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Beyond Switches: Ratcheting a Particle Energetically Uphill with a Compartmentalized Molecular Machine

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Abstract: Here we correlate chemical (covalent), physical (thermodynamic), and statistical (population distribution) descriptions of behavior with the way that two new types of simple molecular machines (the threads of rotaxanes) perform the task of transporting a Brownian substrate (the rotaxane macrocycle) between two distinguishable binding sites. The first machine−substrate ensemble is a [2]rotaxane that operates through a mechanism that intrinsically causes it to change the average position of the macrocycle irreversibly. This contrasts with the behavior of classic stimuli-responsive molecular shuttles that act as reversible molecular switches. The second system is a compartmentalized molecular machine that is able to pump its substrate energetically uphill using the energy provided by a photon by means of an olefin photoisomerization. Resetting this compartmentalized molecular machine does not undo the work it has carried out or the task performed, a significant difference to a simple molecular switch and a characteristic we recognize as "ratcheting" (see Scheme 8). The ratcheting mechanism allows the [2]rotaxane to carry out the transport function envisaged for the historical thought-machines, Smoluchowski's Trapdoor and Maxwell's Pressure Demon, albeit via an unrelated mechanism and using an input of energy. We define and exemplify the terms "ratcheting" and "escapement" in mechanical terms for the molecular level and outline the fundamental phenomenological differences that exist between what constitutes a two-state Brownian switch, a two-state Brownian memory or "flip-flop", and a (two-stroke) Brownian motor. We also suggest that considering the relationship between the parts of a molecular machine and a substrate in terms of "statistical balance" and "linkage" could be useful in the design of more complex systems and in helping to understand the role of individual amino acids and peptide fragments during the directional transport of substrates by biological pumps and motors.

Introduction

In recent years it has proved possible to design synthetic molecular systems in which positional displacements of submolecular components result from moving energetically downhill,[1] but what are the structural features necessary for molecules to convert chemical energy into mechanical work? How can we make a synthetic molecular machine that pumps ions against a gradient, say, or moves itself or a substrate energetically uphill along a track? We know that nature has developed such machines and refined them to a high degree of efficiency[2] and yet the chemistry literature is surprisingly poor when it comes to the fundamental guidelines necessary to invent them. Here we examine the way that some simple molecular machines carry out the task of transporting a particle along a one-dimensional, two minimum, potential energy surface and attempt to correlate the chemical (covalent structure), physical potential (thermodynamic and kinetic properties governed by attractive and repulsive noncovalent interactions), and statistical (population distribution) behavior of the system with aspects of the task performance. The results begin to provide the phenomenological framework necessary for chemists to design more complex compartmentalized molecular-level machines (assemblies of simpler machines that each act as components by performing a set task). It may also prove useful in understanding the roles played by individual submolecular fragments during the operation of biological machines.

The Two-Compartment Brownian Particle "Thought-Machines"

The design of tiny machines capable of transporting Brownian particles selectively between two compartments—i.e., effectively along a one-dimensional, two minimum, potential energy surface—was the subject of several celebrated historical "thought-machines" (Figure 1).[3−7] Both Maxwell's Demon[4] (Figure 1a and b) and Smoluchowski's Trapdoor[5] (Figure 1d) were concerned with trying to set up temperature or pressure gradients in systems containing multiple Brownian particles through their

(1) (a) Balzani, V.; Credi, A.; Raymo, F. M.; Stoddart, J. F. *Angew. Chem., Int. Ed.* **2000**, *39*, 3349−3391. (b) Stoddart, J. F., Ed. Special issue on *Molecular Machines. Acc. Chem. Res.* **2001**, *34*, 409−522. (c) Balzani, V.; Venturi, M.; Credi, A. *Molecular Devices and Machines. A Journey into the Nanoworld*; Wiley-VCH: Weinheim, Germany, 2003. (d) Easton, C. J.; Lincoln, S. F.; Barr, L.; Onagi, H. *Chem. Eur. J.* **2004**, *10*, 3120−3128. (e) Flood, A. H.; Ramirez, R. J. A.; Deng, W. Q.; Muller, R. P.; Goddard, W. A.; Stoddart, J. F. *Aust. J. Chem.* **2004**, *57*, 301−322. (f) Crowley, J. D.; Goshe, A. J.; Steele, I. M.; Bosnich, B. *Chem. Eur. J.* **2004**, *10*, 1944−1955. (g) Kottas, G. S.; Clarke, L. I.; Horinek, D.; Michl, J. *Chem. Rev.* **2005**, *105*, 1281−1376. (h) Kinbara, K.; Aida, T. *Chem. Rev.* **2005**, *105*, 1377−1400. (i) Kay, E. R.; Leigh, D. A. In *Functional Artificial Receptors*; Schrader, T., Hamilton, A. D., Eds.; Wiley-VCH: Weinheim, Germany, 2005; pp 333−406. (j) Kelly, T. R., Ed. Volume on *Molecular Machines*. *Top. Curr. Chem*. **2005**, *262*, 1−236.
(2) *Molecular Motors*; Schliwa, M., Ed.; Wiley-VCH: Weinheim, Germany, 2003.

10.1021/ja057664z CCC: $33.50

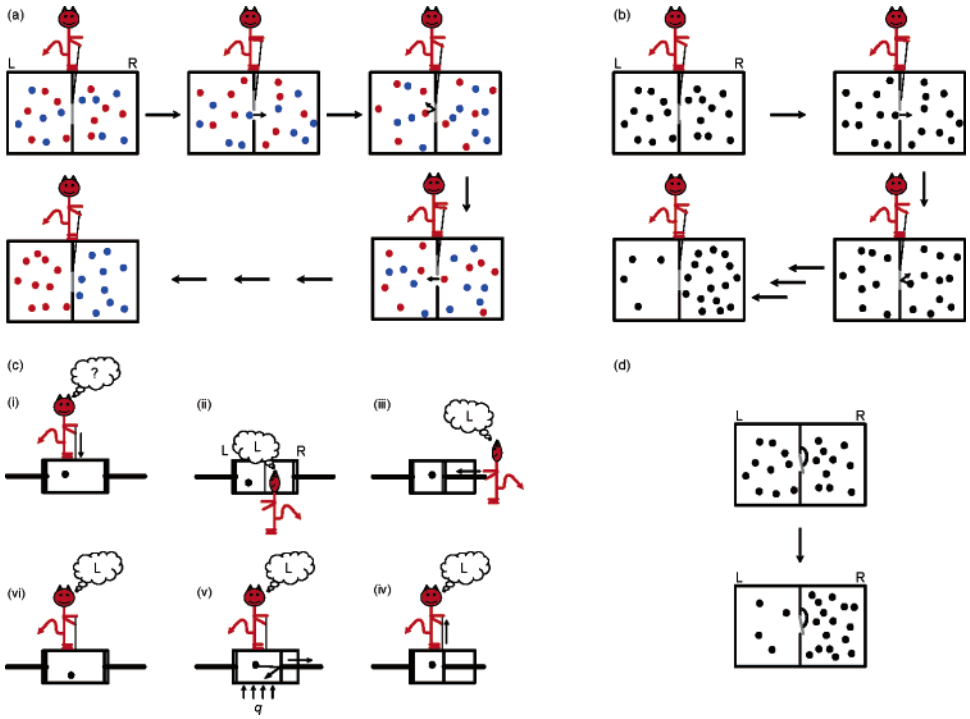


Figure 1. Examples of two-compartment Brownian "thought-machines": (a) Maxwell's "temperature demon" in which a gas at uniform temperature is sorted into "hot" and "cold" molecules.[4] Particles with energy higher than the average are represented by red dots while blue dots represent particles with energies lower than the average. (b) A Maxwellian "pressure demon" in which a pressure gradient would be created if the door was only opened when a particle in the left compartment approached it.[4c] (c) Szilard's Engine, which attempts to do work with a piston using heat drawn from an external reservoir by a pressure demon.[6] (i) Initially, a single Brownian particle occupies a cylinder with a piston at either end. A frictionless partition is put in place to divide the container into two compartments ((i) → (ii), unlinking stimulus). (ii) The demon then detects the particle and determines in which compartment it resides (the left (L) compartment in the depicted example). (iii) Using this information, the demon is able to move the opposite piston into position without meeting any resistance from the particle. (iv) The partition is removed (linking stimulus), allowing (v) the "gas" to expand against the piston, doing work against any attached load. To replenish the energy used by the piston and maintain a constant temperature, heat must flow into the system. To complete the thermodynamic cycle and reset the machine, the demon's memory of where the particle was must be erased ((vi) → (i)). (d) Smoluchowski's Trapdoor: an "automatic" pressure demon. The directionally discriminating behavior is carried out by a wholly mechanical device, a trapdoor that is intended to open when hit from one direction but not the other (note, this still involves the communication of information between the particle and the machine; the demon is incorporated into the door mechanism).[5]

controlled exchange between two compartments; Szilard's Engine[6] (Figure 1c) endeavored to utilize the pressure exerted by one Brownian particle located in one of two compartments to do work. The behaviors of all four "Gedankenmaschinen" were considered without an external energy source (other than a heat reservoir at the same temperature as the Gedankenmaschine system)—their purpose was to test the nature of the

(3) *Maxwell's Demon 2. Entropy, classical and quantum information, computing*; Leff, H. S., Rex, A. F., Eds.; Institute of Physics Publishing: Bristol, U.K., 2003.

(4) The first (a) private and (b) public written discussions of the "temperature demon" were as follows: (a) Maxwell, J. C. *Letter to P. G. Tait, 11 December 1867*. Quoted in Knott, C. G. *Life and Scientific Work of Peter Guthrie Tait*; Cambridge University Press: London, 1911; pp 213−214. (b) Maxwell, J. C. *Theory of Heat*; Longmans, Green and Co.: London, 1871; Chapter 12. (c) Maxwell introduced the idea of a "pressure demon" in a later (undated) letter to Tait, also quoted in Knott, C. G. *Life and Scientific Work of Peter Guthrie Tait*; Cambridge University Press: London, 1911; pp 214−215 and ref (3). A pressure demon is able to operate in a system linked to a constant-temperature reservoir with the sole effect of using energy transferred as heat from that reservoir to do work (see Szilard's engine, Figure 1c, ref 6). This is in conflict with the Kelvin-Planck form of the Second Law, whereas the temperature demon challenges the Clausius definition.

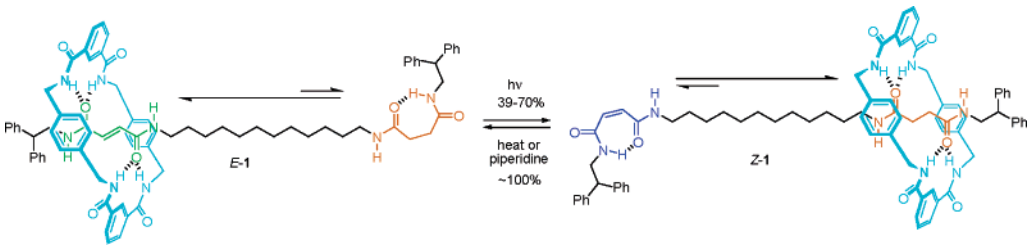
(5) Smoluchowski's Trapdoor [(a) von Smoluchowski, M. *Phys. Z.* **1912**, *13*, 1069−1080. (b) von Smoluchowski, M. *Vortgage über die Kinetische Theorie der Materie und der Elektrizitat*; Planck, M., Ed.; Teubner und Leipzig: Berlin, 1914; pp 89−121] aims to transport particles selectively from the left compartment to the right in Figure 1d. However, in the absence of a mechanism whereby the trapdoor can dissipate energy, it will be at thermal equilibrium with its surroundings. This means it must spend much of its time open, unable to influence particle transport. Rarely, it will be closed when a particle approaches from the right and will open on collision with a particle coming from the left—doing its job as intended. Such events are balanced, however, by the door snapping shut on a particle from the right, pushing it into the left chamber. Overall, the probability of a particle moving from left to right is equal to that for moving right to left and so the trapdoor cannot accomplish its intended function adiabatically.

(6) Szilard, L. *Z. Phys.* **1929**, *53*, 840−856.

(7) Feynman, R. P.; Leighton, R. B.; Sands, M. *The Feynman Lectures on Physics*; Addison-Wesley: Reading, MA, 1963; Vol. 1, Chapter 46.

