Functional nanomachines: Recent advances in synthetic molecular machinery

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A R T I C L E   I N F O
Article history:
Received 31 October 2017
Revised 8 December 2017
Accepted 11 December 2017
Available online 14 December 2017

Keywords:
Molecular machinery
Mechanically interlocked architectures
Non-interlocked architectures
Molecular motors
Nano-machines

A B S T R A C T
A mini-review: As the top-down approach for miniaturisation of technology reaches its inherent limitations, robust strategies to build nanoscale machinery components, which have the ability to convert an input energy into motion, from the molecular level up, become increasingly important. Nature is certainly the most proficient in the control of molecular level motion; nevertheless, many successes have been enjoyed in the pursuit of mimicking key aspects of nature’s molecular machines, including two state switches, ion pumps, unidirectional rotary motors and molecular robots that can move molecular cargo. This mini-review outlines some of the most impressive recent examples towards this end.

Biological molecular machines capable of performing motion and transport (for example F₁F₅ adenosine triphosphate (ATP) synthase and flagella (rotary), dynein/kinesin and myosin (translatory)), are integral to biological systems. Synthetic analogues could find use in nanoscale device applications such as robotics, medical diagnostics and medicine delivery, environmental remediation and high density information storage and processing amongst others. As such, synthetic chemists have taken inspiration from biological systems and have been investigating synthetic molecular machinery components for more than 20 years.

The development of synthetic molecular machinery requires control over translational and/or rotary motion (the two most fundamental movements) on command, and in a reliable and reversible manner. For the most part this has been achieved using mechanically interlocked architectures (MIAs). These interlocked systems are held together via mechanical bonds rather than more tradition covalent bonds. Two of the more prevalent types of MIAs are catenanes and rotaxanes. Catenanes consist of two or more macrocyclic rings linked via a mechanical bond whereas rotaxanes are composed of a macrocyclic ring threaded onto an axle with ‘stoppers’ blocking dethreading/dissociation at either end. Due to the mechanical bonding inherent in MIAs these molecules are promising structures for molecular machine-type applications because, in principle, they permit the controlled movement and positioning of the interlocked components with respect to one another. For their pioneering work on template methods for the synthesis of MIAs and the exploitation of some of these interlocked molecules for the development of functional molecular machines, Sauvage and Stoddart were awarded the 2016 Nobel prize in Chemistry.

As there are now many different template methods available for the synthesis of MIAs, the majority of the most impressive synthetic molecular machines to date have been MIAs. However, the generation of large, complicated, machine like interlocked systems can still be difficult. Recognizing this many groups have focused on exploiting...
Mechanically interlocked architectures

