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Halogen bonding rotaxanes for nitrate recognition in aqueous media

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Targeting the biologically and environmentally important nitrate anion, halogen bonding (XB) has been incorporated into three novel [2]rotaxane structural frameworks *via* an axle component containing covalently linked 3,5-bis-iodotriazole pyridine -pyridinium motifs. This has enabled the recognition of nitrate in aqueous media containing up to 90% water with equivalent binding affinity to chloride, illustrating the potency of XB for anion recognition in highly competitive aqueous solvent mixtures.

Introduction

Stimulated by the crucial roles that anions play in chemical, biological and environmental processes, the field of anion recognition has grown dramatically over the last couple of decades with reports of a vast array of synthetic hosts capable of binding anions in organic and aqueous media.[1-5] Recently, halogen bonding (XB),[6] has been introduced into anion host systems as an alternative to the prevalent hydrogen bond (HB), typically resulting in a dramatic enhancement in anion binding strength as well as noteworthy changes in selectivity.[7] Advantageously, XB is comparable in strength to HB, demands strict directionality of interaction, and its pH-independence and solvent resistance provide significant benefits for the binding of anions in aqueous media.[8, 9] Nonetheless, while anion receptors exploiting XB interactions are relatively rare,[10-14] integrating XB motifs into mechanically interlocked anion host systems has facilitated anion recognition in organic–aqueous media and pure water.[15-21]

Of particular biological and environmental importance is the nitrate anion, which has been implicated in blue baby syndrome (methemoglobinemia) and its anthropogenic overuse in arable farming has led to eutrophication of dams and lakes. Various acyclic tripodal systems,[22, 23] macrocyclic receptors[24] and trigonal cages[25, 26] have been demonstrated to accommodate the oxoanion's trigonal planar geometry, employing spatially-oriented HB amide motifs to complex each of the three nitrate oxygen atoms; however, all these host systems only function in organic solvents.[27] Indeed, receptors capable of nitrate recognition in aqueous media are exceptionally scarce. To the best of our knowledge, two [2]rotaxanes and a [2]catenane host containing respectively, a bis-triazolium acridine axle component, and covalently linked isophthalamide-3,5-bis-amide pyridinium axle and macrocycle motifs are the only examples, binding nitrate in aqueous 45:45:10 $CDCl_3$:CD_3OD:D_2O solution.[28-30]

In an effort to exploit the stringent directionality of XB as a means of elevating the strength and selectivity of nitrate anion recognition in higher percentage water containing solvent media and taking into account our previous nitrate selective interlocked HB host design, herein we report the synthesis of three XB [2]rotaxane anion receptors which incorporate two XB 3,5-bis-iodotriazole pyridine or pyridinium donor sites into the axle component, one of which is demonstrated to bind nitrate in 90% water (9:1 D_2O: CD_3COCD_3).

Results and discussion

Synthesis

The synthesis of the crucial XB axle component of the target [2]rotaxane required the incorporation of two XB 3,5-bis-iodotriazole pyridine or pyridinium donor sites while the macrocycle component was prepared *via* standard procedures.[31] Initially, attempts were made to prepare unsymmetrically functionalised axle precursors *via* various alkyne functional group protection methods. Sonogashira reaction[32, 33] between commercially available 3,5-dibromo-pyridine and 2-methylbut-3-yn-2-ol afforded **1** in 79% yield. Subsequent Sonogashira reaction[32, 33] with TBDMS-acetylene gave the unsymmetrically protected 3,5-diethynyl pyridine **2** in 87% yield. However, selective deprotection of **2** with 2-hydroxy propane and TBDMS protecting groups was problematic. Whilst the 2-hydroxy propyl protecting group could easily be selectively cleaved in the presence of TBDMS by refluxing **2** with NaOH in toluene, the use of TBAF to remove TBDMS either resulted in the unexpected removal of the 2-hydroxy propyl protecting group instead (**2** to **3**) or the