(8) For the realization of Feynman's ratchet-and-pawl in molecular form see: (a) Kelly, T. R.; Tellitu, I.; Sestelo, J. P. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1866−1868. For nonadiabatic molecular versions which unidirectionally rotate see: (b) Kelly, T. R.; De Silva, H.; Silva, R. A. *Nature* **1999**, *401*, 150−152. (c) Leigh, D. A.; Wong, J. K. Y.; Dehez, F.; Zerbetto, F. *Nature* **2003**, *424*, 174−179. (d) Hernández, J. V.; Kay, E. R.; Leigh, D. A. *Science* **2004**, *306*, 1532−1537. For other types of rotary molecular motors see: (e) Koumura, N.; Zijlstra, R. W. J.; van Delden, R. A.; Harada, N.; Feringa, B. L. *Nature* **1999**, *401*, 152−155. (f) Koumura, N.; Geertsema, E. M.; Meetsma, A.; Feringa, B. L. *J. Am. Chem. Soc.* **2000**, *122*, 12005−12006. (g) Koumura, N.; Geertsema, E. M.; van Gelder, M. B.; Meetsma, A.; Feringa, B. L. *J. Am. Chem. Soc.* **2002**, *124*, 5037−5051. (h) Geertsema, E. M.; Koumura, N.; ter Wiel, M. K. J.; Meetsma, A.; Feringa, B. L. *Chem. Commun.* **2002**, 2962−2963. (i) van Delden, R. A.; Koumura, N.; Harada, N.; Feringa, B. L. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 4945−4949. (j) ter Wiel, M. K. J.; van Delden, R. A.; Meetsma, A.; Feringa, B. L. *J. Am. Chem. Soc.* **2003**, *125*, 15076−15086. (k) van Delden, R. A.; Koumura, N.; Schoevaars, A.; Meetsma, A.; Feringa, B. L. *Org. Biomol. Chem.* **2003**, *1*, 33−35. (l) ter Wiel, M. K. J.; van Delden, R. A.; Meetsma, A.; Feringa, B. L. *J. Am. Chem. Soc.* **2005**, *127*, 14208−14222. (m) Pijper, D.; van Delden, R. A.; Meetsma, A.; Feringa, B. L. *J. Am. Chem. Soc.* **2005**, *127*, 17612−17613. (n) ter Wiel, M. K. J.; van Delden, R. A.; Meetsma, A.; Feringa, B. L. *Org. Biomol. Chem.* **2005**, *3*, 4071−4076. (o) van Delden, R. A.; ter Wiel, M. K. J.; Pollard, M. M.; Vicario, J.; Koumura, N.; Feringa, B. L. *Nature* **2005**, *437*, 1337−1340. (p) Fujita, T.; Kuwahara, S.; Harada, N. *Eur. J. Org. Chem.* **2005**, 4533−4543. (q) Kuwahara, S.; Fujita, T.; Harada, N. *Eur. J. Org. Chem.* **2005**, 4544−4556. (r) Fletcher, S. P.; Dumur, F.; Pollard, M. M.; Feringa, B. L. *Science* **2005**, *310*, 80−82. (s) Lin, Y.; Dahl, B. J.; Branchaud, B. P. *Tetrahedron Lett.* **2005**, *46*, 8359−8362.

Scheme 1. Previously Reported[13j] [2]Rotaxane, **1**, that Functions as a Stimuli-Responsive Molecular Shuttle[a]



[a] At 254 nm the photostationary state is 61:39 *E*:*Z*,[13j] at 312 nm it is ~50:50, and at 350 nm with a benzophenone sensitizer it is 40:60 *E*:*Z*[13j] and can be increased up to 30:70 *E*:*Z*[20j] for some derivatives.

Second Law of Thermodynamics, not to see how a working Brownian machine could be achieved (that was probably first discussed[7,8] by Feynman). However, modern synthetic routes allow us to make molecules in which the Brownian motion of substrates *does* occur between two well-defined locations, e.g., rotaxane-based molecular shuttles. This enables us to re-visit the question of how to transport a Brownian particle between two distinguishable sites, not from the point of view of doing so adiabatically, but rather to see how such a task can be performed by a molecular-level machine.

Rotaxanes and Molecular Shuttles

Rotaxanes are chemical structures in which one or more macrocycles are mechanically prevented from de-threading from linear chains by bulky "stoppers".[9] Even though the rings are not covalently attached to the threads, rotaxanes are molecules—not supramolecular complexes—as covalent bonds must be broken in order to separate the components from each other.[9,10] The interactions generally used to direct the synthesis of rotaxanes often "live-on" in the product, providing a well-defined binding site or "station" for the ring on the thread. If two or more stations are present on a thread with a traversable path between them, the rotaxane can be considered a "molecular shuttle"[11] in which the ring is incessantly and randomly exchanged between the binding sites.[12] Stimuli-responsive molecular shuttles are rotaxanes in which the net position of the macrocycle on the thread (i.e., the statistical distribution of the ring between the stations) changes in response to external triggers (light,[13] heat,[14] electrons,[15] chemical,[16] pH,[17] binding events,[18] etc.). Generally, the external stimulus alters the structure of one of the binding sites so as to change the relative binding affinities of the stations for the macrocycle, placing the system out of co-conformational[19] equilibrium. Relaxation toward the new global minimum subsequently occurs by the macrocycle moving along the thread. A typical example[13j] of a light-switchable amide-based molecular shuttle is shown in Scheme 1.

However, we can also think of stimuli-responsive molecular shuttles in another way; we can consider just the thread portion of such a molecule as a machine that directionally transports a particle—the interlocked macrocycle—between two sites (compartments) on a one-dimensional potential energy surface.[20] The significance of considering a rotaxane in this way is that over

(9) (a) Schill, G. *Catenanes, Rotaxanes and Knots*; Academic Press: New York, 1971. (b) Amabilino, D. B.; Stoddart, J. F. *Chem. Rev.* **1995**, *95*, 2725−2828. (c) *Molecular Catenanes Rotaxanes and Knots*; Sauvage, J.-P., Dietrich-Buchecker, C. O., Eds.; Wiley-VCH: Weinheim, Germany, 1999.

(10) Hannam, J. S.; Lacy, S. M.; Leigh, D. A.; Saiz, C. G.; Slawin, A. M. Z.; Stitchell, S. G. *Angew. Chem., Int. Ed.* **2004**, *43*, 3260−3264.

(11) (a) Anelli, P. L.; Spencer, N.; Stoddart, J. F. *J. Am. Chem. Soc.* **1991**, *113*, 5131−5133. For the first example of an amide-based molecular shuttle see: (b) Lane, A. S.; Leigh, D. A.; Murphy, A. *J. Am. Chem. Soc.* **1997**, *119*, 11092−11093.

(12) The key feature of a rotaxane architecture from the point of view of molecular-level machines is that movement of the macrocycle in any direction other than along the thread is resisted by enormous steric forces up until the breaking point of covalent bonds in the macrocycle or the thread. This is a fundamentally different situation to a host−guest complex when, following de-complexation from the binding site, the motion of the ring is not restricted in any dimension and it is free to exchange with others in the medium. Simple host−guest/supramolecular systems cannot function as nanoscale mechanical machines unless restrictions on the exchange of the unbound species with the bulk apply (as happens with kinetically stable pseudo-rotaxanes) or the binding event brings about a mechanical (i.e., conformational) change in one of the molecular components. Similarly, molecules that are not kinetically stable—this includes some rotaxanes that are thermodynamically stable but kinetically labile—cannot behave as molecular machines if they exchange components with the bulk quicker than the time scale of their stimuli-induced change of position. Molecular machines designed to exploit motion have to be kinetically associated with their substrates throughout the operation of the machine.

(13) For examples of photochemically responsive molecular shuttles see: (a) Benniston, A. C.; Harriman, A. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1459−1461. (b) Benniston, A. C.; Harriman, A.; Lynch, V. M. *Tetrahedron Lett.* **1994**, *35*, 1473−1476. (c) Benniston, A. C.; Harriman, A.; Lynch, V. M. *J. Am. Chem. Soc.* **1995**, *117*, 5275−5291. (d) Murakami, H.; Kawabuchi, A.; Kotoo, K.; Kunitake, M.; Nakashima, N. *J. Am. Chem. Soc.* **1997**, *119*, 7605−7606. (e) Armaroli, N.; Balzani, V.; Collin, J.-P.; Gaviña, P.; Sauvage, J.-P.; Ventura, B. *J. Am. Chem. Soc.* **1999**, *121*, 4397−4408. (f) Ashton, P. R.; Ballardini, R.; Balzani, V.; Credi, A.; Dress, K. R.; Ishow, E.; Kleverlaan, C. J.; Kocian, O.; Preece, J. A.; Spencer, N.; Stoddart, J. F.; Venturi, M.; Wenger, S. *Chem. Eur. J.* **2000**, *6*, 3558−3574. (g) Wurpel, G. W. H.; Brouwer, A. M.; van Stokkum, I. H. M.; Farran, A.; Leigh, D. A. *J. Am. Chem. Soc.* **2001**, *123*, 11327−11328. (h) Brouwer, A. M.; Frochot, C.; Gatti, F. G.; Leigh, D. A.; Mottier, L.; Paolucci, F.; Roffia, S.; Wurpel, G. W. H. *Science* **2001**, *291*, 2124−2128. (i) Stanier, C. A.; Alderman, S. J.; Claridge, T. D. W.; Anderson, H. L. *Angew. Chem., Int. Ed.* **2002**, *41*, 1769−1772. (j) Altieri, A.; Bottari, G.; Dehez, F.; Leigh, D. A.; Wong, J. K. Y.; Zerbetto, F. *Angew. Chem., Int. Ed.* **2003**, *42*, 2296−2300. (k) Abraham, W.; Grubert, L.; Grummt, U. W.; Buck, K. *Chem. Eur. J.* **2004**, *10*, 3562−3568. (l) Murakami, H.; Kawabuchi, A.; Matsumoto, R.; Ido, T.; Nakashima, N. *J. Am. Chem. Soc.* **2005**, *127*, 15891−15899. (m) Schmidt-Schäffer, S.; Grubert, L.; Grummt, U. W.; Buck, K.; Abraham, W. *Eur. J. Org. Chem.* **2006**, 378−398. (n) Wang, Q.-C.; Ma, X.; Qu, D.-H.; Tian, H. *Chem. Eur. J.* **2006**, *12*, 1088−1096. (o) Balzani, V.; Clemente-León, M.; Credi, A.; Ferrer, B.; Venturi, M.; Flood, A. H.; Stoddart, J. F. *Proc. Natl. Acad. Sci. U.S.A.* **2006**, *103*, 1178−1183.

(14) For an example of entropy-driven shuttling see: Bottari, G.; Dehez, F.; Leigh, D. A.; Nash, P. J.; Pérez, E. M.; Wong, J. K. Y.; Zerbetto, F. *Angew. Chem., Int. Ed.* **2003**, *42*, 5886−5889.