Mechanical interlocked machines are becoming more and more sophisticated. An important feature of biological molecular machinery is the ability to drive systems away from equilibrium states. An elegant MIA mimicking characteristics of biological systems such as membrane carrier proteins, which act to drive ions or small molecules against charge and/or concentration gradients, recently reported by Stoddart and co-workers. The artificial “molecular pump” produced was able to utilise a flashing energy ratchet mechanism. The pump function was based on the formation of a rotaxane through consecutive addition of cationic macrocycles, increasing the local concentration of small charged macrocycles. The structure of the pump consists of a dumbbell/thread featuring a dimethylpyridinium at one end linked to a 4,4’-bipyridinium unit, followed by an isopropylphenylene “stopper” moiety (Fig. 2). The second larger 2,6-diisopropylphenyl “stopper” was linked to the thread through a 1,2,3-triazole and a C11 alkyl chain. When the tetracationic macrocycles, cyclobis-(paraquat-p-phenylene) (CBPQT4+) and the dumbbell/thread components are combined in solution, they initially repel each other due to coulombic repulsion forces. However, upon reduction of the CBPQT4+ rings to CBPQT2+, and simultaneously the reduction of the 4,4’-bipyridinium units to 4,4’-bipyridinium* units, the stabilising radical-radical pimerisation processes promote the threading of the macrocycles onto the cationic recognition site forming thermodynamically stable tris-radical tricationic complexes. Upon oxidation of these components there are strong electrostatic repulsion forces, meaning they must be driven apart. However, dethreading was not observed as the coulombic repulsion of the two cationic sections of the thread is too high. Instead the CBPQT4+ macrocycle was forced over the so-called energetic ‘speed bump’ unit, the isopropylphenylene group, and onto the C11 alkyl chain. The threading of the CBPQT4+ rings onto the methylene chain was confirmed through proton nuclear Overhauser effect and diffusion ordered spectroscopy (NOESY and DOSY) experiments. Upon repeating the reduction process a second CBPQT4+ ring was threaded onto the [2]rotaxane generating a new high energy [3]rotaxane featuring two cationic macrocycles. Daisy chain (DC) motifs (Fig. 3a) have been reported a number of times since the first examples in the late 1990’s and are recognised as a useful tool in the realization of synthetic molecular muscles/actuators. Coutrot and co-workers recently reported a tetra-interlocked architecture (a hetero-[4]rotaxane, Fig. 3b) which comprised a [2]DC linked to two [2]rotaxanes. The system was designed to undergo two different reversible molecular motions upon alteration of the pH. The architecture was synthesised in the hope of generating multiple different motions within a single MIA, something of importance if the complexity of biological molecular machinery is ever to be rivaled. A pseudo-[2]DC was accessed via self-sorting of a dibenzo-24-crown-8 (DB24C8) macrocycle (green) bearing an oligomethylene chain beginning with an ammonium cationic recognition (pink) site to form a hermaphroditic dimer. A pseudo-[2]rotaxane is similarly prepared by threading of unsubstituted DB24C8 rings onto a thread bearing an alkylne at one end and a di-tert-butyl substituted anilinium (red) stopper group at the other, where the anilinium cation acts as a recognition site for the macrocycle. The oligomethylene chains of the pseudo-[2]DCs are terminated by azide groups allowing them to undergo a copper-catalysed azide-alkyne cycloaddition (CuAAC) with the supplied alkylene. This process results in both the formation of a tetra-interlocked architecture and simultaneously generated a third unoccupied recognition site on each thread component. Methylolation of the 1,2,3-triazole units generated cationic triazolium sites (blue). The DB24C8 macrocycles have the strongest interaction with the ammonium groups as they possess a +1 charge and two protons with which to hydrogen bond with the oxygen atoms of the cycle. The N-methyltriazolium stations however do not have the ability to hydrogen bond and therefore it was rationalized the macrocycles will only reside there upon deprotonation of either the ammonium or the anilinium sites. The anilinium sites also possess a +1 charge and two protons but are more easily deprotonated than the ammonium sites, therefore under basic conditions (1M NaOH) the unsubstituted DB24C8 units, initially at the anilinium stations, will be shuttled to the triazolium stations. NMR studies confirmed that the DB24C8 can be shuttled from the anilinium to the triazolium stations via cycling between acidic (HCl) and basic (1M NaOH) conditions. However, disappointingly the authors could not find appropriate conditions to effect the extension and contraction of the [2]DCs component of the hetero-[4]rotaxane machine. The model [2]DC that does not feature the extra DB24C8 macrocycles was able to extend and contraction when treated with acid and base. However, the ammonium stations of the hetero-[4]rotaxane machine could not be deprotonated despite treatment with a vast excess of sodium hydroxide. The authors suggest that a combination of steric and electronic factors make the deprotonation impossible in their system. The work clearly shows that as MIAs become more complicated, control over the machine like molecular motion can be more difficult to design.

