Neutral [2]rotaxane host systems that recognise halide anions in aqueous solvent mixtures†

James M. Mercurio,a Fergus Tyrrell,a James Cooksonb and Paul D. Beer*a

Four pyridine N-oxide axle containing [2]rotaxanes have been synthesised via an anion templated threading-followed-by-stoppering strategy and shown to be the first examples of neutral interlocked host systems capable of recognising halide anions in aqueous solvent mixtures.

Inspired by the fundamental roles that negatively charged species play in a vast array of chemical, biological, medical and environmental processes, the field of anion supramolecular chemistry has expanded enormously in recent years. Incorporating numerous non-covalent interactions, such as electrostatics, hydrogen bonding, Lewis acid–base, anion–π interactions, and more recently halogen bonding into acyclic and macrocyclic host frameworks has allowed for a panoply of anion receptors to be developed. However, the challenge of raising the degree of recognition to that of biotic systems remains a significant one. In an effort to meet this challenge we have embarked on the anion templated construction of positively charged interlocked host molecules and demonstrated their ability to bind anions in aqueous solvent media. In this communication, we report the first examples of neutral interlocked [2]rotaxane host systems that are capable of recognising halide anions in aqueous solvent mixtures.

We have used the pyridine N-oxide motif as an axle component in the synthesis of [2]rotaxane structures through alkali metal and lanthanide metal cation-templation, whereas hydrogen bonding interactions have been exploited recently in [2]pseudorotaxane assemblies with pyridine N-oxide threading derivatives. The macrocyclic component of the target rotaxane host system was designed to contain two isophthalamide motifs, which serve to facilitate interpenetration with a 3,5-bis-amide pyridine N-oxide thread, where the stability of the resulting pseudorotaxane assembly would be augmented via anion binding, in particular with chloride (Fig. 1).

The preparation of four novel bis-isophthalamide macrocycles 7–10 was achieved via a common multi-step pathway as described in the ESI† (see S2). Preliminary 1H NMR experiments were performed to investigate pseudorotaxane formation between macrocycles 7–9 and a 3,5-bis(hexylamide) pyridine N-oxide derivative 11 alone, and in the presence of one equivalent of TBAI, in 1:1 CDCl3–CD3CN (see ESI† S4.1). Importantly, both in the absence and presence of chloride, the macrocycle hydroquinone protons δ are shifted upfield significantly when pyridine N-oxide thread 11 is added to macrocycle 8. This is the result of aromatic donor–acceptor interactions between the macrocycle and threading species, indicative of pseudorotaxane formation. It is noteworthy that the magnitude of this perturbation is relatively larger when chloride is present, giving evidence for a templating effect. In addition, the internal isophthalamide protons α and γ can be seen to shift downfield. This arises from hydrogen bonding interactions between these protons and the pyridine N-oxide oxygen donor atom and hydrogen bonding interactions with the same oxygen donor atom and chloride when the halide anion is present. Analogous 1H NMR pseudorotaxane titration experiments with macrocycles 7 and 9 revealed similar hydroquinone and isophthalamide perturbations, suggesting interpenetrative formation with 11.

Quantitative 1H NMR titration experiments monitoring the hydroquinone protons δ of the respective macrocycle gave titration...
data (see ESI,† S4.2) from which 1 : 1 stoichiometric association
costants10 were determined by WinEQNMR21 (see ESI,† S4.3).
All the macrocycles were found to form stable interpenetrative
assemblies with 11 in 1 : 1 CDCl3–CD3CN, through the combination
of favourable pyridine N-oxide – isophthalamide macrocycle
hydrogen bonding and aromatic donor–acceptor interactions.
Importantly, the apparent association constants obtained for
pseudorotaxane formation in the presence of chloride were
found to be >104 M−1 in the same solvent mixture demonstrating
a significant enhancement of the stability of interpenetrative
assembly when the macrocycle binds the halide anion.

The synthesis of the target interlocked [2]rotaxane systems was
achieved by a copper(i) catalysed cycloaddition azide–alkyne (CuAAC)
click stoppering reaction, as shown in Scheme 1. Equimolar
amounts of bis-azide axle precursor 12,8 the respective macrocycle
and TBACl, together with two equivalents of alkyne-functionalised
terphenyl stopper 1312 and three equivalents of DIPEA were stirred
in chloroform solution in the presence of a catalytic amount of
Cu(MeCN)4PF6 and TBTA at room temperature for 24 hours. After
purification by preparative thin layer chromatography, [2]rotaxanes
14–17 were isolated in 9%, 17%, 16% and 16% yields respectively
and characterised by 1H NMR spectroscopy and high resolution
mass spectrometry, with their interlocked nature confirmed by
two-dimensional 1H–1H ROESY spectroscopy (see ESI,† S5). It is
important to note that when the syntheses were repeated in the
absence of chloride, no rotaxane product was isolated which
serves to highlight the crucial templating role the halide anion is
playing in the mechanical bond forming process.

The rotaxanes possess two isophthalamide binding sites and so
can in principle adopt two different conformations via
the macro-
cycle component undergoing a pirouetting motion around the
pyridine N-oxide axle (Scheme 2). Evidence for this dynamic process

was obtained from a low temperature VT 1H NMR investigation of
rotaxane 15 in 1 : 1 CDCl3–CD3OD. Significant broadening of both
the macrocycle and axle isophthalamide protons and, importantly,
the macrocycle hydroquinone protons is observed as the tempera-
ture of the sample is lowered from 298 K to 198 K (see ESI,† S6.1)
indicating the interlocked structure is dynamic on the NMR time-
scale and at room temperature is switching between the two
possible conformations.

