Clipping and Stoppering Anion Templated Synthesis of a [2]Rotaxane Host System

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A new [2]rotaxane host system containing nitro-isophthalamide macrocycle and polyether functionalised pyridinium axle components is prepared via clipping and stoppering synthetic methodologies using chloride anion templation. After removing the chloride anion template, 1H NMR titration experiments reveal the unique interlocked host cavity to be highly selective for binding chloride and bromide in preference to basic oxoanions in competitive aqueous solvent mixtures. The rotaxane host system proved to be a superior anion complexant in comparison to the individual macrocycle and axle components. The anion binding affinity of the novel rotaxane is also investigated via molecular dynamics simulations and in general the structural data obtained corroborates the experimental solution anion recognition behaviour.

Introduction
Inspired by potential nanotechnological applications as components of molecular machines and switches, the innovative design and construction of interlocked molecules is an area of ever increasing research activity.[1] In spite of this huge interest the potential exploitation of these molecules to function as molecular recognition and sensory reagents has been largely overlooked which is surprising given their unique, topologically, constrained three dimensional host cavities can be engineered to bind specific guest species during their template-driven syntheses.[2]

With this in mind we have undertaken a research programme with the objective of exploiting the cavities of rotaxanes and catenanes for anion recognition purposes.[3, 4] An anion templating strategy has been developed in which a pyridinium chloride ion-pair is used as an axle threading component through an isophthalamide macrocycle for interweaved molecular assembly.[5, 6] Herein a new rotaxane host system which contains a nitro-isophthalamide macrocycle and polyether appended pyridinium axle components is described, prepared via clipping and stoppering anion templation synthetic methodologies. Anion binding studies reveal the unique interlocked host cavity to be highly selective for binding chloride and bromide in preference to basic oxoanions in competitive aqueous solvent mixtures.

Results and Discussion
Synthetic Strategy: Two complementary synthetic strategies were employed for the anion templated synthesis of a new [2]rotaxane, clipping (Scheme 1a) and stoppering (Scheme 1b).

Scheme 1. (a) Clipping and (b) stoppering strategies of anion templated isophthalamide-pyridinium rotaxane synthesis.
Scheme 2. Synthesis of pyridinium chloride ion-pair thread 3-Cl.

The macrocycle, macrocycle precursor, axle and threading components required for the respective synthetic procedures are shown in Scheme 1. It was anticipated that either ring closing metathesis of a vinyl appended isophthalamide receptor encircling a stopped pyridinium chloride axle, or urethane stoppering of a pyridinium chloride thread-isophthalamide macrocycle pseudorotaxane assembly, would generate the target [2]rotaxane.

Bis-vinyl macrocycle precursor 1 and macrocycle 2 were prepared using modified literature procedures. [5] The synthetic route used to prepare the new threading component 3-Cl is shown in Scheme 2. Diethylene glycol was stirred with 0.25 equivalents of tosyl chloride to give the mono-tosylated derivative 5 in 74% yield after column chromatography. Compound 5 was then refluxed with 4-hydroxyphenylacetamide in the presence of potassium carbonate to give the polyether derivative 6 in good yield. Hydrolysis of the secondary amide group was achieved with sodium hydroxide in an EtOH/H2O solvent mixture to give amine 7 which was then reacted with 3,5-pyridinedicarboxylic acid using N-(3-dimethylaminopropyl)-N’-ethylcarbodiimide hydrochloride (EDC·HCl) and 1-hydroxybenzotriazole (HOBt) as coupling reagents to give the bis-amide compound 8 in 47% yield. Alkylation of the pyridine ring with iodomethane gave the pyridinium iodide derivative 3-I in 92% yield. The pyridinium chloride thread 3-Cl could be obtained in quantitative yield using an Amberlite chloride exchange column.

The synthetic route used to synthesise the stopped pyridinium thread needed for rotaxane synthesis using a clipping methodology is shown in Scheme 3. Two equivalents of isocyanate terphenyl stopper compound 9 [7] were stirred with 8 and a catalytic amount of dibutyltin dilaurate in dichloromethane to afford 10 in 73% yield. This was then alkylated using trimethyloxonium tetrafluoroborate to afford the pyridinium tetrafluoroborate derivative 4-BF4 in 92% yield. Anion exchange was achieved by washing 4-BF4 with a saturated aqueous solution of NH4Cl to give stopped pyridinium chloride axle 4-Cl in quantitative yield.
Rotaxane synthesis via the clipping method: Initial rotaxane synthesis attempts focused on a clipping strategy, in which ring closing metathesis of a vinyl appended macrocycle precursor around the stoppered pyridinium thread 4-C1 would afford the desired interlocked architecture. Equimolar amounts of bis-vinyl appended macrocycle precursor 1 and stoppered pyridinium chloride axle 4-C1 were mixed in dry CH2Cl2. Grubbs’ 2nd generation catalyst (5 % by weight) was added to the mixture and the rotaxane chloride salt 11-C1 was isolated in 55 % yield by column chromatography using 96:4 CH2Cl2/MeOH as eluent (Scheme 4).