Chiu and co-workers have reported on the first discrete cyclic [3] and [4]DCs, which exhibited extension and contraction motions in two and three dimensions respectively (Fig. 4). These “molecular muscles” were attained through synthesis of a monomeric species featuring a series of rigid thread components separating a 2,2'-bipyridine (bpy) binding site (pink) perpendicular to the thread and a binding pocket within a pyridyl macrocycle (orange) which was co-linear to the thread. A terminal amine group at the opposite end of the thread to the macrocyclic unit allowed addition of a stopper unit (blue) and simultaneous formation of a diphenylurea recognition site (green). Addition of an equimolar amount of Zn2+ ions to the monomer templated the formation of the interlocked systems. Subsequent reaction with bis(trifluoromethyl)isocyanate capped the thread component capturing both the [3] and [4] MIAs, depending on the length and flexibility of the linker unit. The rigidity of the threads meant that the smaller [2]DCs could not form, unless the linker, X, was made long enough as to allow sufficient bending of alkynyl units. The synthesis process generated the ‘extended’ molecular muscles as the Zn2+ ions were bound between the 2,2’-bpy and macrocyclic units. Removal of the Zn2+ ions (using N,N,N’,N”-tetraakis(2-pyridylmethyl)ethylenediamine (TPEN)) led to the formation of the con-
tracted co-conformers as shown by $^1$H NMR spectroscopy. With the Zn$^{2+}$ ions removed the pyridyl macrocycles shuttled to the urea moieties of the thread and hydrogen bonded with the ethylene glycol units of the macrocycles stabilizing the contracted co-conformation. Reintroduction of Zn$^{2+}$ ions established the initial extended co-conformation and the process could be cycled back-and-forth. The percentage variation in distances between the urea groups in the contracted and extended forms were found to be 23 and 36% for the [c3] and [c4]DCs respectively; comparable to the value of 27% in human muscle tissue.

There are now many examples of DC motifs in the literature but very few translate the molecular-level muscle-like motions into macroscopic motion. Recently Giuseponne and co-workers devised a method to polymerise, via hydrogen bonding motifs, a [c2]DC (Fig. 5). A pseudo rotaxane [c2]DC was formed through recognition of alkyne substituted crown ether macrocycles with cationic secondary ammonium sites. The mechanical bond captured using the CuAAC “click” reaction to add an azide featuring DAD (donor-acceptor-donor) hydrogen bonding motif which was large enough to act as the stopper group. Methylation of the 1,2,3-triazole units formed during the “click” reaction provided a second cationic station within the [c2]DC. $^1$H NMR studies confirmed that the addition of acid or base to the [c2]DC would lead to reversible extension and contraction of the “muscle”. Molecular modeling suggested that the reversible motion of the [c2]DC monomer generated an approximately 1.2–1.6 nm change in length. Addition of a ditopic
bis(urate) linker molecule that features a complementarity ADA hydrogen motif resulted in the formation of supramolecular [c2] DC polymers (Fig. 5). It was also shown, using AFM and TEM that the polymers formed fibers. TEM experiments suggested that the fibers maintained the ability to reversibly extend and contract when exposed to acid and base meaning the actuation was now greatly exaggerated as many rotaxane dimers were joined.

Using the same type of [c2]DC monomer Giuseponne and co-workers have generated covalent cross linked polymers and showed the gels that result can be reversibly expanded and contracted when treated with acid and base.47

The impressive examples discussed until now have all been generated from rotaxane type architectures. However, catenanes have also been exploited to develop sophisticated synthetic molecular machines. Leigh and co-workers have produced a chemically fueled molecular motor exhibiting directionality which is autonomous (Fig. 6).48 The [2]catenane system features a large macrocycle (the track, shown in black) that contains two fumaramide recognition sites (green) and a smaller benzylic amide macrocycle (blue). The interaction of the benzylic amide macrocycle with the two fumaramide recognition sites is energetically equivalent as such there are two equally low energy positions the smaller macrocycle will move between powered via Brownian motion (one station is deuterated for 1H NMR discrimination). Neighboring the fumaramide recognition sites are fluorenyl ‘stopper’ groups which exhibit substantial steric bulk meaning the small macrocycle cannot pass between the two recognition sites while both stopper groups are attached. The stopper groups are attached and cleaved via different mechanisms but both reactions occur under basic conditions. The key to this system displaying unidirectional motion is the rate constant for the attachment reaction which is altered by the proximity of the small macrocycle to the reaction centre. When the small macrocycle is close to one of the stopper attachment sites the steric hinderance lowers the rate of the attachment reaction at that site (i.e. $k_{\text{close-attach}} < k_{\text{far-attach}}$). Meanwhile the cleavage mechanism is initiated via proton extraction from the tertiary fluorenyl carbon which is five bonds remote from the ‘track’ meaning the cleavage rate constant is unaffected by the small macrocycles presence (i.e. $k_{\text{close-cleave}} = k_{\text{far-cleave}}$). Together this leads to a system where the detachment/re-attachment