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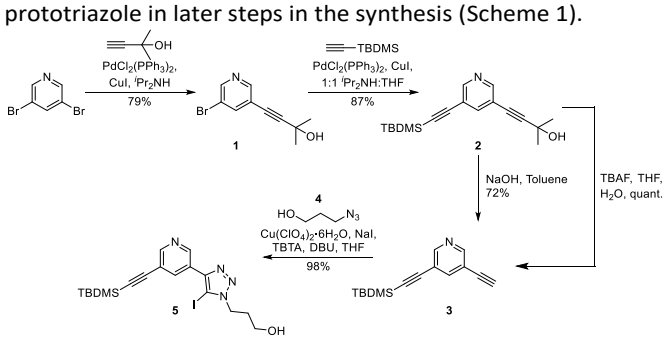
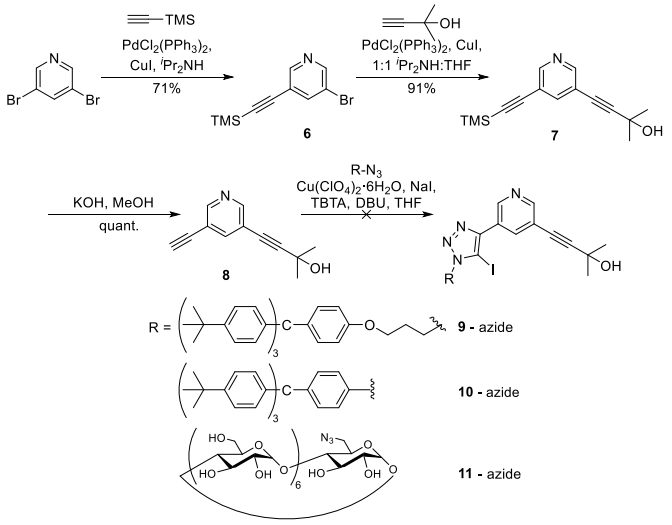
decomposition of the iodotriazole group, for example, in **5** to a prototriazole in later steps in the synthesis (Scheme 1).



Scheme 1: Stepwise alkyne protection and deprotection steps using TBDMS and 2-hydroxy propyl protecting groups.

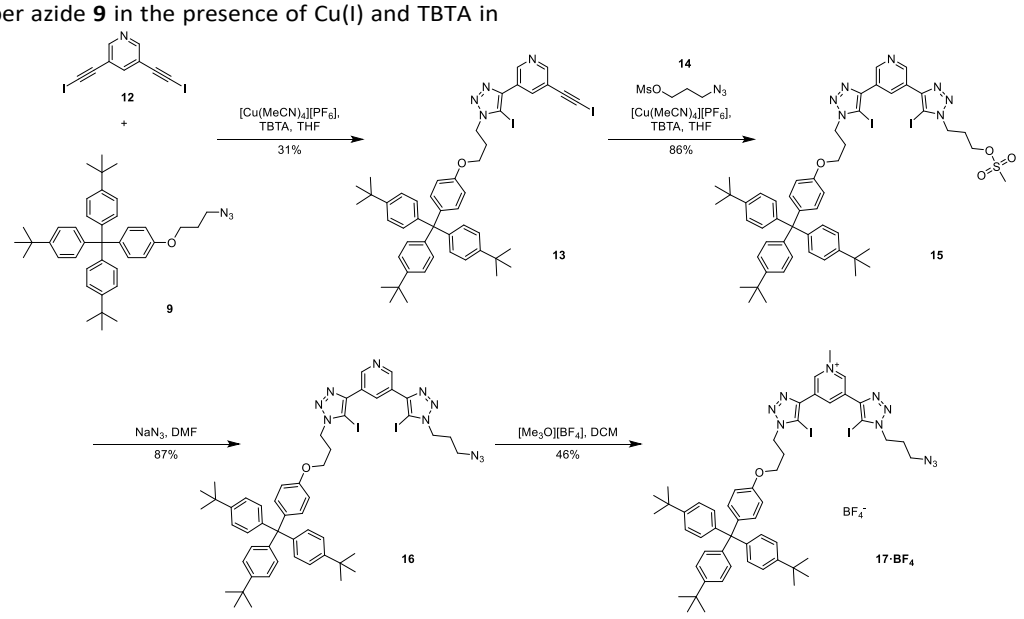
Since the TMS protecting group offered a more labile alternative to TBDMS, and could be selectively deprotected in the presence of the 2-hydroxy propyl protecting group, the TMS analogue of **2** was prepared using an initial Sonogashira reaction[32, 34] between 3,5-dibromopyridine and TMS-acetylene to afford **6** in 79% yield. Thereafter, Sonogashira reaction[32] with 2-methylbut-3-yn-2-ol gave **7** in 91% yield. The TMS protecting group was selectively deprotected using KOH in MeOH, quantitatively giving **8**, which was reacted with various stopper azides (terphenyl-propyl **9**, terphenyl-aryl **10** and permethylated β-cyclodextrin **11**) using a one-pot iodo-CuAAC click reaction.[35] Unfortunately, the click reactions to stopper the mono-deprotected alkyne were unsuccessful (Scheme 2) with the recovery of only starting materials after purification.

