

Expanding the Scope of the Anion Templated Synthesis of Interlocked Structures

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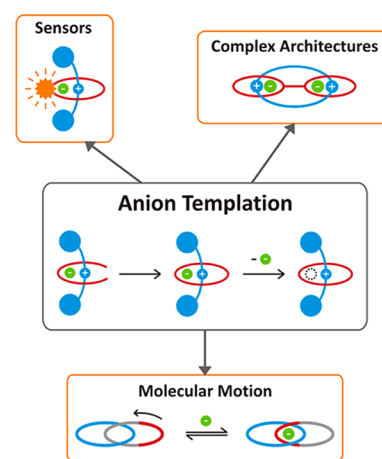
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CONSPECTUS

Nature achieves impressively strong and selective complexation of small molecule anions through the elaborate binding sites of sophisticated proteins. Inspired by these examples, we have developed an anion templation strategy for the synthesis of mechanically interlocked host structures for anion recognition applications. Upon removal of the discrete anionic templating species, such host systems possess unique, three-dimensional, geometrically restrained cavities containing convergent hydrogen bond donor atoms. Such structures exhibit high affinity binding selectivity toward complementary anions.

This Account describes recent advances in this anion templation methodology, demonstrating the versatility and scope of this approach, and progressing to more diverse architectures. Specifically, we have prepared an expansive range of interlocked hosts with enhanced anion recognition properties, such as the ability to operate effectively in competitive aqueous media. We have produced these structures through the utilization of a new anion templated amide condensation synthetic method and through the incorporation of a range of different anion binding motifs, such as groups capable of effective solution-phase halogen bonding interactions. Importantly, direct comparisons between halogen bonding and hydrogen bonding systems reveal impressively magnified anion recognition properties for halogen bonding interlocked host systems. We have also employed the anion templation strategy successfully to construct selective electrochemical and luminescent anion sensors, as well as architectures of increasing complexity, such as a triply interlocked capsule and a handcuff catenane. The synthesis of these latter examples presents greater challenges; however, such molecules offer additional applications in higher order recognition and sensing and in switchable molecular devices.

Having established anion templation as a viable synthetic route to interlocked architectures, we have used this strategy to fabricate a multitude of innovative structures. The key principles of this approach are the ability of anionic species to template the association of carefully designed components, and of the resulting molecular framework with its interlocked host cavity to display impressive anion recognition selectivity. Mechanically interlocked structures have numerous potential applications in nanotechnology. Therefore, the continuing development of effective synthetic methods, especially those which yield functional systems, is of great interest in the broad interdisciplinary field of supramolecular chemistry.



Introduction

The challenge of constructing molecular architectures of increasing complexity has inspired many supramolecular chemists to test the limits of existing synthetic methods as well as explore novel approaches. Primarily motivated by their potential nanotechnological applications as molecular switches and machines,^{1–3} a number of innovative and effective cationic and neutral templation strategies developed over the past 25 years have enabled the preparation of a variety of mechanically interlocked structures of

impressive diversity.^{4,5} In spite of this, the potential of their unique topological cavities in host–guest chemistry has been largely neglected, especially for the recognition of anions.

Anions are ubiquitous in Nature and fundamentally important to a range of biological processes; hence, the construction of potent anion receptors and sensors is of great interest.⁶ Nature's strong and highly selective binding of sulfate and phosphate anions in water is achieved by a network of hydrogen bonds buried deeply inside specific proteins.^{7,8} These binding sites are in protected microenvironment pockets,

facilitating the total encapsulation of the anionic guest species. This suggests that in order to significantly “raise the bar” in anion selectivity exhibited by current abiotic receptors,⁶ more elaborate three-dimensional systems are required, such as interlocked host structures. Compared with cationic or neutral templation methods, however, the construction of interlocked architectures using discrete anion templates is considerably underdeveloped. Consequently, one of the research themes of our group over the past decade or so has been to establish anion templation as a viable route to interlocked structures with the goal of preparing host systems exhibiting selective anion recognition and sensing properties.

Beginnings of Interweaving Anion Templation

Our research into anion templation began with the discovery that a 3,5-bis-amide-pyridinium chloride ion pair forms an orthogonal complex with a neutral isophthalamide derivative via halide hydrogen bonding interactions (Figure 1a).⁹ This arrangement is reminiscent of Sauvage's copper(II) templated systems,¹⁰ in which the tetrahedral ligand requirement of the metal center mediates the association of phenanthroline components (Figure 1b).

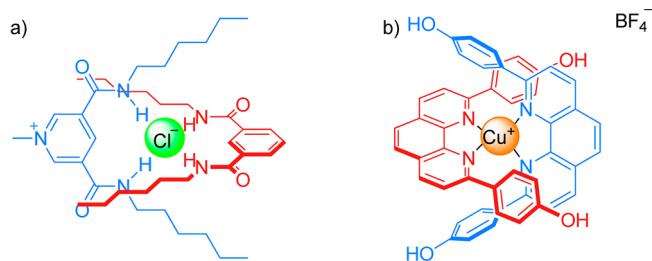


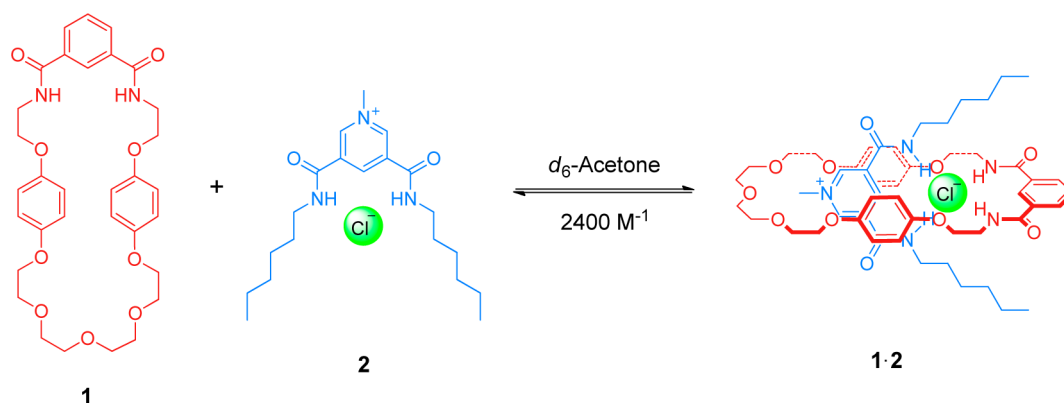
FIGURE 1. Orthogonal association of components around a) a chloride template, and b) a copper(II) template.

Initially, this association was utilized to form an anion templated pseudorotaxane by incorporating the isophthalamide motif into a macrocycle (Scheme 1).⁹ While the chloride anion templates this assembly, further stabilization is achieved from aromatic donor–acceptor interactions between the electron-rich hydroquinone groups of macrocycle **1** and the electron-deficient pyridinium thread **2**, and secondary hydrogen bonding between the macrocycle polyether oxygen atoms and the pyridinium *N*-methyl protons.

The progression from interpenetrated assemblies to interlocked structures, for example, rotaxane **3**, required the use of Grubbs'-catalyzed ring closing metathesis (RCM) to “clip” a bis-vinyl-appended macrocycle precursor around a terphenyl-stoppered pyridinium chloride axle (Scheme 2).¹¹ Upon exchange of the halide template to the noncoordinating hexafluorophosphate, such structures possess unique three-dimensional binding cavities, which exhibit favorable selective anion recognition for the chloride template as larger basic oxoanions are unable to penetrate the binding pocket. Importantly, this is a reversal of the selectivity exhibited by the pyridinium axle.

In 2007, we published an Account detailing “first-generation” receptor systems based on the 3,5-bis-amide-pyridinium motif and employing RCM as the sole method of interlocked structure formation.¹² This Account will discuss our efforts since then to expand the scope of the anion templated synthesis of interlocked structures. Namely, the utilization of alternative synthetic strategies and different anion binding motifs, including those for solution-phase halogen bonding, the incorporation of electrochemically active and luminescent reporter groups to achieve selective anion sensing, and the fabrication of interlocked architectures capable of anion-induced molecular motion and of increasing complexity.

SCHEME 1. Formation of Anion Templated Pseudorotaxane Assembly **1·2**



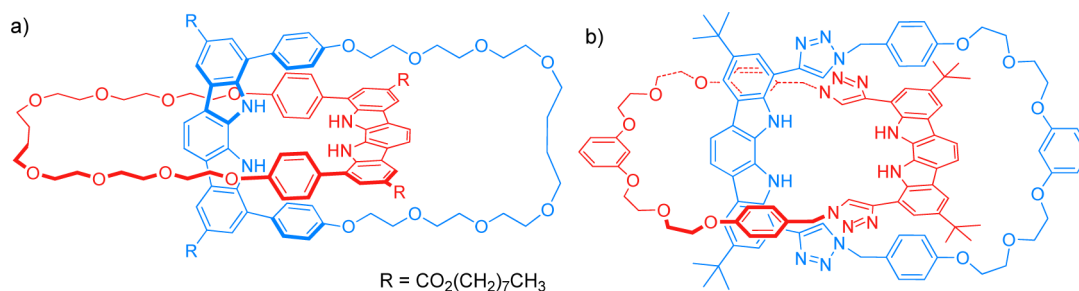
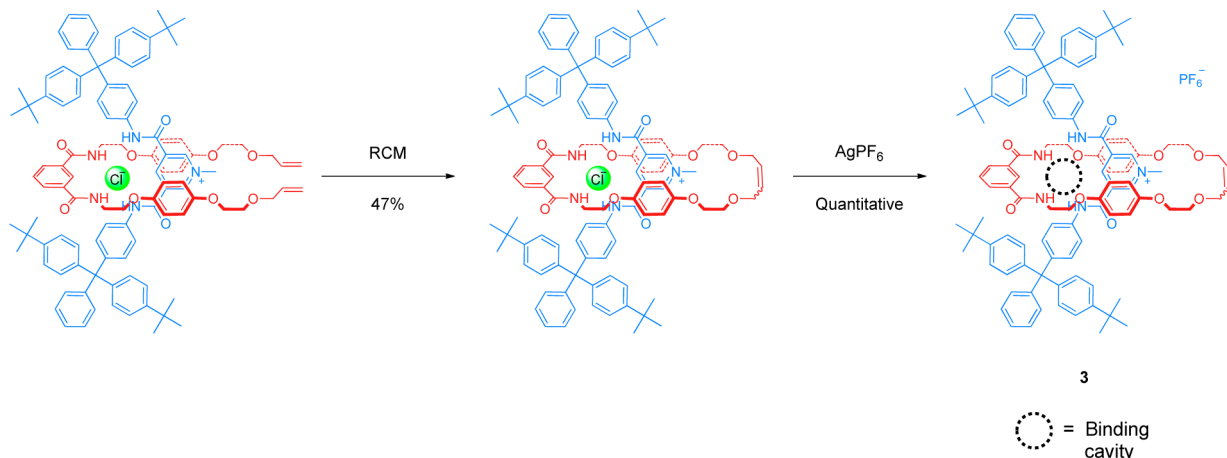


FIGURE 2. Indolocarbazole-based catenanes reported by (a) Jeong et al. and (b) Li and Li.

