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Strong and Selective Halide Anion Binding by Neutral Halogen Bonding [2]Rotaxanes in Wet Organic Solvents

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Abstract: The design and construction of *neutral* interlocked host molecules for anion recognition are rare. Using an active-metal template approach, the preparation of a family of neutral halogen bonding rotaxanes containing two, three and four iodotriazole groups integrated into the macrocycle and axle components is achieved. In spite of the interlocked hosts' neutrality, such rotaxane systems are capable of binding halide anions strongly and selectively in wet organic solvent mixtures. Importantly, halide binding strength and selectivity can be modulated by varying the number and position of the halogen bond-donor iodotriazole groups within the interlocked cavity; the rotaxane containing the largest number of halogen bond donor groups exhibits the highest halide anion binding affinities. Through solvent medium percentage water content variation, neutral XB donor-mediated anion binding strength is also demonstrated to be highly sensitive to solvent polarity.

Introduction

Mechanically-interlocked molecules (MIM) such as rotaxanes and catenanes have progressed from compounds of aesthetic interest and curiosity to an active area of contemporary chemical research, with applications in nanotechnology,^[1–8] drug delivery,^[9–12] catalysis,^[13–15] materials science^[16–21] and molecular recognition^[22–25]. Amongst the supramolecular interactions which imbue interlocked host systems with their unique recognition properties for anion guest species, halogen bonding (XB), the highly-directional attractive non-covalent interaction between an electron-deficient halogen atom and a Lewis base,^[26,27] remains the least exploited. Rare examples of XB donor groups incorporated into the framework of MIMs have been demonstrated to dramatically augment anion binding affinities under highly-competitive aqueous conditions,^[28–30] as well as enhancing the anion binding induced shuttling behaviour in two-station rotaxanes^[31] compared to their hydrogen bonding (HB) analogues. Although these proof-of-concept studies have set the stage for further exploitation of XB MIMs, their often challenging construction^[32] necessitates the development of complementary synthetic methodologies.

Herein, utilising an active-metal template synthetic strategy, we report the synthesis and anion binding properties of a family of *neutral* [2]rotaxanes containing two, three and four XB-donor iodotriazole groups integrated into their macrocycle and axle components (Figure 1). By varying the positions and number of convergent XB donor iodotriazole units within the interlocked anion binding cavity, notable differences in anion binding

affinities and selectivity trends are observed. Importantly, even without the benefit of Coulombic attractions these neutral XB rotaxanes are capable of strong and selective halide anion binding in wet organic solvents containing up to 5 % water by volume.

Results and Discussion

Synthesis of neutral XB [2]rotaxanes

An active metal template approach was used to prepare the neutral XB [2]rotaxanes, where a metal catalyst coordinated endotopically within the cavity of a XB macrocycle forms a covalent bond from appropriately functionalised half-axle components through the macrocycle itself.^[33] This protocol has previously allowed a plethora of MIMs, including molecular knots,^[34] [2]catenanes,^[35,36] [2]-^[37–42] and higher-order rotaxanes^[43–46], to be synthesized with impressive facility and yields. By exploiting the endo/exo-conformational flexibility of a bis-iodotriazole-containing macrocycle component, we recently adapted the active metal template methodology to construct an anion binding XB rotaxane host^[47]. Building on this preliminary work, we designed two different XB macrocycle regioisomers, containing iodotriazole units substituted at the 1,2- and 1,3-positions of a benzene spacer with the potential to facilitate both XB-mediated anion binding via their Lewis acidic iodine atoms, as well as Lewis basic triazole-nitrogen-coordination of the metal catalyst. The copper(I)-catalysed azide-alkyne cycloaddition (CuAAC) reaction was then employed to furnish the target neutral XB rotaxanes.

The synthesis of XB macrocycles **4** and **5**, summarised in Scheme 1, follows a general protocol where bis-iodotriazole macrocycle precursors (**7** and **8**) were synthesized initially from 1,3- or 1,2-diethynylbenzene. Following quantitative deprotection of the methoxymethyl acetal (MOM) protecting group under acidic conditions, macrocycle ring-closing was performed between bis-phenol derivatives **9** and **10** with triethylene glycol-bis-tosylate **11** under basic conditions to afford macrocycles **4** and **5** in 32 and 20 % yields respectively following chromatographic purification (see Supporting Information for full synthetic details).

