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Beyond switches: Rotaxane- and catenane-based synthetic molecular motors*

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Abstract: Nature uses molecular motors and machines in virtually every significant biological process, but learning how to design and assemble simpler artificial structures that function through controlled molecular-level motion is a major challenge for contemporary physical science. The established engineering principles of the macroscopic world can offer little more than inspiration to the molecular engineer who creates devices for an environment where everything is constantly moving and being buffeted by other atoms and molecules. Rather, experimental designs for working molecular machines must follow principles derived from chemical kinetics, thermodynamics, and nonequilibrium statistical physics. The remarkable characteristics of interlocked molecules make them particularly useful for investigating the control of motion at the molecular level. Yet, the vast majority of synthetic molecular machines studied to date are simple two-state switches. Here we outline recent developments from our laboratory that demonstrate more complex molecular machine functions. This new generation of synthetic molecular machines can move continuously and progressively away from equilibrium, and they may be considered true prototypical molecular motors. The examples discussed exemplify two, fundamentally different, "Brownian ratchet" mechanisms previously developed in theoretical statistical physics and realized experimentally in molecular-level devices for the first time in these systems.

Keywords: molecular machines; rotaxanes; catenanes; nanotechnology; Maxwell's demon; noncovalent interactions.

INTRODUCTION

The widespread use of controlled molecular-level motion in key natural processes [1] is inspiring scientists to try to create synthetic devices that mimic the function of these amazing natural systems [2]. Despite the sophistication of modern synthetic chemistry, however, it is far from obvious to see how to design such machines because the established rules of macroscopic mechanical engineering are entirely inapplicable at the molecular level. Unlike their macroscopic counterparts, the components of molecular machines experience constant thermal fluctuations and buffeting in the form of Brownian motion; they exhibit almost instantaneous thermal relaxation times with respect to their surroundings; the effect of gravity on these machines is insignificant; they have large surface-area-to-volume ratios that often lead to attractive interactions; and when in solution, they move in an extremely viscous environment where inertia is negligible and instantaneous forces are all-important (i.e., under conditions of low Reynolds number) [3].

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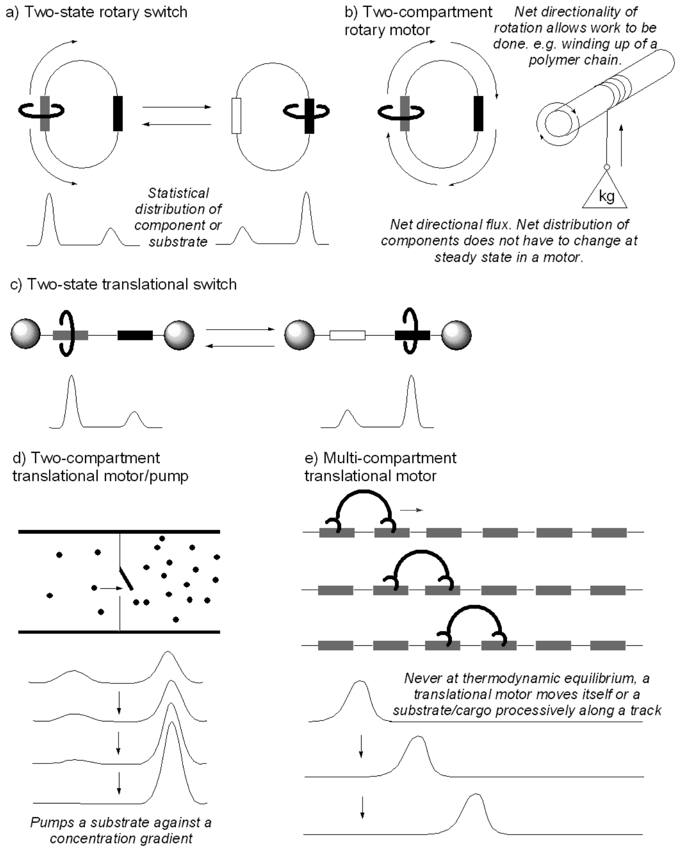
In general terms, this combination of factors leads to a central tenet: while the macroscopic machines we encounter in everyday life may provide the inspiration for what we might like molecular machines to achieve, drawing too close an analogy for how they might do it is likely to be a poor design strategy. The "rules of the game" at large and small length scales are simply too different [2d,f,3,4]. It seems sensible, therefore, to try to design molecular machines that make use of the inherent random motion present at small length scales, rather than make structures that have to fight against thermal energy. Clever design of covalent architectures can restrict this random motion to selected degrees of freedom; switchable noncovalent interactions offer a means of addressing molecular machine components; and self-assembly processes may be used to organize molecular mechanical devices into functional materials.

Care must also be taken to define and categorize molecular machines phenomenologically, and not based on perceived similarities to macroscopic mechanical components [2f]. When describing molecular behavior scientifically, the standard dictionary definitions meant for everyday use are not always appropriate for a regime that the definitions were never intended to cover. The difference between a "motor" and a "switch" as basic molecular machine types, for example, is significant because motor and



a) Two-state rotary switch

b) Two-compartment rotary motor

Net directionality of rotation allows work to be done. e.g. winding up of a polymer chain.