![Fig. 3. a) Generic cartoon representation of a [c2]daisy chain exhibiting two recognition sites, one of which is stimuli responsive, and b) chemical structure and cartoon representation of Coutrot and co-workers’ tetra-interlocked MIA. i) acid, ii) base, iii) excess base.](image-url)
acid (Cl3CCO2H), the ammonium site is protonated, becoming a hydrazone stopper group. When the [2]catenane is treated with a disulfide stopper group and a methylated triazolium station incorporated into it, there is an information ratchet. Upon cleavage of both stoppers, the small macrocycle is occupying the far recognition site. This results in a 180° rotation of the motor to produce one of two isomers after one irradiation. 

Non-interlocked machines

While many of the most impressive synthetic molecular machines to date have been MIAs, they tend to come along with various synthetic challenges. As such other workers have looked to exploit non-interlocked systems to design functional synthetic machines. While many groups have contributed to the area, as outlined in the introduction the pioneering work of Feringa and co-workers showed that suitably designed overcrowded alkenes could be used to generate light-driven unidirectional molecular motors and lead to Prof. Feringa sharing the 2016 Nobel prize in Chemistry. Feringa and co-workers have devised and reported a number of light-driven unidirectional rotary motor molecules comprising overcrowded alkenes.

These rotary motors exhibit helicity (P or M) and/or stereocentres (R or S), with these features largely credited with being the key factors in generating unidirectional rotation. These molecular motors are able to undergo E/Z isomerisation upon irradiation with ultraviolet light, followed by thermal helix inversion (THI). These consecutive processes, allow for overall unidirectional rotation where the central chirality of the rotor determines the direction of rotation. In 2015 Feringa and co-workers reported a ‘third generation’ molecular motor (Fig. 7) comprising two overcrowded alkenes such that the central carbon atom is no longer chiral but maintains a pseudo-asymmetry due to the possibility of either an E or Z alkene either side of the molecule. When this motor was irradiated with 365 nm light at 173 K, one of the two alkenes underwent photocatalysis E/Z isomerization, and then subsequent THI of that alkene upon warming to room temperature. All of the isomers (Fig. 7) of the achiral motor were readily separated using supercritical fluid chromatography. Then, the R(ZM)(E,P) isomer was taken through a reaction cycle. 1H NMR and CD experiments showed that this process gave a mixture of two isomers after one ‘cycle’ performed on a single isomer (e.g. one ‘cycle’ produced both the R,E,E and R,Z,Z isomers starting from pure R(ZM)(E,P)). This confirmed that for one irradiation and THI cycle just one alkene of a rotor would isomerise, resulting in approximately one quarter rotation relative to the central ‘stator’, followed by a one half rotation in the same direction upon THI. The rotor can therefore undergo repeated unidirectional rotations upon irradiation with UV light at room temperature. Despite the described system having no selectivity for which alkene of the rotor undergoes isomerism in a given ‘cycle’, this work demonstrates that chirality is not necessary for unidirectional rotation; however some form of asymmetry seems necessary.

More recently Feringa and co-workers reported a molecular motor capable of locked synchronous unidirectional rotation, moving in an analogous manner to the Moon around the Earth, as only one side of the Moon always faces us. The motor design is based on the second generation overcrowded alkene motors, with a fluorene stator and an indanyl rotor with an appended naphthalene moiety (Fig. 8). In order to achieve locked synchronous rotation, two energetic barriers had to be balanced; the barrier to biaryl rotation (BR) of the naphthalene rotor had to be low enough to occur at reasonable temperatures. This allowed the system to move to the ammonium station via the hydrazone site. When the system is then treated with base the amine becomes deprotonated and the triazolium station becomes the preferred binding site. However, now under basic conditions the hydrazone stopper group is kinetically inert, while the disulfide barrier becomes dynamic, leading to migration of the small macrocycle to the triazolium site, completing a 360° rotation. Each repeated chemical fuel input cycle allows for, mostly (87%) unidirectional rotary motion.

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unidirectional rotation of the naphthalene moiety about the stator through the photochemically driven cycles without allowing the naphthalene to rotate such that the opposite face of the biaryl rotor was facing the stator. The mode of rotation was supported by Density Functional Theory (DFT) calculations and confirmed primarily by circular dichroism and variable temperature $^1$H NMR combined with Eyring analyses.

