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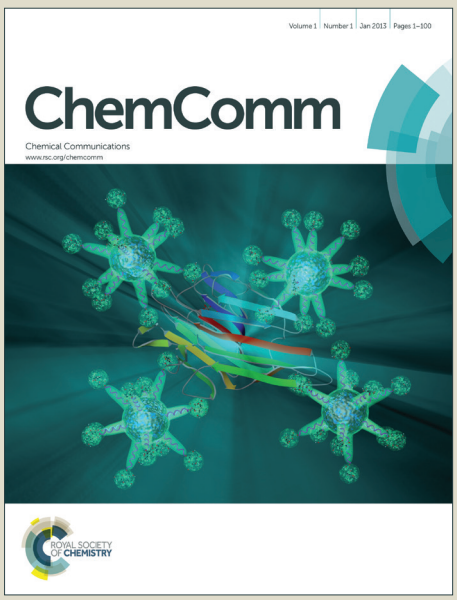

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Halogen Bonding Assisted Selective Removal of Bromide

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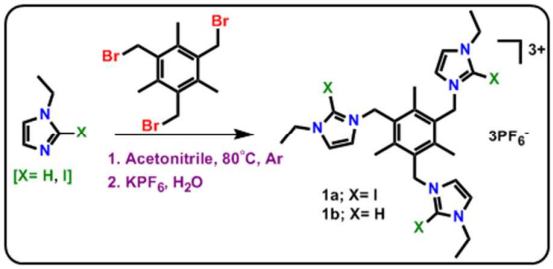
A new benzene platform based tripodal halogen bond (XB) donor receptor, 1a has shown selectivity towards bromide over chloride and other interferring anions. Importantly, bromide selectivity of 1a has been utilized towards the selective removal of bromide (complex 1) from a mixture of interfering anions *via* competitive crystallization process.

Anion coordination chemistry is largely dominated by hydrogen bonding (HB) interactions for over the years.[1-4] However, halogen bonding (XB) is an emerging new genre in the area of supramolecular chemistry and also in designing anion receptors.[5-14] In brief, halogen bonding (XB) is termed as a directional non-covalent attractive interaction between an electrophilic halogen atom and a Lewis base.[10, 11, 15] The positive electrostatic potential is developed due to dislocation of electron density *via* formation of carbon-halogen (C-X) bond. The electron density distributions around these atoms are anisotropic in nature and thus electropositive region exists in the extension of halo-carbon bond which is termed as σ- hole. Strength of halogen bonding depends on the polarizability of the halogen attached to the receptor. Hence C-I bond is found to be more polarizable over C-Br bond. Recently, halogen bonding is utilized for specific anion recognition, despite of XB's diversified implementation towards molecular recognition,[16-22] crystal engineering,[13, 23-26] non-covalent organo-catalysis,[27-29] anion transport[30, 31] and interlocked molecule formation.[32-35] One of the initial reports of anion recognition by halogen bonding interaction is reported by Resnati *et al.* which represents formation of interpenetrated net *via* $I^-\cdots$I-perfluorocarbon interaction[36] and later on recognition of alkali halide with a hetero-ditopic neutral receptor.[37] Till date, different XB motifs which become popular for anion recognition are; iodo-pentafluorobenzene,[18] iodoperfluoroarene,[38, 39] 5-iodo-1,2,3-triazole[40, 41] and 2-halo imidazoles.[42-45] Thus, both neutral and charged receptors are designed for anion recognition through XB. Importantly, Beer *et al.* have reported the first example of 2-halo imidazole substituted macrocyclic receptor for selective recognition of Br^- *via* halogen bonding in aqueous media.[42] It is important to mention that 5-iodo-1,2,3-triazole based multidentate receptor has been utilized for carbon-bromine bond activation[46] and *ortho* substituted iodoperfluoroarene based tripodal XB donors has shown selectivity towards halides.[38] Herein, we report a benzene scaffold based 2-iodo imidazole substituted tripodal XB donor receptor for selective recognition of bromide over chloride, iodide and other competitive anions both in solution as well as in solid states. Further, reversal of the selectivity trend is demonstrated by changing the receptor to its HB (2-H-imidazole) congener. High affinity of the XB donor (1-ethyl-2-iodo-imidazole) enables it to selectively crystallize bromide in presence of competitive anions. To the best of our knowledge, this represents the first example of selective removal of bromide from a solution of competitive anions through XB interactions.