Statistical distribution of component or substrate

Net directional flux. Net distribution of components does not have to change at steady state in a motor.

c) Two-state translational switch

d) Two-compartment translational motor/pump

e) Multi-compartment translational motor

Never at thermodynamic equilibrium, a translational motor moves itself or a substrate/cargo processively along a track

Pumps a substrate against a concentration gradient

Fig. 1 The fundamental difference between a "switch" and a "motor" at the molecular level. Both translational and rotary switches influence a system as a function of the switch state. They switch between two or more, often equilibrium, states. Motors, however, influence a system as a function of the trajectory of their components or a substrate. Motors function repetitively and progressively on a system; the effect of a switch is undone by resetting the machine. (a) Two-state rotary switch. (b) Two-compartment rotary motor. (c) Two-state translational switch. (d) Two-compartment translational motor or pump. (e) Multi-compartment translational motor.

switch become descriptors of very different types of behavior at molecular length scales, not simply iconic images (Fig. 1). A switch influences a system as a function of state whereas a motor influences a system as a function of the trajectory of its components or the substrate. Returning a molecular-level switch to its original position undoes any mechanical effect it has on an external system (naturally, the molecules heat up their surroundings as the energy from the switching stimulus is dissipated); when the components of a rotary motor return to their original position through a different pathway to the one they left by (i.e., a 360° directional rotation), a physical task performed by the machine is not inherently undone (for example, the rotating components could be used to wind up a polymer chain). Although mechanical switches can use energy to do work, that task is undone by resetting the switch to its original state. A motor, on the other hand, is a machine that can do work repetitively and progressively on a system [5].

MOLECULAR MECHANICAL SWITCHES

In recent years, it has proved relatively straightforward to design molecular switches [2]—synthetic molecular systems where positional changes of submolecular components occur by moving energetically downhill toward an equilibrium position. In this pursuit, interlocked molecules [6] such as catenanes and rotaxanes have proved particularly useful. The mechanical bond in these structures severely restricts the relative degrees of freedom of the interlocked components in several directions, while often permitting motion of extraordinarily large amplitude in an allowed vector. In a rotaxane, for example, one or more macrocycles are mechanically prevented from dethreading from a linear unit by bulky "stoppers", restricting significant submolecular motions of the mechanically interlocked components to only two modes, namely, random movement of the ring back and forth along the thread ("shuttling") and nondirectional rotation around the thread ("pirouetting"). A molecular shuttle is a rotaxane in which the thread contains two (or more) macrocycle-binding sites ("stations") connected by a traversable pathway. Provided sufficient thermal energy is available to break the intercomponent interactions at each site, the ring moves randomly between the two stations. On average, however, the macrocycle spends more time on the station with the higher binding affinity (i.e., the molecule tends to adopt a particular preferred co-conformation [7]).

But random motion—even cleverly restricted random motion—is not enough to create a molecular machine. The Principle of Detailed Balance [8] tells us that no useful task can be performed by random transport or exchange processes. Rather, an input of energy is required to break detailed balance and control how the motion occurs. In a "stimuli-responsive molecular shuttle" (Fig. 2), one of the stations is chemically altered, changing its binding affinity for the macrocycle. This "balance-breaking" step puts the ring distribution momentarily out of equilibrium, before thermal energy allows the system to relax to its new equilibrium position by biased Brownian motion. Reversing the chemical change can similarly result in a second change in the average ring position, restoring the starting distribution.

To date, a number of switchable molecular shuttles, operating using a range of different stimuli, have been reported. These systems have even been successfully interfaced with the macroscopic world by harnessing the mechanical switching process to control various properties in a variety of materials [2f,9]. However, these are simple two-state switches, the most basic and functionally limited type of machine mechanism [10], in which the ring distribution is always at or relaxing toward equilibrium, inextricably linked to the state of the thread. In contrast, biological motors and machines are able to drive chemical systems away from equilibrium [1].

Over the past decade, the benzylic amide class of catenanes and rotaxanes has proven remarkably versatile for the construction of switch-like molecular machines [11]. In the current review, we will discuss our most recent results on extending this ability to create more sophisticated molecular machines that can perform functions more akin to molecular motors than switches.

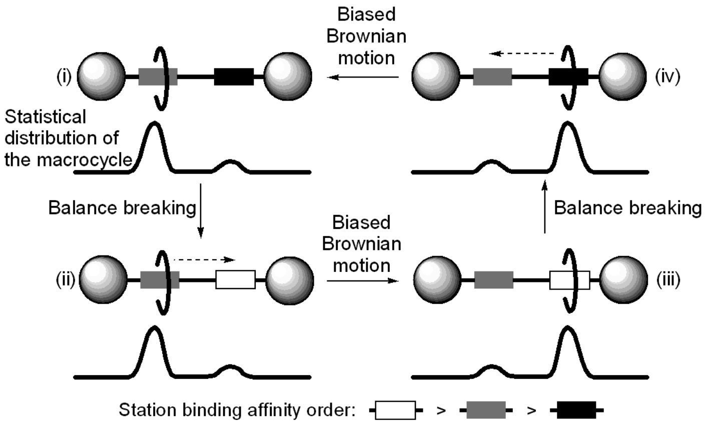


Fig. 2 Translational submolecular motion in a stimuli-responsive molecular shuttle: (i) the macrocycle initially resides on the preferred station (gray); (ii) a reaction occurs (black → white), which changes the relative binding potentials of the two stations such that, (iii) the macrocycle "shuttles" to the now preferred station (white). If the reverse reaction (white → black) now occurs (iv), the components return to their original positions.