Since stepwise alkyne protection/deprotection synthetic techniques could not be used to prepare the axle component, the synthesis of target XB [2]rotaxanes **19·PF$_6$** and **20·(PF$_6$)$_2$** was reliant upon an initial statistical stoppering step shown in Scheme 3. Employing a modification of the copper(I)-catalysed azide-iodoalkyne cycloaddition (CuAAC) click reaction,[36, 37] an equimolar mixture of 3,5-diiodoethynyl pyridine **12** and terphenyl stopper azide **9** in the presence of Cu(I) and TBTA in THF afforded the mono-substituted precursor **13** in 31% yield. Reaction of azido-propyl-mesylate **14** with **13** using the same CuAAC conditions gave the intermediate **15** in 86% yield. Substitution of the mesylate to produce azide **16** was achieved with NaN_3 in 87% yield and methylation with $[Me_3O][BF_4]$ gave the pyridinium tetrafluoroborate salt **17·BF$_4$** in 46% yield.



Scheme 2: Selective alkyne protection and deprotection steps using TMS and 2-hydroxy propyl protecting groups.

The synthesis of rotaxanes **19·PF$_6$** and **20·(PF$_6$)$_2$** is shown in Scheme 4. The synthesis of [2]rotaxane **19·PF$_6$** was achieved in 32% yield using a chloride anion-templated mono-stoppering CuAAC click methodology: equimolar amounts of **13** and **17·BF$_4$** were mixed with 10 equivalents of isophthalamide macrocycle **18** in the presence of Cu(I), TBTA and one equivalent of TBA·Cl. Methylation of [2]rotaxane **19·PF$_6$** with CH_3I afforded the dicationic [2]rotaxane **20·(PF$_6$)$_2$** in 37% yield after anion exchange to the non-coordinating hexafluorophosphate anion.



Scheme 3: Synthesis of axle component precursors **13** and **17·BF$_4$**.

