Rotaxane and Catenane Host Structures for Sensing Charged Guest Species

Matthew J. Langton and Paul D. Beer*

Chemistry Research Laboratory, Department of Chemistry, University of Oxford, Mansfield, Oxford OX1 3TA, United Kingdom

CONSPECTUS: The promise of mechanically interlocked architectures, such as rotaxanes and catenanes, as prototypical molecular switches and shuttles for nanotechnological applications, has stimulated an ever increasing interest in their synthesis and function. The elaborate host cavities of interlocked structures, however, can also offer a novel approach toward molecular recognition: this Account describes the use of rotaxane and catenane host systems for binding charged guest species, and for providing sensing capability through an integrated optical or electrochemical reporter group. Particular attention is drawn to the exploitation of the unusual dynamic properties of interlocked molecules, such as guest-induced shuttling or conformational switching, as a sophisticated means of achieving a selective and functional sensor response. We initially survey interlocked host systems capable of sensing cationic guests, before focusing on our accomplishments in synthesizing rotaxanes and catenanes designed for the more challenging task of selective anion sensing.


In our group, we have developed the use of discrete anionic templation to prepare mechanically interlocked structures for anion recognition applications. Removal of the anion template reveals an interlocked host system, possessing a unique three-dimensional geometrically restrained binding cavity formed between the interlocked components, which exhibits impressive selectivity toward complementary anionic guest species.

By incorporating reporter groups within such systems, we have developed both electrochemical and optical anion sensors which can achieve highly selective sensing of anionic guests. Transition metals, lanthanides, and organic fluorophores integrated within the mechanically bonded structural framework of the receptor are perturbed by the binding of the guest, with a concomitant change in the emission profile. We have also exploited the unique dynamics of interlocked hosts by demonstrating that an anion−induced conformational change can be used as a means of signal transduction. Electrochemical sensing has been realized by integration of the redox-active ferrocene functionality within a range of rotaxane and catenanes; binding of an anion perturbs the metallocene, leading to a cathodic shift in the ferrocene/ferrocenium redox couple.

In order to obtain practical sensors for target charged guest species, confinement of receptors at a surface is necessary in order to develop robust, reuseable devices. Surface confinement also offers advantages over solution based receptors, including amplification of signal, enhanced guest binding thermodynamics and the negation of solubility problems. We have fabricated anion-templated rotaxanes and catenanes on gold electrode surfaces and demonstrated that the resulting mechanically bonded self-assembled monolayers are electrochemically responsive to the binding of anions, a crucial first step toward the advancement of sophisticated, highly selective, anion sensory devices.

Rotaxane and catenane host molecules may be engineered to offer a superior level of molecular recognition, and the incorporation of optical or electrochemical reporter groups within these interlocked frameworks can allow for guest sensing. Advances in synthetic templation strategies has facilitated the synthesis of interlocked architectures and widened their interest as prototype molecular machines. However, their unique host−guest properties are only now beginning to be exploited as a
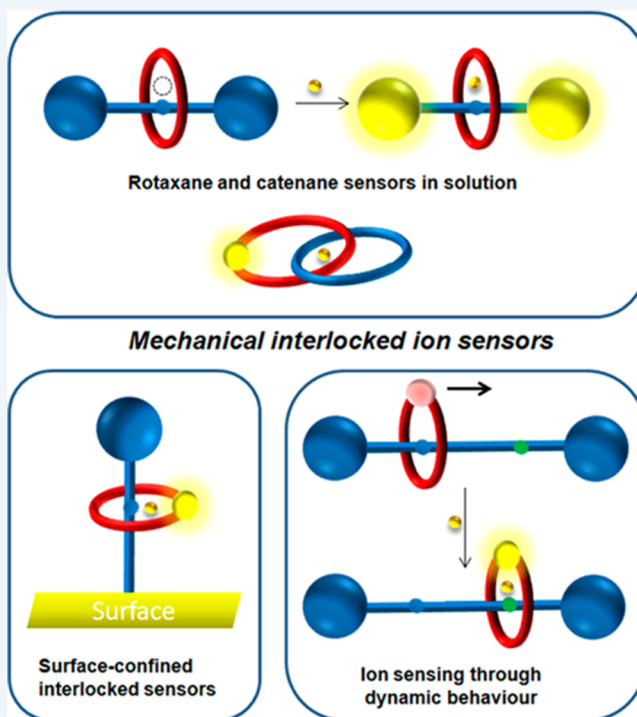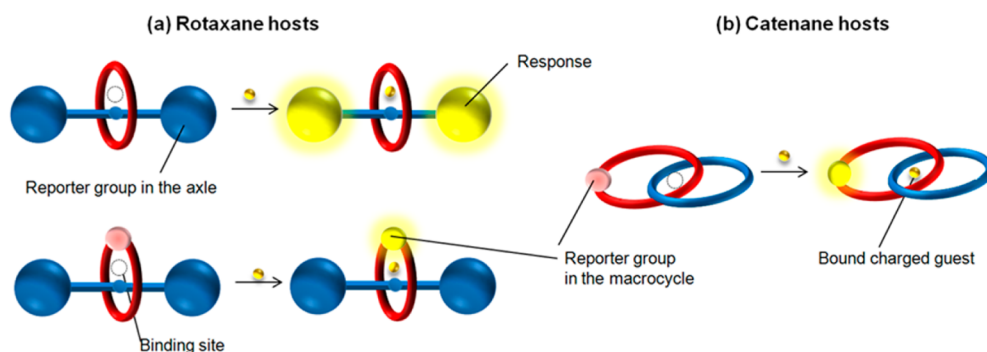
Figure 1. Schematic representation of (a) rotaxane and (b) catenane hosts functionalized with optical or electrochemical reporter groups for sensing of charged guests.

sophisticated approach to chemical sensing. The development of functional host–guest sensory systems such as these is of great interest to the interdisciplinary field of supramolecular chemistry.

INTRODUCTION

The unique topology and dynamic behavior of interlocked molecular architectures, including rotaxanes and catenanes, has been the subject of intense recent research. Controlling the novel dynamics of these structures represents the crucial first step toward the goal of their development into molecular machines, as the building blocks of proposed nanotechnological applications.[1−4] The possibility of using interlocked molecules in molecular guest recognition and sensing, however, has remained largely overlooked. This is surprising since interlocked hosts have been shown to exhibit superior levels of molecular recognition, including enhanced selectivity and binding affinities, compared to that of analogous noninterlocked systems.[5,6] With the potential for being ideal candidates for chemical sensor design, this Account focuses on rotaxane and catenane interlocked hosts functionalized with optical or electrochemical reporter groups incorporated in either the macrocycle or axle components, that are capable of sensing charged guest species (Figure 1).

This paradigm is initially discussed in relation to cation recognition and sensing by rotaxanes and catenanes, before exploring anion sensing both in solution and at a surface-confined monolayer by optical and electrochemical means. Particular attention is drawn to the exploitation of the unusual dynamics of interlocked structures, such as molecular shuttling (Figure 2), which can also serve as a novel means of achieving a selective sensory response.

ROTAXANES AND CATENANES FOR CATION SENSING

Using rotaxanes and catenanes as a means of binding and sensing cationic guests remains relatively underdeveloped, yet the inspirational examples presented here demonstrate the impressive range of possibilities offered by this approach. Particular attention is drawn to the use of the cation guest as a means of stimulating a dynamic response within the interlocked system, which, when coupled to a signaling output, offers a sophisticated way of selectively sensing the cationic guest.

In a pioneering paper published in 1996, Swager and co-workers demonstrated the preparation of a conducting polyrotaxane polymer using Cu^+ or Zn^{2+} cation templation
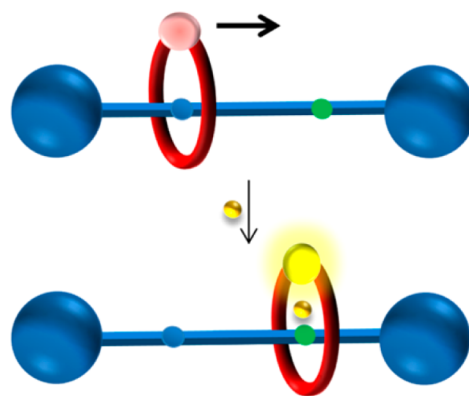

Figure 2. Schematic representation of a rotaxane molecular shuttle for charged guest sensing.

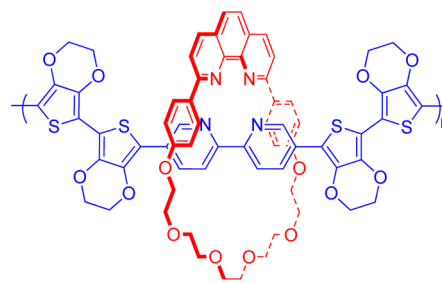(Figure 3).[7,8] The conductivity of the metal-free rotaxane polymer was found to be inferior to that of the metal-

Figure 3. Swager's cation-sensing polyrotaxane.

complexed analogue, while addition of metal ions resulted in significant red-shifting of the UV−vis absorption in CH_2Cl_2 solution. As a result, the metal-free polymer could act as a sensor for Cu^+ ions, through both conductivity and optical responses. Crucially, the noninterlocked thiophene-derived polymer backbone displayed no change in the UV−vis absorption spectra upon exposure to a solution of metal cations, demonstrating that the rotaxane structure is key to the cation-sensing capability of the system.

More recently, a range of pseudorotaxane and rotaxane host systems have been reported, capable of sensing *alkali* metal cations.

