Exercising Demons

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The widespread use of controlled molecular-level motion in natural processes[1] is inspiring scientists to try to create synthetic devices that mimic the function of these amazing natural systems.[2] 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 where everything is constantly moving and being buffeted by other atoms and molecules.[3] The issues involved with controlling motion at the molecular level have consequently occupied the minds of scientists since as far back as the middle of the 19th Century.

Maxwell's Demon

James Clerk Maxwell, arguably one of the most important and influential scientists of all time,[4] 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 science but 'Maxwell's Demon',[5] an offshoot of his work on the kinetic theory, has had its own extraordinary impact.[6] 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 (Figure 1), 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 (Figure 1a). If the demon can perform such a 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 (Figure 1b).

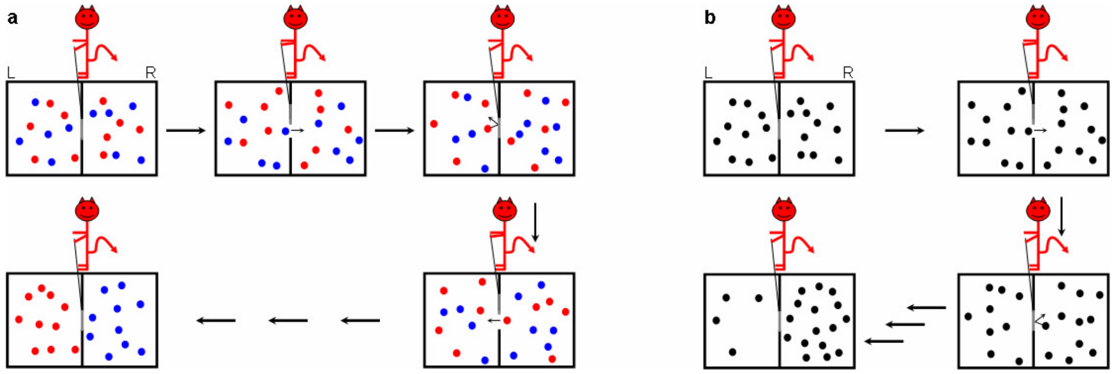


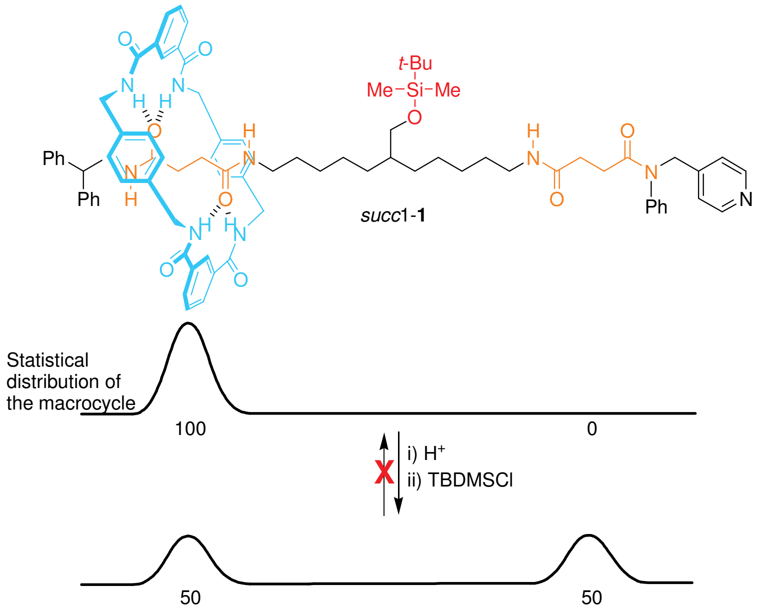
Figure 1. The Maxwell Demon thought experiments. **a** Maxwell's 'temperature demon'[5a,b] in which a gas at uniform temperature is sorted into 'hot' (red) and 'cold' (blue) molecules. The demon opens the gate between the compartments when it detects a cold particle approaching the gate from the left 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'[5c] 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.

Compartmentalized Molecular Machines: Driving Away from Equilibrium

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. The architecture of rotaxane-based molecular shuttles restricts significant submolecular motions to only two modes, namely random movement of the ring back and forth along the thread ('shuttling') and nondirectional rotation around the thread ('pirouetting'). But random motion – even cleverly restricted random motion – is not enough to create a molecular machine. An input of energy is required to control how the motion occurs. The net transport of macrocycles between different regions in rotaxanes has previously been demonstrated in molecules called 'stimuli-responsive molecular shuttles'.[7] However, these are simple two-state switches, the most basic and functionally limited type of machine mechanism[8] in which the ring distribution is always at, or relaxing towards, 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] just like Maxwell's Demon.