Giuseponne and co-workers incorporated Feringa’s second generation molecular motor into a polymer gel and showed that irradiation leads to coiling/contraction of the gel network. The contraction was confirmed using AFM microscopy and small-angle X-ray scattering (SAXS) experiments. The light driven process lead to the collapse of the gel but it was not reversible. Giuseponne and co-workers have gone on to show that by incorporating a light sensitive modulator subunit within the “motor-gel” they can contract and then expand the gel network using different wavelengths of light.

Very recently, light driven molecular motors developed by Feringa and co-workers were adapted by Tour et al. for the purpose of mechanically opening cell membranes. The nanomotors were synthesised with peptide sequences appended on each side of the stator unit. Two different peptides were utilised, one chosen for its selective interaction with particular transmembrane receptors of PC-3 human prostate cancer cells, and the other with the protein GRP78, which targets receptors on PC-3 human prostate cancer cells. A variety of other nanomotors were synthesised as control models, including two with different pendant fluorophores on the stator to track their movement, two with smaller molecular sizes, one with a stator but no rotor, and one with a significantly slower motor. UV-light activation of the nanomotors with fluorophores in the presence of live cells, caused nanomechanical induced entry into the cells, as evidenced by fluorescence imaging. One of the smaller control nanomotors was shown to significantly increase cell necrosis upon UV exposure while the other did so to a lesser extent, presumably due to lessened cell membrane interaction. The control nanomotors which had no rotor, and which underwent very slow rotations did not increase the rate of cell death upon UV exposure. Additionally, the authors irradiated the peptide substituted nanomotors in the presence of the PC-3 cells and also untargeted control cells. The motors bearing sequences known to interact with the protein GRP78, showed increased necrosis of PC-3 cells with no increase for the control cells during UV irradiation, however the other peptide substituted motors showed no selectivity. This work demonstrates how carefully designed molecular machines could, one day, selectively interact with cells within living organisms and be used to kill diseases with minimal harm to the host organism.

While the non-interlocked systems above have generated unidirectional rotation of small molecular entities exploiting light as the stimuli, there are few examples where this was achieved through use of chemical stimulus. Feringa and co-workers have also reported a unidirectional molecular motor based on a redox cycle of palladium, driven by chemical input. The motor molecule itself possesses a sterically crowded C–C bond between two aryl groups due to the ortho-substituents which have dual functions in hindering rotation of the bond, but also specific interactions with palladium (Fig. 9). The system exists as two atropisomers ($S$, $M$) and ($S$, $P$), where the $S$ denotes the chirality of the sulfur atom and $M$ and $P$ denote the chirality about the biaryl C–C bond. The system was shown to act as a molecular motor as the ‘upper’ aryl group (blue) could be rotated through chemical stimulus. Upon addition of palladium(II) to the ($S$, $M$) atropisomer, the sulfur atom binds the palladium ion, acting as a directing group for the C–H insertion of the palladium in the ortho position of the ‘upper’ aryl group. Before C–H insertion, the barrier to rotation about the biaryl C–C bond was significant, but once the palladium(II) complex forms, the barrier is greatly reduced. Furthermore, it was shown the ($R$, $M$) isomer (note the palladium takes precedence, therefore changing the stereochemical
assignment about the sulfur) would form preferentially in equilibrium with the \((R, P)\) isomer. Upon reduction of the palladium (II) using a hydride source \((\text{NaBH(OAc)}_3)\) the \(\text{C–H}\) bond reformed, giving the \((S, P)\) isomer, along with elimination of the palladium (0) species. This process corresponds to a 180° rotation of the motor and was achieved in 45% yield. To complete the 360° cycle and return to the \((S, M)\) rotamer, palladium(0) was reintroduced (using \(\text{Pd}_2\text{dba}_3\) where \(\text{dba} = \text{dibenzylideneacetone}\)), the sulfur ligand directs the oxidative addition of the palladium across the ortho \(\text{C–Br}\) bond of the ‘upper’ rotor unit, again making rotation about the biaryl \(\text{C–C}\) bond possible. Satisfyingly the equilibrium set up between the \((R, P)\) and \((R, M)\) atropisomers lies towards the \((R, M)\) isomer, meaning upon reintroduction of the \(\text{C–Br}\) bond via addition of \(\text{N-bromosuccinimide (NBS)}\), the motor achieved a 360° unidirectional rotation where the second 180° turn occurred in 42% yield. The system is not autonomous as it requires the input of the chemical fuels to change the Pd oxidation states. However, further optimization of the reaction processes and chemical fuels may lead to fully autonomous unidirectional rotation in the future.