MAXWELL'S DEMON

Although the development of molecular machines is a scientific area of great contemporary interest and extraordinary recent growth [2], the notion of harnessing the random Brownian motion of molecular-level objects to create mechanical machines dates back to a time when ideas surrounding the statistical nature of matter and the laws of thermodynamics were first being formulated.

The Scottish physicist James Clerk Maxwell, arguably one of the most important and influential scientists of all time [12], both proposed the electromagnetic theory of light and was instrumental in developing the kinetic theory of gases. These two theories have become cornerstones of modern physical

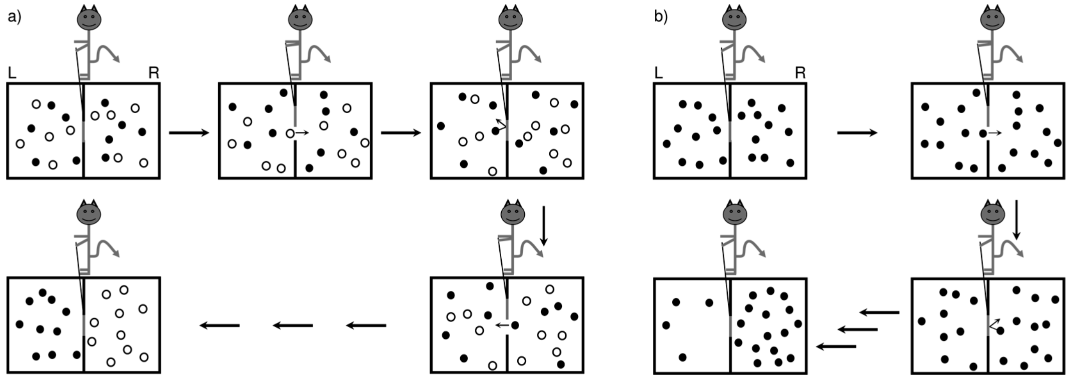


Fig. 3 The Maxwell's demon thought experiments. (a) Maxwell's "temperature demon" [13a,b] in which a gas at uniform temperature is sorted into "hot" (black) and "cold" (white) molecules. The demon opens the gate between the compartments when it detects a cold particle approaching the gate from the left or a hot particle coming from the right, thus separating the particles according to their thermal energy and creating a temperature differential between the compartments. (b) A Maxwellian "pressure demon" [13c] in which a concentration gradient is established by the gate being opened only when a particle approaches it from the left. In both versions of the thought experiment, the idea is that the demon's actions involve no work being done (using a frictionless gate which he opens and closes very slowly), but as the end-result is a reduction in the entropy of the gas, this is in conflict with the Second Law of Thermodynamics.

science, but “Maxwell’s demon” [13], an offshoot of his work on the kinetic theory, has had its own extraordinary impact [14]. Time and again it has captured the imagination and interest of scientists in different fields, profoundly influencing the development of statistical and quantum physics, information theory, computer science, and cybernetics.

In the original version of Maxwell’s thought experiment (Fig. 3), a tiny intelligent being—a “demon”—is able to open and close a gate connecting two boxes filled with gas so as to allow only fast (“hot”) gas molecules to flow into one box and only slow (“cold”) gas molecules into the other—creating a temperature difference between the two compartments (Fig. 3a). If the demon can perform this task without expending any energy, then such a result would be in violation of the Second Law of Thermodynamics. Maxwell appreciated that other types of “sorting demon” could be imagined that would also violate the Second Law, for example, a system that allowed particles to pass between compartments in one direction, but not the other without an energy input (Fig. 3b).

The ensuing debates, analyses, and recapitulations [14,15] of this apparent paradox have served to fuel interest in the rectification of random molecular-level motion to produce useful work (i.e., to drive systems away from equilibrium *without* breaking the Second Law of Thermodynamics). In recent years, these speculative constructs have given way to a new field of statistical physics concerned with the formal analysis of “ratchet” mechanisms, which mathematically describe how random thermal fluc-

