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Chloride Recognition in Aqueous Media by a Rotaxane Prepared via a New Synthetic Pathway

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In spite of the rapid growth of the anion supramolecular chemistry field in recent years,[1] the strategic use of anions as templating reagents for the designed assembly of molecular architectures remains largely underdeveloped.[2] This maybe a consequence of their perceived diffuse nature (small charge/radius ratio), pH dependence, and high solvation energies. In particular this is especially the case in the construction of mechanically bonded molecules which have potential nanotechnological applications as molecular switches, machines, and sensors.[3] Regarding the latter we have undertaken a research program with the objective of exploiting the unique topological cavities of rotaxanes and catenanes in anion host–guest chemistry.[4] By coupling anion recognition with ion-pairing we have utilized the chloride anion to facilitate the interpenetration of pyridinium, imidazolium, and guanidinium cationic threads through the annulus of an isophthalamide macrocycle. This has led to the chloride anion templated preparation of rotaxane and catenane systems[5] by Grubbs' first-generation catalyzed ring-closing metathesis (RCM)[6] reactions. Despite the success achieved in the synthesis of these interlocked structures by RCM, there are various limitations to using Grubbs' first-generation catalyst, such as incompatibility with certain ligating functional groups capable of coordinating to the ruthenium metal like pyridyl, that necessitates the exploration of alternative synthetic routes. Herein we describe the preparation of a novel [2]rotaxane, which consists of a pyridyl macrocycle wheel and pyridinium axle components, by a new synthetic pathway that involves anion templation in combination with favorable π–π stacking interactions (Figure 1). In addition preliminary anion binding studies reveal that the rotaxane exhibits an impressive high affinity for chloride in aqueous solvent media in preference to basic oxoanions.

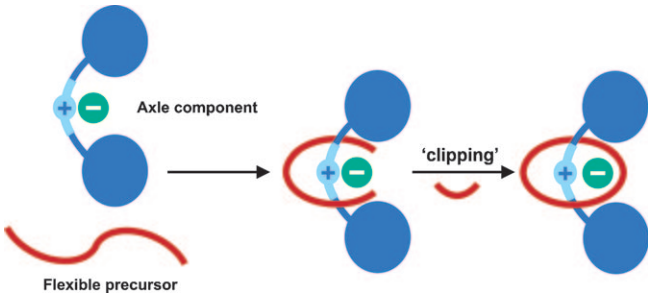
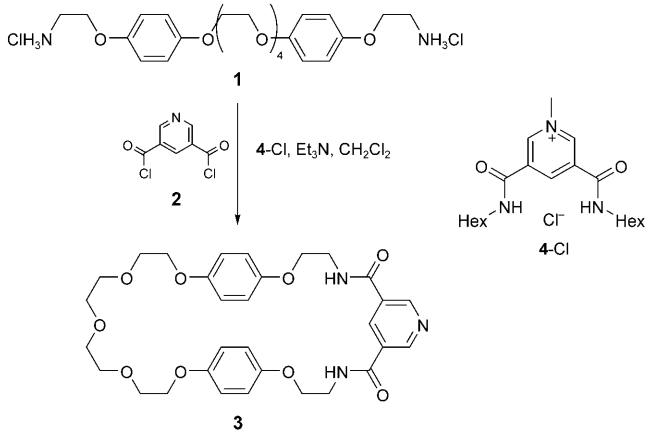


Figure 1. Schematic representation of rotaxane synthesis.

Whilst investigating the synthesis of the target pyridyl-containing macrocycle **3** by the condensation reaction of bisamine **1**[7] with 3,5-bis(chlorocarbonyl) pyridine **2** in dry CH_2Cl_2, the yield of macrocyclization doubled from 21% to 42% when the reaction was undertaken in the presence of 3,5-bis-hexylamide-substituted pyridinium derivative **4**-Cl[8] (Scheme 1). This suggests favorable π–π stacking between the positively charged electron-deficient pyridinium group



Scheme 1. Synthesis of macrocycle **3**.