The $^1$H NMR spectrum of rotaxane 11-Cl in CDCl$_3$ as compared with that of macrocycle 2 and axle 4-Cl is shown in Figure 1. Significant upfield shifts and splitting of the nitro-isophthalamide macrocyclic hydroquinone protons H$_e$ ($\Delta \delta = 0.34$ ppm) and H$_f$ ($\Delta \delta = 0.63$ ppm) was observed in the spectrum of 11-Cl. This is indicative of $\pi$-$\pi$ stacking between the positively charged pyridinium motif and the hydroquinone aromatic rings, which is characteristic of interpenetration.\[9\]

Downfield shifts were also observed for the macrocyclic nitro-isophthalamide amide H$_i$ ($\Delta \delta = 1.54$ ppm) and aryl protons H$_j$ ($\Delta \delta = 0.68$ ppm) and H$_k$ ($\Delta \delta = 0.13$ ppm) which is indicative of anion binding. Moreover, an upfield shift of the pyridinium amide axle protons H$_d$ ($\Delta \delta = 0.94$ ppm) was observed. This is a result of the polarisation of the chloride anion towards the amide proton donor groups of the macrocycle which in turn reduces the strength of the hydrogen bonding interaction between the anion and the amide groups of the pyridinium cation axle. The disappearance of the characteristic multiplets associated with the vinyl protons of reactant 1 and the appearance of a singlet at 6.09 ppm corresponding to the cyclised double bonds (See ESI) is typical of a successful RCM reaction. Furthermore, a downfield shift was observed for N-methyl pyridinium proton H$_a$ ($\Delta \delta = 0.24$ ppm) of the rotaxane which is indicative of hydrogen bonding interactions between the methyl group of the pyridinium axle and the macrocyclic polyether ring.

Fig. 1. Selected region of the $^1$H NMR (500 MHz, 298 K, CDCl$_3$) spectra of (a) macrocycle 2, (b) rotaxane 11-Cl and (c) thread molecule 4-Cl. For proton labelling see Scheme 4.

The structure of rotaxane 11-Cl was further investigated using ROESY $^1$H-$^1$H NMR spectroscopy in CDCl$_3$. The spectrum shown in Figure 2 highlights through-space proton-proton correlation signals arising from aromatic stacking interactions between macrocycle and axle components of the rotaxane. Near in space correlations between the para-pyridinium H$_c$ and aryl protons H$_e$ and H$_f$ of the pyridinium axle molecule and the hydroquinone proton H$_e$ of the macrocycle is a result of stabilising $\pi$-$\pi$ stacking interactions between the positively charged electron deficient pyridinium motif and the macrocyclic electron rich hydroquinone groups. Similarly through space correlations between the aryl protons (H$_j$ and H$_k$) of the axle molecule and the macrocyclic nitro-isophthalamide protons (H$_i$ and H$_d$) are indicative of a $\pi$-$\pi$ stacking interaction between the electron-rich aryl groups and...
Fig. 2. ROESY spectrum of 11-Cl in CDCl₃ at 298 K, showing the through space correlation between macrocycle and pyridinium axle via π-π stacking and hydrogen bonding.

the electron-deficient nitro-isophthalimide group of the macrocycle. In addition, strong through space interactions between pyridinium N-methyl protons Hₙ and polyether protons (Hₐ, Hₗ and Hₜ) were observed indicative of hydrogen bonding interactions between the pyridinium methyl group and the oxygen atoms of the macrocyclic polyether.

Rotaxane synthesis via the stoppering method: In order to assess whether the synthesis of the same rotaxane could be achieved via a stoppering method, anion templated pseudorotaxane formation between 3-Cl and 2 was investigated initially by ¹H NMR (Scheme 5).

