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Halogen bonding-enhanced electrochemical halide anion sensing by redox-active ferrocene receptors†

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The first examples of halogen bonding redox-active ferrocene receptors and their anion electrochemical sensing properties are reported. Halogen bonding was found to significantly amplify the magnitude of the receptor's metallocene redox-couple's voltammetric responses for halide sensing compared to their hydrogen bonding analogues in both acetonitrile and aqueous–acetonitrile solvent media.

The ability to detect halides such as chloride and bromide in aqueous solvent mixtures is crucial in many aspects of medicine, industrial processes and environmental analyses. For instance, chloride is a key indicator of fecal contamination in the environment and has vast applications in industry ranging from anti-freezing agents to metal processing, while bromide is used in sedatives and as an anticonvulsant in medicine, as well as in the photographic industry.[1] As such, artificial halide sensors, which are receptor molecules that give a detectable optical or electrochemical output signal upon halide binding, have received much scientific attention in recent years.[2–4] Electrochemical sensors in particular, are especially sought after due to their innate high sensitivity and facile integration into applicable devices.[5] These receptor molecules typically contain ferrocene as the redox-active moiety due to its chemical stability, favourable voltammetric characteristics and large synthetic repertoire, allowing it to be readily incorporated into a myriad of molecular architectures.[6–12] As a result, ferrocene-containing anion sensors utilising hydrogen bonding (HB), Coulombic interactions, as well as Lewis acid and metal coordination have been reported.[13–15]

Halogen bonding (XB), a highly-directional attractive non-covalent interaction between a Lewis-acidic halogen atom and a Lewis base,[16] is a recent addition to the toolkit of supramolecular anion binding in solution. While its utilisation in solid-state crystal engineering and materials design is well-established,[17,18] its applications in solution-phase self-assembly,[19,20] redox-switching[21] and catalysis[22,23] still remain in their infancy. We have recently demonstrated that XB possesses a high degree of covalency,[24] a feature that has been shown to lend itself to superior iodide[25] and perrhenate[26] anion binding in pure water in comparison to HB analogues. Although anion sensing by XB receptors has been demonstrated *via* UV-vis[27] and fluorescence spectroscopy,[28,29] electrochemical anion sensing by redox-active XB receptors, to the best of our knowledge, is unprecedented. Herein, we describe the synthesis of a family of novel acyclic ferrocene-appended XB donor receptors (Fig. 1), and importantly, demonstrate their significantly enhanced electrochemical anion sensing behaviour in comparison with HB analogues both in organic and organic–aqueous solvent media.

The target receptors were designed to have the redox-active ferrocene motif directly conjugated to XB and HB donor anion binding sites to facilitate efficient electrochemical reporting. Receptors **1.XB** and **1.HB** were prepared using the synthetic procedure shown in Scheme 1. 3,5-Diiodoaniline was converted to its diazonium salt and coupled with ferrocene to form 1-ferrocene-3,5-diiodobenzene (**4**). Sonogashira coupling of **4** with two equivalents of ethynyltrimethylsilane, followed by deprotection of the terminal trimethylsilyl (TMS) groups afforded the bis-ethyne **5** in 96% overall yield. Copper(I)-catalysed azide–alkyne cycloaddition (CuAAC) between **5** and two equivalents of

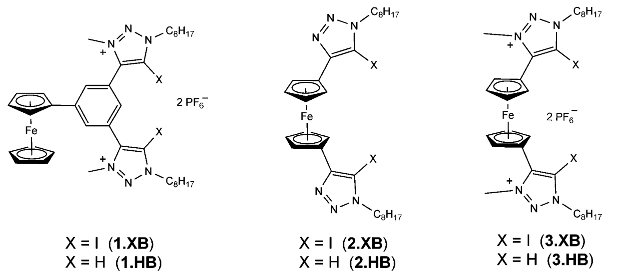

Fig. 1 Structures of the redox-active XB receptors and their HB analogues for electrochemical anion sensing in solution.