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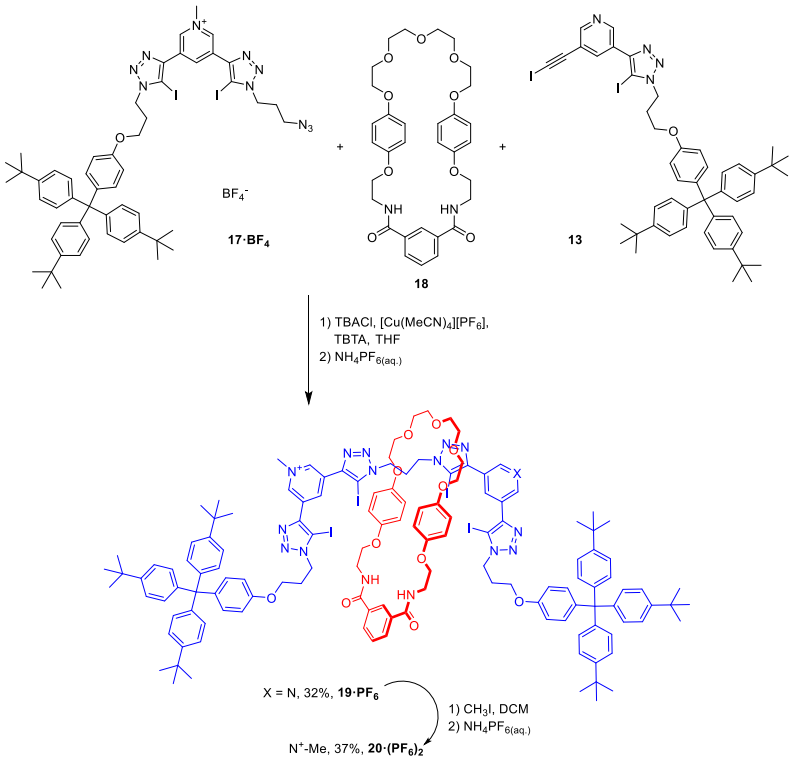
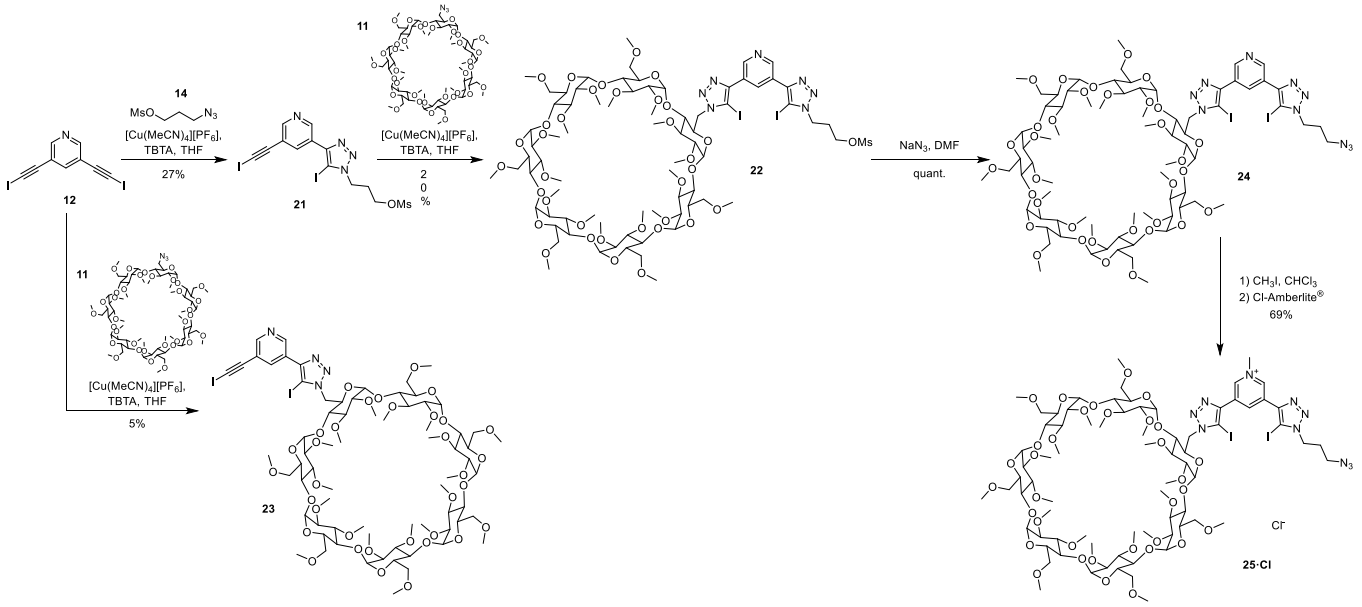


Scheme 4: Synthesis of [2]rotaxanes **19·PF$_6$** and **20·(PF$_6$)$_2$**.

Whilst terphenyl stopper units are suitable for organic and organic–aqueous solvent media, permethylated β-cyclodextrin stopper units are required in order to solubilise a [2]rotaxane analogue in pure water, or solvent mixtures containing a high percentage of water, since permethylation improves the aqueous solubility of β-cyclodextrin.[38, 39] In a similar manner to rotaxanes **19·PF$_6$** and **20·(PF$_6$)$_2$**, β-CD-stoppered rotaxane **27·(OTf)$_3$** was synthesised according to the stepwise procedure shown in Scheme 6 using permethylated β-cyclodextrin functionalised axle component precursors **23** and **25.Cl** (Scheme 5). Mono-substitution of **12** with azido-propyl-mesylate **14** was achieved using the same statistical modified CuAAC conditions for the preparation of **13**, producing **21** in 27% yield. The CuAAC reaction of **21** with azide functionalised permethylated β-cyclodextrin **11**[40-42] gave **22** in 20% yield.‡ Conversion of mesylate **22** to the azide **24** was achieved quantitatively using NaN_3 in DMF. The pyridinium azide axle precursor **25·Cl** was obtained in 69% yield after methylation using CH_3I and subsequent anion exchange to the chloride salt using a chloride-loaded Amberlite® column (Scheme 5).



