Check for updates

FEBS Letters

FEBS PRESS science publishing by scientists

IN A NUTSHELL

Artificial molecular machines and motors—Design and control of nanoscale motion

Leonardo Andreoni[1,2] and Alberto Credi[1,2]

1 Dipartimento di Chimica Industriale "Toso Montanari", Alma Mater Studiorum – Università di Bologna, Bologna, Italy
2 CLAN-Center for Light Activated Nanostructures, Alma Mater Studiorum – Università di Bologna and Consiglio Nazionale delle Ricerche, Bologna, Italy

Correspondence
A. Credi, CLAN-Center for Light Activated Nanostructures, Alma Mater Studiorum – Università di Bologna and Consiglio Nazionale delle Ricerche, via Gobetti 101, 40129 Bologna, Italy
Tel: +39 051 6398320
E-mail: alberto.credi@unibo.it

(Received 30 June 2026, revised 30 July 2026, accepted 31 July 2026)

doi:10.1002/1873-3468.70463

Edited by Dietmar J. Manstein

Artificial molecular machines are multicomponent synthetic systems in which molecular parts undergo controlled motion in response to energy inputs. Inspired by biological molecular motors, these devices show how random nanoscale motion can be biased, directed, and coupled to function. This article introduces the principles of artificial molecular machinery for a broad biochemical audience, focusing on the physical features that distinguish motion at the molecular scale from macroscopic motion. Mechanically interlocked molecules, molecular shuttles, light-driven rotary motors, and supramolecular pumps are discussed as representative systems that convert chemical, electrical, or optical stimuli into switching, rotation, transport, and other functions. Together, they illustrate how chemistry can reproduce, simplify, and extend key concepts underlying dynamic processes in living systems.

Keywords: Brownian motion; catenane; mechanical bond; Ratchet mechanism; rotaxane; supramolecular chemistry

Introduction

Life is a nonequilibrium phenomenon in which endergonic physicochemical processes are sustained by exergonic ones that supply the required energy [1–3]. Complex molecular assemblies such as motor proteins are essential to life because they perform key functions including ATP synthesis, cargo transport, protein synthesis, and DNA replication [4,5]. Myosins, kinesins, ATP synthase, and the bacterial flagellar motor are among the best-studied examples: like macroscopic engines, they continuously convert the energy released by fuel-consuming reactions into mechanical work through directional motion, while dissipating energy to maintain nonequilibrium states.

About four decades ago, chemists began developing synthetic systems that mimic natural molecular motors. These artificial molecular devices use chemical, electrochemical, or photochemical inputs to induce mechanical-like motion of molecular components. The field has evolved from proof-of-principle demonstrations to studies targeting practical applications, and the 2016 Nobel Prize in Chemistry awarded to Jean-Pierre Sauvage [6], Fraser Stoddart [7], and Ben Feringa [8] recognized both the conceptual importance and technological promise of this research.

Molecular devices

In the macroscopic world, a device is an ordered assembly of components constructed to perform a specific function, where each component carries out a simple task and the overall behavior arises from their cooperation (Fig. 1A). This concept can be extended to the molecular level [9–13]: a molecular device can be thought of as a discrete multicomponent system in which individual molecular units—such as chromophores, recognition sites, or redox-active groups—

Abbreviations
ATP, adenosine triphosphate; MIM, mechanically interlocked molecules; PEZ, *E-Z* photoisomerization; THI, thermal helix inversion.

FEBS Letters (2026) © 2026 The Author(s). *FEBS Letters* published by John Wiley & Sons Ltd on behalf of Federation of European Biochemical Societies.
This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

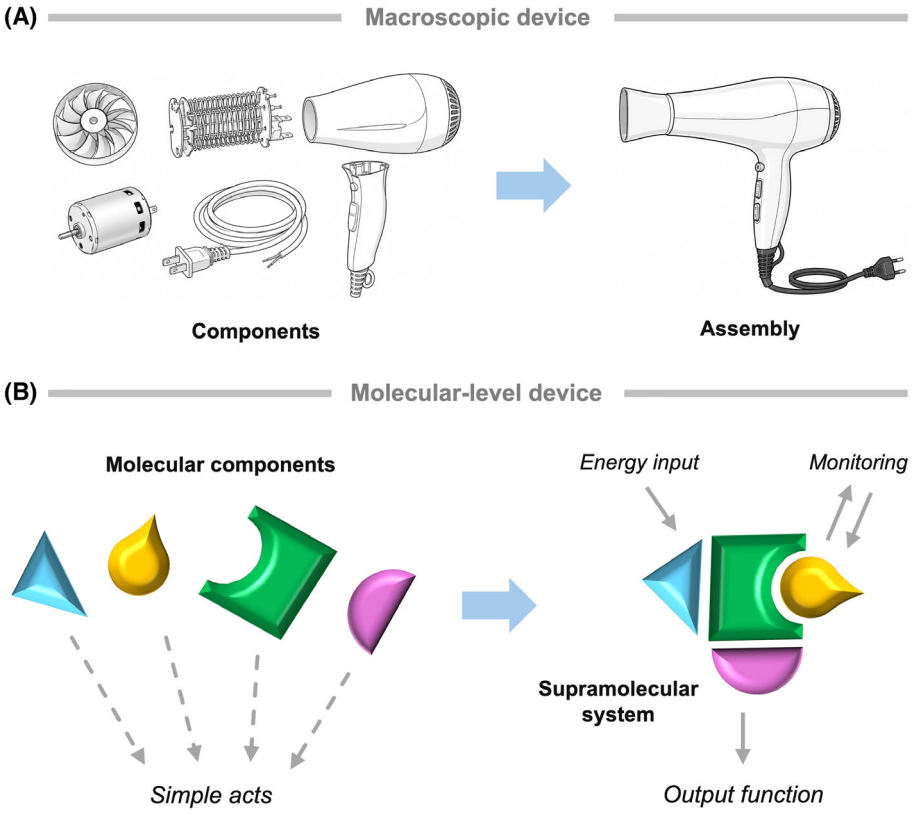


Fig. 1. (A) In the macroscopic world, a device such as a hairdryer is an ordered assembly of components—including a fan, a motor, a heating element, cables and a casing, constructed to perform a function: generating a flow of hot air. (B) This concept can be extended to the molecular level. A molecular device is an ordered assembly of molecular components—that is, a supramolecular system—in which each individual component performs a basic physicochemical task, such as light absorption, ion or molecule binding, electron or proton exchange, or catalysis. The cooperation of the components within the assembly enables the latter to carry out a more complex, potentially useful function that is not accessible to the components taken separately. A molecular machine is a device whose function involves controlled changes in the relative positions of its components; these changes require an energy input, can be repeated over multiple operation cycles, and need to be monitored by appropriate signals and techniques.

interact to process energy or signals and perform a function evidenced by an experimentally observable output (Fig. 1B). The idea of a molecular device emerged when chemists began to regard molecules not only as the smallest entities of a chemical species but also as material objects with a specific size, nontrivial (i.e., nonspherical) shape, and properties that can be organized into functional structures.

Within this framework, a molecular machine is a particular type of device in which the function is directly associated with controlled changes in the relative positions of its components, typically induced by an external stimulus [14]. These changes may involve translational, rotational, or more complex rearrangements and occur through cycles that require both energy input and resetting. A further level of functional specificity is reached in molecular motors, which are machines capable of converting an energy input into directional motion and, in principle, performing work on their surroundings [15–18]. This hierarchical distinction—device, machine, and motor—provides a useful conceptual framework for describing how molecular motion can be organized and coupled to function [19].