1H NMR anion titration experiments were undertaken to
assess the anion binding affinities of the four [2]rotaxanes with
nitro functionalised [2]rotaxane 15 studied initially. Upon
addition of increasing amounts of TBACl to a solution of 15
in 1 : 1 CDCl3–CD3OD protons α, χ, b and f were observed to
shift downfield significantly (Fig. 2).

These downfield shifts are indicative of polarising hydrogen
bonding interactions between these protons and the chloride anion.
The shifting of the axle internal isophthalamide proton b and triazole proton f suggests the axle wraps around and encapsulates the anion, whereas perturbation of macrocycle isophthalamide protons \( z \) and \( \chi \) indicates that anion recognition is occurring at both isophthalamide binding sites of 15 in a dynamic manner. This was confirmed by low temperature VT \( ^1 \)H NMR of a 1:1 mixture of [2]rotaxane 15 and TBACl (see ESI, S6.2) where similar broadening in the aromatic region of the \( ^1 \)H NMR spectra was observed to that in the free rotaxane, indicating that the conformation of 15 is not locked upon chloride binding and both isophthalamide binding sites are accessible to the halide anion.

Similar downfield shifts of protons \( z \), \( \chi \), b and f were observed for the other rotaxane systems with chloride and various other anions. The titration data monitoring the internal isophthalamide proton \( z \) (see ESI, S7) was analysed using the WinEQNMR\(^{2\text{1}}\) curve fitting software to give the 1:1 stoichiometric association constants reported in Table 1.\(^{13}\)

All the rotaxanes exhibit strong binding of halides, especially with chloride and bromide, which are preferentially bound over iodide and dihydrogen phosphate.\(^{14}\) This suggests the interlocked binding cleft within these host systems is of complementary size for the smaller chloride and bromide anions, whereas larger iodide and dihydrogen phosphate anions are presumably too large to penetrate the interlocked binding pocket. It is noteworthy that the strength of halide binding for these neutral interlocked host systems is comparable to that of previously reported charged [2]rotaxanes containing a pyridinium axle component and isophthalamide macrocycle.\(^{15}\)

Taking into account the substantial chloride and bromide association constant values observed, in particular with rotaxane 16, \( ^1 \)H NMR halide anion titrations were repeated in the more competitive 45:45:10 CDCl\(_3\)-CD\(_3\)OD-D\(_2\)O aqueous solvent mixture (see ESI, S8) and the determined association constants are shown in Table 2. Even in an aqueous solvent mixture, the binding of chloride and bromide is still remarkably strong for the neutral [2]rotaxanes, with the strength of halide binding again being comparable to that of previously reported charged pyridinium axle containing rotaxane systems.\(^{3}\) Impressively, chloride and bromide anions are still bound the strongest, in spite of the Hofmeister series bias\(^{16}\) favouring iodide on the basis of relative ease of desolvation, which provides further compelling evidence of the rotaxane host binding domains being of a complementary size-match for the smaller halides.

In summary, four neutral pyridine N-oxide functionalised [2]rotaxanes have been prepared via a chloride anion templated threading-followed-by-stoppering methodology.\(^{1}\) \( ^1 \)H NMR anion titration experiments revealed these [2]rotaxanes are the first examples of neutral interlocked host systems to be capable of recognising halide anions in aqueous solvent mixtures, with a selectivity preference for chloride and bromide anions over iodide and dihydrogen phosphate resulting from their complementary sized interlocked binding domains for the smaller halide anions.

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### Notes and references


13. It is noteworthy that the same association constant values, within experimental error, are obtained by monitoring macrocycle internal isophthalamide proton \( \chi \) and axle internal isophthalamide proton b.

14. \( ^1 \)H NMR anion titrations were also carried out with TBAOAc but WinEQNMR2 could not fit the data.


### Table 1

<table>
<thead>
<tr>
<th>Anion</th>
<th>14</th>
<th>15</th>
<th>16</th>
<th>17</th>
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</thead>
<tbody>
<tr>
<td>Cl(^-)</td>
<td>2720(280)</td>
<td>2790(240)</td>
<td>&gt;10(^4)</td>
<td>3010(340)</td>
</tr>
<tr>
<td>Br(^-)</td>
<td>1230(90)</td>
<td>2050(280)</td>
<td>&gt;10(^4)</td>
<td>2090(20)</td>
</tr>
<tr>
<td>I(^-)</td>
<td>295(22)</td>
<td>667(28)</td>
<td>1700(190)</td>
<td>635(84)</td>
</tr>
<tr>
<td>H(_2)PO(_4)(^-)</td>
<td>129(33)</td>
<td>152(7)</td>
<td>112(7)</td>
<td>671(54)</td>
</tr>
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</table>

1:1 CDCl\(_3\)-C\(_3\)D\(_6\)OD, 298 K, [host] = 2 mM, errors in parentheses.

### Table 2

<table>
<thead>
<tr>
<th>Anion</th>
<th>14</th>
<th>15</th>
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<th>17</th>
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<tbody>
<tr>
<td>Cl(^-)</td>
<td>501(27)</td>
<td>475(15)</td>
<td>552(8)</td>
<td>487(39)</td>
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<tr>
<td>Br(^-)</td>
<td>311(14)</td>
<td>442(6)</td>
<td>466(9)</td>
<td>324(17)</td>
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<tr>
<td>I(^-)</td>
<td>59(3)</td>
<td>92(4)</td>
<td>139(10)</td>
<td>173(32)</td>
</tr>
</tbody>
</table>

45:45:10 CDCl\(_3\)-C\(_3\)D\(_6\)OD-D\(_2\)O, 298 K, [host] = 2 mM, errors in parentheses.