

Heteroditopic Rotaxanes and Catenanes for Ion Pair Recognition

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Abstract: A review of heteroditopic interlocked molecules and their application as receptors for simple inorganic ion pair species. The review details the design and ion recognition properties of the rotaxane and catenane receptors, as well as highlighting some of the experimental challenges; hence, it provides insight into possible future avenues of research in this youthful field.

Keywords: rotaxane; catenane; host-guest recognition; ion pair

1. Introduction

The binding of ionic species by molecular receptors has been a cornerstone of supramolecular chemistry [1–3]. While still being added to, the supramolecular chemical literature possesses vast quantities of work regarding the binding of cationic [4] and anionic [5–7] species. In contrast, the field of *ion pair* recognition [8–11] is much less developed, yet any ion will have associated with it (somewhere) a counter-ion, and it has been recognized that the binding of specific ion pairs may be desirable for applications (beyond simple binding or sensing) such as salt extraction and solubilization [12–19] or symportic transmembrane ion transportation [20,21].

Receptors capable of simultaneously binding a cation and an anion can be classified as either *contact* ion pair or *separated* ion pair receptors. Separated ion pair receptors may be further categorized as either *host-separated* or *solvent-separated*. The binding of one ion typically increases the binding affinity of the receptor for the counter-ion—*positive allostery*—due to the favourable electrostatic interaction between oppositely charged ions. However, there are examples of *negative allostery*, arising from conformational changes induced by the first binding event that have a detrimental impact on the binding site for the counter-ion. The study of ion pair recognition is complicated (in comparison to either cation or anion recognition) due to the number of equilibria that may exist in an ion pair binding system. The receptor may bind either the anion or cation alone, the desired ion pair binding may occur, or the ion pair may precipitate as the extended ionic lattice [22].

It is now well-established that the three-dimensional cavities of mechanically interlocked molecules [23,24] such as rotaxanes (molecules consisting of macrocyclic ring(s) trapped on a stoppered axle [25]) and catenanes (interlocked macrocyclic rings [26]) may act as binding sites for ionic guests [27–30]. In fact, Sauvage reported on the binding affinities for a range of metal cations in his seminal passive metal templated [2]catenane [31], and several research groups have since demonstrated the binding of cations by other rotaxanes and catenanes [32–42]. Numerous anion binding examples have been reported by Beer [43–58] and others [59–62], while Leigh's group has demonstrated anion binding by metalated molecular knots [63,64]. It is notable that the active metal template synthetic strategy (where a metal cation templates self-assembly and mediates the covalent bond formation step leading to capture of the interlocked structure [65,66]) has been used in the preparation of several examples of MIMs capable of cation or anion binding [39,54,56,57].

In contrast to the binding of cations or anions by interlocked molecules, the simultaneous binding of a cation *and* an anion by heteroditopic interlocked molecules is very much an emerging area of research interest. This review charts progress in this field from its roots some 20 years ago in the labs of Bradley D. Smith, to the most recent achievements,



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before concluding with thoughts on future avenues of research. Examples are limited to heteroditopic interlocked molecules that are capable (at least in principle) of the binding of a cation and an anion.

2. Early Examples of Rotaxanes Incorporating Heteroditopic Macrocycles

In 2000, Smith and co-workers reported [67] the preparation of rotaxane **1** utilizing a heteroditopic isophthalamide/crown ether macrobicycle, where installation of the axle component was achieved by application of Vögtle's phenoxide hydrogen bond templation methodology [68] (Figure 1). In Smith's preliminary communication, the freezing out of a single co-conformation of rotaxane **1** in DMSO- d_6 was achieved by addition of KPF₆ with binding of the K⁺ cation in the crown ether.