Motion at the nanoscale

The analogy between macroscopic and molecular devices is useful, but it must be taken with care [20]. The physical factors that govern motion at the molecular scale are fundamentally different from those operating in the everyday world of conventional machines [2–4]. In particular, nanoscale movements are dominated by thermal fluctuations, viscous forces, and continuous interactions with the surrounding medium. Let us first consider thermal fluctuations. At the molecular scale, thermal energy gives rise to a variety of motions,

FEBS Letters (2026) © 2026 The Author(s). *FEBS Letters* published by John Wiley & Sons Ltd on behalf of Federation of European Biochemical Societies.

18733468, 0, Downloaded from https://febs.onlinelibrary.wiley.com/doi/10.1002/1873-3468.70463 by Alberto Credi - CNR Bologna , Wiley Online Library on [11/09/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

including intramolecular vibrations and rotations, conformational fluctuations, and random translational and rotational motion caused by collisions with surrounding molecules (e.g., solvent). The latter types of motion are often discussed, especially in biological and biophysical contexts, in terms of Brownian motion [2–5].

Walking in a hurricane

A characteristic instantaneous power scale associated with thermally driven molecular motion can be estimated by dividing the thermal energy k_BT by a typical molecular vibrational timescale, of the order of a picosecond. At ambient temperature, this gives a value on the order of 10^{-8} W. By comparison, the average power supplied by ATP hydrolysis—the exergonic reaction that fuels many biomolecular devices—is on the order of 10^{-17} W. Thus, at ambient temperature, molecules move incessantly because of thermal fluctuations, whose instantaneous effects can exceed those of individual chemical energy-supplying events by several orders of magnitude [21]. The real challenge for a molecular machine is therefore not to create motion, because motion is already present everywhere at the molecular scale (except in the unattainable limit of 0 K), but to bias random movements so that they become directional and potentially useful.

At equilibrium, however, thermal fluctuations are random and cannot be used, by themselves, to generate net directional motion; otherwise, the Second Law of Thermodynamics would be violated [22]. This principle is closely related to microscopic reversibility, according to which any elementary process must be accompanied by a reverse process following the same microscopic trajectory. At equilibrium, forward and backward processes occur at equal rates, a condition known as detailed balance, thereby preventing the emergence of sustained directional motion. Molecular machines and motors, whether artificial or naturally occurring, overcome this limitation by using energy inputs to maintain their operation away from equilibrium, break detailed balance, and rectify Brownian motion through ratchet-like mechanisms [23–25].

Two conceptually distinct types of ratchet mechanisms are commonly considered: energy ratchets and information ratchets. In an energy ratchet, an external energy input—for example in the form of chemical reactants, electricity, or light—modulates the potential energy landscape of the system, including energy wells and barriers, so that forward motion is favored over backward motion at defined stages of the operating cycle. In an information ratchet, by contrast, directionality arises from state-dependent kinetic gating. For example, a transformation that raises or lowers a barrier occurs at different rates depending on the mechanical state of the motor. Thus, the gate may open preferentially when the moving component is on one side, allowing passage, and close after it has crossed, suppressing the reverse step. Repetition of this sequence biases Brownian motion in one direction.

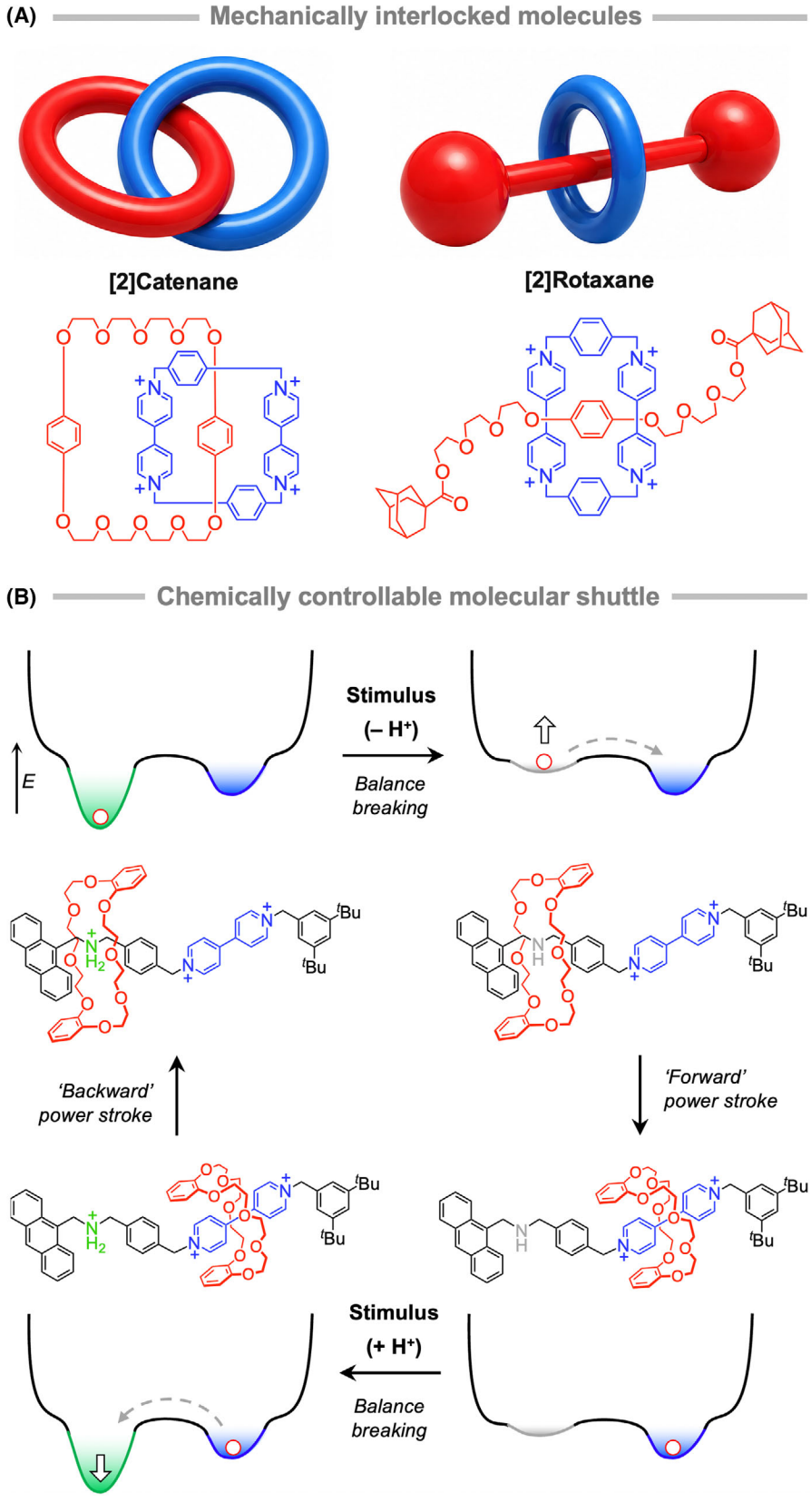
An energy ratchet therefore changes the energy landscape irrespective of the system's state, whereas an information ratchet uses state-dependent rates to select a pathway. Both mechanisms require an energy input to maintain the reaction cycle away from equilibrium, thereby enabling sustained directional motion and energy conversion. A detailed discussion of ratchet mechanisms and their significance for the design of molecular machines is beyond the scope of this article, and the interested reader is referred to specialized reviews on the topic [24,25].

