DESIGN OF PHOTOINDUCED ARTIFICIAL MOTORS: ROTARY CATENANES, MOLECULAR WALKERS, AND SUPRAMOLECULAR PUMPS

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ABSTRACT OF THE DISSERTATION

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Biological motion is a fundamental and very obvious attribute of all living organisms. In a cell, molecular motor proteins are able to perform a myriad of complex functions that make life possible, for example walking along a cytoskeletal track to transport a variety of different types of cargos. Mimicking such sophisticated and complex molecule-based motors from a design and synthesis perspective is certainly a daunting task. However, many scientists have risen to the challenge in the last few decades and have created simple prototypes of molecular machines that are able to move in a processive, unidirectional, and controlled manner. As with biological motors that convert chemical energy into movement, the three motor types described here have been developed to exploit light energy as the fuel source to drive movement. In this context I describe the latest development of rotary catenanes, molecular walkers, and supramolecular pumps.

Introduction

When the field of supramolecular chemistry emerged in the 1970s, scientists began using molecules as opposed to atoms to construct artificial molecular machines. Taking inspiration from nature and the biological world, they implemented this “bottom-up” [1] approach to construct much simpler systems than those found in nature which at their most complex can utilize an energy input and convert it into mechanical work or motion. Motion is fundamentally important to living organisms [2], however, it must be directed and controlled in order to accomplish a function. Energy inputs such as chemical, light, heat, and electricity have all been employed to drive directed and autonomous motion. While chemical fuel reactants are perhaps the most direct and widely used, the use of light energy has been extensively explored [3],[4] for the numerous advantages it presents. First of all, the amount of light energy supplied to a system can be carefully controlled and fine-tuned by modulating the wavelength and intensity. The energy can also be transmitted to the molecules directly without any external influence or physical connectors. Lastly, by using photochemical reactions, less waste is generated, allowing for the design of cleaner, reversible, and more sustainable systems. The exploitation of photochemistry has allowed scientists to develop and construct various molecular motors. Here, we will focus on three types of molecular motors, namely catenane rotary motors, molecular walkers, and supramolecular pumps, all of which are capable of unidirectional movement and can potentially be used

`as molecular devices for responsive materials and surfaces, information storage and processing, drug delivery, etc [5].

Catenane Rotary Motors

Catenanes consist of two or more interlocked rings non-covalently bound. In 1983, Strasbourg chemists Jean-Pierre Sauvage and Christiane Dietrich-Buchecker made a pivotal breakthrough in the design of [2]catenanes (the number in brackets designates the number of interlocked rings), when they developed a “metal-template” strategy for their preparation [6] using copper (I) ions and phenanthroline ligands. They recognized that previously examined 2,9 dianisyl-1,10-phenanthroline ligands (dpp), in the presence of a copper (I) atom, function as molecular “threads” forming a stable tetrahedral coordinated structure [7]. Once the rings cyclize the copper ion can be removed using potassium cyanide to generate a [2]catenane, a molecule of two intertwined rings (figure 1). This metal-ligand template strategy ultimately paved the way for the design and construction of future catenanes. Sauvage was awarded the 2016 Nobel Prize for his efforts and contributions leading to the discovery of molecular machines.

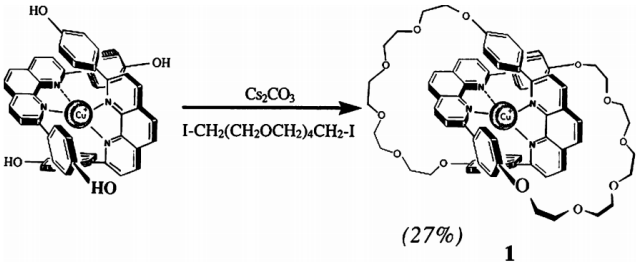

Figure 1: Precursors prepared by Sauvage and coworkers reacted in a double cyclization to produce Cu(I) [2]catenane. Adapted from Sauvage et al [6]

Approximately ten years later, Sauvage and co-workers made another important discovery when they observed that upon oxidation of Cu(I) to Cu(II) the [2]catenane adopts a penta-coordinated geometry as opposed to tetrahedral as with Cu(I). This interconversion of metal oxidation states resulted in translational motion of one ring within the other [8]. A photochemically driven operation was realized a few years later by excitation with 464 nm light in acetonitrile solution [9]. Spectral data shown in figure 2, indicate disappearance of $Cu^{I}N_4$ and subsequent generation of $Cu^{II}N_4$ as the only reaction product in about 20 minutes.