The efficacy of the CuAAC active metal template synthesis for the target neutral XB rotaxanes depends crucially upon facile endotopic coordination of the copper(I) metal catalyst to the XB macrocycles. Hence to ascertain Cu(I) binding, ¹H NMR titration studies were performed where increasing quantities of [Cu(CH₃CN)₄]PF₆ were added to solutions of the macrocycles in [D₂]dichloromethane. For macrocycle **4**, addition of 0.25, 0.50 and 0.75 equivalents of Cu(I) caused its ¹H NMR spectrum to become more complex, accompanied by noticeable signal broadening (Figure 2a), indicating that Cu(I)-binding was slow on the ¹H NMR timescale with multiple complexed species being

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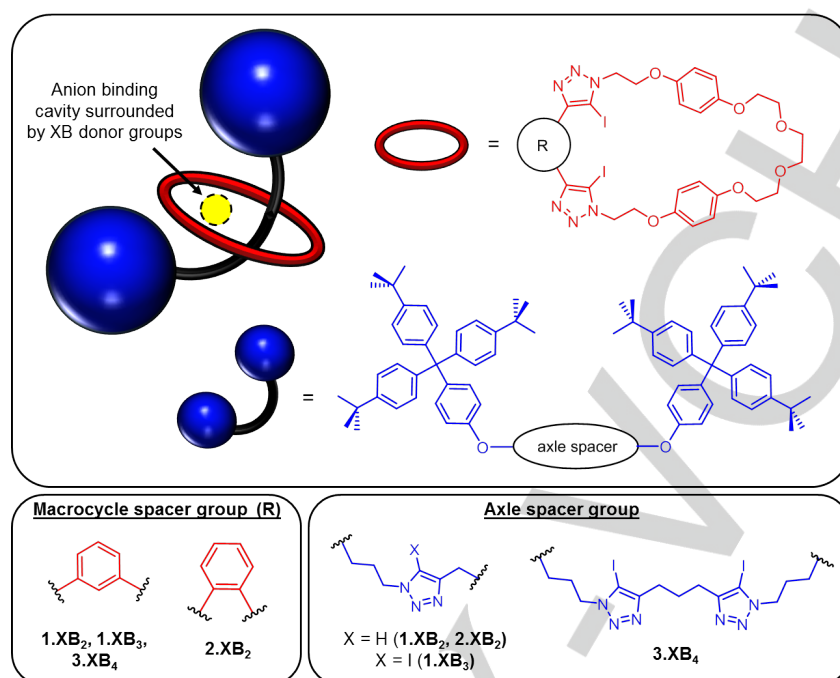
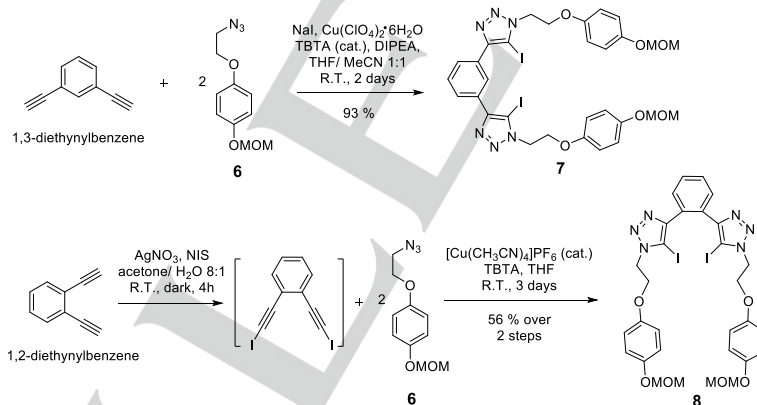
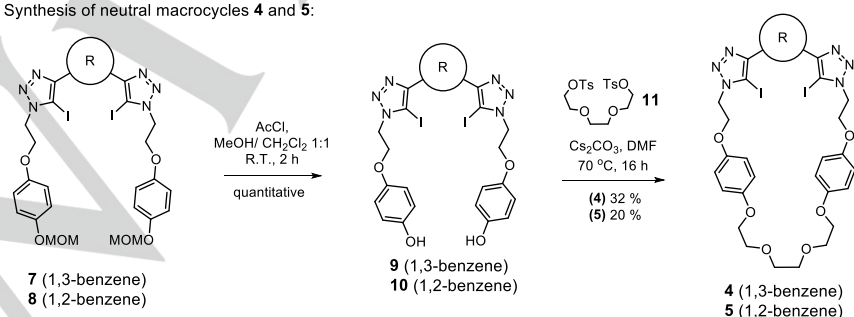


Figure 1. Schematic structures of the neutral XB rotaxanes **1.XB₂**, **2.XB₂**, **1.XB₃** and **3.XB₄** with different numbers and positions of XB-donor iodotriazole groups surrounding the interlocked anion binding cavity.