Sanders and co-workers have used Li^+ cations as a means of templating the formation of a pseudorotaxane assembly in $CHCl_3$, in which a naphthalene-diimide moiety is threaded through a naphthalene-polyether derived macrocycle (Scheme
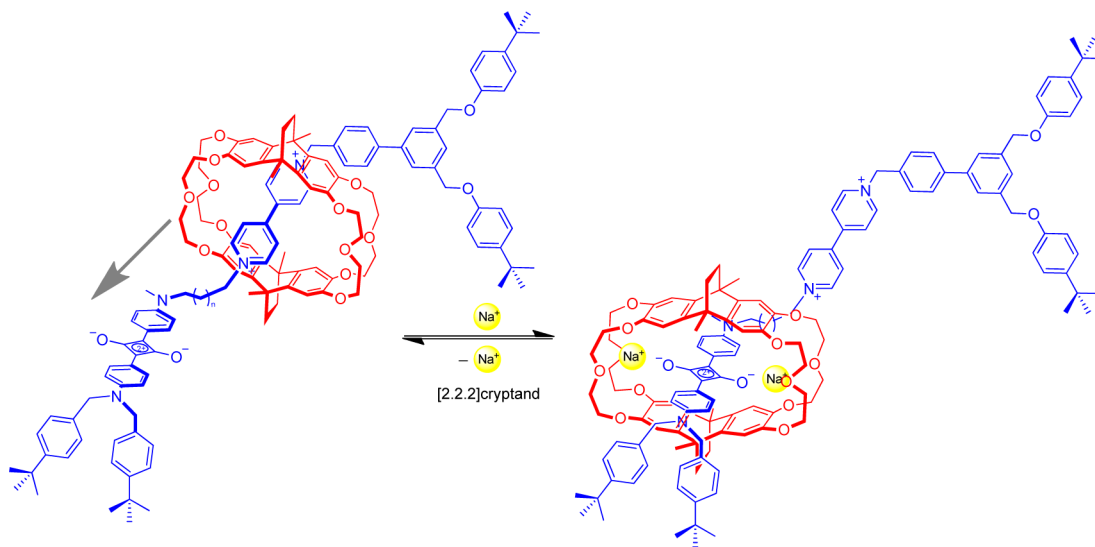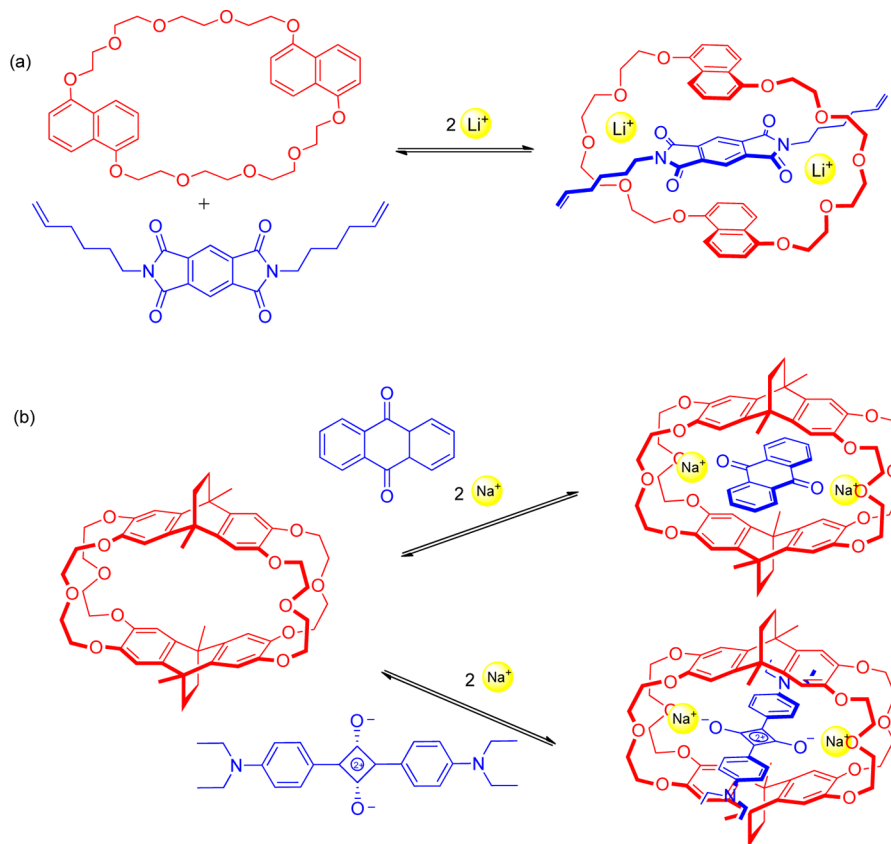
Scheme 1. Optically Responsive Pseudorotaxanes

**Figure 4.** Squaraine based, optically responsive molecular switch.

1a).[9] The enhancement of the donor−acceptor aromatic charge-transfer interactions between the two components results in a visible color change, thus enabling colormetric sensing of Li^{+}.

In a similar manner, Chiu and co-workers described the sodium-templated interpenetration of squarine or anthraquinone dyes within a bis-dibenzo[18]crown-6-derived macrocycle in $CDCl_3/CD_3CN$, which led to enhancement of the dye's fluorescence (Scheme 1b).[10] The system exhibits high selectivity for Na^{+} over the other alkali metal cations: addition

of K^{+} results in no pseudorotaxane formation. The authors extended this principle to prepare a Na^{+} responsive molecular shuttle, in which the same macrocycle translocates and encapsulates the integrated squaraine dye upon Na^{+} addition in CD_3CN, resulting in fluorescence enhancement (Figure 4).[11]

A variety of cation-sensing interlocked hosts have also been synthesized, in which the reporter group is incorporated in one of the interlocked components. Hiratani and co-workers synthesized a fluorescent [1]rotaxane in which the threading component is stopped with an anthracene group (Scheme

Scheme 2. Alkali-Metal-Sensing Rotaxanes

(a)

R = (CH₂)₁₀

(b)
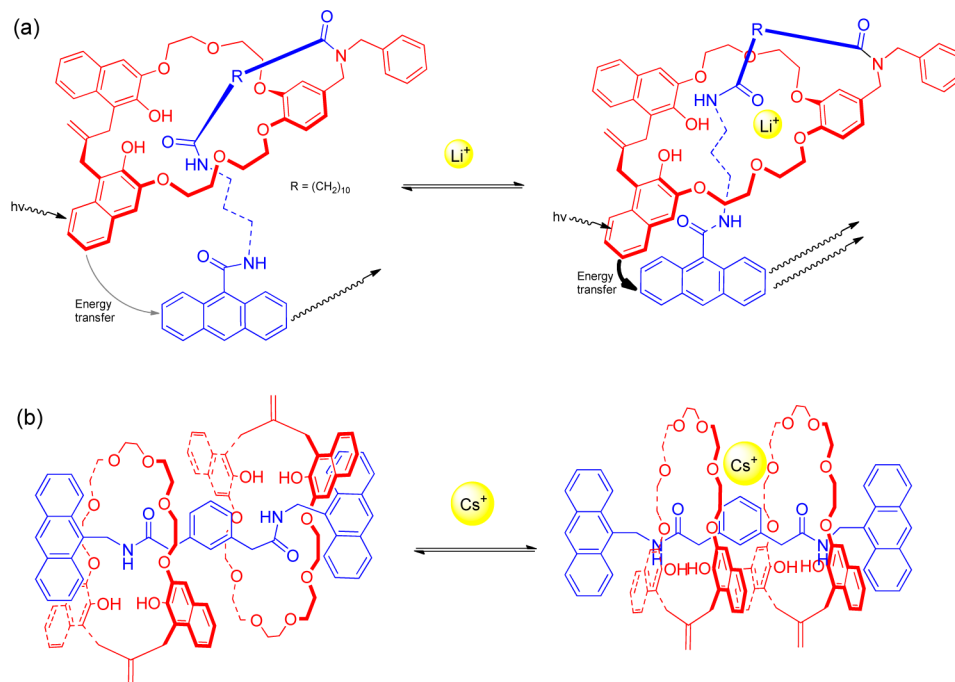
Scheme 3. Optically Signaled Multistation Rotaxane
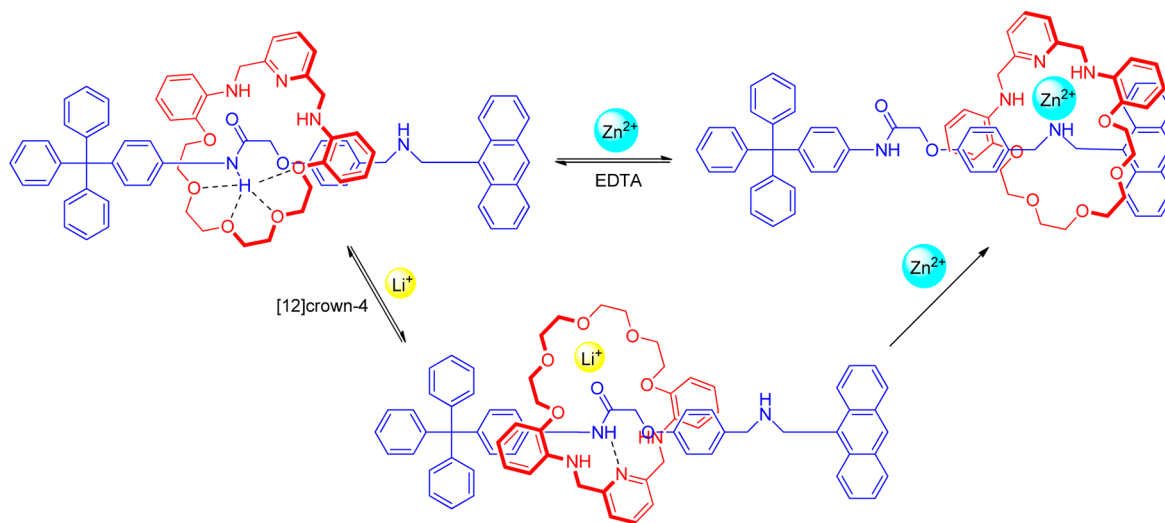
Scheme 4. Zn²⁺ Responsive [2]Catenane

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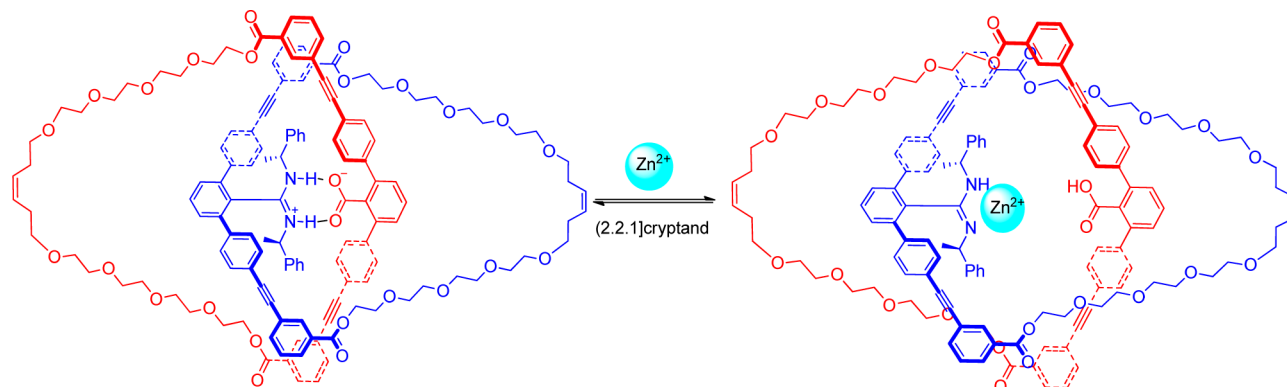
2a).[12] Binding of Li^{+} in CH_2Cl_2/CH_3CN led to a conformational change in which the anthracene fluorophore in the thread is brought into closer proximity to a naphthalene derivative within the macrocycle. Consequently, naphthalene excitation leads to enhanced energy transfer to the anthracene emitter, and thus, Li^{+} binding is detected though emission intensity enhancement. Hiratani also utilized a cation-induced conformational change as a means of modulating the optical response in a [3]rotaxane. The host system, comprising two crown-ether-derived macrocycles threaded onto an anthracene-based axle, binds Cs^{+} between the two macrocycle components in a "sandwich" complex fashion in CH_2Cl_2/CH_3CN, resulting in enhancement of the anthracene emission (Scheme 2b).[13]

Li and co-workers demonstrated that the cation-induced motion of a molecular shuttle may be coupled to a fluorescence response, which can report the location of the macrocycle on a multistation rotaxane (Scheme 3).[14] The anthracene stopper emission in the metal-free rotaxane is partially quenched in 10:1 $CHCl_3/THF$, due to photoinduced electron transfer (PET) from the axle's amine motif. Addition of Li^{+} results in macrocycle rotation, and complete PET quenching of the emission. In contrast, Zn^{2+} causes macrocycle translocation from the axle amide to the amine moiety, concomitant with anthracene emission enhancement due to removal of PET quenching via amine-Zn^{2+} coordination. Cation binding was shown to be fully reversible by the respective addition of Li^{+}/ [12]crown-4 and Zn^{2+}/EDTA.