Swimming in molasses

Another significant issue associated with nanoscale motion is the balance between inertial effects and viscous forces in a fluid [26]. This balance is quantified by the Reynolds number, *Re*, which depends on the density and viscosity of the fluid, and on the size and velocity of the moving body. For a swimmer in water, *Re* is typically on the order of 10^5, meaning that inertial effects dominate over viscous drag: Motion may continue after the applied force has ceased, and propulsion can rely on inertia and momentum transfer to the surrounding fluid. For smaller objects under comparable conditions, *Re* decreases dramatically [27]. In water, *Re* is typically very small for bacteria and becomes vanishingly small for molecules. In this low-Reynolds-number regime, viscous drag dominates over inertia and motion stops immediately after the force has ceased. Thus, for an object as small as a cell or a molecule, moving through a solvent is analogous to a human trying to swim in a medium far thicker than peanut butter.

A crucial consequence of this regime is that reciprocal motion—that is, motion in which the forward and backward trajectories are identical—cannot produce net displacement. This principle is often referred to as the scallop theorem [27]. Accordingly, bacteria do not swim like scallops, but use flagella driven by motor proteins that rotate unidirectionally, acting much like corkscrews [28]. This consideration highlights why unidirectional rotation, unidirectional translation, or more generally nonreciprocal cyclic motion, is essential for achieving useful mechanical effects at the molecular scale.

18733468, 0, Downloaded from https://febs.onlinelibrary.wiley.com/doi/10.1002/1873-3468.70463 by Alberto Credi - CNR Bologna , Wiley Online Library on [11/09/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License



FEBS Letters (2026) © 2026 The Author(s). *FEBS Letters* published by John Wiley & Sons Ltd on behalf of Federation of European Biochemical Societies.

18733468, 0, Downloaded from https://febs.onlinelibrary.wiley.com/doi/10.1002/1873-3468.70463 by Alberto Credi - CNR Bologna , Wiley Online Library on [11/09/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Fig. 2. (A) Schematic representation (top) and structure formula (bottom) of a [2]catenane (left) and a [2]rotaxane (right); the number of interlocked molecular components is indicated in brackets. (B) Operation of a bistable mechanical switch based on a stimuli-responsive rotaxane ('molecular shuttle') [46]. The structure formulas depict a prototypical case of a molecular shuttle operated by pH changes, and the (simplified) potential energy profiles versus the ring-axle relative position highlight how the input stimuli alter the relative depths of two energy minima, which is a basic requirement to build an energy ratchet. The high barriers at each extremity are associated with the stoppers, which prevent dissociation of the ring from the axle. The dashed arrows highlight the shuttling steps, enabled by Brownian motion, whereas the white arrows highlight the changes in the energy profile caused by the stimuli. For each state, the red circle marks the position of the system on the potential energy profile.

Autonomous operation

Motor proteins such as myosin and kinesin [4,5] can exploit ATP hydrolysis to operate continuously—that is, repeat their working cycle—under constant experimental conditions (except for the energy input) and without external intervention. They can do so because they are catalysts for their fuel-processing reaction, and the motor mechanism is strictly related to the catalytic cycle. Therefore, the motor can exploit the fuel as long as it is available. While such an autonomous operation is usual for biomolecular machines, it is still uncommon for artificial ones, which typically rely on resetting stimuli [11,29]. Nonetheless, examples of autonomous artificial molecular machines exploiting chemical [30], electrochemical [31], and photochemical [32] inputs have been reported. The autonomous exploitation of the energy source enables the reactive system to sustain a nonequilibrium state [33–35], which is essential to achieve continuous directional motion.

The mechanical bond

The 2016 Nobel Prize in Chemistry also gave recognition to the rational and efficient synthesis of mechanically interlocked molecules (MIMs), pioneered by Sauvage [6] and Stoddart [7]. In these systems, the molecular components are linked together by mechanical bonds, that is, by entanglements in the three-dimensional space such that the components cannot be separated without breaking or distorting conventional chemical bonds [36,37]. Therefore, the mechanical bond does not occur between atoms and is a formidable tool for the construction of multicomponent molecular architectures in the broader context of molecular-level devices. Mechanical bonds are also found in biological systems [38].

Catenanes and rotaxanes

Archetypal examples of MIMs are catenanes and rotaxanes, which consist at minimum of two interlocked components (Fig. 2A). In a [2]catenane, two molecular rings are linked like the elements of a chain [39], while in a [2]rotaxane, a ring is threaded onto a molecular axle and trapped by bulky extremities ('stoppers') that prevent dethreading [40]. The components are thus permanently associated, even though the noncovalent interactions between them may be relatively weak, or even absent, and dynamically adjustable.

This unconventional connection is important because it combines assembly persistence with large-scale mobility. The components cannot drift apart, yet they remain free to move relative to one another. For example, a macrocycle can shuttle between recognition sites ('stations') on an axle, or one ring of a catenane can adopt different positions relative to another ring, without the whole assembly falling apart. The motion is large in amplitude compared with ordinary conformational fluctuations, but it still occurs within a robust structural framework. Such a combination makes MIMs ideal building blocks for switches, shuttles, transport systems, and responsive assemblies [36,41,42].

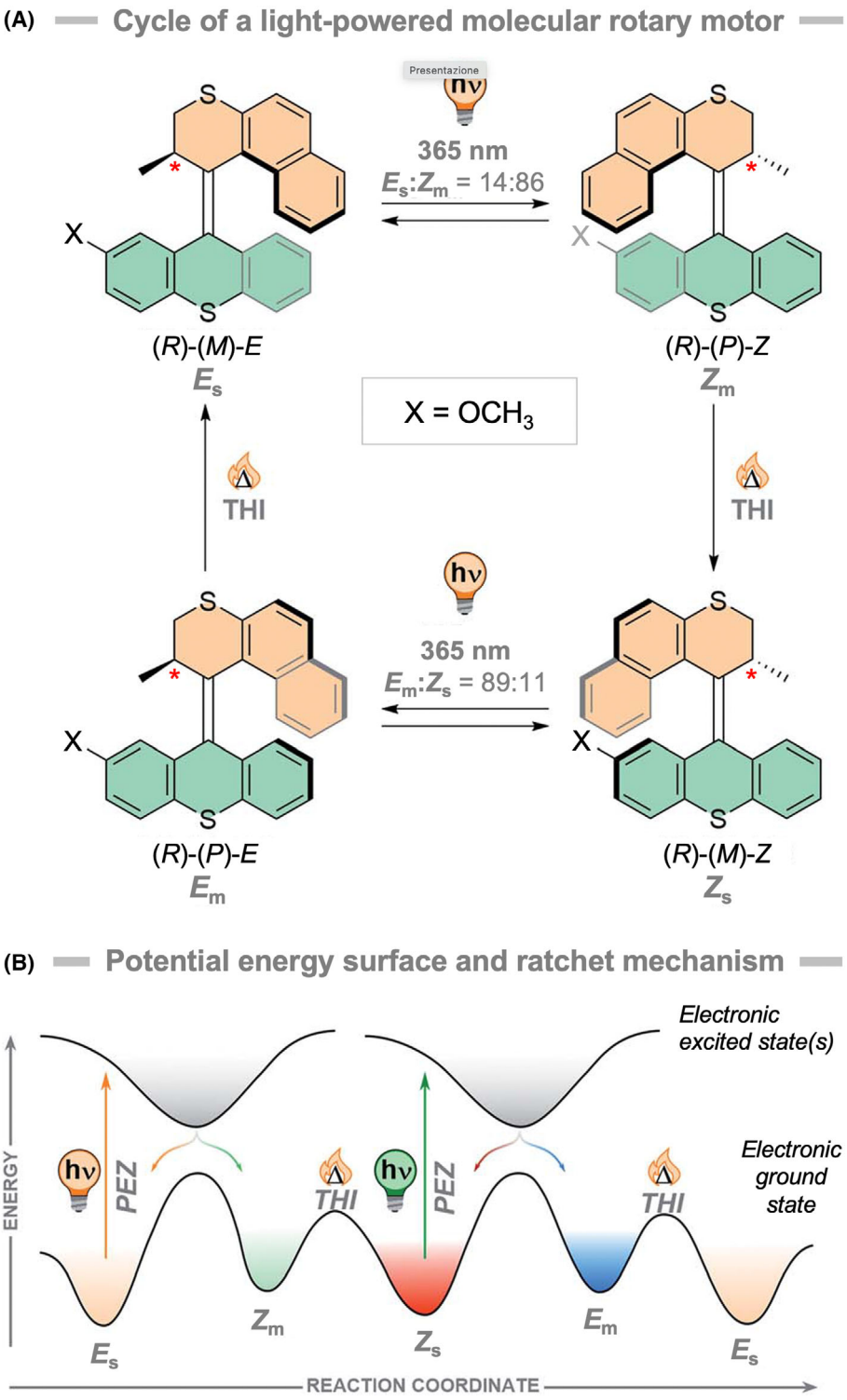
For a biochemical audience, the appeal of the mechanical bond is easy to appreciate. Biological function often depends on controlled rearrangements that occur within a constrained architecture. Proteins switch between conformations without dissociating into their constituent parts. Substrates move through channels and binding sites that are precisely arranged in space. MIMs provide a highly simplified synthetic analog of this principle: their components are organized so that movement is possible, but only along defined pathways and between specific positions.