*Fig. 6.* Leigh and co-workers’ first autonomous chemically fueled, unidirectional molecular motor.
The development of artificial molecular transporters is an important and thought-provoking area in this field as they inherently require a system where two separate functions must be able to occur within the device independently of each other. There have been several recent publications describing molecular transporters which included one based on a bistable rotaxane from Credi and co-workers,\textsuperscript{56} and a light switchable device from Feringa and co-workers.\textsuperscript{57} Feringa’s light driven transporter is capable of transferring an acetyl group from a phenol moiety on one end of a stator to a benzylic amine group 2 nm removed. This is achieved via a thiol terminated ‘arm’ bound to the rotor unit of a second generation overcrowded alkene. The process involves three steps; phenol to thiol acetyl transfer followed by light driven $E/Z$ isomerization and THI of the central alkene which allowed repositioning of the acetyl cargo over the amine functionality. Finally thiol to amine transfer completed the relocation. While this system is elegant and produces minimal waste chemicals, reversibility is not demonstrated. Leigh and co-workers have reported\textsuperscript{58} a molecular ‘robotic...
arm’, able to move a cargo from one platform to another, selectively and reversibly through manipulation of pH (Fig. 10). The stator, with an aldehyde ‘platform’ (red and orange) at either end, was linked to the ‘robotic arm’ (pink) through a central quinolone unit (purple) via a hydrazone linkage to form a pH-responsive rotor unit developed by Aprahamian and co-workers.59 The rotor may adopt one of two conformers where either the pyridine (E isomer) or the ester (Z isomer) of the ‘arm’ will participate in hydrogen bonding with the hydrazono proton along with the quinolone nitrogen on the stator. Control over this E/Z isomerisation is achieved through selective protonation of several functionalities in the system, allowing control over the position of the ‘arm’ over one of the two platforms. 1H NMR analysis allowed the loading, transport, and unloading processes to be followed conveniently as one of the aldehyde platform was deuterated in order to distinguish which of the platforms the cargo was bound to, or if it was bound only to the ‘arm’. The cargo (black) was initially shown to be able to be transported from the deuterated station to the other in three steps and 79% yield. The first of which is kinetic disulphide formation between the end of the robotic arm and the cargo. This macrocyclisation was followed by treatment with 70 eq. of triflic acid which protonates the hydrazono switch, along with facilitating acyl hydrazono exchange, allowing for detachment of the cargo from the station and for rotation of the robotic arm placing the cargo on the other station (red). NMR spectroscopy indicated that this step actually produces a 17:83 mixture of the transporter with the cargo on the first (orange) platform to the transporter with the cargo on the red platform. The cargo can then be detached from the robotic arm upon reduction of the disulphide bond, simultaneously restoring the switch. The reverse process could be completed in 85% efficiency over the three associated steps. Firstly oxidation with iodine reforms the disulphide linkage. Treatment with 5 eq. of triflic acid allowed for the return of >90% of the cargo to the first station, and subsequent reduction of the disulphide bond releases the cargo from the robotic arm.

More recently Leigh and co-workers have modified and repurposed the design of the transporter in order to achieve stereodivergent synthesis through mechanical manipulation of a substrate.60 This programmable molecular machine bears a terminal alkene on the ‘robotic arm’, which allows an α,β-unsaturated aldehyde substrate to be attached, and then positioned over one of two ‘stations’ which feature chiral activating sites of opposite handedness (prolinol silyl ethers). An iminium- or enamine-promoted reaction is able to be initiated through condensation of the substrate with an activating site. The choice of station at each of the asymmetric tandem additions of a nucleophile and an electrophile to the α,β-unsaturated aldehyde determines the stereochemistry of the eventually output product. The same organocatalysis process (without the mechanical directionality) typically only allows access to the syn diastereoisomers, whereas this programmable control allows selective production of any of the four stereoisomeric products, including the anti-isomers.