(15) For examples of electrochemically responsive molecular shuttles see ref 13e, 13o and (a) Bissell, R. A.; Córdova, E.; Kaifer, A. E.; Stoddart, J. F. *Nature* **1994**, *369*, 133−136. (b) Collin, J.-P.; Gaviña, P.; Sauvage, J.-P. *New J. Chem.* **1997**, 525−528. (c) Ballardini, R.; Balzani, V.; Dehaen, W.; Dell'Erba, A. E.; Raymo, F. M.; Stoddart, J. F.; Venturi, M. *Eur. J. Org. Chem.* **2000**, 591−602. (d) Ashton, P. R.; Ballardini, R.; Balzani, V.; Credi, A.; Dress, K. R.; Ishow, E.; Kleverlaan, C. J.; Kocian, O.; Preece, J. A.; Spencer, N.; Stoddart, J. F.; Venturi, M.; Wenger, S. *Chem. Eur. J.* **2000**, *6*, 3558−3574. (e) Altieri, A.; Gatti, F. G.; Kay, E. R.; Leigh, D. A.; Martel, D.; Paolucci, F.; Slawin, A. M. Z.; Wong, J. K. Y. *J. Am. Chem. Soc.* **2003**, *125*, 8644−8654. (f) Long, B.; Nikitin, K.; Fitzmaurice, D. *J. Am. Chem. Soc.* **2003**, *125*, 15490−15498. (g) Kihara, N.; Hashimoto, M.; Takata, T. *Org. Lett.* **2004**, *6*, 1693−1696. (h) Tseng, H.-R.; Vignon, S. A.; Celestre, P. C.; Perkins, J.; Jeppesen, J. O.; Di Fabio, A.; Ballardini, R.; Gandolfi, M. T.; Venturi, M.; Balzani, V.; Stoddart, J. F. *Chem. Eur. J.* **2004**, *10*, 155−172. (i) Flood, A. H.; Peters, A. J.; Vignon, S. A.; Steuerman, D. W.; Tseng, H.-R.; Kang, S.; Heath, J. R.; Stoddart, J. F. *Chem. Eur. J.* **2004**, *10*, 6558−6564. (j) Tseng, H.-R.; Wu, D. M.; Fang, N. X. L.; Zhang, X.; Stoddart, J. F. *ChemPhysChem* **2004**, *5*, 111−116. (k) Steuerman, D. W.; Tseng, H.-R.; Peters, A. J.; Flood, A. H.; Jeppesen, J. O.; Nielsen, K. A.; Stoddart, J. F.; Heath, J. R. *Angew. Chem., Int. Ed.* **2004**, *43*, 6486−6491. (l) Jeppesen, J. O.; Nygaard, S.; Vignon, S. A.; Stoddart, J. F. *Eur. J. Org. Chem.* **2005**, 196−220.

the past decade physicists have developed formal theoretical mechanisms, deeply rooted in nonequilibrium statistical mechanics, which explain how the directional transport of Brownian particles can occur from periodic changes in a potential energy surface (e.g., by applying an oscillating electric field).[21,22] Many different possible types of these theoretical "Brownian ratchet" mechanisms have been suggested, including energy ratchets, information ratchets, flashing ratchets, tilting ratchets, and rocking ratchets.[22] These mechanisms have been successfully applied to the development of transport and separation devices for mesoscopic particles and macromolecules, microfluidic pumping, and quantum and electronic applications[23,24] and have also been shown to successfully account for the general principles that govern the operation of complex biological motors.[24,25] However, to date it is not known how such theoretical mechanisms correlate with the changes that occur in molecular structure during the operation of biological machines. What do individual peptide fragments do in order to bring about transport of an ion or molecule by a Brownian ratchet mechanism and why? We wondered whether examining how these principles can be applied to some much less sophisticated (in terms of function as well as structure) synthetic molecular machines could tell us something about how they might apply to more complex systems, both artificial and natural.

Statistical Balance of a Dynamically Exchangeable Substrate or Quantity (The Principle of Detailed Balance)

If we ignore the normally small population of rings on the spacer, at equilibrium the macrocycle in a molecular shuttle can be considered to continuously fluctuate between the two stations. However, even for a molecular shuttle with two different stations, at equilibrium no net task can be performed by these movements. This is a consequence of the "Principle of Detailed Balance";[26] at equilibrium transitions between any two states take place in either direction at the same rate so that no flux is generated. This rules out the maintenance of equilibria by cyclic

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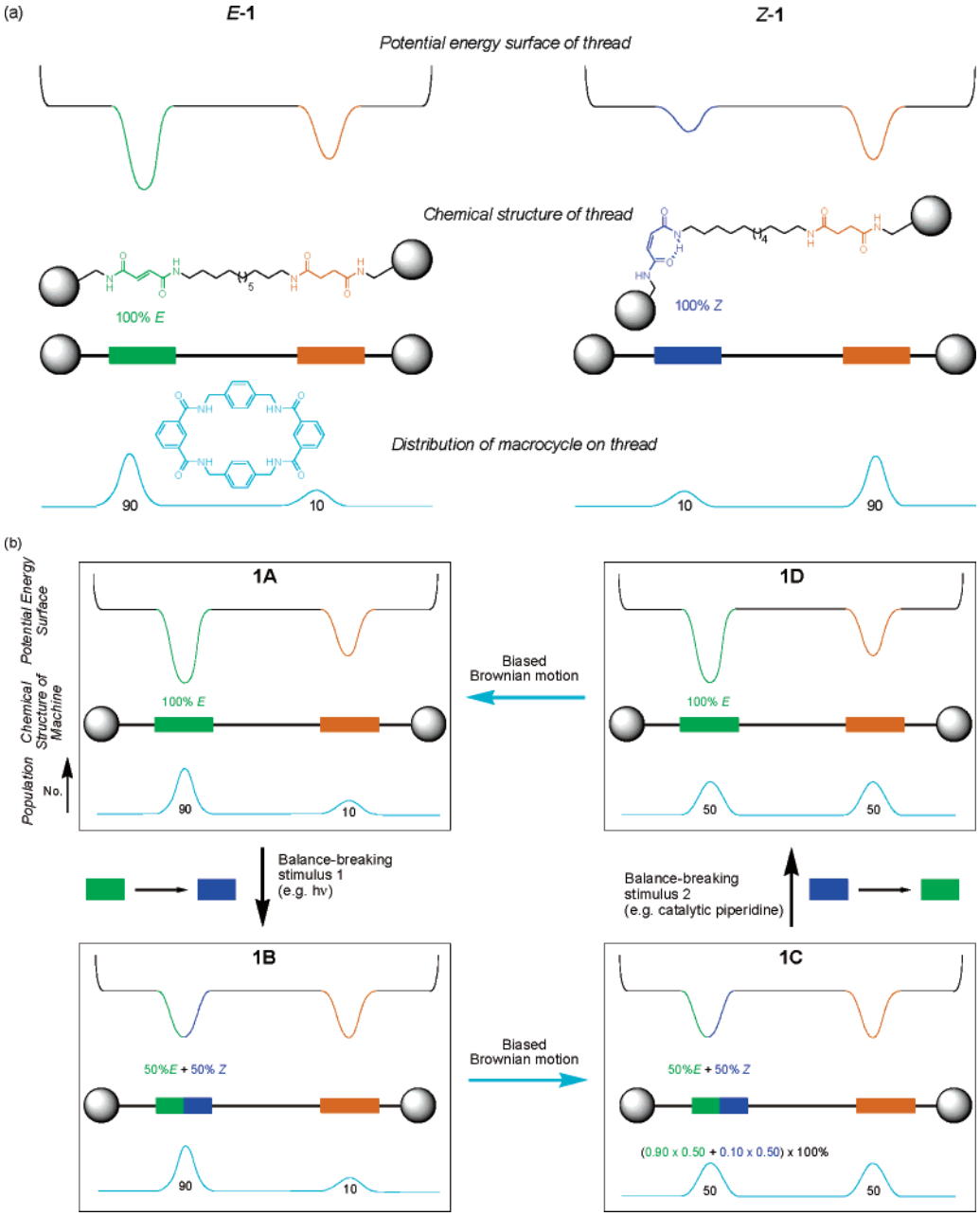
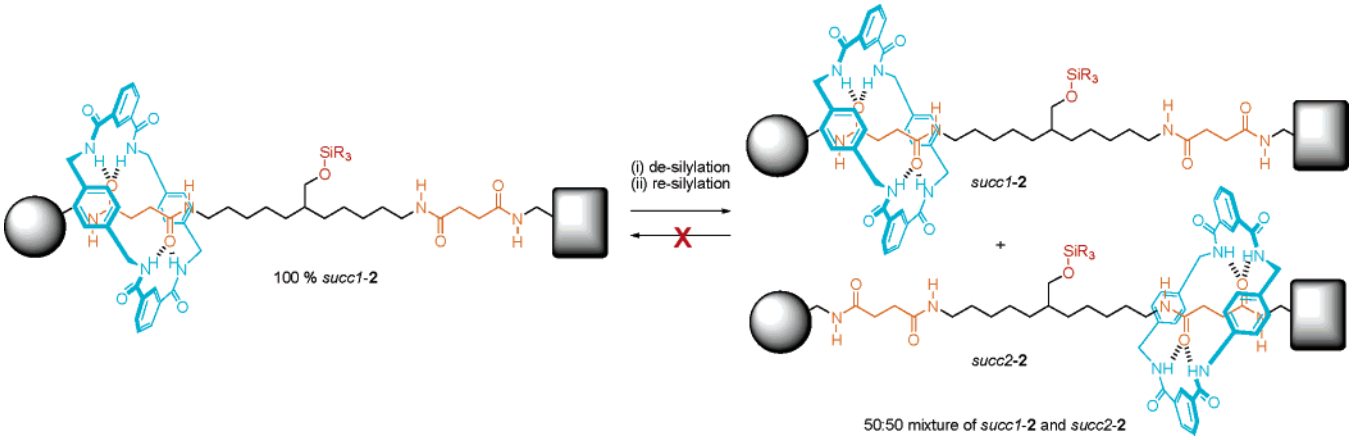
Scheme 2 [a,b]



[a] Description of *E*-**1** and *Z*-**1** in covalent, thermodynamic, and statistical terms, assuming a 90:10 distribution of translational isomers in each olefin diastereomer. [b] "Machine-performance representation" of the forward (**1A** → **1C**) and backward (**1C** → **1A**) operations of machine−substrate system **1**, assuming a 50:50 olefin mixture at the photostationary state. The chemical structure of the machine (thread) is shown at each stage in cartoon form with the fraction of olefin diastereomers indicated in terms of color of a station. The potential energy surface shown is the average potential energy surface of the thread for the macrocycle at that stage of the machine operation, i.e., the appropriately weighted combination of the potential energy surfaces for each of the olefin diastereomers (see (a)) contributing to the mixture. The population trace shows the overall distribution of the substrate over the machine.

processes such as A → B → C → A rather than A⇆B + B⇆C + C⇆A (ref 21b) and is a formal indication that a machine such as Smoluchowski's Trapdoor (Figure 1d) cannot operate (at least not in the way originally envisaged). However, in an out-of-equilibrium system, detailed balance is broken and as the system moves spontaneously toward equilibrium net work *can* be done by the fluxional exchange process. It is well-established that breaking detailed balance is a requirement for doing work with stochastic transport systems.[22] However, we recently pointed out that detailed balance could be considered to result from two separate properties of a system;[8d] the statistical distribution of a quantity (an imbalance in which provides the thermodynamic impetus for net transport) and the ability of that quantity to be dynamically exchanged (which provides the communication necessary for transport to occur). It is no coincidence that all four of the Gedankenmaschinen shown in Figure 1 disconnect the compartments at various stages during their operation in order to try and achieve net particle transportation. The molecular examples in this paper (vide infra) show that the deconvolution of the statistical "balance" and the "linkage" of compartments is useful for establishing the phenomenological nature of ratcheting and escapement (the counterpart to ratcheting) in Brownian transport processes.

Scheme 3. A Type of [2]Rotaxane that can Act as an Irreversible Mechanical Switch[a]



[a] R_3SiO- is a silyl ether that is too bulky to allow macrocycle exchange between the succinamide stations.

Systematic Behavior of Some Simple Molecular Machines

Let us consider how a stimuli-responsive rotaxane such as **1** (Scheme 1) performs the mechanical task of changing the average position of the ring along the thread. So that we can clearly see how the system evolves as this task is performed, we will represent it at each stage (Scheme 2) in terms of the covalent structure of the machine, that is, the thread (chemical status), the average potential energy surface (physical status of the machine, governed by noncovalent interactions—attractive forces between machine and substrate such as H-bonding, and repulsive forces such as steric barriers), and the statistical distribution of the substrate being transported (the macrocycle). In these types of schemes, which we shall call "machine-performance representations", we will use bold numbers to show different systems (**1**, **2**, **3**... etc.) and lettered suffixes to differentiate states of the system (**1A**, **1B**, **1C**.... etc.). In Scheme 2 we assume the photostationary state is 50:50 *E*:*Z* and that the preferred ratio of occupancy between fumaramide (green) and succinamide (orange) stations is 90:10 and between maleamide (dark blue) and succinamide 10:90.

The initial state of the system (**1A**) is statistically balanced. The average position of the macrocycle (from the Boltzmann distribution) is very close to the green station. A photonic stimulus ("balance-breaking stimulus") causes isomerization of some of the olefins from *E* to *Z*, putting the position of the macrocycle in the molecules that are isomerized momentarily out of equilibrium (**1B**, similarly **1D**). The system acts to restore balance through biased Brownian motion of the macrocycles and we arrive at the final state, **1C**. The change in state between **1B** and **1C** (and also between **1D** and **1A**) is not triggered externally; rather it is a thermally activated relaxation step in which the average position of the macrocycle (given by the Boltzmann distributions within the olefin isomers multiplied by their contribution to the photostationary state) moves along the thread toward the orange station. Note, however, that the machine—the thread—cannot use the energy from the photon to perform the transportation task in such a way that the position of the substrate becomes independent of the state of the machine; applying a second stimulus to reset the machine (e.g., adding piperidine to reform the *E*-olefin of the thread) undoes the net displacement of the macrocycle (**1C** → **1A**).