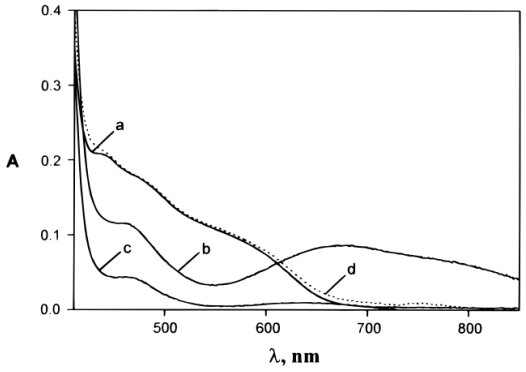

Figure 2 (a) spectral data prior to light excitation, (b) data corresponding to absorption of $Cu^{I}N_4$ in acetonitrile for 20 minutes, (c) after 24 hours in the dark, d) 30 min post addition of ascorbic acid. Adapted from Sauvage et al [9]

Directing motion within the catenanes, however, remained a challenge until 2004 when Leigh and coworkers devised the first light-powered catenane rotary motor that was able to move unidirectionally in either direction using a Brownian [10] ratchet mechanism. This mechanism of operation is quite complex, relying specifically on a flashing ratchet, which is a form of energy ratchet mechanism that involves an asymmetric potential energy landscape consisting of a series of

two alternating minima and maxima. A Brownian particle rests in the absolute minima and it moves directionally along by increasing the minima and decreasing the maxima, as seen in figure 3. This is only made possible through either a chemical, electrical, or photoinduced stimulus [11].

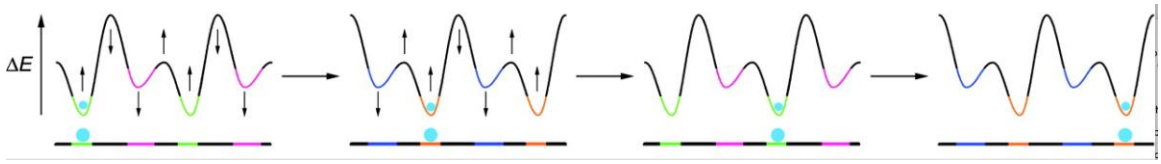

Figure 3: Operation of an energy ratchet with alternating minima and maxima that are modulated to move the black particle directionally. Adapted from Credi et al [12]

A [2]catenane contains a larger ring with different binding sites and a smaller ring that can move based on its affinity for the different binding sites. The relative affinity is altered based on the external energy stimuli applied, which changes the energy landscape, and affords the particle directionality. In the [3]catenane design, Leigh and co-workers exploited the use of a third small macrocyclic ring. Each of these smaller macrocyclic rings mutually prevents each other's movement thereby forcing unidirectional motion [13]. The binding stations on the large ring have vastly different binding affinities for the small macrocycles. The green fumaramide station A forms a stronger bond with the blue macrocyclic ring because they are in the correct geometry for intermolecular hydrogen bonding (figure 4 process 1). The red methyl tertiary fumaramide station B, on the other hand, binds less well because the methyl groups create steric hindrance for the benzylic amide blue macrocycle, preventing proper orientation for bonding. The third binding station, the orange succinic amide ester C, is capable of weak hydrogen bonding due to the inherent flexibility of the molecule and the fact that it

is a poor hydrogen bond acceptor. Lastly, amide station D, represented in dark green, can only very weakly bind relative to the other three stations. Furthermore, the green fumaramide station is positioned right next to a benzophenone unit which acts as a donor chromophore, resulting in the isomerization of station A as opposed to B [13].

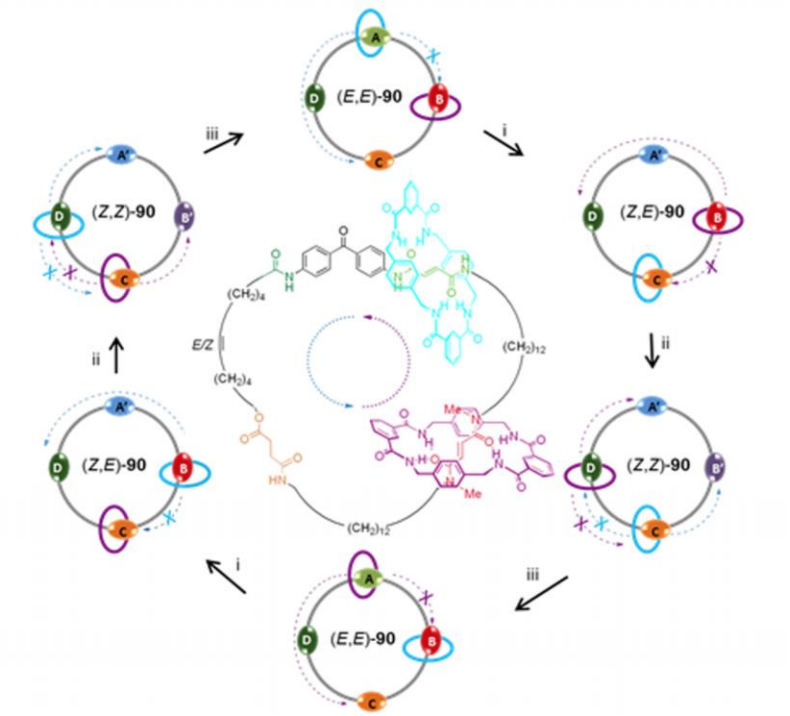

Figure 4: Circumrotation of [3]catenane via photoinduction: i) photoisomerization of fumaramide station A from light green to blue after irradiation with 350 nm of light energy ii) photoisomerization of the tertiary fumaramide station B from red to purple using 254 nm of light iii) back isomerization of A and B binding sites by irradiation with light in the 400-670 nm range . Adapted from Leigh et al [13]