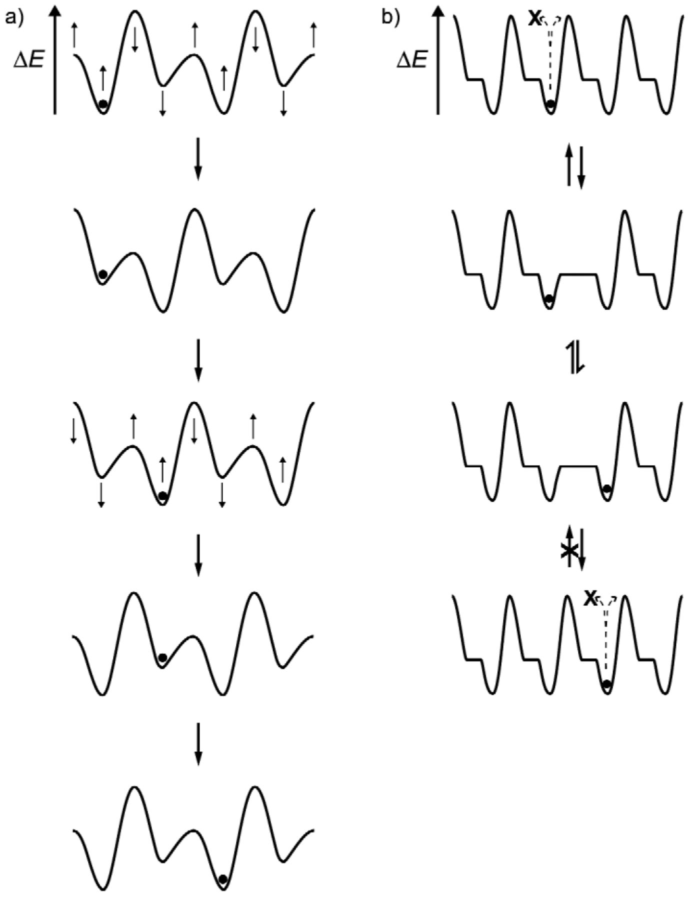


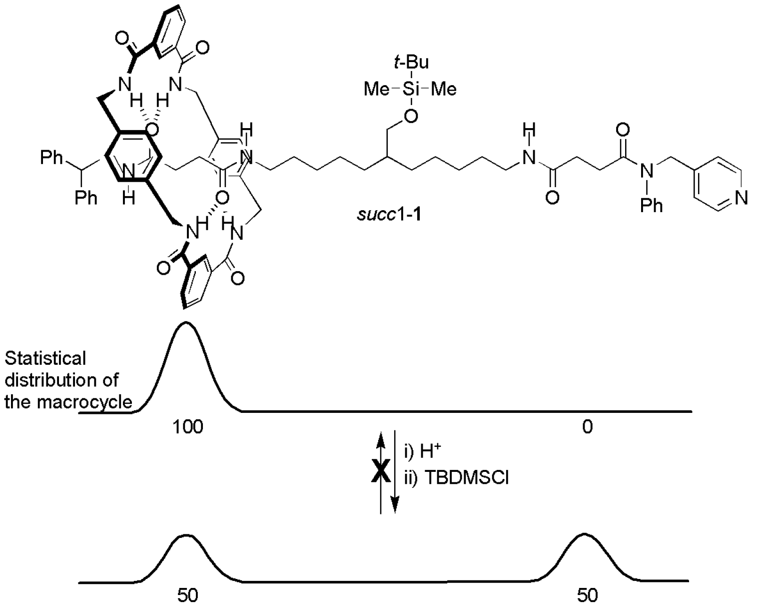
Fig. 4 Schematic examples of (a) an energy ratchet and (b) an information ratchet mechanism for transport of a Brownian particle across a potential-energy surface. In (b) dotted arrows indicate the transfer of information that signals the position of the particle.

tuations may be captured with the help of an energy source and a source of symmetry breaking [16,17]. Two overarching classes of such mechanisms may be discerned. In "energy ratchets" (e.g., Fig. 4a), changes to the energy minima and maxima on an asymmetric potential-energy surface, which are independent of the particle's location, are correlated such that successive thermodynamically driven relaxation steps all occur kinetically biased in the same direction. An "information ratchet", on the other hand, is a mechanism that employs knowledge about the Brownian particle's location to lower activation barriers on the potential-energy surface at appropriate moments so as to allow transport in a given direction (e.g., Fig. 4b).

COMPARTMENTALIZED MOLECULAR MACHINES

Modern synthetic chemistry allows us to revisit the question of how to transport a Brownian particle between two distinguishable sites, not from the point of view of challenging the Second Law of Thermodynamics, but rather to see how such a task can be performed by a working molecular-level machine. In this regard, catenane- and rotaxane-based molecular shuttles provide an ideal basis for a molecular-level experimental realization of the mechanisms recently formalized by physicists. It is no coincidence that Maxwell's demon, and other similar constructs, all employ some means of separating the two compartments, while both energy and information ratchets involve manipulation of activation barriers: to create Brownian machines more sophisticated than simple switches, control over the kinetics for exchange of the substrate between two sites of the machine must be introduced.

Control over shuttling kinetics was introduced in [2]rotaxane **1** to maintain, and then release, a nonequilibrium macrocycle distribution (Scheme 1) [18]. A bulky silyl ether restricts the ring to only one of two structurally identical (but distinguishable) stations. The system starts out statistically unbalanced (*succ1*-**1**, because of the synthetic route used to access it). Removal of the silyl ether is a "linking" operation, which switches "on" dynamic exchange of the macrocycle between the two stations and allows the system to move toward equilibrium. An average displacement of the macrocycle half the distance separating the two stations is the result. This is a molecular-level form of "escapement", the mech-