Upon addition of one equivalent of 3-Cl to a 1:1 CDCl₃/CD₃CN solution of 2, significant upfield shifts and splitting of the macrocyclic hydroquinone protons Hₑ (Δδ = 0.06 ppm) and Hₕ (Δδ = 0.11 ppm) were observed (Figure 3), characteristic of π-π stacking between the positively charged pyridinium motif and the hydroquinone protons.[9] Chloride anion bound induced downfield shifts were also observed for the macrocycle amide protons Hᵢ (Δδ = 0.27 ppm) and aryl protons Hⱼ (Δδ = 0.18 ppm) and Hₖ (Δδ = 0.01 ppm) concomitant with upfield shifts of the amide protons Hᵣ (Δδ = 0.50 ppm) and aromatic pyridinium proton Hᵦ (Δδ = 0.35 ppm) of 3-Cl, all of which is suggestive of pseudorotaxane formation.

Scheme 5. Pseudorotaxane formation of 2 and 3-Cl in 1:1 CDCl₃/CD₃CN
Fig. 3. $^1$H NMR (500 MHz, 298 K, 1:1 CDCl$_3$/CD$_3$CN) spectra of (a) macrocycle 2, (b) pseudorotaxane 12-Cl and (c) pyridinium chloride thread 3-Cl. For proton labelling see Scheme 5.

Taking into account the promising results of the pseudorotaxane study, rotaxane synthesis adopting a stopping strategy was undertaken. An equimolar mixture of 2 and 3-Cl was stirred in 1:1 CH$_2$Cl$_2$/MeCN for 1 hour to facilitate the assembly of the pseudorotaxane. Two equivalents of isocyanate stopper 9 and a catalytic amount of dibutyl tin dilaurate were then added and the resulting mixture was stirred under N$_2$ for 72 hours. Following workup and column chromatography using 96:4 CH$_2$Cl$_2$/MeOH as the eluent the target rotaxane 11-Cl was isolated 21 % yield (Scheme 6).

The yield of the rotaxane obtained by the stoppering method is significantly lower than that obtained by the clipping method (55 %), presumably this is a consequence of the more competitive CH$_2$Cl$_2$/CH$_3$CN solvent mixture (necessary for the solubility of starting materials) used during the stoppering synthesis.

Anion binding studies: In order to investigate the anion binding properties of the rotaxane, the chloride anion templated was removed by washing a CH$_2$Cl$_2$ solution of the chloride salt 11-Cl with 0.1 M NH$_4$PF$_6$(aq) to afford hexafluorophosphate salt 11-PF$_6$ in quantitative yield.[4]

Comparing the $^1$H NMR spectra of the rotaxane salts in CDCl$_3$, significant upfield shifts of isophthalamide and pyridinium protons were observed in the $^1$H NMR spectrum of 11-PF$_6$ due to the loss of hydrogen bonding interactions with the encapsulated templating chloride anion. Anion exchange was also confirmed by $^{19}$F and $^{31}$P NMR spectra.

The anion binding properties of rotaxane 11-PF$_6$ were initially investigated in the solvent mixture 1:1 CDCl$_3$/CD$_3$OD. Upon addition of one equivalent of chloride, significant downfield shifts of para-pyridinium proton of the axle H$_c$ ($\Delta\delta = 0.34$ ppm) and para-aryl proton of the macrocycle H$_j$ ($\Delta\delta = 0.24$ ppm) were observed indicating anion complexation. The binding stoichiometry was determined to be 1:1 host/anion by Job plot analysis. The titration data analysed by WinEQNMR[10] software reveals that rotaxane 11-PF$_6$ complexes Cl$^-$ and Br$^-$ very strongly in this solvent mixture of 1:1 CDCl$_3$/CD$_3$OD ($K_a > 10^4$ M$^{-1}$) (Table 2). In addition 11-PF$_6$ exhibits relatively weaker binding with o xoanions such as SO$_4^{2-}$, HSO$_4^-$, OAc$^-$ and H$_2$PO$_4^-$ due to unfavourable size complementarity. In order to quantify the selectivity of rotaxane 11-PF$_6$ for these halide anions the titration experiments were repeated in the more competitive aqueous solvent mixture of 45:45:10 CD$_3$OD/CDCl$_3$/D$_2$O. Again, upon addition of one molar equivalent of TBA chloride to the rotaxane, significant downfield shifts of para-pyridinium proton H$_c$ ($\Delta\delta = 0.22$ ppm) and para-aryl proton H$_j$ ($\Delta\delta = 0.23$ ppm) of 11-PF$_6$ were observed (Figure 4).
Association constants, determined by WinEQNMR analysis of the titration data (Figure 5), are reported in Table 2. In comparison to macrocycle 2 and axle 4-BF₄ (Table 1), the anion recognition ability of rotaxane 11-PF₆ is enhanced dramatically due to the cooperative hydrogen bond donating ability of the rotaxane cavity containing two orthogonal amide clefts. For example, in 45:45:10 CD₃OD/CDCl₃/D₂O, the rotaxane exhibits a significantly stronger binding affinity for dihydrogen phosphate and acetate anions more weakly. The rotaxane exhibits a significantly stronger binding affinity for dramatically due to the cooperative hydrogen bond donating 5
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Furthermore, in comparison to [2]rotaxanes reported previously which selectively bind chloride in 1:1 CD₂OD/CDCl₃ with association constants of up to \( K_a = 4500 \) M⁻¹,[5] the recognition ability of rotaxane 11-PF₆ for chloride is significantly enhanced (\( K_a > 10^4 \) M⁻¹ in 1:1 CD₂OD/CDCl₃). Even in the aqueous solvent mixture, rotaxane 11-PF₆ still performs as a superior anion host. This suggests that the novel design of the two sets of π-π stacking interactions between the positively charged electron deficient pyridinium motif and the macrocyclic electron rich hydroquinone groups as well as between the electron-rich aryl groups and the electron-deficient nitro-isophthalamide group of the macrocycle, help preorganise the rotaxane’s unique interlocked binding cavity which is of complementary size and shape for selectively binding chloride and bromide in preference to larger oxoanions.