The process begins with the blue macrocycle ring bound to the strongest interacting site A, and the second macrocycle purple ring encircling the second most preferred station B. Upon E→Z photoisomerization of station A, the binding affinity weakens, causing the macrocycle to move in a counterclockwise direction

towards the succinimide ester station, C (figure 4 process 1). Step two involves isomerization of the tertiary fumaramide group, resulting in the purple macrocyclic ring moving to the amide (dark green) station. Movement occurs in a counterclockwise direction due to the blocked pathway by the other (blue) macrocycle. At this point the position of the two small macrocycles is swapped and in order to complete a full 360-degree rotation, the sequence needs to be repeated twice.

DNA Molecular Walkers

The inspiration for designing artificial molecular machines is often based on nature and the biological world. The well-studied and best understood motor proteins are myosin, dynein, and kinesin, all of which “walk” on actin filament or microtubules respectively, to contract our muscles or transport different organelle and vesicle that help to sustain life [14]. While scientists are extensively investigating these natural nanoscale motors, they are a long way from developing artificial ones that can precisely mimic the essential functions required for practical applications. However, there are some defining features shared by all biomolecular walkers that can be implemented in the design of artificial molecular walkers [15]. For example, molecular walkers have to be processive, that is they must remain bound to the track as the walker continues along the molecular scaffold. They must also move unidirectionally towards one end of the track as a result of a ratchet mechanism. Lastly, a highly desired property when thinking about design is that walkers function and move

continuously and autonomously, as long as an energy source is available the entire time [15].

In 2012, chemists at the University of Florida presented the first light-powered DNA walking device that was able to autonomously move with direction and control [16]. The three-part system encompassed a single stranded DNA track (**T)**, four attachment sites labeled **S1, S2, S3**, and **S4,** and a light sensitive walker **W [16] (**figure 5).

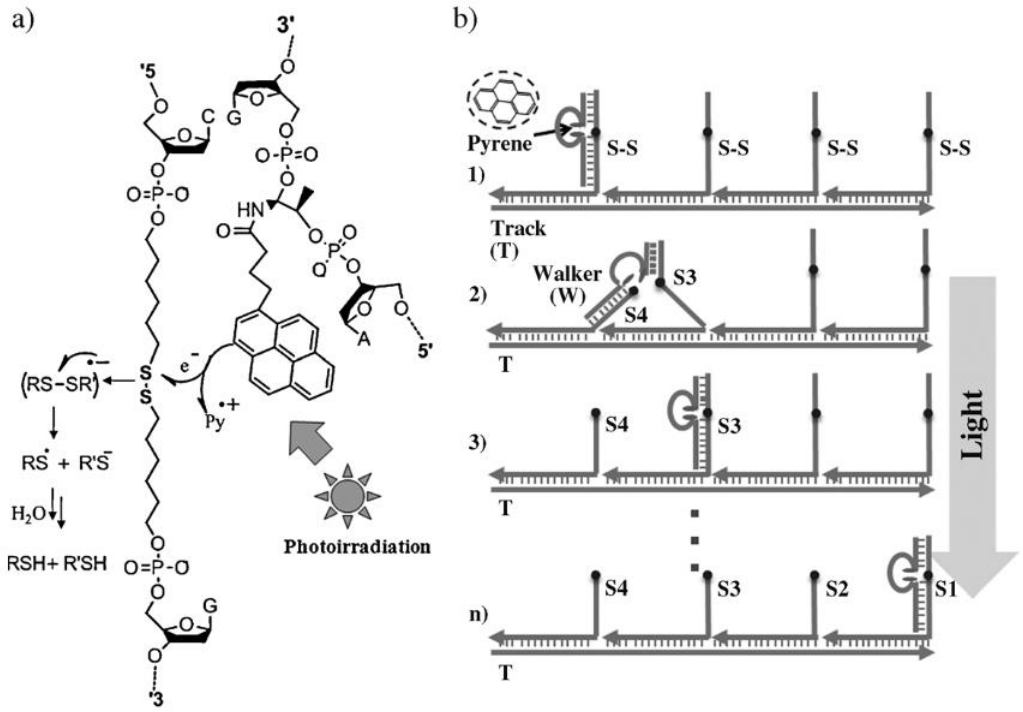

Figure 5: A) photoirradiation of pyrene facilitates in breakage of disulfide bond within the DNA structure. B) Illustration of the walking sequence design using track **T**, four anchorage sites **S1, S2, S3, S4,** and walker **W.** Adapted from You et al. [16]

The four walker attachment sites are bound to a 21-nucleotide track via complementary base pairing recognition tags. The DNA walker is also made up of two complementary legs, linked together by an oligomer body. The

photoinitiator, pyrene moiety, is attached to this DNA oligomer and the walker operates based on a toehold mediated strand displacement design. The long leg of the DNA strand, composed of 16 nucleotide units, stays attached to the extender segment preventing the walker from leaving the track. Upon irradiation at 350nm, energy-rich pyrene transfers electrons to the disulfide bond, causing it to break. Once the bond is broken, the shorter leg detaches and binds to the next available site, which will become the replacement strand. The movement is powered by toehold-mediated strand displacement with the longer leg “stepping” forward to meet the short leg at the new closest anchorage site [16]. The directional movement was verified by running a polyacrylamide gel electrophoresis (PAGE), that showed the anchorage site splitting on the opposite side of the disulfide linker, once the DNA walker steps forward. The dark bands represent the short-cleaved fragments over a period of sixty minutes both in the S4→S1 direction and the reverse.