The vast majority of synthetic machine systems are fully organic in design.30–35 However, metal ions offer different stereochemical preferences to carbon and can also provide interesting redox and/or photophysical properties. As such more and more metal containing machine systems are beginning to appear in the literature.12,36

Sauvage and co-workers have exploited the coordination preference of metal ions to affect the synthesis and controlled molecular motion of MIAs, most notably catenanes.12,36 Similar large amplitude motions in non-interlocked architectures are far less common. Sauvage and co-workers reported a non-interlocked architecture where a 78-membered macrocycle (Fig. 11) was able to be contracted and elongated through either the choice of metal ion, or through the electrochemistry of copper ions.61 The large macrocycle exhibits two bidentate diphenylphenanthrolinone (dpp) binding pockets opposite one another and two terpyridine (terpy) binding pockets oriented perpendicularly to the dpp sites. Addition of one equivalent of Cu(I) ions resulted in formation of the tetrahedral bis-dpp copper(I) complex and thus a ‘figure-of-eight’ shaped entity. Addition of Fe(II) ions results in the octahedral bis-terpy iron(II) complex where the macrocycle has compressed in the perpendicular dimension. Both metal ions could be removed (KCN) and replaced by the other reversibly and quantitatively. Utilising the differing coordination geometry preferences of Cu(I) (tetrahedral) and Cu(II) (5 or 6 coordinate) ions, it was also shown that the reversible electrochemistry of copper ions would affect the same orthogonal contraction/elongation process as the copper ions switched between the different ligand moieties upon oxidation and reduction (Fig. 11b).

Several groups have examined using metals ion as “molecular ball bearings” in machine like systems. Designs based on including metalloccenes, carboranes and lanthanide bis-porphyrins and piano-stool type complexes have all been examined.30–35

Rapenne and co-workers have developed a ruthenium based rotor which can perform unidirectional rotation in both clockwise and anticlockwise directions, through use of a scanning tunneling microscope (STM) tip (Fig. 12).64 The rotor consists of a tripod base (blue) able to bind to a gold surface through thiol linkages (red). On top of the tripod stator a ruthenium ion (dark red) is bound through three coordinating nitrogen atoms. The remaining coordination sites are occupied by a cyclopentadienyl ring rotor unit (dark red) forming a ‘half-sandwich’ complex. Four of the five linear ‘arms’ on the cyclopentadienyl ring are terminated with redox active ferrocene units (orange), while the fifth is truncated, terminating in a methyl group. The rotor unit will rotate freely in both directions at sufficiently high temperatures, but this rotation slows at lower temperatures.
Once grafted to an Au(111) surface, an STM tip was brought within a short enough distance so as to allow electrons to tunnel between the tip and a rotor ‘arm’ upon application of a sufficient potential. When tunneling is allowed to occur between the STM tip and a ferrocene terminated ‘arm’, mostly anticlockwise rotation is observed, and when tunneling occurs through the truncated ‘arm’ only clockwise rotation of the rotor unit is observed. This is explained through the use of DFT calculations which produced a ‘saw tooth like’ potential energy curve when plotted against rotation angle. Excitation of an electron results in population of different LUMO orbitals depending on which ‘arm’ the STM tip is positioned over and thus the saw tooth like potential curve favours rotation in the opposite direction for the different ‘arms’. The authors suggest that asymmetry in the rotation energy potential

Fig. 10. Leigh and co-workers’ molecular ‘robotic arm’, undergoing the reversible molecular motion which allows the transport of cargo.

Fig. 11. a) Sauvage and co-workers’ 78-membered macrocycle and, b) switching of shape between vertically and horizontally disposed complex of tetrahedral Cu(I) (red) and octahedral Cu(II) (green), respectively.
and inelastic tunneling effects enable the unidirectional motion in both clockwise and anticlockwise directions by selectively exciting different subunits of the motor.