Molecular shuttles

The peculiar structure of rotaxanes enables the design of molecular machines in which the ring moves back and forth between two stations ('molecular shuttles', Fig. 2B) [43]. The ring can be made to reside at one station or another by adjusting the relative strength of noncovalent interactions along the axle; changes in protonation, oxidation state, or photoisomerization can alter these interactions (balance breaking), causing the ring to move (power stroke). Early systems established

18733468, 0, Downloaded from https://febs.onlinelibrary.wiley.com/doi/10.1002/1873-3468.70463 by Alberto Credi - CNR Bologna , Wiley Online Library on [11/09/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

the principle of reversible shuttling between two recognition sites [44–47]; later designs showed that shuttling can be associated with catalytic behavior, signal transduction, directional transport, and data storage [48–51]. All these systems have a common underlying physical picture: the ring moves owing to thermal



FEBS Letters (2026) © 2026 The Author(s). *FEBS Letters* published by John Wiley & Sons Ltd on behalf of Federation of European Biochemical Societies.

18733468, 0, Downloaded from https://febs.onlinelibrary.wiley.com/doi/10.1002/1873-3468.70463 by Alberto Credi - CNR Bologna , Wiley Online Library on [11/09/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Fig. 3. (A) Operation cycle of a photochemically driven overcrowded alkene-based motor. The red asterisk denotes the stereogenic carbon atom (*R* configuration), while *M* and *P* are the stereochemical descriptors of the helical structure of the molecule. The combination of two distinct chiral elements—that is, point and helical chirality—gives rise to four different isomeric states and governs the directional rotation of the motor. (B) Simplified potential energy profile corresponding to the rotation cycle, with photochemical $E \leftrightarrows Z$ (PEZ) and thermal helix inversion (THI) steps highlighted. Since E_s/E_m and Z_s/Z_m are diastereomeric—not enantiomeric—pairs, they are endowed with different thermodynamic stabilities. Adapted from Ref. [54].

fluctuations, whose direction is biased through the modulation of a non-symmetric energy landscape with an external stimulus (a distinctive feature of an energy ratchet). Molecular shuttles operated by information ratchet mechanisms have also been reported [52,53].

Molecular rotary motors

The central achievement of a molecular rotary motor is that repeated cycles of energy input and relaxation can produce unidirectional rotation [8,54]. This is a far more demanding problem than reversible switching, as in the case of most molecular shuttles, because it requires a mechanism in which each step of the cycle prepares the system for the next, without simply going back to the previous one. In this context, directionality becomes a fundamental design challenge: while reversible switches explore an energy landscape in a symmetric fashion, motors must bias the travel across the landscape so that repeated cycles lead to net progress. Achieving such behavior requires careful integration of molecular asymmetry, energy input, and kinetic control.

Using light to power unidirectional molecular rotation

The best-known examples are light-driven rotary motors based on overcrowded alkenes, that is, sterically hindered C=C double bonds (Fig. 3A) [55]. In these species, steric congestion forces the two halves of the molecule into a twisted arrangement, giving rise to a helical shape and chirality (*M* or *P*). The clockwise and counterclockwise rotation directions are differentiated by the presence of a stereogenic carbon atom. In the enantiopure species (*R* configuration in Fig. 3A), light absorption by the stable *E* isomer (E_s) causes the $E \leftrightarrows Z$ photoisomerization (PEZ) of the C=C bond, generating a metastable state (Z_m). A subsequent thermal helix inversion (THI) step relieves strain and, by occurring energetically downhill, places the system in the stable Z_s diastereoisomer. Repeating the sequence of photochemical activation ($Zs \leftrightarrows E_m$) and thermal relaxation ($E_m \rightarrow E_s$) results in a complete rotation achieved in a single preferred direction, according to an energy ratchet mechanism (Fig. 3B). Since both E_s and Z_s can be isomerized with light of the same wavelength, the motor can operate autonomously at room temperature under constant illumination.

