As shown in Figure 2, addition of Cl[−] to receptor **1.HB** led to significant downfield perturbations of the triazolium protons signal H_a (Δδ = + 0.20 ppm after 5.0 eqv.) and small upfield shifts for the pyrrolic aromatic protons (H_b) and triazolium methyl groups (Δδ c.a. - 0.02 ppm in both cases). This indicated that chloride was binding primarily in the vicinity of the receptor cleft containing the pyrrole NH proton flanked by the triazolium units, and not hydrogen bonding significantly with the external pyrrolic (H_b) and triazolium protons at the outer periphery of the receptor. With receptor **1.XB**, Cl[−] addition elicited similar small shifts of H_b (Δδ c.a. - 0.02 ppm in both cases) (see Fig. S11, Supporting Information). The lack of proton signals within the anion binding cleft of **1.XB** for monitoring during anion titration experiments precluded determination of reliable anion association constant values using ¹H NMR titration data. Hence anion binding was probed using UV-Vis spectroscopy instead.

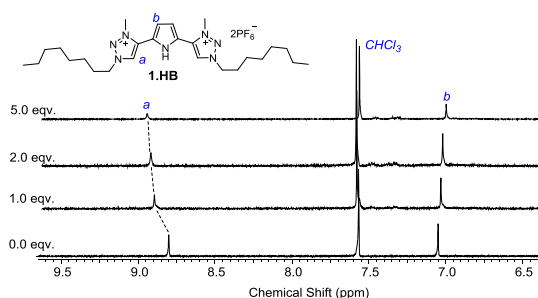


Figure 2. Partial ¹H NMR spectra of receptor **1.HB** in the presence of 0.0, 1.0, 2.0 and 5.0 equivalents of TBACl ([**1.HB**] = 1.5 mM, CDCl₃/CD₃OD/D₂O 45:45:10 v/v, T = 298 K).

Quantitative UV-Vis titration experiments were performed by adding increasing quantities of anions (oxoanions: H₂PO₄[−], SO₄^{2−}, NO₃[−], AcO[−] and ClO₄[−]; halides: F[−], Cl[−], Br[−] and I[−]), as their TBA salts, to receptors **1.XB** and **1.HB** in the competitive solvent media of CH₃CN/ H₂O 9:1 v/v. Both receptors exhibited almost identical peak absorption wavelengths at approximately 300 and 360 nm and molar extinction coefficients, suggesting that the presence of the XB-donor iodine atoms of **1.XB** did not significantly affect the electronic energy levels of the pyrrolic receptor framework.

The binding of anions elicited considerable variations in the UV-Vis response for each receptor (Section S4, Supporting Information), most notably with the lower-energy 360 nm absorption band. With receptor **1.XB**, the presence of Cl[−] (Figure 3A) and Br[−] gave negligible changes to intensity of this absorption peak. In contrast, H₂PO₄[−] (Figure 3B) and SO₄^{2−} (see Supporting Information) both resulted in an initial intensity increase, followed by a dramatic reduction in intensity at higher anion concentrations. Nitrate addition, on the other hand, caused a continual 360 nm peak intensity decrease.

These anion-dependent intensity change observations may indicate the sensitivity of the pyrrole NH...anion HB interactions,⁴⁰ with the most charge dense anion (SO_4^{2-}) producing the most pronounced intensity response. Interestingly, the peak centred at 300 nm underwent bathochromic shifts upon anion binding. This is consistent with anion coordination enforcing greater planarity between the iodo-triazolium units and the pyrrole motif in **1.XB**, which increases the extent of electronic conjugation between them, concomitantly causing an absorption red-shift. Although receptor **1.HB** also showed more pronounced spectral changes with the oxoanions H_2PO_4^- , SO_4^{2-} and NO_3^- than with Cl^- and Br^- ,

unlike **1.XB**, only unidirectional changes upon anion addition were observed suggesting the oxoanions were being bound via different coordination stoichiometries. While both receptors showed no perceptible UV-Vis absorbance changes with ClO_4^- , indicating very weak binding, the addition of 1.0 equivalent of F^- and AcO^- brought about very large spectral perturbations (Figure 3C). Considering their basicity ($\text{pK}_a(\text{aq.})$ of $\text{HF} = 3.2$ and $\text{HOAc} = 4.8$),⁴¹ these changes likely result from deprotonation of the central pyrrole NH proton. Global spectral fitting of the UV-Vis spectroscopy titration data was performed using the BindFit software,⁴² and the calculated association constants are summarised in Table 1.

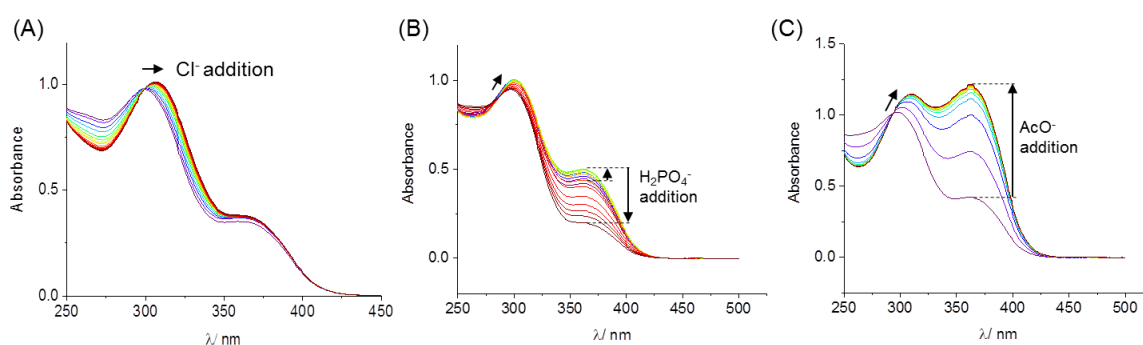


Figure 3. UV-Vis spectra of receptor **1.XB** with increasing quantities of (A) Cl^- ; (B) H_2PO_4^- and (C) AcO^- as their TBA salts ($[\mathbf{1.XB}] = 50 \mu\text{M}$, $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ 9:1, $T = 293 \text{ K}$).

