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PERSPECTIVE

Molecular Machines with Bio-Inspired Mechanisms

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The widespread use of molecular-level motion in key natural processes suggests that great rewards could come from bridging the gap between the present generation of synthetic molecular machines—which by and large function as 'on'/'off' switches—and the machines of the macroscopic world, which utilize the synchronized behavior of integrated components to perform more sophisticated tasks than is possible with any individual switch. Should we try to make molecular machines of greater complexity by trying to mimic machines from the macroscopic world, or instead apply unfamiliar (and no doubt have to discover or invent currently unknown) mechanisms utilized by biological machines? Here we explore some of the advances made to date using bio-inspired machine mechanisms.

molecular machines | molecular motors | catenanes | rotaxanes

Introduction – Technomimetics vs Biomimetics

There are two, fundamentally different, philosophies for designing molecular machinery.[1] One is to scale down classical mechanical elements from the macroscopic world, an approach advocated in many of the Drexlerian designs for nanomachines[2] and also the inspiration behind 'nanocars',[3-7] 'molecular pistons',[8] 'molecular elevators',[9] 'molecular wheelbarrows'[10] and other technomimetic[11] molecules designed to imitate macroscopic objects at the molecular level.[1] An advantage of this approach is that the engineering concepts behind such machines and mechanisms are well understood in terms of their macroscopic counterparts; a drawback is that many of the mechanical principles that complex macroscopic machines are based upon are fundamentally inappropriate for the molecular world.[1,12]

An alternative philosophy is to try to unravel the workings of an already established nanotechnology, biology, and apply those concepts to the design of synthetic molecular machine systems. A potential upside of this, biomimetic, approach is that such designs are clearly well-suited to functional machines that operate at the nanoscale, even when limited, as nature is, to the use of only 20 different building blocks (amino acids), ambient temperatures and pressures, and water as the operating medium. However, a major issue in pursuing this second strategy is that the only 'textbook' we have to follow is unclear: biological machines are so complex that it is often difficult to deconvolute the reasons behind the dynamics of individual machine parts. How and why does each peptide residue move in the way it does in order for kinesin to walk along a microtubule, which conformational, hydrogen bonding and solvation changes are necessary to bring about transport and which only occur as a consequence of other intrinsically required intramolecular rearrangements? Applying fundamental principles deduced from small-scale physics and biomachines is the approach our group has adopted in building molecular machines over the past two decades.[13] Here we outline progress on this path to synthetic nanomachines, the application of bio-inspired mechanisms to the design of molecular machines.

Simple machines

Since Stoddart's invention of the switchable molecular shuttle (Figure 1A),[14] chemists have used molecular switching to perform a variety of 'on'/'off' tasks with synthetic mechanically interlocked molecules.[15-17] Catenane and rotaxane switches have been shown to act as bits in molecular electronics,[18,19] and used for chiroptical switching,[20] fluorescence switching,[21] the writing of information in polymer films,[22] in controlled release delivery systems,[23] switchable catalysts[24] and as 'molecular muscles'[25,26]. However, in order to make molecular machines that can perform more complex tasks it is necessary to integrate the dynamics of individual molecular machine components in a way that achieves more than just the sum of the respective parts.

Compound machines – from switches to ratchets

Prior to the introduction of kinematic theory,[27] scientists and engineers considered there to be six different types of simple mechanical machines.[28] These are the three Archimedian simple machines[29]—the lever, pulley and screw—plus the wheel-and-axle (including gears), inclined plane and wedge. Connecting 'simple machines' in such a way that the output of one provides the input for another can integrate their mechanisms and produce 'compound machines' capable of performing more complex tasks. For example, a pair of scissors can be considered a compound machine consisting of levers (the handles and blades pivoting about a fulcrum) connected to wedges (the cutting edges of the blades). Because matter behaves so differently at different length scales, several types of simple machine cannot perform the same function they execute at macroscopic scales in the low Reynolds number and Brownian-motion-dominated environment that molecular-sized machines operate in. An inclined plane, for example, has no mechanical advantage nor effect on the motion