Scheme 5: Synthesis of axle component precursors **23** and **25·Cl**.

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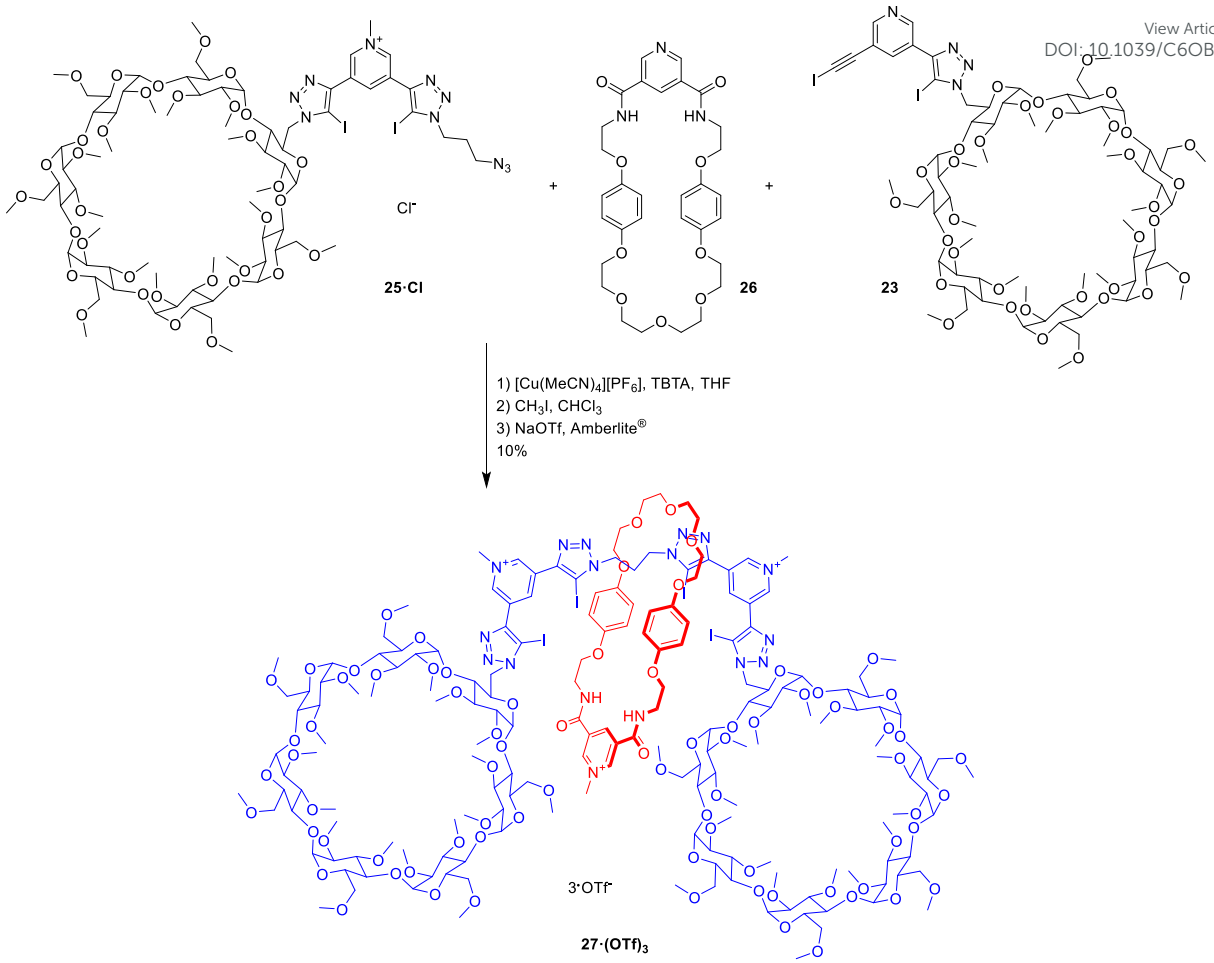

Scheme 6: Synthetic route to prepare [2]rotaxane **27·(OTf)$_3$**.