Yashima and co-workers have reported a [2]catenane containing an amidinium–carboxylate salt-bridge between the two macrocycle components, which locks the optically active catenane in a fixed conformation.[15] The salt bridge can be cleaved upon addition of acid or Zn^{2+} (Scheme 4), resulting in a significant enhancement and red-shifting of the terphenyl fluorescence in 10:1 CH_2Cl_2/THF. The reversible nature of this effect was demonstrated by removal of Zn^{2+} with 2.2.1-cryptand.

INTERLOCKED HOST SYSTEMS FOR SENSING ANIONIC GUESTS

The selective binding and recognition of anions represents a significant challenge, and has necessitated the development of intricate and sophisticated anion receptors over recent years.[16] Anions are less charge dense than comparable isoelectronic cations, display no exploitable ligand-field effects, are pH-dependent, and exhibit high hydration energies. Consequently, simple hydrogen-bonding acyclic receptors only function in aprotic-organic media and in general suffer from modest binding affinities and selectivities. Hence, the ability to bind anions selectively in competitive protic solvents arguably requires a more elaborate approach. Taking inspiration from nature, where phosphate and sulfate binding proteins selectively recognize their oxoanion guests within a buried, solvent-inaccessible binding pocket through an intricate network of hydrogen bonds,[17,18] we have designed interlocked hosts which can encapsulate the anion in a three-dimensional binding site formed between the interlocked components.

The synthesis of such interlocked receptors has required the development of an innovative anion templation approach, which has been a major theme of our group's research over the past decade. Unlike the established field of cation templation, pioneered by Sauvage and co-workers using copper(I) templation,[19,20] and Stoddart with positively charged organic systems,[4] anion templation has been less extensively

researched.[5] Our initial work in this area began with the discovery that an orthogonal complex could be formed between a hydrogen-bond-donating 3,5-bis-amide pyridinium and a neutral isophthalamide motif via chloride anion coordination (Figure 5). This association was initially employed in the
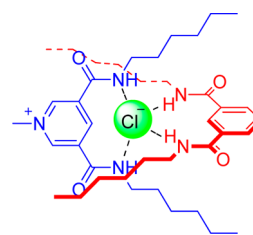

Figure 5. Orthogonal association of hydrogen-bonding components about a chloride anion.

preparation of a chloride-templated pseudorotaxane, by incorporating the isophthalamide motif within the macrocycle (Scheme 5).[21] The interpenetrated association is enhanced by secondary supramolecular interactions, aromatic donor–acceptor interactions and pyridinium-N-methyl-polyether CH–O hydrogen bonding.

Exploiting this strategic anion templation methodology in the construction of rotaxane **1** was achieved using a ring-closing metathesis (RCM) approach by cyclizing a bis-vinyl-appended macrocycle precursor around a terphenyl-stopped pyridinium chloride axle (Scheme 6a).[22] More recently, we have demonstrated alternative routes toward anion-templated interlocked structures: using an amide condensation strategy, rotaxanes **3** and **4** were formed by templating the formation of the macrocycle in the presence of pyridinium chloride axle **2** in yields of 56% and 60%.[23]

Chloride anion templation has also been applied to the synthesis of catenanes[24] and more complex architectures, such as a hand-cuff catenane,[25] Janus [2]rotaxane,[26] and [3]-rotaxanes,[27,28] while bromide,[29] sulfate[30] and nitrate[31] have also been utilized as the templating anions for mechanical bond formation.

Removing the anion template from these interlocked molecular architectures, by exchanging to a noncoordinating anion such as hexafluorophosphate, reveals an anion host system which possesses a three-dimensionally restrained binding cavity formed between the interlocked components. Importantly, such hosts exhibit high selectivity for the templating anion in competitive organic-aqueous solvent mixtures. For example, the dicationic chloride-templated rotaxane **3c** (Scheme 6) is highly selective for Cl^{−} in 65:35 d_6-acetone/D_2O ($K = 500$ $M^{−1}$) over the more basic oxoanions $H_2PO_4^−$ and $AcO^−$ which do not bind since they cannot penetrate the interlocked binding cavity.[32] This is the reverse of the anion selectivity observed for the noninterlocked axle **2**.[22]

We have extended this methodology to prepare interlocked hosts with a variety of hydrogen[16] and halogen[33−35] bonding anion binding motifs, which allows tuning of the anion recognition properties. The use of halogen bonding in solution molecular recognition is relatively underdeveloped;[36] however the localized region of positive charge exhibited by electron-deficient halogen atoms, such as bromine or iodine, can be exploited to form a stringent linear halogen bond to the anion within a rotaxane or catenane host cavity. This can result in notable enhancement of the anion binding strength and

Scheme 5. Chloride-Templated Pseudorotaxane Assembly
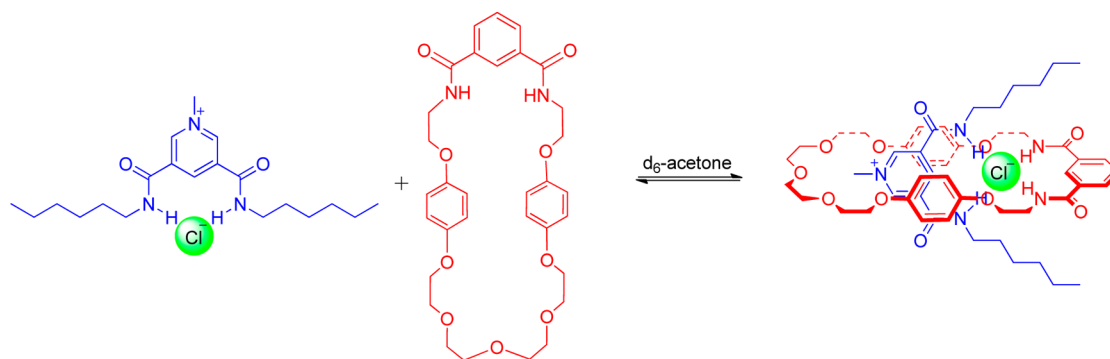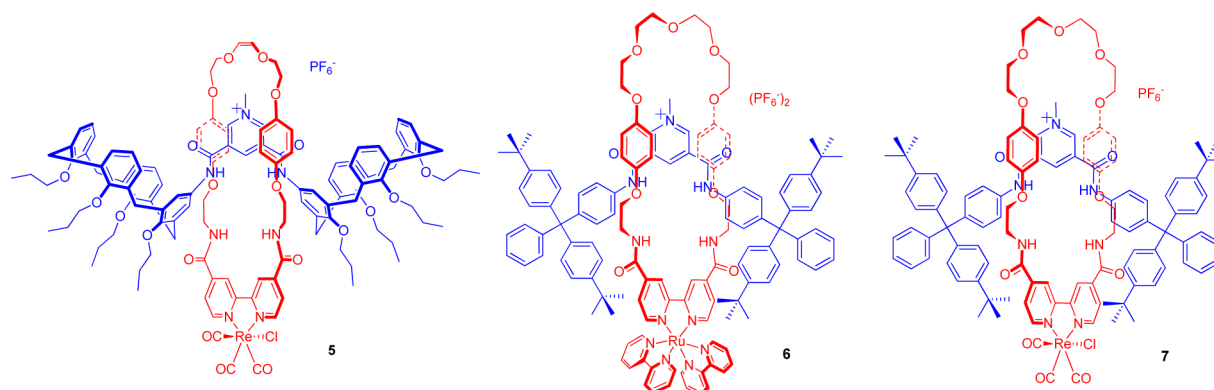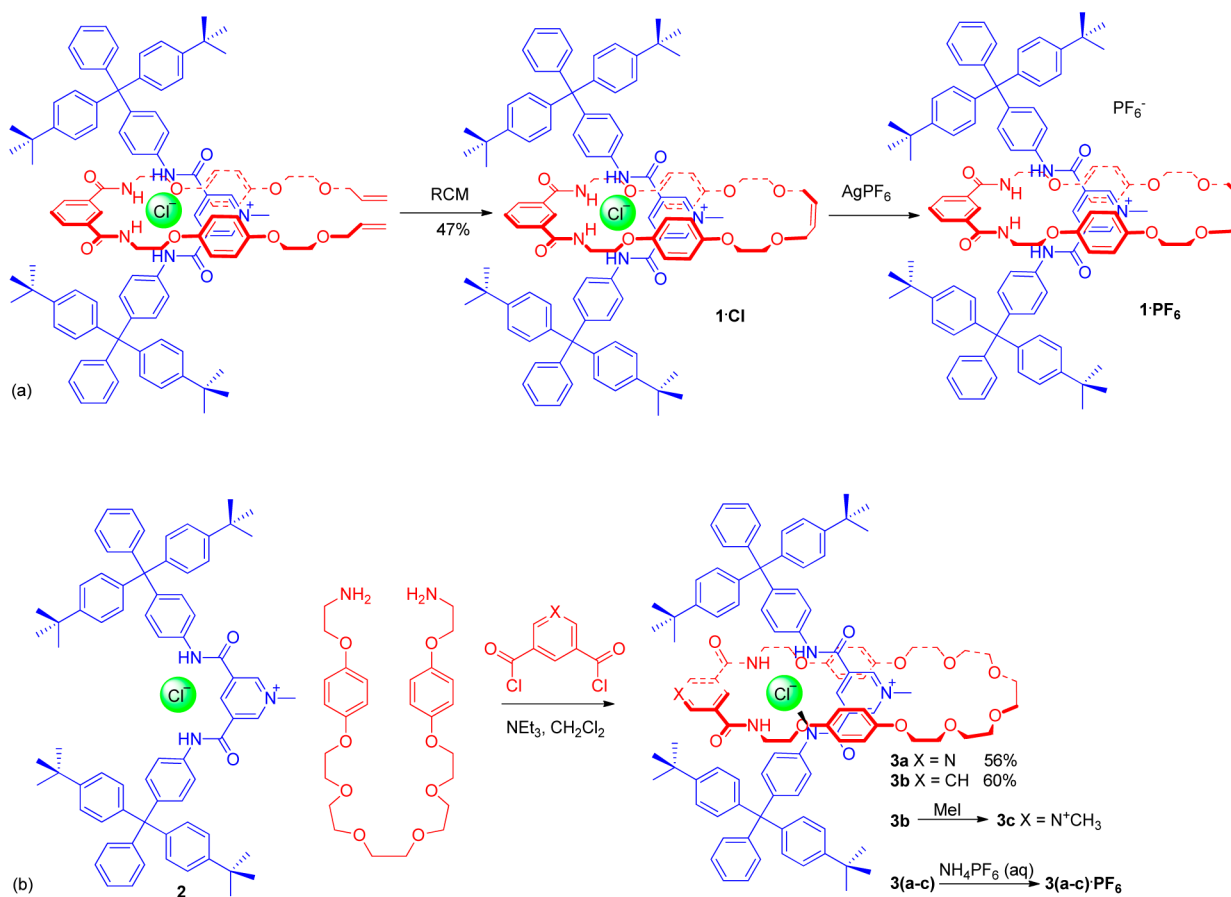

Scheme 6. Chloride-Anion-Templation of Rotaxanes

(a)

(b)

Figure 6. Transition-metal-appended luminescent rotaxane hosts.

