A Potent Halogen-Bonding Donor Motif for Anion Recognition and Anion Template Mechanical Bond Synthesis

Thanthapatra Bunchuay, Andrew Docker, Antonio J. Martinez−Martinez, and Paul D. Beer*

Dedicated to Professor Jean-Marie Lehn on the occasion of his 80th birthday

Abstract: *The covalent attachment of electron deficient perfluoroaryl substituents to a bis-iodotriazole pyridinium group produces a remarkably potent halogen bonding donor motif for anion recognition in aqueous media. Such a motif also establishes halogen bonding anion templation as a highly efficient method for constructing a mechanically interlocked molecule in unprecedented near quantitative yield. The resulting bis-perfluoroaryl substituted iodotriazole pyridinium axle containing halogen bonding [2]rotaxane host exhibits exceptionally strong halide binding affinities in competitive 50% water containing aqueous media, by a factor of at least three orders of magnitude greater in comparison to a hydrogen bonding rotaxane host analogue. These observations further champion and advance halogen bonding as a powerful tool for recognising anions in aqueous media.*

Originating from its exploitation in solid state crystal engineering and in materials design, halogen bonding (XB), the highly directional, attractive intermolecular non-covalent interaction between an electrophilic halogen atom and a neutral or charged Lewis base, has begun to emerge as a powerful complement to the ubiquitous hydrogen bonding (HB) interactions for solution phase applications in catalysis, medicinal chemistry, anion transport, and anion recognition.[1–6] Regarding the latter, we and others have demonstrated that XB hosts often display superior anion affinities and contrasting selectivities in comparison to HB host analogues.[7–11] However, examples of XB host systems that function in competitive aqueous media remain extremely rare due in part to the challenging syntheses of such systems.[12,13] This is especially the case with elaborate XB mechanically interlocked molecules (MIMs) which due to their unique topological three-dimensional and highly preorganised cavities are capable of aqueous anion recognition.[7,14,15] Herein we report a novel, remarkably potent electron deficient perfluoroaryl substituted bis-iodotriazole pyridinium XB donor motif (Figure 1a) which is demonstrated to dramatically increase the strength of XB—anion interactions for recognition in aqueous media and the efficacy for an unprecedented near quantitative high yielding XB MIM synthesis of a rotaxane **1·PF₆** (Figure 1b) using anion templation.

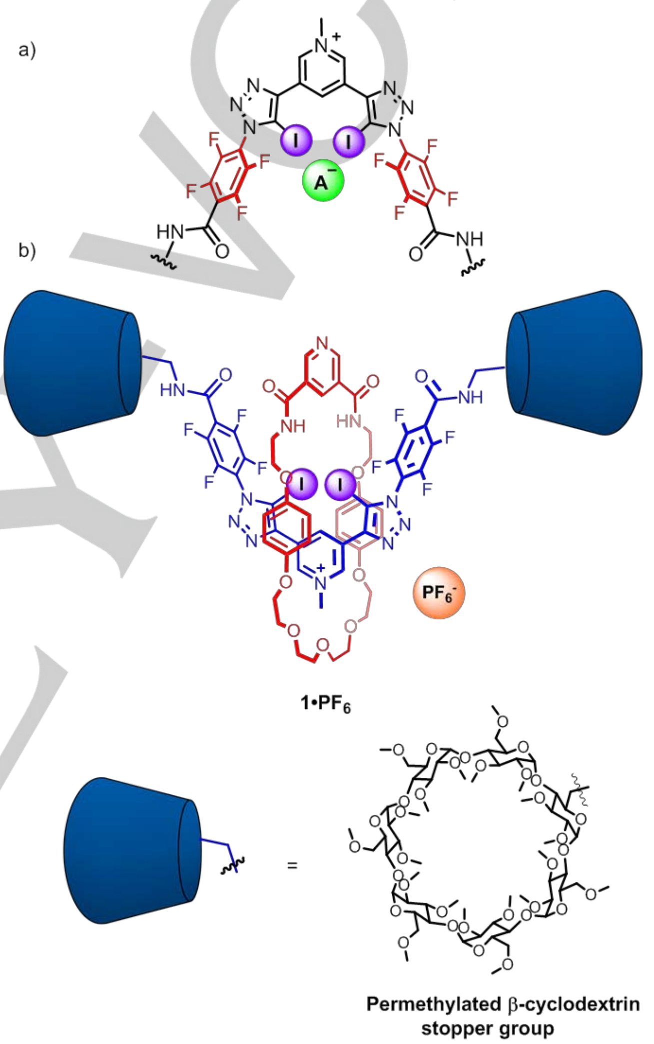

Figure 1. a) Electron deficient perfluoroaryl substituted bis-iodotriazole pyridinium XB donor motif and b) XB [2]rotaxane **1·PF₆**.