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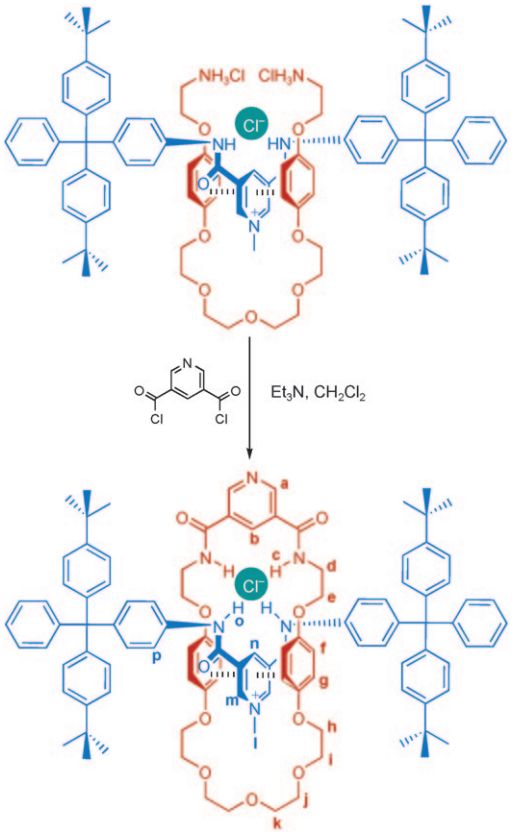
of **4**-Cl and the electron-rich hydroquinone motifs of **1** together with chloride anion templation preorganize the terminal amine functional groups of **1** to favor macrocycle formation.

Indeed given the observed strength of pseudorotaxane formation between macrocycle **3** and **4**-Cl, $K > 10^4\,\text{M}^{-1}$ in CD_2Cl_2 as determined by ^{1}H NMR titration experiments, it was of interest to investigate whether [2]rotaxanes could be synthesized by simply replacing **4**-Cl with an appropriate pyridinium-stoppered axle under the condensation reaction conditions described in Scheme 1.

The synthesis of new [2]rotaxane **6**-Cl was achieved by the addition of 3,5-bis(chlorocarbonyl) pyridine **2** to a mixture of bis-amine **1**, Et_3N, and the stoppered axle component **5**-Cl [5a] in CH_2Cl_2 (Scheme 2). The rotaxane was isolated in 32% yield following preparative thin-layer chromatography.



Scheme 2. Synthesis of [2]rotaxane **6**-Cl.

Evidence for the formation of the [2]rotaxane was initially obtained by ^{1}H NMR spectroscopy. The spectrum of rotaxane **6**-Cl, along with those of the component macrocycle **3** and axle **5**-Cl for comparison are shown in Figure 2.

The [2]rotaxane **6**-Cl displays considerable upfield shifts of the amide protons **o** and *para*-pyridinium proton **n** corresponding to polarization of the chloride ion away from the binding cleft as a result of halide anion recognition by the macrocycle's isophthalamide cavity. This is further signified

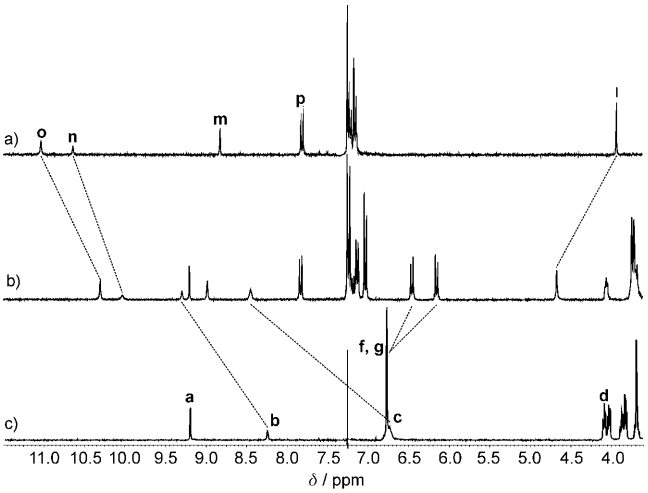


Figure 2. ^{1}H NMR spectra in $CDCl_3$ at 293 K of a) axle **5**-Cl, b) [2]rotaxane **6**-Cl, and c) macrocycle **3**.

by downfield shifts of the amide **c** and cavity isophthalamide proton **b** as they become deshielded by the halide's negative charge. The proton signal associated with the hydroquinone environments, **f** and **g**, of the macrocycle has moved upfield and split appreciably which is characteristic of π–π donor-acceptor interactions between the electron-rich hydroquinones and the positively charged electron-deficient pyridinium motif. Finally, the signal corresponding to the methyl protons **l** of the pyridinium axle has moved significantly upfield, indicative of hydrogen bonding between these protons and the oxygen atoms of the macrocycle's polyether chain.