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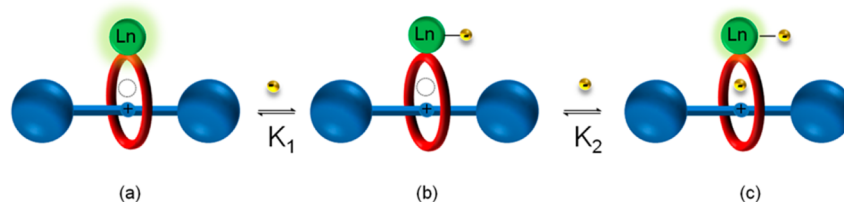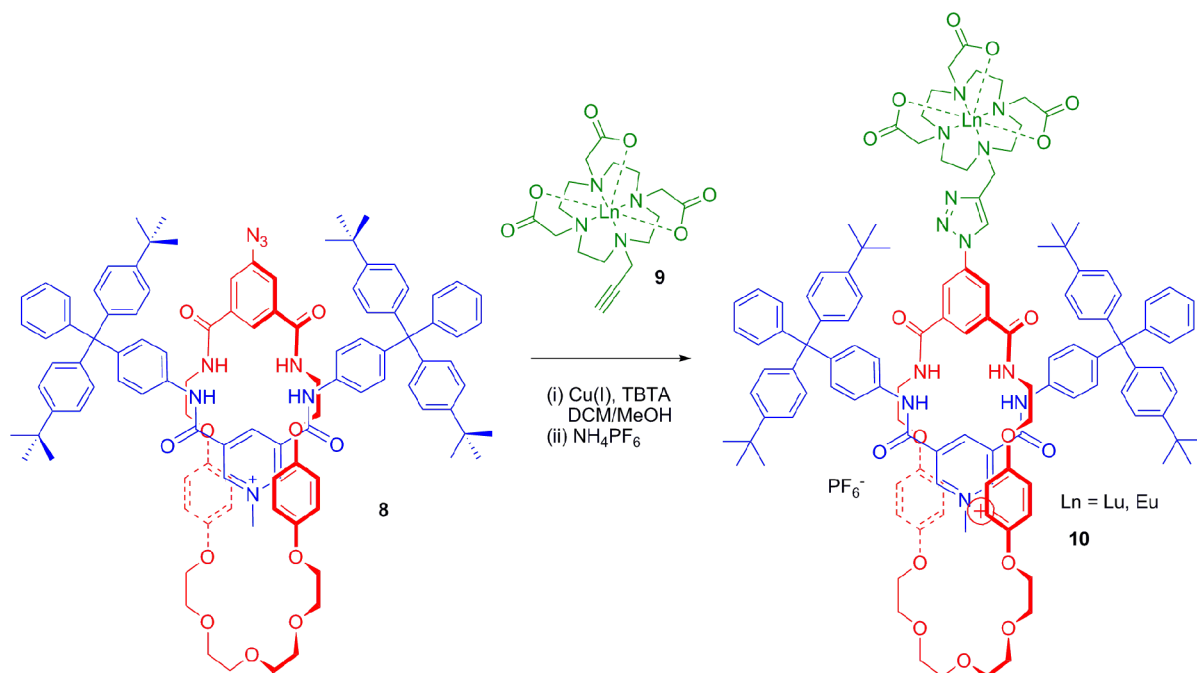**Scheme 7. Synthesis of Lanthanide-Appended Rotaxane 10**

Figure 7. Schematic representation of successive chloride binding to rotaxane **10**.

improved halide anion selectivity relative to the hydrogen-bonding interlocked analogues.

OPTICAL ANION SENSORS

Thus far it has been shown that interlocked anion receptors can be prepared using a versatile anion-templation strategy, and that the unique topology of these structures enables strong and selective binding of complementary anions. By incorporating redox or photoactive reporter groups within either the macrocycle or axle components, the development of an anion sensor which exhibits an electrochemical or optical response upon guest binding may be achieved.

Our first optical anion sensing rotaxane **5** was based on a Re(I)-bipyridyl luminophore incorporated within the macrocycle component, with the axle stoppered with bulky calix[4]arene motifs (Figure 6).[37] Addition of anions to a solution of **5**·PF_6 in acetone resulted in enhancement of the MLCT emission band of the Re(I) center, postulated to be due to increased rigidity of the rotaxane-anion complex which disfavors nonradiative decay processes. Rotaxane **5**·PF_6 was found to be selective for HSO_4^-, an anion that has proved particularly difficult to bind and sense, more strongly than Cl^- and NO_3^- due to its poor hydrogen-bond-acceptor ability.

Recently we have incorporated both Ru(II) and Re(I) into bipyridyl macrocycle-based rotaxanes that are capable of anion sensing in aqueous solvent mixtures.[38] Rotaxanes **6** and **7** (Figure 6), synthesized by chloride templation, were

determined to bind Cl^- selectively over $H_2PO_4^-$ and AcO^- in competitive aqueous-acetone solvent mixtures by ^{1}H NMR titrations. Crucially, photophysical investigations revealed that anion binding was signaled through increasing MLCT emission intensity of both rotaxanes.

We have extended the use of metal luminophores to include lanthanide cations as the anion sensing motif, which are particularly useful in imaging and assay due to their long-lived luminescence. We recently reported the first example of a lanthanide-containing interlocked structure, by preparing [2]rotaxane **10** by a CuAAC "click" reaction of a propargyl-DO3A-lanthanide complex **9** to azide-appended rotaxane **8**, with the aim of exploring the time-gated luminescence detection of complementary anions binding within the rotaxane cavity (Scheme 7).[39] The europium-containing rotaxane exhibited chloride-responsive luminescence behavior, within two independent chloride binding sites: the first chloride anion binds strongly to the lanthanide cation at the axial ninth coordination site, concomitant with dramatic quenching of the hypersensitive $\Delta J = 2$ transition. Further chloride binding within the rotaxane cavity leads to a gradual recovery of the lanthanide emission intensity (Figure 7). This first generation lanthanide-containing rotaxane demonstrated selectivity for Cl^- over both $H_2PO_4^-$ and AcO^-. To further utilize the combination of the optical anion-sensing properties of lanthanide complexes with the selectivity of interlocked anion receptors, we have recently reported the first lanthanide-cation
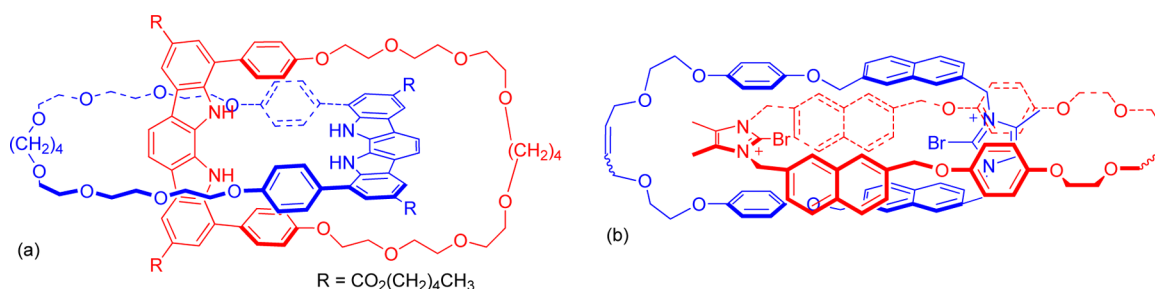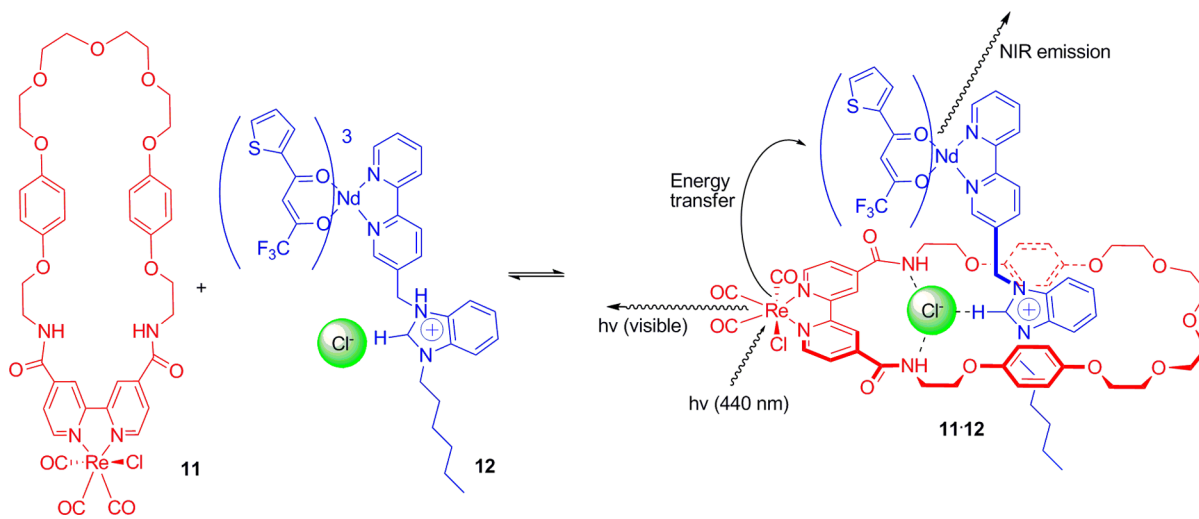
Figure 8. Anion-sensing catenanes containing organic fluorophores.

Scheme 8. Heteronuclear d-f Anion-Templated Pseudorotaxane Assembly 11·12

templation of interlocked structures[40] as a first step to developing more sophisticated lanthanide-rotaxane anion sensors.

Incorporating organic fluorophores within interlocked receptors provides an alternative route to optical anion sensing. Jeong et al. have reported an indolocarbazole-based homo-catenane, that senses chloride selectively over a range of oxoanions in 99:1 acetone/water by means of fluorescence intensity enhancement (Figure 8a).[41] We recently reported an all-halogen bonding catenane assembled using bromide-templation (Figure 8b).[35] The catenane selectively senses chloride and bromide, which bind through the cooperative effect of two halogen bonds, in CH_3CN via modulation of the naphthalene emission. No response was observed upon addition of F^-, I^-, NO_3^-, $H_2PO_4^-$, AcO^-, and HCO_3^-.

