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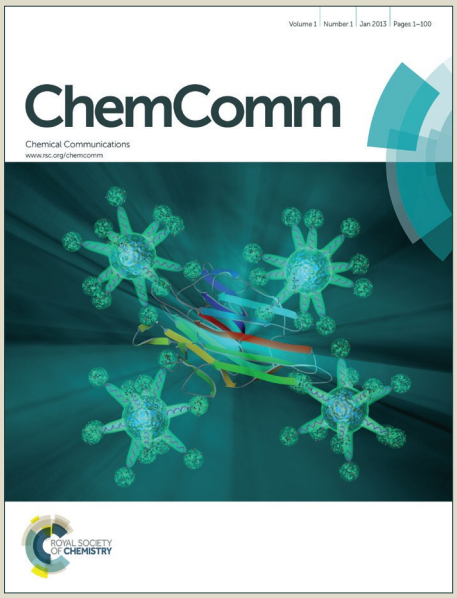

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Enhancing the enantioselective recognition and sensing of chiral anions by halogen bonding ++

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Chiral halogen bonding (*S*)-BINOL based receptors are demonstrated to enhance the enantioselective recognition and sensing of chiral anions compared to their hydrogen bonding analogues. Computational studies attribute this behaviour to the strict linearity of halogen bonding (XB) and steric environment conferred by the XB donor groups bridged by the (*S*)-BINOL motif.

A chiral receptor molecule's ability to selectively recognise one enantiomer of a chiral guest species over the other is a fundamental process of nature. Enantioselective anion binding processes dictate many important biological roles, as different enantiomers often possess contrasting biological activities.[1] A wide range of chiral anions exist in nature, including the α-amino carboxylate anions which function as neurotransmitters and metabolates.[2] In order to understand the subtle processes driving enantioselectivity, theoretical frameworks such as the three-point attachment model[3] and the more recent stereocentre recognition model[4] have been proposed. In these models, supramolecular interactions between the chiral host and anion, which include hydrogen bonding (HB), metal coordination, π–π stacking, electrostatics and even steric repulsions, act in tandem to preferentially bind the anion enantiomer capable of forming the energetically most stable host-guest diastereomeric complex. Although these principles have guided the design and synthesis of artificial chiral receptors in recent years, only modest enantioselectivity has been achieved so far.[5] Nevertheless, these chiral anion receptors have already found diverse applications ranging from analyte sensing[5b, 6] to asymmetric catalysis.[7] With the objective of enhancing enantiodiscrimination, we investigate herein the unprecedented use of halogen bonding (XB) as a tool for solution-phase enantioselective anion recognition.

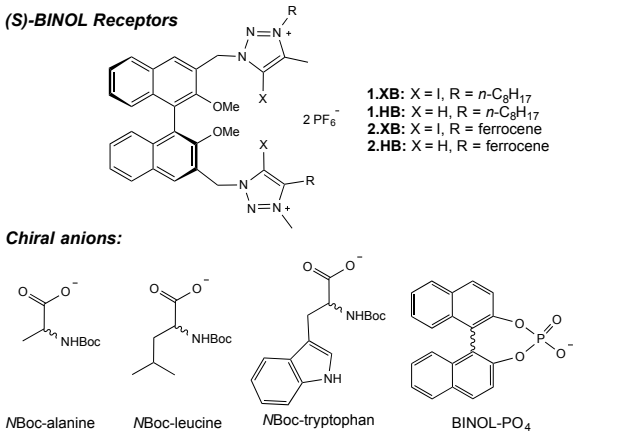

Fig. 1. Structures of the (*S*)-BINOL receptors **1.XB**, **1.HB**, **2.XB** and **2.HB**, as well as the chiral anions used in this study.

Arising from the attractive non-covalent interaction between the electron-deficient σ-hole of a polarised halogen atom and a Lewis-base, XB has been demonstrated to exhibit a degree of covalency comparable to that of transition metal complexes.[8] As a result, receptors containing XB-donor groups have showed remarkable enhancements in the binding of iodide,[9] perrhenate[10] and acetate[8] compared to their HB analogues. In addition, the steric bulk of the XB donor halogen atom constituting the anion binding site, coupled with its stringent requirements of linearity, makes XB a prime candidate for enhancing the enantioselectivity of chiral anion recognition, a process which is fundamentally governed by the geometry of host-guest supramolecular interactions and their relative three-dimensional spatial arrangements. We have thus prepared novel dicationic XB chiral host molecules that contain the (*S*)-1,1'-bi-2-naphthol (BINOL) motif (Fig. 1). Importantly, by simply replacing the hydrogen atoms of the anion-binding triazolium units with iodine, significant improvements in the extent of chiral discrimination between anionic enantiomeric species were achieved. Furthermore, building on earlier work by Tucker and co-workers on redox chiral anion sensing,[11] we have appended ferrocene, as a redox-active reporter group, to the iodotriazolium anion binding units of the BINOL-derived