Table 1. Association constants (M⁻¹) of macrocycle 2 (determined by para-nitro-isophthalamide proton Hj) and axle 4-BF₄ (determined by para-pyridinium proton Hj) with anions in competitive solvents at 298 K (estimated errors less than 10 %).

<table>
<thead>
<tr>
<th>Anion</th>
<th>( 2^\text{[a]} )</th>
<th>4-BF₄ ( \text{[b]} )</th>
<th>2^\text{[c]}</th>
<th>4-BF₄^\text{[c]}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cl⁻</td>
<td>&gt;10⁴</td>
<td>4610</td>
<td>N.B.</td>
<td>140</td>
</tr>
<tr>
<td>Br⁻</td>
<td>&gt;10⁴</td>
<td>1820 (a)</td>
<td>N.B.</td>
<td>120</td>
</tr>
<tr>
<td>AcO⁻</td>
<td>50</td>
<td>475</td>
<td>N.B.</td>
<td>180</td>
</tr>
<tr>
<td>SO₄²⁻</td>
<td>1000</td>
<td>1100</td>
<td>N.B.</td>
<td>45</td>
</tr>
<tr>
<td>F⁻</td>
<td>---</td>
<td>850</td>
<td>---</td>
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</tr>
<tr>
<td>I⁻</td>
<td>---</td>
<td>315</td>
<td>---</td>
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</tr>
<tr>
<td>HSO₄⁻</td>
<td>765</td>
<td>235</td>
<td>---</td>
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</tr>
<tr>
<td>OAc⁻</td>
<td>1040 (a)</td>
<td>180</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>H₂PO₄⁻</td>
<td>355</td>
<td>340</td>
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</tr>
</tbody>
</table>

[a] in 1:1 CD₂OD/CDCl₃ and [b] in 45:45:10 CDCl₃/CD₂OD/D₂O.

Table 2. Association constants (M⁻¹) of 11-PF₆ (determined by para-pyridinium proton Hj) with anions in competitive solvents at 298K (estimated errors less than 10 %).

<table>
<thead>
<tr>
<th>Anion</th>
<th>11-PF₆ ( \text{[a]} )</th>
<th>11-PF₆ ( \text{[c]} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cl⁻</td>
<td>&gt;10⁴</td>
<td>4610</td>
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<td>1820 (a)</td>
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<tr>
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<td>F⁻</td>
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<tr>
<td>I⁻</td>
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<tr>
<td>HSO₄⁻</td>
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<td>355</td>
<td>340</td>
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</table>

[a] in 1:1 CD₂OD/CDCl₃, [b] in 45:45:10 CDCl₃/CD₂OD/D₂O and [c] determined by ortho-nitroisophthalamide proton Hj.

Modelling studies: The anion binding ability of 11⁻ was also investigated by means of molecular mechanics and molecular dynamics (MD) simulations carried out for Cl⁻, Br⁻, SO₄²⁻, OAc⁻ and H₂PO₄⁻ anion associations using the AMBER 11 software package.[11] The [2]rotaxane and o xo anions were described with force field parameters taken from GAFF[12] and RESP atomic charges.[13] Remaining computational details are given in supplementary material.