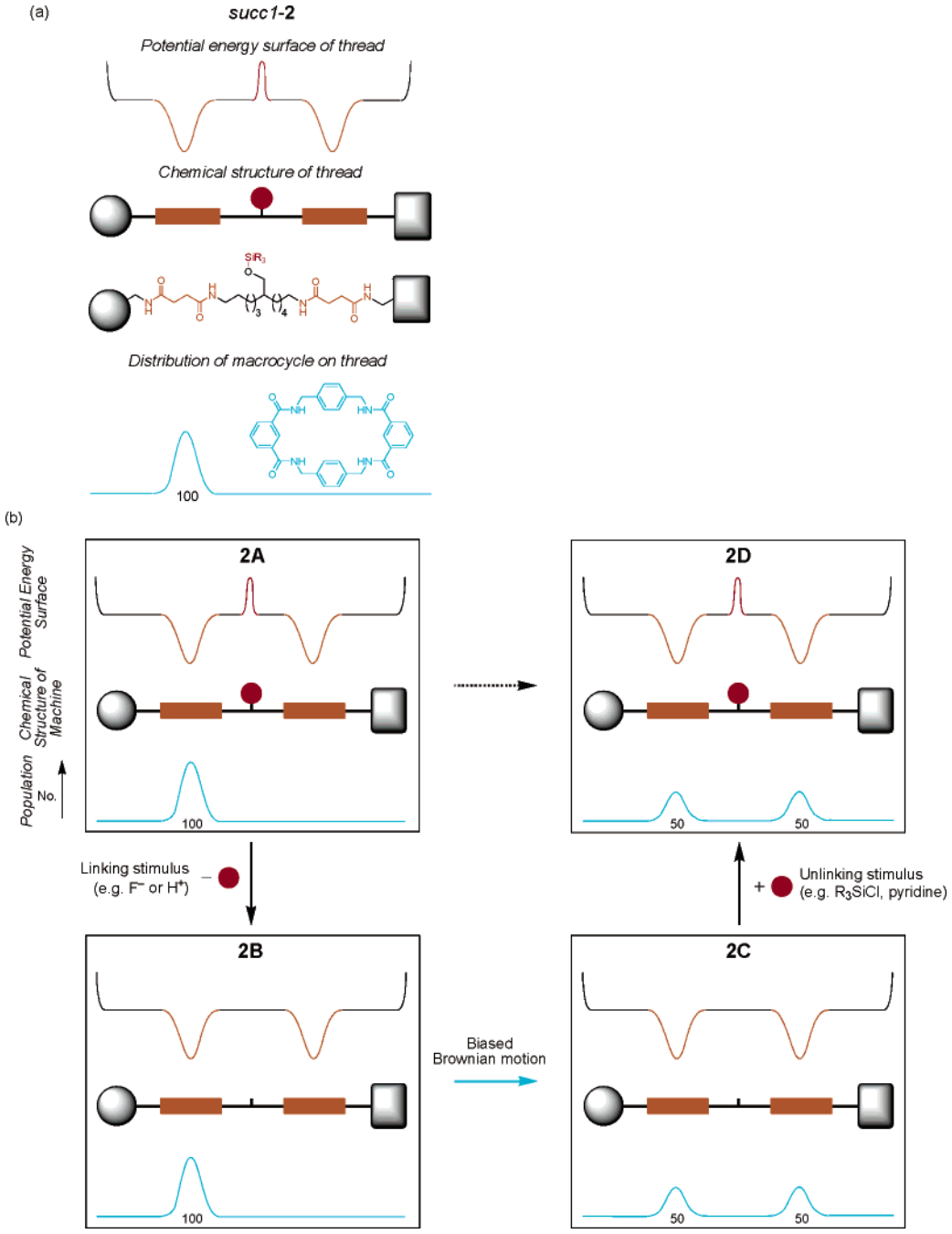
Now let us consider a new type of rotaxane system, **2**, in which a stimuli-induced change of position of the macrocycle also occurs but through a clearly different mechanism to the previous shuttle (Scheme 3). In **2** the two stations are structurally identical (but distinguishable—note the differently depicted stoppers) and a bulky group acts as a barrier which prevents the ring from moving between them. If we start with 100% of the rings on the first station, *succ1*-**2**,[27] and then remove the barrier, the system moves toward equilibrium, causing an average displacement of the macrocycle of half the distance separating the two stations.

Again, we can see how this system evolves more clearly using a "machine-performance representation" (Scheme 4). Unlike system **1**, machine−substrate system **2** starts out statistically unbalanced (**2A**). The stimulus required is also different from that used in the first system: a "linking stimulus" lowers the barrier between the two stations (**2B**), allowing the system to fulfill the impetus to restore balance and move to equilibrium by biased Brownian motion of the macrocycle (**2C**, note that the energy well-depths of the two stations are the same; the macrocycle is not held more tightly by the station it moves to). Raising the barrier by applying an "unlinking stimulus" resets the machine—the thread—but this time the task it has performed is *not* undone (**2D**). However, we note that if we try applying the linking stimulus again after the machine is reset, the machine does not change the average position of the macrocycle because the system is already statistically balanced (Scheme 4).

This stimuli-induced irreversible net change of position of the macrocycle represents a new type of molecular shuttle in phenomenological terms and so we prepared an experimental example, **3**, in single translational isomer form (*succ1*-**3**) according to Scheme 5. The unoccupied thread, **4**, was also synthesized as a comparison for ^{1}H NMR purposes. To be able to distinguish between the two succinamide stations through ^{1}H NMR spectroscopy but still keep them similar in terms of macrocycle binding affinity, the terminal right-hand side (as depicted in Scheme 5) amide group was derivatized with a

(27) The nomenclature used to denote individual rotaxane configurational and translational isomers follows conventions introduced in previous papers (e.g., ref 8d). Namely, a bolded compound number refers to a given structural formula irrespective of functional group configuration or position of the macrocycle; a prefix *E* or *Z* describes the configuration of the olefin; a prefix *succ1*, *succ2*, *fum*, or *mal* denotes the position of the macrocycle in a particular translational isomer.

Scheme 4 [a,b]



[a] Description of *succ1*-**2** in covalent, thermodynamic, and statistical terms. [b] "Machine-performance representation" of a [2]rotaxane that acts as an irreversible mechanical switch. **2A**: The macrocycle is locked on one of the two energetically identical but distinguishable stations by a large kinetic energy barrier. **2B**: A linking stimulus lowers the barrier. **2C**: The thermal bath restores equilibrium via biased Brownian motion. **2D**: An unlinking stimulus resets the machine. Note that repeating the cycle of chemical reactions would not change the distribution of the macrocycle for a second time.

phenyl group. Aryl-substituted tertiary amides preferentially adopt an *anti*-arrangement of the alkyl groups so there is no complication with slowly interconverting rotamers in the ^{1}H NMR spectra.[28,29] (Tertiary aryl-substituted fumaramide groups are excellent templates for benzylic amide macrocycle rotaxane formation.[30]) A 4-picolyl fragment provides the necessary bulk for the rest of the stopper.

The synthetic route to *succ1*-**3** is worthy of some comment. The "gated" spacer that separates the two stations was prepared by double alkylation (orthogonal amine protecting groups) and subsequent Krapcho decarboxylation[31] of dimethyl malonate (Scheme 5, i−v). A fumaramide group was then attached, both to maximize the yield of rotaxane formation (step viii, 68%) and to provide a common route for the synthesis of *fum-E*-**5** (vide infra). Unmasking of the Fmoc-protected amine, followed by coupling with a succinic acid derivative (step ix), was

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(29) Note that there is no indication of multiple tertiary amide rotamers in the ^{1}H NMR spectrum of **4** (Figure 2a). For example, only one signal is observed for H_q.
(30) Leigh, D. A.; Nash, P. J. Manuscript in preparation.
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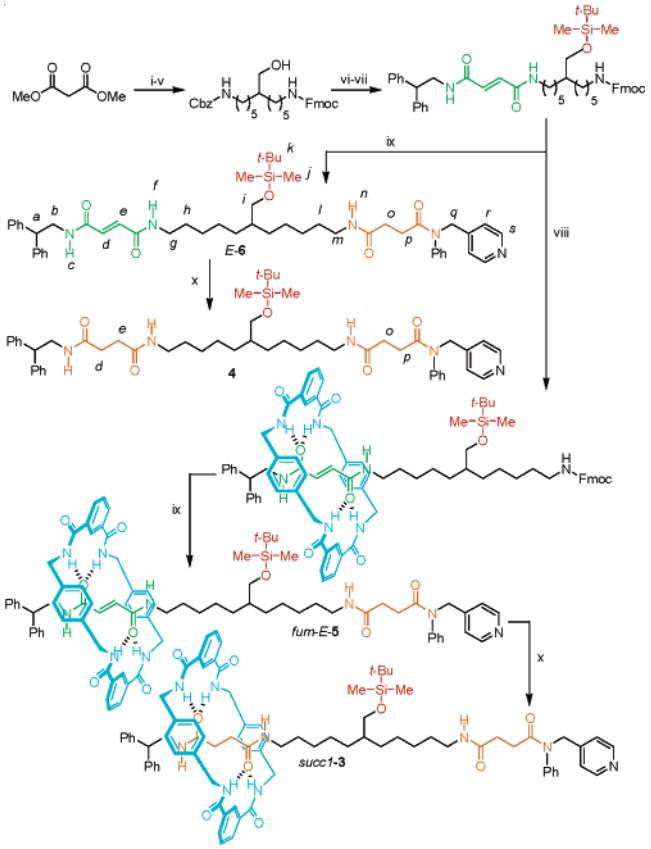
Scheme 5. Synthesis of Single Translational Isomer [2]Rotaxanes *succ1*-**3** and *fum-E*-**5** and the Corresponding Threads, **4** and *E*-**6**[a]

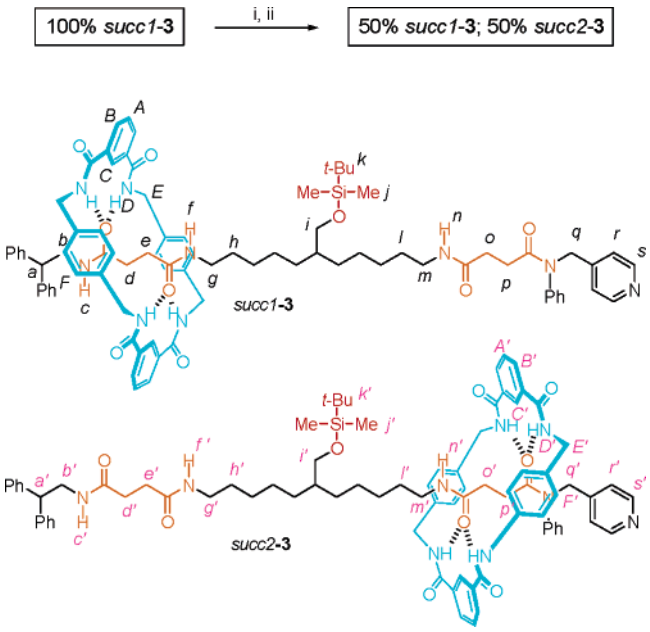


[a] Reaction conditions (unless otherwise stated, reactions were carried out at room temperature): (i) a. NaH, THF, 0 °C to rt, 1 h; b. Bu_4NI, *N*-benzyloxycarbonyl-5-bromo-1-pentylamine, THF, reflux, 12 h, 88%. (ii) a. NaH, THF, 0 °C to rt, 1 h; b. Bu_4NI, *N*-allyloxycarbonyl-5-bromo-1-pentylamine, THF, reflux, 12 h, 58%. (iii) LiCl, DMSO, H_2O, 160 °C, 4 h, 66%. (iv) Diisobutylaluminum hydride (1 M in toluene), THF, −78 °C, 4 h, 68%. (v) a. $PhSiH_3$, $Pd(PPh_3)_4$, CH_2Cl_2, 45 min; b. fluorenylmethylchloroformate (Fmoc-Cl), Et_3N, 0 °C, 30 min, 56%. (vi) a. H_2, 10% Pd/ C, HCl (1 M in Et_2O), MeOH, 1 atm, 1 h; b. (*E*)-3-(2,2-diphenylethylcarbamoyl)-acrylic acid, 1-[3-dimethylaminopropyl]-3-ethylcarbodiimide hydrochloride (EDCI·HCl), 1-hydroxybenzotriazole hydrate (HOBt·H_2O), Et_3N, CH_2Cl_2, 0 °C to rt, 2 h, 60%. (vii) *tert*-Butyldimethylsilyl chloride (TBDMSCl), imidazole, 4-(dimethylamino)pyridine (DMAP), CH_2Cl_2, 1 h, 63%. (viii) *p*-Xylylenediamine, isophthaloyl dichloride, Et_3N, $CHCl_3$, 3 h, 68%. (ix) a. Piperidine, THF:CH_3CN (1:3), 2.5 h; b. 4-oxo-4-(phenyl(pyridin-4-ylmethyl)amino)butanoic acid, EDCI·HCl, HOBt·H_2O, Et_3N, CH_2Cl_2, 0 °C to rt, 14 h, 47% (*E*-**6**), 48% (*fum-E*-**5**). (x) H_2, 10% Pd/C, THF, 1 atm, 6 h, 90% (**4**), 90% (*succ1*-**3**). Full experimental procedures can be found in the Supporting Information.

followed by hydrogenation (step x) of the fumaramide moiety. Perhaps surprisingly, the macrocycle appears to offer no significant protection to the thread functionality in this step,[32] which readily affords the two station rotaxane, **3**, as a single translational isomer, *succ1*-**3** (however, careful solvent selection is necessary to avoid cleavage of the silyl ether[33]).