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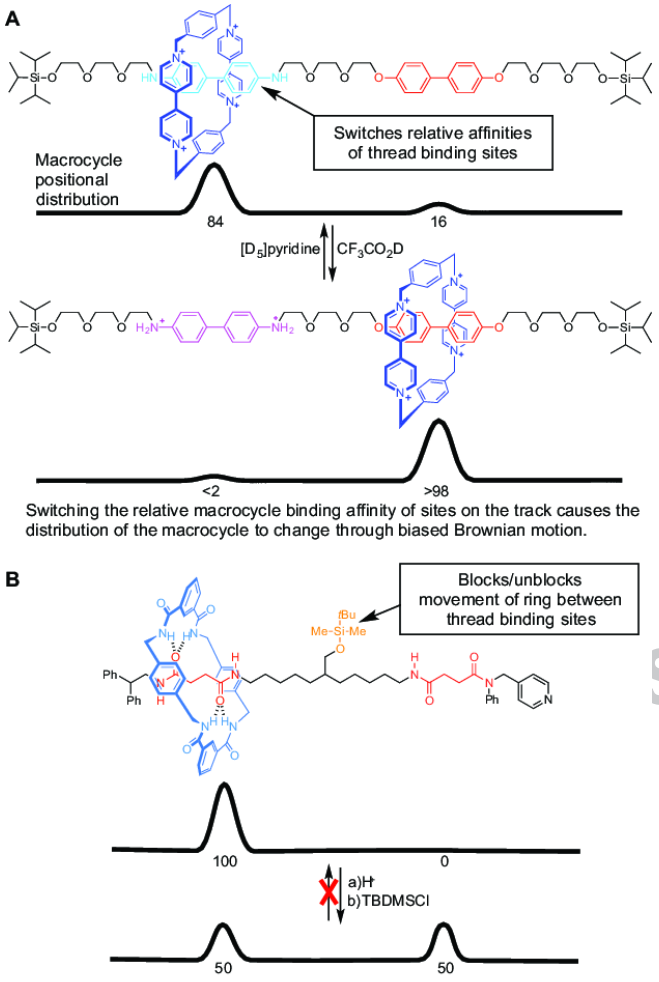

Fig. 1. Simple molecular machine mechanisms. (A) Switching of the thermodynamically favored ring position in a molecular shuttle,[25] a process used in numerous[1,13-26] functional rotaxane switches. (B) Blocking/unblocking of the ring movement between the compartments of a rotaxane.[30] Both actions result in biased Brownian motion of the ring along the track. However, note that the consequence of the switching operation in (A) (i.e. the change in the distribution of the macrocycle) is undone by reversing the switch state, whereas the result of the unblocking action in (B) is not undone by simply re-attaching the blocking group.

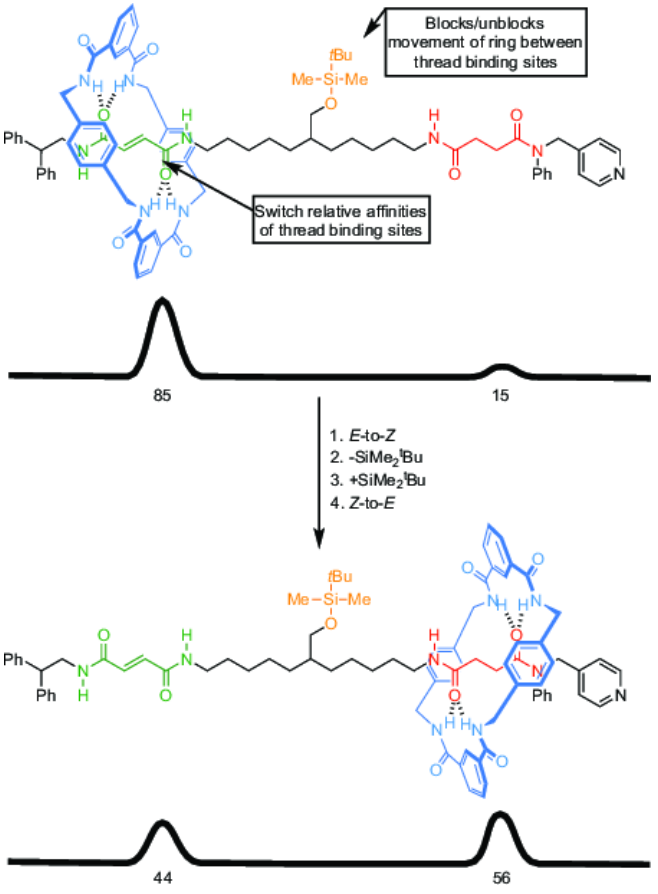

Fig. 2. A compound molecular machine.[30] Note that the thread is structural identical in both states of the machine shown, only the distribution of the macrocycle differs. Combining (and synchronizing the operation of) a switch for the thermodynamically favored position of the macrocycle on the axle with the attachment/release of a blocking group enables the macrocycle distribution to be driven away from its equilibrium value, a task that cannot be accomplished by a simple machine process.

of a molecular object; it is the height of an energy barrier, not its shape, that determines the ease (i.e. rate) at which a barrier to molecular motion is overcome.[1]

In a regime where inertia and momentum are irrelevant in mechanical terms, the basic mechanisms of molecular machines include switching of relative binding affinities at different sites and modifying the kinetics for changes of position of components that occur by random thermal motion (Figure 1), as well as binding-release mechanisms, catalytic action, etc. To produce compound molecular machines capable of more advanced task performance than simple molecular machines one can follow a similar strategy to that of making compound machines in the macroscopic world, namely connect the actions of simple molecular machines in ways that the output of one machine action provides an input for the next.