Synthesis of macrocycle precursors **7** and **8**:



Synthesis of neutral macrocycles **4** and **5**:



Scheme 1. Synthesis of XB macrocycle regioisomers **4** and **5** containing the iodotriazole units substituted at the 1,3- and 1,2-positions of the benzene spacer respectively (OMOM = OCH₂OCH₃).

formed in solution. However, the presence of 1.0 equivalent of Cu(I) led to a noticeable simplification and sharpening of the spectrum, with clear desymmetrisation now observed and the signal arising from H_b shifting upfield and splitting into two distinct doublets. This suggested that Cu(I) was bound in an asymmetric manner to **4**, likely via only one of the iodotriazole groups at any one time. In stark contrast, having the iodotriazole units positioned *ortho*- to each other in macrocycle **5** resulted in Cu(I) binding being *fast* on the NMR timescale, with slight spectral signal broadening observed (Figure 2b). Instead, the ¹H NMR signals arising from the benzene spacer (H_A and H_B) exhibited initial *upfield* perturbations up to 0.5 equivalents of Cu(I), which then moved *downfield* in the opposite direction with higher concentrations of Cu(I) present. This suggested that macrocycle **5** initially bound Cu(I) with a 2:1 host-guest binding stoichiometry which subsequently converted to 1:1 stoichiometry with increasing Cu(I) concentration.^[48,49] Binding was found to be too strong to be quantified ($K_{2:1} > 10^4 \text{ M}^{-1}$) by WinEQNMR2 analysis.^[50] Notably, no perturbations of the polyether region of either macrocycle was seen during the titrations, clearly indicating that Cu(I) was bound exclusively by the iodotriazole groups.

To further understand how the iodotriazole units were ligating Cu(I), a qualitative UV-Vis titration was performed with macrocycle **4** and [Cu(CH₃CN)₄]PF₆ in dichloromethane. As shown in Figure 3, an increase in the intensity of the absorbance band at 290 nm resulted from addition of up to 0.5 equivalents of Cu(I), with a distinct isobestic point seen at 260 nm. Subsequent further addition of up to 1.0 equivalent of Cu(I) resulted in a decrease in intensity of the 290 nm band accompanied by a new isobestic point at 272 nm. These UV-Vis titration observations are similar to those seen for Cu(I)-(proto)triazole complex formation, attributed to significant perturbations to the HOMO-LUMO energy gap of the triazole ligands resulting from direct *N*-coordination.^[51] Taken together with the ¹H NMR binding studies, this suggests the iodotriazole motifs of macrocycle **4** are acting as *N*-donor ligands for Cu(I) coordination where the *meta*-positioned iodotriazole groups are too far apart spatially to allow bidentate coordination of the Cu(I) species between the triazole nitrogen donor atoms.

Having determined that XB macrocycles **4** and **5** were capable of strong binding to Cu(I), the CuAAC active metal template synthesis of rotaxanes was attempted. A dichloromethane solution containing an equimolar mixture of macrocycle **4** and [Cu(CH₃CN)₄]PF₆, with a five-fold excess of azide **12** and terminal alkyne **13**, was stirred under an inert atmosphere of N₂ for 24 hours. Complete consumption of the azide and alkyne starting material was observed within this time interval, and pleasingly, the presence of rotaxane **1.XB₂** in the reaction mixture was also clearly evident from electrospray ionisation mass spectrometry analysis of the crude reaction mixture ($m/z = 1981 [\text{M} + \text{H}]^+$). Following demetallation with a basic aqueous solution of ethylenediaminetetraacetate (EDTA) and chromatographic purification, rotaxane **1.XB₂** was isolated in a yield of 41 % (Scheme 2). An analogous synthetic procedure with macrocycle **5** produced rotaxane regioisomer **2.XB₂** in 30% yield.^[52] It is noteworthy that the successful XB rotaxane syntheses demonstrates the conformational flexibility of both

macrocycles enabling endo-Cu(I)-iodotriazole complexation for MIM formation via CuAAC reaction.