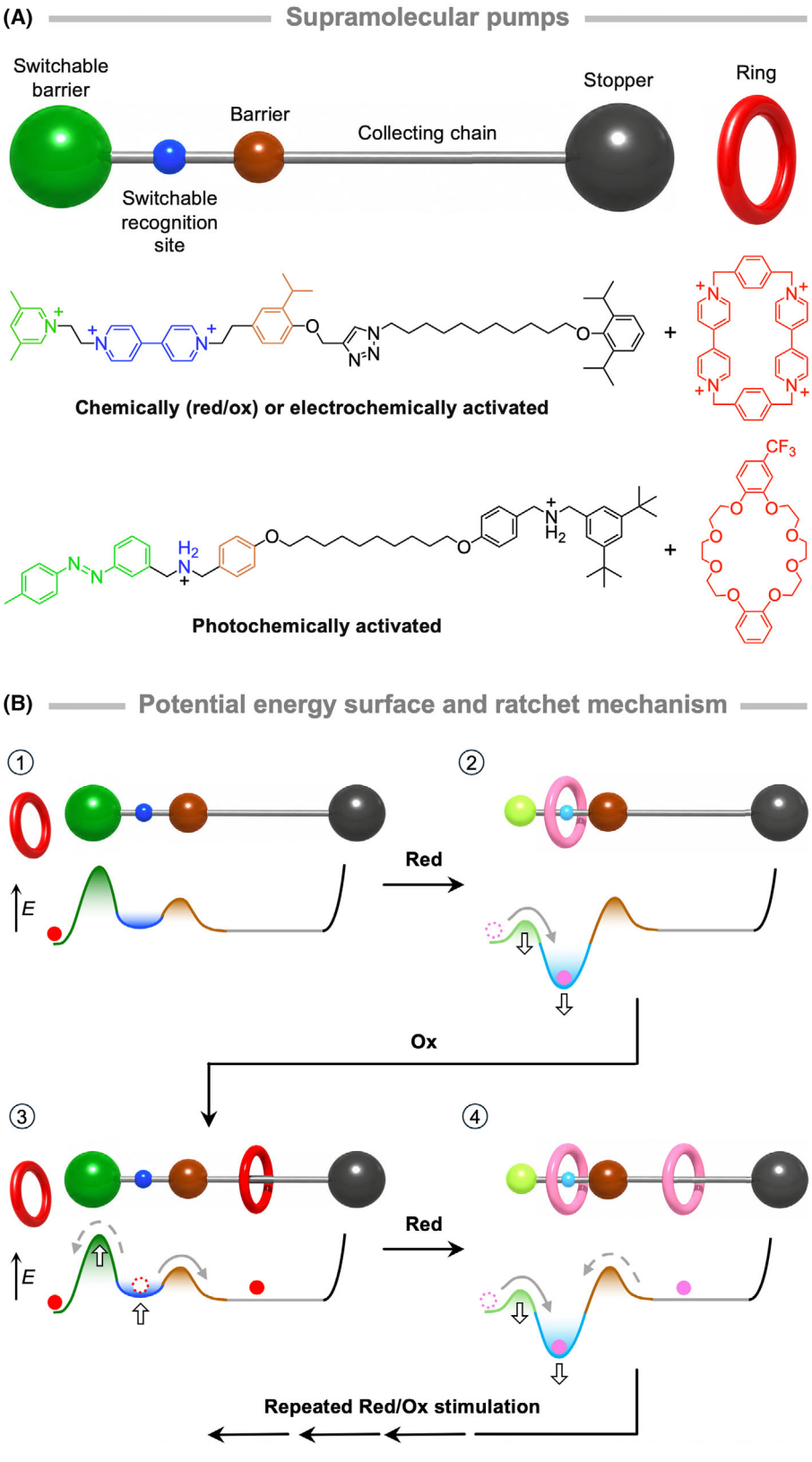
The conceptual importance of these motors lies in the relationship between structure, asymmetry, and energy dissipation [54]. Light does not simply flip the molecule between two equivalent forms: it allows the system to access an excited-state pathway unavailable under thermal equilibrium conditions. Directionality emerges because, owing to molecular design, thermal relaxation of the photogenerated species is irreversible and return along the same route is prevented.

This pattern is reminiscent of biological energy transduction. Protein motors do not move by coasting through space like tiny propellers; rather, they move by passing through a sequence of nonequivalent states linked to energy-releasing chemical events [4,5]. The steps are individually small, but together they produce directional motion. Artificial rotary motors follow the same logic in a stripped-down synthetic setting. They make evident, in a particularly elegant form, the general principle that motion becomes directional when random fluctuations are coupled to an energy-consuming cycle with built-in asymmetry.

Recent work has pushed these motors beyond proof-of-principle demonstrations. Structural modifications have tuned their absorption toward longer wavelengths, improved their speed, enabled operation on solid surfaces and in porous structures, and made it possible to couple their motion to more remote functional effects [56–58]. Rotation can now be transmitted to neighboring axes, influence the handedness of larger structures, or progressively increase conformational strain and topological complexity in linked systems [59–62] up to the synthesis of MIMs [63]. Very recently, molecular rotary motors have been used to investigate noninvasively the mechanical response of cells [64]. Such studies are important because they ask a deeper question: what can molecular motion accomplish once it is generated?

Light is particularly well-suited as an energy source for these systems because it allows precise control over when and where energy is delivered, while avoiding the accumulation of chemical waste products. It can be

18733468, 0, Downloaded from https://febs.onlinelibrary.wiley.com/doi/10.1002/1873-3468.70463 by Alberto Credi - CNR Bologna , Wiley Online Library on [11/09/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License



FEBS Letters (2026) © 2026 The Author(s). *FEBS Letters* published by John Wiley & Sons Ltd on behalf of Federation of European Biochemical Societies.

18733468, 0, Downloaded from https://febs.onlinelibrary.wiley.com/doi/10.1002/1873-3468.70463 by Alberto Credi - CNR Bologna , Wiley Online Library on [11/09/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Fig. 4. (A) Schematic representation and examples of rotaxane-based supramolecular pumps based on energy ratchets and activated by chemical, electrochemical (top) [76] or photochemical (bottom) [80] inputs. (B) Stimuli-induced modulation of the (simplified) potential energy profile versus the ring-axle relative position for the chemically or electrochemically activated supramolecular pump shown in (A). The full and dashed arrows represent, respectively, the pumping steps, enabled by Brownian motion, and the kinetically unfavorable competing steps. The color changes (dark/light green, blue/cyan, red/pink) and white arrows highlight the stimuli-induced chemical modification of the molecular components and the corresponding variations in the energy maxima and minima, which form the basis of the energy ratchet. For each state, the disk(s) indicate(s) the position of the molecular ring(s) with respect to the potential energy profile. The photochemically activated pump shown in (A) operates following the same principles, although with a slightly different logic.

delivered remotely, cleanly, and with high spatial and temporal precision. Light offers a selectivity that is highly attractive for operating synthetic systems in complex environments because only molecules that absorb at the chosen wavelength are addressed. These features explain why light-driven molecular rotary motors have been shown to function in many different environments, and why photochemical control has become central to other classes of artificial molecular devices and machines [19,29,65].

Other classes of photochemically [66–68] and chemically [69,70] driven molecular rotary motors have been described. Catenane-based rotary motors, in which one ring can be made to travel directionally along the other in response to chemical [71], electrochemical [72], and/or photochemical [73] stimuli have also been reported.

Supramolecular pumps

Among the many functions performed by biological molecular machines, transport occupies a particularly important place [2–5,74]. Cells continuously move ions, metabolites, proteins, and other molecular cargoes across membranes and between compartments. These processes are rarely sustained by diffusion alone; instead, they often require specialized molecular assemblies that use chemical energy to transport substrates directionally, frequently against concentration gradients. Ion pumps, membrane transporters, and ATP-dependent translocases are prominent examples of such systems.

Reproducing directional transport in wholly synthetic systems represents a major challenge for molecular engineering. Whereas a molecular switch simply interconverts two states, a pump must repeatedly move a substrate in a preferred direction while preventing its spontaneous return. In other words, transport requires not only motion but also control over the sequence of events by which that motion occurs [24,25].

Artificial supramolecular pumps based on rotaxane-type architectures provide one of the most compelling demonstrations of this concept (Fig. 4) [75]. In a typical implementation [76–80], a macrocyclic ring interacts with a molecular axle that can be switched by external stimuli (e.g., chemical reactants, electricity, or light). The axle contains a stimuli-responsive barrier, a stimuli-responsive recognition site for the ring, a passive barrier and a collecting chain terminated by a stopper (Fig. 4A). Under one set of conditions, threading of the ring onto the axle is unfavored. Upon application of the energy input, both the kinetic barriers and the thermodynamic stability of the available states are modified. As a result, the probabilities of threading, translation along the axle, and dethreading become unequal. Although the ring continues to undergo thermally driven Brownian motion, the overall transport cycle becomes biased in one direction. Repeated input-triggered modulation of the potential energy profile leads to the net translocation of macrocycles from solution onto the axle through an energy ratchet mechanism (Fig. 4B). The case of photochemically driven supramolecular pumps is particularly interesting because they operate autonomously [81] and sustain dissipative nonequilibrium stationary states whose composition depends on the intensity of the energy input [82], despite their unsophisticated chemical structure and modular design [83].