Rotaxane **27·(OTf)$_3$** was prepared using the chloride anion-templated CuAAC click reaction (Scheme 6): mixing equimolar quantities of the two axle precursors **23** and **25·Cl** with 10 equivalents of the pyridine bis-amide macrocycle[21] **26** in the presence of Cu(I) and TBTA in THF. The rotaxane was purified using preparative thin layer chromatography (silica, 8% MeOH in $CHCl_3$). Post-rotaxane methylation using CH_3I in $CHCl_3$, and subsequent anion exchange to the water-soluble, non-coordinating triflate salt using a triflate-loaded Amberlite® column, afforded the [2]rotaxane **27·(OTf)$_3$** in 10% yield over 3 steps. The tricationic [2]rotaxane **27·(OTf)$_3$** was characterised by ^{1}H, ^{13}C, ^{19}F as well as 2D COSY NMR spectroscopy, high resolution mass spectrometry, and the interlocked nature of the [2]rotaxane was confirmed by 2D ROESY NMR spectroscopic analysis (See ESI).

Anion binding studies

As a consequence of limited quantities of the mono- and di-cationic [2]rotaxanes **19·PF$_6$** and **20·(PF$_6$)$_2$**, respectively, and the tricationic permethylated β-cyclodextrin stopper-axle appended [2]rotaxane **27·(OTf)$_3$**, anion binding studies were restricted to chloride and nitrate ^{1}H NMR titration experiments. Whilst anions were titrated as their tetrabutylammonium (TBA) salts for rotaxanes **19·PF$_6$** and **20·(PF$_6$)$_2$**, they were added as their sodium salts for the water-soluble rotaxane **27·(OTf)$_3$**. In the case of the monocationic [2]rotaxane **19·PF$_6$**, a preliminary titration with TBA·NO_3 in 45:45:10 $CDCl_3$:CD_3OD:D_2O showed no evidence of binding the oxoanion. Consequently, titrations were repeated in 1:1 $CDCl_3$:CD_3OD, and chemical shifts were monitored for the protons *i* and *3*, incumbent on the anion binding cavity of the rotaxane, as well as protons *j* and *k* (Figure 1a). Analogous titrations for the dicationic [2]rotaxane host **20·(PF$_6$)$_2$** were conducted in 45:45:10 $CDCl_3$:CD_3OD:D_2O. Upfield chemical shifts were observed for the pyridinium internal (*i* and *p*) and external (*j,k* and *q,r*) protons, whilst a downfield shift was observed for the isophthalamide proton *3*. Figure 1b shows the downfield shift for proton *j,k* of **20·(PF$_6$)$_2$** upon addition of anions. Since the receptor **27·(OTf)$_3$** was only partially soluble in pure water, the anion binding studies were conducted in 9:1 D_2O:acetone-d_6. Upon addition of chloride, noteworthy downfield shifts were observed for the various pyridinium protons (*j,k* , *l*, *2* and *4*), whilst proton *3* shifted upfield (Figure 1c). In contrast, modest upfield shifts were detected for all pyridinium protons upon addition of nitrate to the interlocked host **27·(OTf)$_3$**. Job plot approximations and WinEQNMR2[43] analysis of the titration data for [2]rotaxanes **19·PF$_6$**, **20·(PF$_6$)$_2$** and **27·(OTf)$_3$** determined the 1:1 stoichiometric association

constants for Cl^- and NO_3^- (Table 1), which were determined to be independent of the proton monitored for a given anion and are compared with the previously mentioned bis-amide HB analogue **28·PF$_6$** (Figure 2).[29]