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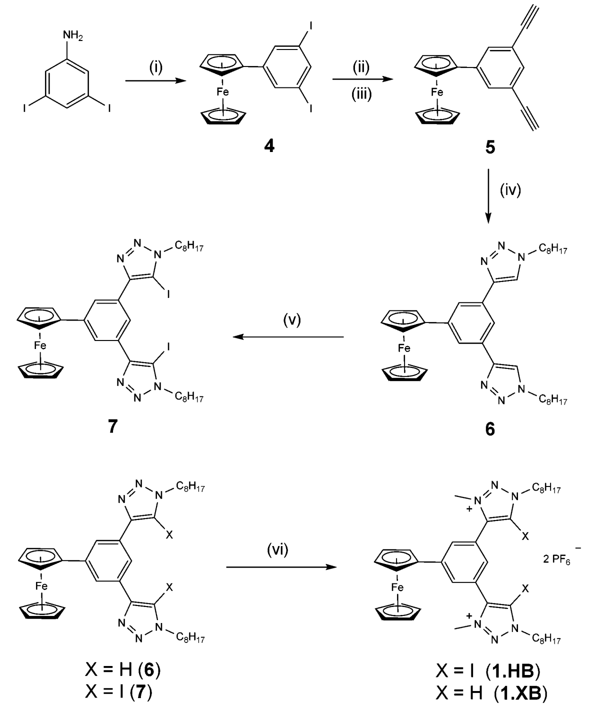
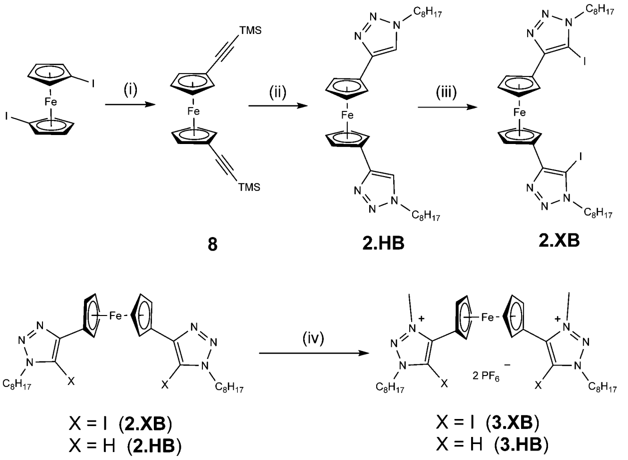


Scheme 1 Synthesis of dicationic receptors **1.XB** and **1.HB**. (i) HCl, $NaNO_2$, 0 °C, 1 h then ferrocene, toluene, 16 h, R.T., 33%; (ii) ethynyltrimethylsilane, NEt_3, $Pd(PPh_3)_2Cl_2$ (cat.), CuI (cat.), THF, microwave, 100 °C, 1 h, 97%; (iii) K_2CO_3, MeOH, R.T., 3 h, 96%; (iv) octyl azide, $Cu(MeCN)_4PF_6$ (cat.), TBTA (cat.), NEt_3, CH_2Cl_2, R.T., 16 h, 85%; (v) *n*-BuLi, THF, −78 °C, 1 h then I_2, R.T., 1 h, 75%; (vi) $[Me_3O][BF_4]$, CH_2Cl_2, R.T., 16 h, **1.XB** 76%, **1.HB** 80%.

octyl azide gave the bis-prototriazole derivative **6**. Thereafter, capitalising on the acidity of the triazole functionality,[30] regioselective triazole deprotonation of **6** was achieved using *n*-butyllithium. Following quenching with molecular iodine, **7** was obtained in a good yield of 75%. Bis-methylation of receptor precursors **6** and **7** with trimethyloxonium tetrafluoroborate, followed by anion exchange, afforded receptors **1.HB** and **1.XB** respectively as hexafluorophosphate salts.

The 1,1′-bis-substituted ferrocene receptors **2.XB**, **2.HB**, **3.XB** and **3.HB** were synthesised *via* a similar route starting from 1,1′-diiodoferrocene (Scheme 2). Following Sonogashira coupling with two equivalents of ethynyltrimethylsilane, the product **8** was deprotected *in situ* with tetrabutylammonium (TBA) fluoride and reacted immediately with two equivalents of octyl azide to give **2.HB**, which was then converted directly to **2.XB** with *n*-butyllithium and iodine. Dicationic receptors **3.HB** and **3.XB**, were prepared *via* alkylation with trimethyloxonium tetrafluoroborate, and anion exchanged to the hexafluorophosphate salts.