++ *Dedicated to the memory of Professor Roger J. Mortimer (1956-2015).*

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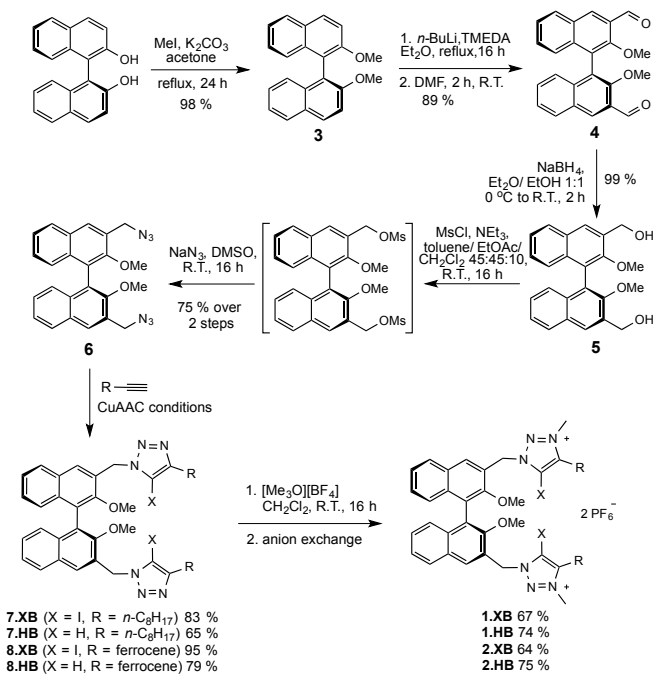
receptor to demonstrate, for the first time, the XB-mediated electrochemical redox discrimination of chiral anions.

The synthetic route undertaken for the construction of the chiral XB and HB (*S*)-BINOL receptors is shown in Scheme 1. 3,3'-Bis-aldehyde functionalisation of methoxy-protected (*S*)-BINOL[†] **3** was achieved by *ortho*-lithiation using tetramethylethylenediamine (TMEDA) and *n*-butyllithium, followed by reaction with *N,N*-dimethylformamide.[12] Reduction of bis-aldehyde **4** with sodium borohydride afforded the bis-primary alcohol **5** in near-quantitative yield. Reaction of **5** with methanesulfonyl chloride, followed by azide substitution using sodium azide gave the bis-azide (*S*)-BINOL synthon **6**. The bis(iodotriazole)-containing receptor precursors **7.XB** and **8.XB** were prepared directly from **6** using a one-pot copper(I)-catalysed azide-alkyne cycloaddition (CuAAC) protocol[13] with two equivalents of the appropriate terminal alkyne. Bis-methylation using trimethyloxonium tetrafluoroborate, followed by anion exchange with hexafluorophosphate-loaded Amberlite™ resin afforded the dicationic chiral receptors **1.XB** and **2.XB** in yields of 67 % and 64 % respectively. An analogous procedure involving standard 'proto-Click' conditions was undertaken to prepare **1.HB** and **2.HB.**



Scheme 1. Synthesis of dicationic (*S*)-BINOL receptors.

The solution-phase chiral anion recognition properties of the chiral receptors were investigated using ^{1}H NMR titration experiments where increasing quantities of chiral anions (Fig. 1), as tetrabutylammonium (TBA) salts, were added to a solution of the receptor in acetonitrile-water 99:1. In addition to amino acid derivatives, the enantioselectivity of the receptors towards chiral BINOL-derived phosphates, which have diverse applications in asymmetric catalysis,[14] was investigated as well. Interestingly, with receptors **1.XB** and **1.HB**, ^{1}H NMR titration experiments revealed that addition of a chiral anion influenced the proton shift perturbations of the BINOL core differently. For instance, addition of *N*Boc-(*S*)-leucine to **1.XB** led to downfield shifts of the signal corresponding to H_e, whereas H_a undergoes a slight upfield shift (Fig. 2)[§]. In contrast, the H_a and prototriazole H_f signals of **1.HB** were shifted downfield slightly in the presence of the same chiral anion, while H_e showed negligible movement throughout the titration experiment. Using a 1:1 stoichiometric host-guest binding model, non-linear regression analysis of the ^{1}H NMR titration data using the WinEQNMR2 software[15] determined the association constants summarised in Table 1.