The structures of chloride and polyatomic anions assembled with rotaxane 11 were generated in the gas phase via an MD quenching approach. Among the 2000 docking conformations saved for the 11⁻-Cl complex, the structures of the most populated cluster revealed a similar binding arrangement as found in other related rotaxane systems.[56,14] As illustrated in Fig. 6 with a representative structure, the chloride anion establishes concomitantly four N-H•••Cl hydroxide bonds with the axle pyridinium motif and macrocyclic nitro-isophthalamide unit, which adopt an orthogonal binding arrangement stabilized by π-π stacking interactions between the pyridinium moiety and the two hydroquinone rings of the macrocycle. In addition, the...
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Fig. 6. A representative energy minimised syn-syn co-conformation of 11-Cl complex showing two sets of π-π stacking interactions between the aromatic rings of macrocycle and axle components. The carbon atoms of the macrocycle are in gray and of the axle in orange. The majority of C-H hydrogen atoms have been omitted for clarity and the N-H•••Cl hydrogen bonds are drawn as yellow dashed lines.

electron-deficient nitro-isophthalamide cleft is also involved in π-π stacking interactions with one electron-rich oxyaniline group of the thread leading to a three-dimensional rotaxane binding cavity. In conformational analysis no co-conformations involving the simultaneous π-π stacking of the two oxyaniline groups was observed. The molecular mechanics structure of 11-Cl is entirely consistent with the solution NMR structural findings. Equivalent topological binding scenarios between the polyatomic anions OAc−, SO42− and H2PO4− and 11 were also clustered.

Afterwards, selected low energy structures of rotaxane halide (Cl− and Br−) and oxoanion (SO42−, OAc− and H2PO4−) complexes were immersed in periodic cubic boxes of a CHCl3/CH3OH/H2O (45:45:10) explicit solvent mixture and their dynamic structural behaviours were evaluated by MD simulations for 15 ns. The starting structure of 11-Br complex was obtained from the 11-Cl counterpart replacing chloride with the bromide anion.

Selected snapshots taken from the MD simulations of rotaxane halide and oxoanion complexes showing the anions surrounded by their 2nd solvent shells (see below) are presented in Figs. 7 and 8 respectively. In Cl−, Br− and OAc− complexes, the pyridinium and isophthalamide clefts are assembled in an almost orthogonal fashion held by four uninterrupted hydrogen bonds established with the anions. In SO42− and H2PO4− associations, the rotaxane orthogonal arrangement is assisted by multiple N-H•••O hydrogen bonds based on the intermittent swapping of all the oxygen atom interactions, which contributes to the weakening of the oxoanion-rotaxane binding.

The distances between the pyridinium motif and the hydroquinone rings of the macrocycle (Cpy•••Cphyd) and between the nitro-isophthalamide cleft and the two axle’s oxyaniline rings (Ciso•••Coxy) were monitored during the course of MD simulations. The average values with their standard deviations, reported in Table 3, show that the two sets of π-π stacking interactions between the aromatic rings of the macrocycle and axle components found in the gas phase are preserved in solution over the entire time of the MD simulations carried out with the different anions. In addition, the two sets of Cpy•••Cphyd average distances reported, one shorter and other extensively longer (for instance 4.01 and 9.71 Å in 11-Cl complex) show that only one axle’s electron rich oxyaniline ring is face to face with the electron deficient nitro-isophthalamide ring of the macrocycle while the other is faraway from the rotaxane binding cavity.
The distance from the anion (A') to the centre of binding cavity (C_N4), determined by the four nitrogen binding sites from the two amide clefts, was also evaluated and their average values together with the standard deviations are also given in Table 3. The chloride (1.50 Å) is located preferentially inside of the binding pocket whereas the bromide anion (1.65 Å) has a propensity to remain barely outside of the binding cavity. In contrast, the average distances for sulphate (2.55 Å) and dihydrogen phosphate (2.52 Å) reveal that these polyatomic anions are too large in size to enter into the three dimensional rotaxane binding cavity. Furthermore, the larger standard deviations of this structural parameter indicate that rotaxane 11 binds these anions weakly. The carboxylate group of the more basic oxoanion OAc' is on average only 1.62 Å away from the binding cavity. Nevertheless, as with the other two polyatomic anions and in contrast with the monoatomic ones, the acetate methyl group is clearly located outside of the rotaxane binding pocket, as can be seen clearly in Fig. 8. It is noteworthy, that the Cl' anion having the shorter A'•••C_N4 distance is more strongly bonded to the rotaxane system than the remaining anions, which is in agreement with experimental binding data (see Table 2).