■ EXPLOITING THE DYNAMICS OF INTERLOCKED HOST SYSTEMS FOR AN OPTICAL ANION SENSING RESPONSE

The rotaxane anion sensors reviewed thus far possess a common sensing mechanism in which there is direct electronic communication between the reporter group and the cavity bound anionic guest. Rotaxane and catenane hosts offer another means of signal transduction, however, in which the anion-binding event modulates the dynamic interactions between the mechanically bonded components, which can result in a measurable optical response. In the next section we review the initial work carried out by us and others in demonstrating this paradigm.

We first demonstrated this idea in a chloride-templated pseudorotaxane assembly 11·12 in which photoinduced energy transfer between a macrocyclic Re(I)bipyridyl-sensitizer 11 and a luminescent lanthanide complex appended to a chloride-benzimidazolium thread 12 signaled the formation of the interpenetrative assembly (Scheme 8).[42] It was demonstrated initially that by using a thread which contained either no lanthanide cation, or a gadolinium cation that was unable to undergo energy transfer with the Re(I)-bipyridyl center, an enhancement of the Re-bipyridyl-MLCT band was observed upon pseudorotaxane formation. However, addition of neo-dymium thread 12 resulted in a significant reduction in the MLCT emission, with the concomitant appearance of a near-IR lanthanide emission band due to energy transfer between the MLCT excited state and the lanthanide complex. This Forster energy transfer process is dependent on the distance between the two metal centers, and thus only occurs upon pseudorotaxane formation, which in turn occurs only in the presence of specific anion templates.

Anion-induced molecular shuttling, in which binding of an anion guest leads to macrocycle translocation from one station to another along the axle component of a rotaxane, can be exploited to provide a further mechanism of signal trans-duction. This proposition has been realized by Smith and co-workers, who demonstrated that the addition of chloride to a squaraine-derived rotaxane caused macrocycle trans-location away from the dye moiety, with concomitant modulation of the fluorescence intensity. They had previously reported that by encapsulating a squaraine dye (which emits at deep red wavelengths and is desirable for biological imaging applica-tions) within a macrocycle to form a pseudorotaxane assembly,

the fluorescence quantum yield of the dye is decreased 3-fold.[43] An analogous [2]rotaxane, **13**, which incorporates the squaraine dye within the axle, was prepared by stoppering of a pseudorotaxane assembly. This rotaxane host system was demonstrated to act as a reversible optical chloride sensor in CHCl₃ (Figure 9): chloride binding to the triazole motif
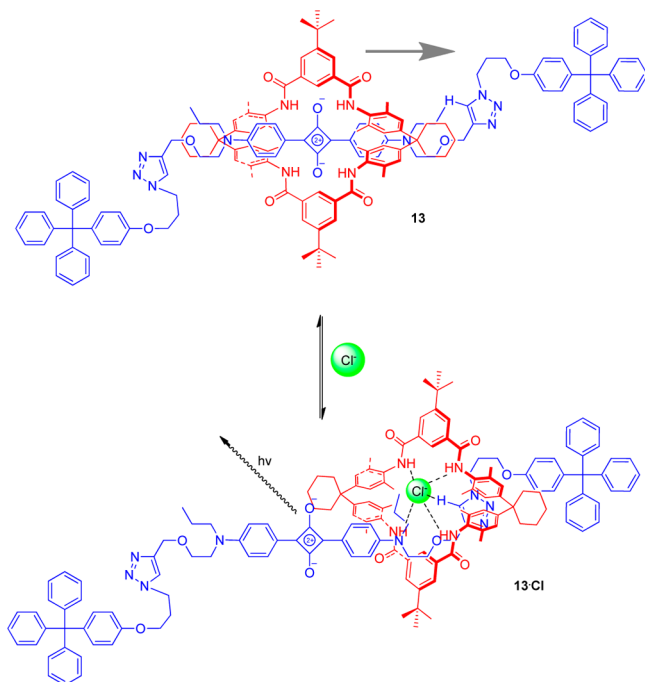

Figure 9. Smith's chloride-sensing squaraine rotaxane shuttle.

induces translocation of the macrocycle away from the squaraine motif, resulting in restoration of the fluorescence intensity.[44] The process is reversed when chloride is removed. Recently, this concept has been extended to include ratiometric chloride sensing.[45]

With the aim of developing an anion-responsive molecular switch which exhibits optical signaling, we have synthesized naphthalimide-triazolium rotaxane **14** which undergoes selective anion-induced unidirectional shuttling behavior upon addition of Cl⁻ or Br⁻ in CHCl₃ (Figure 10).[46] The macrocycle initially resides over the naphthalimide group, due to aromatic donor–acceptor interactions with the electron-rich hydroquinones on the macrocycle; however, the formation of an anion binding cavity requires the translocation to the axle's triazolium motif. Complete macrocycle translocation occurs only in the presence of the smaller halide anions, and importantly, the change in naphthalimide-hydroquinone donor–acceptor interactions upon macrocycle shuttling is signaled by changes in the rotaxane's UV–vis absorption band.

Lin and co-workers have very recently reported a diketopyrrolopyrrole (DPP) based rotaxane which can selectively sense F⁻ via both a colormetric and fluorescence response.[47] Fluoride anions bind within the amide binding cavity of the macrocycle component of rotaxane **15** (Figure 11). Further equivalents of F⁻ result in deprotonation of the amides, and shuttling of the macrocycle toward the axle DPP-fluorophore, concomitant with fluorescence quenching and a color change. The response is selective for F⁻ over a range of anions, including other halides, NO₃⁻, H₂PO₄⁻, and AcO⁻ in DMSO.
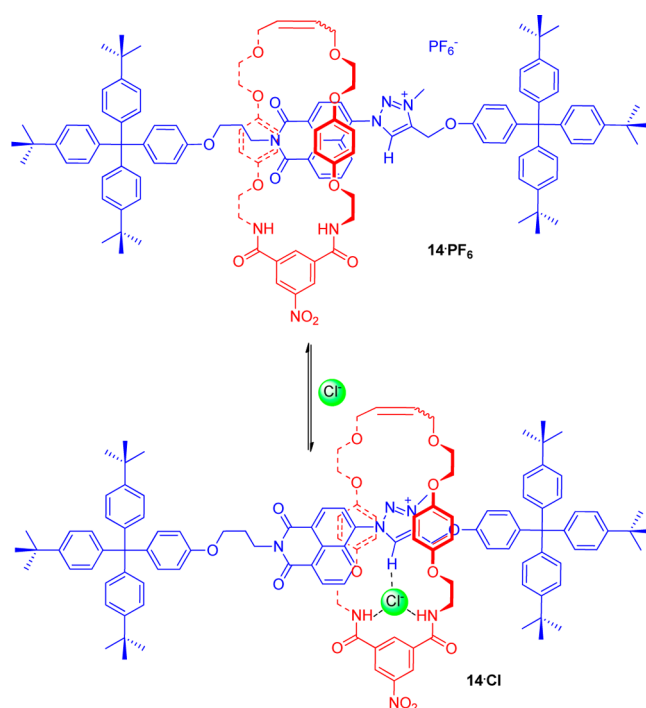

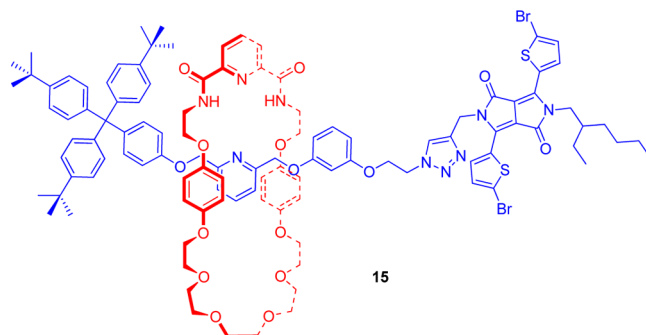**Figure 10.** Naphthalimide-derived anion-responsive rotaxane shuttle.

Figure 11. Diketopyrrolopyrrole-based [2]rotaxane shuttle for fluoride sensing.

The previous four examples demonstrate that an anion-induced change in geometry or co-conformation can be used as an approach to achieving an anion-selective optical response. With this in mind, we designed a [3]rotaxane host, containing a fluorescent naphthalene motif for optical anion sensing, that was able to undergo a conformational change upon anion binding.[28] Selective recognition of sulfate in 45:45:10 CDCl₃/ CD₃OD/D₂O by rotaxane **16** resulted in a conformational change where the sulfate anion is bridged between the two macrocycle components in a 1:1 "sandwich" complex (Figure 12). The anion is held in close proximity to the naphthalene moiety which resulted in a dramatic fluorescence quenching in CHCl₃. In contrast, Cl⁻ binds within the two rotaxane cavities, leading to a modest emission enhancement.

■ **SOLUTION-BASED ELECTROCHEMICAL ANION SENSING BY INTERLOCKED HOST SYSTEMS**

Over the years, there has been much interest in developing anion receptors capable of selectively sensing anions via electrochemical methods, and our previous research in this area has focused on incorporating ferrocene within anion-
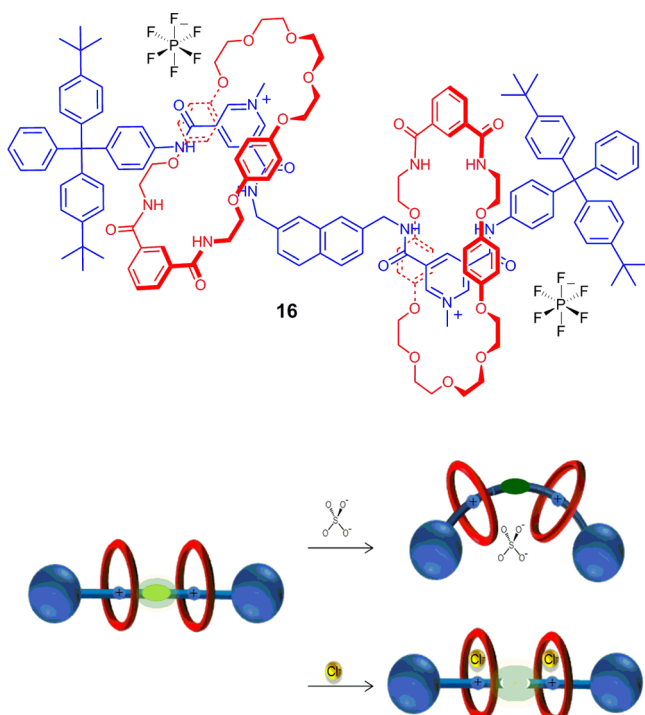
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Figure 12. Schematic representation of anion binding in fluorescent [3]rotaxane **16**.

receptor systems.[48] Anion binding typically results in a cathodic shift in the ferrocene/ferrocenium redox couple due to stabilization of the ferrocenium state by the anionic guest.