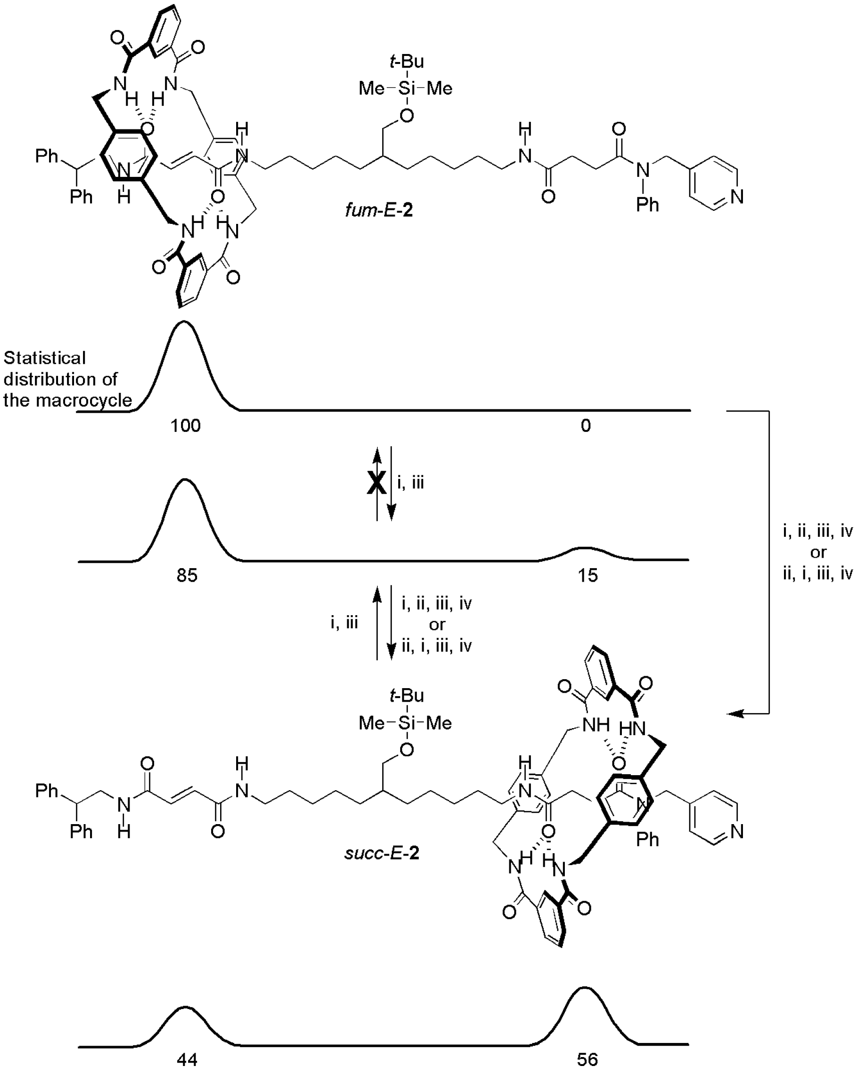


Scheme 1 Operation of a compartmentalized Brownian molecular machine that acts as an irreversible switch [18]. TBDMS = *tert*-butyldimethylsilyl.

anistic element that controls the release of potential energy to drive mechanical motion in clocks and other macroscopic mechanical devices.

Reinstating the barrier (an "unlinking" operation, resetting the machine), or even removing it a second time, has no further effect on the average position of the macrocycle, because the system is now statistically balanced. This stimuli-induced irreversible net change of position of the macrocycle represents a new type of molecular shuttle in phenomenological terms: its operation is irreversible and the state of the machine (the thread) does *not* determine the position of the substrate.

Combining control over exchange between the two stations (kinetics, as in **1**) with the ability to modulate their relative binding affinities (thermodynamics, as in previous molecular shuttle systems, see Fig. 2) produced a machine that can move a substrate distribution away from equilibrium (Scheme 2) [18]. [2]Rotaxane **2** can be made statistically balanced (85 % of the macrocycles on the fumaramide station; 15 % on the succinamide station) and unlinked (and therefore not in equilibrium) by



Scheme 2 Operation of a compartmentalized molecular machine, **2**, which corresponds to a two-state Brownian flip-flop [18]. Operation steps: (i) Desilylation (80 % aqueous acetic acid); (ii) *E* → *Z* photoisomerization ($h\nu$ at 312 nm); (iii) resilylation (TBDMSCl); and (iv) *Z* → *E* thermal isomerization (catalytic piperidine).

simply removing and reattaching the silyl group (Scheme 2, steps i and iii). Irradiation at 312 nm provides a balance-breaking stimulus, generating a 49:51 *E*:*Z* photostationary state. Subsequent removal of the kinetic barrier (“linking stimulus”) then allows balance to be restored by biased Brownian motion of the ring toward the new equilibrium distribution. Reinstating the barrier (“unlinking stimulus”) makes the system unlinked and not in equilibrium although statistically balanced. The resetting step (a different balance-breaking stimulus, to promote the $Z \rightarrow E$ olefin isomerization) makes the system statistically unbalanced, unlinked and not in equilibrium. Following this operational cycle, ~56 % of the macrocycles are located on the succinamide station—the thread has performed the task of directionally changing the net position of the macrocycle, and since the succinamide station binds the macrocycle more weakly than the fumaramide station, the thread has moved the macrocycle energetically uphill! The transportation of the macrocycle in **2** is repeatedly reversible between the statistically balanced 85:15 and statistically unbalanced 44:56 ratios of *fum-E*-**2** to *succ-E*-**2**. Significantly, in **2**, as in **1**, the thread itself returns to its initial state without restoring the initial macrocycle distribution—it is only from the history of the operations that the distribution can be known. This behavior amounts to “ratcheting”, a characteristic of the operating mechanism of many biological molecular machines. The behavior of **2** is characteristic of a two-state “flip-flop” component in electronics, and therefore **2** is the first example of a new class of molecular machine—a two-state Brownian flip-flop.