Further insights on the binding affinity of 11 for halides and oxoanions can be acquired by counting the number of methanol, water and chloroform molecules of the competitive aqueous solvent mixture around the anions along the MD simulations. The average number of solvent molecules found in the first and the second solvent shells are listed in Table 4.

In rotaxane complexes, apart from sulphate all the anions are preferentially solvated in the first and second solvation shells by methanol molecules. In 11-SO_4^{2-} association, the anion is mostly surrounded by water molecules in both solvent shells. As would be expected, chloroform solvates poorly the anions and the number of solvent molecules only increases near the solution bulk. This is particularly evident in the second solvent shells of OAc' and H_2PO_4^{2-} with average number of chloroform molecules of 1.6 and 2.6, respectively.
These numbers are understandable taking into account that the methyl acetate group and the phosphate anion are located outside the binding pocket and are therefore exposed to the solvent. However, the cut-off used for the solvent second shell (5.0 Å) is near the solvent bulk approach and the subsequent discussion will be limited to the first methanol and water solvent shells. As shown above, the rotaxane 11 shields the halide anions from the solvent mixture leading to a small average number of methanol molecules of 1.4 for chloride and 1.6 for bromide. In contrast, the inorganic polyatomic anions, located outside of the binding pocket, are exposed to the polar solvents and their solvent shells are composed of a significant number of solvent molecules: 4.9 water molecules for sulphate and 2.9 methanol molecules for dihydrogen phosphate. Naturally, the $\pi$-$\pi$ distances and the solvation strength of association depends largely on the number of water molecules within the oxoanion solvation shells.

Conclusions

A novel [2]rotaxane, containing nitro-isophthalamide macrocycle and polyether appended pyridinium axle components, has been synthesised via both clipping and stoppering synthetically using an anion templation strategy. The rotaxane is characterised by $^1$H NMR, ROESY $^1$H-$^1$H NMR spectroscopy and ESI mass spectrometry. Through space correlation studies reveal that two sets of $\pi$-$\pi$ stacking interactions between the aromatic rings of macrocycle and axle components form a topologically unique three dimensional binding cavity. This structural feature is corroborated by molecular dynamics simulations carried out in a competitive aqueous solvent medium. After removing the chloride anion template, $^1$H NMR titration experiments reveal this preorganised interlocked host to be highly selective for binding chloride and bromide in preference to basic oxoanions in competitive aqueous solvent mixtures. The rotaxane host system proved to be a superior anion complexant in comparison to the individual macrocycle and axle components, and other isophthalamide-pyridinium rotaxane systems reported previously. The molecular dynamics structural data show that the superior binding affinity of the rotaxane for chloride and bromide anions in comparison with polyatomic oxoanions can be rationalised by the halide anions penetrating the interlocked binding pocket which protects them from solvent molecules. Since the oxoanions are unable in size to be encapsulated within the binding pocket, the strength of association depends largely on the number of water molecules within the oxoanion solvation shells.

Experimental

Materials and Instruments

Dry solvents were obtained by purging with nitrogen and then passing through a MBraun MPS-SP-800 column. Water was deionised and microfiltered using a Milli-Q® Millipore machine. All tetrabutylammonium (TBA) salts, silver hexafluorophosphate, Grubbs’ 2nd generation catalyst were stored in a vacuum desiccator over phosphorus pentoxide prior to use. Triethylamine was distilled from and stored over potassium hydroxide. Triethyl chloride was distilled over triphenyl phosphate. All other solvents and commercial grade reagents were used without further purification unless otherwise noted.

Column chromatography was performed on silica gel (160-200 mesh), and thin-layer chromatography (TLC) was performed on preparative silica gel GF plates with UV254 (1000 microns, Analtech, USA). $^1$H, $^{13}$C, $^{19}$F and $^{31}$P NMR spectra were recorded on a Varian Mercury VX300 or Varian Unity Plus 500 spectrometer. Mass spectrometry was performed on a Bruker microTOF (ESI) or a Waters Micromass MALDI micro MX (MALDI-TOF) mass spectrometer. Microwave reactions were carried out using a Biotage Initiator 2.0 microwave.