SCHEME 2. Anion Templated Synthesis of Rotaxane **3** Using Grubbs'-Catalyzed Ring Closing Metathesis (RCM)



Recently, two other research groups have employed similar methods to synthesize interlocked anion receptors, namely, the chloride-selective, indolocarbazole-based catenanes reported by Jeong et al.¹³ and Li and Li¹⁴ (Figure 2).

An Alternative Anion Templatation Synthetic Strategy

To develop the anion templatation strategy further and prepare hosts with enhanced recognition properties, we have recently established a novel amide condensation route. Specifically, the formation of macrocycle **4** was found to be templated by 3,5-bis-amide-pyridinium chloride thread **2**,¹⁵ with rotaxanes **6** and **7** synthesized in yields of 56% and 60% when the appropriate macrocyclization reactions were carried out in the presence of stoppered axle **5** (Scheme 3).¹⁶ Amide condensation methods have been employed previously for interlocked structure formation, notably by Hunter,¹⁷ Vögtle et al.,¹⁸ and Leigh et al.¹⁹ We have, however, demonstrated that our approach operates through an anion templatation mechanism due to the formation of an intermediate assembly produced via binding to the halide template by the axle and half-formed macrocycle (represented in Scheme 3).

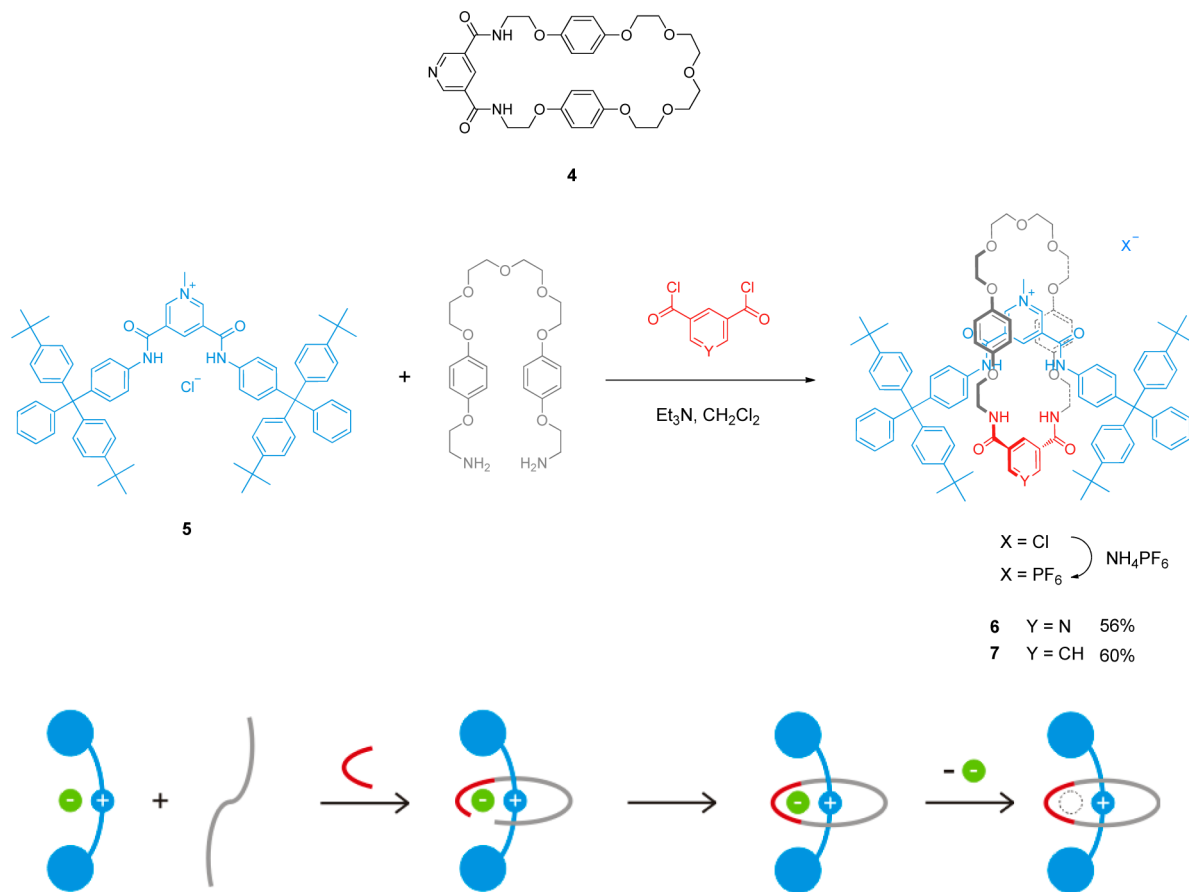
This association is further stabilized by the secondary hydrogen bonding and donor–acceptor interactions discussed above, and importantly, substantially lower yields were observed in analogous reactions without the sources of potential halide templates.¹⁶

The anion recognition properties of the systems constructed via this method can be compared with the analogous systems synthesized using RCM, for example, rotaxanes **3** and **7**. While the binding of chloride by **3** is able to be quantified in 1:1 CDCl₃/CD₃OD (Table 1), the same interaction is too strong with rotaxane **7** ($K > 10^4 \text{ M}^{-1}$) and the addition of 10% D₂O in the solvent media is necessary to obtain an accurate association constant using ¹H NMR spectroscopy. The enhanced chloride binding strength exhibited by **7** compared with **3** is due to the hydrogen bonding interactions between the axle pyridinium *N*-methyl protons and the macrocycle polyether oxygens which are reduced in **3** due to the presence of the vinyl group. Increased stabilization from these interactions favors the preorganization of the interlocked cavity in the correct orientation for anion binding.

As in previous systems, rotaxane **7** displays selectivity for the chloride template over the larger, more basic oxoanions

TABLE 1. Association Constants, K (M^{-1}), of Rotaxanes **3**, **7**, and **8** with Anions^a

anion	3	7		8
	1:1 CDCl ₃ /CD ₃ OD	1:1 CDCl ₃ /CD ₃ OD	45:45:10 DCl ₃ /CD ₃ OD/D ₂ O	65:35 <i>d</i> ₆ -acetone/D ₂ O
Cl ⁻	1130	>10 ⁴	1190	500
H ₂ PO ₄ ⁻	300		120	NB ^b
OAc ⁻	$K_{11} = 100, K_{12} = 40$		180	NB ^b

^aErrors < 10%. ^bNB = no binding.**SCHEME 3.** Macrocycle **4** and the Synthesis of Rotaxanes **6** and **7** via an Anion Templated Amide Condensation Route

dihydrogen phosphate and acetate in 45:45:10 CDCl₃/CD₃OD/D₂O. The X-ray crystal structure of the chloride salt of rotaxane **7** (Figure 3) illustrates the ability of the halide guest species to bind within the rotaxane host cavity, facilitating optimum complexation with the convergent axle and macrocycle N–H and C–H hydrogen bond donors. The presence of different binding modes for the halides and oxoanions, internal and external to the constrained rotaxane cavity, is supported by both molecular dynamics simulations¹⁶ and differential ¹H NMR shifts in the signal corresponding to the *para*-pyridinium proton of **7** (Figure 4). While chloride binding within the interlocked cavity induces a downfield shift due to a C–H hydrogen bonding

interaction, upfield shifts were observed with the oxoanions, due to a substantial change in rotaxane co-conformation to assist the peripheral association of the larger oxoanion guest species.

Stronger chloride complexation and more definitive selectivity over the oxoanions can be achieved by preparing a doubly charged system, bis-pyridinium rotaxane **8** (Figure 5a).¹⁶ Impressively, in the highly polar 65:35 *d*₆-acetone/D₂O solvent mixture, **8** is capable of binding chloride with an association constant of 500 M⁻¹, while no binding was observed with either dihydrogen phosphate or acetate (Table 1). The scope of this synthetic method has also been demonstrated by synthesizing

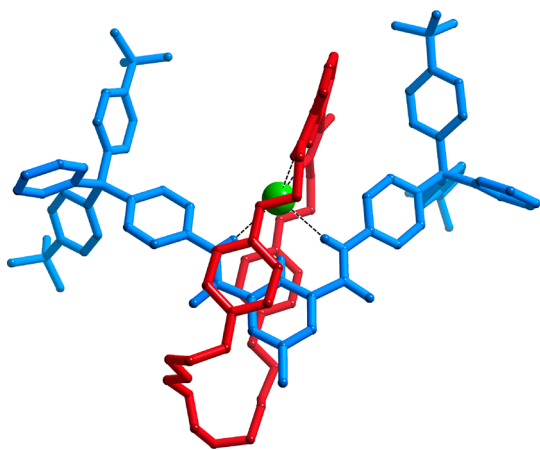


FIGURE 3. X-ray crystal structure of the chloride salt of rotaxane **7**.

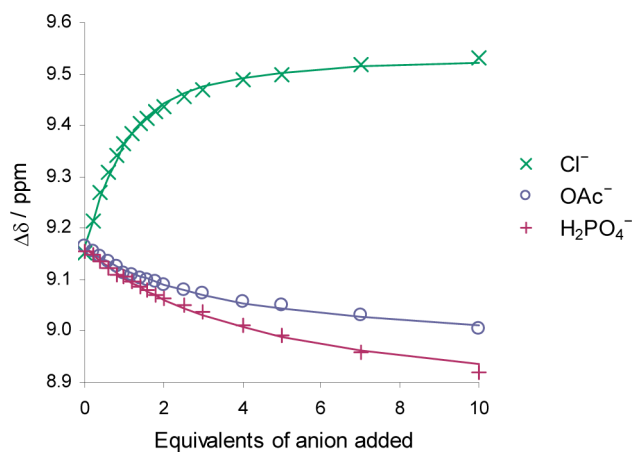


FIGURE 4. Shifts of the *para*-pyridinium proton in rotaxane **7** upon anion addition in 45:45:10 $\text{CDCl}_3/\text{CD}_3\text{OD}/\text{D}_2\text{O}$. Symbols represent data points, lines represent binding isotherms.

related catenane systems such as **9** (Figure 5b),²⁰ and adjusting the macrocycle binding cleft to prepare both sulfonamide-containing rotaxane **10**¹⁶ (Figure 5c) and *meta*-xylenediamide rotaxane **11**²¹ (Figure 5d).

Incorporating Different Binding Motifs: Hydrogen Bonding

The desire to incorporate different anion binding motifs into interlocked host structural frameworks is driven by the possibility of influencing significantly the recognition properties of these systems. For example, the high yielding synthesis of pyridinium nicotinamide homocatenane **12** using RCM was mediated by sulfate as the templating anion (Scheme 4).²² This system was the first sulfate templated interlocked structure and displayed selective recognition for this templating anion over chloride, bromide and acetate in 1:1 $\text{CDCl}_3/\text{CD}_3\text{OD}$.