The system functions (Scheme 6) as predicted in Scheme 4. De-silylation of *succ1*-**3** (Scheme 6, step i) followed by re-silylation (step ii) afforded a ∼1:1 mixture of the two translational isomers of **3**. Note, because *succ1*-**3** and *succ2*-**3** are not in equilibrium with each other, unlike *fum-E*-**1** and *succ-*

Scheme 6. Chemical Representation of the Irreversible Net Translocation of the Macrocycle that Occurs through the Transformation *succ1*-**3** → [*succ2*-**3** + *succ1*-**3**] (50:50 ± 2)[a]



[a] Reaction conditions: (i) 80% aqueous acetic acid, 60 °C, 1 h. (ii) TBDMSCl, imidazole, DMAP, CH_2Cl_2, rt, 1 h.

E-**1** for example (Scheme 1), the translational isomers of **3** are actually diastereoisomers.[10] The ^{1}H NMR spectra of the machine in the absence of the substrate (i.e., the free thread, Figure 2a),[29] the machine−substrate ensemble in its initial state (Figure 2b), and after application of the linking and unlinking stimuli (Figure 2c) are shown in Figure 2.

Again, let us consider what the mechanism of operation of the machine is: The stimuli applied to **3** switch "on" and "off" whether the stations are able to exchange the macrocycle or not. Linking of two parts of the machine which interact with the substrate allows the system to move toward equilibrium, that is, toward a statistically balanced state. This is a molecular-level form of "escapement", the element of the mechanism that controls the release of potential energy to drive mechanical motion in clocks and other macroscopic mechanical devices.[34]

Let us combine the features of the first two rotaxanes, **1** and **3**, to invent a third type of molecular machine system, **5**, and see how it functions. Rotaxane **5** was synthesized as a single configurational and translational isomer, *fum-E*-**5**, along with the corresponding thread *E*-**6**, according to Scheme 5. The reaction profile of this rotaxane is outlined in Scheme 7 in standard chemical terms and its performance as a machine−substrate ensemble is shown in Scheme 8.

The xylylene rings of the macrocycle shield the regions of the thread that they encapsulate and the resulting shifts in the ^{1}H NMR spectra are diagnostic of the position of the macrocycle on the thread.[13j] Thus, the operation of the machine and its effect on the substrate can be followed by ^{1}H NMR spectroscopy (Figure 3). In particular, it is instructive to observe the change in intensity of the unoccupied fumaramide station protons $H_{d'}$ and $H_{e'}$ (H_d and H_e in *E*-**6**) during the operation of the machine. In the free thread they appear as a pair of doublets at 6.86 and

(32) Parham, A. H.; Windisch, B.; Vögtle, F. *Eur. J. Org. Chem.* **1999**, 1233−1238.
(33) Sajiki, H.; Ikawa, T.; Hattori, K.; Hirota, K. *Chem. Commun.* **2003**, 654−655.
(34) (a) Britten, F. J. *Escapements: Their Actions Constructions and Proportion*; Arlington Book Co: U.S.A., 1985. (b) Gazeley, W. J. *Clock and Watch Escapements*; Robert Hale & Co.: 1999.

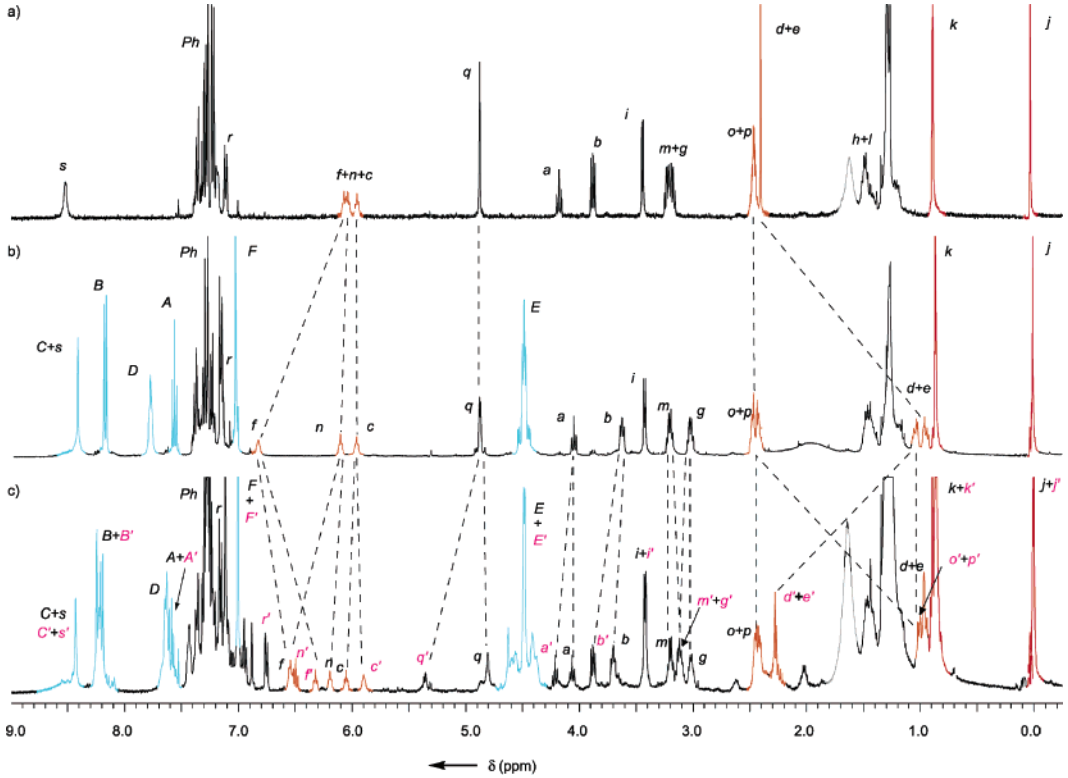


Figure 2. ^{1}H NMR spectra (400 MHz, $CDCl_3$, 298 K) of (a) free thread **4**, (b) *succ1*-**3**, and (c) mixture of translational isomers *succ1*-**3** and *succ2*-**3** after the two-step operation (Scheme 6, (i) and (ii)). Integration shows the *succ1*-**3**:*succ2*-**3** ratio in (c) is 50:50 (±2%). The ^{1}H NMR assignments and coloring correspond to the labeling in Schemes 5 and 6. Residual water peaks are shown in gray.

7.02 ppm (Figure 3a); they are absent in the spectrum of pure *fum*-*E*-**5** (Figure 3b); in the statistically balanced (unlinked) system (Figure 3c) they account for ~15% of the overall population; in the final ratcheted system (Figure 3d) they are ~56% of the reaction mixture.

So, in Scheme 8, the two parts of the machine start out (**5A**) statistically balanced (85% of the macrocycles on the fumaramide station; 15% on the succinamide station) and unlinked (and therefore not in equilibrium). A balance-breaking stimulus ($h\nu$ at 312 nm,[35] which generates a 49:51 ±2% *E*:*Z* photostationary state by ^{1}H NMR, not shown) is applied, giving **5B**. Removal of the barrier ("linking stimulus"; 80% aqueous acetic acid) gives **5C** and allows balance to be restored through moving to equilibrium by biased Brownian motion of the ring (**5D**). Restoring the barrier ("unlinking stimulus"; TBDMSCl, base) makes the system (**5E**) unlinked and not in equilibrium, although statistically balanced. The resetting step (a different balance-breaking stimulus; catalytic piperidine, to promote the $Z \rightarrow E$ olefin isomerization) makes the system statistically unbalanced, unlinked, and not in equilibrium (**5F**).

After the operational cycle of the machine (i.e., **5F**) the unoccupied fumaramide station protons $H_{d'}$ and $H_{e'}$ account for ~56% of the reaction mixture (Figure 3d).[36] Given that the photostationary state from irradiation of *E*-**5** at 312 nm is 49:51 ±2% *E*:*Z*, and that the statistically balanced distribution of the macrocycle is 85:15 between the *fum* and *succ* stations of *E*-**5** (Figure 3c), the final 44:56 *fum*-*E*-**5**:*succ*-*E*-**5** ratio indicates that the equilibrium distribution of translational isomers between the *mal* and *succ* stations in the de-silylated (linked) derivative of *Z*-**5** is ~5:95 in CH_2Cl_2 at room temperature.[37] The transportation of the macrocycle in **5** is repeatedly reversible between the statistically balanced 85:15 and statistically unbalanced 44:56 ratios of *fum*-*E*-**5** to *succ*-*E*-**5**.[38]

The thread has therefore successfully 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!—and the machine, the thread, has returned to its initial state. We recognize this behavior as "ratcheting", a characteristic of the operating mechanism of many biological molecular machines. For the first time, we have a molecular shuttle which is more sophisticated in terms of task performance than a simple mechanical switch. The compartmentalized machine achieves this result by applying four different stimuli which govern in turn the thermodynamics and the kinetics for transport between the two stations: balance-breaking 1; linking; unlinking; balance-breaking 2 (resetting—of the machine, not the substrate).[39]

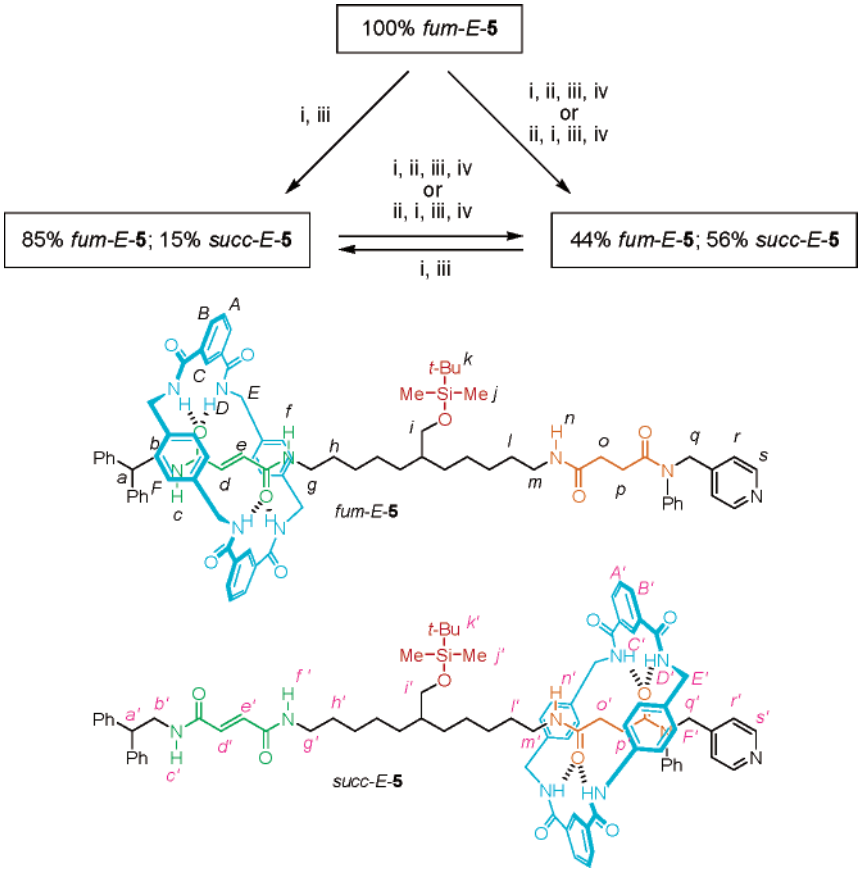
(35) Some degradation of rotaxane **5** occurs upon irradiation at 254 nm; however, at 312 nm no degradation or side reactions are apparent and the photostationary state is 49:51 ± 2 *E*:*Z* by ^{1}H NMR spectroscopy.