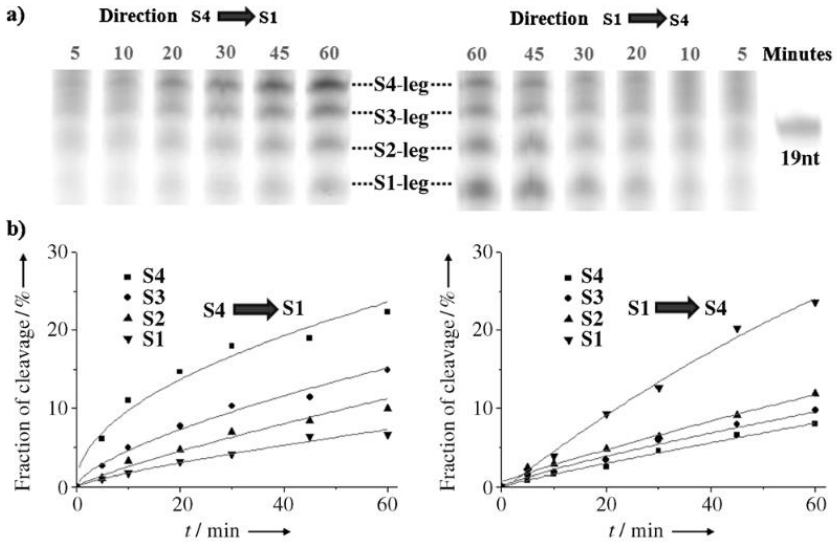

Figure 6: Directional movement of the walker towards the successive anchorage sites. A: PAGE data showing the cleaved fragments over 60minute period. B:

Line graph quantifying the cleavage fraction as a percentage over irradiation time Adapted from You et al [16].

The short strand prefers a stepwise motion to the next available anchorage site, it will not hop or skip a site. Progressive stepwise motion from S1 to S2 to S3 to S4 of the walker was confirmed using fluorescence resonance energy transfer or FRET (figure7). FRET is a widely used technology for elucidating biomolecular processes at a sub-nanometer scale, allowing the investigation of static and dynamic systems such as DNA walkers [17].

The mechanism is distance-dependent and involves a non-radiative transfer of excitation energy from a donor fluorophore to a closely located acceptor fluorophore. In this case, 6-carboxyfluorescin (6-FAM fluorophores) was used as the donor and covalently labeled on the longer leg of the walker, while cyanine fluorescent dye Cy5, an acceptor for FAM, was attached to anchorage site S3. In order for the acceptor to absorb the energy, the walker must step onto the S3 site, since the efficiency of FRET depends on the close proximity of the donor and acceptor. Fluorescent intensity proved to be greatest for Cy5 at S3 due to the shorter distance. The progressive nature of the system was demonstrated in that movement of the walker from the S4 to S1 direction resulted in faster peak fluorescent intensity due to the one step required to reach S3 from S4 as opposed to the S1 to S4 direction where S3 was two steps away from S1(figure 7) [16]. Site S2 was also labeled with an acceptor fluorophore, TAMRA, 5-Carboxytetramethylrhodamine to further aid in monitoring fluorescence intensity sequentially.

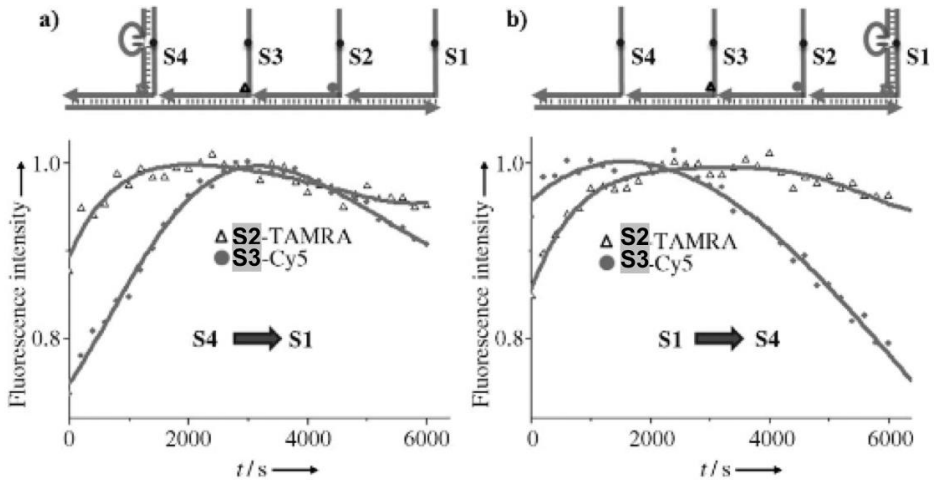

Figure 7: Graphical FRET assay representation of the progressive movement. Donor fluorophore FAM labeled walker moves on anchorage sites 2 and 3 both labeled with a suitable acceptor, TAMRA and Cy5 respectively Adapted from You et al [16].