The triazole group has received intense recent attention due to its accessibility via the copper(I)-catalyzed alkyne–azide cycloaddition (CuAAC) reaction, as well as its C–H hydrogen bonding capabilities. We have integrated this motif into an interlocked host using the novel 3,5-bis(triazole)-pyridinium functionality within catenane **13** (Figure 6a),²³ and this system was found to exhibit substantially enhanced halide selectivity in comparison with the analogous amide catenane **14** (Figure 6b).²⁴ While the two receptors display similar chloride affinities (Table 2), catenane **13** binds dihydrogen phosphate much more weakly than **14**. This increased halide-oxoanion discrimination arises from the unique nature of the bis-triazole bis-amide interlocked cavity. Furthermore, as alternatives to the pyridinium motif, the positively charged heterocycles triazolium and imidazolium, both capable of anion complexation through electrostatic and C–H hydrogen bonding interactions, have been successfully incorporated into the axle components of rotaxane host structures which display selective anion recognition properties.^{25,26}

Incorporating Different Binding Motifs: Halogen Bonding

Electron-deficient halogen atoms, most commonly bromine and iodine, have been shown to act as electrophiles due to the existence of a highly localized region of positive charge. Halogen bonding was, however, until very recently, mainly restricted to crystal engineering and materials applications.²⁷ The rapid expansion in the use of halogen bonding in solution-phase molecular recognition processes has included developments in anion binding as Lewis basic anions can act as excellent halogen bond acceptors, with a range of suitable acyclic^{28–31} and macrocyclic^{32,33} anion host systems reported by our group and others. The interest in this interaction arises from its comparison with hydrogen bonding – comparable in strength but with more strictly linear geometrical requirements. Moreover, halogen bonding appears to be highly suited for exploitation in competitive polar media and polar/aqueous solvent mixtures.

To establish the use of halogen bonding in facilitating anion templated interpenetrative assembly, bromoimidazolium thread **15** was demonstrated to form a pseudorotaxane with isophthalamide macrocycle **19** (Figure 7).³⁴ Thread **15** exists as a tight ion pair due to charge-assisted halogen bonding between the bromo-imidazolium group and the chloride counteranion, and halide complexation to the macrocycle hydrogen bond donors mediates the assembly of pseudorotaxane **15**·**19** along with stabilizing donor–acceptor interactions. This process was proven to be anion

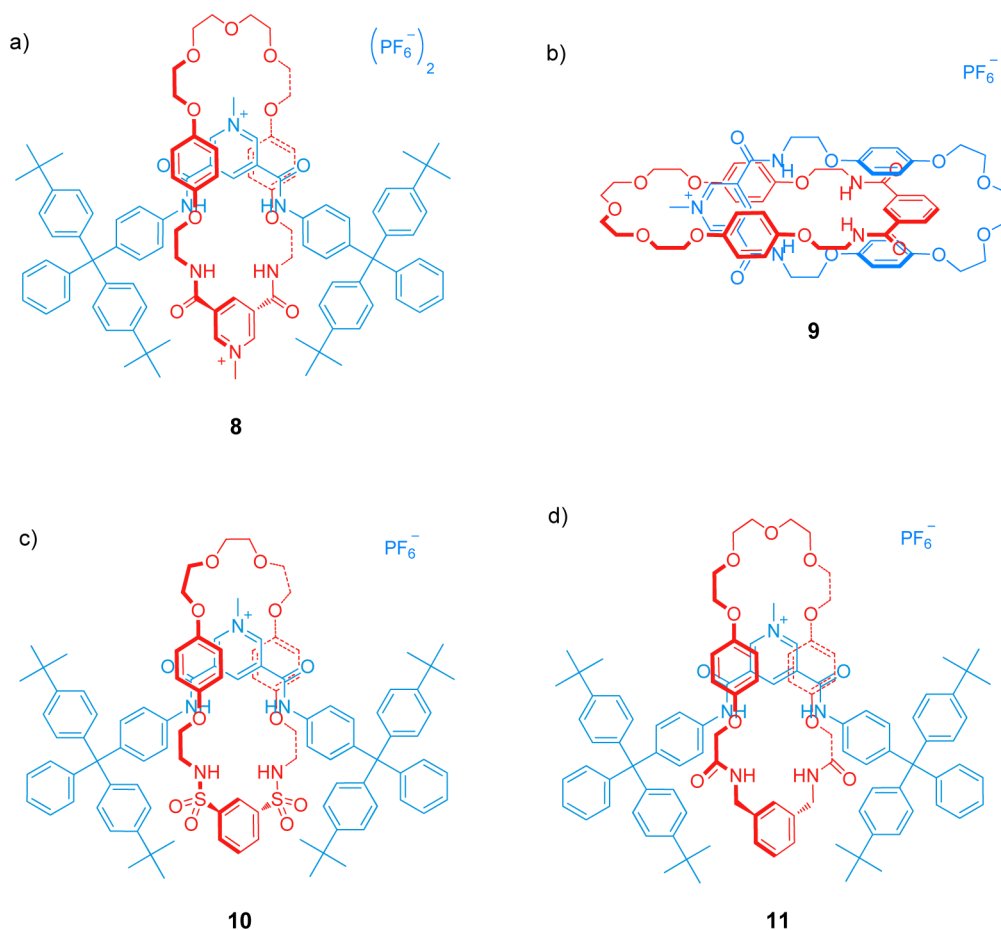


FIGURE 5. (a) Doubly charged bis-pyridinium rotaxane **8**, (b) catenane **9**, (c) sulfonamide rotaxane **10**, and (d) *meta*-xylenediamide rotaxane **11**.

templated as the hexafluorophosphate salt of thread **15** did not form a pseudorotaxane with macrocycle **19**.

Importantly, the stability of this assembly was found to be significantly enhanced compared to the analogous protic-imidazolium system using 4,5-dimethylimidazolium thread **16** (Table 3). Furthermore, the increased linear requirements of halogen bonding compared with hydrogen bonding were demonstrated by the related bis-bromo thread **17** displaying no affinity for macrocycle **19**, while the related bis-protic thread **18** formed a stable pseudorotaxane, tolerating the divergent nature of the imidazolium hydrogen bond donors.

A similar enhancement in anion templated pseudorotaxane stability was also observed with iodo-triazolium thread **20** compared with protic-analogue **21** (Figure 8 and Table 3).³⁵ In this system, bromide was found to be the most effective halide template for interpenetrative assembly using ¹H NMR spectroscopic titration experiments, with apparent association constants of 1188 M⁻¹ for **19**·**20** and 610 M⁻¹ for **19**·**21** in CDCl₃.

Encouraged by these halide anion templated halogen bonding pseudorotaxane findings, rotaxane **22** (Figure 8) was prepared by bromide templation.³⁵ This was the first interlocked structure to use halogen bonding to control the assembly process, and its solid-state crystal structure illustrates the increased steric considerations which arise from incorporating a large halogen atom within the molecular frameworks of interlocked structures.

Initial anion recognition studies in 1:1 CDCl₃/CD₃OD revealed that rotaxane **22** binds bromide anions at least an order of a magnitude stronger than the analogous protic-triazolium rotaxane²⁵ ($K > 10^4$ M⁻¹). Pleasingly, this result, enhanced binding strength with halogen bonding, is in agreement with the pseudorotaxane findings. In addition, despite the apparent exposed nature of the interlocked cavity in the solid-state, rotaxane **22** did exhibit considerable selectivity between halide anion guest species in 45:45:10 CDCl₃/CD₃OD/D₂O with 1:1 association constants of 457, 1251, and 2228 M⁻¹ for chloride, bromide, and iodide respectively. This unusual binding preference for the

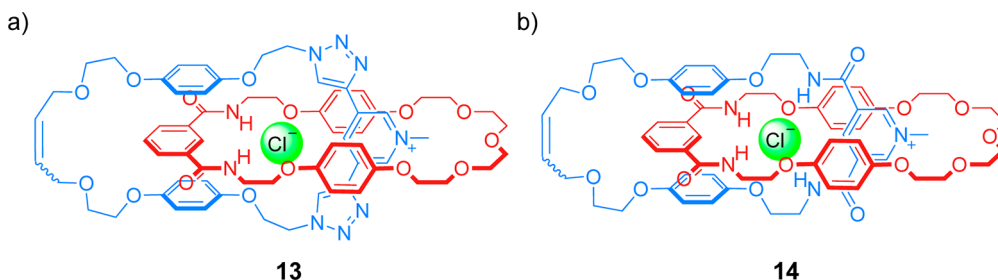
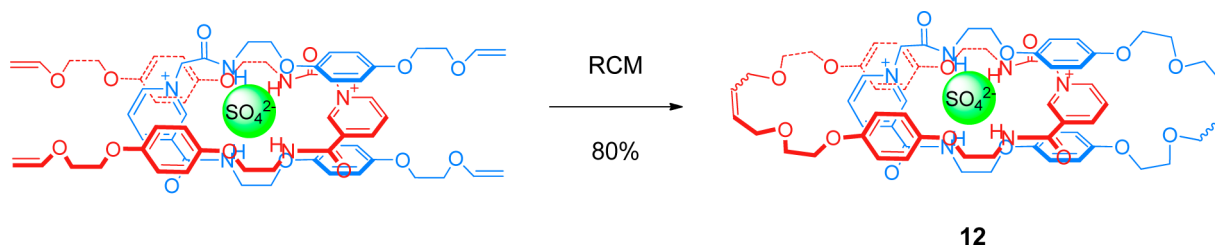


FIGURE 6. (a) Triazole-containing catenane **13** and (b) amide-containing catenane **14**.

SCHEME 4. Sulfate Templated Synthesis of Pyridinium Nicotinamide Homocatenane **12**



larger iodide is thought to arise from a combination of the exact geometrical requirements of the mixed halogen- and hydrogen-bonding cavity, its relative accessibility, and the greater lipophilicity of iodide given the aqueous content of the media.

Returning to the bromo-imidazolium motif, we have reported the synthesis of a bromide anion templated homocatenane **23** capable of selective anion recognition solely via halogen bonding (Scheme 5).³⁶ The inclusion of naphthalene spacers within component design was influenced by the desire to create a larger, enclosed interlocked host cavity than in rotaxane **22**, as well as the potential for these motifs to act as fluorescent reporter groups.

This potential was confirmed using fluorescence spectroscopy in acetonitrile, with catenane **23** displaying significant changes in its emission spectrum upon chloride and bromide binding. A range of other anions were also tested, however, no fluorescence perturbations were observed, nor upon addition of any of the anions to the component macrocycle. This impressive selectivity, complete sensing discrimination for these two halides, is thought to arise from the properties of the preorganized interlocked cavity. Only anions which can penetrate the binding domain perturb the naphthalene emission, with chloride bound substantially more strongly than bromide (3.71×10^6 and $1.48 \times 10^5 \text{ M}^{-1}$, respectively).

