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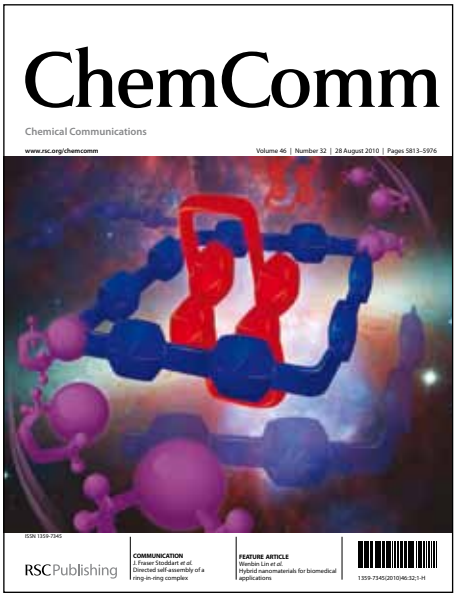

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ARTICLE TYPE

Axle component separated ion-pair recognition by a neutral heteroditopic [2]rotaxane

Richard C. Knighton and Paul D. Beer*

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A neutral heteroditopic pyridine N-oxide axle containing [2]rotaxane, synthesised *via* sodium cation templation, displays cooperative recognition of alkali metal cation-halide anion ion-pairs in an unprecedented axle component separated ion-pair binding fashion.

As a consequence of the paramount importance of charged species in chemical, biological, environmental and industrial processes, the construction of receptors for cation and anion recognition is an area of supramolecular chemistry that is forever expanding. There is compelling evidence that the binding affinities and selectivity trends of monotopic receptor systems for charged guests are in some instances influenced significantly by the nature of counterions. With this in mind attention has turned towards the innovative design of heteroditopic receptors which through favourable cooperative electrostatic interactions, allosteric effects and preorganisation, have been shown to enhance the efficacy of charged guest recognition with promising applications as superior extraction and membrane transport agents.[1, 2]

Heteroditopic receptors can be divided into two classes, where the cation and anion are bound as a contact or a separated ion-pair. The additional challenge to the construction of separated ion-pair receptors lies in the requirement to overcome the electrostatic interaction between the constituent cation or anion from its counterpart.[3] Mechanically interlocked molecules can be fabricated to contain topologically unique three dimensional cavities for molecular recognition and sensing applications.[4-6] In this communication, we report the first example of a neutral heteroditopic interlocked rotaxane host system which is capable of binding alkali metal halides as 'axle-separated' ion-pairs whereby halide anion binding affinity is enhanced by the presence of the alkali metal cation.[7]

[a] *Chemistry Research Laboratory, Department of Chemistry, University 40 of Oxford, Mansfield Road, Oxford, OX1 3TA (UK); E-mail: paul.beer@chem.ox.ac.uk*

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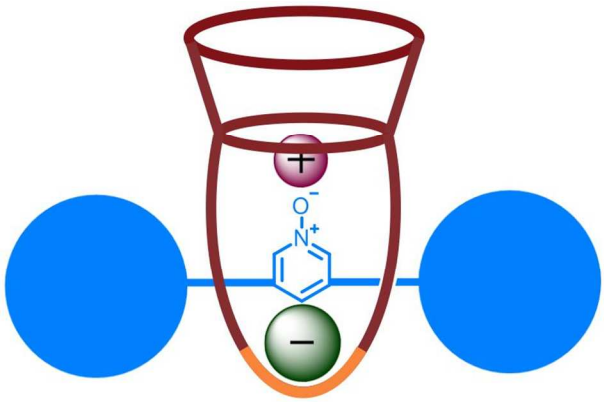
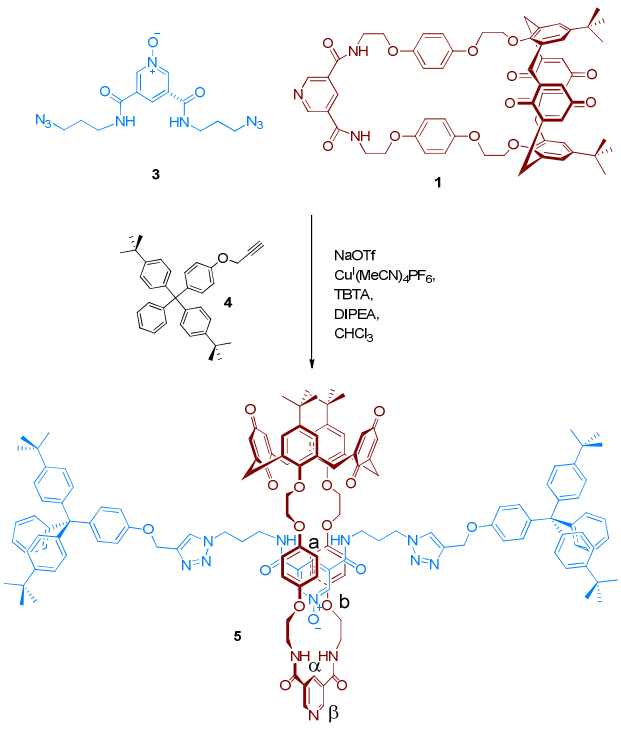