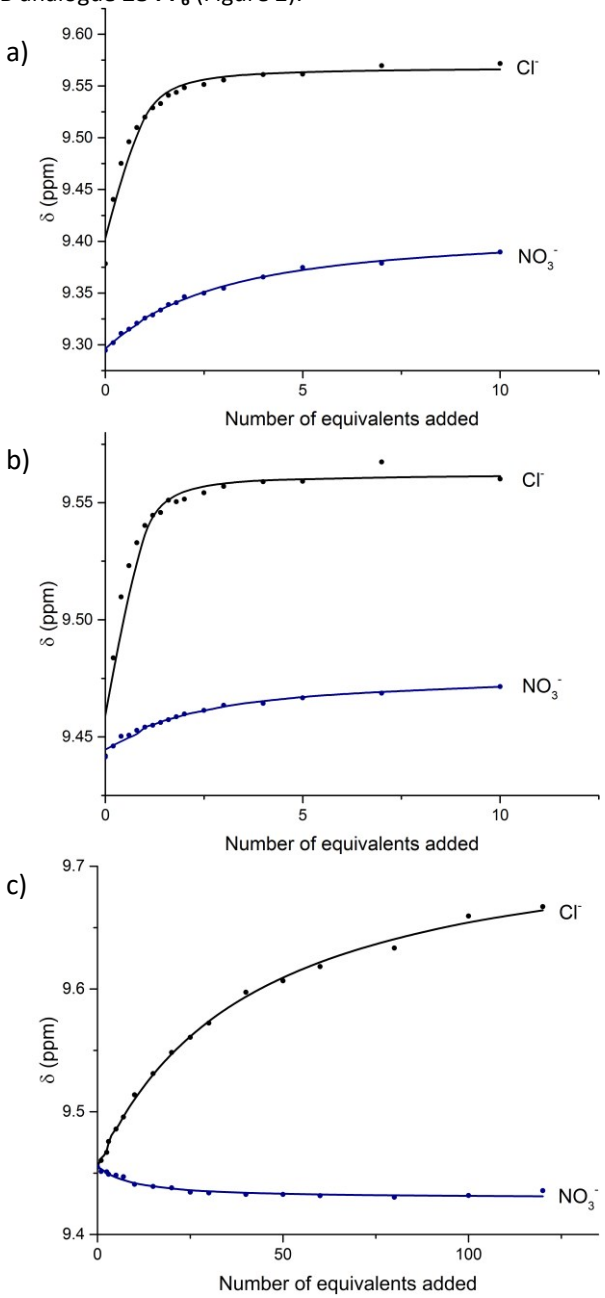

Figure 1: Anion binding titrations: (a) **19·PF$_6$** following pyridinium proton *j* (1:1 $CDCl_3$:CD_3OD), (b) **20·(PF$_6$)$_2$** following the external pyridinium protons *j,k* in the aqueous solvent mixture 45:45:10 $CDCl_3$:CD_3OD:D_2O, and (c) **27·(OTf)$_3$** following pyridinium proton *j*. Experimental titration data (circles) with WinEQNMR2[43] fitted binding isotherms indicated as lines (298 K).

The [2]rotaxane **19·PF$_6$** shows strong binding for chloride in 1:1 $CDCl_3$:CD_3OD. Although binding for nitrate is much weaker than chloride by an order of magnitude, indicating chloride selectivity, the [2]rotaxane host displays notable binding for the oxoanion in this competitive solvent mixture. Moreover, this represents only the second example of nitrate binding by an interlocked halogen-bonding receptor.[44]

In the relatively more competitive aqueous mixture 45:45:10 $CDCl_3$:CD_3OD:D_2O, the dicationic XB [2]rotaxane **20·(PF$_6$)$_2$** binds chloride so strongly (K_a > 10^4 M^{-1}) that it was not possible to determine an accurate K_a value. This is in stark contrast to the previously reported all hydrogen-bonding [2]rotaxane analogue **28·PF$_6$** which exhibited much weaker chloride binding affinity (K_a = 490 M^{-1}). The binding for nitrate with the XB rotaxane **20·(PF$_6$)$_2$** is weaker (K_a = 364 M^{-1}), however, considering the challenge that nitrate recognition represents with its low basicity, the relative strength of association in this aqueous mixture is noteworthy. Interestingly, the halogen-bonding [2]rotaxane **20·(PF$_6$)$_2$** bound nitrate with comparable strength to the previously reported all hydrogen-bonding [2]rotaxane analogue **28·PF$_6$** (K_a = 430 M^{-1}).[29]

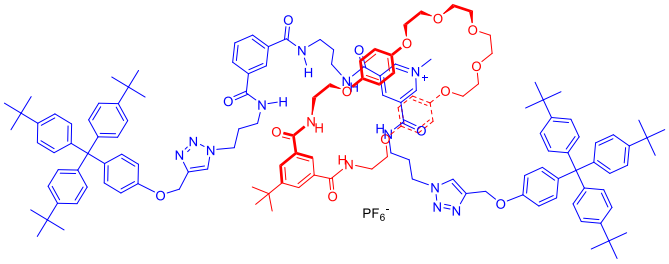

Figure 2: Structure of the previously reported HB [2]rotaxane **28·PF$_6$** for nitrate.[29]

Table 1: Association constants (K_a)[a] determined for **19·PF$_6$**, **20·(PF$_6$)$_2$** and **27·(OTf)$_3$** with various anions as either their TBA or Na salts, compared with the bis-amide HB analogue **28·PF$_6$**.