Syntheses

Synthesis of 8: A solution of 7 (0.50 g, 2.5 mmol), 3,5-pyridine-dicarboxylic acid (0.21 g, 1.3 mmol), 3-N,N-dimethylaminopropyl-N'-ethylcarbodiimide hydrochloride (EDC) (0.51 g, 2.7 mmol), 1-hydroxybenzotriazole (HOBt) (0.36 g, 2.7 mmol) and triethylamine (0.5 mL, 3.6 mmol) in 1:1 CH$_3$Cl$_2$/THF (100 mL) was stirred under N$_2$ for 24 hours. After this time the solvent was concentrated in vacuo and the residue was purified by column chromatography using 4:1 CH$_3$Cl$_2$/MeOH as the eluent to give the pure product as a pale white solid (0.31 g, 47 %); $^1$H NMR (300 MHz, DMSO-$_d_6$, 298 K): $\delta$ 10.49 (2H, s, -NH$_2$), 9.23 (2H, d, $^3$J = 1.8Hz, ArH), 8.79 (1H, t, $^2$J = 2.1Hz, $^4$J = 3.7Hz ArH), 7.69 (4H, d, $^3$J = 9.1Hz, ArH), 6.97 (4H, d, $^3$J = 9.1Hz, ArH), 4.65 (4H, t, -OH$_2$), 4.10-4.07 (4H, m, -CH$_2$), 3.76-3.73 (4H, m, -CH$_2$-), 3.52-3.49 (8H, m, -CH$_2$$_2$); $^{13}$C NMR (75 MHz, DMSO-$_d_6$, 298 K): $\delta$ 163.4, 155.5, 151.2, 134.9, 132.3, 130.7, 122.4, 114.9, 72.9, 69.4, 67.7, 60.7; ESI-MS (m/z): [M + Na]$^+$ 548.004, C$_{12}$H$_{16}$N$_2$O$_6$Na (calc. 548.003).

Synthesis of 3-I: Compound 8 (0.30 g, 0.57 mmol) was dissolved in excess iodomethane (5 mL) and acetone (20 mL) and was refluxed under N$_2$ for 48 hours. After this time, diethyl ether (50 mL) was added and the filtration was performed on a Biotage Initiator 2.0 microwave. The compound was isolated to give the pure product as a yellow solid (0.35 g, 92 %); $^1$H NMR (300 MHz, DMSO-$_d_6$, 298 K): $\delta$ 11.09 (2H, s, -NH$_2$), 9.23 (1H, s, ArH), 9.68 (2H, s, ArH), 7.77 (4H, d, $^3$J = 9.1 Hz, ArH), 7.02 (4H, d, $^3$J = 9.1 Hz, ArH), 4.65 (2H, t, -OH$_2$), 4.49 (3H, s, -CH$_2$-), 4.12-4.09 (4H, m, -CH$_2$), 3.76-3.73 (4H, m, -CH$_2$), 3.53-3.48 (8H, m, -CH$_2$$_2$); $^{13}$C NMR (125 MHz, CD$_3$OD, 298 K): $\delta$ 160.7, 157.7, 148.3, 142.7, 133.5, 132.1, 123.7, 115.8, 73.8, 70.7, 68.9, 62.2, 49.9; ESI-MS (m/z): [M - I]$^+$ 540.2354, C$_{12}$H$_{16}$N$_2$O$_6$ (calc. 540.2340).

Synthesis of 3-Cl: A solution of 3-I (0.35 g, 0.52 mmol) in...
Synthesis of 5:

A solution of 4 (0.3067 g, 0.103 mmol) and 4-Cl (0.156 g, 0.103 mmol) were dissolved in dry dichloromethane (20 mL) and stirred under N₂ for 30 minutes. Grubbs' catalyst 2nd generation (5 mg) was then added and the mixture was stirred for 48 hours. The solvent was removed in vacuo and the residue was purified by column chromatography using 96:4 CH₂Cl₂/MeOH as the eluent to give the pure product as a yellow solid (0.121 g, 55%).

Synthesis of 11 by stoppering method: A solution of 2 (0.0670 g, 0.0993 mmol) and 3-Cl (0.0572 g, 0.0993 mmol) in 1:1 CH₂Cl₂/MeCN (20 mL) was stirred under N₂ for one hour.