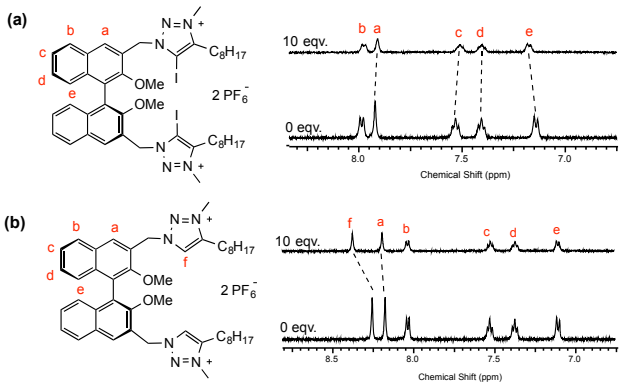


Fig. 2. Partial ^{1}H NMR spectra of receptors (a) **1.XB** (a) and (b) **1.HB** in the presence of 0 and 10 equivalents of TBA[*N*Boc-(*S*)-leucine] (500 MHz, CD_3CN/D_2O 99:1, T = 298 K).

Table 1. Anion association constants (K / M^{-1}) of receptors towards (*S*)- and (*R*)-enantiomers and their enantioselectivities (K_S/K_R).[a]

	1.XB			1.HB		
	K_S	K_R	K_S/K_R	K_S	K_R	K_S/K_R
*N*Boc- Ala	620 (25)	727 (56)	0.85 (0.07)	58 (1)	63 (2)	0.92 (0.03)
*N*Boc- Leu	680 (3)	1041 (60)	0.65 (0.05)	68 (3)	74 (4)	0.92 (0.06)
*N*Boc- Trp	1661 (72)	990 (82)	1.67 (0.16)	34 (3)	37 (3)	0.92 (0.11)
BINOL-PO_4	1394 (115)	924 (67)	1.51 (0.17)	92 (2)	89 (2)	1.03 (0.03)

[a] 1:1 stoichiometric association constants were calculated from ^{1}H NMR titration data in in CD_3CN/D_2O 99:1 at 298 K using the WinEQNMR2 software[15] by monitoring H_e for **1.XB** and H_f for **1.HB**. All anions were added as their TBA salts. Errors (±) are in parentheses.

As shown in Table 1, all chiral anions exhibited remarkably superior binding strength with **1.XB** than with **1.HB**, with more than an order of magnitude enhancement in association constant values observed in all cases. Most importantly, other than enhancing the strength of anion binding, the presence of XB donor groups on the receptor led to significantly improved enantioselectivity of chiral anions. From Table 1, **1.XB** gave selectivities of more than 1.5 times for one enantiomer over the other with the exception of *N*Boc-alanine. The degree of enantioselectivity displayed by **1.XB** was greater with chiral amino acid carboxylates containing bulkier R-group substituents: the sterically-bulky indole moiety of *N*Boc-tryptophan resulted in the largest selectivity of 1.7 times with preference for the (*S*)-enantiomer ($K_S > K_R$). On the other hand, the (*R*)-enantiomers of *N*Boc-alanine and *N*Boc-leucine were

preferentially bound to **1.XB** compared to the (*S*)-enantiomers. Interestingly, hydrogen bonding receptor **1.HB** showed almost no enantioselectivity with all the chiral anion pairs investigated.

Analogous ^{1}H NMR titrations performed on the bis-ferrocene functionalised receptor **2.XB** with *N*Boc-leucine in 99:1 acetonitrile-water revealed identical enantioselectivity (K_S/K_R = 0.70 ± 0.04) with **1.XB** (see ESI), demonstrating that the rigid ferrocene units at the receptor's termini influenced enantioselectivity negligibly. The electrochemical sensing properties of **2.XB** were studied by square-wave voltammetry (SWV) in a 0.1 M $TBAPF_6$ electrolyte solution in acetonitrile using a $Ag/AgNO_3$ reference electrode.[16] **2.XB** displayed redox quasi-reversibility of the ferrocene/ ferrocenium redox couple ($E_{1/2}$ = 0.425 mV)[#]. In the presence of the anion enantiomers[||], significant $E_{1/2}$ cathodic perturbations of the halogen bonding receptor's ferrocene/ ferrocenium redox couple were observed (see ESI). It is noteworthy that with *N*Boc-leucine and BINOL-PO_4 (Table 2), the stronger-binding enantiomer, as listed in Table 1, elicited the larger magnitude of cathodic shift, due to its greater stabilisation of the ferrocenium oxidation state. Importantly, the ratio of ΔE_S to ΔE_R is in good agreement with K_S/K_R (Table 1) within experimental error, underscoring the reliability of electrochemical anion sensing for chiral discrimination as well.