A smaller light-driven synthetic molecular walker with the ability to move in either direction along a four foothold track was first developed and reported by Leigh and coworkers [18]. The system, very similar in construction to a previously synthesized chemically fueled walker by the same group [19], consists of a molecular track with four binding stations and a walker unit containing two different functional sites that bind to the track (figure 8a). The walker features two feet that respond with movement in response to different chemical conditions and reversibly bind to different stations on the track. For example, under acidic conditions, the disulfide bond between one foot of the walker and the track remains locked while the hydrazone unit of the other foot is free to move and detach (figure 8b). Under basic conditions, this foot-track dynamic reverses,

ultimately allowing for movement in two different directions, forward and backward.

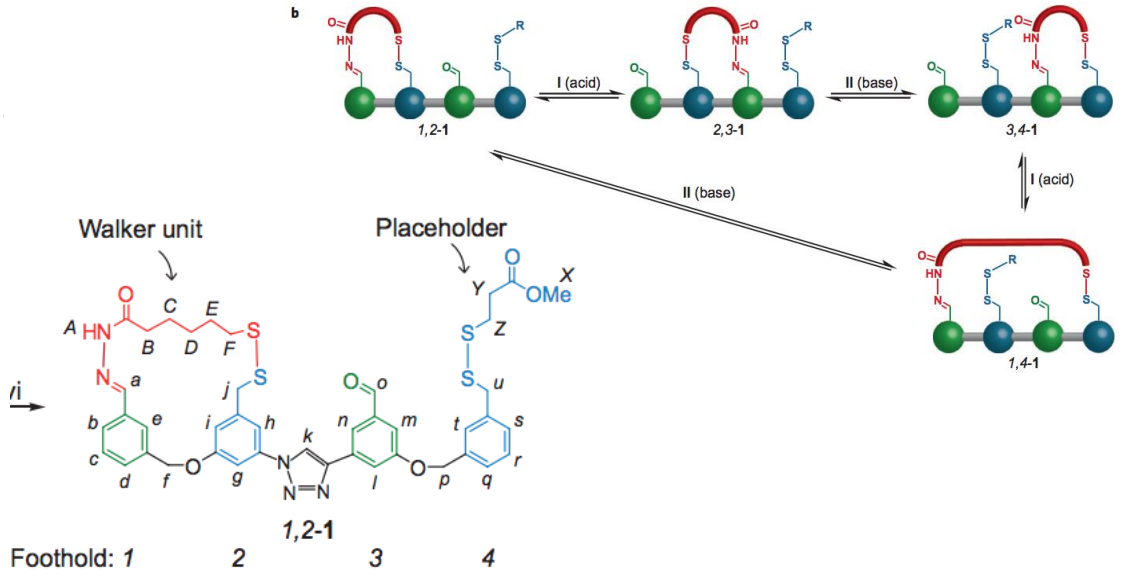

Figure 8a: molecular walker **1,2-1** (numbering designates binding region on track of the walker unit) 8b: operating mechanism based on selectively labile “feet” between the walker (red) and the track. The sequence shows the reversible movement of the walker from left to right under acidic and basic conditions, respectively, Adapted from Leigh et al [19].

The one major difference between the chemically driven system and the light induced one (figure 9) is the introduction of a stilbene unit between one of the internal aldehydes of the molecule and the disulfide binding station of the track. Upon irradiation with UV or visible light, the stilbene unit isomerizes from E-> Z, causing significant ring strain of the constitutional isomer (blue and green units) in which the walker unit bridges with the stilbene linkage. This isomerization provides the necessary momentum for the walker to effectively step or bind onto the stilbene group.

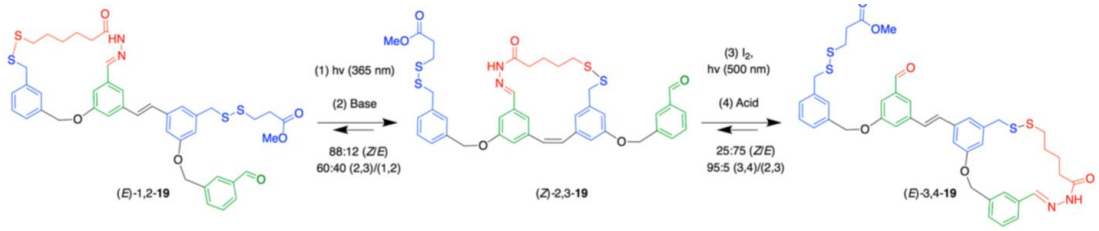

Figure 9: Red walker molecule moving along a four station (blue and green) track. The walker moves after photoisomerization of the stilbene moiety results in ring strain between the walker and the track. The numbers used in the descriptor molecules indicate the stations linked to the walker. The walker moves from station 1 and 2 to 3 and 4 ; Adapted from Credi et al [12]

The general direction the walker takes is ultimately dependent on the sequence of the applied stimuli. The acidic or basic conditions control the detachment of the “foot” of the walker from the track, and photoirradiation controls the isomerization of the stilbene unit to increase or decrease ring strain between the walker and the constitutional isomer track [12].