The thermodynamically unfavorable substrate distribution produced in **2** is precisely the result envisaged for Maxwell’s pressure demon (Fig. 3b), yet here it is achieved by an entirely different mechanism that is ignorant of the position of the Brownian particle. Rather, the rotaxane machine carries out a sequence of four steps (independent of the position of the particle) which govern in turn the thermodynamics and the kinetics for transport between the two stations: balance-breaking 1, linking, unlinking, balance-breaking 2 (Fig. 5).

Examining the behavior of these simple devices reveals four fundamental mechanistic elements that are involved in the operation of any compartmentalized Brownian machine (ratcheting, escapement, balance-breaking, and linking/unlinking) and suggests how these can be combined in different ways to create different types of device [18]. There are three basic types of Brownian machine that act through various combinations of these four processes: Brownian switches (e.g., switchable molecular shuttles), Brownian flip-flops (e.g., rotaxane **2**), and Brownian motors.

The latter is a machine that can repetitively and progressively change the distribution or position of a Brownian substrate, during which the machine is reset without restoring the original distribution or

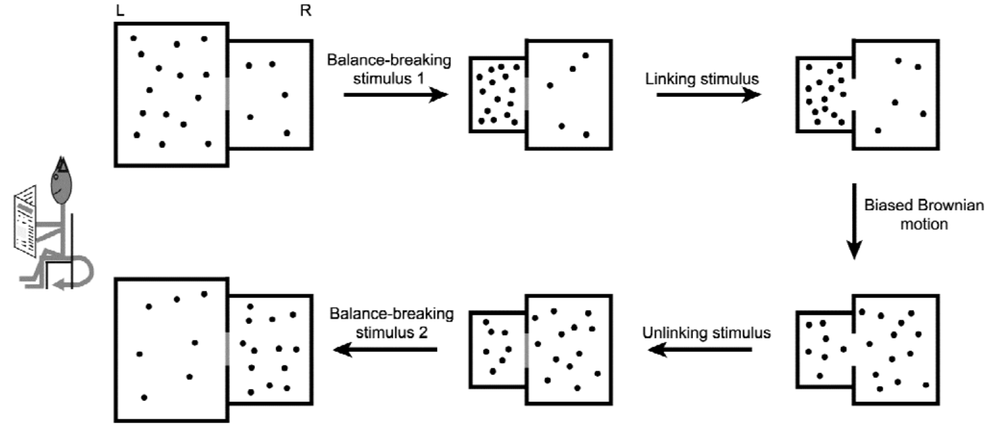
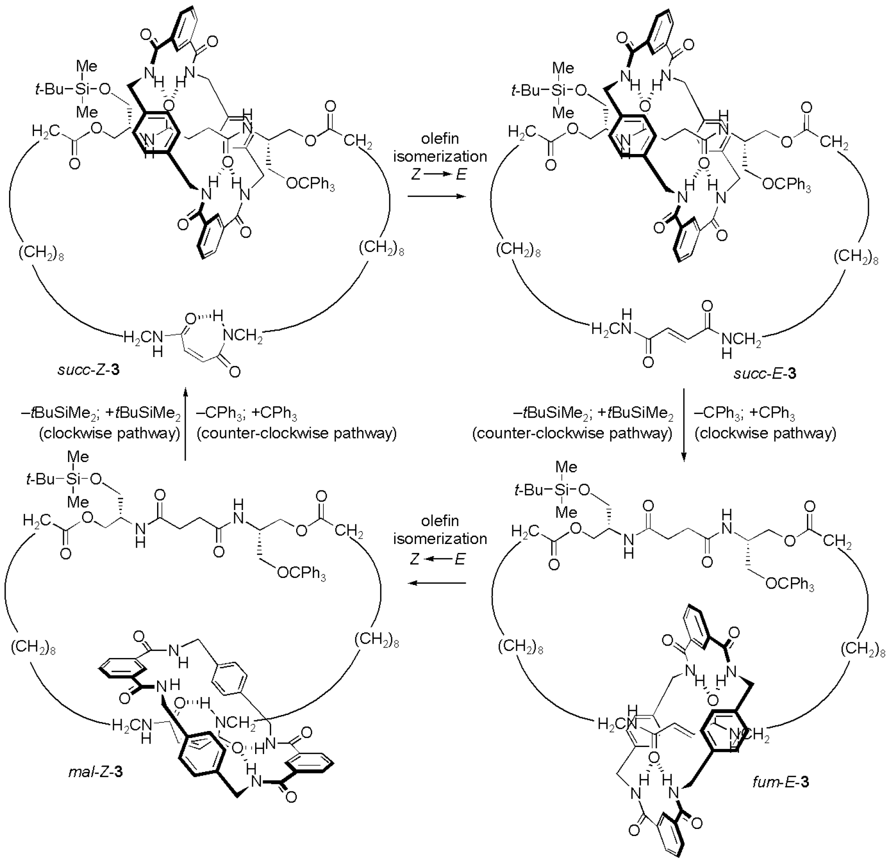