Scheme 1 Synthetic strategy of **1a** & **1b**.

The bromide salt of benzene based tripodal XB (**1a**) & HB (**1b**) donor ligands are synthesized by slow addition of 1-ethyl 2-iodo imidazole and 1-ethyl imidazole respectively into the solution of 1,3,5-tris(bromomethyl)-2,4,6-trimethylbenzene in acetonitrile (ACN) at 80°C for 24 h under argon atmosphere (Scheme 1). Then the solution is evaporated to dryness and the dry mass is dissolved in water. Addition of excess aqueous KPF_6 solution results the precipitation of PF_6 salt as colorless solid which are filtered and dried in vacuum to obtain **1a** (XB donor, yield 72%) and **1b** (HB donor, yield 90%) as analytically pure products.

ITC studies are carried out with **1a** and **1b** in dry acetonitrile at 298K. Tetra-butyl-ammonium salts of corresponding guest anions

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Electronic Supplementary Information (ESI) available: [Synthesis & characterization data, crystallographic tables, bonding parameters of complexes 1, 2, 3, ITC & NMR titration profiles and details, SEM-EDX images. CCDC numbers, 1049817 (complex 1), 1049818 (complex 2), 1049819 (complex 3)]. See DOI: 10.1039/x0xx00000x

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Host	Guest	Stoichio-metry	Association constants (K, M^{-1})	ΔH (kJ/mol)	T*ΔS (kJ/mol)	ΔG (kJ/mol)
1a	Chloride	1:3	K1= $6.00*10^4$ K2= $9.43*10^3$ K3= $9.55*10^2$ β= $(5.40 \pm 0.4)*10^{11}$	ΔH1 = -6.9 ΔH2 = -14.6 ΔH3 = -6.0	T*ΔS1 = 20.4 T*ΔS2 = 8.1 T*ΔS3 = 11.0	ΔG1 = -27.3 ΔG2 = -22.7 ΔG3 = -17.0
1a	Bromide	1:3	K1= $5.93*10^5$ K2= $1.61*10^4$ K3= $1.16*10^3$ β= $(1.11 \pm 0.08)*10^{13}$	ΔH1 = -6.5 ΔH2 = -8.0 ΔH3 = -12.8	T*ΔS1 = 26.4 T*ΔS2 = 15.9 T*ΔS3 = 4.6	ΔG1 = -32.9 ΔG2 = -23.9 ΔG3 = -17.5
1a	Iodide	1:3	K1= $5.41*10^4$ K2= $2.62*10^3$ K3= $7.51*10^1$ β= $(1.06 \pm 0.04)*10^{10}$	ΔH1 = -6.2 ΔH2 = -10.0 ΔH3 = -15.3	T*ΔS1 = 20.8 T*ΔS2 = 9.5 T*ΔS3 = -4.6	ΔG1 = -27.0 ΔG2 = -19.5 ΔG3 = -10.7
1b	Chloride	1:1	$1.37*10^5$	-4.8	24.6	-29.3
1b	Bromide	1:1	$3.35*10^4$	-2.5	23.3	-25.8

Table 1: Association constants (K1, K2 & K3) and ΔG values obtained from ITC titration experiments with TBACl, TBABr and TBAI with the **1a** and **1b** in dry ACN at 298K. β represents the overall thermodynamic formation constant whose unit is M^{-3}. The 1:1 stoichiometry data are fitted in one set of site model and 1:3 stoichiometry data are fitted in sequential sites model. The standard deviation of β is calculated with data from repetitive experiments.