(36) Note how the chemical shifts of some of the protons (e.g., H_d and H_e) in *fum*-*E*-**5** change among Figures 3b, 3c, and 3d, illustrating the sensitivity of the H-bonding between the macrocycle and thread to factors such as moisture, concentration, and possibly, impurities.

(37) This calculation assumes that both translational isomers of de-silylated *Z*-**5** are re-silylated at the same rate. If this is not true, if the position of the macrocycle on a station affects the rate of the unlinking reaction, then it is possible to produce a nonbalanced distribution of the macrocycle through just controlling kinetic energy barriers with the position of the ring—an "information ratchet" (ref 25b).

(38) The pure single translational isomer *fum*-*E*-**5** cannot be regenerated by the operation of the machine but it can be separated from the reaction mixture at any stage using standard purification protocols.

Scheme 7. Chemical Representation of the Operation of Machine−Substrate System **5**[a]



[a] Reaction conditions: (i) 80% aqueous acetic acid, 60 °C, 1 h. (ii) *hν* at 312 nm (5 × 5 min irradiation),[35] CH_2Cl_2, rt. (iii) TBDMSCl, imidazole, DMAP, CH_2Cl_2, rt, 1 h. (iv) Piperidine, CH_2Cl_2, rt, 12 h, quantitative.

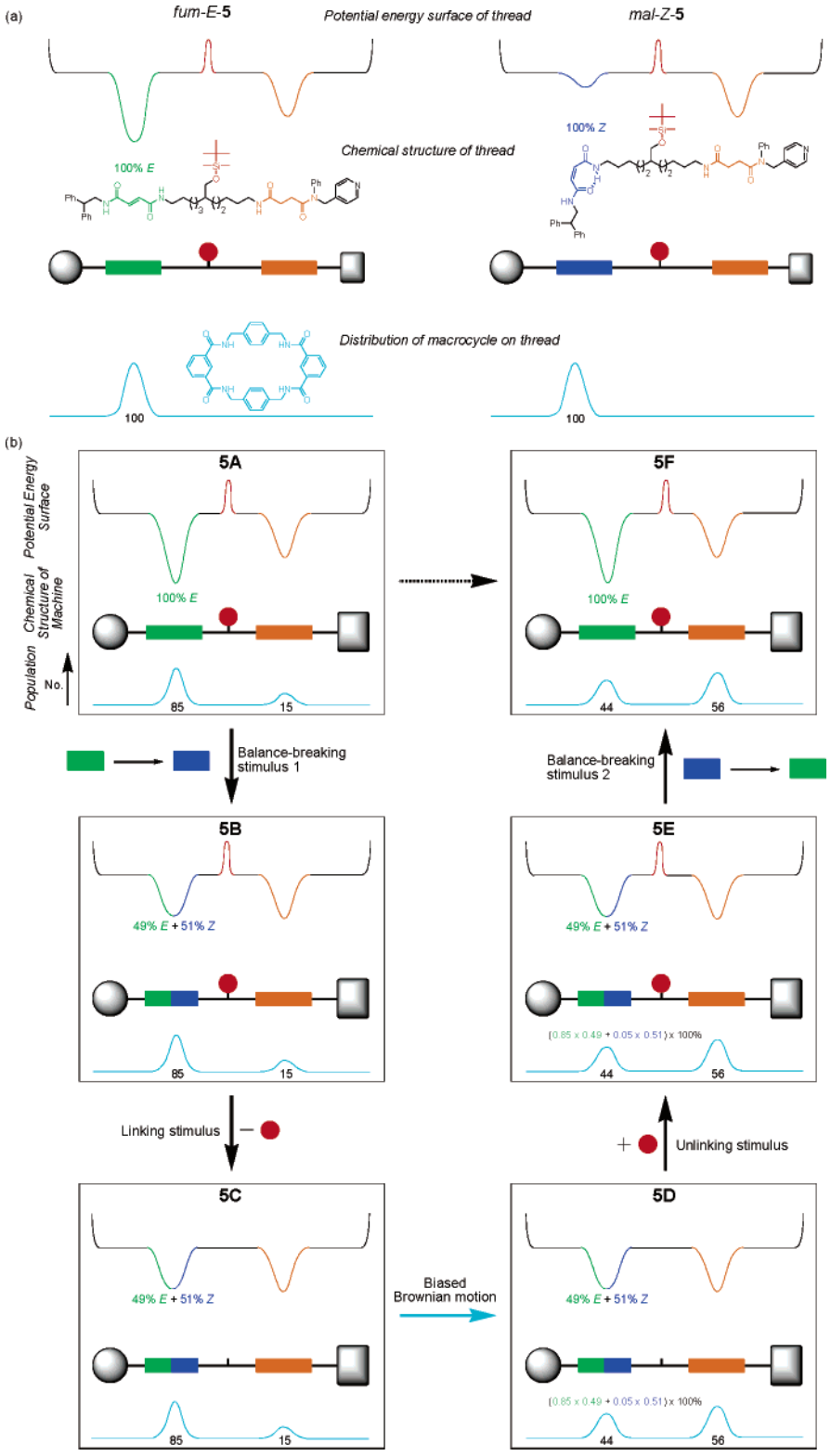
Through its operation in Scheme 7/8, rotaxane **5** establishes a thermodynamically unfavorable concentration gradient of the macrocycle between the compartments. This is the function envisaged for the thought-machine pressure demons shown in Figures 1b and 1d, albeit featuring many machines each acting on one Brownian particle in the case of the rotaxane rather than a single machine acting on many Brownian particles. However, the way in which **5** achieves this result is very different from either Gedankenmaschine design. During the operation of **5** the Brownian particle's position does not determine when or whether the linking stimulus is applied. This would require the communication of information regarding the particle's position to the machine, which *is* possible but would correspond to an "information ratchet"[25b] mechanism. Rather the rotaxane machine carries out its operations independent of the position of the particle by varying the potential energy surface minima as well as maxima in a partial so-called "energy ratchet"[25b,8d] mechanism (Figure 4).

As mechanical work is done by its operation, is it correct to categorize **5** as a molecular motor? No. Although the machine component of **5** acts to transport a substrate energetically uphill and can be reset without undoing the work done on the substrate, it cannot do so repetitively—a key requirement of a motor—because the succinamide compartment cannot be emptied of the ratcheted substrate. The escapement of the ratcheted quantity is the missing element required for **5** to operate for a second time without undoing the previously performed task by the action of resetting the machine.[40] This feature is present in a previously reported[8d] [2]catenane, **7**, in which the larger macrocycle acts as a motor that repetitively transports the small macrocycle directionally around itself according to a cyclic reaction scheme (Scheme 9). As with **5**, the olefin isomerization reactions in Scheme 9 are balance-breaking steps (depending on where one starts in the scheme, either can be considered to reset the machine); the manipulation of the trityl and silyl protecting groups are pairs of linking−unlinking steps which determine the pathway through which escapement of the ratcheted substrate occurs. Thus, the molecular machine in Scheme 9 operates by the following sequence: [balance-breaking 1; escapement (pathway A); ratcheting; balance-breaking 2 (reset machine); escapement (pathway B); ratcheting]$_n$.

(39) Starting from state **5A**, the linking and initial balance-breaking stimuli can be applied in either order (or simultaneously) in Scheme 8 for the task to be performed by the machine on the substrate, i.e., net transport of the macrocycle along the thread. In fact, any orthogonal transformations that transpire between two unlinking operations are commutative. Indeed, in a classic energy ratchet mechanism (ref 25b)—say using an oscillating electric field to directionally transport a charged particle—the linking/unlinking and balance-breaking steps happen simultaneously which, of course, would have exactly the same effect as doing them sequentially as envisaged in Scheme 8. Balance-breaking and linking/unlinking steps also occur simultaneously during the operation of molecular shuttles containing cyclodextrins incorporated onto azobenzene or stilbene threads (refs 13d, 13i, 13l, 13n, 20b, 20c, 20d, 20f, and 20g).

(40) Although escapement occurs during the operation of **5**, it is not escapement of a quantity that had been previously ratcheted by the operation of the motor. Prior to escapement, the macrocycles located on the olefin station in **5** have only been statistically unbalanced by the action of the motor, not ratcheted.

Scheme 8 [a,b]



[a] Description of *fum*-*E*-**5** and *mal*-*Z*-**5** in covalent, thermodynamic, and statistical terms. [b] "Machine-performance representation" of a compartmentalized molecular machine that can transport a substrate energetically uphill and be reset without undoing the task. **5A**: Initially balanced and unlinked. **5B**: Unbalanced and unlinked. **5C**: Unbalanced and linked (detailed balance is broken). **5D**: Balanced and linked. **5E**: Balanced and unlinked. **5F**: Unbalanced and unlinked. Note the chemical structure of the thread in **5F** is identical to that in **5A**—the machine has been reset—but the population distribution of the macrocycle has changed. The machine has successfully utilized the energy of the photon, via the olefin isomerization reactions, to do the work required to transport the substrate energetically uphill. The stimuli correspond to the reaction conditions given in Scheme 7.

Although rotaxane **5** does not fulfill the requirements for a motor, neither is it a simple switch since the machine part can be reset without influencing the distribution of the substrate. Significantly, examining the state of the machine (the rotaxane thread) in **5** does not provide information regarding the state (distribution) of the substrate. It is only from the history of the

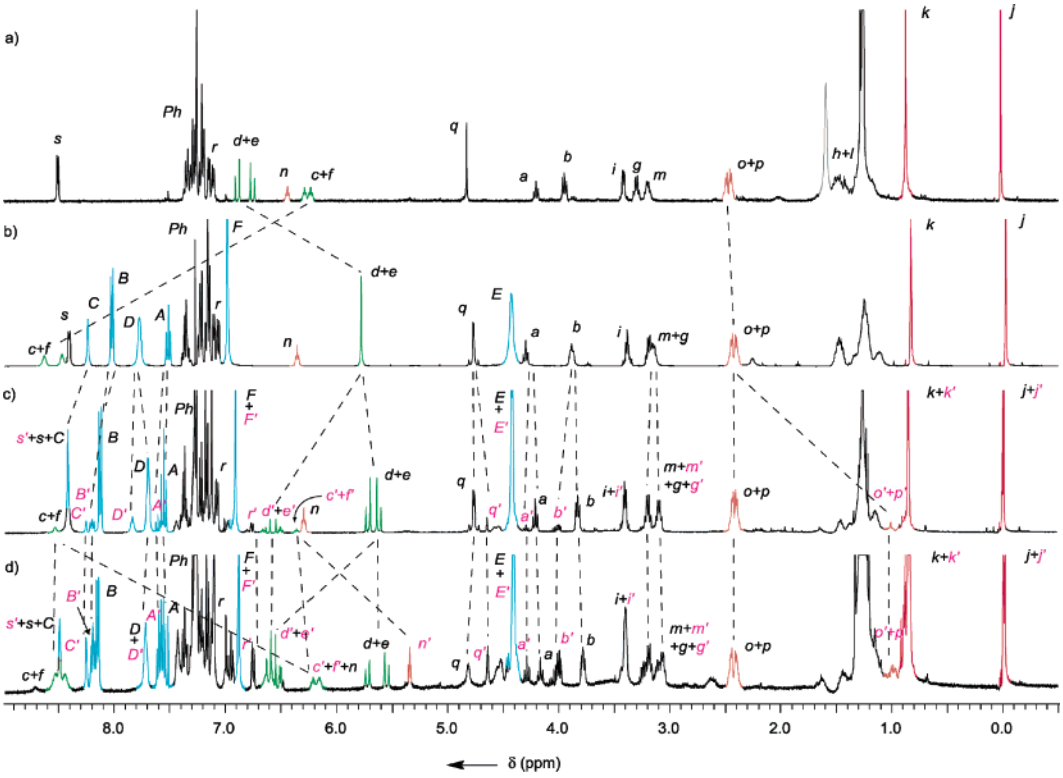


Figure 3. ^{1}H NMR spectra (400 MHz, $CDCl_3$, 298 K) of (a) free thread *E*-**6**, (b) *fum*-*E*-**5**, (c) statistically balanced *E*-**5**, the 85:15 mixture of *fum*-*E*-**5** and *succ*-*E*-**5** that results from desilylation/resilylation of *fum*-*E*-**5** (Scheme 7, (i) and (iii)), and (d) 44:56 (±2%) mixture of *fum*-*E*-**5** and *succ*-*E*-**5** that results from the four-step operation of the machine, either starting from *fum*-*E*-**5** or the 85:15 *fum*-*E*-**5**:*succ*-*E*-**5** statistically balanced mixture (Scheme 7, (i), (ii), (iii), (iv) or (ii), (i), (iii), (iv); Scheme 8, **5A** → **5F**). The ^{1}H NMR assignments and coloring correspond to the labeling in Schemes 5 and 7. Residual water peaks are shown in gray.