Fig. 5 The operation of rotaxane **2** in Scheme 2 is the experimental realization (albeit in non-adiabatic form) of the transportation task required of Maxwell’s pressure demon. There is, however, no role for an information-gathering demon in this mechanism.

position of the substrate. The mechanism illustrated in Fig. 5 can be extended to create a continuously operating Brownian motor working via an energy ratchet mechanism. Such a device has been realized in the form of [2]catenane **3** (Scheme 3). This molecule is the first example of a reversible synthetic rotary molecular motor, in which the smaller ring (light blue) can be directionally rotated around the larger one by 360° in either direction [19].

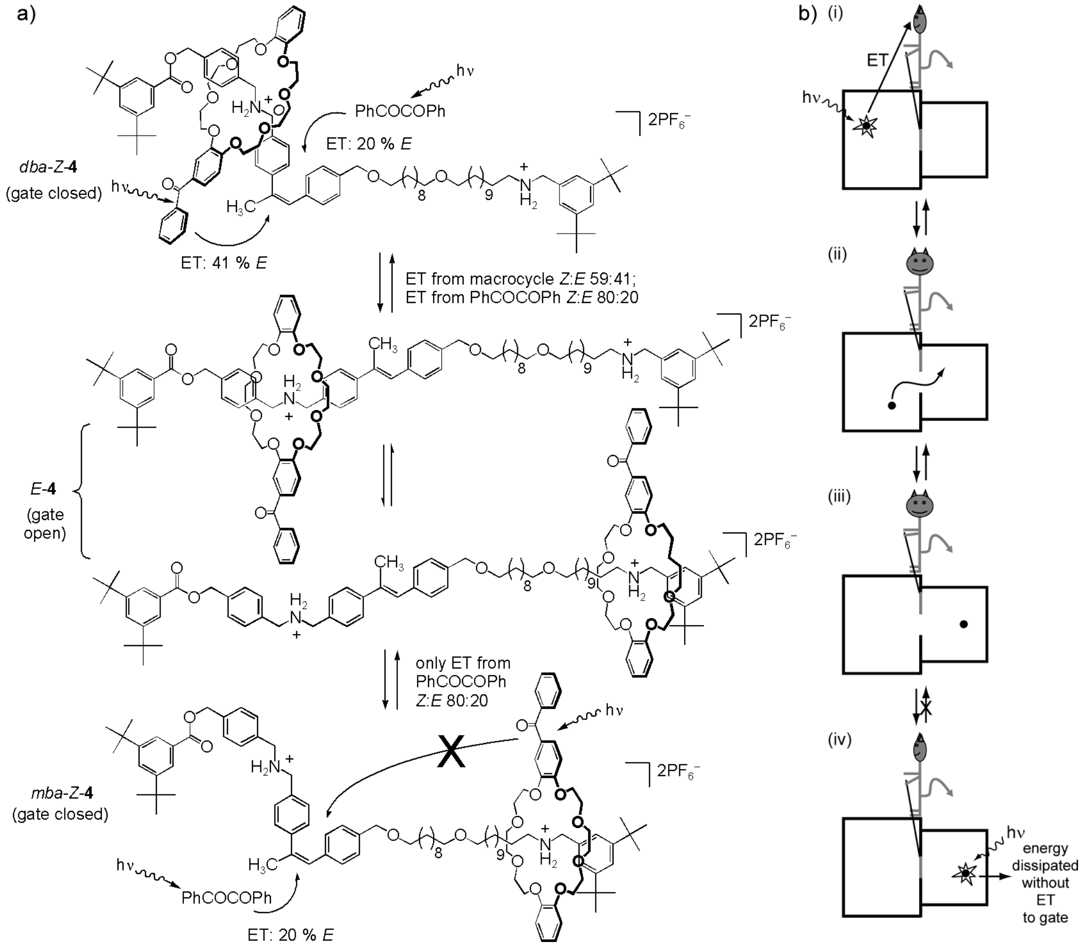
The analysis of this deceptively simple molecule provides experimental insight into how an energy input is essential for directional rotation of a submolecular fragment by Brownian motion. Even though no net energy is stored in the system, there has to be some processing of chemical energy for net rotation to be directional over a statistically significant number of molecules—a requirement that is absent if the equivalent motion is non-directional. The amount of energy conversion required to induce directionality has an intrinsic lower limit, which corresponds to the difference in binding energy of the fumaramide and maleamide binding sites, the same value that determines the directional efficiency of rotation and the maximum amount of work the motor can theoretically perform in a single cycle [19].



Scheme 3 Reversible [2]catenane rotary motor **3**, which works via an energy ratchet mechanism [19].