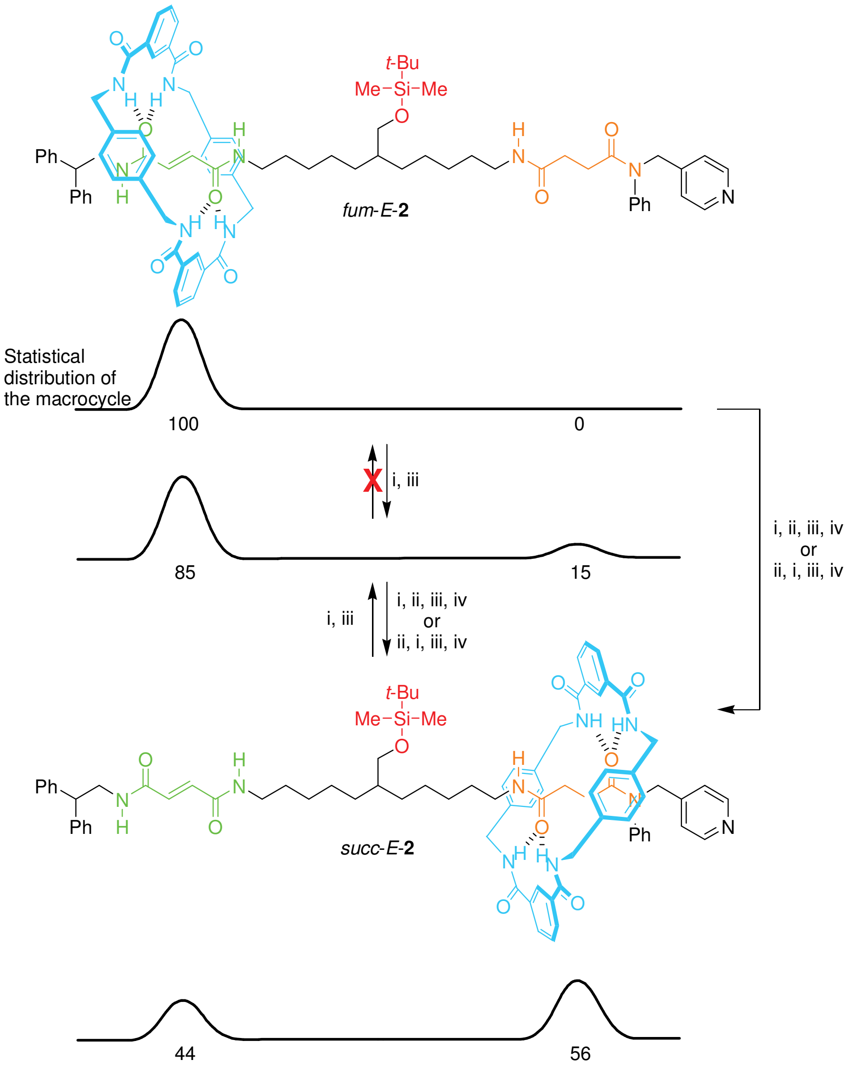
It is no coincidence that Maxwell's Demon, and other similar constructs, all employ some means of separating the two compartments: to create Brownian machines more sophisticated than simple switches, control over the kinetics for exchange of the substrate between two sites of the machine must be introduced.

Control over shuttling kinetics was introduced in [2]Rotaxane **1** to maintain, and then release, a nonequilibrium macrocycle distribution (Scheme 1).[9] A bulky silyl ether restricts the ring to only one of two structurally identical (but distinguishable) stations. Removing this group results in an average displacement of the macrocycle half the distance separating the two stations. Reinstating the barrier, or even removing it a second time, has no further effect on the average position of the macrocycle. This device represents a new type of molecular shuttle in phenomenological terms: its operation is irreversible and the state of the thread does *not* determine the position of the substrate.



Scheme 1. Operation of a compartmentalized Brownian molecular machine that acts as an irreversible switch.[9] TBDMS = *tert*-butyldimethylsilyl.

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) produced a machine that can move a substrate distribution away from equilibrium (Scheme 2).[9] In **2**, the thread performs the task of directionally changing the net position of the macrocycle, and since the succinamide (orange) station binds the macrocycle more weakly than the fumaramide (green) station, the thread moves the macrocycle energetically uphill! Significantly, the thread itself returns to its initial state without restoring the initial macrocycle distribution – it is only from the history of the machine’s operations that the distribution can be known. The behaviour 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.



Scheme 2. Operation of a compartmentalized molecular machine **2** which corresponds to a two-state Brownian flip-flop.[9] Operation steps: (i) Desilylation (80% aqueous acetic acid); (ii) *E*→*Z* photoisomerization (hν at 312 nm); (iii) resilylation (TBDMSCl); and (iv) *Z*→*E* thermal isomerization (catalytic piperidine).