The anion recognition properties of the dicationic ferrocene-appended receptors were studied *via* ^{1}H NMR titration experiments by adding increasing quantities of Cl^- and Br^- as their TBA salts to the receptor solutions (see ESI†).‡ Initial titrations of **1.HB** with Cl^- and Br^- in d_3-acetonitrile determined 1 : 1 association constants of (909 ± 14) M^{-1} and (404 ± 4) M^{-1} respectively. However, both halides were bound very strongly by **1.XB** in the same solvent ($K_a > 10^4$ M^{-1}), clearly demonstrating the superiority of XB for anion recognition in solution. Analogous ^{1}H NMR titrations in the more competitive solvent mixture of 9 : 1 acetonitrile–D_2O revealed that the addition of chloride or bromide caused significant downfield perturbations of the receptor's internal aromatic proton H_a (Fig. 2A), suggesting that anion binding was occurring in the binding cavity flanked by the triazoliums moieties. WinEQNMR2[31] analysis of the titration data determined 1 : 1 stoichiometric association constants summarised in Table 1. Notably, both chloride and bromide were bound much more strongly to the halogen bonding receptor **1.XB** than **1.HB**, with more than an order of magnitude enhancement in the association constant observed in the case of bromide.



Scheme 2 Synthesis of 1,1′-substituted ferrocene receptors. (i) Copper(II) acetate hydrate, $Pd(PPh_3)_2Cl_2$ (cat.), $^iPr_2NH$, ethynyltrimethylsilane, THF, microwave, 100 °C, 1 h, 68%; (ii) octyl azide, TBAF, $Cu(MeCN)_4PF_6$ (cat.), TBTA (cat.), NEt_3, CH_2Cl_2, R.T., 2 days, 77%; (iii) *n*-BuLi, THF, −78 °C, 1 h then I_2, R.T., 1 h, 90%; (iv) $[Me_3O][BF_4]$, CH_2Cl_2, R.T., 16 h, **3.XB** 50%, **3.HB** 59%.

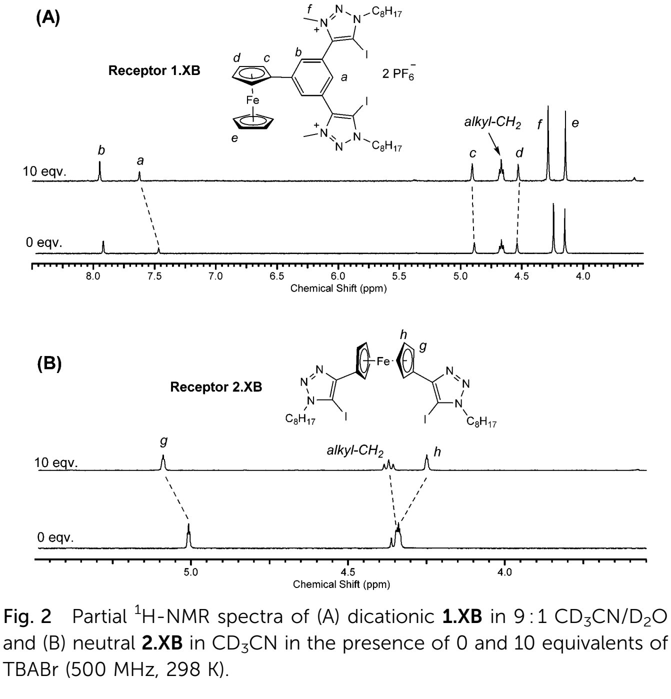


Fig. 2 Partial ^{1}H-NMR spectra of (A) dicationic **1.XB** in 9 : 1 CD_3CN/D_2O and (B) neutral **2.XB** in CD_3CN in the presence of 0 and 10 equivalents of TBABr (500 MHz, 298 K).

