Project no. **[505487-1]**

Project acronym: **BIOMACH**

Project full name: **"Molecular Machines – Design and Nano-Scale Handling of Biological Antetypes and Artificial Mimics"**

Instrument type: **SPECIFIC TARGETED RESEARCH PROJECT**

Priority name: [NMP-2002-3.4.1.1-3: Molecular and bio-molecular mechanisms and engines]

BIOMACH Plan of Dissemination of Knowledge M25-M29

Due date of deliverable: **15.09.2007**

Actual submission date:

Start date of project: **01.03.2004** Duration: **3 years + 3 months**

Organisation name of lead contractor for this deliverable: **FZK-INT**

Involved Partners: **CIAM, ETHZ, TU/d-MB, ULP, TU/e, IGC-GC, ETHZ, EPFL, AMOLF**

Project co-funded by the EC within the Sixth Framework Programme (2002-2006)		
Dissemination Level		
PU	Public	X
PP	Restricted to other programme participants (including the Commission Services)	
RE	Restricted to a group specified by the consortium (including the Commission Services)	
CO	Confidential, only for members of the consortium (including the Commission Services)	

Section 1 – Exploitable knowledge and its Use

Overview table Patents

Exploitable Knowledge (description)	**Exploitable product(s) or measure(s)**	**Sector(s)** of application	Timetable for commercial use	Patents or other IPR protection	**Owner** & Other Partner(s) involved
1.new synthetic procedures to synthesize tpy alternatives	*chemical compounds and precursors*	*Chemcial/Pharmaceutical applications*	- -	*A materials patent is planned for 2008*	***Partic. FZK-INT(owner)***

Section 2 – Dissemination of knowledge

Overview table dissemination actions

Planned /actual Dates	**Type**	**Type of audience**	**Countries addressed**	**Size of audience**	**Partner responsible /involved**
Sep 2006	*Press release(press)*	*Research/General Public*	**1**	*sever. th.*	*MPI*
June 2006	*Film/video Press release(press/radio/TV)*	*General public*	**1**	*Several millions*	*FZK-INT*
October 2006	*Film/video Press release(TV)*	*General public*	**1**	*Several millions*	*FZK-INT*
March 2007	*Film/video Press release (radio)*	*General public*	**1**	*Several millions*	*Tu/e*

5. **“Everything starts with recognition” press release of the Max-Planck-Society, Munich, Germany, 2006**

MAX PLANCK SOCIETY

Press Release

News C / 2007 (49) April 23rd, 2007

Everything starts with Recognition

Scientists track at the atomic scale how individual molecules recognise each other

A human body has more than 10 to the power of 27 molecules with about one hundred thousand different shapes and functions. Interactions between molecules determine our structure and keep us alive. Researchers at the Max Planck Institute for Solid State Research in Stuttgart in collaboration with scientists from the Fraunhofer Institute in Freiburg and the King's Collage London have followed the interaction of only two individual molecules to show the basic mechanism underlying recognition of dipeptides. By means of scanning tunnelling microscopy movies and theoretical simulations they have shown how dynamic interactions induce the molecular fit needed for the transfer of structural information to higher levels of complexity. This dynamic picture illustrates how recognition works at the very first steps, tracking back the path in the evolution of complex matter. (Angewandte Chemie international April 20th 2007)

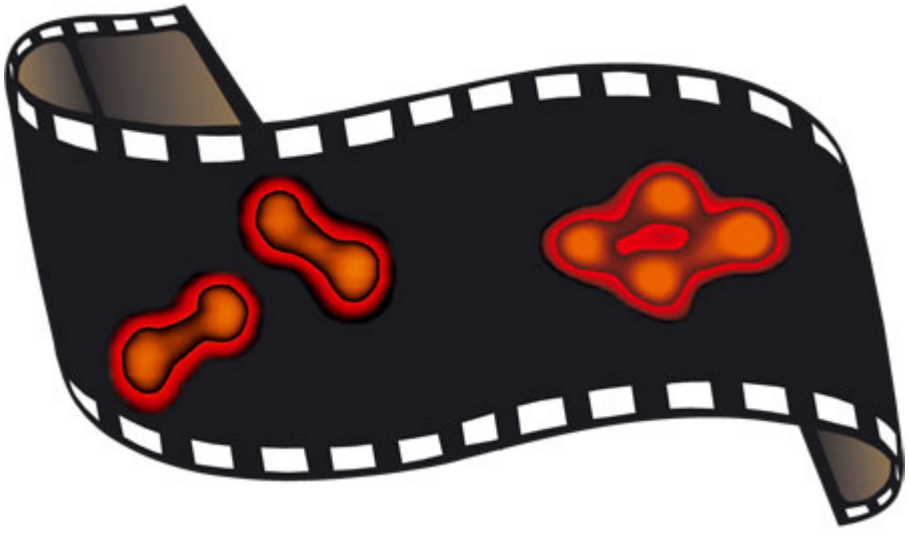

Fig.: *An STM image of individual L and D Di-phenylalanine molecules adsorbed onto Cu (110). A human body has more than one thousand trillion trillion molecules with about one hundred thousand different shapes and functions. The researchers have followed the interaction between two molecules to show the basic mechanism underlying chiral recognition.*

Image: Max Planck Institute for Solid State Research

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If one thinks that there are thousands of times more molecules forming our body than stars in the universe it is astonishing how all these molecules can work together in such an organised and efficient way. How can our muscles contract to make us walk? How can food be metabolised every day? How can we use specific drugs to relieve pain?