Table 1. Anion association constants K_a/M^{-1} of receptors **1.XB** and **1.HB**.^a

Anion	pK_a^b	K_a/M^{-1}	
		1.XB	1.HB
F^-	3.2	— ^c	— ^c
Cl^-	-7.0	1390 (30)	630 (10)
Br^-	-9.0	2660 (40)	— ^d
I^-	-10.0	— ^e	— ^d
H_2PO_4^-	2.1	$K_{1:1} = 3460$ (60) $K_{1:2} = 70.4$ (0.2)	1210 (9)
SO_4^{2-}	2.0	$K_{1:1} = 7700$ (200) $K_{2:1} = 9900$ (200)	$K_{1:1} = 5450$ (40) $K_{1:2} = 4710$ (70)
ClO_4^-	-10.0	— ^d	— ^d
NO_3^-	-1.3	44.7 (0.2)	96.5 (0.7)
AcO^-	4.8	— ^c	— ^c

^aA 1:1 host-guest binding model, unless otherwise stated, was used to determine K_a values from global fitting of UV-Vis titration spectra using BindFit;⁴² $K_{1:2}$ and $K_{2:1}$ represent association constants for a host-guest 1:2 and 2:1 binding stoichiometry respectively; anions were added as their TBA salts ($[\text{host}] = 50 \mu\text{M}$, $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ 9:1, $T = 293 \text{ K}$); errors (\pm) are shown in parentheses; ^b pK_a values are for the conjugate acids reported in water by Smith and March;⁴¹ ^cNo reliable association constants could be obtained due to receptor deprotonation; ^dBinding too weak to be quantified; ^eComplex equilibria.

Comparing the anion binding affinities of **1.XB** and **1.HB** in Table 1 reveal the important influences of XB interactions on anion association. Firstly, **1.XB** exhibited superior binding

strength compared to its HB analogue for all halides and oxoanions, with the exception of NO_3^- . Secondly, both receptors displayed contrasting anion binding trends for Cl^- and Br^- . With **1.XB**, Br^- was bound more strongly than Cl^- , attributed to the greater energetic ease of dehydration of the former anion, as well as the inherent preference of XB interactions towards 'softer' halides. In contrast, receptor **1.HB** showed only detectable binding for the most charge-dense and Lewis basic halide Cl^- . Notably, the Cl^- and Br^- anion affinities observed with both pyrrolic receptors are greatly augmented compared with previously-reported HB and XB dicationic receptor analogues containing the benzene-3,5-bis[(iodo)triazolium] anion binding motif in the same solvent mixture.⁴³

Binding of the tetrahedral oxoanions to both receptors appears to be driven largely by the anions' charge densities, with K_a values decreasing in the order of $\text{SO}_4^{2-} > \text{H}_2\text{PO}_4^- \gg \text{ClO}_4^-$. Despite the sensitivity of the pyrrolic-NH HB donor motif to anion basicity, this factor does not account for the observed binding affinities with these anions. This is most evidently seen from the similar K_a values of **1.HB** towards Cl^- and H_2PO_4^- despite the latter being much more basic (Table 1).⁴¹ Once again, the influences of XB are seen from the augmented affinities and different anion binding stoichiometries of both receptors with H_2PO_4^- and SO_4^{2-} .⁶ Importantly, both these tetrahedral oxoanions are preferentially bound by **1.XB** compared to halides despite their much greater free energies of hydration,⁶ which may be attributed to the wider XB bidentate bite angle being of complementary size for the

larger oxoanions. Also, in spite of its smaller size and hydration energy,⁶ trigonal-planar NO_3^- is bound weakly by both receptors.

In conclusion, the first pyrrole-containing XB receptor has been synthesised and demonstrated to bind anions in aqueous solvent media. Receptor **1.XB** is especially notable for being a very rare example of a simple acyclic XB host molecule capable of preferentially recognising and sensing the strongly-hydrated tetrahedral oxoanions H_2PO_4^- and SO_4^{2-} over spherical halide anions in a protic solvent system which may be attributed to host-guest size-complementarity. Significantly, while HB interactions between the anion guest and the pyrrole NH unit could augment anion affinities, charge-assisted XB interactions are largely influencing the observed anion binding properties of **1.XB**. The development of XB anion receptors for strong and selective recognition of anions is continuing in our laboratories.

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Conflicts of interest

There are no conflicts to declare.

Notes and references

- § The different binding stoichiometries for H_2PO_4^- and SO_4^{2-} with **1.XB** are reflective of their different charges and charge densities, with SO_4^{2-} forming (**1.XB**)₂(SO_4) host-guest 2:1 complexes at low anion concentrations similar to those observed by Horng et. al. (*New J. Chem.*, 2017, **41**, 2249–2254), while preferentially forming 1:1 complexes in the presence of greater anion excess (see Section S4, Supporting Information). On the other hand, the singly-charged nature of H_2PO_4^- disfavours (**1.XB**)₂(H_2PO_4) host-guest 2:1 complex formation due to electrostatic repulsion.
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