Table 1 Anion association constants (K_a/M^{-1})[a]

	Cl^-	Br^-
1.XB[b]	286 (13)	1139 (87)
1.HB[b]	77 (2)	86 (3)
2.XB[c]	72 (2)	53 (1)
2.HB[c]	4.0 (0.3)	3.0 (0.3)
3.XB[b]	312 (21)	1024 (15)
3.HB[b]	94 (3)	100 (3)

[a] 1 : 1 stoichiometric association constants were calculated from ^{1}H NMR titrations at 298 K using the WinEQNMR2 software[31] by monitoring the following protons: **1.XB** and **1.HB** – the internal aromatic proton H_a was monitored; **2.HB** and **3.HB** – triazole and triazolium protons respectively (signals for ferrocene protons were not monitored for **2.HB** and **3.HB** as their perturbations were too small for reliable association constants to be obtained); **2.XB** and **3.XB** – ferrocene proton H_g. Anions were added as their TBA salts. Errors (±) are given in parentheses and are >10%. [b] Titrations were performed in 9 : 1 CD_3CN/D_2O. [c] Titrations were performed in pure CD_3CN as no binding was observed in the presence of water.

While ^{1}H NMR titrations showed that the dicationic receptors **3.XB** and **3.HB** bound both chloride and bromide in 9 : 1 acetonitrile–D_2O, no binding was observed for the neutral receptors **2.XB** and **2.HB** in this solvent mixture. Hence, the titrations for the neutral receptors were performed in pure acetonitrile instead.§ For all 1,1′-substituted ferrocene receptors (**2.XB**, **2.HB**, **3.XB** and **3.HB**), addition of halides caused a downfield signal shift of the ferrocene protons immediately adjacent to the triazole/triazolium moieties (H_g in Fig. 2B) and an upfield shift of H_h. This was clearly indicative that effective electronic communication of anion binding to the ferrocene moieties was occurring. Interestingly, despite the rotary flexibility of the 1,1′-substituted ferrocene motif,[32] no desymmetrisation of the ^{1}H NMR spectra were observed upon halide titration, suggesting that the halide was bound in a cooperative fashion between both triazole/triazolium moieties of each receptor (Fig. 2B). Once again, the XB receptors bound halides much more strongly than their HB analogues. However notably, a reversal of halide binding preference was observed in the aqueous solvent mixture (Table 1). In acetonitrile, the neutral receptor **2.XB** showed a slight preference for chloride binding over bromide, due to the higher charge density of the former guest. However in the presence of water, a distinct preference for bromide was observed for **3.XB** over chloride, presumably arising from Hofmeister bias where the relatively more charge-diffuse bromide anion is more poorly hydrated.[33]

The electrochemical anion sensing properties of the ferrocene-appended receptors were studied by cyclic voltammetry (CV) in an acetonitrile electrolyte solution of 0.1 M $TBAPF_6$ with a $Ag/AgNO_3$ reference electrode.[34]

Receptors **1.XB**, **1.HB**, **2.XB** and **2.HB** displayed electrochemical quasi-reversibility of the respective ferrocene/ferrocenium redox couple (see ESI†) with $E_{1/2}$ values of 260, 250, 220 and 160 mV respectively relative to the $Ag/AgNO_3$ electrode in acetonitrile. Both **1.XB** and **2.XB** exhibited more anodic $E_{1/2}$ values compared to their HB analogues, consistent with the electron-withdrawing nature of the iodine atoms thermodynamically disfavouring oxidation of the coupled ferrocene unit. Surprisingly, receptors **3.XB** and **3.HB** did not show any evidence of electrochemical oxidation across the entire potential window accessible in the electrolyte solution (see ESI†). This could be attributed to the cationic triazolium groups attached directly to the ferrocene units, causing their oxidation to be so highly disfavoured that their oxidation potentials lie beyond the accessible solvent potential window.

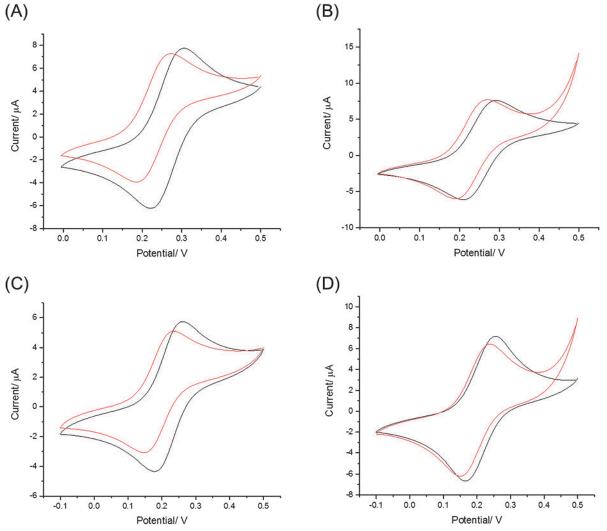


Fig. 3 CVs of (A) **1.XB** with TBACl; (B) **1.XB** with TBABr; (C) **2.XB** with TBACl and (D) **2.XB** with TBABr. In all spectra, the CVs in the presence of 0 and 10 equivalents of halide are represented by the black and red curves respectively (potentials compared to the $Ag/AgNO_3$ reference electrode).