Further characterization of the structure of [2]rotaxane **6**-Cl was obtained from ESMS, ^{13}C NMR, and 2D ^{1}H NMR ROESY spectroscopy (see Supporting Information).

To probe the anion binding cavity of [2]rotaxane **6** it was necessary to remove the chloride anion from the interlocked binding domain. It was exchanged for the non-coordinating hexafluorophosphate anion in quantitative yield by repeated washing of a solution of **6**-Cl in $CHCl_3$ with $NH_4PF_{6(aq)}$ solution. Anion exchange was observed to have no significant effect on the position of the cationic pyridinium axle component within the pyridyl macrocyclic wheel, as demonstrated by the observed splitting of hydroquinone protons, **f** and **g**, in the ^{1}H NMR spectra of **6**-PF_6. The only significant difference in the $CDCl_3$ ^{1}H NMR spectra of the two rotaxanes is both sets of amide signals are observed to move significantly upfield upon removal of the chloride templating anion.

The anion binding properties of the rotaxane **6**-PF_6 were investigated by titrating with TBA salts of Cl^-, Br^-, $H_2PO_4^-$, and OAc^- initially in 1:1 $CDCl_3$:CD_3OD. The chemical shift perturbations of the *ortho*-pyridinium proton **m** and *para*-pyridinium proton **n** were monitored as a function of the equivalents of anion added. WinEQNMR[9] analysis of the titration data gave association constant values for 1:1 rotaxane/anion stoichiometric complexes shown in Table 1.

The rotaxane is selective for chloride in preference to the more basic oxoanions. It is noteworthy that chloride is very

Table 1. Association constants, K, of [2]rotaxane **6**-PF_6 with Cl^-, Br^-, $H_2PO_4^{<M->}$, and OAc^- in 1:1 $CDCl_3$:CD_3OD, and 45:45:10 $CDCl_3$:CD_3OD:D_2O at 293 K. Error < 10%.

Anion	Cl^-	Br^-	$H_2PO_4^-$	OAc^-
K (M^{-1}) in 1:1 $CDCl_3$:CD_3OD	$>10^4$	–[a]	720	520
K (M^{-1}) in 45:45:10 $CDCl_3$:CD_3OD:D_2O	1500	780	60	110

[a] winEQNMR was unable to obtain association constant value.

strongly bound in this methanol–chloroform solvent mixture, so strongly in fact that winEQNMR was unable to determine an association constant value. Analogous anion titration experiments were therefore undertaken in the presence of 10% water and association constant values calculated. Table 1 shows that even in this competitive aqueous solvent medium the rotaxane is an efficient complexant of chloride and the oxoanions are only weakly bound. These results suggest the unique interlocked cavity of rotaxane **6**-PF_6 is of complementary size and shape for chloride, whereas the larger oxoanions are unable to penetrate the rotaxane's binding pocket.

Interestingly, whereas chloride anion binding by the rotaxane results in a downfield perturbation of the pyridinium proton **n**, addition of bromide and oxoanions by contrast resulted in significant upfield shifts of this proton. This indicates a different type of binding mode is taking place with these larger anionic guest species resulting in an unfavorable distortion of the interlocked binding cavity and reduction of complex stability.

In summary a new synthetic route for [2]rotaxanes has been developed. A combination of chloride anion templation and favorable π–π donor–acceptor interactions assembles flexible bis-amine acyclic precursor wheel and pyridinium axle components in such a fashion that a subsequent acid chloride condensation reaction results in rotaxane formation. Simple variation of the nature of the acid chloride can lead to a range of rotaxanes being prepared which contain interlocked cavities of variable dimensions. Taking into account the new [2]rotaxane's impressive selective recognition of chloride in aqueous solvent media highlights the real potential such interlocked molecular host systems might have in anion chemical sensor technological applications.

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Keywords: anions · molecular recognition · rotaxanes · supramolecular chemistry · template synthesis

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