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In order to investigate whether XB halide anion binding potency could be tuned via the covalent attachment of suitable electron withdrawing substituents, the synthesis of a series of XB acyclic receptors consisting of a 3,5-bis-iodotriazole pyridinium motif functionalized with methylene linked benzylic and ester groups, and aryl linked benzene and perfluorinated benzene ester groups was undertaken initially. The monocationic pyridinium XB receptors **2·PF₆**, **3·PF₆**, **4·PF₆**, and **5·PF₆** (Figure 2) were prepared via copper(I)-catalysed azide-alkyne cycloaddition (CuAAC) reactions between appropriate azides and 3,5-diiodoethynylpyridine, subsequent methylation with iodomethane and anion exchange. (The synthetic details are described in the SI). The halide anion binding properties of the XB acyclic receptors, studied by ^{1}H-NMR titration experiments in d_6-DMSO, revealed chloride to form the strongest complexes correlating with halide charge density (Table 1).

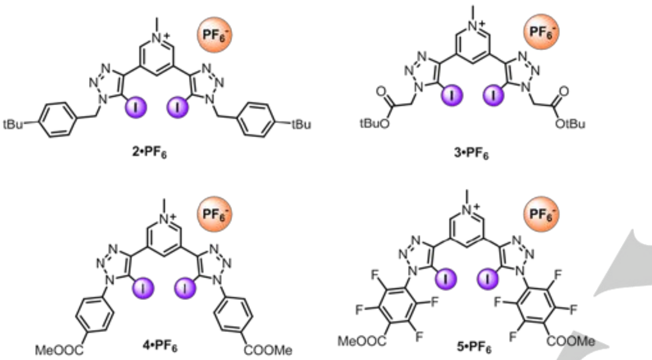


Figure 2. Structures of monocationic acyclic XB bis-iodotriazole pyridinium receptors as their hexafluorophosphate salts (PF_6^-).

It is noteworthy that the largest association constant magnitudes were observed with the perfluorinated arene functionalized receptor **5·PF₆** with all halides. This result highlights the inductive effect of the electron withdrawing perfluoroaryl spacer motifs polarising the iodine atoms of the bis-iodotriazole XB donor groups facilitating strong XB-anion interactions.

Table 1. Anion association constant (K_a/M^{-1}) acyclic pyridinium bis-iodotriazole receptors in d_6-DMSO.[a]

Anion[a]	**2·PF₆**[1]	**3·PF₆**	**4·PF₆**	**5·PF₆**
Cl^-	387	403	429	1395
Br^-	238	206	277	491
I^-	146	62	98	190

[a] Anions added as their TBA salts, values of K_a determined using the WinEQNMR2 software[16] using a 1:1 host-guest binding model; errors (±) less than 10%. d_6-DMSO, T = 298 K.

Single crystals suitable for X-ray diffraction studies were obtained for the halide salts **5·Cl** and **5·I**. In both structures the acyclic receptor adopts a close triazole–I conformation encapsulating the anion guest through strong halogen bond-halide interactions (Figure 3, see SI for CCDC) as indicated by triazole–I···X⁻ interatomic distances significantly shorter than the sum of the van der Waals radii (see Table 2).[17]