The first such compound molecular machines were introduced over the period 2003-2007.[30-33] An example is the rotaxane shown in Figure 2.[30] This combines the switching of the thermodynamically favored position of the ring (brought about by *E-Z* isomerization of the olefin binding site) with steric blocking of ring movement (caused by the presence of the silyl ether). By synchronizing these two simple machine processes (1. *E*-to-*Z* isomerization, 2. removal of the silyl ether, 3. re-attachment of the silyl ether, 4. *Z*-to-*E* isomerization) it is possible to achieve something that neither of the individual machine processes can accomplish in isolation, namely drive the macrocycle distribution away from its equilibrium value of 85:15 (*fumarmide*:*succinamide occupation*) to 44:56 (*fumarmide*:*succinamide occupation*). The profundity and generality of this outcome should not be underestimated: Simply removing the terminal stopper groups creates a molecular pump; connecting the ends so that the output of the machine mechanism becomes the next input creates a rotary motor. The same motor-mechanism is responsible for each type of machine.

A similar combination of switching of the relative affinity of the ring for different sites on an axle, with subsequent addition of a blocking group to lock in the change of position of the ring, was

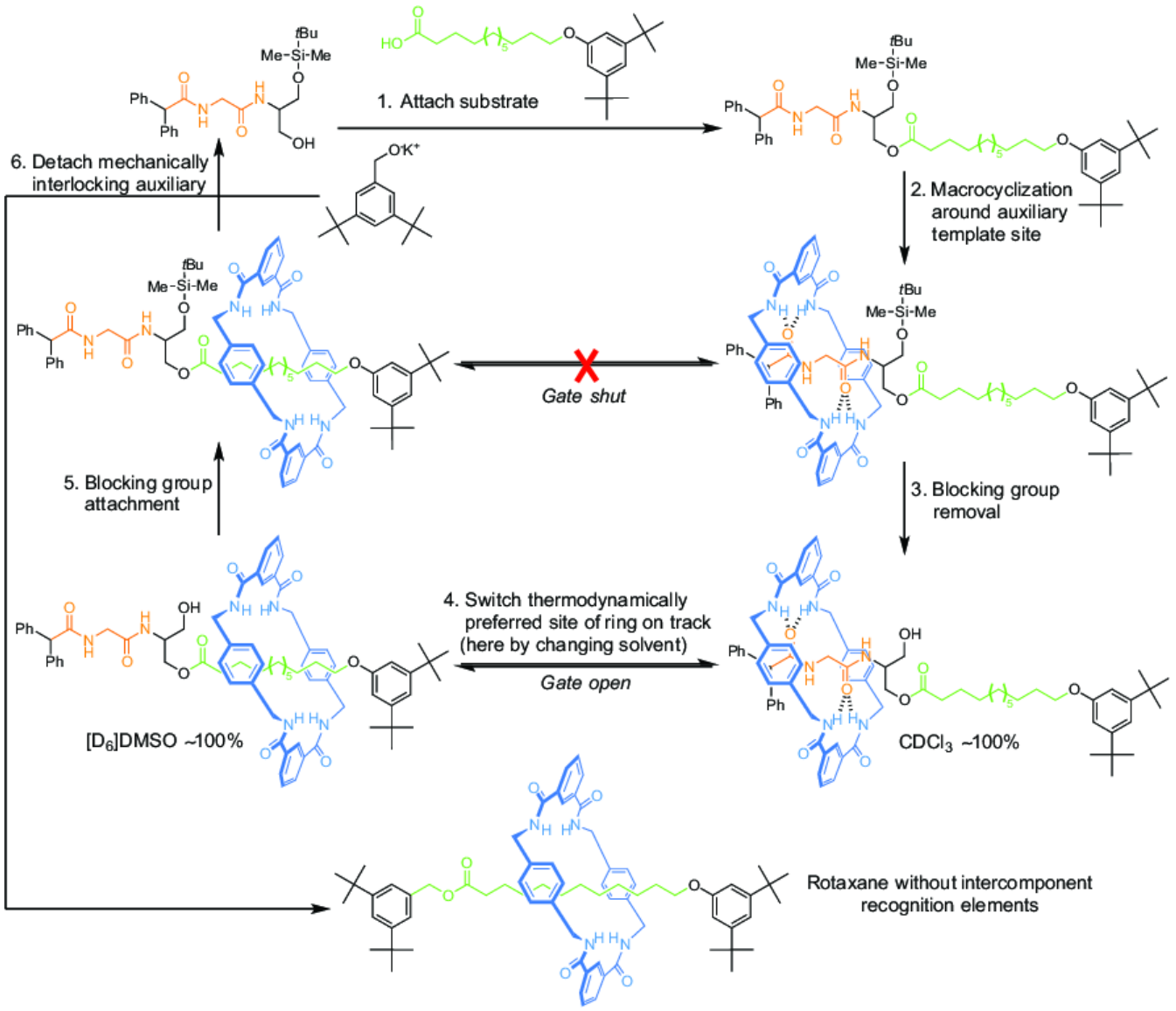

Fig. 3. Synthesis of a [2]rotaxane without intercomponent recognition elements by ratcheted transport of a macrocycle along a track.[34] Efficient synthetic strategies to mechanically interlocked compounds without recognition elements were otherwise unavailable prior to the invention of active template synthesis.[35,36]