Last decade Bosnich and Crowley began to devise systems featuring 1,1'-diaryl substituted ferrocene derivatives, which exhibited π-stacking of the two ‘arms’ in the syn-conformer. These could be stimulated to extend into the anti-conformer upon application of a stimulus, harnessing the ‘ball bearing’ feature of ferrocene and exploiting it for reversible controlled molecular motion (Fig. 13).

Initially a system involving 1,1'-bis[3-pyridyl]ferrocene was synthesised with the switching mechanism proposed to be protonation of the ring nitrogen causing coloumbic repulsion of the two ‘arms’. However, it was found that protonation of both nitrogens did not cause the system to assume the anti-conformer, leading to the conclusion that the repulsion of a 1+/0 system was not sufficient to overcome the attractive π-system interactions of the ‘arms’. A second generation system was thus developed involving the replacement of one of the 3-pyridyl ‘arms’ with a 2,2'-bipy unit. This allowed for complexation of a palladium(II) ion, creating a 1+/2+ system and therefore increasing the repulsive forces between the ‘arms’. The extension/contraction process here was achieved through exchanging the two substituents bound to the palladium ion. In order to assume the contracted syn-conformer, chloride ions were utilised to create a neutral ‘arm’ such that the system became 1+/0, and the ‘arms’ would preferentially undergo π-stacking. Upon addition of silver, the chloride ions were removed and subsequently replaced with pyridine, allowing the system to reassume the anti-conformer due to the 1+/2+ charge repulsion.

Building on that initial work Crowley and co-workers have developed electrochemically switchable ferrocene rotor systems. In 2015, Crowley and co-workers reported an electrochemically induced expansion and contraction process within a 1,1'-bipyridyl disubstituted ferrocene rotor, which in its native state exhibited π-π stacking interactions between the 2,2'-bipy ‘arms’ (Fig. 14a). More recently, the same authors reported a larger triple tiered di-ferrocene folding ruler (Fig. 14b), able to operate under analogous conditions. Addition of copper(I) ions bound by 6,6'-dimesityl-2,2'-bipy ligands, the heteroleptic bis-copper(I) extended complex shown was generated as the steric bulk of the dimesityl groups prevent formation of the corresponding homoletic complexes. Oxidation of the copper ions to Cu(II) alters the coordination sphere preference of the metal ion from tetrahedral to a higher coordinate sphere. By supplying a tridentate ligand (terpy) in solution, it was shown the copper ions, upon oxidation, would leave the 2,2'-bipy units of the ferrocene rotor in favour of terpyridine to form the 5-coordinate copper(II) complex, and allow the rotor to adopt the contracted syn-state. Reversible molecular extension and contraction is thereby generated upon repeated oxidation/reduction cycles of the copper ions with no degradation of the system.

Conclusion

As outlined in this mini-review the level of sophistication and elegance of many synthetic molecular machines has continued to rise over the past few years. Additionally, the award of the 2016 Nobel Prize in chemistry to Sauvage, Stoddart and Feringa for their pioneering contributions to this young field has further increased the visibility of the area. While there are now many different functioning designs of switches and motors reported in the literature efforts to develop new systems are still prevalent. However, simply focusing on new types of synthetic machines will not necessarily lead to applications of these systems. In order for the vast potential of these machines to be fully realized efforts need to turn to incorporation of these nano-machines into condensed phases via either attachment on surfaces or dispersion in polymer/gel networks. This should allow for the molecular level motion of the machines to be harnessed to perform macroscopic work. Additionally, efforts to design systems that operate far-from-equilibrium should also be
pursued. The future is bright and further exploration and innovation into controlling motion at these tiny length scales, will likely lead to novel technological solutions in the near future.

Acknowledgments

JAF thanks the University of Otago for a Ph.D. scholarship. JDC thanks the Marsden Fund (Grant no. UOO1124) and the University of Otago (Division of Sciences Research Grant) for supporting this work. The authors thank the University of Otago for additional funding.

References

15. Denis M, Goldup SM. 2017, 1, 0061.

Fig. 14. Schematic of electrochemical expansion and contraction of Crowley’s ferrocene-based molecular actuators (a) double tier and (b) triple tier. Hydrogen atoms and counterions of solid state structures and terpyridine omitted for clarity.