Table 2. Cathodic shifts of the ferrocene/ferrocenium redox couples (ΔE / mV) of **2.XB** upon addition of 5.0 equivalents of chiral anions in dry acetonitrile.[a]

	ΔE_S	ΔE_R	$\Delta E_S/\Delta E_R$ [b]
*N*Boc- Ala	-57	-63	0.90 (0.11)
*N*Boc- Leu	-55	-77	0.71 (0.08)
BINOL-PO_4	-55	-38	1.5 (0.2)

[a] Anions added as TBA salts, T = 293 K. Electrolyte: 0.1 M $TBAPF_6$ in dry acetonitrile. [b] Errors of $\Delta E_S/\Delta E_R$ calculated based on estimated measurement errors of ± 5 mV for ΔE values.

Further insights into the enantioselectivity of **1.XB** and **1.HB** towards the chiral anion guests were obtained through molecular dynamics (MD) simulations, followed by DFT calculations. MD simulations were carried out with **1.XB** complexes with the AMBER14 software suite[17] using the General Amber Force Field (GAFF)[18] parameters for the receptors **1.XB** and **1.HB**, and the *S* and *R* anion guests of *N*Boc amino acid derivatives and BINOL-PO_4. The two C–I···O putative halogen bonding interactions were described with the σ-hole of each iodine bonded to the triazolium binding moieties represented by a positively charged extra point[19] (computational details in ESI). Subsequently, the structures of the eight chiral complexes of **1.XB**, previously obtained by quenched MD (see ESI), were immersed in periodic cubic boxes composed of a mixture of CH_3CN/H_2O 99:1 (1426 and 42 molecules of CH_3CN and H_2O, respectively) with two PF_6^- and one TBA counter-ions. The dynamic behaviour of the diastereoisomeric complexes was ascertained through three independent MD runs of 100 ns each. The chirality of receptor **1.XB** was preserved throughout the whole simulation time, with the inter-annular C_{OMe}-C-C-C_{OMe} torsion angle ranging between 39.2 and 136.8°.

In these MD simulations, **1.XB** maintains with the chiral anionic substrates two convergent and highly-directional halogen bonds. However, significant aqueous solvation of the chiral guests' anionic O atoms (*via* HO–H···O_{anion} hydrogen bonds) and **1.XB**'s binding site was found, with the water molecules able to establish putative HB (HO–H···I) and XB interactions (C-I···OH_2) with the iodine atoms of **1.XB**. This results in sporadic interruptions of the C-I···O_{anion} XB interactions and leads to an increase of the $I_{COM,host}$···$O_{COM,anion}$ distance (where $I_{COM,host}$ and $O_{COM,anion}$ are the centres of mass of **1.XB**'s binding units and of the anion's oxygen binding sites, respectively, as defined in ESI Section S5.1). In addition, in the complexes with the *N*Boc-tryptophan enantiomers, a triazolium ring of **1.XB** and the indole moiety of the amino acid derivative adopt, along several ns simulation periods, approximately parallel dispositions, consistent with the existence of sporadic π–π stacking interactions (ESI Video S1). This result indicates that these interactions may enhance the enantioselectivity of **1.XB** for *N*Boc-(*S*)-tryptophan, in line with the ^{1}H NMR binding data.

The binding strength ($\Delta\Delta E_{bind(S,R)}$) of **1.XB** towards the chiral anion enantiomers can be estimated using the equation:

$$\Delta\Delta E_{bind(S,R)} = \langle E\rangle_{complex,S} - \langle E\rangle_{complex,R}$$

where $\langle E\rangle_{complex,X}$ represents the average molecular mechanics (MM) energy of the solvated diastereoisomeric complexes, directly obtained from the MD simulations. This energy difference corresponds to the relative binding enthalpy of the anion enantiomers and also takes into account the interactions with the solvent molecules. Significantly, the $\Delta\Delta E_{bind(S,R)}$ energy differences (see Table S5-1) are entirely consistent with ^{1}H NMR binding data as evident by the linear fitting with R^2 = 0.99 obtained when the K_s/K_R ratios are plotted against the $\Delta\Delta E_{bind(S,R)}$ values (Fig. S5-5). Furthermore, the van der Waals (vdW) energy difference between *S* and *R* enantiomers $\Delta\Delta E_{vdW(S,R)}$ follow the same trend of $\Delta\Delta E_{bind(S,R)}$, with a roughly linear relationship, suggesting that differences in the steric interactions between **1.XB** and the chiral anions play a role in anion binding enantioselectivity.