Supramolecular Pumps

Supramolecular pumps can be described as linear motors composed of a molecular ring that can be directionally transported as a substrate on an asymmetrical molecular axle [20]. The design is based on a pseudo-rotaxane structure where the ring and axle molecules can undergo threading and dethreading, slipping in and out of at least one end of the axle. Rotaxanes, on the other hand, are unable to disassemble because they contain two bulky dumbbell ends or stoppers on either side of the molecular axle.

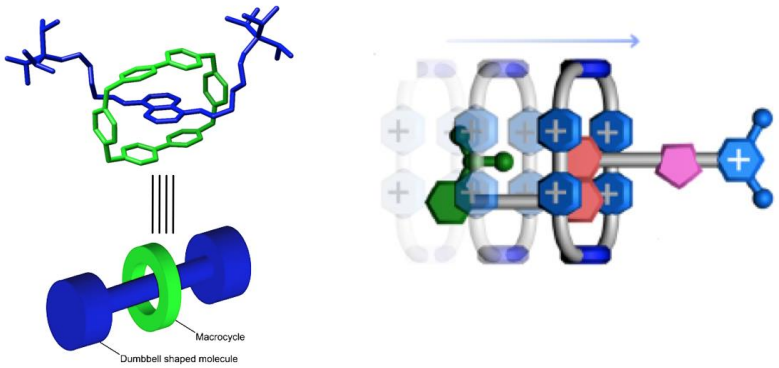

Figure 10 Left: Dumbbell shaped rotaxane consisting of macrocyclic ring and asymmetrical axle. Right: Pseudorotaxane, rotaxane type structure allowing for slippage (threading/dethreading) at the end of the less bulk end group; Adapted from Stoddart et al [21]

The common theme uniting the design and development of molecular machines is they must have unidirectional movement powered by some external stimulus, and the transport must be controlled and going against a concentration gradient [22]. The importance of fulfilling these requirements cannot be overstated as the nanoscale dynamics of biological machines within cells are ultimately responsible for the existence of life [23].

In 2013, Nobel laureate J. Fraser Stoddart and coworkers devised the first example of a redox powered molecular pump, in the form of a [2]pseudorotaxane (figure 11a) [21]. The [2]pseudorotaxane is composed of a **CBPQT^{4+}** (cyclobis(paraquat-p-phenylene) macrocycle and an asymmetrical axle **D1^{+}**, which contains a π-donating 1,5-dioxynaphthalene DNP recognition site in the center, a neutral 2-isopropylphenyl group on one end and a positively charged 3,5-dimethylpyridinium unit on the opposite end (figure 11a). The redox properties of the CBPQT^{4+} ring significantly alter its affinity for the charged and

neutral molecules on the axle, changing the relative heights of the kinetic energy barriers and depth of the energy wells, and allowing for passage of the ring in a unidirectional manner. When the macrocycle is oxidized to its tetracationic state, it becomes a strong π- electron acceptor [24] so it's association onto the ring and interaction with the central π-electron donor DNP unit is greatly favored. However, in order to reach the DNP unit and move into a favorable minimum energy state, it must first pass through one of the two dumbbell stoppers on each end. Passage via the positively charged 3,5-dimethylpyridinium moiety is very unlikely due to strong Coulombic repulsion [21] so movement of the ring occurs over the bulky neutral isopropylphenyl terminus. Herein lies the basis for unidirectional threading. Upon reduction of the macrocycle to its radical states, the ring passes over the dimethylpyridinium unit and dissociates as a result of two factors: firstly, the Coulombic repulsion between the 3,5 dimethylpyridinium unit and the ring is significantly reduced and secondly, the π- electron donor-acceptor interaction between the DNP unit and the ring is not nearly as strong as when the ring is oxidized. Re-oxidation of the ring allows the system to revert back to its fully charged state with free $CBPQT^{4+}$ and $D1^{+}$ able to proceed through another repetitive cycle.