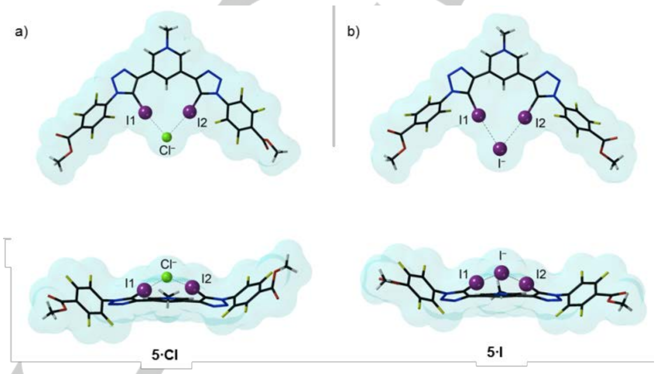


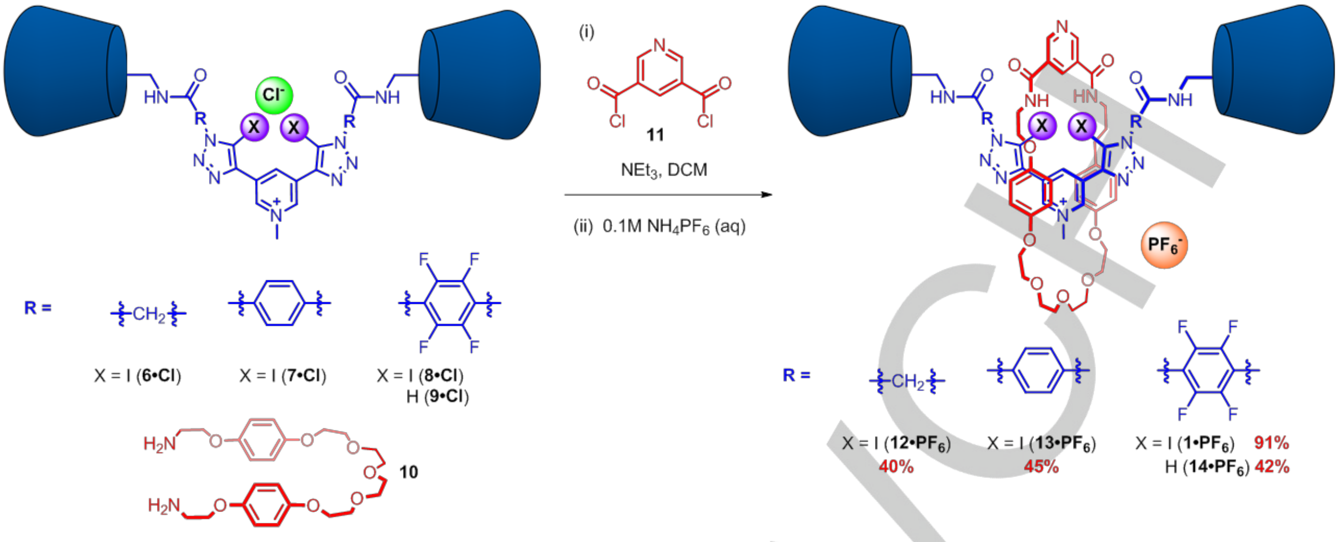
Figure 3. Structures of monocationic acyclic XB bis-iodotriazole pyridinium receptors **5⁺** as the; a) chloride and b) iodide salt.

Table 2. XB bond lengths and percentage shortening of the sum of the van der Waals radii (%VdW).[17]

Guest Anion	**interatomic distances (I···X⁻/Å)[a]**	**%vdW**
Cl^-	3.1419(6), 3.0079(6)	83%, 79%
I^-	3.4010(3), 3.3522(3)	81%, 80%

[a] Calculated errors given in parenthesis.

The XB donor bis-iodotriazole pyridinium structural motifs of the acyclic receptors were integrated into a bis-permethylated β-cyclodextrin stoppered axle component for respective XB [2]rotaxane construction using a chloride anion template amide condensation clipping rotaxanation reaction. Axles **6·Cl**, **7·Cl**, **8·Cl** were each stirred with an equimolar amount of bis-amine macrocycle precursor **10**[18] and NEt_3 in dry CH_2Cl_2 at 0ºC, whereupon addition of 3,5-bis-chlorocarbonyl pyridine **11** afforded, after purification by preparative thin layer silica gel chromatography and anion exchange to their PF_6^- salts, the target XB [2]rotaxanes **12·PF₆**, **13·PF₆** and **1·PF₆** in respective isolated yields of 40%, 45% and 91% (Scheme 1). In contrast, the combined effect of XB and perfluoroaryl group incorporation in effective rotaxane formation was further highlighted by a significantly lower 42% isolated yield of the HB rotaxane **14·PF₆**, obtained from using perfluoroaryl HB **9·Cl** axle as a template, compared to the 91% yield of XB rotaxane **1·PF₆**.