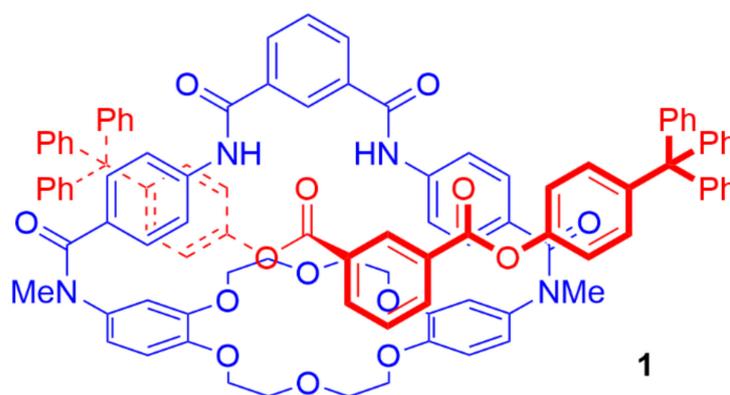


Figure 1. Structure of Smith's original rotaxane **1** containing a heteroditopic isophthalamide/crown ether macrobicycle in the absence of coordinating ions.

In a subsequent full paper, comparisons were made with rotaxanes consisting of isomeric macrobicycles and axles [69]. Yields of 3–20% with respect to rotaxane formation were achieved when the reaction was run in a polar solvent system of 5:1 THF/DMF, used to avoid precipitation of the macrobicycle/KCl complex. At room temperature, in polar solvents (e.g., DMSO- d_6 or acetone- d_6), the ¹H NMR spectra of the rotaxanes are broad. Titration of TBACl in DMSO- d_6 /CD₃CN (3:1), in the absence and presence of KBPh₄, revealed that the chloride ion is bound within a pocket arising from the macrocycle and axle components, the anion being held in place by hydrogen bonds to the N-H amide groups (Figure 2).

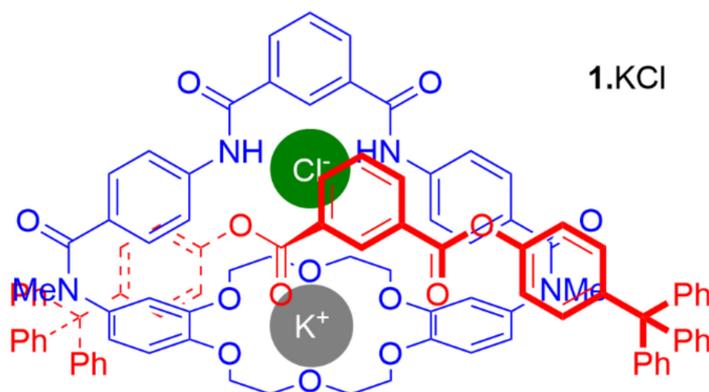


Figure 2. Proposed binding mode of KCl by Smith's original rotaxane **1**.

In the absence of K⁺, rotaxane **1** binds chloride six times more strongly than the free macrobicycle ($K = 300 \text{ M}^{-1}$ vs. 50 M^{-1}). The authors attribute this observation to the inability of a DMSO molecule to compete with chloride in the sterically more constricted rotaxane cavity. Notably, the presence of 1 equivalent K⁺ led to no variation in chloride ion

affinity for rotaxane **1** (unlike for the free macrobicyclic where a positive allosteric effect is observed). This is likely to be due to the axle of rotaxane **1** insulating the through-space attractive electrostatic interaction between the bound K^+ and Cl^- .

Orozco and Luque undertook a molecular dynamics study of the co-conformational behaviour of rotaxane **1** [70]. In chloroform, rotaxane **1** was calculated to exist in a mixture of co-conformations including some with hydrogen bonds between the axle $C=O$ and macrocycle $N-H$ groups. In contrast, in DMSO, no hydrogen bonded co-conformations were identifiable, presumably due to the macrocycle $N-H$ groups hydrogen bonding to the DMSO solvent molecules. The modelling revealed that the axle experiences notable changes in anisotropic shielding, which is consistent with the broad 1H NMR signals observed experimentally. Adding a Na^+ cation, bound within the crown ether, reduces co-conformational flexibility by interactions of the axle with the cation.