The thermodynamically unfavourable substrate distribution produced in **2** is precisely the result envisaged for Maxwell's pressure demon (Figure 1b), yet here it is achieved by an entirely different mechanism that is ignorant of the position of the Brownian particle (Figure 2).

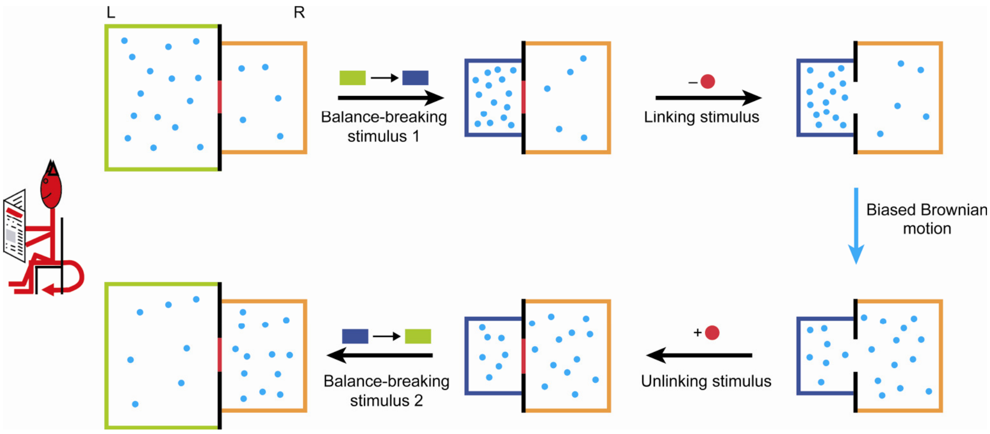
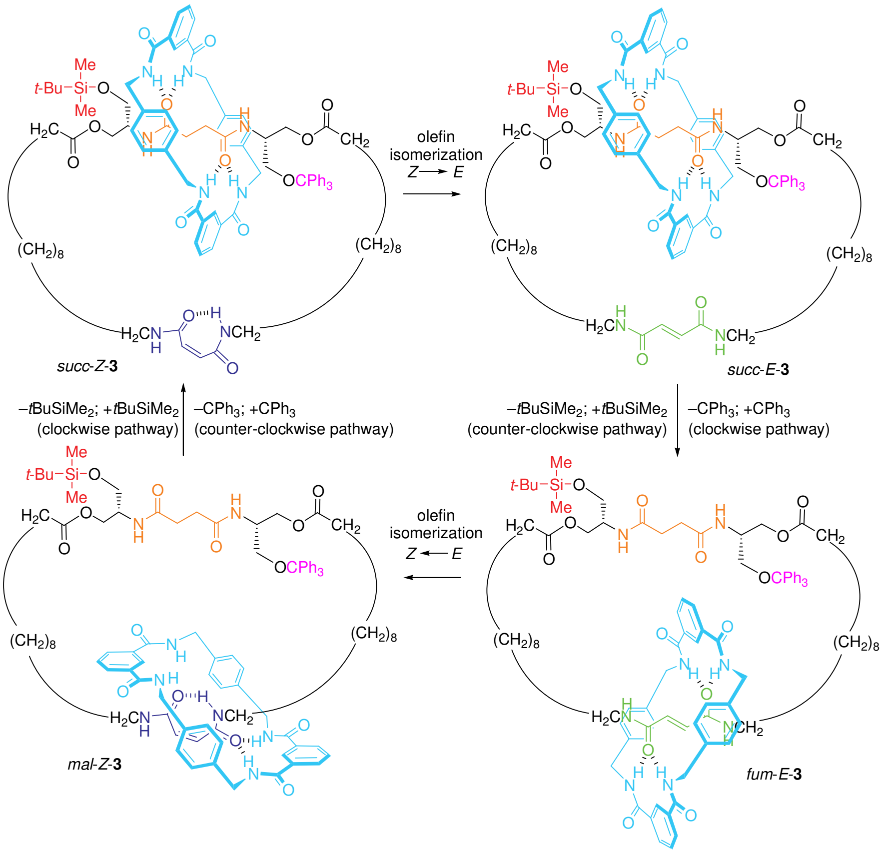


Figure 2. The operation of rotaxane **2** in Scheme 2 is the experimental realization (albeit in non-adiabatic form) of the transportation task required of Maxwell's pressure demon. There is no role for an information-gathering demon in this mechanism.