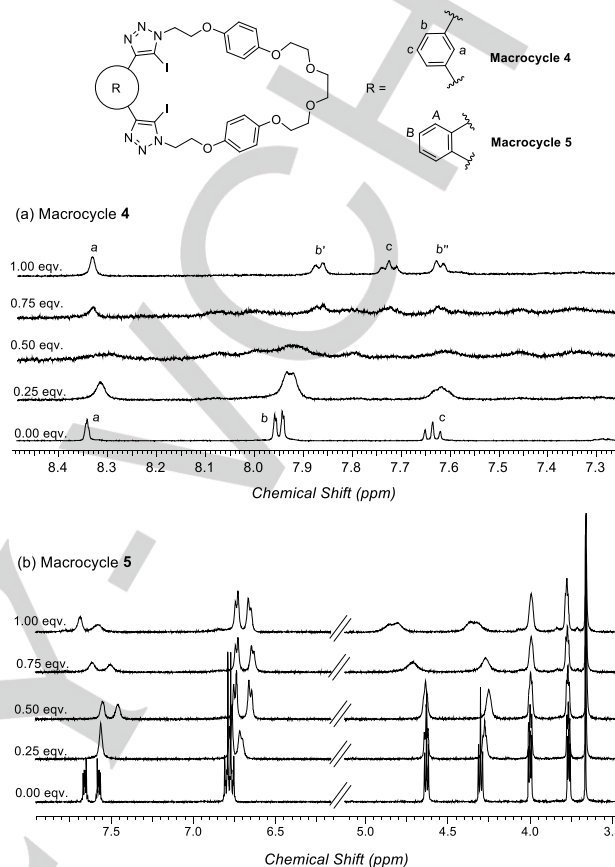


Figure 2. Partial ¹H NMR spectra of macrocycle regioisomers (A) **4** and (B) **5** in the presence of increasing quantities of [Cu(CH₃CN)₄]PF₆ ([macrocycle] = 1.0 mM, CD₂Cl₂, T = 298 K).

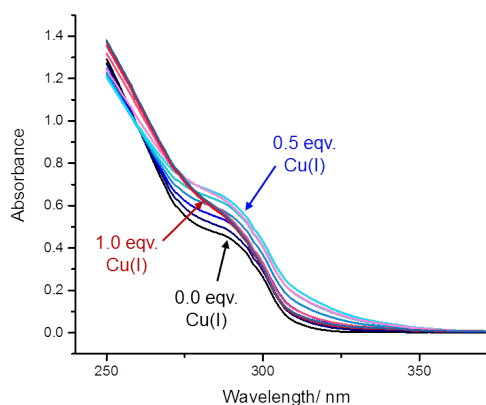
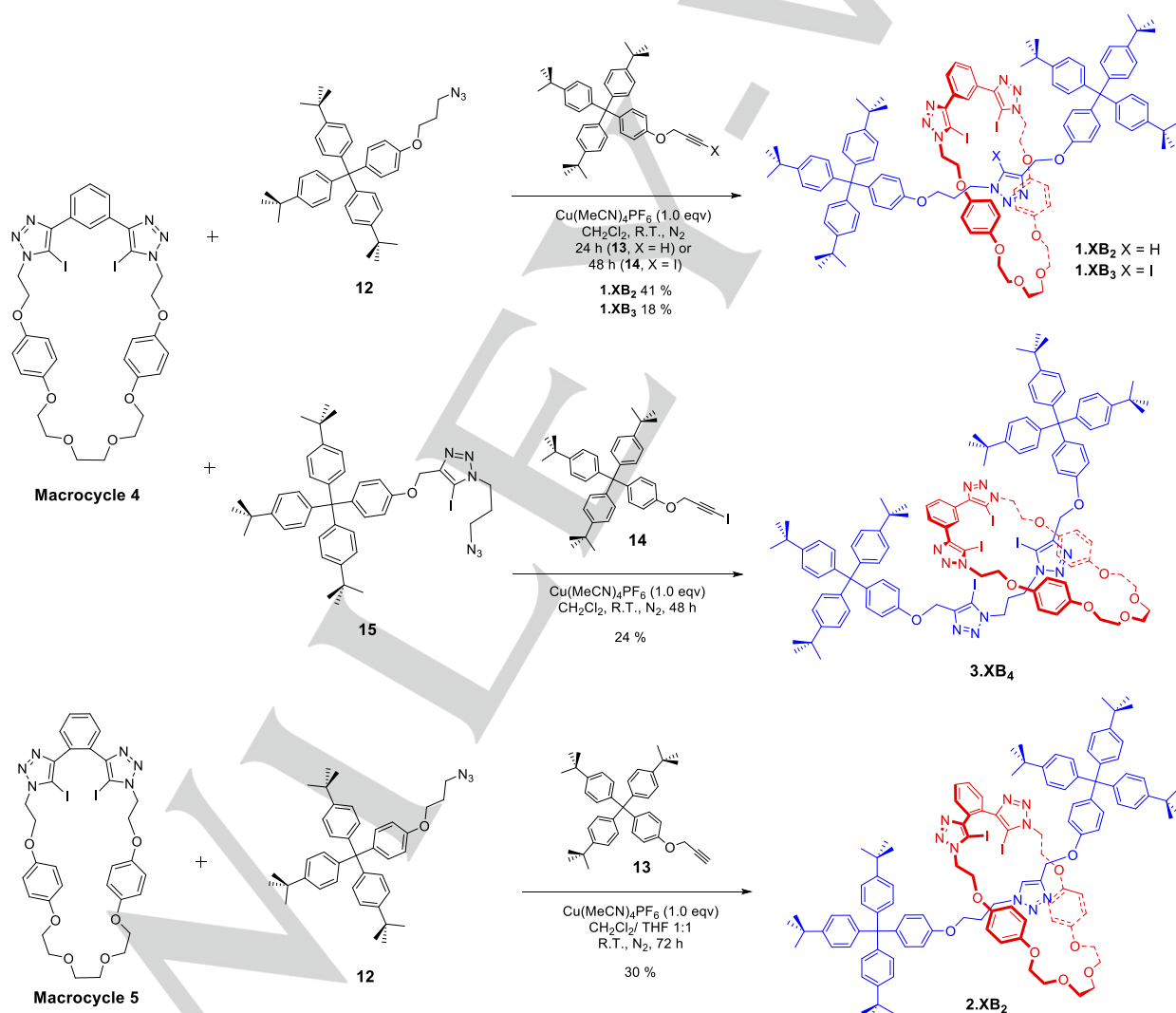