We note that a related rotaxane **2** was subsequently prepared by Moustrou and co-workers [71] (Figure 3). The researchers included binaphthopyrans in the stoppers of the rotaxane. The photochemical properties of rotaxane **2** (when dissolved in acetonitrile) are perturbed by the addition of Na^+ ; there is an increase in the absorbance of the open form of the chromene chromophore, while there is a decrease in absorbance of the closed form.

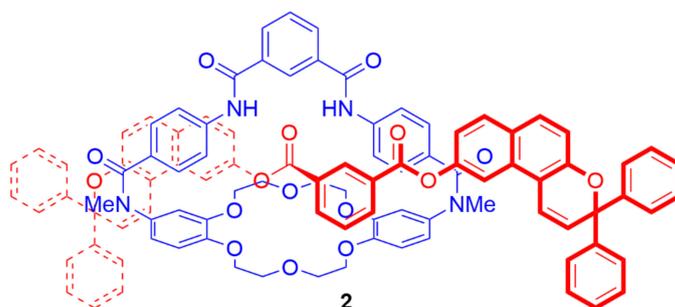


Figure 3. Structure of Moustrou's rotaxane **2** with chromene stoppers in their closed form.

Smith's group also reported the preparation of rotaxane **3**, where the axle possessed an acetal linkage (Figure 4a) [72]. The yield of the formation was 15% (notably no rotaxane was formed when using the 2,6-pyridyl analogue of the macrobicyclic). In $DMSO-d_6$, in the presence of 1 equivalent of $NaBF_4$, there was no observed enhancement in chloride binding at the isophthalamide ($K_{no\ cation} = K_{with\ Na^+} = 2\ M^{-1}$) and only modest enhancement with KBF_4 ($K_{with\ K^+} = 5\ M^{-1}$). It is notable that this mirrors trends with the free macrobicyclic ($K_{no\ cation} = 5\ M^{-1}$, $K_{with\ Na^+} = 5\ M^{-1}$, $K_{with\ K^+} = 15\ M^{-1}$), and the lack of a significant positive allosteric effect probably reflects the larger distance between the isophthalamide and crown ether in the macrobicyclic in comparison to that in original rotaxane **1**. Rotaxane **4** with a longer axle was also prepared (Figure 4b). In $DMSO-d_6$, the lipophilic alkyl portion of the axle resides within the macrocycle cavity. However, the addition of perchlorate salts of a range of cations (Na^+ , K^+ , Ba^{2+} , Ag^+) does not lead to movement of the axle.

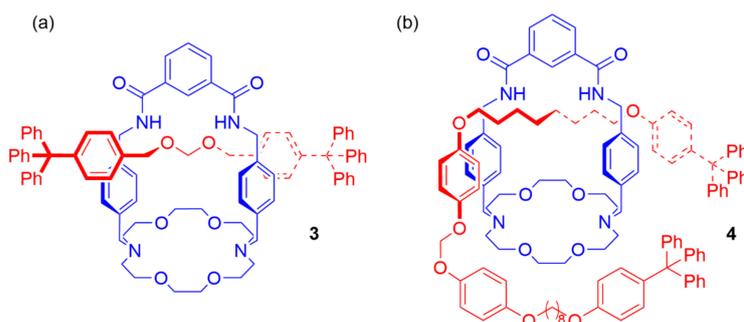


Figure 4. Structures of Smith's acetal axle rotaxanes **3** (a) and **4** (b).

3. Ion-Induced Motion in Rotaxanes and Catenanes Incorporating Heteroditopic Macrocycles

After a gap of almost a decade from the studies above, Beer's research group reported on the synthesis of several interlocked molecules that incorporated a heteroditopic calix[4]diquinone-isophthalamide macrobicyclic and subsequent studies of the ion-induced motion of the interlocked components. While no ion pair binding studies were detailed, we have chosen to include these examples for completeness.