The significance of these systems lies in their ability to achieve active molecular transport. Rather than merely changing conformation or position reversibly, they capture molecular components from the surrounding environment and move them to locations that would not be populated efficiently by spontaneous diffusion alone [84,85]. In this respect, supramolecular pumps are conceptually analogous—albeit still much less sophisticated—to biological transporters that use ATP hydrolysis, ion gradients, or redox reactions to drive substrates across membranes or between cellular compartments. The next stage will be the incorporation of these synthetic pumps into bilayer membranes that separate solution compartments, such as in vesicles, to investigate whether energy-driven pumping can create a concentration gradient across these compartments [86,87].

18733468, 0, Downloaded from https://febs.onlinelibrary.wiley.com/doi/10.1002/1873-3468.70463 by Alberto Credi - CNR Bologna , Wiley Online Library on [11/09/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Outlook

Artificial molecular machines remain far simpler than biological motors and transport systems. They do not yet approach the efficiency, adaptability, or level of integration achieved by the molecular machinery of living organisms. Nevertheless, the progress made over the past four decades has established a set of general design principles that allow controlled molecular motion to be generated, directed, and coupled to function.

One of the most important lessons emerging from this field is that molecular motion is not an end in itself. Rotaxane shuttles, catenanes, rotary motors, and supramolecular pumps are valuable because they demonstrate how motion can be linked to switching, transport, catalysis, information processing, energy storage, and materials response. In this respect, artificial molecular machines are evolving from elegant molecular constructions into functional systems capable of performing increasingly complex tasks. A major challenge now is the integration of molecular machines into larger chemical, supramolecular, and biological environments, such that their motion can influence processes occurring across multiple length scales. The transmission and amplification of molecular-level movements into collective behavior, adaptive materials, transport processes, or measurable macroscopic effects represent some of the most active and promising directions in current research.

For biochemists and molecular biologists, these systems offer more than technological promise. They provide simplified and highly controllable models for investigating fundamental concepts that are central to living systems, including Brownian motion, energy transduction, directional transport, kinetic asymmetry, and operation away from equilibrium. By reducing these phenomena to their essential components, artificial molecular machines help reveal the physical principles that underlie biological functions.

At the same time, the objective of molecular nanotechnology should not be to reproduce biological machinery exactly. Natural molecular machines operate primarily through chemically fuelled reaction cycles because living organisms possess sophisticated metabolic networks capable of supplying reagents and removing waste products continuously. Despite the remarkable progress made in recent years, reproducing such conditions in artificial systems is still a formidable challenge. Synthetic molecular machines, in contrast, can exploit alternative energy inputs such as light or electricity, which can be delivered remotely, modulated with high precision, and used without generating chemical waste. These opportunities have no close equivalent in most biological systems and may ultimately lead to forms of molecular function that are distinct from those found in nature.

The challenge ahead is therefore not only to understand how biological molecular machines work but also to explore what synthetic molecular machinery can uniquely achieve. This will require the development of systems in which controlled molecular motion is integrated with transport, catalysis, self-assembly, materials properties, and interactions with complex biological environments. In this sense, molecular machines and motors represent both a source of inspiration from biology and a route toward new kinds of responsive molecular systems.

Acknowledgments

This work was supported by the EU ('MonaLisa' Marie Skłodowska-Curie Doctoral Network) and the University of Bologna. Open access publishing facilitated by Universita di Bologna, as part of the Wiley - CRUI-CARE agreement.

Author contributions

AC conceptualized the study. LA and AC collected the articles for the literature review, and prepared and revised the manuscript text and figures.

References

1 Mann S (2008) Life as a nanoscale phenomenon. *Angew Chem Int Ed* **47**, 5306–5320.
2 Goodsell DS (2004) Bionanotechnology: Lessons from Nature. Wiley, Hoboken, NJ.
3 Jones RAL (2004) Soft Machines: Nanotechnology and Life. Oxford University Press, Oxford.
4 Goodsell DS (2009) The Machinery of Life. 2nd edn. Copernicus, New York, NY.
5 Schliwa M and Woehlke G (2003) Molecular motors. *Nature* **422**, 759–765.
6 Sauvage J-P (2017) From chemical topology to molecular machines (Nobel lecture). *Angew Chem Int Ed* **56**, 11080–11093.
7 Stoddart JF (2017) Mechanically interlocked molecules (MIMs) – molecular shuttles, switches, and machines (Nobel lecture). *Angew Chem Int Ed* **56**, 11094–11125.
8 Feringa BL (2017) The art of building small: from molecular switches to motors (Nobel lecture). *Angew Chem Int Ed* **56**, 11060–11078.
9 Lehn J-M (1988) Supramolecular chemistry – scope and perspectives. Molecules, supermolecules, and molecular devices (Nobel lecture). *Angew Chem Int Ed Engl* **27**, 89–112.

FEBS Letters (2026) © 2026 The Author(s). *FEBS Letters* published by John Wiley & Sons Ltd on behalf of Federation of European Biochemical Societies.

18733468, 0, Downloaded from https://febs.onlinelibrary.wiley.com/doi/10.1002/1873-3468.70463 by Alberto Credi - CNR Bologna , Wiley Online Library on [11/09/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