Electrochemical Anion Sensing

With the objective of selectively sensing anions via electrochemical methods, previous research in our group has been

TABLE 2. Association Constants, K (M^{-1}), of Catenanes **13** and **14** with Chloride and Dihydrogen Phosphate^a

anion	13	14
Cl^-	680	730
H_2PO_4^-	49	$K_{11} = 480, K_{12} = 520$

^aErrors < 10%.

undertaken to incorporate ferrocene as an appropriate reporter group within anion receptor systems.³⁷ Binding can perturb the metallocene redox center sufficiently to result in cathodic shifts in the ferrocene/ferrocenium oxidation potential as the anion stabilizes the oxidized ferrocenium state. To exploit the selective recognition properties of anion templated interlocked structures, the ferrocene motif was integrated into rotaxane and catenane host structural frameworks. In preliminary work, an anion templated bis-ferrocene rotaxane self-assembled monolayer (SAM) was shown to exhibit an electrochemical response to chloride anions.^{12,38} Since then, various new methods of ferrocene-attachment have been achieved.

Ferrocene was incorporated either as pentaphenylferrocene stopper groups within a pyridinium axle component in rotaxane **24**,³⁹ appended onto the isophthalamide macrocycle component of rotaxane **25**,⁴⁰ or similarly onto one of the macrocycles in the first ferrocene-containing catenane **26**⁴¹ (Figure 9). All three systems were constructed using chloride anion templation, and the interlocked natures of these structures were confirmed by diagnostic ^1H NMR spectra and intercomponent ^1H – ^1H NMR ROESY couplings,

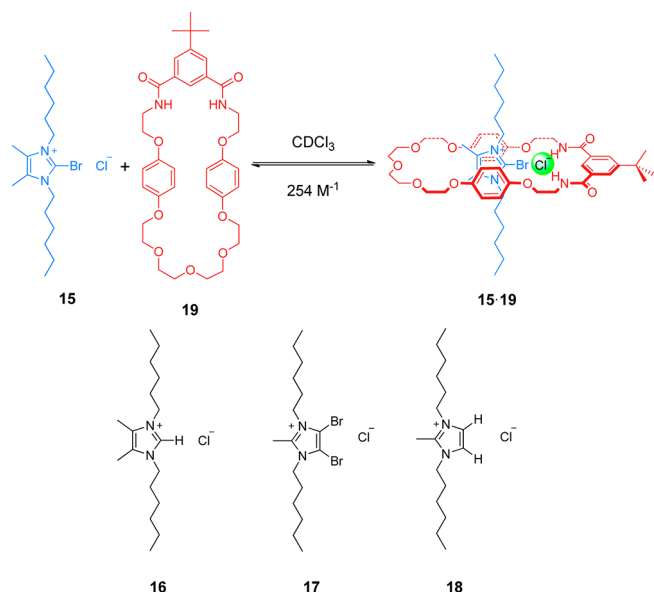


FIGURE 7. Threads **15–18**, macrocycle **19**, and pseudorotaxane **15–19**.

TABLE 3. Apparent Association Constants, K (M^{-1}), for Pseudorotaxane Formation between Threads 15–18 and 20–21 and Macrocycle 19 in $CDCl_3$ ^a

macrocycle	threads					
19	15	16	17	18	20	21
	254	97	NA ^b	245	1188	610

^aErrors < 10%. ^bNA = no association.

as well as X-ray crystal structures of the chloride salts of rotaxane **24** and catenane **26** (Figure 10).

Rotaxanes **24** and **25** and catenane **26** were all found to selectively bind chloride over oxoanions dihydrogen phosphate, benzoate, and hydrogen sulfate using ¹H NMR titration experiments in 1:1 $CDCl_3/CD_3OD$ (Table 4). Interestingly, the chloride binding affinity of rotaxane **25** was considerably higher than that displayed by both **24** and **26**. It is thought that the increased acidity of the N–H protons of the pyridinium axle component of **25**, due to direct attachment of the terphenyl stoppers, compared with the aliphatic bis-amide-pyridinium groups within **24** and **26** is responsible for these differences.

Solubility considerations required the use of alternative 1:1 CH_2Cl_2/CH_3CN or CH_3CN solvent conditions in electrochemical anion sensing investigations (Table 5). Selective characteristic responses with chloride were observed, in which the maximum cathodic shift in the respective ferrocene redox couple occurred after one equivalent of halide, in contrast with the oxoanions which required many more equivalents to achieve sensing saturation. Importantly, these findings are in agreement with the NMR studies,

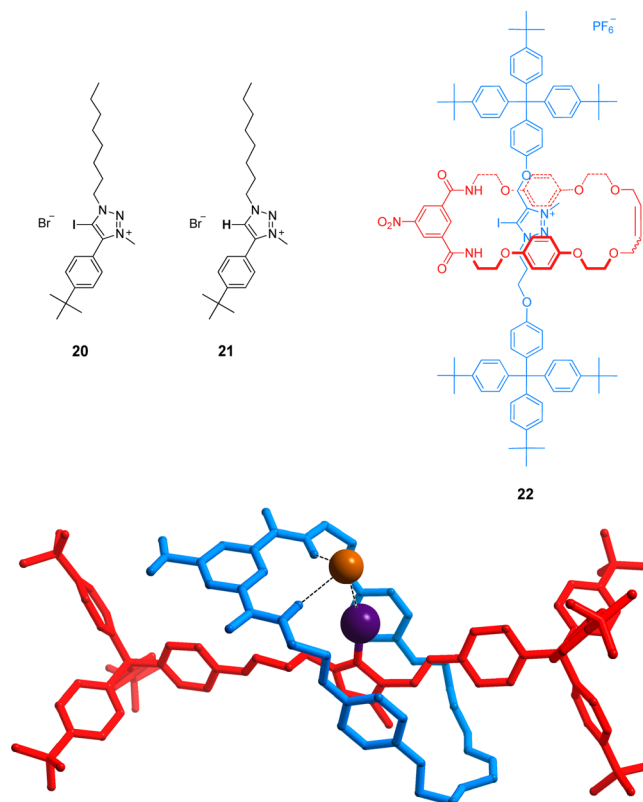


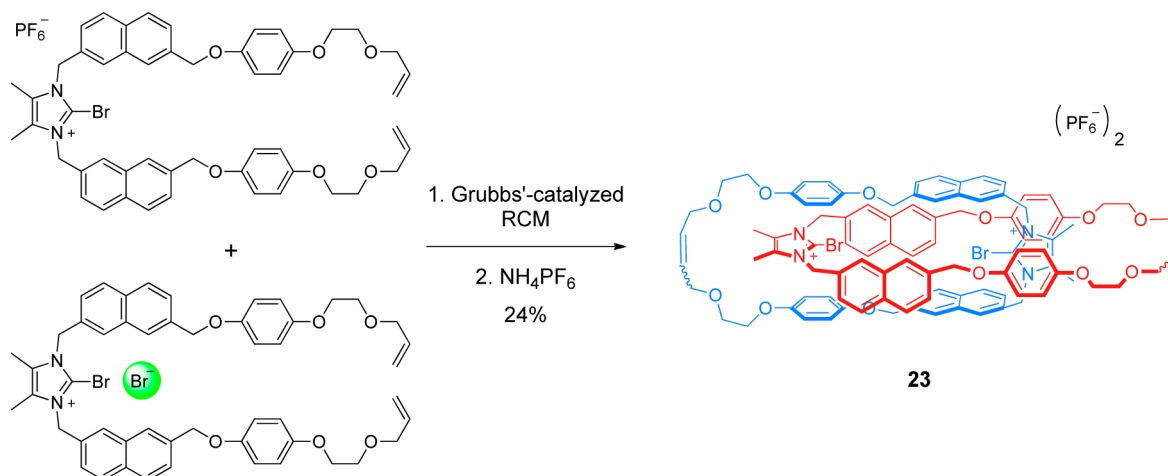
FIGURE 8. Threads **20** and **21**, and iodo-triazolium rotaxane **22** and X-ray crystal structure of the bromide salt of **22**.

indicating a preference for strong chloride binding within the interlocked cavities of **24–26**.

Surface-based sensor devices have a number of advantages when compared with solution-phase analogues, including reusability, the avoidance of solubility problems, and the potential for beneficial amplification effects, and hence, a surface-confined analogue of catenane **26** was fabricated (Scheme 6).⁴¹ Thiol functionalities allow for adsorption of pyridinium derivative **27** onto a gold electrode, and this reaction was carried out in the presence of 10 equiv of ferrocene-appended macrocycle **28** to bias the association equilibrium toward pseudorotaxane, and ultimately catenane formation. Evidence for formation of SAM **29** was obtained using cyclic voltammetry, ellipsometry, and high resolution X-ray photoelectron spectroscopy. Surprisingly, the inability to remove the chloride template negated anion sensing studies. This dramatically amplified SAM halide binding strength is postulated to be due to the high degree of surface preorganization in the doubly attached catenane system.

Luminescent Anion Sensing

Returning to fluorescent sensing methods, which are desirable due to inherent high sensitivity, previous work within

SCHEME 5. Bromide Templated Synthesis of Bromo-Imidazolium Homocatenane **23** Using Halogen Bonding

the group has included anion sensing using acyclic and macrocyclic luminescent transition metal receptors.^{37,42} Rotaxanes **30** and **31** (Figure 11) were synthesized using the new amide condensation method to incorporate the 4,4'-bis-amide-2,2'-bipyridyl group for rhenium(I) and ruthenium(II) complexation.⁴³

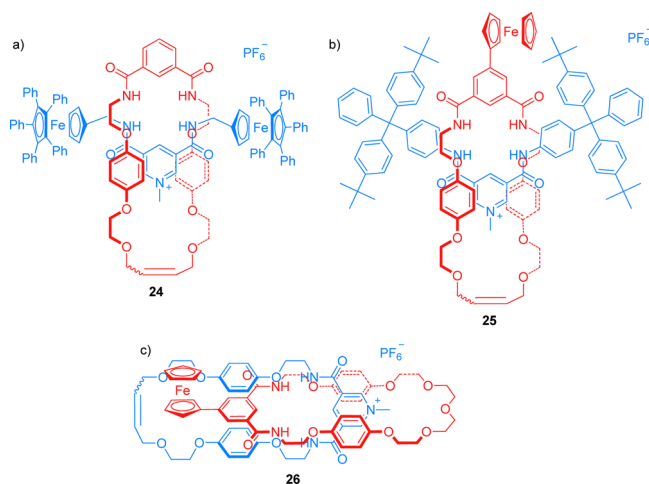


FIGURE 9. (a) Pentaphenylferrocene-stoppered rotaxane **24**, (b) ferrocene-appended rotaxane **25**, and (c) ferrocene-appended catenane **26**.