used to synthesize rotaxanes without permanent recognition elements between macrocycle and thread (Figure 3).[34] Hydrogen-bond-directed assembly of a benzylic amide macrocycle around a peptide 'mechanical interlocking auxiliary' efficiently generates a [2]rotaxane (Figure 3, step 2). Removal of a bulky silyl ether allows the ring to access the full length of the thread (Figure 3, step 3). In chloroform the macrocycle hydrogen bonds to the peptide, but in dimethylsulfoxide (DMSO) the solvent competes for the amide hydrogen bonding sites (of both macrocycle and thread) and the alkyl chain minimizes its area exposed to polar solvent by burying itself within the macrocycle cavity (Figure 3, step 4). The change of position of the ring on the thread is locked by resilylation (Figure 3, step 5) and the auxiliary removed by transesterification (Figure 3, step 6) to leave a [2]rotaxane with no residual recognition elements between macrocycle and thread.

By adding escapement mechanisms to the system shown in Figure 2 and other related compound machines, the components of [2]catenanes[31] and [3]catenanes[32] could be directionally rotated, the first examples of Brownian ratchet mechanisms being introduced into the designs of synthetic molecular machines[31-33]. The idea of using unbiased thermal fluctuations to drive directed motion has its origins in the visionary works of von Smoluchowski[37] and Feynman[38], and a theoretical description of energy and information ratchets had been described[39,40] for (bio)molecular systems by Astumian in the 1990s. In the early 2000s our group recognized that molecular rings mechanically locked onto linear or cyclic axles (the catenane and rotaxane architectures pioneered by Sauvage[16] and Stoddart[17] in the 1980s and 90s) could be considered as Brownian particles (the rings) on a potential energy surface (the axle) and their dynamics thus controlled by incorporating Brownian ratchet mechanisms into synthetic molecular machine designs: '*The way in which the principles of an energy ratchet can be applied to a catenane architecture is not to consider the whole structure as a molecular*