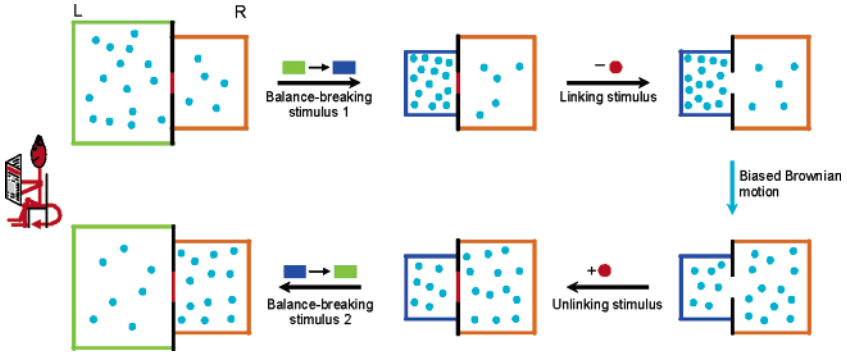
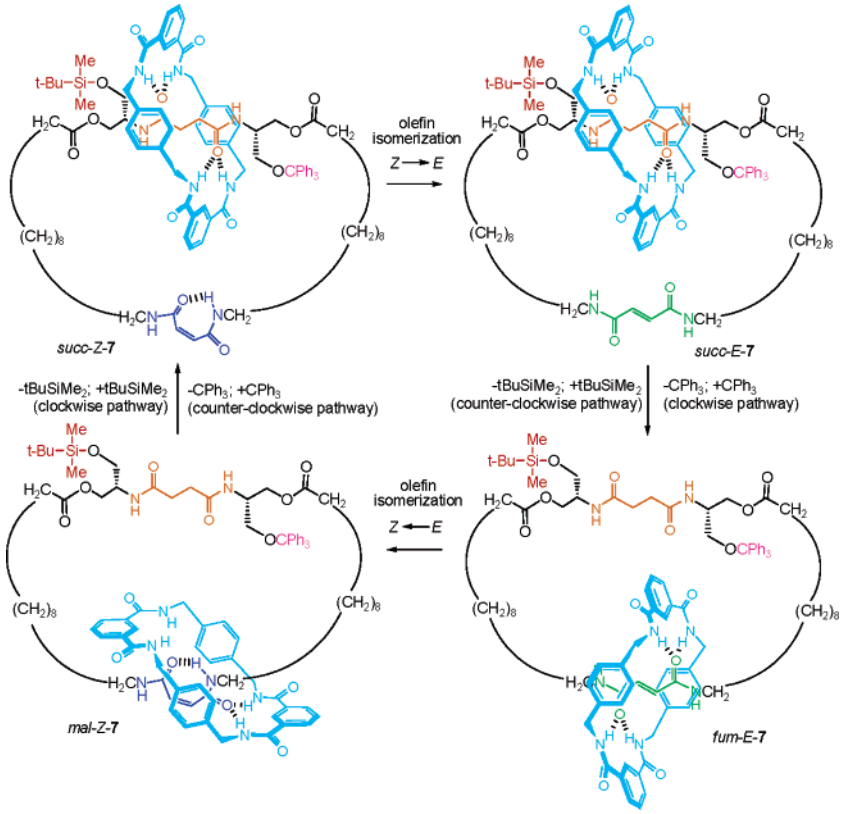


Figure 4. The operation of machine−substrate **5** in Schemes 7 or 8 is the experimental realization (albeit nonadiabatic) of the transportation task required of Smoluchowski's Trapdoor[5] (Figure 1d) and Maxwell's Pressure Demon[4c] (Figure 1b). The mechanistic equivalent of the illustrations from Figure 1 is shown above. The colors of the compartments, particles, and door are the same as the corresponding elements of **5**. The initially balanced (in proportion to the sizes of the two compartments) distribution of the Brownian particles between the left (L) and right (R) compartments becomes statistically unbalanced by a change in volume of the left-hand compartment. Opening the door allows the particles to redistribute themselves according to the new size ratio of the compartments. Closing the door ratchets the new distribution of particles. Restoring the left-hand compartment to its original size then results in a concentration gradient of the Brownian particles across the two compartments. There is no role for an information-gathering demon in this mechanism.

machine's operations that the distribution of the substrate can be known; in other words, the net position of the macrocycle in rotaxane **5** is a consequence of a form of sequential logic. This type of logic is different from that utilized in most of the Boolean logic chemical systems investigated to date, which feature combinational logic (the outputs are solely a function of the inputs at that moment in time).[41] In fact, the behavior of **5** is characteristic of a two-state (one bit) memory or "flip-flop" component in electronics.[42] A flip-flop maintains its effect on a system indefinitely until an input pulse operates on it, causing its output to change to a new indefinitely stable state according to defined rules.[43] Different variants include T-, S-R-, J-K-, and D-type flip-flops. We suggest that a molecule such as **5** should be termed a "two-state" Brownian flip-flop because the substrate must exist in one of two compartments

(41) Combinational logic circuits (NAND, NOR, OR, XOR, EOR, two- and three-input INH, etc.) are assembled by connecting combinations of AND, NOT, and OR gates in various ways. These, in turn, are assembled by connecting simple "on"−"off" switches in various ways. See: (a) Ben-Ari, M. *Mathematical Logic for Computer Science*; Prentice-Hall: Hemel Hempstead, 1993. For reviews on molecular-scale combinational logic systems see: (b) Raymo, F. M. *Adv. Mater.* **2002**, *14*, 401−414 and (c) de Silva, A. P.; McClenaghan, N. D. *Chem. Eur. J.* **2004**, *10*, 574−586. For the sequential operation of combinational logic gates see: (d) de Silva, A. P.; Dixon, I. M.; Gunaratne, H. Q. N.; Gunnlaugsson, T.; Maxwell, P. R. S.; Rice, T. E. *J. Am. Chem. Soc.* **1999**, *121*, 1393−1394 and (e) Raymo, F. M.; Giordani, S. *Org. Lett.* **2001**, *3*, 3475−3478.

Scheme 9. Previously Reported[8d] Synthetic Molecular Rotary Motor **7** that Operates through a Full Brownian Ratchet Mechanism



in each molecule. However, there is an important difference that arises because of the statistical nature of a two-state Brownian flip-flop compared to the digital nature of its electronic counterpart. If we wish to utilize the effect of *many* molecules of **5** on a system, the operation of the flip-flop can vary the bulk population distribution of the substrate between the two compartments over a continuum from 85:15 to 44:56 *fum*:*succ* by modifying the balance-breaking reaction parameters (e.g., by changing the time for which the photoisomerization stimulus is applied). If, on the other hand, we use a *single* molecule of **5** to influence a system, its effect is strictly binary—the molecule is in one state or the other—with the *fum*:*succ* ratios corresponding to the *probability* that the substrate will be in a particular compartment given the history of the inputs. In contrast, an electronic flip-flop is always utilized as a single entity in a circuit and its effect is therefore always binary.

Language Necessary To Describe the Operation and Mechanisms of Molecular-Level Mechanical Machines

Up to now the categorization of molecules as machines by chemists has largely been iconic—the structures "look" like pieces of machinery—or they are so-called because they carried out a function that in the macroscopic world would require a machine to perform it.[1] However, as function and mechanism replace imagery as the driving force behind advances in this field, the use of language needs to become more phenomenologically based. For this reason, on the basis of the systems described in this paper and those developed previously by ourselves, Kelly, Feringa, Stoddart and others,[8,10,13−18] we suggest below definitions for four significant phenomenological terms (ratcheting, escapement, balance, and linkage) that are crucial for machines that operate by controlled Brownian motion. Ratcheting is an often used, but previously ill-defined, process in chemical terms. Unfortunately, this vagueness has led to the term sometimes being applied to describe phenomena that are unrelated to Brownian ratchet mechanisms. Escapement is the counterpart to ratcheting and, as far as we are aware, has only rarely been used to describe molecular-level events. The statistical balance of a dynamic substrate and whether the parts of the machine acting on the substrate allow exchange of the substrate or not appear to be key factors that determine whether the machine can perform a task or not. In fact, it appears that the behavior of a molecular machine toward a substrate can be defined by the changing relationship (linked/unlinked; balanced/unbalanced) between the parts of machine interacting with the substrate.

(i) "Ratcheting" is the capturing of a positional displacement of a substrate through the imposition of a kinetic energy barrier which prevents the displacement being reversed when the thermodynamic driving force is removed. The key feature of ratcheting is that the ratcheted part of the system is not linked with (i.e., not allowed to exchange the substrate with) any part of the system that it is ratcheted from. Ratcheting is a crucial requirement for allowing a Brownian machine to be reset without undoing the task it has performed. An example of

(42) (a) Malvino, A. P.; Brown, J. A. *Digital Computer Electronics*, 3rd ed.; Glencoe: Lake Forest, 1993. (b) Mitchell, R. J. *Microprocessor Systems: An introduction*; Macmillan: London, 1995.

(43) A series of stimuli-responsive molecular shuttles have been shown to exhibit relatively long-lived nonequilibrium ("metastable") states when operating in self-assembled monolayers or a polymer electrolyte or at low temperatures (see refs 15i, 15j, and 15k). This may account for the junction hysteresis observed in solid-state electronic devices that utilize such rotaxanes (refs 20k−n). Kinetically stable nonequilibrium co-conformations have also been observed in cyclodextrin-based shuttles; see refs 13l and 16d.

