Nitrate anion templated assembly of a [2]rotaxane for selective nitrate recognition in aqueous solvent mixtures†

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The exquisite anion guest selectivity displayed by nature in phosphate and sulfate binding proteins is accomplished through a three-dimensional convergent array of hydrogen bond donors and acceptors, arranged in an optimized geometry for recognition of the complementary oxoanion.† In our group we have developed the use of discrete anion templates for the formation of interlocked molecular architectures, utilising chloride,7 bromide8 and sulfate9 as the templating anions. The resulting interlocked host molecules can encapsulate anions between the interlocked components, with a high degree of selectivity for the templating anion, through convergent hydrogen bond donors reminiscent of those found in anion binding proteins in nature.

Herein we report the first example of the use of nitrate as a template for the formation of interpenetrated and interlocked molecular architectures.10 Discrete nitrate anion templated pseudorotaxane formation of a suitably designed threading component within a macrocycle is demonstrated initially. Stoppering of the pseudorotaxane assembly led to the construction of a [2]rotaxane host system, which displays excellent selectivity for nitrate in aqueous–polar organic solvent mixtures over a range of other, more basic, mono-charged oxoanions.

Our strategy was to design a complementary threading component that contains two hydrogen bonding recognition sites for forming hydrogen bonds to two of the oxygen atoms of the nitrate anion. The remaining oxygen atom would thus be free to interact with a suitable hydrogen bonding motif that is integrated into a macrocycle component and facilitate the trigonal nitrate anion templated assembly of a rotaxane (Fig. 1).

The possibility of using nitrate as a pseudorotaxane templating anion was investigated initially using the asymmetrical bidentate isophthalamide-3,5-bis-amide pyridinium containing thread 2·PF6.

Fig. 1 Schematic representation of a nitrate templated [2]rotaxane, with two hydrogen bonding recognition sites in the axle (blue and green) and one in the macrocycle (red), forming a complementary binding site for the trigonal nitrate anion between the interlocked components.
(Scheme 1), terminated with non-interacting hexyl chains (see ESI† for synthesis). Macrocycle 1, incorporating an isophthalamide motif to coordinate to the nitrate anion, and hydroquinone groups to provide secondary stabilization through aromatic donor–acceptor interactions with the electron deficient pyridinium moiety of the thread, was prepared according to literature procedures.11

Initial 1H NMR pseudorotaxane assembly studies were undertaken in d6-acetone (Fig. 2). Addition of TBANO3 to a solution of macrocycle 1 led to downfield shifts of the isophthalamide amide protons and internal proton b, indicating coordination of the oxoanion within the amide binding cleft. Upon addition of one equivalent of thread 3PF6, downfield shifts of the thread protons 1, 4 and amides were observed, which is indicative of nitrate binding, and demonstrates that both the isophthalamide and pyridinium isophthalamide moieties are involved in hydrogen bonding to the nitrate anion. Importantly, the observed upfield perturbation and increased splitting of the macrocycle hydroquinone protons c and d is characteristic of aromatic donor–acceptor interactions between the electron rich hydroquinone groups in the macrocycle and the positively charged electron deficient pyridinium group in the thread, confirming the formation of the pseudorotaxane 1·2·NO3 (Scheme 1).

The successful formation of the nitrate templated pseudorotaxane 1·2·NO3 suggested that the synthesis of a [2]rotaxane would be possible using nitrate templation, via a stoppering strategy. To this end bis-azide functionalized axle precursor 3NO3 was prepared (see ESI†) for a copper(i) catalysed azide–alkyne (CuAAC) click stoppering reaction with a suitable alkyne functionalized stopper. Synthesis of rotaxane 5NO3 was achieved by mixing 1 equiv. of 3NO3 with 1.1 equiv. of macrocycle 1 in 4:1 CH2Cl2-acetone to form the initial pseudorotaxane assembly. Addition of catalytic Cu(CH3CN)4PF6 and 2.2 equiv. of stopper alkyne 4 gave a crude product whose 1H NMR spectrum revealed that the rotaxane was formed in approximately 35% yield (Scheme 2). Purification by size exclusion chromatography and silica gel chromatography gave rotaxane 5NO3 in an isolated yield of 24%, which was fully characterized by 1H, 13C and ROESY NMR, and high resolution electrospray mass spectrometry (see ESI†). Importantly, an analogous reaction conducted in the absence of nitrate with 3PF6 gave no evidence of rotaxane formation, which highlights the crucial templating role of the nitrate anion.12

The 1H spectra of rotaxane 5NO3, macrocycle 1 and axle precursor 3NO3 are compared in Fig. 3. It is noteworthy that the

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**Scheme 1** Assembly of nitrate templated pseudorotaxane 1·2·NO3.