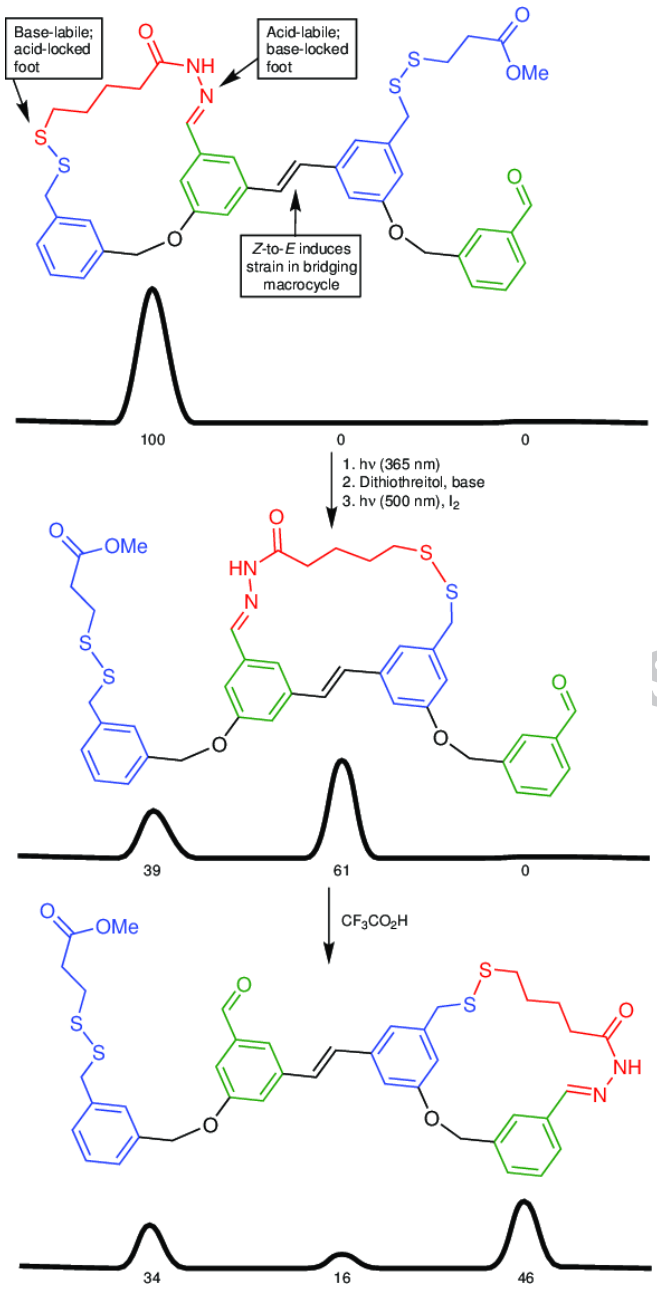

Fig. 4. A molecule that 'walks' directionally along a molecular track using a light-fueled energy ratchet mechanism.[45] The *E*/*Z* state of the stilbene molecular switch modulates the strain in the walker as it bridges the central footholds; synchronizing the stilbene switching with labilizing the orthogonal foot-track interactions generates directional transport of the walker along the track.

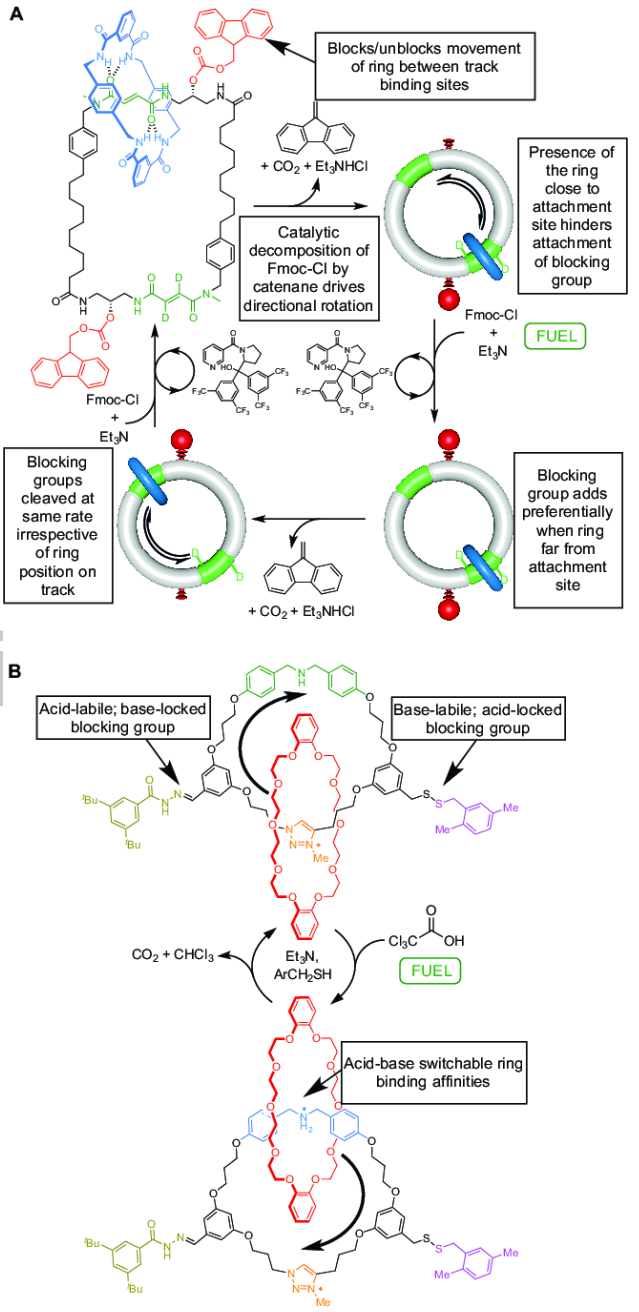

Fig. 5. Compound molecular machines with multiple simple machine mechanisms that operate in synchronized fashion through a common input. (A) A chemically-fuelled molecular motor that runs autonomously in the presence of Fmoc-Cl.[48] The rate of addition of an Fmoc blocking group to a free OH group on the track is faster when the site of attachment is not hindered by the presence of the macrocycle, meaning that blocking groups attach to the track faster with respect to one face of the macrocycle than the other, biasing the brownian motion of the ring in one direction (an information ratchet mechanism). (B) A molecular motor driven by pulses of Cl_3CCO_2H.[49] The base-catalyzed decarboxylation of Cl_3CCO_2H changes the environment from acidic to basic; the thermodynamically favored position of the ring and the lability of the blocking groups switches with the change in acidity (an energy ratchet mechanism).