In 2011, Leontiev, Beer and co-workers reported on the preparation of a rotaxane **5** containing a calix[4]diquinone-isophthalamide macrobicyclic and a 3,5-bis-amide methyl pyridinium axle component, prepared by chloride anion templation and copper-catalyzed alkyne-azide cycloaddition (CuAAC) "click" stoppering (Figure 5) [73]. The hexafluorophosphate salt was shown to bind cations in dichloromethane–acetonitrile system mixtures (and anions in chloroform/methanol). While no dramatic changes in conformation are observed upon addition of monovalent cations such as Na^+ and K^+ , the addition of Ba^{2+} displaces the pyridinium unit of the axle, tentatively indicating coordination of the triazole to the alkaline earth metal cation bound by the calix[4]diquinone. This process can be reversed by the addition of $(\text{TBA})_2\text{SO}_4$ to precipitate out insoluble BaSO_4 . Related catenane systems were prepared by Grubbs' catalyzed ring closing metathesis of methyl and benzyl pyridinium threads functionalized with terminal vinyl groups [74]. As the hexafluorophosphate salt, binding of Ba^{2+} leads to co-conformational partial rotation of the pyridinium ring, reversible upon the addition of $(\text{TBA})_2\text{SO}_4$.

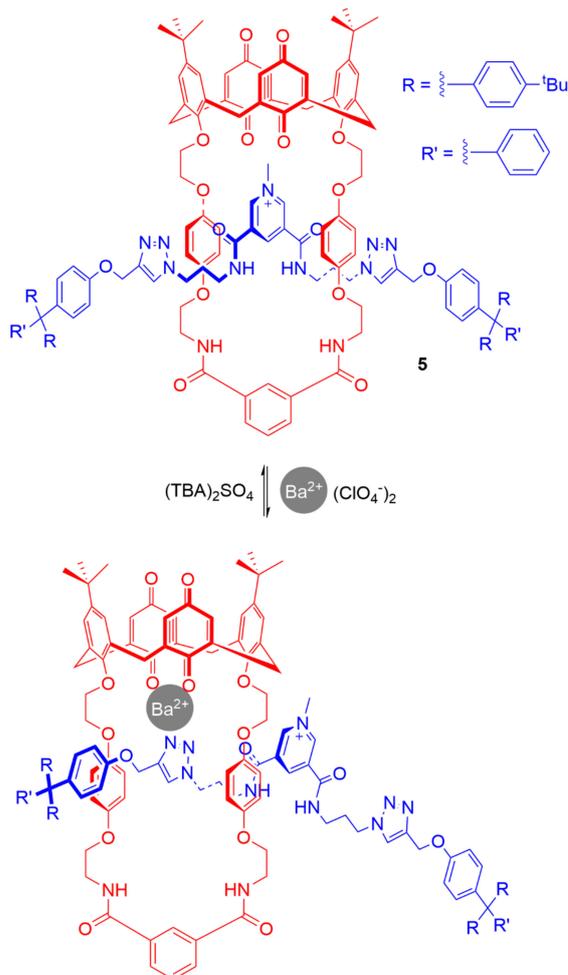


Figure 5. Barium cation-induced motion in Leontiev and Beer's calix[4]diquinone–isophthalamide macrobicyclic rotaxane **5**.

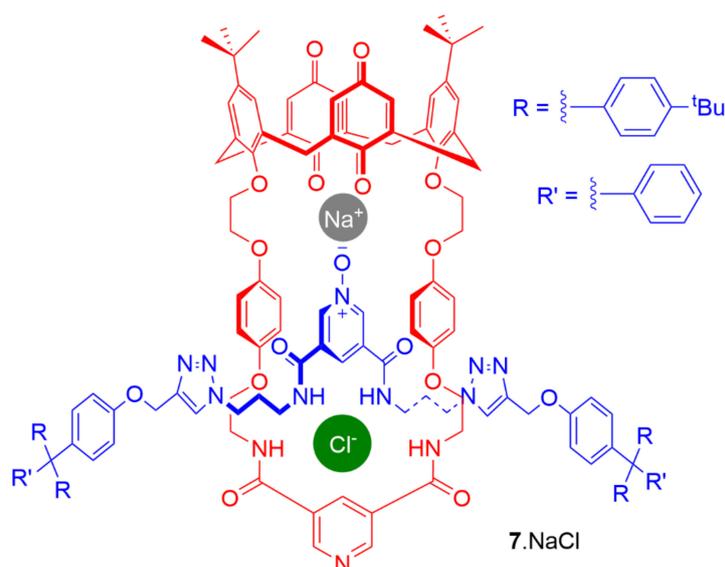


Figure 7. Knighton and Beer's rotaxane **7** exhibiting axle separated cooperative ion pair binding.