Figure 1 - Cartoon representation of proposed heteroditopic [2]rotaxane capable of axle-separated ion-pair binding.

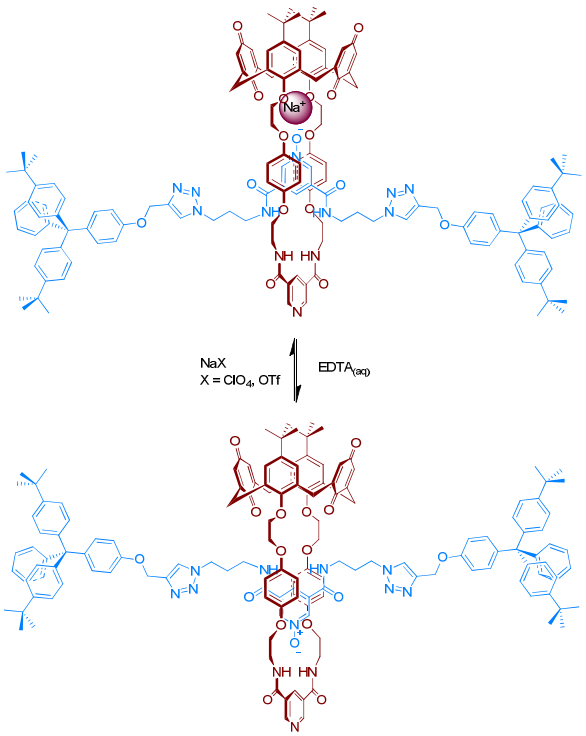
We have recently exploited alkali[8] and lanthanide metal cation,[9] and chloride anion templation[10] to prepare rotaxanes containing a pyridine N-oxide axle component. The target heteroditopic rotaxane contains a heteroditopic macrocycle which consists of a calix[4]diquinone cation recognition site covalently linked to a 3, 5-bis amide functionalised pyridine anion binding motif, together with a pyridine N-oxide axle component where the resulting interlocked host system is designed to recognise alkali metal cation-halide anion ion-pairs in an unprecedented 'axle-separated' ion-pair binding fashion (Figure 1).

The synthesis of the new heteroditopic macrocyclic component **1** of the rotaxane was achieved *via* a multi-step pathway[11, 12] as described in the supporting information (see ESI for synthesis and X-ray crystal structure). Preliminary ^{1}H NMR experiments were undertaken to confirm pseudorotaxane formation between macrocycle **1** and 3,5-bis-hexyl-amide pyridine N-oxide thread derivative **2** in $CDCl_3$ in the presence of one equivalent of sodium cation (see ESI, **S4.1**). Upon addition of the pyridine N-oxide thread **2** broadening and upfield shifts of macrocycle hydroquinone protons δ were observed, indicative of interpenetration.