Figure 3. UV-Vis spectra of macrocycle **4** in the presence of 0.1 equivalents increment of [Cu(CH₃CN)₄]PF₆ up to 1.0 equivalent. Changes from 0.0 to 0.5 equivalents of Cu(I) are shown in shades of blue, while those between 0.6 to 1.0 equivalents are shown in shades of red ([macrocycle **4**] = 50 μM, T = 293 K, CH₂Cl₂).

^1H NMR spectroscopic characterisation of rotaxanes **1.XB₂** and **2.XB₂** show unequivocal evidence that both rotaxanes retain their interlocked nature following removal of the Cu(I)-template (see Supporting Information). Compared with their respective macrocycles **4** and **5**, diagnostic upfield perturbations and increased splitting of the macrocycle hydroquinone proton resonances were seen, arising from aromatic donor-acceptor interactions between the electron-rich hydroquinone and relatively electron-deficient axle triazole motifs. Furthermore, both rotaxanes also show significant upfield signal shifts for the alkyl protons on the axle component immediately adjacent to the triazole unit, as compared to the free axle itself. This is presumably due to the shielding effect from the aromatic ring currents of the macrocycle hydroquinone groups present in close spatial proximity. Additional evidence of the interlocked nature of **1.XB₂** and **2.XB₂** was obtained from two-dimensional ^1H - ^1H ROESY experiments, with numerous cross-peaks

observed from the through-space interactions between the respective axle and macrocycle components (see Supporting Information).

Following the successful Cu(I)-templated synthesis of rotaxanes **1.XB₂** and **2.XB₂** via the proto-'Click' CuAAC reaction, the analogous iodo-'Click' reactions using an iodoalkyne axle precursor **14** with azide-functionalised congeners **12** and **15** were undertaken. Despite identical conditions (Scheme 2), the iodo-'Click' reaction was found to be less facile, requiring up to 48 hours for complete consumption of azide and iodoalkyne starting materials. In both cases, neutral rotaxanes **1.XB₃** and **3.XB₄**, containing three and four iodo-triazole units flanking the rotaxane's anion binding cavity respectively, were isolated in similar yields of ca. 20%. Full characterisation of all rotaxanes were obtained using ^1H and ^{13}C NMR, 2D ROESY spectroscopy, as well as high-resolution mass spectrometry (see Supporting Information).



Scheme 2. Active metal template CuAAC synthesis of neutral XB rotaxanes containing two (**1.XB₂** and **2.XB₂**), three (**1.XB₃**) and four (**3.XB₄**) XB-donor iodo-triazole units.

¹H NMR Anion Binding Studies

The anion binding properties of neutral XB rotaxane regioisomers **1.XB₂** and **2.XB₂** were initially investigated by ¹H NMR titration experiments, where increasing quantities of tetrabutylammonium (TBA) anion salts were added to solutions of the respective rotaxanes in [D₆]acetone.

As shown in Figure 4, the addition of chloride resulted in large downfield perturbations ($\Delta\delta > 0.2$ ppm over 10 equivalents of chloride) of the axle triazole proton (H₄) for both **1.XB₂** and **2.XB₂**, indicating that the halide is bound in the vicinity of the rotaxane binding cavity. Smaller upfield perturbations of the aromatic protons on the macrocycle component's benzene spacer (H_b and H_c for **1.XB₂**; H_B for **2.XB₂**) were seen as well, which likely result from donation of electron density from the chloride anion guest *via* halogen bonding-anion interactions. In addition, small downfield perturbations of the axle alkyl proton environments immediately adjacent to the triazole (H₃ and H₅) were also observed for both rotaxanes, possibly due to their proximity to the anion binding site which may result in weak hydrogen bonding interactions with the bound anion. However, it is noteworthy that in general, much more pronounced proton signal shifts were observed in the ¹H NMR spectra of **1.XB₂** than **2.XB₂** upon chloride binding, suggesting a greater degree of conformational change. This is most clearly seen for the macrocyclic proton signal H_e, which showed a significant upfield shift of 0.2 ppm in the presence of 10 equivalents of chloride for

1.XB₂, while barely any shifts were observed for the same proton signal of **2.XB₂**.