machine, but rather to view one macrocycle as a motor that transports a substrate—the other ring—directionally around itself'[31].[1] This led to the first energy ratchets (directional transport caused by varying potential energy minima and maxima independent of the position of the particle on the potential energy surface),[31,32] the first information ratchets (directional transport caused by kinetics dependent on the position of the particle),[33,41,42] the first linear molecular motors,[30,33] and a second type, after the Feringa overcrowded alkenes,[7] of rotary molecular motors.

Such molecular motor mechanisms have been improved and expanded upon by us and others over the last decade,[43-49] including DNA motors,[43] ratcheted small-molecule walkers[44,45] (Figure 4) and pumps[46,47], with the most recent examples of

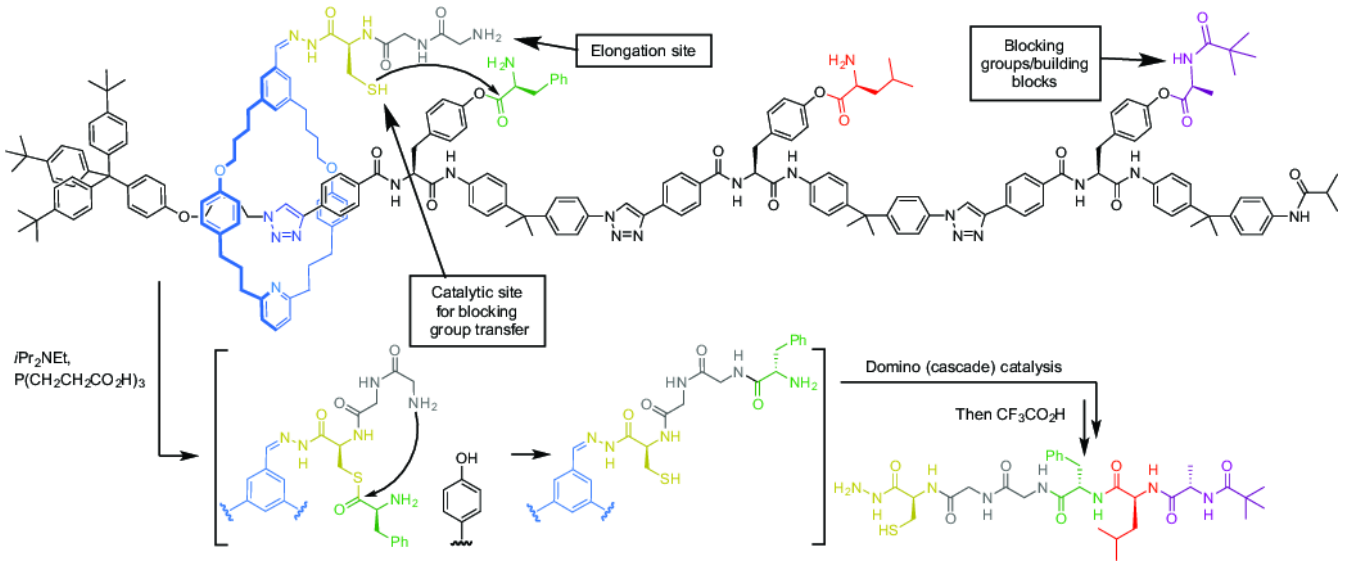

Fig. 6. A compound molecular machine that assembles a tripeptide of specific sequence by travelling along a track loaded with α-amino acid building blocks.[51]