Beer's group followed this work by synthesizing rotaxanes that bind d-block metal cations (Figure 8) [77]. Rotaxanes **8–10** were prepared by a Cu^{2+} directed passive metal template strategy: an isophthalamide/tris-amine macrocycle was pre-metallated with the copper cation, before interlocked axle formation by the stoppering of a coordinating bipyridyl or pyridyl axle precursor. The anion binding sites comprise convergent hydrogen bond donors, or mixed hydrogen bond and C-I halogen bond donor groups. The cation binding site consist of the macrocycle tris-amine with axle bipyridine or pyridyl and carbonyl oxygen groups.

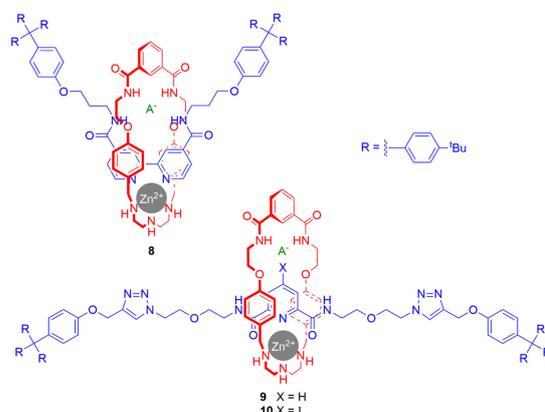


Figure 8. Beer's tris-amine macrocycle rotaxanes **8–10** exhibiting axle separated cooperative ion pair binding.

^1H NMR titration experiments revealed cooperative binding of halide and nitrate anions in the presence of a co-bound Zn^{2+} cation in 1:1 $\text{CDCl}_3/\text{CD}_3\text{OD}$. For the bipyridyl axle rotaxane **8**, in the absence of Zn^{2+} , no binding of halide anions is observed; this is attributed to a lack of preorganization and electrostatic effects. For the Zn^{2+} metallated pyridyl axle rotaxanes, there is little difference in the anion association constants between the all-hydrogen-bonding **9** and the halogen-bonding-containing **10** (e.g., $K_{\text{Cl}^-} = 500 \text{ M}^{-1}$ and 535 M^{-1} , $K_{\text{Br}^-} = 925 \text{ M}^{-1}$ and 1080 M^{-1} , respectively, in 45:45:10 $\text{CDCl}_3/\text{CD}_3\text{OD}/\text{D}_2\text{O}$).

Ghosh and co-workers have extensively investigated heteroditopic rotaxanes based on related tris-acylated nitrogen macrocycles. For example, for tris-acylated rotaxane **11**, rotameric behaviour of the acetyl groups in 9:1 $\text{CDCl}_3/\text{CD}_3\text{CN}$ solution may be impeded upon addition of Na^+ (or Li^+) cation (Figure 9) [78]. The addition of 18-crown-6 (or

12-crown-4) reveals the regeneration of the dynamic behaviour of the tertiary amide groups. Adapting this rotaxane structure to include fluorophores allows for study using UV-vis [79] and fluorescence [80] spectroscopies, to generate cation sensory systems. More recently, inclusion of NDI in related rotaxane (and catenane) structures, allowed for interaction with fluoride or cyanide to be detected by absorption and emission [81]. To emphasize, none of these studies focused on the binding of ion pairs.