Our first interlocked structures for electrochemical sensing incorporated ferrocene either on the periphery of the

macrocycle component (rotaxane **17**[49] and catenane **19**[50]), or in the axle by utilizing a pentaphenylferrocene stopper component in rotaxane **18** (Figure 13).[51] All three structures were prepared by chloride anion-templation, using ring-closing metathesis of a suitable bisvinyl appended macrocycle precursor, and exhibited a common selectivity for Cl^- over HSO_4^-, BzO^-, and $H_2PO_4^-$. Importantly, Cl^- selectivity was also manifested in the electrochemistry, with the maximum cathodic shift of the Fc/Fc$^+$ couple occurring after addition of 1 equiv of Cl^- in CH_3CN. In contrast, the addition of excess oxoanion was required to achieve a maximum response. 1,1'-Disubstituted ferrocene was incorporated within the axle component of [3]rotaxane **20**, which was shown to electrochemically sense anionic guests in 0.1 M NH_4PF_6/CH_3CN.[27] Binding of Cl^- and SO_4^{2-} occurs in a similar way to [3]rotaxane **16**; Cl^- binds in a 2:1 stoichiometry within the two interlocked cavities, while the divalent sulfate anion leads to a 1:1 "sandwich" complex, with concomitant cathodic shift of the ferrocene/ferrocenium redox couple of 55 and 265 mV, respectively.

We have also recently integrated the porphyrin motif as an electrochemical antenna within rotaxane host systems (Figure 14).[52] Both rotaxanes **21** and **22** were responsive to Cl^-, resulting in a cathodic shift of the first porphyrin oxidation waves of 50 and 23 mV, respectively after 2 equiv of anion in CH_2Cl_2/CH_3CN.

■ SURFACE CONFINED INTERLOCKED ARCHITECTURES FOR ANION SENSING

While interlocked structures have been extensively studied in the solution phase, and their ability to function as molecular shuttles and ion sensors has been demonstrated, the fabrication of such molecules into workable devices for proposed
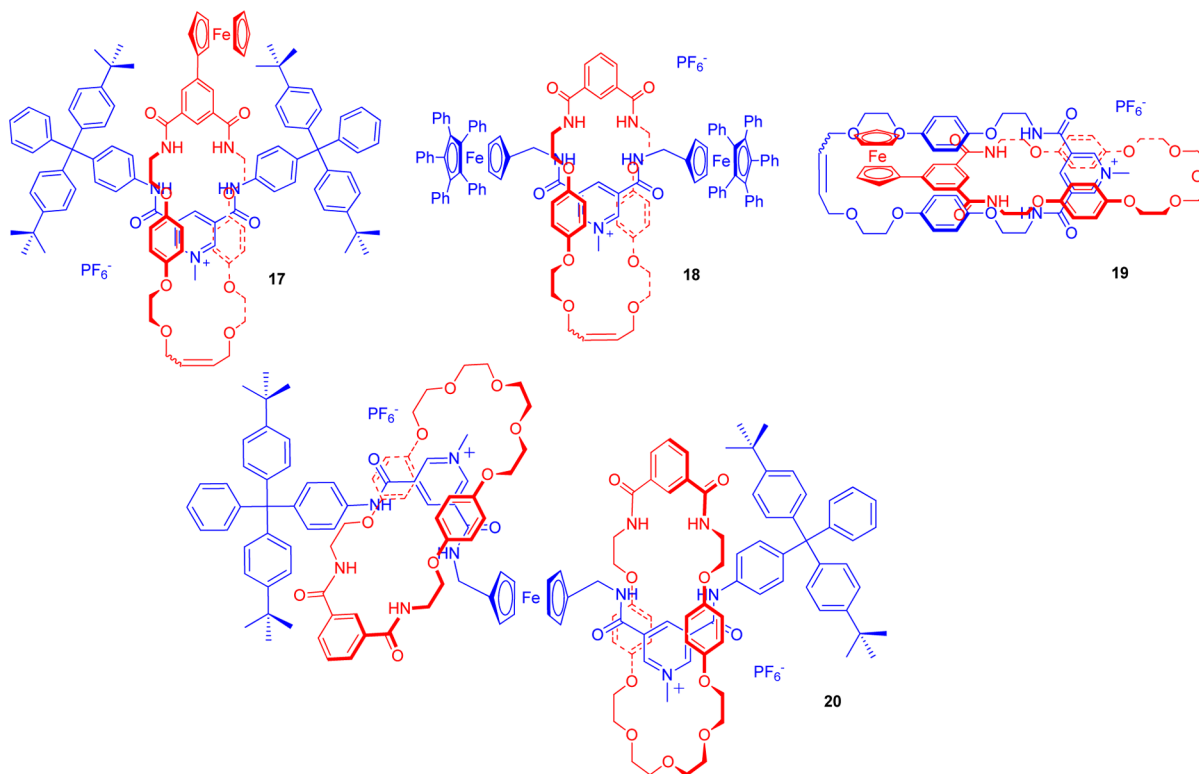

Figure 13. Ferrocene-functionalized interlocked hosts.

1944

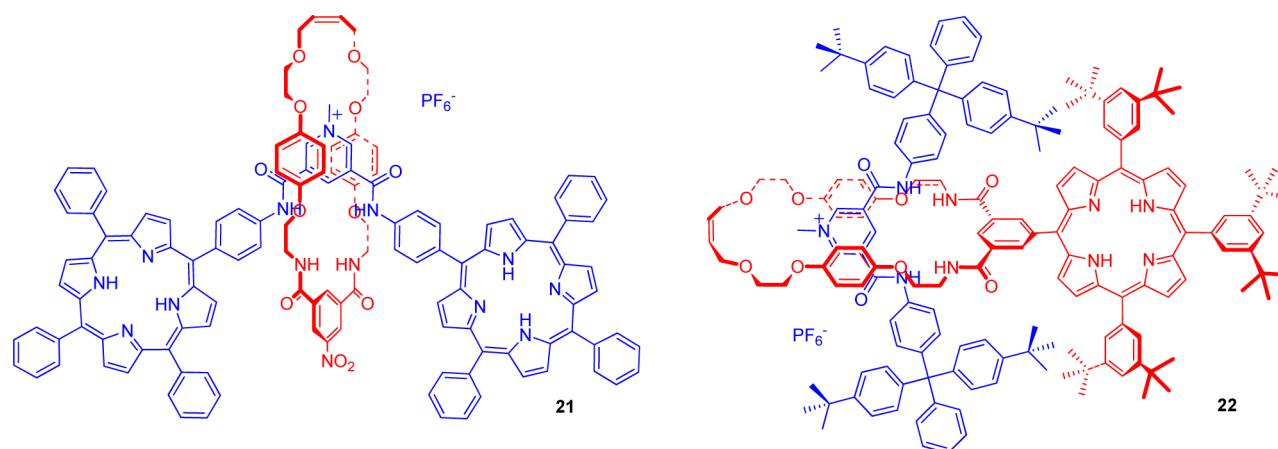dx.doi.org/10.1021/ar500012a | *Acc. Chem. Res.* 2014, 47, 1935–1949

Figure 14. Porphyrin-functionalized rotaxanes for electrochemical anion sensing.

applications in sensing or data storage is in its infancy. Central to addressing this challenge is the interfacing of these molecules with a supportive optically transparent or electroactive surface. The formation of two-dimensional self-assembled monolayers (SAMs) represents a means of amplifying molecular-level properties to the macroscopic scale. From the point of view of host−guest sensing, SAMs offer the possibility of generating a robust, reusable anion-responsive surface (Figure 15) which can
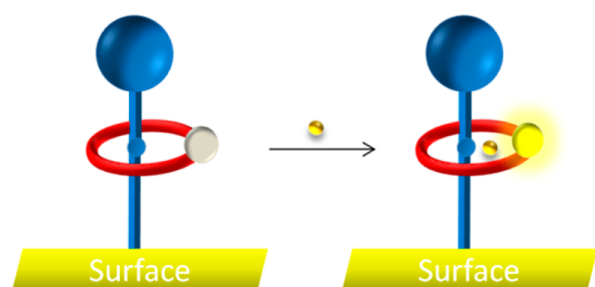

Figure 15. Schematic representation of a surface-appended rotaxane anion sensor.

be integrated into a device capable of operating in a wide variety of solution-based environments. Furthermore, confinement of host species at a surface can significantly enhance the

thermodynamics of host−guest interactions, in part due to the preorganization of the receptors at the surface.

There have been several examples of surface-attached interlocked molecular architectures reported in the literature to date;[53−56] however, sensory applications are rare. We reported the first example of a sensory rotaxane-SAM that was redox-active in 2007.[57] A chloride-templated pseudorotaxane assembly **23·24** was initially prepared in solution by mixing ferrocene-functionalized macrocycle **24** and an ion-pair threading component **23** in which the bulky stopper component is the redox-active pentaphenylferrocene motif (Scheme 9). Immersing a gold electrode into this solution led to the formation of rotaxane-SAM **25**, from which the Cl^- anion template could be removed by washing with $NH_4PF_{6(aq)}$ to reveal the chloride-responsive adlayer. The ferrocene moiety of the macrocycle demonstrated a selective voltammetric response to the presence of Cl^- ($\Delta E \sim 40$ mV) in a 0.1 M NH_4PF_6/CH_3CN electrolyte solution, even in the presence of a 100-fold excess of competing oxoanions, such as $H_2PO_4^-$. The crucial importance of the interlocked nature of the SAM was demonstrated when comparing the electrochemical response to that of the free, noninterlocked, components in solution: thread **23·PF₆** exhibited small cathodic shifts in the presence of both Cl^- and the oxoanions, while macrocycle **24** displayed a selective and strong response ($\Delta E \sim 45$ mV) for the oxoanions, the reverse of the observed Cl^- selectivity of the rotaxane SAM.