Analogous ¹H NMR titrations with bromide, iodide and sulfate caused similar perturbations to the rotaxanes' proton signals to those observed with chloride, suggesting complexation in the vicinity of the rotaxane binding cavity. Sulfate, in particular, was able to elicit dramatic downfield shifts of axle triazole proton H₄ ($\Delta\delta = +1.95$ ppm from 0 to 10 equivalents, Figure S3-3 in Supporting Information), clearly indicating very close association of the anion around the interlocked binding cavity. By monitoring the perturbations of axle triazole H₄, non-linear regression analysis determined host-guest association constants summarised in Table 1.

Both rotaxanes **1.XB₂** and **2.XB₂** were found to bind anions following the selectivity trend $\text{SO}_4^{2-} > \text{Cl}^- > \text{Br}^- > \text{I}^-$, in order of decreasing charge density and basicity (Table 1). For rotaxane **1.XB₂**, the convergent halogen bonding interactions arising from the *meta*-positioned iodotriazole units on the macrocycle benzene spacer, as predicted computationally,^[53] resulted in all anions being bound very strongly with 1:1 host-guest binding stoichiometry. This suggests rotaxane **1.XB₂** binds anions via an induced-fit mode, where the axle and macrocycle components can adjust their positions relative to each other to accommodate anion guest size variation.

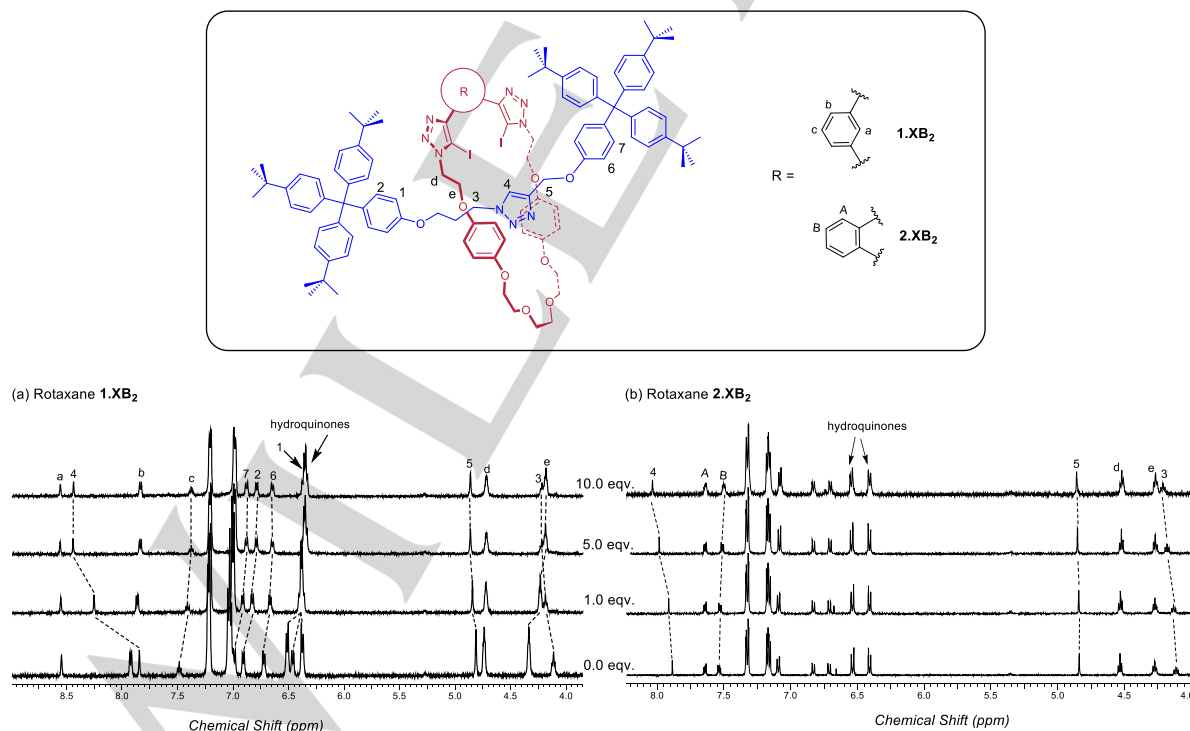


Figure 4. Partial ¹H NMR spectra of rotaxanes **1.XB₂** and **2.XB₂** in the presence of 0.0, 1.0, 5.0 and 10.0 equivalents of chloride ([rotaxanes] = 1.0 mM, [D₆]acetone, T = 298 K).