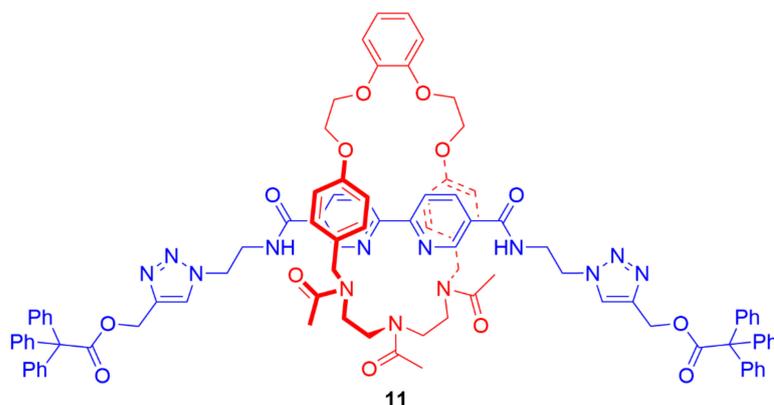


Figure 9. Ghosh's tris-acylated rotaxane **11** lockable using alkali metal cations.

Very recently, Beer and co-workers have reported on lithium halide recognition (Figure 10) [82]. A family of related rotaxanes **12–14** were prepared by CuAAC “click” active metal template methodology, including one example (**14**) which has a fully halogen bonding anion pocket. Coordination of Li^+ by the macrocyclic pyridyl and the axle triazole, polarizes and preorganizes the potential anion binding donor groups. LiBr is bound more strongly than LiI in $\text{CD}_3\text{CN}/\text{CDCl}_3$ solvent mixtures for all three rotaxanes prepared, with the all-halogen bonding rotaxane binding bromide strongest ($K_{\text{with 1 eq Li}^+} > 10^4 \text{ M}^{-1}$ in 3:7 $\text{CD}_3\text{CN}/\text{CDCl}_3$).

Previously, Goldup and Joliffe had reported an active metal templated rotaxane **15** that contained a urea within the axle component (Figure 11) [83]. However, when neutral, rotaxane **15** was not able to bind anions as anticipated at the urea. Single crystal X-ray crystallography revealed the urea N-H hydrogen bonding to the bipyridyl nitrogens of the macrocyclic component. The addition of a proton (by use of HBF_4) allows for the binding of a range of anions in 1:1 $\text{CDCl}_3/\text{CD}_3\text{CN}$ by disruption of these intercomponent hydrogen bonds. The authors reported rotaxane **15** as an ion pair binding system, i.e., treating the proton as a cation.

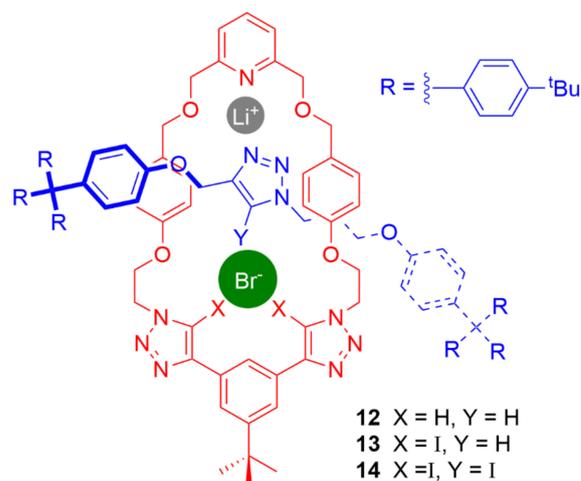


Figure 10. Beer's active metal templated rotaxanes **12–14** capable of selective lithium bromide recognition.

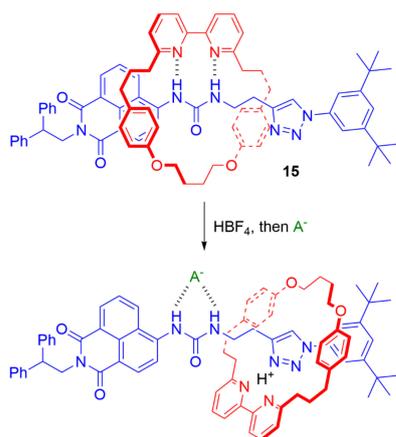


Figure 11. Revealing of anion binding site by proton induced shuttling in Goldup and Joliffe's urea containing active template metallated rotaxane **15**.