As the MD simulations with **1.HB** resulted in water-assisted host-guest decomplexation (data not shown), the relative anion binding strengths of **1.HB** and **1.XB** were compared through DFT calculations at the M06-2X theory level (see ESI, Sections S6.2 and S6.9). The optimised structures of **1.XB** and **1.HB** complexes with *N*Boc-(*S*)-tryptophan enantiomers are shown in Fig. 3, while the structures of all complexes are presented in Figs. S5-6 (**1.XB**) and S5-7 (**1.HB**). For both enantiomers of *N*Boc-tryptophan, additional π–π interactions were also observed between the indole ring and the triazolium units of either receptor, in agreement with the earlier MD simulation results for the **1.XB**'s complexes.

The distribution of the electrostatic potential (V_S) of both chiral free receptors was calculated and mapped onto their electron density surfaces, (ESI, Fig S5-8, Section S6.9). **1.XB** presents two highly positive values ($V_{S,max}$) of 612 and 606 kJ/mol in front of each C-I binding unit. The V_S computed for **1.HB** also has two $V_{S,max}$, of 638 and 616 kJ/mol, close to the C–H binding units. The regions of high V_S on **1.XB**

are localised mainly at the σ-hole positions on the iodine atoms, while those for **1.HB** are much broader, spreading across the binding sites. Indeed, the C–I···O angles in **1.XB** complexes, ranging from 169.3 to 177.7°, show that the XB interactions are highly directional, while the C–H···O angles in the complexes of **1.HB**, varying between 101.5 and 167.9°, deviate significantly from linearity (see ESI Table S5-2). These important differences in directionality between XB and HB may account for the enhanced enantioselectivity shown by **1.XB** over **1.HB**.

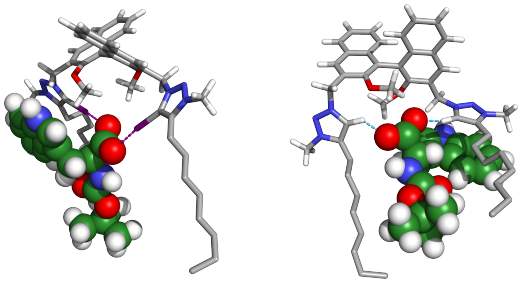


Fig. 3. DFT optimised structures for complexes of *N*Boc-(*S*)-tryptophan with **1.XB** (left) and **1.HB** (right). The XB and HB interactions are depicted as purple and light blue dashed lines, respectively.

The degree of covalency of the XB and HB interactions with the anions was assessed using Wiberg Bond Indices (WBI, see ESI, Table S5-3 and Section S6.9). The WBI values for the XB interactions range between 0.24 and 0.33, while for the HB ones these values are much lower, from 0.03 to 0.07. The linearity of the XB interactions, along with a high degree of covalency, leads to a higher binding affinity of **1.XB** towards the chiral oxoanions when compared with **1.HB**.

In conclusion, the first chiral XB receptors were synthesised and shown to significantly enhance enantioselective anion binding and electrochemical sensing behaviour compared to their protic analogues. Computational modelling indicates that the strict linearity of XB and host-guest steric interactions play dominant roles in the enhanced chiral recognition behaviour. The exploitation of halogen bonding for chiral recognition and analyte sensing is continuing in our laboratories.

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Notes and references

† Methoxy-protected BINOL receptors were used for this study as preliminary binding studies using free BINOL-OH receptors resulted in deprotonation upon addition of basic carboxylate anions in MeCN/H_2O 99:1.

§ The assignment of the aromatic proton signals of the BINOL core was performed using 1D NOESY experiments (ESI).

2.HB showed poor electrochemical reversibility which negated chiral anion sensing experiments being undertaken (see ESI).

|| No reliable electrochemical data could be obtained for *N*Boc-tryptophan due to oxidation of the indole motif.[20]

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