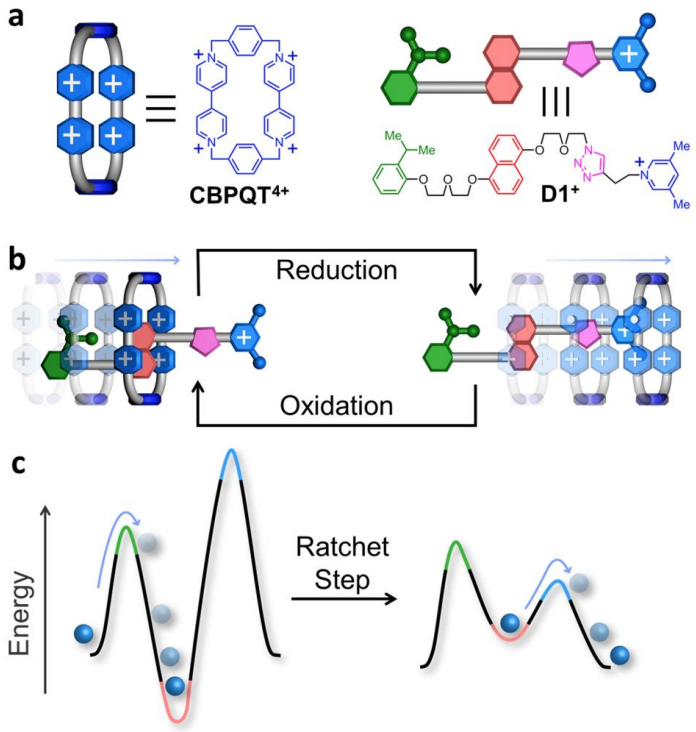

Figure 11 (a): Structural composition of [2]pseudorotaxane formed by a $CBPQT^{4+}$ macrocyclic ring and a $D1^{+}$ dumbbell comprised of sterically bulky yet neutral 2-isopropylphenyl group (green), pi-electron donating 1,5 dioxynaphthalene site (red), and a positively charged 3,5dimethylpyridinium moiety (blue). (b) Unidirectional threading of the ring upon exploitation of its redox properties. (c) Demonstration of unidirectional passage upon reduction or oxidation of the macrocycle via energy ratchet mechanism. Reduction results in the potential energy minimum increasing (red trough) and the potential energy maximum decreasing (blue peak) causing the ring to dethread directionally. Adapted from Stoddart et al [21]

Chemical, electrochemical, and optical energy stimuli have been employed to drive this system from left to right. Zinc (Zn) dust was used as the reducing agent, capable of converting $CBPQT^{4+}$ to $CBPQT^{2(\bullet+)}$ radical. The tetracationic ring was reformed by oxidation in air. When a reductive voltage of -700mV was applied to a solution of **$D1^{+}$**, **$CBPQT^{4+}$**, and methyl viologen (**V^{2+}**), a redox active organic compound, the group observed maximum absorptions for radical formation, indicating the presence of [2]pseudorotaxane [21]. After confirming that the pseudorotaxane directionally threads and dethreads using chemical and

electrochemical drivers the group aimed to establish a process via light stimulation using a photoredox reaction. They employed $[Ru(bpy)_3]^{2+}$ (bpy=2,2'-bipyridine) as the photosensitizer in the presence of phenothiazine (ptz), which acts an electron transfer mediator. The mechanism proposed is illustrated in figure 12 below [21].

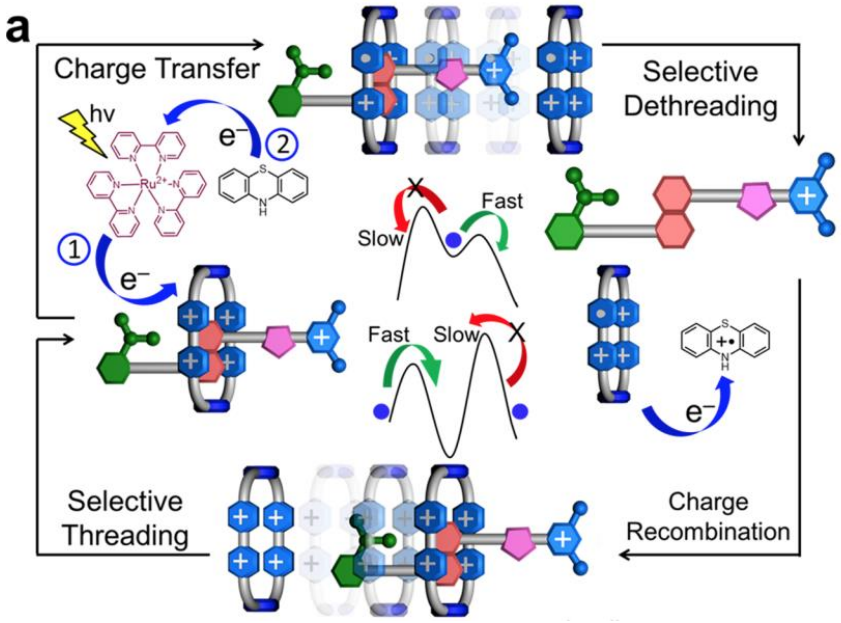

Figure 12 (a): mechanism for the photochemically induced redox-driven [2]pseudorotaxane based on macrocycle $CBPQT^{4+}$ and axle $D1^{+}$. Adapted from Stoddart et al [21]