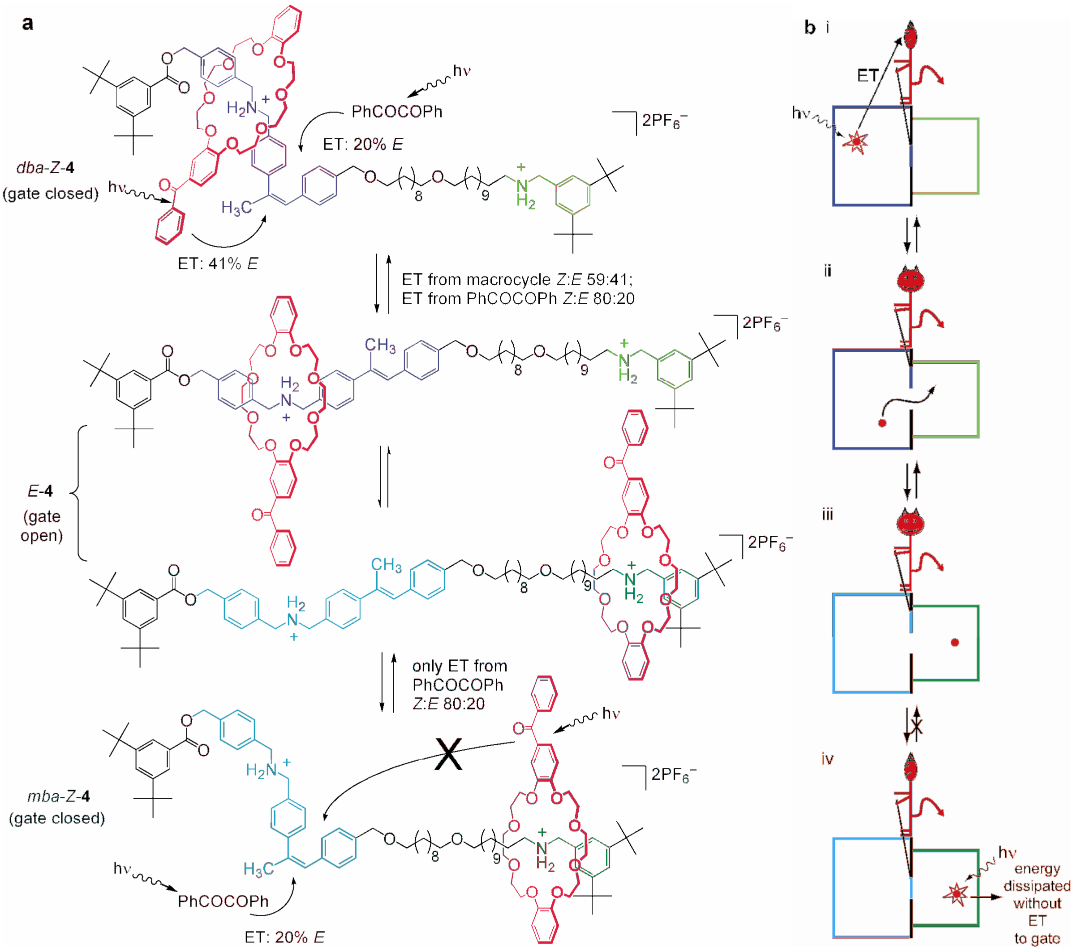
Examining the behaviour of these simple devices reveals four fundamental mechanistic elements that are involved in the operation of any compartmentalized Brownian machine (ratcheting, escapement, balance and linkage) and suggests how these can be combined in different ways to create different types of device.[9] The mechanism illustrated in Figure 2 has been applied to create a continuously operating molecular machine, [2]Catenane **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 (Scheme 3).[10]



Scheme 3. Reversible [2]catenane rotary motor **3**.[10]

Exercising Demons: Using Information to Direct Brownian Motion

Molecular machines **2** and **3** are able to move a distribution of Brownian particles away from equilibrium, yet there is no role for information in their operation. 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).[11]



Scheme 4. A photo-operated molecular information ratchet.[11] **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 (green), intramolecular energy transfer (ET) from the macrocycle is inefficient and intermolecular ET from benzil dominates. When the macrocycle is on the *dba* binding site (blue), both ET mechanisms can operate. **b** Cartoon illustration of the operation of **4** as a Maxwellian pressure demon[5c]: **i** Photo-induced excitation of a particle signals its position in the blue 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** Photo-induced excitation of the particle in the green 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 signalling 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 blue compartment spend much more time close to the gate than those in the green compartment, the number of rings in the green compartment increases upon the shining of light on the molecules and the particle distribution is directionally driven further and further away from equilibrium.

Exorcising Demons

In formulating his thought experiment, Maxwell was only interested in illustrating the statistical nature of the Second Law, but subsequent generations of inventors and philosophers have been fascinated by its implications for the creation of a perpetual motion machine. 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[12] but it was eventually understood through an extension of Landauer's Principle[13] 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 behaviour 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.[11]

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 recognise 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 revolutionise 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 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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