10 Lehn J-M (1995) Supramolecular Chemistry – Concepts and Perspectives. Wiley-VCH, Weinheim, Germany.
11 Balzani V, Credi A and Venturi M (2002) The bottom-up approach to molecular-level devices and machines. *Chem Eur J* **8**, 5524–5532.
12 Balzani V, Credi A and Venturi M (2002) Controlled disassembling of self-assembling systems: toward artificial molecular-level devices and machines. *Proc Natl Acad Sci USA* **99**, 4814–4817.
13 Balzani V, Credi A and Venturi M (2008) Molecular Devices and Machines – Concepts and Perspectives for the Nanoworld. Wiley-VCH, Weinheim, Germany.
14 Balzani V, Credi A, Raymo FM and Stoddart JF (2000) Artificial molecular machines. *Angew Chem Int Ed* **39**, 3348–3391.
15 Browne WR and Feringa BL (2006) Making molecular machines work. *Nat Nanotechnol* **1**, 25–35.
16 Erbas-Cakmak S, Leigh DA, McTernan CT and Nussbaumer AL (2015) Artificial molecular machines. *Chem Rev* **115**, 10081–10206.
17 Kassem S, van Leeuwen T, Lubbe AS, Wilson MR, Feringa BL and Leigh DA (2017) Artificial molecular motors. *Chem Soc Rev* **46**, 2592–2621.
18 Pezzato C, Cheng C, Stoddart JF and Astumian RD (2017) Mastering the non-equilibrium assembly and operation of molecular machines. *Chem Soc Rev* **46**, 5491–5507.
19 Baroncini M, Silvi S and Credi A (2020) Photo- and redox-driven artificial molecular motors. *Chem Rev* **120**, 200–268.
20 Coffey TS and Krim J (2006) C_{60} molecular bearings and the phenomenon of nanomapping. *Phys Rev Lett* **96**, 186104.
21 Astumian RD and Hänggi P (2002) Brownian motors. *Phys Today* **55**, 33–39.
22 Astumian RD (2012) Microscopic reversibility as the organizing principle of molecular machines. *Nat Nanotechnol* **7**, 684–688.
23 Hoffman PM (2012) Life's Ratchet. How Molecular Machines Extract Order from Chaos. Basic Books, New York, NY.
24 Sangchai T, Al Shehimy S, Penocchio E and Ragazzon G (2023) Artificial molecular ratchets: tools enabling endergonic processes. *Angew Chem Int Ed* **62**, e202309501.
25 Borsley S, Leigh DA and Roberts BMW (2024) Molecular ratchets and kinetic asymmetry: giving chemistry direction. *Angew Chem Int Ed* **63**, e202400495.
26 Astumian RD (2007) Design principles for Brownian molecular machines: how to swim in molasses and walk in a hurricane. *Phys Chem Chem Phys* **9**, 5067–5083.
27 Purcell EM (1977) Life at low Reynolds number. *Am J Phys* **45**, 3–11.
28 Lauga E (2011) Life around the scallop theorem. *Soft Matter* **7**, 3060–3065.
29 Corra S, Curcio M and Credi A (2023) Photoactivated artificial molecular motors. *JACS Au* **3**, 1301–1313.
30 Wilson MR, Solá J, Carlone A, Goldup SM, Lebrasseur N and Leigh DA (2016) An autonomous chemically fuelled small-molecule motor. *Nature* **534**, 235–240.
31 Ragazzon G, Malferrari M, Arduini A, Secchi A, Rapino S, Silvi S and Credi A (2023) Autonomous non-equilibrium self-assembly and molecular movements powered by electrical energy. *Angew Chem Int Ed* **62**, e202214265.
32 Balzani V, Clemente-Leon M, Credi A, Ferrer B, Venturi M, Flood AH and Stoddart JF (2006) Autonomous artificial nanomotor powered by sunlight. *Proc Natl Acad Sci USA* **103**, 1178–1183.
33 Giuseppone N and Walther A, eds (2021) Out-of-Equilibrium (Supra)Molecular Systems and Materials. Wiley-VCH, Weinheim, Germany.
34 Ragazzon G and Prins LJ (2018) Energy consumption in chemical fuel-driven self-assembly. *Nat Nanotechnol* **13**, 882–889.
35 Sachini B, Corra S, Curcio M, Groppi J and Credi A (2025) Defying chemical equilibrium with light. *Trends Chem* **7**, 372–383.
36 Bruns CJ and Stoddart JF (2016) The Nature of the Mechanical Bond: From Molecules to Machines. Wiley, New York, NY.
37 Stoddart JF (2009) The chemistry of the mechanical bond. *Chem Soc Rev* **38**, 1802–1820.
38 Beeren SR, McTernan CT and Schaufelberger F (2023) The mechanical bond in biological systems. *Chem* **9**, 1378–1412.
39 Dietrich-Buchecker CO, Sauvage J-P and Kintzinger J-P (1983) Une nouvelle famille de molécules: les métallo-caténanes. *Tetrahedron Lett* **24**, 5095–5098.
40 Ashton PR, Grognuz M, Slawin AMZ, Stoddart JF and Williams DJ (1991) The template-directed synthesis of a [2]rotaxane. *Tetrahedron Lett* **32**, 6235–6238.
41 Bonnet S, Collin J-P, Koizumi M, Mobian P and Sauvage J-P (2006) Transition-metal-complexed molecular machine prototypes. *Adv Mater* **18**, 1239–1250.
42 Andreoni L, Taticchi C, Sachini B and Credi A (2026) Molecular devices based on the mechanical bond: recent advances. *Coord Chem Rev* **553**, 217583.
43 Silvi S, Venturi M and Credi A (2009) Artificial molecular shuttles: from concepts to devices. *J Mater Chem* **19**, 2279–2294.
44 Anelli PL, Spencer N and Stoddart JF (1991) A molecular shuttle. *J Am Chem Soc* **113**, 5131–5133.
45 Bissell RA, Cordova E, Kaifer AE and Stoddart JF (1994) A chemically and electrochemically switchable molecular shuttle. *Nature* **369**, 133–137.

FEBS Letters (2026) © 2026 The Author(s). *FEBS Letters* published by John Wiley & Sons Ltd on behalf of Federation of European Biochemical Societies.

18733468, 0, Downloaded from https://febs.onlinelibrary.wiley.com/doi/10.1002/1873-3468.70463 by Alberto Credi - CNR Bologna , Wiley Online Library on [11/09/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