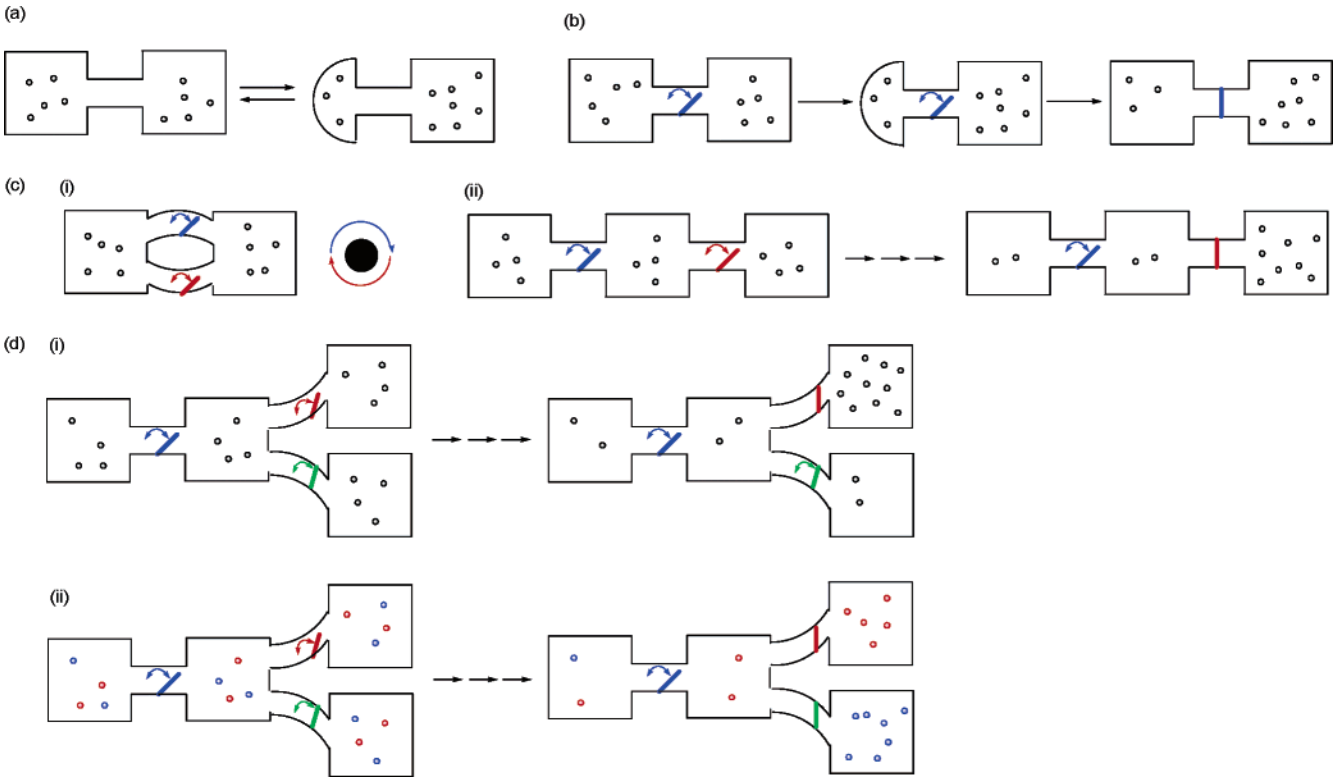


Figure 5. Schematic representations of some already realized (a−c(i)) and possible (c(ii), d) types of multicompartment molecular-level machines. (a) A two-state Brownian switch. (b) A two-state Brownian memory or flip-flop (shown operating through a partial energy ratchet mechanism; other mechanisms are also possible to achieve the same machine function). (c) Examples of Brownian motors: (i) a two-stroke rotary motor; (ii) a three-compartment translational motor. (d) Compartmentalized molecular-level machines that combine ratcheting and escapement with Boolean logic operations: (i) a four-compartment Brownian machine that pumps a substrate in a given (variable) direction. Deciding which one of the red or green gates is used for ratcheting determines whether the substrate is transported to the top compartment or the bottom. (ii) A four-compartment Brownian machine that sorts and separates different ions (e.g., red = Na^+; blue = K^+). A logic operation providing selective access through each of the red and green gates ensures one type of ion is pumped into each compartment.

ratcheting is the unlinking step **5D** → **5E** in Scheme 8. Because it is used to kinetically stabilize an ultimately thermodynamically unfavorable state, ratcheting is intrinsically associated with a sequential logic sequence applied to a Brownian substrate.

(ii) "Escapement" is the (directional) release of a ratcheted substrate in a statistically unbalanced system by lowering a kinetic energy barrier (i.e., by linking). The key feature of escapement is that it requires the linking of two unbalanced parts of a system that were previously unlinked. An escapement step must be subsequently ratcheted in order for a machine to be able to do work repetitively on a substrate. An example of escapement is the de-silylation step during the operation of the irreversible molecular shuttle *succ1*-**3** (Scheme 6, step (i)) or the analogous step for system **5** (**5B** → **5C**, Scheme 8).

(iii) "Balance" is the thermodynamically preferred distribution of an exchangeable quantity or substrate over a machine or parts of a machine. The impetus for net transportation of a substrate comes from balance being broken. (Note that "balance" being broken is not the same as "detailed balance" being broken; "balance" is the thermodynamic driving force for "detailed balance" to be broken.)

(iv) "Linkage" is the communication necessary for transportation of a substrate to occur between parts of a machine. However, the ability to exchange the substrate between the linked parts is not in itself enough for a task to be performed; there must also be a driving force for it to occur (vide supra). Linking and unlinking operations are purely kinetic parameters and so can be accomplished by simply changing the rate of reactions rather than introducing or removing physical steric or electronic barriers.

Types of Compartmentalized Molecular Machines

During development of the terminology necessary to describe molecular-level behavior scientifically, the standard dictionary definitions meant for everyday use are not always appropriate for regimes that the definitions were never intended to cover. As we have seen through the examples given in this paper, the difference between a molecular motor and a molecular switch is fundamental and profound because "motor" and "switch" become different phenomenological descriptors at Brownian length scales, not just iconic classifications of macroscopic objects. As another example, simple switches that operate through biasing Brownian motion do not stay in the same state if the thermodynamic driving force is turned off and it is important to distinguish them from other Brownian machines that do. Indeed, we can identify three different fundamental types of simple Brownian machines that act through various combinations of balance-breaking, linking/unlinking, ratcheting, and escapement steps—a Brownian switch (Figure 5a), a Brownian flip-flop (Figure 5b), and a Brownian motor (Figure 5c). Each of these machine types can also function as components in more complex molecular-level machines (Figure 5d).

(a) A "Two-state (or multistate) Brownian switch" is a machine which can reversibly change the distribution of a Brownian substrate (a moiety which undergoes Brownian motion) between two (or more) distinguishable sites as a

function of state of the machine. It does this by biasing the Brownian motion of the substrate (Figure 5a). Classic stimuli-responsive molecular shuttles, such as *E*/*Z*-**1** and those listed in refs 13−18 and 20, are examples of two-state (or three-state[14]) Brownian switches.

(b) A "Two-state (or multi-state) Brownian flip-flop" is a machine which can reversibly change the distribution of a Brownian substrate between two (or more) distinguishable sites and can be reset without restoring the original distribution of the substrate (Figure 5b). The statistical distribution of the substrate cannot be determined from the state of the flip-flop (unlike a switch, which influences a substrate as a function of state) but rather is determined by the history of operation of the machine, i.e., through a form of sequential logic. Rotaxane **5** is an example of a two-state Brownian flip-flop. It operates through a partial Brownian ratchet mechanism[44] consisting of the following steps applied to a pair of compartments: balance-breaking, escapement, ratcheting, and resetting of the machine (a second balance-breaking step). The original substrate distribution is restored by an escapement−unlinking sequence.

(c) A "Brownian motor" is a machine which can repetitively and progressively change the distribution of a Brownian substrate, during which the machine is reset without restoring the original distribution of the substrate (Figure 5c). Like a flip-flop, a Brownian motor affects a system as a function of the pathway that the machine takes, not as a function of state. Catenane **7** (Scheme 9) is an example of a two-stroke rotary Brownian motor (Figure 5c (i)).[8d] The substrate is repetitively transported between two sites via two alternating pathways. We shall shortly report on the synthesis and operation of a linear three compartment Brownian motor (Figure 5c (ii)).[45]

(d) By combining the three fundamental Brownian machine types which work through combinations of balance-breaking, linking/unlinking, ratcheting, and escapement with other combinational and/or sequential operations based on Boolean logic, machines that can carry out more complex functions, such as variable, directional, travel (Figure 5d (i)), and "sorting and separating" (Figure 5d (ii)), can be envisaged.

Apart from allowing a large amplitude one-dimensional motion to be considered independently of other movements, there is nothing special about rotaxanes in terms of mechanical mechanisms.[12,46] The relationships described in this paper are applicable to any type of molecular-level construct, with controlled motion possible in a kinetically associated structure in two or three dimensions as well as just one. They may also be useful in understanding the changes involved in biological machines as they bring about movement, function, and the transport of Brownian substrates (molecules and ions) in 1-D channels, across membranes, and between parts of a protein.

To appreciate the technological potential of controlled molecular-level motion, one only has to consider that it lies at the heart of virtually every biological process. When we learn how to build synthetic structures that can rectify random dynamic processes and interface their effects directly with other molecular-level substructures and the outside world, it will add a new dimension to functional molecule and materials design. An improved understanding of biological pumps, motors, and other cellular machines will surely also follow.

Experimental Procedures for the Operation of Machine−Substrate Systems 3 and 5

Machine−Substrate System 3. Step (i). A solution of [2]rotaxane *succ1*-**3** (80 mg, 0.057 mmol) in aqueous acetic acid (80%, 10 mL) was heated at 60 °C for 1 h. The reaction mixture was concentrated under reduced pressure and traces of acetic acid were removed with a toluene azeotrope (3 × 50 mL). To remove non-rotaxane impurities, the crude reaction mixture was filtered through a plug of silica gel (neat dichloromethane followed by dichloromethane:methanol 95:5) and the solvent removed under reduced pressure to furnish fully de-silylated material.

Step (ii). The de-silylated product from step (i) was dissolved in dichloromethane (20 mL) and treated with imidazole (70 mg, 1.0 mmol), *tert*-butyl-dimethylsilyl chloride (90 mg, 0.60 mmol), and a catalytic amount (5.0 mg) of 4-(dimethylamino)pyridine and the mixture stirred at room temperature for 1 h. To remove non-rotaxane impurities, the crude reaction mixture was filtered through a plug of silica gel (neat dichloromethane followed by dichloromethane:methanol 98:2) and the solvent removed under reduced pressure. The ^{1}H NMR spectrum in $CDCl_3$ of the isomeric mixture of *succ1*-**3** and *succ2*-**3** resulting from this two-step operation is shown in Figure 2c.

Machine−Substrate System 5. Step (i). A solution of [2]rotaxane *fum-E*-**5** (30 mg, 0.021 mmol) in aqueous acetic acid (80%, 2.0 mL) was heated at 60 °C for 1 h. The reaction mixture was concentrated under reduced pressure and traces of acetic acid were removed with a toluene azeotrope (3 × 5 mL). To remove non-rotaxane impurities, the crude reaction mixture was filtered through a plug of silica gel (neat dicholormethane followed by dichloromethane:methanol 95:5) and the solvent removed under reduced pressure to furnish fully de-silylated material.

Step (ii). A solution of the de-silylated product from step (i) (20 mg) in dichloromethane (50 mL) was placed in a quartz vessel, degassed with argon (3 × 5 min), and irradiated at 312 nm using a multilamp photoreactor for five successive 5 min sessions. The progress of the reaction was monitored by ^{1}H NMR spectroscopy. The photostationary state was reached after 20 min (4 × 5 min irradiations). The reaction mixture was concentrated under reduced pressure and used directly in the next step.

Step (iii). The de-silylated photoisomerized material (20 mg) was dissolved in dichloromethane (2.0 mL) and treated with imidazole (20 mg, 0.29 mmol), *tert*-butyldimethylsilyl chloride (26 mg, 0.17 mmol), and a catalytic amount (5.0 mg) of 4-(dimethylamino)pyridine. The reaction mixture was stirred for 2 h, during which time a colorless precipitate appeared. Water (2 mL) was added and the reaction mixture extracted with dichloromethane (5 mL). The organic layer was separated, washed with brine (saturated, 5 mL), dried over Na_2SO_4, and concentrated under reduced pressure to furnish the crude re-silylated isomeric mixture of rotaxanes. To remove non-rotaxane impurities, the mixture was filtered through a plug of silica gel (petroleum ether:ethyl acetate 8:2 followed by dichloromethane:methanol 8:2). This mixture was concentrated under reduced pressure and used directly in the next step.

Step (iv). To a solution of the re-silylated isomeric mixture of four rotaxanes from step (iii) (20 mg) in dichloromethane (1.0 mL) was added piperidine (100 μL, 1.0 mmol). The reaction was stirred for 12 h. To remove non-rotaxane impurities, the crude reaction mixture was filtered through a plug of silica gel (neat dichloromethane followed by

(44) Since the method of operation of **5** involves varying the relative heights of energy minima and maxima irrespective of the position of the macrocycle, this is a partial "energy ratchet" mechanism (ref 25b). Other types of mechanisms are known (see ref 22), for example, an "information ratchet" which achieves directional transport of a Brownian substrate by varying the relative heights of energy maxima using information provided by the position of the substrate (ref 25b).

(45) Chatterjee, M. N.; Goldup, S.; Kay, E. R.; Leigh, D. A. Manuscript in preparation.

(46) Indeed, their branched topologies rule out rotaxanes as architectures for the particular examples of compartmentalized machines shown in Figure 5d (i) and (ii).

dichloromethane:methanol 8:2) and the solvent removed under reduced pressure. The ^{1}H NMR spectrum in $CDCl_3$ of the isomeric mixture of *fum*-*E*-**5** and *succ*-*E*-**5** obtained after the four-step operation is shown in Figure 3d. An essentially identical ^{1}H NMR spectrum was obtained upon reversing the sequence of steps (i) and (ii).

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Supporting Information Available: Experimental procedures and spectroscopic data for *succ1*-**3** and *fum*-*E*-**5** and their precursors. This material is available free of charge via the Internet at http://pubs.acs.org. See any current masthead page for ordering information and Web access instructions.

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