Scheme 1. [2]Rotaxane synthesis *via* chloride template amide condensation

Clearly the perfluorinated benzene functionalized XB axle **8·Cl** acts as the most efficient anion template for rotaxane synthesis as evidenced by the impressive 91% yield of [2]rotaxane **1·PF₆**. By contrast, the axles containing the non-fluorinated aromatic and alkyl spacers result in [2]rotaxane formation in the typical yield range for the anion template method of 40-60%.[7,15,18] Taking into account the chloride anion association constant data shown in Table 1, where the acyclic XB receptor **5·PF₆** by virtue of the electron-withdrawing perfluoroaryl spacer motifs forms the strongest association with chloride, there is an obvious correlation of chloride anion association strength with yield of rotaxane formation. Notably, the observed > 90% yield for the preparation of [2]rotaxane **1·PF₆** via this XB anion template clipping method matches the highest yields obtained for MIM formation using metal cation , π-donor-π-acceptor and hydrogen bond templates. [19–26]

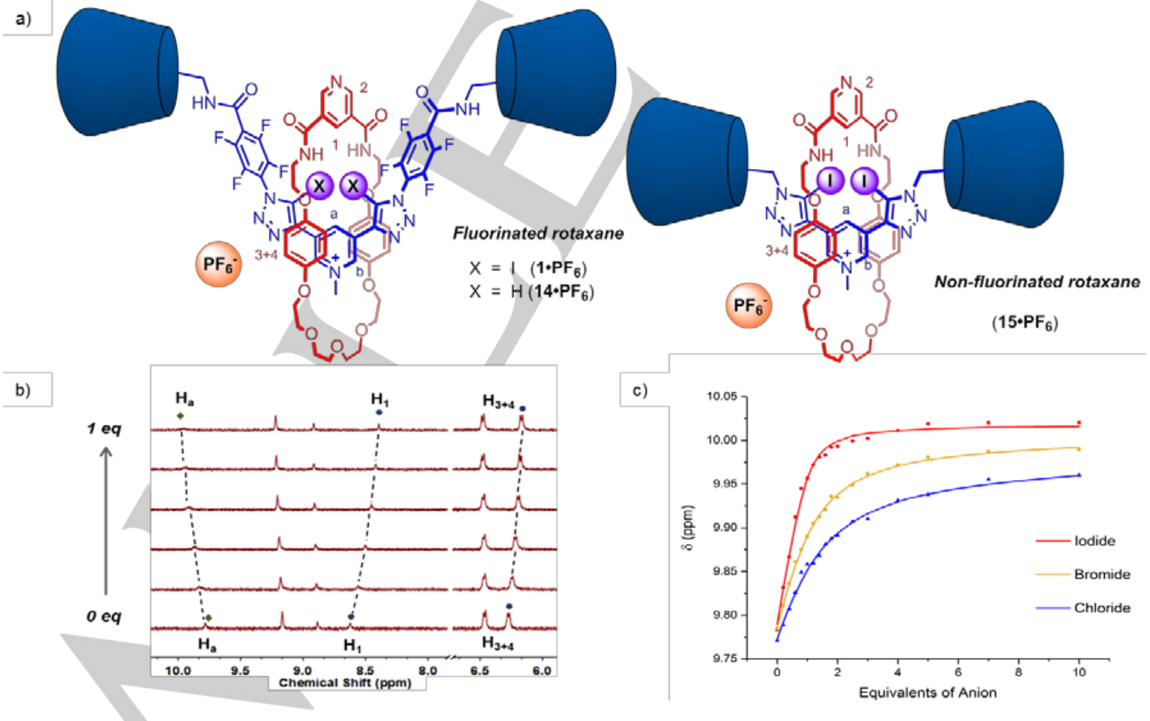


Figure 4 a) Perfluorinated and non-fluorinated [2]rotaxane host molecules b) Truncated ^{1}H-NMR of **1·PF₆** in D$_2$O:*d*$_6$-Acetone (1:1) upon addition of iodide anion as its TBA salt. c) Anion Binding isotherm of **1·PF₆**, [host] = 1mM and [guest] = 50 mM (500MHz, 298K).

Table 3. Anion association constant (K_a/M^{-1}) for acyclic and [2]rotaxane hosts in D_2O:d_6-Acetone (1:1).[a]

Entry	Receptors	K_a (M^{-1}) in 1:1 D_2O/d_6-Acetone		
		Chloride	**Bromide**	**Iodide**
Perfluorinated Hosts				
1	Monocationic XB Perfluoroaryl Rotaxane **$1\cdot PF_6$**	930	1727	$>10^5$
2	Monocationic HB Perfluoroaryl Rotaxane **$14\cdot PF_6$**	NB[b]	NB[b]	63
Non-fluorinated Hosts				
3	Monocationic XB Rotaxane **$15\cdot PF_6$**	150	436	1036

[a] Anions added as TBA salts, errors (±) less than 10%, 1:1 association constants calculated using WinEqNMR2 software,[2] monitoring the perturbation of the internal pyridinium proton H_a (500MHz, 298K). [b] NB =No binding.