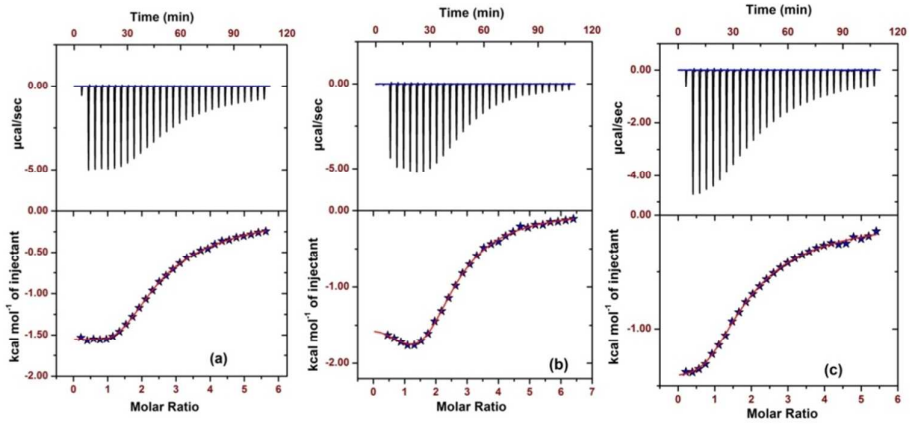

Fig. 1: ITC titration profiles of **1a** with (a) Br^-, (b) Cl^-, (c) I^-. Solvent; dry ACN at 298K.

are used for the calorimetric titration experiments. Details of the ITC experiments are mentioned in the ESI. In order to find out the proper fitting model for ITC data fitting, we have carried out ^{13}C-NMR titration studies with **1a** (27.90 mmol) and TBACl (399.5 mmol) in DMSO-d_6. Here we have monitored the down field shift of carbon atom attached to Iodine center. In **1a**, this iodine attached carbon is located at 101.32 ppm in DMSO-d_6 which is confirmed by ^1H-^{13}C HMBC, ^1H-^{13}C HSQC and DEPT-^{13}C spectroscopies (Fig. 3S – 5S, ESI). This carbon is found to shift 8.28 ppm after addition of 3.2 equivalents of TBACl and after that it is saturated. The anion equivalent plot of ^{13}C-NMR titration confirms the host: guest binding model as 1:3 (Fig. 16S – 17S, ESI).Thus we have chosen 1:3 stoichiometry (sequential sites model, n = 3) for data fitting in ITC (Fig. 28S – 30S, ESI). However, one set of site model to fit the ITC data resulted poor fitting (Fig. 33S - 35S, ESI). The 1:3 binding stoichiometry indicates the cleft binding of guests. Table 1 shown preference towards Br^- (K1 = $5.93*10^5$ M^{-1}) over Cl^- (K1 = $6.00*10^4$ M^{-1}) and I^- (K1 = $5.41*10^4$ M^{-1}). Also, the overall thermodynamic stability constant (β) of Br^- (β = $1.11*10^{13}$ M^{-3}) is found to be much higher compared to that of Cl^- (β = $5.40*10^{11}$ M^{-3}) and I^- (β = $1.06*10^{10}$ M^{-3}) in case of **1a.** The binding of first guest (Cl^-/Br^-/I^-) to**1a** is always found to be entropy driven which indicates liberation

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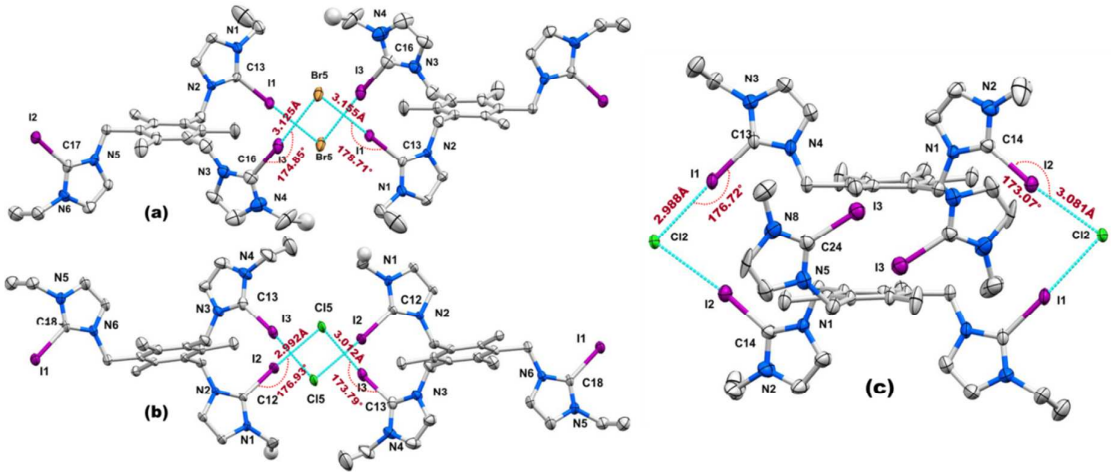