Upon addition of chloride and bromide, cathodic perturbations of the respective ferrocene/ferrocenium redox couples were observed for the electrochemically-active receptors (Fig. 3).¶ As noted previously with HB ferrocene-based receptors in general, this arises from halide anion binding stabilising the ferrocenium oxidation state.[13] In acetonitrile, chloride elicited a larger cathodic shift than bromide in all cases, due to the fact that bromide is more charge-diffuse (Table 2). Most importantly, the XB receptors exhibited significantly larger magnitudes of cathodic shifts in comparison to the HB analogues. For example with **2.XB**, chloride and bromide exhibited cathodic shift values of 30 mV and 18 mV respectively, compared with **2.HB** displaying a small cathodic perturbation of only 6 mV with chloride and no response at all on addition of bromide. Due to the extensive aromatic conjugation of the receptors, a through-bond mechanism is likely to account for the communication between the anion binding site

Table 2 Cathodic shifts of the ferrocene/ferrocenium redox couples ($\Delta E_{1/2}$/mV) of redox-active receptors upon addition of 10 equivalents of chloride and bromide in dry acetonitrile[a]

	$\Delta E_{1/2}$/mV[b]	
	Cl^-	Br^-
1.XB	−32	−19
1.HB	−17	−11
2.XB	−30	−18
2.HB	−6	0

[a] Anions were added as their TBA salts, T = 293 K. Electrolyte: 0.1 M $TBAPF_6$ in dry acetonitrile. [b] Error estimated to be ±5 mV.

and the ferrocene unit.[13] As evidenced from X-ray Absorption Spectroscopy (XAS) investigations,[24] the significant contribution of covalency exhibited by halogen bonding-halide interactions in acyclic and catenane XB receptors may also be responsible for the enhanced cathodic shift magnitudes observed with the present XB ferrocene receptors.

In order to investigate the effects of water on the redox sensing capabilities of the XB receptors for chloride and bromide, analogous CV experiments were undertaken in a 9 : 1 acetonitrile–water mixture with 0.1 M $TBAPF_6$ electrolyte. Although no redox response was observed with the neutral receptors **2.XB** and **2.HB** in this aqueous solvent mixture, the dicationic halogen bonding receptor **1.XB** was capable of sensing the halides *via* modest cathodic shifts of 12 mV and 15 mV for chloride and bromide anions respectively. In comparison, the hydrogen bonding dicationic receptor **1.HB** displays a smaller cathodic perturbation of only 6 mV for both halides, reflecting the weaker binding of **1.HB** with chloride and bromide in the presence of water compared to **1.XB** as shown in Table 1.

In conclusion, we have synthesised the first redox-active XB anion receptors, and demonstrated that they are capable of electrochemically sensing chloride and bromide in both acetonitrile and aqueous–acetonitrile solvent media. Most importantly, in all cases, XB enhanced the recognition and sensitivity of halide electrochemical sensing as compared with HB, as manifested by significantly larger cathodic $\Delta E_{1/2}$ perturbations of the respective receptor's ferrocene/ferrocenium redox couple. The application of XB to electrochemical analyte sensing and in device fabrication is continuing in our laboratories.

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Notes and references

‡ The binding of iodide was not investigated by ^{1}H NMR titrations as it is not possible to perform electrochemical anion titrations with the anion due to its low oxidation potential.

§ Dicationic receptor **3.XB** exhibited very strong binding with chloride and bromide in pure acetonitrile ($K_a > 10^4$ M^{-1}).

¶ The addition of increasing equivalents of TBA fluoride, dihydrogen phosphate and sulphate salts to acetonitrile solutions of the receptors led to a gradual loss of electrochemical reversibility (see ESI†). The disappearance of both the oxidation and reduction waves suggested that an EC process was taking place. A similar loss of reversibility in the presence of these anions was also noted for HB ferrocene-appended isophthalamide receptors.[35]

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