**Scheme 2** Synthesis of rotaxane 5·NO3 via nitrate templation.

**Fig. 2** 1H NMR spectra of (a) macrocycle 1, (b) macrocycle 1 + 1 equiv. TBANO3, (c) pseudorotaxane 1·2·NO3, (d) thread 2·PF6 in d6-acetone (500 MHz). For atom labels see Scheme 1.
macrocyclic hydroquinone protons c and d are split and shifted upfield, which are diagnostic of the aromatic donor–acceptor interactions between the hydroquinones in the macrocycle and the axle pyridinium motif, and confirms the interlocked nature of the rotaxane. Further evidence is obtained in the 1H NMR ROESY spectrum, in which multiple through space interactions between the macrocycle and axle are observed (see ESI†). Anion exchange to the non-coordinating hexafluorophosphate salt, in preparation for anion recognition studies, was achieved by washing a solution of the rotaxane 5NO3 in CH2Cl2 with aqueous NH4PF6. The anion recognition properties of rotaxane 5PF6 were investigated using 1H NMR titration experiments in a competitive aqueous–organic solvent mixture of 45 : 45 : 10 CDCl3–CD3OD–D2O. Upon binding of nitrate the internal pyridinium axle proton 1 proton is strongly perturbed upfield (Δδ = 0.19 ppm after 10 equiv.) which is diagnostic of the nitrate anion binding within the rotaxane cavity. Addition of other oxoanions led to smaller perturbations of axle proton 1 (Table 1). WinEQNMR213 analysis of the titration data, monitoring proton 1, enabled the determination of 1 : 1 stoichiometric anion association constants shown in Table 1.

The trigonal nitrate anion was found to bind strongly within the rotaxane host’s complementary tridentate hydrogen bond donor binding cavity in this competitive aqueous–organic solvent mixture. Impressive selectivity for nitrate was observed over a range of other more basic oxoanions: the pseudo-trigonal hydrogen carbonate anion bound considerably more weakly, and acetate and dihydrogenphosphate resulted in very weak binding, which in the case of acetate was too weak to be quantified.

The selectivity for nitrate over acetate is particularly impressive, given that acetate is 105 times more basic,14 and reflects in part the geometric complementarity of the rotaxane binding cavity for nitrate. To the best of our knowledge this is the first example of a synthetic anion receptor capable of this level of nitrate selectivity in aqueous solvent mixtures over other mono-charged oxoanions.

The spherical chloride anion, which is of comparable size to nitrate but lacks the trigonal geometric preference, was found to bind with a similar affinity to nitrate. Addition of the larger Br– anion led to very small perturbations of the internal binding cavity proton 1, and the binding could not be quantified. Analogous titrations with axle precursor 3PF6 and NO3–, AcO– and Cl–, revealed no binding of the two oxoanions in the same solvent mixture, but significantly stronger binding of Cl– (150 M−1). This serves to further highlight the importance of the interlocked cavity in remarkably enhancing the strength of nitrate binding with respect to the non-interlocked pyridinium axle, and the crucial role the unique three-dimensional binding domain plays in achieving the shape selectivity for the trigonal nitrate anion, by encapsulating the oxoanion guest.

In summary, we have demonstrated the first example of nitrate anion templation for the formation of interlocked molecular architectures, through the preparation of a [2]rotaxane. Removal of the nitrate template affords an interlocked host system which displays unprecedented binding affinity and selectivity for nitrate over other oxoanions of significantly higher basicity, in a competitive aqueous–organic solvent mixture. The exploitation of nitrate as a templating reagent in the synthesis and development of interlocked anion receptors and sensors is continuing in our laboratories.

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