The halide anion recognition properties of XB monocationic rotaxanes together with a HB rotaxane analogue and axle were investigated using ^{1}H-NMR titration experiments in D_2O:d_6-acetone (1:1). With all XB rotaxanes the addition of halide anion caused significant perturbations of interlocked cavity proton resonances (H_a and H_1) (Figure 5b). The downfield shift of the axle component internal pyridinium proton (H_a) and the upfield shift of the internal pyridine proton (H_1) from the macrocycle component were monitored as a function of equivalents of anion added (Figure 5c). WinEQNMR2 analysis of the titration data for both **$1\cdot PF_6$** and **$14\cdot PF_6$** revealed 1:1 stoichiometric association constants for halide anions (Table 3).

In the highly competitive 50% aqueous mixture, the halogen bonding rotaxane **$1\cdot PF_6$** displays remarkably strong binding for Cl^-, Br^-, and I^- anions. Indeed, the association constant for iodide binding is $>10^5$ M^{-1}, whilst those of bromide and chloride are 1727 M^{-1} and 930 M^{-1} (Table 3, Entry 1), respectively. This preferential binding to the larger and less highly hydrated halide anions is presumably governed by the Hofmeister series bias.[27–29] In contrast, the halide anion recognition strength of the hydrogen bonding rotaxane analogue **$14\cdot PF_6$**, where iodotriazole groups are substituted with C—H prototriazole motifs is dramatically diminished, demonstrating only very weak affinity to I^- and no binding for Cl^- and Br^- (Table 3, Entry 2). The remarkable enhancement of halide complexation by XB **$1\cdot PF_6$** rotaxane by at the very least three orders of magnitude in comparison to HB rotaxane **$14\cdot PF_6$** illustrates again the superiority of halogen bonding over hydrogen bonding in aqueous anion recognition.[7,9,12–15]

Finally, in an effort to elucidate the effect of incorporating the perfluoroaryl motif into the axle component of **$1\cdot PF_6$,** the halide anion binding properties of monocationic XB rotaxane **$15\cdot PF_6$** were determined (Table 3 Entry 3). As expected, **$1\cdot PF_6$** demonstrates notable enhancement of halide binding, with the strength of iodide complexation at least two orders of magnitude greater than **$15\cdot PF_6$** rotaxane (Table 3, Entry 1 and 3), which can be attributed to the rigid, electron deficient and hydrophobic nature of the perfluoroaryl substituents of the pyridinium bis-iodotriazole axle component of **$1\cdot PF_6$**, facilitating in particular the amplified potency of XB donor – halide anion interactions.

In conclusion, the covalent attachment of electron deficient perfluoroaryl substituents to a bis-iodotriazole pyridinium group produces a powerful halogen bonding donor motif capable of halide anion recognition in aqueous media. For the first time, a near quantitative isolated yield of a discrete anion template directed assembly of a MIM host structure is achieved via exceptionally strong XB donor—chloride interactions. Moreover, the chloride anion association strength of the axle component's XB donor motif correlates with rotaxane formation yield. Importantly, anion binding studies in competitive 50% water containing aqueous media reveal the monocationic XB rotaxane **$1\cdot PF_6$** to exhibit remarkable halide binding affinities at least three orders of magnitude greater than a HB rotaxane analogue. These observations provide further evidence for highlighting XB as a novel tool for achieving anion recognition in aqueous media.

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Keywords: Anion Recognition • Halogen Bonding • Rotaxanes • Supramolecular

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COMMUNICATION

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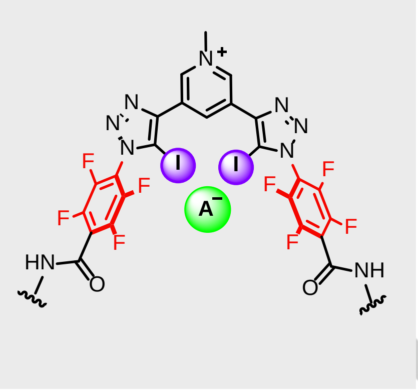

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