The recognition and sensing properties of **30** and **31** were studied using ¹H NMR and photophysical investigations in aqueous acetone mixtures (9:1 to 7:3 acetone/water), and, as expected, both systems were found to exhibit considerable binding selectivity for chloride over dihydrogen phosphate and acetate. Importantly, these recognition events were signaled by significant enhancements in the respective metal–ligand complexes luminescent emissions. Examples of interlocked structures displaying fluorescent anion sensing behavior are relatively rare,^{13,44,45} and operation in

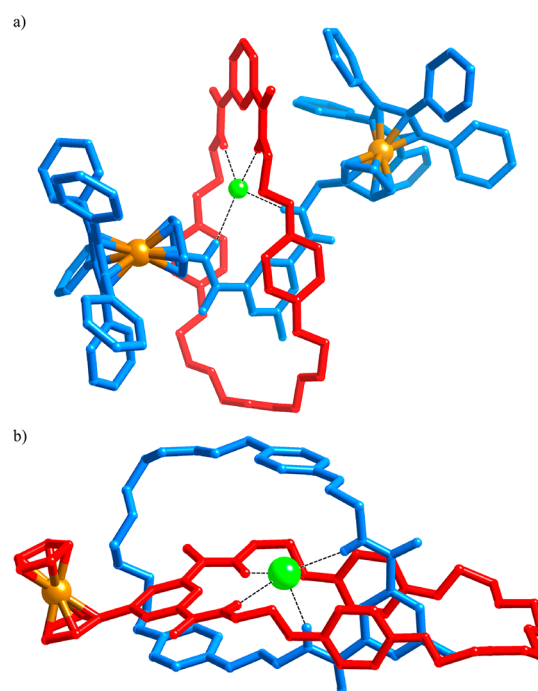


FIGURE 10. X-ray crystal structures of the chloride salts of (a) rotaxane **24** and (b) catenane **26**.

TABLE 4. Association Constants, K (M^{-1}), of Ferrocene-Containing Rotaxanes **24** and **25** and Catenane **26** with Anions in 1:1 $CDCl_3/CD_3OD^a$

anion	rotaxane 24	rotaxane 25	catenane 26
Cl^-	1780	4200	1900
$H_2PO_4^-$	350	640	350
BzO^-	490	640	190
HSO_4^-	1040	1560	1100

^aErrors < 10%.

aqueous solvent media is vital in the development of this area.

Anion-Induced Molecular Motion

The potential for mechanically interlocked molecules to act as molecular-scale switchable devices, even “machines”, arises from their ability to undergo reversible molecular motion through changes in the relative positions of the constituent parts. The use of molecular recognition events such as anion binding to induce this behavior is, however, relatively underdeveloped. By incorporating an orthogonal set of noncovalent intercomponent interactions into our target systems, we have been able to successfully synthesize interlocked structures capable of effective anion-induced molecular motion.

This principle is illustrated by the anion-induced shuttling behavior of rotaxane **32** (Scheme 7),⁴⁶ synthesized via chloride templation using the CuAAC reaction to stopper a 2,6-bis-imidazolium-pyridine axle. In the absence of a coordinating anion, **32** exists with the macrocycle residing preferentially over one of the two axle triazole groups due to hydrogen bonding interactions between the macrocycle

isophthalamide motifs and the axle carbonyl oxygen atoms. Upon chloride addition, a considerable macrocycle

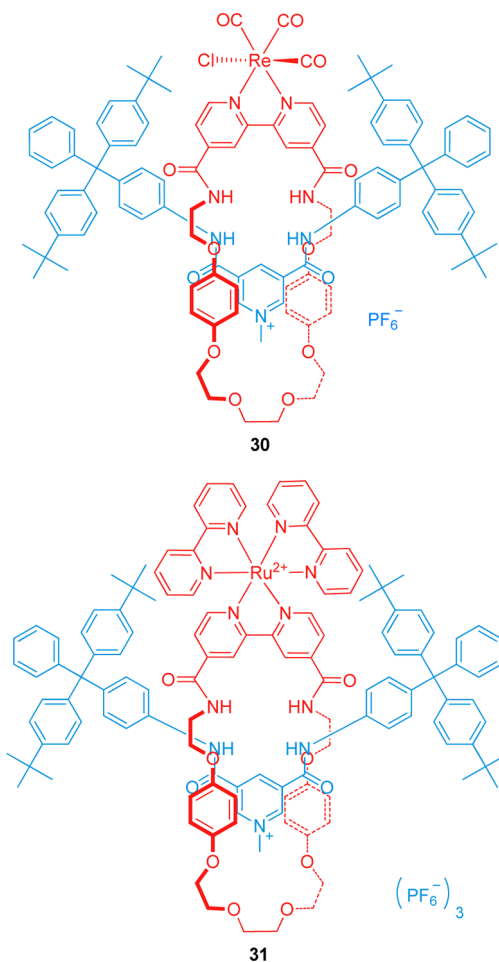
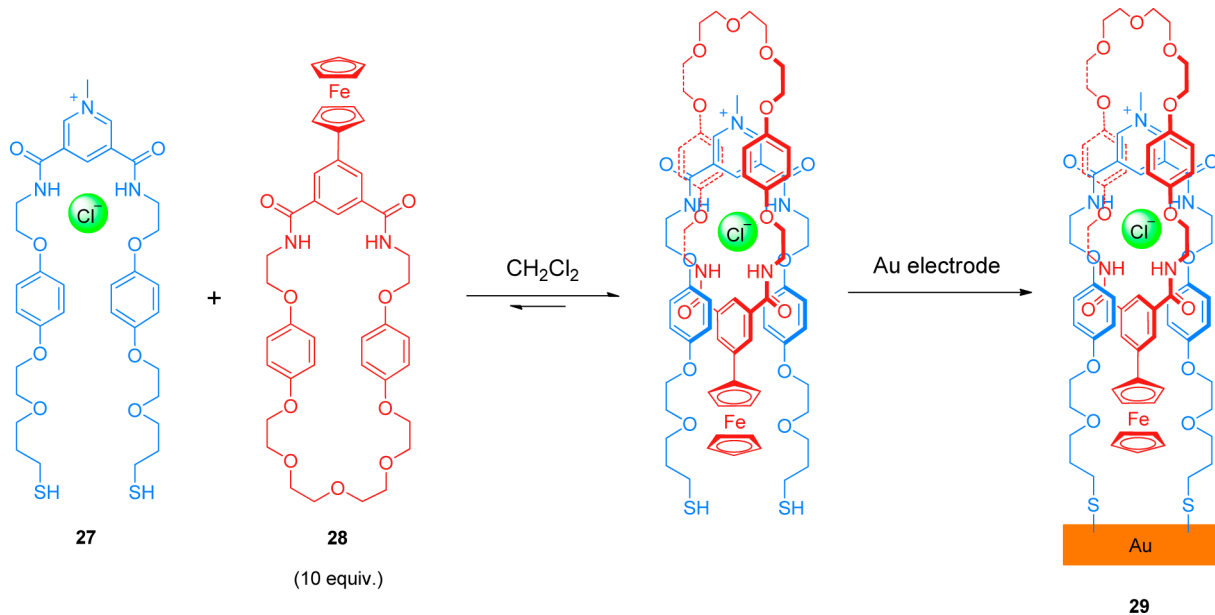


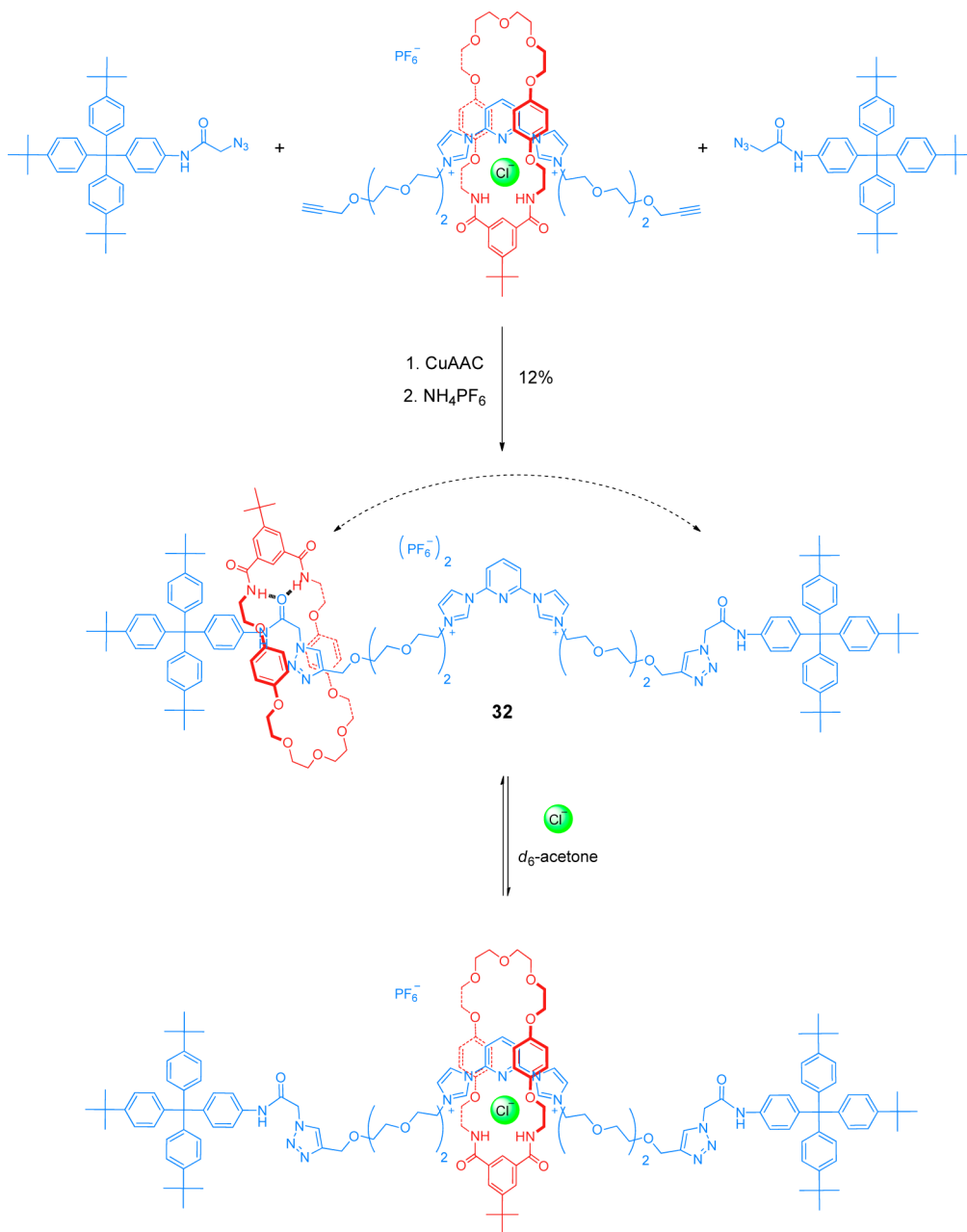
FIGURE 11. Transition metal appended luminescent rotaxanes **30** and **31**.