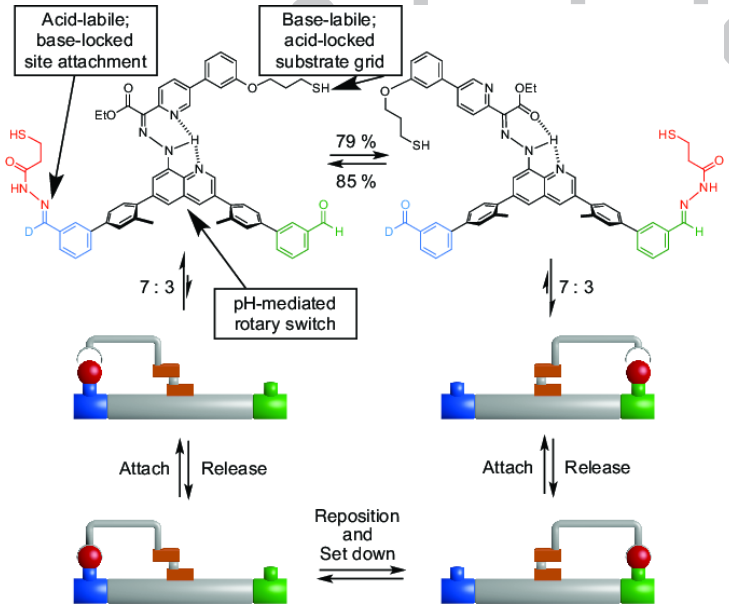

Fig. 7. Multi-stage operation of a bidirectional small-molecule transporter that uses a rotary switch to control a molecular robotic arm.[56]

chemically-fueled catenane and rotaxane motors featuring autonomous operation[48] (Figure 5A) and directionality of the component movements synchronized to the addition of a chemical fuel[49] (Figure 5B). These latter developments are particularly significant as they demonstrate how several simple machine processes can be integrated and made to work together using a single energy input. Biological motors are driven by catalysis of a chemical reaction based on information ratchet mechanisms.[50] The molecular motor shown in Figure 5A works in identical fashion: the components are directionally driven by catalysis of the decomposition of Fmoc-Cl by the catenane. It is the first example of the implementation of an information ratchet to continuously drive cyclic motion in a synthetic molecular machine. The molecular motor shown in Figure 5B illustrates that pulses of a chemical fuel can also be used to drive energy ratchet motors.

Other types of compound molecular machine

Compound molecular machines are not limited to ratchet mechanisms, the integration of other simple molecular machine processes can produce other advanced functions. The combination of blocking groups that are removed in a particular order because of a rotaxane's structure, together with a pendant strand that possesses both a regenerable catalytic site and an elongation site, has been used to make rotaxanes in which the macrocycle moves directionally along the track, removing and adding together building blocks in a predetermined order to form a sequence-defined oligomer (Figure 6).[51-53] In the rotaxane shown in Figure 6 the macrocycle carries a thiolate group that iteratively removes amino acids in sequence from the strand and transfers them to a peptide-elongation site through native chemical ligation as the macrocycle moves along the track. It is reminiscent of (although much simpler than) the task performed by the ribosome and of some aspects of the way that biology

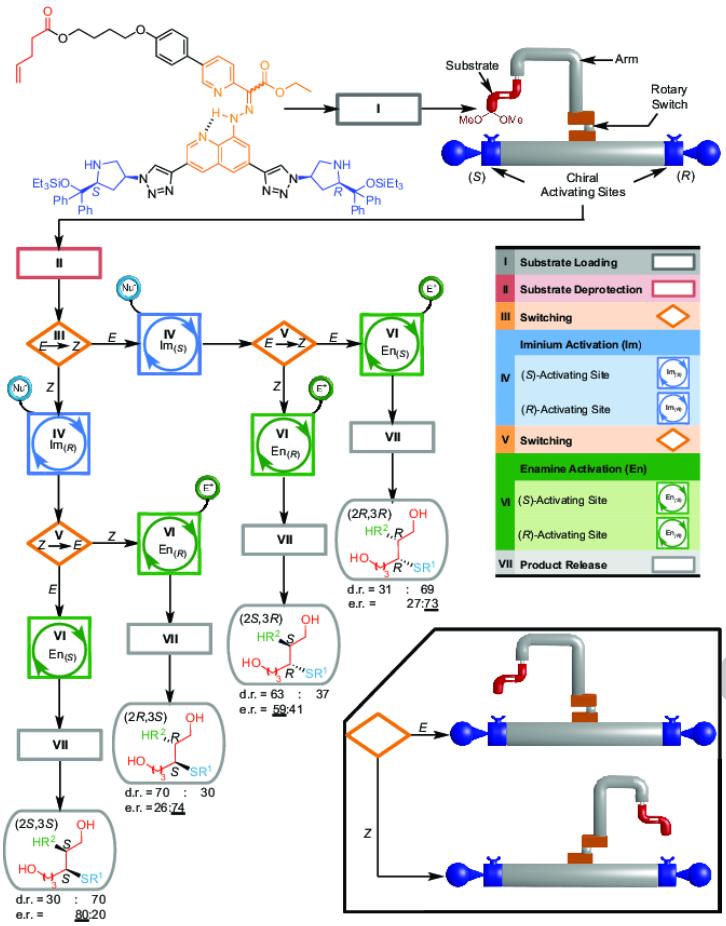

Fig. 8. Programable synthesis of any one of four stereoisomers by a small-molecule robot.[58] Using a thiol nucleophile for the first reaction (iminium activation of the substrate by the machine) and an electron-poor alkene electrophile for the second reaction (enamine activation of the substrate by the machine) any of the four possible products can be selectively made by the robot in one pot through different programing.

makes sequence polymers in general, i.e. by using molecular machines that move along tracks in order to direct the sequence that monomers are assembled.