Table 1. Association constants (K_a / M^{-1}) of various anions with rotaxanes **1.XB₂** and **2.XB₂** in [D₆]acetone.^[a]

Anion	Rotaxane 1.XB₂	Rotaxane 2.XB₂
Cl ⁻	4384 (322)	89 (4)
Br ⁻	2139 (68)	64 (2)
I ⁻	902 (57)	34 (1)
SO ₄ ²⁻	> 10 ⁴	$K_{2:1} = 211$ (3) ^[b] $K_{1:1} = 425$ (7)

[a] Axle triazole proton H_a monitored for both rotaxanes. Values of K_a are determined by the WinEQNMR2 software^[50] using a 1:1 host-guest binding model unless otherwise stated. Errors (\pm) are in parentheses and are < 10 %. [b] Values of K_a calculated using BindFit^[54] following a host-guest 2:1 binding model. ([rotaxanes] = 1.0 mM, 500 MHz, $T = 298$ K).

The importance of the relative positions of the iodotriazole motifs on the macrocycle can be seen by comparing the binding properties of rotaxanes **1.XB₂** and **2.XB₂**, which reveal several notable differences (Table 1). Firstly, **1.XB₂** binds all anions with much greater affinities than **2.XB₂**, with more than an order-of-magnitude enhancement in association constant values in all cases. Unlike **1.XB₂**, where there is sufficient space to allow both iodotriazoles to bind the anion via convergent XB interactions, the 1,2-position of **2.XB₂** likely causes too much steric constraints for both bulky iodotriazoles groups to interact in a cooperative fashion. In addition, the more sterically-encumbered and constrained macrocycle geometry of **2.XB₂** may also reduce the likelihood of the anion being encapsulated within the rotaxane binding cavity. In combination, these factors may account for the significant diminished anion affinity of **2.XB₂** compared to **1.XB₂**. The consequence of these geometric factors can be most clearly seen with the ¹H NMR sulfate binding studies where rotaxane **2.XB₂** initially showed a host-guest 2:1 binding mode at low concentrations of the anion, which subsequently became 1:1 upon further addition of sulfate (see Figure S3-4 in Supporting Information).

A ¹H NMR titration study between rotaxane **1.XB₃** and chloride in [D₆]acetone revealed downfield shifts of the macrocycle internal aromatic proton H_a , axle alkyl proton H_5 , as well as the stopper proton H_6 (same proton assignments as **1.XB₂** in Figure 4). This suggested the bound chloride anion is perching above the plane of the macrocycle just below the stopper proximal to it, likely due to the steric bulk of the three XB-donor iodine atoms preventing anion coordination within the rotaxane cavity itself. It is noteworthy that strong chloride binding was observed, with negligible shifts in the NMR spectra seen after 1.0 equivalent of chloride. By monitoring the perturbations of macrocycle aromatic proton H_a , WinEQNMR2 analysis^[50] determined a 1:1 stoichiometric association constant of >10⁴ M⁻¹,

making **1.XB₃** one of the strongest *neutral* halogen bonding anion receptors reported to date.^[27] Importantly, in comparison to **1.XB₂**, by simply replacing a single proton on the axle triazole component of the rotaxane with an iodine atom, a dramatic enhancement in the strength of chloride anion association is observed with **1.XB₃**, confirming the notable influential involvement of additional halogen bonding upon the overall halide recognition process.

Encouraged by the strong anion binding behaviour of rotaxanes **1.XB₂** and **1.XB₃** in acetone, the effects of the addition of water on their anion binding properties together with rotaxanes **2.XB₂** and **1.XB₄** was investigated. As shown in Table 2, analogous ¹H NMR anion titrations in the presence of 2 % D₂O in [D₆]acetone by volume with **1.XB₂** and **1.XB₃** led to a reversal of anion binding selectivity trend, with iodide now being the most strongly bound anion in both cases (*vide infra*). As expected from the modest anion affinities in *d*₆-acetone, rotaxane **2.XB₂** exhibited no evidence of anion binding behaviour in this aqueous solvent mixture.

Table 2. 1:1 Stoichiometric association constants (K_a / M^{-1}) of various anions with rotaxanes **1.XB₂**, **1.XB₃** and **3.XB₄** in [D₆]acetone-D₂O solvent mixtures.^[a]

	2 % D ₂ O in acetone		5 % D ₂ O in acetone	
	1.XB₂	1.XB₃	3.XB₄	3.XB₄
Cl ⁻	114 (6)	280 (6)	496 (2)	25 (2)
Br ⁻	371 (25)	461 (11)	1200 (4)	224 (8)
I ⁻	533 (7)	617 (27)	1101 (68)	562 (44)
SO ₄ ²⁻	38 (3)	19 (1)	— ^[b]	— ^[c]

[a] Anions added as TBA salts, errors (\pm) given in parentheses. 1:1 association constants calculated using WinEQNMR2 software^[50] monitoring the perturbations of the axle triazole protons for **1.XB₂** and the internal aromatic macrocycle proton H_a for the other rotaxanes (500 MHz, [D₆]acetone, 298 K). [b] No binding; [c] Not performed.