TABLE 5. Cathodic Shifts, $\Delta E_{1/2}$ (mV), of Fc/Fc⁺ or Ppfc/Ppfc⁺ Redox Couple upon Anion Addition of Ferrocene-Containing Rotaxanes **24** and **25** and Catenane **26**

anion	rotaxane 24		rotaxane 25		catenane 26	
	1 equiv	10 equiv	1 equiv	10 equiv	1 equiv	5 equiv
Cl ⁻	-20	-20	-20	-20	-20	-20
H ₂ PO ₄ ⁻	-35	-115	-10	-100	-25	-85
BzO ⁻	-20	-65	-15	-25	<10	<10
HSO ₄ ⁻	-20	-40	-15	-40	-10	-25

SCHEME 6. Synthesis of Ferrocene-Containing Catenane SAM **29**



SCHEME 7. Synthesis and Chloride-Induced Shuttling Behavior of 2,6-Bis-imidazolium-pyridine Rotaxane **32**

translocation event occurs to allow for cooperative anion complexation by the macrocycle and axle binding motifs. Evidence for the interlocked co-conformations is obtained primarily from rationalization of ^1H NMR shifts and definitive changes in the observed 2D ^1H - ^1H NMR ROESY couplings.

For the development of anion-induced switchable molecular devices, it is advantageous for systems to exhibit unidirectional motion, selectivity between coordinating anions, and optical or electrochemical signaling. For example, naphthalimide triazolium rotaxane **33** contains an asymmetrical axle which facilitates unidirectional shuttling upon

anion addition (Scheme 8).⁴⁷ Donor-acceptor interactions between the electron-rich hydroquinone groups of the macrocycle and the electron-deficient axle naphthalimide motif, along with complementary isophthalamide-carbonyl hydrogen bonds, are responsible for the initial rotaxane co-conformation. Subsequent molecular motion is driven by anion complexation within the rotaxane host cavity created by macrocycle translocation, with selectivity displayed for the smaller halides chloride and bromide over iodide and oxoanions acetate and dihydrogen phosphate in 4:1 $\text{CDCl}_3/\text{CD}_3\text{OD}$, both in the strength of binding and the extent of the

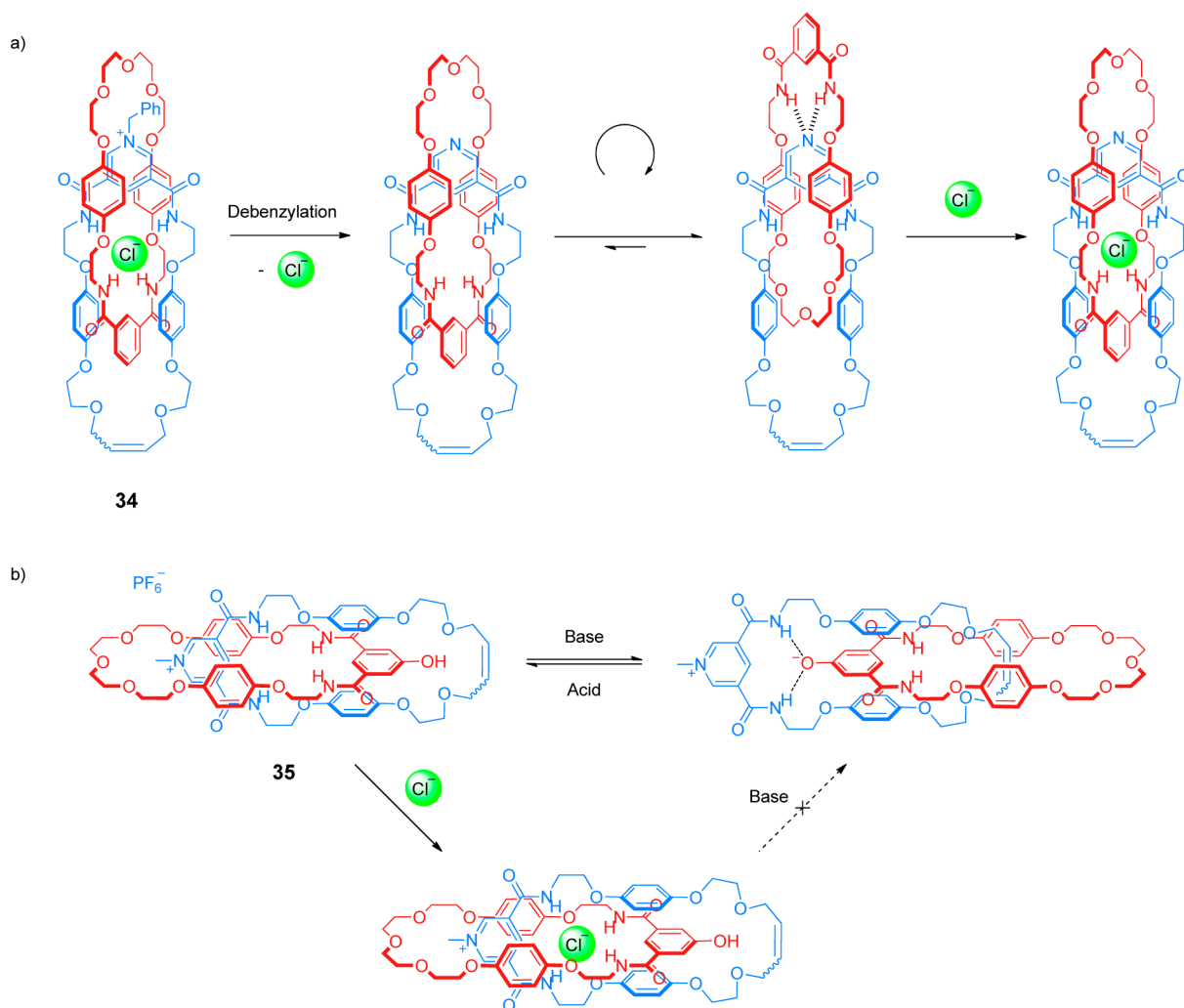
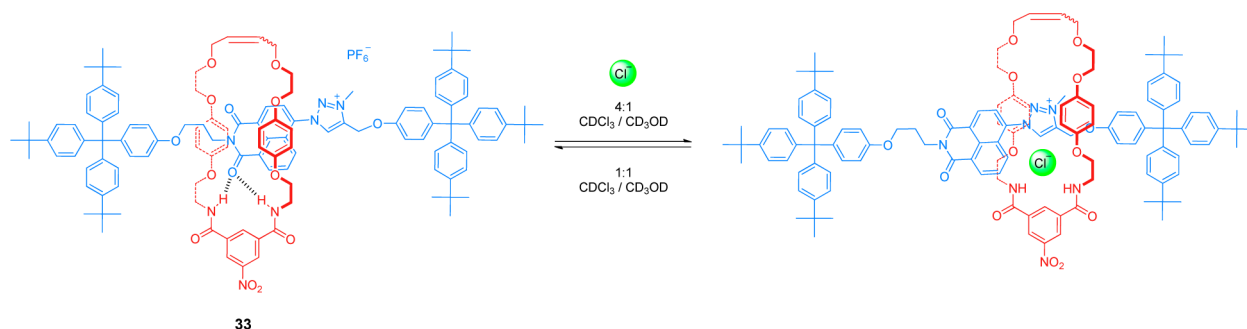


FIGURE 12. Controlled pirouetting motions exhibited by (a) catenane **34** and (b) catenane **35**.

SCHEME 8. Anion and Solvent Controlled Shuttling of Naphthalimide Rotaxane **33**



co-conformational change. Molecular motion was able to be reversed by protic solvent addition, increasing the competitive nature of the media and hence sufficiently weakening the anion recognition interactions. Furthermore, while the macrocycle translocation is relatively small in this system, the changes in the hydroquinone–naphthalimide donor–acceptor

interactions are signaled effectively by perturbations in the rotaxane absorbance band detectable by UV/vis spectroscopy.

In addition to rotaxane shuttling, catenane ring circumrotation, “pirouetting”, is another mode of interlocked structure molecular motion, and catenanes **34**⁴⁸ and **35**⁴⁹ both undergo this type of behavior (Figure 12). Debenzylation of

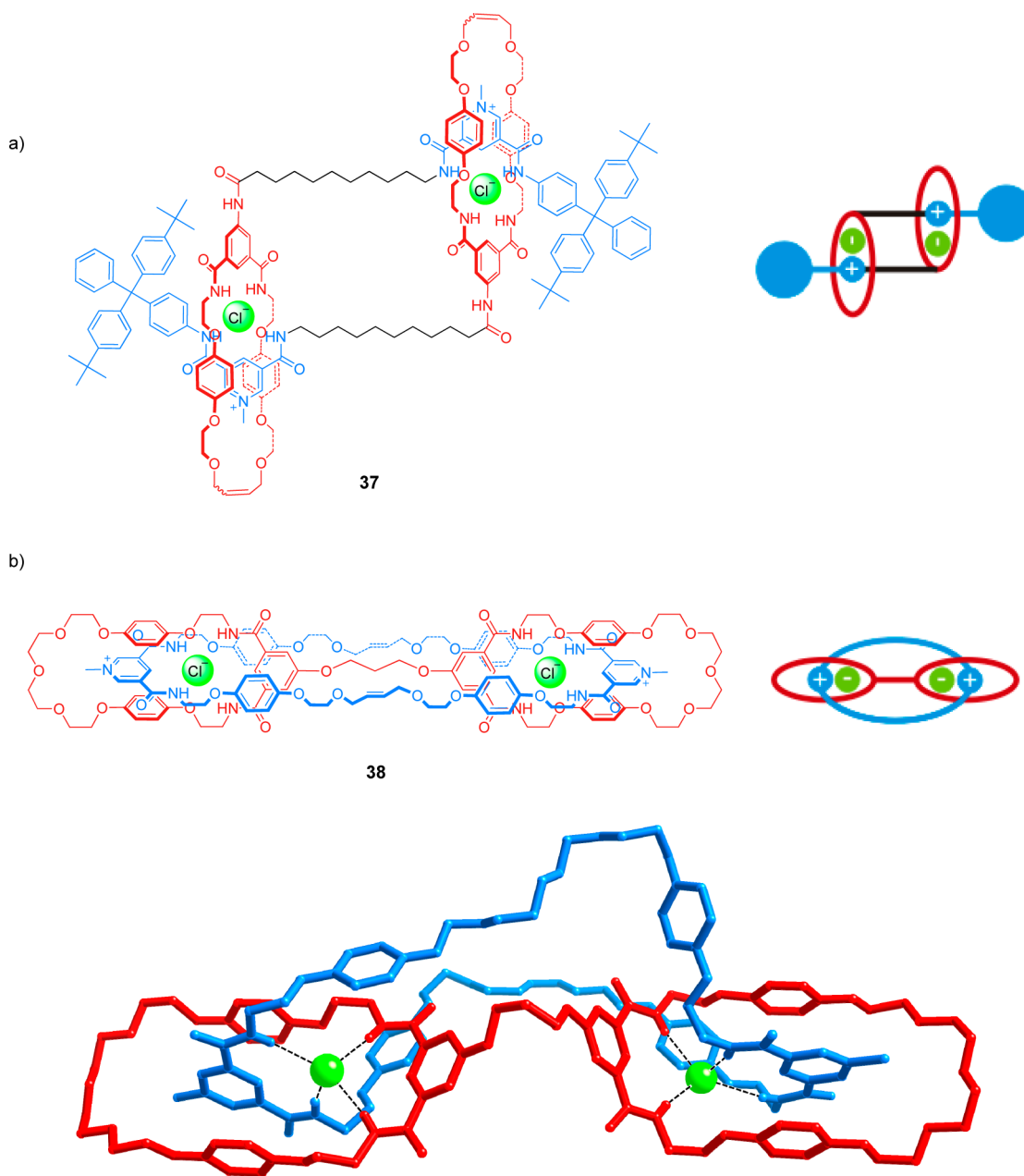
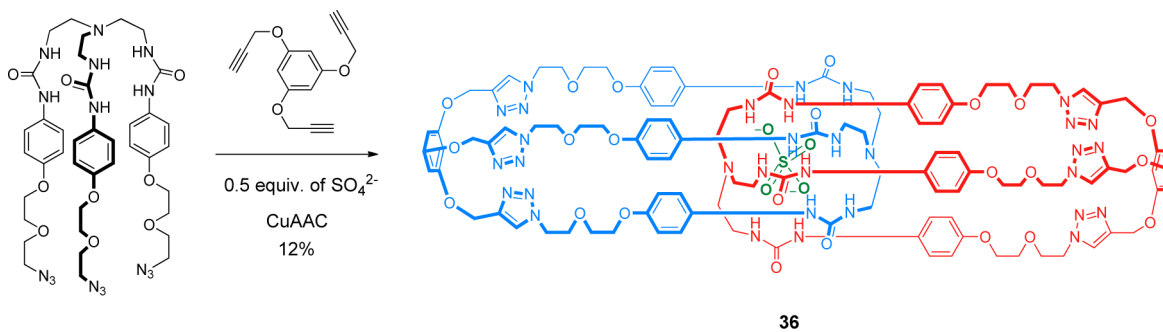