Molecular robotics

The mechanical manipulation of matter at atomic length-scales has fascinated scientists since it was proposed by Feynman in his celebrated lecture '*There's Plenty of Room at the Bottom*'.[54] Indeed, the concept of using molecules to manipulate other molecules in robotic fashion is an intriguing one that has some precedence in biology: for example, in metazoan fatty acid synthase a growing fatty acid chain, tethered to an embedded carrier protein, is passed between enzyme domains in the protein superstructure in a manner reminiscent of the way a robotic arm manipulates objects on a factory assembly line.[55] By integrating the actions of several simple molecular machine functions—two distinct gripping/release actions (substrate-to-machine and substrate-to-platform) and positional switching of a 'robotic arm'—a compound molecular machine has been produced that is able to selectively transport a molecular cargo in either direction between two spatially distinct, chemically similar, sites on a molecular platform without the substrate ever exchanging with others in the bulk (Figure 7).[56]

With this machine transport of the substrate is controlled by inducing sequential conformational and configurational changes within an embedded hydrazone rotary switch[57] that steers the robotic arm. When the substrate is being moved through a change in position of the arm, the substrate-arm linkage is kinetically locked and the substrate-platform bond labile. When the substrate is released by the arm, the substrate-platform bond is kinetically locked in placed. By controlling the order that each simple machine function occurs, it is possible to program the molecular machine to selectively transport the substrate either from left-to-right or from right-to-left in a one-pot reaction sequence. In chemical terms this is the selective synthesis of constitutional isomers through intramolecular rearrangements that can be induced to proceed in either direction, something that is difficult or impossible to achieve in any other way.

Just as biological molecular machines position substrates in order to direct chemical reaction sequences it is possible to adapt this type of machine to produce different outputs from a series of molecular-robot-mediated chemical reactions. The compound molecular machine moves a substrate between different activating sites to achieve different product outcomes from chemical synthesis (Figure 8).[58] The molecular robot can be programmed to stereoselectively produce, in a sequential one-pot reaction, an excess of any of the four possible diastereoisomers from the addition of a thiol and an alkene to an α,β-unsaturated aldehyde in a tandem reaction process. The stereodivergent synthesis includes access to diastereoisomers that cannot be selectively synthesized through conventional iminium-enamine organocatalysis.

Outlook

Molecules that resemble in their appearance machines familiar to us from our everyday world have seductive appeal, but numerous mechanical mechanisms that work at the macroscopic

scale are physically impossible at the molecular level (including pendulums, spring-loaded trapdoors, pistons, crankshafts, the internal combustion engine, inclined planes, wedges, etc). Others machine parts scale down in some respects but not others. For example, the rotation of the aromatic ring blades of interdigitated triptycene residues can be coupled in the same way as meshed mechanical cogwheels, the rotors look and behave in that respect like gears.[59] However, mechanical gears are designed to move with uniform angular velocity within macroscopic compound machines and this can never be the case for rotors within molecular machines. Such issues make extrapolation of mechanical machine concepts to the molecular level fraught with difficulty. Indeed, many of the current generation of technomimetic molecular machines are really iconic models of machines, that is they look like but do not function as the original object does, in the same way that a model aeroplane does not fly like a jumbo jet.[60] Few, if any, technomimetic molecular machines are analogic models, resembling the parent machine in behavior as well as form.

The alternative is to design nanomachines that work in broadly the same way as biology. As with classical engineering, a route to machine complexity is to integrate the actions of several simple machine processes to generate advanced functions that cannot be achieved by the action of any of the machine parts individually. Given that most complex machine mechanisms cannot be scaled to the environments that molecular machines operate in, it may prove difficult for technomimetic designs to produce nanomachines that are significantly more advanced in terms of mechanism than the rudimentary systems made to date. Yet all of biology is based on molecular machines that use (and appear to require) non-trivial mechanisms to carry out the sophisticated and useful tasks they perform. Through adopting the basic principles of how such machines work, bio-inspired mechanisms can enable the construction of molecular machines that are more than just switches, with compound mechanisms based on the integration of several simple working parts.

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