Fig. 2: Single crystal X-ray structures represent XB interactions in (a) complex **1**; (b) complex **2** and (c) complex **3**.

of more numbers of solvent molecules in the system. Hence, the T*ΔS1 value is found to be much higher compared to that of T*ΔS2 and T*ΔS3 in all the cases. It is evident from ITC studies that selectivity order of **1a** is Br^- > Cl^- > I^-. We have also carried out ITC studies with **1b** and all the above anions but reliable data are only obtained in cases of Cl^- and Br^-. The binding of I^-, NO_3^- and AcO^- are found to be too weak to be reliably quantified by ITC studies. In case of **1b**, both Cl^- and Br^- have found to be binding the receptor in 1:1 stoichiometry (one set of site model). This means that the guest anions are capable enough to fit in the inner cavity of the receptor which is fenced by three arms. However, the binding constant of Cl^- (log K = 5.14, Fig. 32S, ESI) is found to be higher compared to that of Br^- (log K = 4.53, Fig. 31S, ESI). Binding of Cl^- and Br^- with **1b** are found to be exothermic as well as entropy driven with entropic contribution towards ΔG at 298K is found to be 24.6 kJ/mol and 23.3 kJ/mol for Cl^- and Br^- respectively. Thus, the 1:1 stoichiometry of binding of HB donor receptor **1b** is altered to 1:3 by introducing C-I bond instead of C-H in imidazole centers. This shows that alteration of substitution on imidazole scaffold from C-H (**1b**) to C-I (**1a**) enforces the selectivity from Cl^- to Br^-. Further ITC studies with the monodentate analogue of **1a**, i.e. **1c** is carried out where it shows slightly higher formation constant with Br^- ($2.66*10^3$ M^{-1}) compared to Cl^- ($2.12*10^3$ M^{-1}) and I^- ($1.49*10^3$ M^{-1}) (ESI, Fig. 41S- 46S, Table 4S). Thus, an order of magnitude higher K1 in **1a** with Br^- compared to Cl^- and I^- could be attributed to the conformation of **1a** in solution and its better interactions with Br^-.

^{1}H-NMR titration studies have also been employed to investigate the binding affinity of **1b** towards halides and other relevant anions in ACN-d_3 at 298K. Qualitative ^{1}H-NMR study of **1b** has shown shift of acidic imidazole proton with gradual addition of different guest anions (Cl^-, Br^-, I^-, CH_3COO^- and NO_3^-). Like that of ITC, the stoichiometry of binding in ^{1}H-NMR titration is found to be 1:1

Ligand	Anions	Association constants (log K)	ΔG (kJ/mol)
1b	Cl^-	4.68	-26.7
	Br^-	3.87	-22.1
	I^-	2.90	-16.5
	NO_3^-	2.87	-16.4
	AcO^-	3.43	-19.6

Table 2: Association constants obtained from ^{1}H-NMR titrations of **1b** with anionic guests. The titrations were carried out in ACN-d_3 at 298K.

(host: guest) in all the cases which is evident from anion equivalents plots (Fig. 18S - 23S, ESI). F^-, HSO_4^- and $H_2PO_4^-$ have exhibited precipitation of the receptor-anion adduct after addition of only 0.25 equivalent of guests. Association constants with different anions are calculated in 1:1 model by monitoring the downfield shift of H_a proton using WINEQNMR2.[47] In case of **1b**, Cl^- has shown highest stability constant (logK = 4.68) with down field shift of H_a proton up to 1.87 ppm (Fig. 18S). The stability constant (log K) of Br^- with **1b** is found to be 3.87 with down field shift up to 1.54 ppm (Fig. 19S). Other anions, I^-, AcO^- and NO_3^- have comparatively lower binding affinity with respect to Cl^- and Br^-. Details of the binding constant values are tabulated in Table 2. By means of ^{1}H-NMR titration studies it is evident that **1b** has selectivity towards Cl^- with a selectivity order of Cl^- > Br^- > AcO^- > I^- ~ NO_3^-. Thus, ^{1}H-NMR titrations and ITC studies both have indicated selectivity of **1b** towards Cl^- over Br^- with 1:1 binding stoichiometry. In case of **1a**, protons have not shifted with gradual addition of TBABr and TBAI. Even the shift of these protons with gradual addition of TBACl is insignificant (Fig. 24S – 25S, ESI).