EXERCISING DEMONS

Molecular machines **2** and **3** are able to move a distribution of Brownian particles away from equilibrium by switching the relative energies of adjacent compartments in concert with altering the kinetics for transport between them, yet there is no role for information in their operation. They operate via energy ratchet mechanisms, in which knowledge about the position of the Brownian particle is not required. We have recently demonstrated another fundamentally new type of motor mechanism that more closely mimics the mechanism of Maxwell's demon. Using light energy, [2]rotaxane **4** is able to transmit information about the position of the macrocycle in a manner that allows transport of this unit in a particular direction (Scheme 4) [20].



Scheme 4 A photo-operated molecular information ratchet [20]. (a) Irradiation of rotaxane **4** at 350 nm interconverts the different forms of **4** and, in the presence of benzil (PhCOCOPh), drives the ring distribution away from its thermodynamic minimum without ever changing the binding strengths of the macrocycle or ammonium binding sites. When the macrocycle is on the *mba* binding site (drawn at right here), intramolecular ET from the macrocycle is inefficient and intermolecular ET from benzil dominates. When the macrocycle is on the *dba* binding site (drawn at left), both ET mechanisms can operate. (b) Cartoon illustration of the operation of **4** as a Maxwellian pressure demon [13c]: (i) Photoinduced excitation of a particle signals its position in the left-hand compartment by ET to the demon operating the gate. (ii) & (iii) The demon opens the gate and the particle shuttles incessantly between the two compartments by Brownian motion until the gate shuts, trapping the particle at random in one of them. (iv) Photoinduced excitation of the particle in the right-hand compartment is ignored by the demon and the energy of the excited state is dissipated as heat.

An α-methyl stilbene in the rotaxane thread acts as a "gate" for passage of the crown ether macrocycle: the *E*-stilbene isomer allows free movement of the ring, while the *Z*-stilbene blocks its motion. Under irradiation, the triplet sensitizer benzil produces a high proportion of the gate-closed *Z*-form. The benzophenone-like substitution on the macrocycle, however, means that it too can act as a photosensitizer, so that it can signal its presence to the gate by energy transfer (ET). This signaling is distance dependent and triggers a process that opens the gate, momentarily allowing the rings to pass, before the gate is returned to its closed state. Because the rings in the left-hand compartment spend much more time close to the gate than those in the right-hand compartment, the gate is more likely to be opened by rings moving from left to right. For an ensemble of such machines, the particle distribution is driven further and further away from equilibrium, providing a non-adiabatic realization (in terms of both task and mechanism) of Maxwell's pressure demon in molecular form.

EXORCISING DEMONS

In formulating his thought experiment, Maxwell was only interested in illustrating the statistical nature of the Second Law, and while the demon may be considered the progenitor of modern, thermodynamically consistent, Brownian ratchet mechanisms, subsequent generations of inventors and philosophers have also been fascinated by its implications for the creation of a perpetual motion machine [14]. Such a machine is impossible, of course, and is not what rotaxane **4** achieves. The solution as to why an input of energy is *always* necessary took more than a century to fully resolve [21], but it was eventually understood through an extension of Landauer's principle [22] on the thermodynamic cost of computation: any device that is able to process and act upon information has an inherent energy requirement that always saves the Second Law. As the behavior of **4** can be understood in clear chemical terms, it is possible in this experimental system to pin-point precisely how information is traded for energy [20]. The energy cost of information transfer is met by externally supplied photons and the effectiveness of the mechanism depends directly upon the efficiency of the ET to the closed gate from the excited state of a benzophenone macrocycle that is located in the left-hand compartment (*dba*-*Z*-**4**, Scheme 4(b)(i)). This process triggers an olefin isomerization, which *must* involve energy dissipation during relaxation processes on both the excited- and ground-state potential-energy surfaces. As the excited state of *dba*-*Z*-**4** is quenched by ET to open the gate, therefore, the information regarding the probable position of the macrocycle is erased on decay of the initial, vertically excited state to the perpendicular intermediate. Thus, the part of the mechanism of **4** that intrinsically requires dissipation of energy is equivalent to the erasure of the information known to a gate-operating demon, in agreement with Bennett's resolution [21] of the Maxwell's demon paradox.

This is the first example of a synthetic molecular machine designed to operate via an information ratchet mechanism, where knowledge of the object's position is used to control its transport away from equilibrium and fundamentally different to the energy ratchet mechanism employed by **2** and **3**.

NANOMACHINES AND NANOTECHNOLOGY

As with many fundamental developments in science, it is not clear in exactly what ways synthetic molecular-level machines are ultimately going to change technology. Perhaps the best way to appreciate their potential is to recognize that over four billion years of evolution Nature has decided to use molecular-level machines at the heart of virtually every significant biological process. In stark contrast, none of mankind's present-day technologies (with the exception of liquid crystals) exploit controlled molecular-level motion in any way at all. When we learn how to make use of this inherent feature of nanoscale matter, it will revolutionize many aspects of functional molecule and materials design, while an improved understanding of physics and biology will surely also follow. Here, we have elucidated the first two general mechanisms for moving molecular components away from equilibrium, exemplified in a number of devices of varying complexity. The principles derived, however, are not restricted to the design of functional catenanes and rotaxanes but, rather, can be applied to any structural class of molecular machine and indeed other chemical processes that operate far from equilibrium.

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