Scheme 9. Fabrication of a Chloride-Responsive Rotaxane SAM
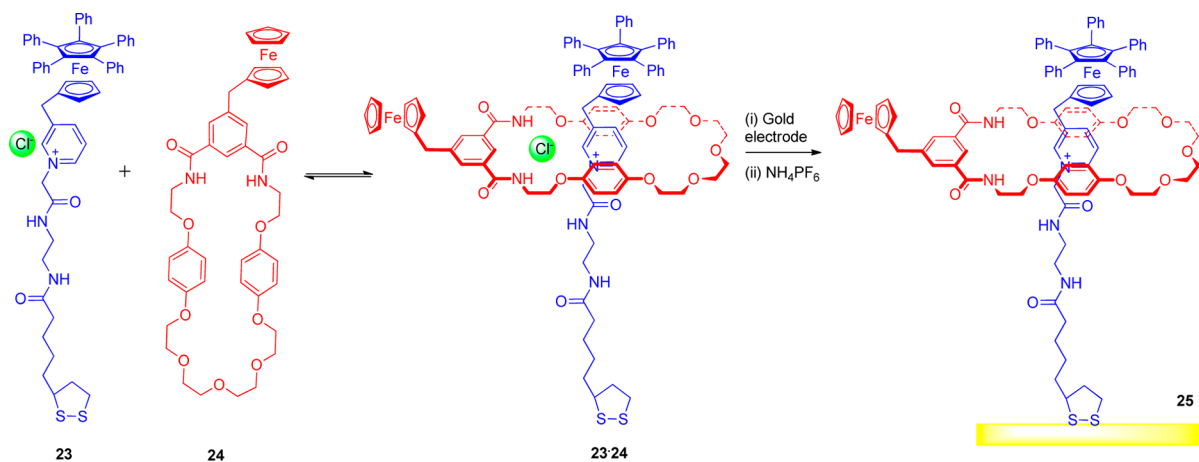
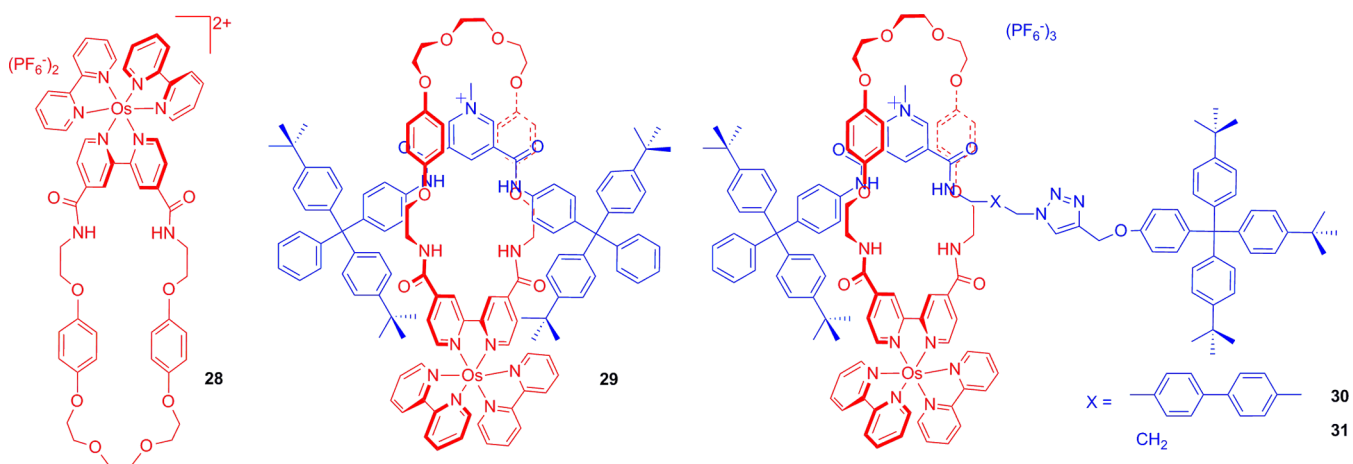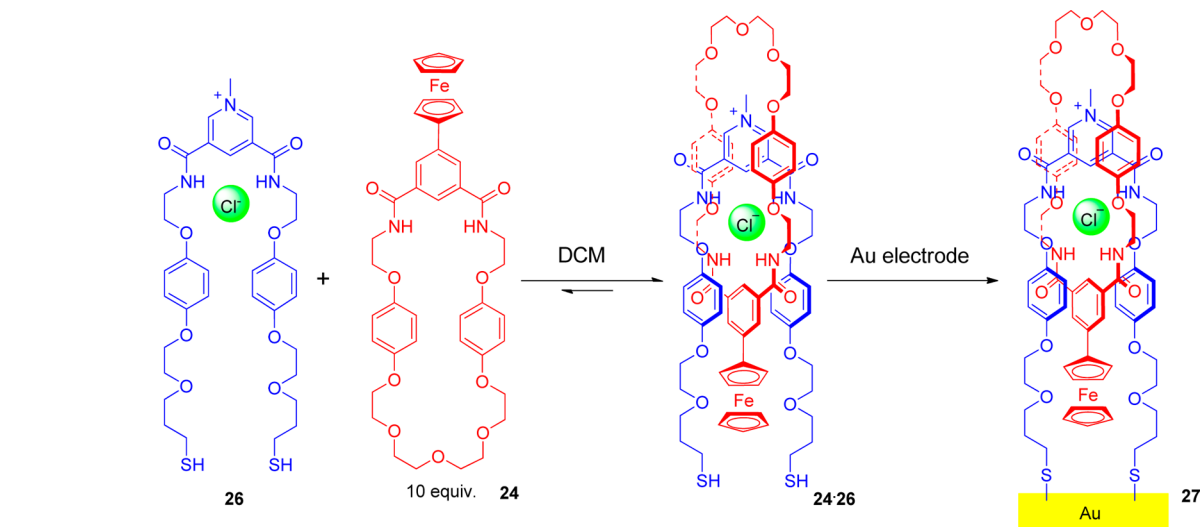**Scheme 10. Surface-Assembled Ferrocene Catenane 26**

Figure 16. Osmium-functionalized rotaxanes for optical and electrochemical anion sensing.

Scheme 11. Fabrication of Surface-Assembled Osmium Rotaxane
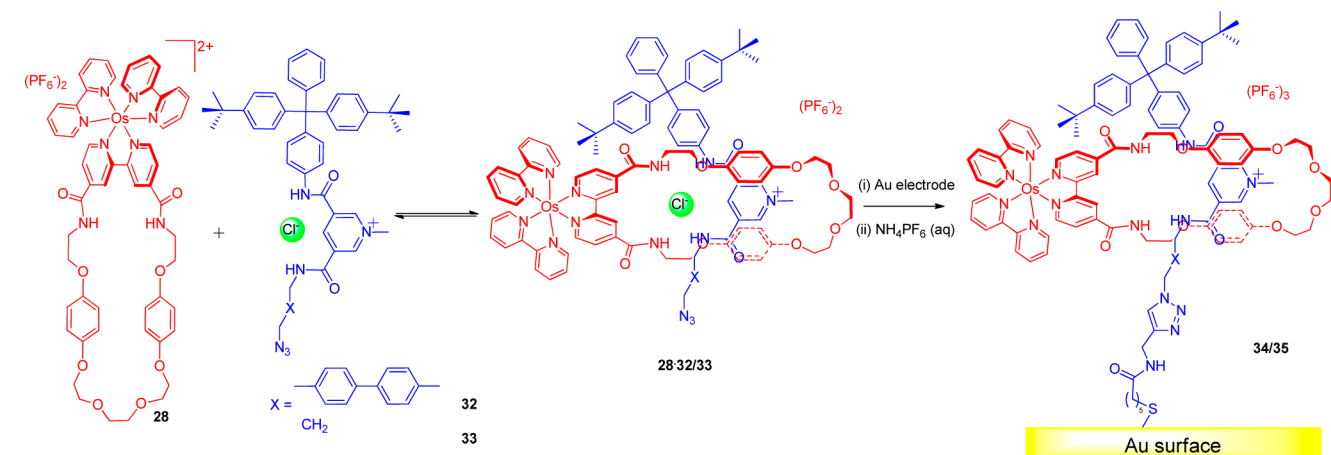
We have also demonstrated the self-assembly of a catenane host system on a gold surface. A pseudorotaxane assembly 24· 26 was preformed in solution between ferrocene-appended macrocycle 24 and bis-thiol-appended pyridinium-chloride 26, which, upon exposure to a gold surface, afforded the surface-confined catenane 27 (Scheme 10),[50] the analogue of catenane

19 discussed earlier. The high degree of preorganization of catenane 27 at the surface, however, coupled with poor solvent access prevented the removal of the Cl⁻ anion template, and thus inhibited the exploration of the anion sensing capabilities.

Recently, we developed a family of rotaxane hosts that contain an osmium(II) bipyridyl-derived macrocycle, capable of

sensing anions via both luminescence and electrochemistry.[58] Three distinct rotaxanes were prepared by Cl⁻ templation, comprising macrocycle **28** and axles of different lengths (Figure 16).

^{1}H NMR anion-binding studies of the rotaxanes revealed a strong selectivity for Cl⁻ over AcO⁻ and $H_2PO_4^-$, while anion binding was demonstrated to perturb the osmium-bipyridyl-MLCT luminescence. Surface-bound analogues of rotaxanes **34** and **35** were prepared on an alkyne-terminated SAM by a CuAAC click reaction of the pseudorotaxane assembly (Scheme 11). Removal of the Cl⁻ template revealed the surface-immobilized rotaxane to selectively bind and sense Cl⁻ electrochemically via a cathodic shift of the $Os^{2+/3+}$-bipyridyl redox couple in CH_3CN.

CONCLUDING REMARKS

In this Account, we have demonstrated that suitably designed mechanically interlocked molecules can be used to bind charged guest species, and by incorporating optical or electrochemical reporter groups the bound guest can be sensed. The superior selectivity of interlocked hosts compared to their acyclic analogues makes them ideal candidates for developing ion-selective sensors, and importantly, their unusual dynamics can be exploited as a means of obtaining a functional sensor response. While the molecular architectures presented here are complex and intricate, the development of high yielding templating strategies has made rotaxanes and catenanes synthetically accessible, and the prudent choice of such receptors is often necessary when dealing with the selective recognition of more challenging targets, such as anionic guests. Having developed the use of anion templation to synthesize interlocked anion receptors, we have prepared a wide range of anion-sensing rotaxanes and catenanes, incorporating a variety of reporter groups for both optical and electrochemical sensing, including transition metals, lanthanides, and organic chromophores. We have also developed more complex rotaxane architectures that can undergo anion-induced conformational changes or molecular motion, as a means of obtaining a functional sensor response.

Ultimately, the fabrication of such devices on to surfaces is required to prepare robust anion-sensing devices, and we have recently approached this challenge through the preparation of redox-active rotaxane and catenane architectures on gold surfaces, which can act as selective chloride sensors. While the study and application of the host–guest chemistry of interlocked receptors remains in its infancy, the examples presented in this Account highlight the exciting potential of rotaxane and catenanes as sophisticated and selective sensors for practical application.

AUTHOR INFORMATION

Corresponding Author

*E-mail: paul.beer@chem.ox.ac.uk.

Notes

The authors declare no competing financial interest.

Biographies

Matthew Langton graduated from Lincoln College, University of Oxford with a first class honors degree in Chemistry (MChem) in 2011. He remained in Oxford for graduate studies with Paul Beer, and is in the third year of his DPhil. His research interests center around

anion recognition and sensing, with particular focus on developing water-soluble and lanthanide-functionalized rotaxane sensors.

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.

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REFERENCES

(1) van Dongen, S. F. M.; Cantekin, S.; Elemans, J. A. A. W.; Rowan, A. E.; Nolte, R. J. M. Functional Interlocked Systems. *Chem. Soc. Rev.* **2014**, *43*, 99−122.

(2) Balzani, V.; Credi, A.; Silvi, S.; Venturi, M. Artificial Nanomachines Based on Interlocked Molecular Species: Recent Advances. *Chem. Soc. Rev.* **2006**, *35*, 1135−1149.

(3) Kay, E. R.; Leigh, D. A.; Zerbetto, F. Synthetic Molecular Motors and Mechanical Machines. *Angew. Chem., Int. Ed.* **2007**, *46*, 72−191.