Host-guest complex formation through XB in solid state is evident in case of **1a** (Fig. 2) *via* the isolation of Br^- complex, **1** and Cl^- complex, **2**. Single crystals suitable for X-ray diffraction studies are obtained through concerted vapor diffusion and layering technique between DCM and DMF both in cases of complexes **1** (yield 75%) &

2 (yield 55%). The unit cell of complexes **1** and **2** contains one unit of **1a**, two halides (Br^- / Cl^-) and one PF_6^-unit. In **1**, one of the bromides (Br5) is halogen bonded to two C-I bonds (C13-I1 and C16-I3) and another bromide (Br4) is further halogen bonded to C17-I2 and such XB continues to form a two-dimensional infinite arrangement. Likewise the case of complex **1**, complex **2** also exhibits XB between C-I bonds (C12-I2 and C13-I3) and chloride (Cl5) center. Here also, the remaining Cl^- (Cl4) is further XB to C18-I1 to form a two-dimensional infinite arrangement. The average XB distances in complex **1** & **2** ranges from 2.92Å – 3.15Å and the angles range from 173° - 179° which match well with the parameters reported in literature. The XB distances are found to be strong as I···X distance ranges between 78% - 82% of the sum of the van der wall radii.[42] The XB distances in complex **2**, are found to be shorter compared to that of complex **1** due to the change of guest from Br^- and Cl^-. Fig. 2 & Table 1S summarize the XB bond angles and distances together.

The ITC studies reveal that **1a** has selectivity towards Br^- over other competing anions like, Cl^-, I^- in solution. This solution state selectivity is directly implemented in competitive crystallization in DCM/DMF binary solvent. We have found that in presence of competing guests like Cl^-, I^-, ReO_4^-, HSO_4^-, NO_3^- in solution, **1a** crystalize out Br^- selectively (yield 60%) *via* XB to form host-guest adduct, **1** which is confirmed by single crystal X-ray crystallographic and SEM- EDX studies (Table 3S & Fig. 40S, ESI). Furthermore, we wanted to check whether **1a** is capable to bind Br^- selectively in presence of various equivalence of Cl^- in the system (Table 3S). Results show gradual decrease in Br^- removal upon increasing equivalent of Cl^- into the system. Such type of competitive selectivity towards Br^- is not reported with synthetic anion receptor till date. Moreover, **1a** is also capable of removing Cl^- in presence of interfering anions except Br^- as complex **3** (Table 3S, batch 7, yield 35%) whose structural features are different from that of complex **2** (Fig. 2).

In conclusion, selective recognition of bromide in solution state through XB with receptor **1a** is observed which is established by ITC studies. ^{13}C- NMR titration study have also confirmed 1:3 host: guest binding stoichiometry. Solution state selectivity towards Br^- is further manifested in solid state, *via* selective removal of Br^- from solution of interfering anions and also in presence of up to 90% (weight equiv.) of Cl^-. **1a** has shown highest overall thermodynamic stability constant (β) in the order of 10^{13} (M^{-3}) with Br^- in acetonitrile. Further, selectivity reversal between HB donor receptor **1b** and XB donor receptor **1a** is also observed.

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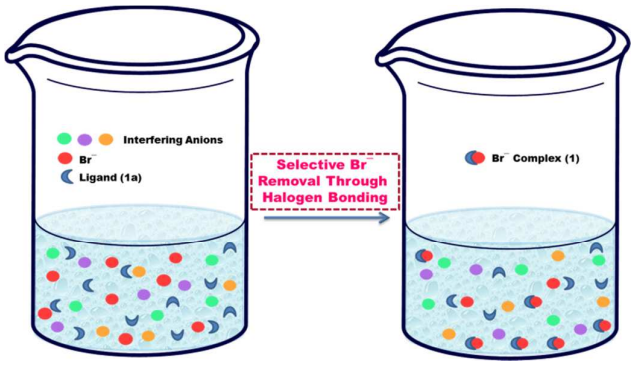

Selective removal of bromide from the mixture of competing anions through a XB donor receptor *via* halogen bonding interactions.