Ballester and co-workers have demonstrated ion pair binding by a pyridine-*N*-oxide axle/bis(calix[4]pyrrole) macrocycle-containing rotaxane **16** (Figure 12) [84]. Intriguingly, in chloroform, rotaxane **16** bound both anions and their tetraalkylammonium counter-cations, and when an excess of salt was added, the 1:1 complex of rotaxane and salt converted to a 1:2 complex. Very recently the researchers have studied the binding behaviour in more depth by variation of solvent (specifically acetone and chloroform/methanol mixtures) and have found in these more competitive solvents that the principal binding event is anion binding [85].

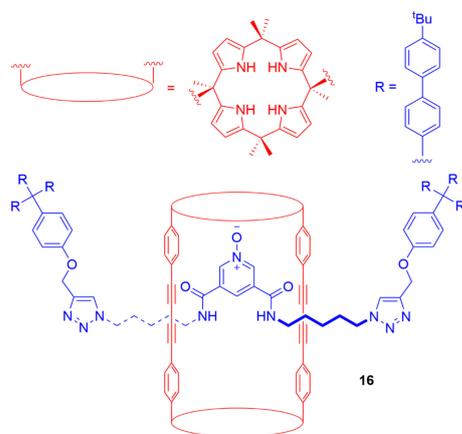


Figure 12. Ballester's pyridine-*N*-oxide rotaxane **16** using a bis(calix[4]pyrrole) macrocycle.

5. Heteroditopic Catenanes Binding Ion Pairs

To date, very few demonstrations of catenanes binding ion pairs have been reported. In 2011, while working in Beer's laboratories, one of us (N.H.E.), reported the crystal structure of a neutral catenane **17**, serendipitously binding a sodium cation/chloride anion ion pair. The chloride anion is held in a convergent amide hydrogen bonding cleft, while the alkali metal cation is coordinated between the pyridyl nitrogen of one macrocycle and two glycol oxygen atoms of the other ring (Figure 13) [86].

More recently, Knighton and Beer have reported on another crystal structure of a catenane simultaneously binding a sodium cation and chloride anion (Figure 14) [87]. Catenane **18** was prepared by reacting the bis(pentafluorophenyl) ester of 3,5-pyridinedicarboxylic-1-oxide acid with a bis-amine in the presence of a sodium-metallated methyl pyridinium calix[4]diquinone macrobicyclic. Catenane **18** was isolated in a modest 7% yield, with a crystal structure revealing chloride binding within a convergent amide hydrogen bonding pocket, with the sodium cation coordinated by the calix[4]diquinone and pyridine-*N*-oxide.

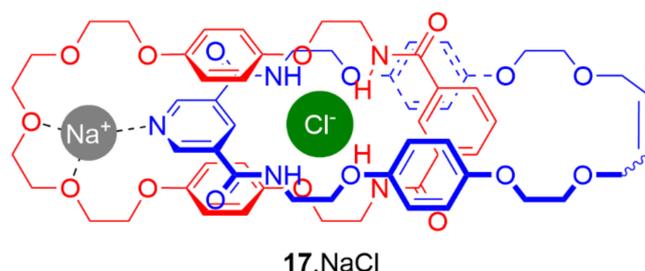


Figure 13. Evans and Beer's neutral pyridyl catenane **17** that serendipitously exhibited ion pair binding in the solid state.