FIGURE 13. (a) Janus [2]rotaxane **37** and (b) handcuff catenane **38**.

SCHEME 9. Synthesis of Triply Interlocked Capsule **36**



34 and removal of the chloride template yields a neutral catenane which primarily adopts a pirouetted co-conformation due to pyridine-isophthalamide hydrogen bonding (Figure 12a). Chloride addition in d_6 -acetone requires the reversal of this rotation and “locks” the catenane in the co-conformation which allows for halide binding in the interlocked cavity. In contrast, the pirouetting of catenane **35** is mediated by acid/base stimuli by virtue of the 5-hydroxy-isophthalamide group (Figure 12b). When this group is protonated, aromatic donor–acceptor interactions are optimized, while upon deprotonation the phenolate anion chelates to the pyridinium amide protons, resulting in the contrasting co-conformation. Similarly to catenane **34**, chloride complexation “locks” the system in such a way to prevent this base-mediated molecular motion.

Interlocked Architectures with Increased Complexity

As the synthesis of [2]rotaxanes and [2]catenanes has been facilitated greatly by the number of available templation strategies, attention is being increasingly turned to more topologically diverse interlocked architectures. While these structures test the limits of strategic templation, they can also offer additional benefits in the form of unique binding domains and “higher order” intercomponent interactions.

Sulfate templated capsule **36** (Scheme 9),⁵⁰ maintains the precedent of containing two components which both contribute to one anion templation/recognition site, but is *triplly* interlocked due to the tripodal nature of the precursor. The symmetrical ^1H NMR spectrum of **36** and extensive NMR DOSY experiments confirm the formation of the intended two-component capsule. In fact, the templating anion is bound so strongly by the array of 12 hydrogen bond donor atoms from the convergent urea motifs that it was unable to be completely removed. An interesting comparison can be made between this structure and the sulfate binding protein found in *Salmonella typhimurium* in which the target anion is shielded from the surrounding media and held by seven hydrogen bonds.⁶

Progressing to two-component structures with *two* templation sites, “Janus” [2]rotaxane (or [c2]daisy chain) **37**⁵¹ and “handcuff” catenane **38**⁵² are shown in Figure 13. Both of these systems contain similar components composed of the same functional groups, and were constructed using chloride anion templation and RCM. By controlling the exact arrangement of these groups within the constituent parts, however, we were able to design and synthesize the two topologically distinct architectures. A Janus [2]rotaxane consists of two interlocked components which both contain a monostoppered axle section covalently attached to a

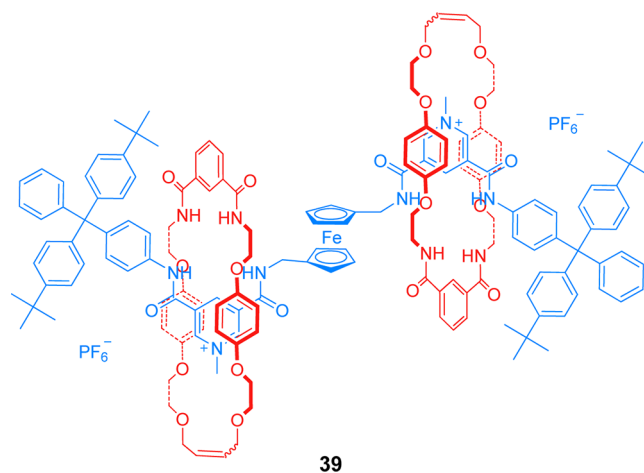


FIGURE 14. Ferrocene-containing [3]rotaxane **39**.

macrocycle. By contrast, in a handcuff catenane two covalently linked macrocycles have a single macrocycle passing through both rings. A solid-state X-ray crystal structure for handcuff catenane **38** was obtained, allowing for visualization of this system's unusual topology. For both **37** and **38**, no product was able to be isolated from the reaction mixtures in the absence of the chloride templating species, highlighting the crucial importance of the halide template.

To utilize “exotic” anion templated interlocked structures for functional applications, we are exploring the potential for “higher order” anion sensing behavior, for example, that displayed by ferrocene-containing [3]rotaxane **39** (Figure 14).⁵³ In this system, a ferrocene reporter group is integrated within a symmetrical axle component between two anion templation sites. The amide condensation method described above was employed in the efficient synthesis of **39**, isolated in a yield of 37%. ^1H NMR titrations in 45:45:10 $\text{CDCl}_3/\text{CD}_3\text{OD}/\text{D}_2\text{O}$ revealed that while a 1:2 host:guest stoichiometry is observed for chloride anion binding, one in each pyridinium–isophthalamide cavity, the larger sulfate anionic guest species cannot efficiently penetrate a single cavity but is able to interact with both binding sites peripherally in a 1:1 complexation mode due to the rotational flexibility of ferrocene. Preliminary electrochemical studies showed anion-induced cathodic shifts in the ferrocene/ferrocenium redox couple, with contrasting behavior in response to chloride and sulfate addition further supporting the proposed differential binding modes.

Concluding Remarks

We have successfully expanded the scope of the anion templation strategy for the fabrication of mechanically interlocked structures, in particular in the synthesis of host

systems with enhanced anion recognition properties by utilizing an alternative synthetic method and by the integration of different anion binding motifs, including those for halogen bonding. Furthermore, we have constructed selective electrochemical and luminescent sensors, as well as innovative molecular motion and “higher-order” interlocked structures. Importantly, the key anion templation principles have proved sufficiently versatile and robust throughout these investigations. Namely, the orthogonal association of components mediated by a discrete anion template is followed by interlocked structure formation, and removal of the template yields a binding cavity which discriminates between anionic guest species on the basis of size and shape complementarity.

An area which we believe will be most fruitful in our present and future research focuses on the synthesis of hosts capable of recognition and sensing in solvent media with increased aqueous content. In addition, given the intense interest being shown in supramolecular chemistry at the interface between solution and solid phases, the anion templated surface-attachment of functional systems to produce practical molecular devices has the potential to provide a multitude of nanotechnological advances.

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BIOGRAPHICAL INFORMATION

Graeme Spence graduated from the University of Cambridge with a first class honors degree in Natural Sciences (Chemistry) in 2008. He has recently finished his D.Phil. studies under Professor Beer at Oxford and has begun postdoctoral work with Professor Bradley Smith in University of Notre Dame, Indiana.

Paul Beer obtained a Ph.D. from King's College London in 1982 with Dr. C. Dennis Hall. After a Royal Society European Postdoctoral Fellowship with Professor J.-M. Lehn and a Demonstratorship at the University of Exeter, he was awarded a Lectureship at the University of Birmingham in 1984. In 1990, he moved to the University of Oxford, where he was made a University Lecturer and Tutorial Fellow at Wadham College, and became a Professor of Chemistry in 1998. His research interests include coordination and supramolecular chemistry.