The effects of increasing the number of XB donor groups around the rotaxane binding cavity on anion binding in the presence of water can be clearly seen by comparing the binding properties of rotaxanes **1.XB₂**, **1.XB₃** and **3.XB₄** (Table 2). Having three convergent iodotriazole motifs contributing to the interlocked binding site of **1.XB₃**, in comparison to two with rotaxane **1.XB₂**, results in an enhancement in anion binding strength for all the halides except sulfate. Incorporating a further iodotriazole motif in the axle design of rotaxane **3.XB₄** led to an approximate two-fold increase in the magnitudes of the association constants for all halides in the same solvent mixture, clearly demonstrating the additive effects of increasing numbers of convergent XB donor groups on anion binding strength. Interestingly, a modest binding preference for bromide was also

observed over iodide. When analogous titrations with **3.XB₄** and azide, acetate, nitrate, perchlorate or sulphate were performed in a solution of 2% D₂O in [D₆]acetone, no evidence of binding was observed (see Supporting Information Fig. S3-8), suggesting that the interlocked binding cavity surrounded by four XB donor groups is complementary for spherical halides, in particular bromide, over other possible anion geometries. Repeating the halide binding studies in the more competitive aqueous solvent mixture of 5 % D₂O in [D₆]acetone shows that neutral rotaxane **3.XB₄** displays a distinct Hofmeister bias binding trend with iodide selectivity (Table 2), underscoring the importance of anion hydration in the binding process.

Commenting further on the importance of hydration in determining the anion affinities and selectivities by these neutral XB rotaxanes, introducing just 2 % water by volume in acetone led to a significant reduction in anion binding strength of **1.XB₂** in particular for the more hydrated anions chloride and sulfate. Clearly, these results show that the stabilities of the XB rotaxane-anion complexes are highly dependent on solvent polarity, which contrasts the observations by Hunter and co-workers regarding the solvent-independence of XB interaction strengths.^[56] In their study, XB association constants between neutral molecular iodine and tetramethylthiourea decreased only by a factor of three-fold when the solvent was changed from *n*-octane to methanol.^[57] While the different XB-donor properties of molecular iodine and iodotriazoles may play a part in accounting for the observed contrasting solvent dependency, the augmented sensitivity of XB-anion binding affinity to solvent polarity highlights the much higher solvation energies of anions as compared with neutral species. This is especially the case with protic solvents, where anions are significantly more sensitive to changes in the solvent's hydrogen bond-donor ability. Notably, Table 2 shows the stabilities of neutral XB rotaxane-anion complexes with 'soft' and poorly-hydrated anions such as iodide are relatively less sensitive to variations in solvent polarity, behaving more similarly to the neutral XB donor-acceptor associated species in Hunter's study.

Conclusions

Novel XB macrocycles have been shown to promote the CuAAC active metal template synthesis of a family of *neutral* XB rotaxanes containing different numbers of convergent iodotriazole groups surrounding the interlocked anion binding cavity. ¹H NMR binding studies reveal the XB iodotriazole groups are found to contribute in an additive manner to increase the strength of the rotaxane-anion complex. This design feature enables these neutral XB interlocked hosts to exhibit impressively strong and selective halide anion binding affinities, even without the benefits of charge assistance, in the presence of water. In addition, comparing the halide anion association constant values in the presence of increasing quantities of water reveals that neutral XB donor-mediated anion binding is highly sensitive to solvent polarity. The application of active metal template synthesis to construct XB rotaxanes nicely complements our strategic anion templation approach,^[58–60] and

opens up new possibilities for the design and preparation of elaborate XB interlocked receptors capable of strong anion binding for various analytical and nanotechnological applications.

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Keywords: anion binding • halogen bonding • rotaxanes • supramolecular chemistry • neutral

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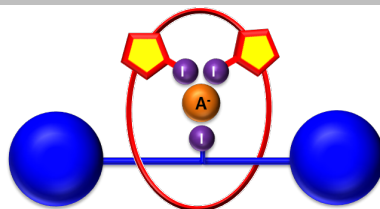
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Layout 1:

FULL PAPER

A family of neutral halogen bonding rotaxanes have been prepared which show remarkably strong binding and selectivity for halides in water-acetone solvent mixtures. Halide binding strength and selectivity can be modulated by varying the number and position of the halogen bond-donor iodotriazole groups within the interlocked host cavity, as well as changing the solvent polarity.



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Strong and Selective Halide Anion Binding by Neutral Halogen Bonding [2]Rotaxanes in Wet Organic Solvents