Anion	K_a (M^{-1})[a]			
	19·PF$_6$[b]	**20·(PF$_6$)$_2$**[c]	**27·(OTf)$_3$**[d]	**28·PF$_6$**[c]
Cl^-	7970(1890)	> 10^4	112(16)	490
NO_3^-	374(31)	364(38)	114(4)	430

[a]Estimated standard errors are given in parentheses. Association constants calculated using WinEQNMR2 (298 K),[43] [b]1:1 $CDCl_3$:CD_3OD, [c]45:45:10 $CDCl_3$:CD_3OD:D_2O, [d]9:1 D_2O:acetone-d_6. Errors estimated to be < 10%.

The tricationic [2]rotaxane **27·(OTf)$_3$** binds both chloride and nitrate in competitive aqueous 9:1 D_2O:acetone-d_6 with equal strength: $K_a(Cl^-)$ = 112 and $K_a(NO_3^-)$ = 114 M^{-1}. The incorporation of additional positive charge makes the [2]rotaxane capable of recognising both anions in 90% water, and results in enhanced anion binding ability when compared to the mono- and dicationic [2]rotaxanes. Although the anion binding cavity is evidently complementary towards the trigonal geometry of nitrate, it does not preclude the binding of the spherical halide anion. Presumably, a more rigid axle component joining the two bis-iodotriazole pyridinium groups would preorganise the host to a greater extent and improve the selectivity for nitrate over chloride (and other halide anions). Nonetheless, whilst the receptor shows no selectivity between chloride and nitrate, increasing the percentage of water from 10% to 90% appears to have a much more detrimental influence upon chloride anion binding than the nitrate oxoanion, which reflects the higher hydration enthalpy of chloride ($\Delta H_{hyd}(Cl^-)$ = −381 kJ mol^{-1} vs $\Delta H_{hyd}(NO_3^-)$ = −314 kJ mol^{-1}).[27, 45] Indeed, the relatively strong binding of nitrate in

this aqueous mixture presents an important step towards nitrate recognition in pure water.

Conclusions

With the objective of demonstrating XB nitrate anion recognition in aqueous media, three novel XB [2]rotaxane anion host systems comprising of XB axle components containing two 3,5-bis-iodotriazole pyridine or pyridinium units and HB isophthalamide or bis-amide pyridinium macrocycles were prepared *via* a chloride anion-templated mono-stoppering methodology.

^{1}H NMR chloride and nitrate anion binding investigations revealed all three [2]rotaxanes to exhibit an affinity for both anions. Nitrate was bound in solutions containing increasing proportions of water, which correlated with increasing positive charge of the [2]rotaxane host system. While in the case of the monocationic [2]rotaxane **19·PF$_6$**, a significantly higher affinity and selectivity for chloride was observed in 1:1 $CDCl_3$:CD_3OD, the tricationic permethylated β-cyclodextrin-stoppered [2]rotaxane **27·(OTf)$_3$** displayed equivalent binding affinity for chloride and nitrate in 9:1 D_2O:acetone-d_6. Importantly, increasing the solvent water percentage from 10% to 90% was shown to have a greater effect upon the binding of chloride than the oxoanion, and correlates with their relative energies of hydration. Whilst the trigonal design of the interlocked XB anion binding site complements the geometry of nitrate, it is still able to accommodate the spherical chloride anion, possibly owing to flexibility in the axle component. These results however represent a significant step towards achieving selective nitrate recognition and illustrate the impressive potential of XB receptors for anion recognition in aqueous media.

Acknowledgements

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Notes and references

‡ Substitution was ordered in this way due to inclusion of **12** within the cavity of the pCD stopper **11**, which also explains the reduced yield of the unsymmetrically substituted intermediate **22**. However, a nominal quantity of **23** was obtained from the CuAAC click reaction between **12** and **11**, which constituted one half of the axle component.

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