The synthesis of the target rotaxane was accomplished using a threading-followed-by-stoppering strategy utilising the copper-catalysed azide-alkyne cycloaddition (CuAAC) reaction. The macrocycle **1** was stirred with equimolar amounts of axle



Scheme 1 - Synthesis of heteroditopic [2]rotaxane 5 by a threading-followed-by-stoppering strategy



Scheme 2 - Molecular pirouetting of heteroditopic [2]rotaxane upon addition of sodium cations

precursor **3**[9] and sodium perchlorate, together with two equivalents of alkyne functionalised terphenyl stopper **4**[12] and diisopropylethylamine (DIPEA) in chloroform solution in the presence of catalytic amount of $Cu(MeCN)_4PF_6$ and TBTA at room temperature for 36 hours (Scheme 1). After sequestration of the metal template and purification by size-exclusion and preparative thin layer chromatography the target [2]rotaxane **5** was isolated in 62% yield and characterised by ^1H and ^{13}C NMR spectroscopy and high resolution mass spectrometry, with the interlocked nature confirmed using ^1H-^1H ROESY spectroscopy (see ESI, **S3.1**).

It is noteworthy that the role of the sodium cation is crucial in the formation of the interlocked structure; when the synthesis was repeated in the absence of the metal the yield of rotaxane was significantly reduced to <10%.[13] It was found that upon removal of the sodium cation metal template from the resultant [2]rotaxane using EDTA that a molecular motion occurs; in the presence of the alkali metal the pyridine N-oxide is coordinated to the metal cation with the axle pyridine N-oxide oxygen pointing towards the calixdiquinone moiety. Upon removal of the template however, the pyridine N-oxide motif pirouettes within the macrocyclic cavity, forming hydrogen bonds with the 3, 5-bis amide functionalised pyridine motif of the macrocycle (Scheme 2) as determined by ^1H-^1H ROESY spectroscopy (see ESI, **S3.2**).

Preliminary ^1H NMR anion titration experiments were undertaken to determine the affinity of the rotaxane to halides in the *absence* of a metal cation. Upon addition of increasing amounts of TBACl to a solution of [2]rotaxane **5** in $CDCl_3/CD_3OD$ (4:1) the internal and external bis-amide pyridyl and pyridine N-oxide protons *a,b* and *α, β* of the respective macrocycle and axle were observed to shift downfield (Figure 2). The downfield shifts of *a* and *α* are indicative of a polarising hydrogen bonding interaction of these protons with the chloride anion. The shift of both these protons suggests the halide anion is binding within the interlocked amide cavity of the rotaxane formed between axle and macrocycle components.[14] Similar downfield shifts of *a,b* and *α, β* were also observed for the other halides. The titration data was analysed using the WinEQNMR2[15] program, monitoring the internal axle proton *a*, to determine 1:1 stoichiometric association constants reported in Table 1.

In the absence of a metal cation the observed halide binding affinities are modest and are all of comparable magnitude. This may be rationalised by consideration of the rotaxane having to undergo conformational reorganisation where upon pirouetting of the axle results in favourable inter-component axle pyridine N-oxide-macrocycle bis-amide pyridyl hydrogen bonds being broken in order bind the halide anion.

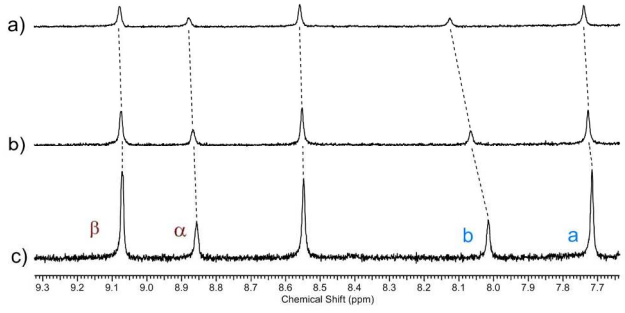


Figure 2 - *^1H NMR spectra of a) rotaxane 5 plus 3 equivalents of TBA.Cl; b) rotaxane 5 plus 1 equivalent of TBA.Cl; c) rotaxane 5 (500 MHz, 4:1 $CDCl_3/CD_3OD$, 298 K)*

Table 1 - Association constants Ka (M^{-1}) for rotaxane **5** in the presence of a metal cation (4:1 $CDCl_3/CD_3OD$, 298 K) ;errors in parentheses; Alkali metals cations added as $LiPF_6$, NaOTf and KPF_6.