(4) Fang, L.; Olson, M. A.; Benítez, D.; Tkatchouk, E.; Goddard, W. A., III; Stoddart, J. F. Mechanically Bonded Macromolecules. *Chem. Soc. Rev.* **2009**, *39*, 17−29.

(5) Spence, G. T.; Beer, P. D. Expanding the Scope of the Anion Templated Synthesis of Interlocked Structures. *Acc. Chem. Res.* **2013**, *46*, 571−586.

(6) Caballero, A.; Zapata, F.; Beer, P. D. Interlocked Host Molecules for Anion Recognition and Sensing. *Coord. Chem. Rev.* **2013**, *257*, 2434−2455.

(7) Zhu, S. S.; Carroll, P. J.; Swager, T. M. Conducting Polymetallorotaxanes: A Supramolecular Approach to Transition Metal Ion Sensors. *J. Am. Chem. Soc.* **1996**, *118*, 8713−8714.

(8) Zhu, S. S.; Swager, T. M. Conducting Polymetallorotaxanes: Metal Ion Mediated Enhancements in Conductivity and Charge Localization. *J. Am. Chem. Soc.* **1997**, *119*, 12568−12577.

(9) Kaiser, G.; Jarrosson, T.; Otto, S.; Ng, Y.-F.; Bond, A. D.; Sanders, J. K. M. Lithium-Templated Synthesis of a Donor−Acceptor Pseudorotaxane and Catenane. *Angew. Chem., Int. Ed.* **2004**, *43*, 1959−1962.

(10) Hsueh, S.-Y.; Lai, C.-C.; Liu, Y.-H.; Peng, S.-M.; Chiu, S.-H. Highly Selective Na+-Templated Formation of [2]Pseudorotaxanes Exhibiting Significant Optical Outputs. *Angew. Chem., Int. Ed.* **2007**, *46*, 2013−2017.

(11) Hsueh, S.-Y.; Lai, C.-C.; Chiu, S.-H. Squaraine-Based [2]-Rotaxanes That Function as Visibly Active Molecular Switches. *Chem.—Eur. J.* **2010**, *16*, 2997−3000.

(12) Hiratani, K.; Kaneyama, M.; Nagawa, Y.; Koyama, E.; Kanesato, M. Synthesis of [1]Rotaxane via Covalent Bond Formation and Its Unique Fluorescent Response by Energy Transfer in the Presence of Lithium Ion. *J. Am. Chem. Soc.* **2004**, *126*, 13568−13569.

(13) Nagawa, Y.; Suga, J.; Hiratani, K.; Koyama, E.; Kanesato, M. [3]Rotaxane Synthesized via Covalent Bond Formation Can Recognize Cations Forming a Sandwich Structure. *Chem. Commun.* **2005**, 749−751.

(14) Zhou, W.; Li, J.; He, X.; Li, C.; Lv, J.; Li, Y.; Wang, S.; Liu, H.; Zhu, D. A Molecular Shuttle for Driving a Multilevel Fluorescence Switch. *Chem.—Eur. J.* **2008**, *14*, 754−763.

(15) Nakatani, Y.; Furusho, Y.; Yashima, E. Amidinium Carboxylate Salt Bridges as a Recognition Motif for Mechanically Interlocked

Molecules: Synthesis of an Optically Active [2]Catenane and Control of Its Structure. *Angew. Chem., Int. Ed.* 2010, 49, 5463–5467.

(16) Lankshear, M. D.; Beer, P. D. Interweaving Anion Templation. *Acc. Chem. Res.* 2007, 40, 657–668.

(17) Luecke, H.; Quiocho, F. A. High Specificity of a Phosphate Transport Protein Determined by Hydrogen Bonds. *Nature* 1990, 347, 402–406.

(18) Pflugrath, J. W.; Quiocho, F. A. Sulphate Sequestered in the Sulphate-Binding Protein of Salmonella Typhimurium Is Bound Solely by Hydrogen Bonds. *Nature* 1985, 314, 257–260.

(19) Sauvage, J.-P.; Dietrich-Buchecker, C. O. *Molecular Catenanes, Rotaxanes and Knots*; Wiley-VCH: Weinheim, 1999.

(20) Sauvage, J.-P.; Dietrich-Buchecker, C. O. *Tetrahedron Lett.* 1983, 24, 5091–5094.

(21) 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.

(22) 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.

(23) Hancock, L. M.; Beer, P. D. Chloride Recognition in Aqueous Media by a Rotaxane Prepared via a New Synthetic Pathway. *Chem.—Eur. J.* 2008, 15, 42–44.

(24) 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.* 2011, 47, 1725–1727.

(25) 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.

(26) 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.

(27) 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.

(28) Langton, M. J.; Beer, P. D. Sulfate-Selective Binding and Sensing of a Fluorescent [3]Rotaxane Host System. *Chem.—Eur. J.* 2012, 18, 14406–14412.

(29) 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.

(30) Mullen, K. M.; Beer, P. D. Sulfate Anion Templation of Macrocycles, Capsules, Interpenetrated and Interlocked Structures. *Chem. Soc. Rev.* 2009, 38, 1701–1713.

(31) Langton, M. J.; Duckworth, L. C.; Beer, P. D. Nitrate Anion Templated Assembly of a [2]rotaxane for Selective Nitrate Recognition in Aqueous Solvent Mixtures. *Chem. Commun.* 2013, 49, 8608–8610.

(32) 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.

(33) 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.

(34) 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.

(35) 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.

(36) Beale, T. M.; Chudzinski, M. G.; Sarwar, M. G.; Taylor, M. S. Halogen Bonding in Solution: Thermodynamics and Applications. *Chem. Soc. Rev.* 2013, 42, 1667–1680.

(37) Curiel, D.; Beer, P. D. Anion Directed Synthesis of a Hydrogensulfate Selective Luminescent Rotaxane. *Chem. Commun.* 2005, 1909–1911.

(38) 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.

(39) Allain, C.; Beer, P. D.; Faulkner, S.; Jones, M. W.; Kenwright, A. M.; Kilah, N. L.; Knighton, R. C.; Sørensen, T. J.; Tropiano, M. Lanthanide Appended Rotaxanes Respond to Changing Chloride Concentration. *Chem. Sci.* 2012, 4, 489–493.

(40) Zapata, F.; Blackburn, O. A.; Langton, M. J.; Faulkner, S.; Beer, P. D. Lanthanide Cation-Templated Synthesis of Rotaxanes. *Chem. Commun.* 2013, 49, 8157–8159.

(41) Chae, M. K.; Suk, J.; Jeong, K.-S. A Catenated Anion Receptor Based on Indolocarbazole. *Tetrahedron Lett.* 2010, 51, 4240–4242.

(42) Sambrook, M. R.; Curiel, D.; Hayes, E. J.; Beer, P. D.; Pope, S. J. A.; Faulkner, S. Sensitised near Infrared Emission from Lanthanides via Anion-Templated Assembly of D−f Heteronuclear [2]-pseudorotaxanes. *New J. Chem.* 2006, 30, 1133–1136.

(43) Gassensmith, J. J.; Baumes, J. M.; Smith, B. D. Discovery and Early Development of Squaraine Rotaxanes. *Chem. Commun.* 2009, 6329–6338.

(44) Gassensmith, J. J.; Matthys, S.; Lee, J.; Wojcik, A.; Kamat, P. V.; Smith, B. D. Squaraine Rotaxane as a Reversible Optical Chloride Sensor. *Chem.—Eur. J.* 2010, 16, 2916–2921.

(45) Collins, C. G.; Peck, E. M.; Kramer, P. J.; Smith, B. D. Squaraine Rotaxane Shuttle as a Ratiometric Deep-Red Optical Chloride Sensor. *Chem. Sci.* 2013, 4, 2557–2563.

(46) Spence, G. T.; Pitak, M. B.; Beer, P. D. Anion-Induced Shuttling of a Naphthalimide Triazolium Rotaxane. *Chem.—Eur. J.* 2012, 18, 7100–7108.

(47) Raju, M. V. R.; Lin, H.-C. A Novel Diketopyrrolopyrrole (DPP)-Based [2]Rotaxane for Highly Selective Optical Sensing of Fluoride. *Org. Lett.* 2013, 15, 1274–1277.

(48) Beer, P. D.; Cadman, J. Electrochemical and Optical Sensing of Anions by Transition Metal Based Receptors. *Coord. Chem. Rev.* 2000, 205, 131–155.

(49) Evans, N. H.; Beer, P. D. A Ferrocene Functionalized Rotaxane Host System Capable of the Electrochemical Recognition of Chloride. *Org. Biomol. Chem.* 2010, 9, 92–100.

(50) Evans, N. H.; Rahman, H.; Leontiev, A. V.; Greenham, N. D.; Orlowski, 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.

(51) Evans, N. H.; Serpell, C. J.; White, N. G.; Beer, P. D. A 1,2,3,4,5-Pentaphenylferrocene-Stoppered Rotaxane Capable of Electrochemical Anion Recognition. *Chem.—Eur. J.* 2011, 17, 12347–12354.

(52) Brown, A.; Beer, P. D. Porphyrin-Functionalised Rotaxanes for Anion Recognition. *Dalton Trans.* 2011, 41, 118–129.

(53) Berná, J.; Leigh, D. A.; Lubomska, M.; Mendoza, S. M.; Pérez, E. M.; Rudolf, P.; Teobaldi, G.; Zerbetto, F. Macroscopic Transport by Synthetic Molecular Machines. *Nat. Mater.* 2005, 4, 704–710.

(54) Klajn, R.; Fang, L.; Coskun, A.; Olson, M. A.; Wesson, P. J.; Stoddart, J. F.; Grzybowski, B. A. Metal Nanoparticles Functionalized with Molecular and Supramolecular Switches. *J. Am. Chem. Soc.* 2009, 131, 4233–4235.

(55) Richter, S.; Poppenberg, J.; Traulsen, C. H.-H.; Darlatt, E.; Sokolowski, A.; Sattler, D.; Unger, W. E. S.; Schalley, C. A. Deposition of Ordered Layers of Tetralactam Macrocycles and Ether Rotaxanes on Pyridine-Terminated Self-Assembled Monolayers on Gold. *J. Am. Chem. Soc.* 2012, 134, 16289–16297.

(56) Zhao, L.; Davis, J. J.; Mullen, K. M.; Chmielewski, M. J.; Jacobs, R. M. J.; Brown, A.; Beer, P. D. Anion Templated Formation of Pseudorotaxane and Rotaxane Monolayers on Gold from Neutral Components. *Langmuir* 2009, 25, 2935–2940.

(57) 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.

(58) Lehr, J.; Lang, T.; Blackburn, O. A.; Barendt, T. A.; Faulkner, S.; Davis, J. J.; Beer, P. D. Anion Sensing by Solution- and Surface-

Assembled Osmium(II) Bipyridyl Rotaxanes. *Chem.—Eur. J.* **2013**, *19*, 15898−15906.