Isocyanate stopper 9 (0.0943 g, 0.199 mmol) and dibutyltin dilaurate (Sn catalyst) (0.0630 g, 0.0995 mmol) were then added and the mixture was stirred under N₂ for 72 hours. After this time the solvent was removed in vacuo and the residue was purified by column chromatography column using 25:1 CH₂Cl₂/MeOH as the eluent to give the pure product as a yellow solid (44.7 mg, 21%); ¹H NMR (500 MHz, CDCl₃, 298 K): δ 10.08 (2H, s, -NH₂), 9.93 (1H, s, Ar), 9.12 (1H, s, NO₂-), 8.99 (2H, s, ArNO₂), 8.97 (2H, s, ArH), 8.56 (2H, s, -NH₂), 7.71 (4H, d, J = 8.8 Hz, ArH), 7.30-7.20 (34H, m, ArH), 6.75 (4H, d, J = 8.8 Hz, ArH), 6.18-6.17 (2H, m, CH=CH₂), 6.15 (4H, d, J = 8.8 Hz, ArH), 4.49 (3H, s, -CH₃), 3.47-3.45 (4H, m, -CH₂-), 2.45-2.43 (4H, m, -CH₂-), 1.44-1.43 (4H, m, -CH₂-), 4.00-3.99 (4H, m, -CH₂-), 3.83-3.77 (20H, m, -CH₂-), 1.26 (36H, s, -CH₃). ¹³C NMR (125 MHz, CDCl₃, 298 K): δ 164.3, 158.3, 156.7, 153.5, 153.3, 152.0, 148.5, 148.3, 147.1, 145.4, 143.7, 142.2, 136.9, 135.6, 135.1, 131.5, 131.1, 131.0, 129.6, 129.0, 127.2, 125.9, 125.6, 124.1, 117.5, 115.5, 112.4, 114.5, 114.4, 70.8, 69.7, 69.5, 69.4, 68.1, 67.6, 65.0, 64.2, 63.6, 49.2, 41.4, 34.2, 31.3; ESI-MS (m/z): [M + Na]⁺ 2109.0201, C₁₂₃H₁₄₀N₁₀O₁₀Na (calc. 2109.0133).

Synthesis of 11-PF₆: A solution of 11-CI (0.085 g, 0.040 mmol) in chloroform (5 mL) was washed with 0.1 M NH₄PF₆aq (10 × 2 mL) and water (2 × 2 mL). The organic layer was dried over magnesium sulfate, filtered and the solvent removed in vacuo to give the pure product as a yellow solid (0.086, 96%); ¹H NMR (500 MHz, 1:1 CDCl₃/CD₂OD, 298 K): δ 9.28 (1H, s, NO₂-), 9.10 (2H, s, ArH), 8.83-8.81 (3H, s, ArH & NO₂-), 7.57 (4H, m, ArH), 7.29-7.07 (34H, m, ArH), 6.81 (4H, m, ArH), 6.49 (4H, d, J = 8.8 Hz, ArH), 6.36 (4H, d, J = 9.2 Hz, ArH), 6.08-6.07 (2H, m, CH=CH₂), 4.48 (3H, s, NC₃H₃), 4.31-4.30 (4H, m, -CH₂-), 4.13-4.11 (4H, m, -CH₂-), 4.08-4.06 (4H, m, -CH₂-), 3.84-3.79 (12H, m, -CH₂-), 3.74-3.72 (4H, m, -CH₂-), 1.27 (36H, s, -CH₃), 1.26 (36H, s, -CH₃). ¹³C NMR (125 MHz, CDCl₃, 298 K): δ 164.8, 158.6, 156.6, 153.5, 152.4, 148.5, 148.3, 147.1, 145.5, 143.7, 142.2, 136.9, 135.6, 135.1, 131.5, 131.1, 131.0, 129.6, 129.0, 127.2, 125.9, 125.6, 124.1, 117.5, 115.5, 112.4, 114.5, 114.4, 70.8, 69.7, 69.5, 69.4, 68.1, 67.6, 65.0, 64.2, 63.6, 49.2, 41.4, 34.2, 31.3; ESI-MS (m/z): [M - Cl]⁻ 2109.0133.
All NMR titration experiments were conducted on an Oxford Instruments Varian Unity Plus 500 MHz spectrometer, at 298 K. Initial sample volumes were 600 μL. The starting concentration of the host was 2 mM for all titrations. All anions were added as their TBA salts (0.06 M in 1.0 mL). 17 aliquots of the TBAX solutions (corresponding to 0, 0.2, 0.4, 1.0, 2.0, 3.0, 4.0, 5.0, 7.0, 10.0 equivalents of added guest) were added until a total of 10 equivalents of the anion had been added. Spectra were recorded after each addition, and the sample shaken thoroughly before measurement.

Stability constants were obtained by analysis of the resulting titration data using the WinEQNMR[10] computer program. Estimates for each binding constant, the limiting chemical shifts and the complex stoichiometry were also added to the input file. The various parameters were refined by non-linear least-squares analysis to achieve the best fit between observed and calculated chemical shifts. The parameters were varied until the values for the stability constants converged. Comparison of the calculated binding isotherm with that obtained experimentally demonstrated that the model used was appropriate.

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