	Cation	Association Constant/ M^{-1}	Cooperativity Factor[a]
Cl^-	None	71 (7)	-
	Li^+	80 (3)	1.1
	Na^+	1079 (33)	15.1
	K^+	676 (85)	9.5
Br^-	None	88 (8)	-
	Li^+	166 (6)	1.9
	Na^+	930 (134)	10.6
	K^+	633 (91)	7.2
I^-	None	92 (12)	-

[a] Cooperativity factor is calculated by K_{obs} (anion, ion pair)/K_{obs} (anion, free)

Analogous halide anion titration experiments were undertaken in the presence of an alkali metal cation with the expectation that the bound metal cation would help preorganise the rotaxane through conformational reorganisation and, in addition through favourable electrostatic interactions, increase the interlocked host's anion binding affinity. Anion titrations were performed in the presence of one equivalent of an alkali metal cation as non-coordinating hexafluorophosphate and triflate salts and WinEQNMR2 analysis of the titration data determined 1:1 stoichiometric association constant values shown in Table 1 (see ESI, **S4.3** and Figure 3 for anion-binding curves and ^{1}H NMR spectra respectively).

It is noteworthy that a significant increase in the magnitudes of chloride and bromide anion association constants is observed in the presence of sodium and potassium.[16] In the case of chloride the cooperativity factor in the presence of sodium cations is over 15-fold, suggesting a high degree of host-guest binding complementarity between the heteroditopic rotaxane and the sodium chloride ion-pair. Chloride binding affinity is also enhanced by almost an order of magnitude in the presence of potassium. Large cooperativity factors are also noted for bromide, of 10.6 and 7.2 for sodium and potassium respectively. With lithium, a modest increase in the strength of bromide anion binding was observed although no significant enhancement of the binding affinity of chloride was noted.

In summary a *neutral* heteroditopic [2]rotaxane has been synthesised via a sodium cation templated threading-followed-by-stoppering methodology. The resultant rotaxane host system has been demonstrated to act as either a monotopic or heteroditopic host for halide anions or alkali metal halide ion-pairs respectively. It was found that upon the addition of sodium and potassium alkali metal cations the chloride and bromide anion binding affinities were significantly amplified due to conformational reorganisation of the host and favourable electrostatic contributions, with the greatest complementary found for sodium chloride, displaying over an order of magnitude enhancement for the halide in the presence of the metal cation. This increase in binding affinity occurs from greater preorganisation of the receptor when a cation is bound and operates through an unprecedented 'axle-separated' recognition of the ion-pair by the heteroditopic rotaxane host.

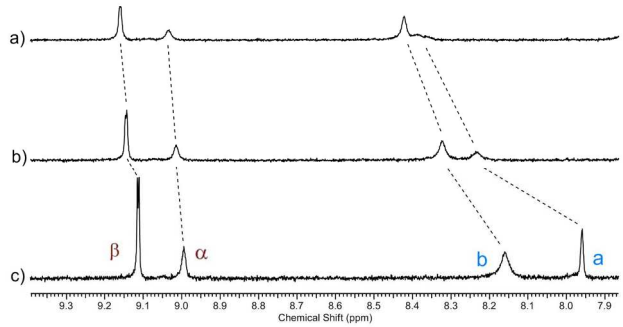


Figure 3 - *^{1}H NMR spectra of a) rotaxane **5**.NaOTf plus 3 equivalents of TBA.Cl; b) rotaxane **5**.NaOTf plus 1 equivalent of TBA.Cl; c) rotaxane **5**.NaOTf (500 MHz, 4:1 $CDCl_3/CD_3OD$, 298 K)*

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