46 Ashton PR, Ballardini R, Balzani V, Baxter I, Credi A, Fyfe MCT, Gandolfi MT, Gómez-López M, Martínez-Díaz MV, Piersanti A *et al.* (1998) Acid-base controllable molecular shuttles. *J Am Chem Soc* **120**, 11932–11942.
47 Armaroli N, Balzani V, Collin J-P, Gaviña P, Sauvage J-P and Ventura B (1999) Rotaxanes incorporating two different coordinating units in their thread: synthesis and electrochemically and photochemically induced molecular motions. *J Am Chem Soc* **121**, 4397–4408.
48 Blanco V, Leigh DA, Marcos V, Morales-Serna JA and Nussbaumer AL (2014) A switchable [2]rotaxane asymmetric organocatalyst that utilizes an acyclic chiral secondary amine. *J Am Chem Soc* **136**, 4905–4908.
49 Ragazzon G, Schäfer C, Franchi P, Silvi S, Colasson B, Lucarini M and Credi A (2018) Remote electrochemical modulation of p*K*a in a rotaxane by co-conformational allostery. *Proc Natl Acad Sci USA* **115**, 9385–9390.
50 Lewandowski B, De Bo G, Ward JW, Papmeyer M, Kuschel S, Aldegunde MJ, Gramlich PME, Heckmann D, Goldup SM, D'Souza DM *et al.* (2013) Sequence-specific peptide synthesis by an artificial small-molecule machine. *Science* **339**, 189–193.
51 Green JE, Choi JW, Boukai A, Bunimovich Y, Johnston-Halperin E, DeIonno E, Luo Y, Sheriff BA, Xu K, Shin YS *et al.* (2007) A 160-kilobit molecular electronic memory patterned at 10^{11} bits per square centimetre. *Nature* **445**, 414–417.
52 Serreli V, Lee CF, Kay ER and Leigh DA (2007) A molecular information ratchet. *Nature* **445**, 523–527.
53 Alvarez-Pérez M, Goldup SM, Leigh DA and Slawin AMZ (2008) A chemically-driven molecular information ratchet. *J Am Chem Soc* **130**, 1836–1838.
54 Pooler DRS, Lubbe AS, Crespi S and Feringa BL (2021) Designing light-driven rotary molecular motors. *Chem Sci* **12**, 14964–14986.
55 Koumura N, Zijlstra RWJ, van Delden RA, Harada N and Feringa BL (1999) Light-driven monodirectional molecular rotor. *Nature* **401**, 152–155.
56 Kudernac T, Ruangsupapichat N, Parschau M, Maciá B, Katsonis N, Harutyunyan SR, Ernst K-H and Feringa BL (2011) Electrically driven directional motion of a four-wheeled molecule on a metal surface. *Nature* **479**, 208–211.
57 Chen J, Leung FKC, Stuart MCA, Kajitani T, Fukushima T, van der Giessen E and Feringa BL (2018) Artificial muscle-like function from hierarchical supramolecular assembly of photoresponsive molecular motors. *Nat Chem* **10**, 132–138.
58 Danowski W, van Leeuwen T, Abdolahzadeh S, Roke D, Browne WR, Wezenberg SJ and Feringa BL (2019) Unidirectional rotary motion in a metal–organic framework. *Nat Nanotechnol* **14**, 488–494.
59 Li Q, Fuks G, Moulin E, Maaloum M, Rawiso M, Kulic I, Foy JT and Giuseppone N (2015) Macroscopic contraction of a gel induced by the integrated motion of light-driven molecular motors. *Nat Nanotechnol* **10**, 161–165.
60 Štacko P, Kistemaker JCM, van Leeuwen T, Chang M-C, Otten E and Feringa BL (2017) Locked synchronous rotor motion in a molecular motor. *Science* **356**, 964–968.
61 Perrot A, Moulin E and Giuseppone N (2021) Extraction of mechanical work from stimuli-responsive molecular systems and materials. *Trends Chem* **3**, 926–942.
62 Kathan M, Crespi S, Thiel NO, Stares DL, Morsa D, de Boer J, Pacella G, van den Enk T, Kobauri P, Portale G *et al.* (2022) A light-fuelled nanoratchet shifts a coupled chemical equilibrium. *Nat Nanotechnol* **17**, 159–165.
63 Wachsmuth T, Kluifhooft R, Müller M, Zeiss L and Kathan M (2025) A molecular machine directs the synthesis of a catenane. *Science* **389**, 526–531.
64 Kumar R, Fernandez-Yague MA, Bessaguet A, Lee H, Giuseppone N, García AJ and del Campo A (2026) An opto-actuated hydrogel for cell mechanoactuation and real-time force monitoring. *Adv Sci* **13**, e11538.
65 Ceroni P, Credi A and Venturi M (2014) Light to investigate (read) and operate (write) molecular devices and machines. *Chem Soc Rev* **43**, 4068–4083.
66 Greb L and Lehn J-M (2014) Light-driven molecular motors: imines as four-step or two-step unidirectional rotors. *J Am Chem Soc* **136**, 13114–13117.
67 Guentner M, Schildhauer M, Thumser S, Mayer P, Stephenson D, Mayer PJ and Dube H (2015) Sunlight-powered kHz rotation of a hemithioindigo-based molecular motor. *Nat Commun* **6**, 8406.
68 Nicoli F, Taticchi C, Lorini E, Borghi S, Aleotti F, Silvi S, Credi A, Garavelli M, Muccioli L, Baroncini M *et al.* (2026) Wavelength-steered directional rotation in an autonomous light-driven molecular motor. *Nat Chem* **18**, 1171–1177. doi: 10.1038/s41557-025-02045-x
69 Borsley S, Kreidt E, Leigh DA and Roberts BMW (2022) Autonomous fuelled directional rotation about a covalent single bond. *Nature* **604**, 80–85.
70 Liu H-K, Roberts BMW, Borsley S, Adams RW, Whitehead GFS, Hasija A and Leigh DA (2026) Chiral catalysis-driven rotary molecular motors. *Nat Chem* **18**, 1178–1185. doi: 10.1038/s41557-025-02050-0
71 Lu C-H, Cecconello A, Elbaz J, Credi A and Willner I (2013) A three-station DNA catenane rotary motor with controlled directionality. *Nano Lett* **13**, 2303–2308.
72 Zhang L, Qiu Y, Liu W-G, Chen H, Shen D, Song B, Cai K, Wu H, Jiao Y, Feng Y *et al.* (2023) An electric molecular motor. *Nature* **613**, 280–286.
73 Hernández JV, Kay ER and Leigh DA (2004) A reversible synthetic rotary molecular motor. *Science* **306**, 1532–1537.

FEBS Letters (2026) © 2026 The Author(s). *FEBS Letters* published by John Wiley & Sons Ltd on behalf of Federation of European Biochemical Societies.

18733468, 0, Downloaded from https://febs.onlinelibrary.wiley.com/doi/10.1002/1873-3468.70463 by Alberto Credi - CNR Bologna , Wiley Online Library on [11/09/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

74 Gadsby DC (2009) Ion channels versus ion pumps: the principal difference, in principle. *Nat Rev Mol Cell Biol* **10**, 344–352.
75 Qiu Y, Feng Y, Guo QH, Astumian RD and Stoddart JF (2020) Pumps through the ages. *Chem* **6**, 1952–1977.
76 Cheng C, McGonigal PR, Schneebeli ST, Li H, Vermeulen NA, Ke C and Stoddart JF (2015) An artificial molecular pump. *Nat Nanotechnol* **10**, 547–553.
77 Amano S, Fielden SDP and Leigh DA (2021) A catalysis-driven artificial molecular pump. *Nature* **594**, 529–534.
78 Lee ACK, Feng YN, Enciso AE, Violi JP, Donald WA, Stoddart JF and Kim DJ (2026) An aqueous artificial molecular pump. *Chem* **12**, doi: 10.1016/j.chempr.2025.102693
79 Pezzato C, Nguyen MT, Kim DJ, Anamimoghadam O, Mosca L and Stoddart JF (2018) Controlling dual molecular pumps electrochemically. *Angew Chem Int Ed* **57**, 9325–9329.
80 Nicoli F, Taticchi C, Corra S, Tranfić Bakić M, Baroncini M, Silvi S, Groppi J and Credi A (2026) An artificial molecular pump powered by light. *Angew Chem Int Ed* **65**, e8103353.
81 Ragazzon G, Baroncini M, Silvi S, Venturi M and Credi A (2015) Light-powered autonomous and directional molecular motion of a dissipative self-assembling system. *Nat Nanotechnol* **10**, 70–75.
82 Corra S, Tranfić Bakić M, Groppi J, Baroncini M, Silvi S, Penocchio E, Esposito M and Credi A (2022) Kinetic and energetic insights into the dissipative non-equilibrium operation of an autonomous light-powered supramolecular pump. *Nat Nanotechnol* **17**, 746–751.
83 Canton M, Groppi J, Casimiro L, Corra S, Baroncini M, Silvi S and Credi A (2021) Second-generation light-fueled supramolecular pump. *J Am Chem Soc* **143**, 10890–10894.
84 Qiu YY, Song B, Pezzato C, Shen DK, Liu WQ, Zhang L, Feng YN, Guo QH, Cai K, Li WXY *et al.* (2020) A precise polyrotaxane synthesizer. *Science* **368**, 1247–1253.
85 Seale JSW, Sharma S, Lee CK, Han H, Jaynes T, Roth EW, Shafie S, Qiu YY, Malaisrie L, Bardot MI *et al.* (2025) Active transport of macrocycles into micelles using molecular pumps. *Angew Chem Int Ed* **64**, e202512899.
86 Watson MA and Cockroft SL (2016) Man-made molecular machines: membrane bound. *Chem Soc Rev* **45**, 6118–6129.
87 Johnson TG and Langton MJ (2023) Molecular machines for the control of transmembrane transport. *J Am Chem Soc* **145**, 27167–27184.

18733468, 0, Downloaded from https://febs.onlinelibrary.wiley.com/doi/10.1002/1873-3468.70463 by Alberto Credi - CNR Bologna , Wiley Online Library on [11/09/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License