In figure 12, $[Ru(bbpy)_3]^{2+}$ is first irradiated with 450 nm of light. Upon absorption of a photon, it is excited to its robust and long lived triplet state (^{3}MLCT metal-to-ligand charge transfer) $[Ru(bpy)_3]^{3+}$. At this point, intermolecular electron transfer occurs from the ruthenium complex to the macrocyclic $CBPQT^{4+}$component of the pseudorotaxane, which in the process reduces the ring to its radical cation $CBPQT^{(2+)(\bullet+)}$. The phenothiazine (ptz) reacts with the excited ruthenium complex, reducing it back to $[Ru(bbpy)_3]^{2+}$, all the while it

becomes oxidized and the reduced macrocycle dethreads unidirectionally. This can only occur if dethreading happens at a faster rate than the ptz^{+} is able to retrieve an electron from free $CBPQT^{2+(\bullet+)}$, because once CBPQT is oxidized back to $CBPQT^{4+}$, the psuedorotaxane regenerates, and undergoes selective threading, passing through the 2-isopropylphenyl terminus [21].

There has only been one other reported system using a photoactive moiety that upon irradiation can change the interaction of the macrocycle and axle in a pseudorotaxane type design to drive unidirectional movement. This was accomplished by Alberto Credi and coworkers who devised a system composed of a known [25] dibenzo[24]crown-8 macrocyclic ring **15** and an axle formed of a dibenzylammonium $\mathbf{14^{+}}$ recognition site with two azobenzene terminal units [26] (figure 13). The energetics of the system can be controlled via photoisomerization of the azobenzene functionality. In fact, when isomerization from $\mathbf{(E,E)\text{-}14^{+}}$ to $\mathbf{(Z,Z)\text{-}14^{+}}$ occurred, the threading and dethreading rate decreased, resulting in a loss of stability of the entire complex [26]. A second axle $\mathbf{16^{+}}$ was synthesized by the same group following previous observations in order to create a system where the macrocyclic ring **17** is able to pass through the axle at a rate between that of the E-and Z- azobenzene termini [20].

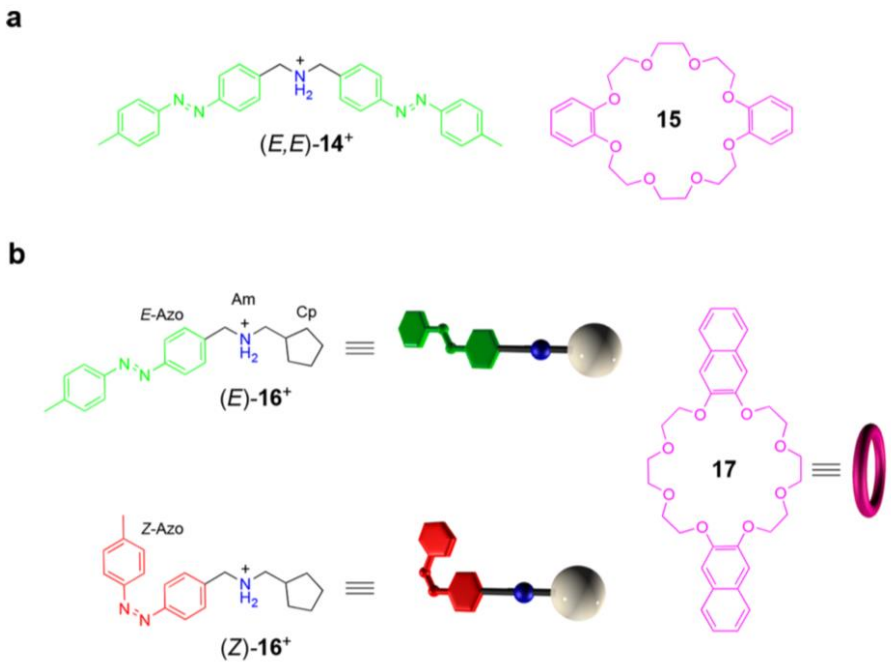

Figure 13 (a): Structural conformation of axle **14**$^{+}$ in its E,E configuration along with dibenzo[24]crown-8 macrocyclic ring. (b) Isomerization of synthesized axle **16**$^{+}$ capable of slipping into the macrocyclic ring **15** at a faster rate than that over the Z-Azobenzene moiety of **Z-16**$^{+}$**.** Adapted from Credi et al [12].

Unfortunately, in order to dissociate ring **15** from the axle to complete the threading and dethreading cycle, a chemical stimulus needed to be used as the binding affinity of the axle **16** was not altered upon photoisomerization. Consequently, to create a stronger binding interaction, macrocycle **17** was synthesized, which was able to move from one end of axle **16** to the other, clearly altering both the kinetic and thermodynamics of the system [20].

Conclusion

While scientists have yet to rival nature in the level of complexity and sophistication of molecule-based motors, they have certainly implemented various strategies towards the design of systems intended to, at the very least, emulate some of the basic characteristics of motor protein dynamics such as

processive, unidirectional, and controlled movement away from equilibrium. This has resulted in an overview of the most recent progress in the design of multicomponent synthetic systems capable of performing non-trivial mechanical movements in a directionally controlled manner, particularly through photochemical induced stimuli.

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