During the peer review of this manuscript, Beer and co-workers published the first detailed report on solution phase ion pair recognition studies with catenanes (Figure 15) [88]. Catenanes **19** and **20** were prepared using an adaptation of Chiu's alkali metal templation methodology [89,90], clipping shut Na^+ templated pseudorotaxanes by use of the CuAAC "click" reaction. Both catenanes, therefore, possess a single multidentate alkali metal cation binding site arising from the glycol sections of the interlocked rings and—in theory—two bidentate halogen bond donor binding sites for halide anions. However, based on quantitative ^1H NMR titrations carried out in 1:1 $\text{CDCl}_3/\text{CD}_3\text{CN}$, catenane **20** only exhibits enhanced 1:1 binding of bromide and iodide in the presence of 1 equivalent of Na^+ or K^+ cation. Catenane **19** demonstrated similar anion binding behaviour with 1 equivalent of K^+ , but with 1 equivalent of Na^+ the binding of a second equivalent of halide anion could be detected. Based on crystallographic evidence, this observation was attributed to the Na^+ cation being coordinatively unsaturated when bound by the shorter glycol chains of **19**. The first equivalent of anion, therefore, coordinates strongly to the cation, before a second equivalent of anion halogen bonds to one of the two bis-iodotriazoles. In addition to these studies, the researchers demonstrated both catenanes were able to extract solid halide salts (NaBr and NaI for **19** and KBr and KI for **20**) into chloroform.

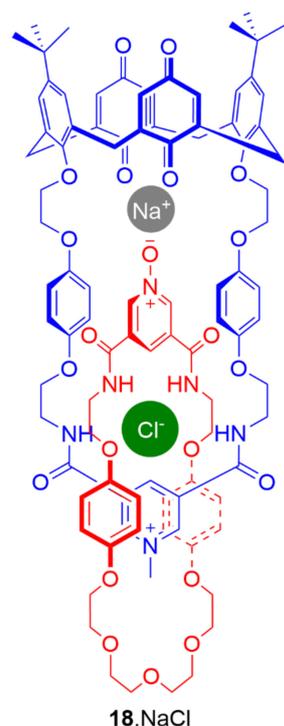


Figure 14. Knighton and Beer's ion pair catenane **18** exhibiting separated ion pair binding in the solid state.

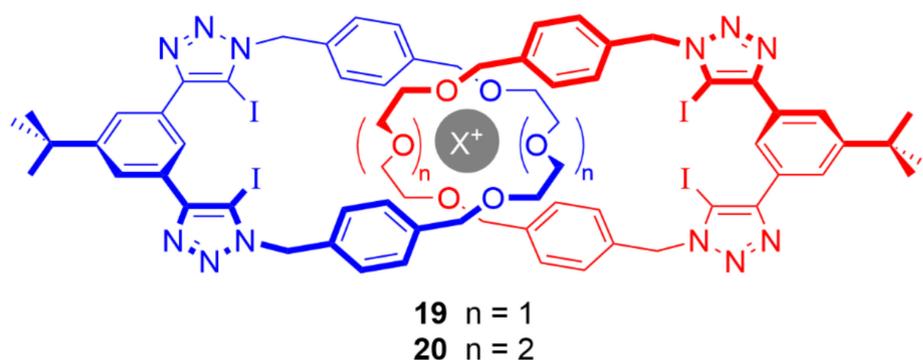


Figure 15. Beer and co-workers' alkali metal cation templated catenanes **19** and **20**, capable of solution phase binding, and extraction of, ion pairs.

6. Conclusions

It has been shown that, in solution and the solid state, interlocked molecules are capable of binding ion pairs. However, studies have been surprisingly limited considering the number of cation and anion binding interlocked molecules that have been reported over the same period. We attribute this to the synthetic challenge of preparing interlocked molecules capable of binding more than one ion, as well as the perennial ion pair recognition problem of salt precipitation during titration studies. There has been a strong (if not exclusive) focus on alkali metal halide ion pairs, but we anticipate that a wider range of ion pair guests will be targeted in future investigations, including enantioselective ion pair recognition (which, in turn, opens up the possibility of ion pair induced asymmetric catalysis). We also predict that attention will turn to deploying interlocked molecular hosts for ion pairs in other applications, such as sensing and transportation, in our own laboratories and elsewhere.

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Data Availability Statement: Not applicable—as this work is a literature review, there is no new data underpinning this publication.

Conflicts of Interest: The authors declare no conflict of interest.

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