FOOTNOTES

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REFERENCES

- Kay, E. R.; Leigh, D. A.; Zerbetto, F. Synthetic Molecular Motors and Mechanical Machines. *Angew. Chem., Int. Ed.* **2007**, *46*, 72–191.
- Coskun, A.; Banaszak, M.; Astumian, R. D.; Stoddart, J. F.; Grzybowski, B. A. Great expectations: can artificial molecular machines deliver on their promise? *Chem. Soc. Rev.* **2012**, *41*, 19–30.
- Balzani, V.; Credi, A.; Venturi, M. *Molecular devices and machines: concepts and perspectives for the nanoworld*; Wiley-VCH: Weinheim, Germany, 2008.
- Forgan, R. S.; Sauvage, J.-P.; Stoddart, J. F. Chemical Topology: Complex Molecular Knots, Links, and Entanglements. *Chem. Rev.* **2011**, *111*, 5434–5464.
- Sauvage, J. P.; Dietrich-Buchecker, C. *Molecular catenanes, rotaxanes and knots: a journey through the world of molecular topology*; Wiley-VCH: Weinheim, Germany, 1999.
- Sessler, J. L.; Gale, P. A.; Cho, W.-S. *Anion Receptor Chemistry*; Royal Society of Chemistry: Cambridge, 2006.
- Luecke, H.; Quijoco, F. A. High specificity of a phosphate transport protein determined by hydrogen bonds. *Nature* **1990**, *347*, 402–406.
- Pflugrath, J. W.; Quijoco, F. A. Sulphate Sequestered in the Sulphate-Binding Protein of Salmonella Typhimurium is Bound Solely by Hydrogen Bonds. *Nature* **1985**, *314*, 257–260.
- Wisner, J. A.; Beer, P. D.; Drew, M. G. B. A Demonstration of Anion Templation and Selectivity in Pseudorotaxane Formation. *Angew. Chem., Int. Ed.* **2001**, *40*, 3606–3609.
- Stoddart, J. F. The Master of Chemical Topology. *Chem. Soc. Rev.* **2009**, *38*, 1521–1529.
- Wisner, J. A.; Beer, P. D.; Drew, M. G. B.; Sambrook, M. R. Anion-Templated Rotaxane Formation. *J. Am. Chem. Soc.* **2002**, *124*, 12469–12476.
- Lankshear, M. D.; Beer, P. D. Interweaving Anion Templation. *Acc. Chem. Res.* **2007**, *40*, 657–668.
- Chae, M. K.; Suk, J.-M.; Jeong, K.-S. A Catenated Anion Receptor Based on Indolocarbazole. *Tetrahedron Lett.* **2010**, *51*, 4240–4242.
- Zhao, Y.; Li, Y.; Li, Y.; Zheng, H.; Yin, X.; Liu, H. Construction of an Interpenetrated Structure of Macrocycles. *Chem. Commun.* **2010**, *46*, 5698–5700.
- Hancock, L. M.; Beer, P. D. Chloride Recognition in Aqueous Media by a Rotaxane Prepared via a New Synthetic Pathway. *Chem.—Eur. J.* **2009**, *15*, 42–44.
- Hancock, L. M.; Gilday, L. C.; Carvalho, S.; Costa, P. J.; Félix, V.; Serpell, C. J.; Kilah, N. L.; Beer, P. D. Rotaxanes Capable of Recognising Chloride in Aqueous Media. *Chem.—Eur. J.* **2010**, *16*, 13082–13094.
- Hunter, C. A. Synthesis and Structure Elucidation of a New [2]-Catenane. *J. Am. Chem. Soc.* **1992**, *114*, 5303–5311.
- Vögtle, F.; Meier, S.; Hoss, R. One-Step Synthesis of a Fourfold Functionalized Catenane. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1619–1622.
- Johnston, A. G.; Leigh, D. A.; Nezhad, L.; Smart, J. P.; Deegan, M. D. Structurally Diverse and Dynamically Versatile Benzylic Amide [2]Catenanes Assembled Directly from Commercially Available Precursors. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1212–1216.
- Hancock, L. M.; Gilday, L. C.; Kilah, N. L.; Serpell, C. J.; Beer, P. D. A New Synthetic Route to Chloride Selective [2]Catenanes. *Chem. Commun.* **2010**, *47*, 1725–1727.
- Evans, N. H.; Serpell, C. J.; Beer, P. D. A Meta-Xylenediamide Macrocyclic Containing Rotaxane Anion Host System Constructed by a New Synthetic Clipping Methodology. *New J. Chem.* **2011**, *35*, 2047–2053.
- Huang, B.; Santos, S. M.; Felix, V.; Beer, P. D. Sulfate Anion-Templated Assembly of a [2]Catenane. *Chem. Commun.* **2008**, 4610–4612.
- White, N. G.; Beer, P. D.; Catenane Host, A System containing Integrated Triazole C-H Hydrogen Bond Donors for Anion Recognition. *Chem. Commun.* **2012**, *48*, 8499–8501.
- Sambrook, M. R.; Beer, P. D.; Wisner, J. A.; Paul, R. L.; Cowley, A. R. Anion-Templated Assembly of a [2]Catenane. *J. Am. Chem. Soc.* **2004**, *126*, 15364–15365.
- Mullen, K. M.; Mercurio, J.; Serpell, C. J.; Beer, P. D. Exploiting the 1,2,3-Triazolium Motif in Anion-Templated Formation of a Bromide-Selective Rotaxane Host Assembly. *Angew. Chem., Int. Ed.* **2009**, *48*, 4781–4784.
- Spence, G. T.; Serpell, C. J.; Sardinha, J.; Costa, P. J.; Félix, V.; Beer, P. D. Investigating the Imidazolium–Anion Interaction through the Anion-Templated Construction of Interpenetrated and Interlocked Assemblies. *Chem.—Eur. J.* **2011**, *17*, 12955–12966.
- Metrangolo, P.; Meyer, F.; Pilati, T.; Resnati, G.; Terraneo, G. Halogen Bonding in Supramolecular Chemistry. *Angew. Chem., Int. Ed.* **2008**, *47*, 6114–6127.
- Vargas Jentzsch, A.; Emery, D.; Mareda, J.; Metrangolo, P.; Resnati, G.; Matile, S. Dtopic Ion Transport Systems: Anion– π Interactions and Halogen Bonds at Work. *Angew. Chem., Int. Ed.* **2011**, *50*, 11675–11678.
- Chudzinski, M. G.; McClary, C. A.; Taylor, M. S. Anion Receptors Composed of Hydrogen- and Halogen-Bond Donor Groups: Modulating Selectivity With Combinations of Distinct Noncovalent Interactions. *J. Am. Chem. Soc.* **2011**, *133*, 10559–10567.
- Sarwar, M. G.; Dragisic, B.; Sagoo, S.; Taylor, M. S. A Tridentate Halogen-Bonding Receptor for Tight Binding of Halide Anions. *Angew. Chem., Int. Ed.* **2010**, *49*, 1674–1677.

- 31 Mele, A.; Metrangolo, P.; Neukirch, H.; Pilati, T.; Resnati, G. A Halogen-Bonding-Based Heteroditopic Receptor for Alkali Metal Halides. *J. Am. Chem. Soc.* **2005**, *127*, 14972–14973.
- 32 Caballero, A.; White, N. G.; Beer, P. D. A Bidentate Halogen-Bonding Bromoimidazolophane Receptor for Bromide Ion Recognition in Aqueous Media. *Angew. Chem., Int. Ed.* **2011**, *50*, 1845–1848.
- 33 Zapata, F.; Caballero, A.; White, N. G.; Claridge, T. D. W.; Costa, P. J.; Félix, V.; Beer, P. D. Fluorescent Charge-Assisted Halogen-Bonding Macrocyclic Halo-Imidazolium Receptors for Anion Recognition and Sensing in Aqueous Media. *J. Am. Chem. Soc.* **2012**, *134*, 11533–11541.
- 34 Serpell, C. J.; Kilah, N. L.; Costa, P. J.; Félix, V.; Beer, P. D. Halogen Bond Anion Templated Assembly of an Imidazolium Pseudorotaxane. *Angew. Chem., Int. Ed.* **2010**, *49*, 5322–5326.
- 35 Kilah, N. L.; Wise, M. D.; Serpell, C. J.; Thompson, A. L.; White, N. G.; Christensen, K. E.; Beer, P. D. Enhancement of Anion Recognition Exhibited by a Halogen-Bonding Rotaxane Host System. *J. Am. Chem. Soc.* **2010**, *132*, 11893–11895.
- 36 Caballero, A.; Zapata, F.; White, N. G.; Costa, P. J.; Félix, V.; Beer, P. D. A Halogen-Bonding Catenane for Anion Recognition and Sensing. *Angew. Chem., Int. Ed.* **2012**, *51*, 1876–1880.
- 37 Beer, P. D. Transition-Metal Receptor Systems for the Selective Recognition and Sensing of Anionic Guest Species. *Acc. Chem. Res.* **1998**, *31*, 71–80.
- 38 Bayly, S. R.; Gray, T. M.; Chmielewski, M. J.; Davis, J. J.; Beer, P. D. Anion Templated Surface Assembly of a Redox-Active Sensory Rotaxane. *Chem. Commun.* **2007**, 2234–2236.
- 39 Evans, N. H.; Serpell, C. J.; White, N. G.; Beer, P. D. A 1,2,3,4,5-Pentaphenylferrocene-Stopped Rotaxane Capable of Electrochemical Anion Recognition. *Chem.—Eur. J.* **2011**, *17*, 12347–12354.
- 40 Evans, N. H.; Beer, P. D. A Ferrocene Functionalized Rotaxane Host System Capable of the Electrochemical Recognition of Chloride. *Org. Biomol. Chem.* **2011**, *9*, 92–100.
- 41 Evans, N. H.; Rahman, H.; Leontiev, A. V.; Greenham, N. D.; Orłowski, G. A.; Zeng, Q.; Jacobs, R. M. J.; Serpell, C. J.; Kilah, N. L.; Davis, J. J.; Beer, P. D. Solution and Surface-Confined Chloride Anion Templated Redox-Active Ferrocene Catenanes. *Chem. Sci.* **2012**, *3*, 1080–1089.
- 42 Vickers, M. S.; Martindale, K. S.; Beer, P. D. Imidazolium Functionalised Acyclic Ruthenium(II) Bipyridyl Receptors for Anion Recognition and Luminescent Sensing. *J. Mater. Chem.* **2005**, *15*, 2784–2790.
- 43 Hancock, L. M.; Marchi, E.; Ceroni, P.; Beer, P. D. Anion Sensing in Aqueous Media by Photo-Active Transition-Metal Bipyridyl Rotaxanes. *Chem.—Eur. J.* **2012**, *18*, 11277–11283.
- 44 Curiel, D.; Beer, P. D. Anion Directed Synthesis of a Hydrogensulfate Selective Luminescent Rotaxane. *Chem. Commun.* **2005**, 1909–1911.
- 45 Gassensmith, J. J.; Matthys, S.; Lee, J.-J.; Wojcik, A.; Kamat, P. V.; Smith, B. D. Squaraine Rotaxane as a Reversible Optical Chloride Sensor. *Chem.—Eur. J.* **2010**, *16*, 2916–2921.
- 46 Serpell, C. J.; Chall, R.; Thompson, A. L.; Beer, P. D. Chloride Anion Triggered Motion in a Bis-Imidazolium Rotaxane. *Dalton Trans.* **2011**, *40*, 12052–12055.
- 47 Spence, G. T.; Pitak, M. B.; Beer, P. D. Anion-Induced Shuttling of a Naphthalimide Triazolium Rotaxane. *Chem.—Eur. J.* **2012**, *18*, 7100–7108.
- 48 Evans, N. H.; Serpell, C. J.; Beer, P. D. A [2]Catenane Displaying Pirouetting Motion Triggered by Debenzylation and Locked by Chloride Anion Recognition. *Chem.—Eur. J.* **2011**, *17*, 7734–7738.
- 49 Ng, K.-Y.; Felix, V.; Santos, S. M.; Rees, N. H.; Beer, P. D. Anion Induced and Inhibited Circumrotation of a [2]Catenane. *Chem. Commun.* **2008**, 1281–1283.
- 50 Li, Y.; Mullen, K. M.; Claridge, T. D. W.; Costa, P. J.; Felix, V.; Beer, P. D. Sulfate Anion Templated Synthesis of a Triply Interlocked Capsule. *Chem. Commun.* **2009**, 7134–7136.
- 51 Evans, N. H.; Beer, P. D. A Janus [2]Rotaxane Synthesized by Using an Anion-Templated Clipping Methodology. *Chem.—Eur. J.* **2011**, *17*, 10542–10546.
- 52 Evans, N. H.; Serpell, C. J.; Beer, P. D. Chloride Anion Templated Synthesis and Crystal Structure of a Handcuff Catenane. *Angew. Chem., Int. Ed.* **2011**, *50*, 2507–2510.
- 53 Evans, N. H.; Serpell, C. J.; Beer, P. D. A Redox-Active [3]Rotaxane Capable of Binding and Electrochemically Sensing Chloride and Sulfate Anions. *Chem. Commun.* **2011**, *47*, 8775–8777.