To work as a perfect machine, our body ultimately relies on the capability of each little part (molecule) to know a specific function and location out of countless possibilities. To do this, molecules carry information in different ways. An international team at the Max Planck Institute for Solid State Research in Stuttgart, in collaboration with scientists from the Fraunhofer Institute in Freiburg and the King's College London are seeking to find out how the information can be passed on at the very first steps: from the single molecule level to structures of increasing complexity and functionality.

The key to understanding all biological processes is recognition. Each molecule has a unique composition and shape that allows it to interact with other molecules. The interactions between molecules let us - as well as bacteria, animals, plants and other living systems - move, sense, reproduce and accomplish the processes that keep all living creatures alive.

A very common example of recognition can be experienced in daily life whenever one meets someone and shakes right hands. In principle, one can also shake left hands; the fact that we do it with the right has historically been a sign of peace, used to show that both people hold no weapon. But, have you ever attempt to shake the right hand of a person using your left hand? No matter how the two hands are oriented, you will never fit your left hand with the right hand of your friend.

Many molecules can recognise each other and transfer information exactly in the same way, they can either be "right handed" (D) or "left handed" (L). This property called "chirality" is a spectacular way to store information: a chiral molecule can recognise molecules that have the same chirality (same "handedness", L to L or D to D) and discriminate the ones of different chirality (L to D and D to L).

Probably one of the most exciting mysteries of Nature is why the building blocks of life, i.e. amino acids (the building blocks of proteins) are exclusively present in the chiral L form and sugars (which constitute DNA) are all in the D form. Once more, the reason for this preference is "historical", but this time goes back millions of years till the origins of the biological world. Scientists believe that current life forms could not exist without the uniform chirality ("homochirality") of these blocks, because biological processes need the efficiency in recognition achieved with homochiral substances. In other words, the separation of molecules by chirality was the crucial process during the Archean Era when life first emerged.

Researchers of the Max Planck Institute for Solid State Research have now used the "nanoscopic eye" of a scanning tunnelling microscope to make movies following how two adsorbed molecules (diphenylalanine, the core recognition motif of Alzheimer amyloid polypeptide) of the same chirality can form structures (pairs, chains) while molecules of different chirality discriminate and cannot form stable structures.

As it occurs when you shake the hand of your friend, the fact that the two homochiral hands are complementary by shape is not enough, you both have to dynamically adapt and adjust your hands to reach a better fit, a comfortable situation. By a combination with theoretical simulations done at Kings College London, the researchers have shown for the first time this dynamic mechanism of how two molecules "shake hands" and recognise each other by mutually induced conformational changes at the single molecule level.

We live in houses, wear clothes and read books made of chiral cellulose. Most of the molecules that mediate the processes of life like hormones, antibodies and receptors are chiral. Fifty of the top hundred best-selling drugs worldwide are chiral. With this contribution to the basic mechanism of chiral recognition, the researchers have not only tracked back to the very first steps in the evolution of living matter but have also shed light on our understanding and control of synthetic (man-made) materials of increasing complexity.

Related Links:

6. **“Towards Devices powered by biomolecular motors” by Henry Hess, perspective article, Science, May, 2006**

mutant is phenotypically similar to the *aux1* mutant, which suggests that both genes act in the same process. Dharmasiri *et al.* now provide an explanation for this phenotypic similarity by identifying AXR4 as an endoplasmic reticulum–resident protein required for proper AUX1 sorting to the plasma membrane. AXR4 appears specific for AUX1 trafficking, because other membrane proteins such as the PINs are not mislocalized in the *axr4* mutant. Interestingly, in the root tissues examined, the only cell types affected by the *axr4* mutation were those in which AUX1 localization is polar. In the lateral root cap, where AUX1 is uniformly distributed, there are no obvious effects in the *axr4* mutant background, whereas in the epidermis and protophloem where AUX1 is polarly localized, AUX1 is retained in the endoplasmic reticulum. This suggests that AXR4 plays a specific tissue-dependent role in the polar sorting of AUX1 to a particular plasma membrane face, rather than a general chaperone-like function. The biochemical basis for AXR4 action is not yet clear. Apart from a predicted transmembrane motif and a putative α/β hydrolase fold, AXR4 does not contain any known protein domains.

These discoveries demonstrate clear tissue-specific elements in the membrane targeting of both PIN and AUX1. So far, however, there is no evidence of any coordination of these events, although there is some suggestion of common elements because both are sensitive to the protein traffic inhibitor brefeldin A (*13*, *17*). As the mechanisms for polar localization of these proteins are revealed, it will be interesting to see the extent to which they are independent.

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10.1126/science.1127659

MATERIALS SCIENCE

Toward Devices Powered by Biomolecular Motors

Biomolecular motors can be used in nanometer-scale devices to perform mechanical work. This approach will assist the development of active nanostructures.

Henry Hess

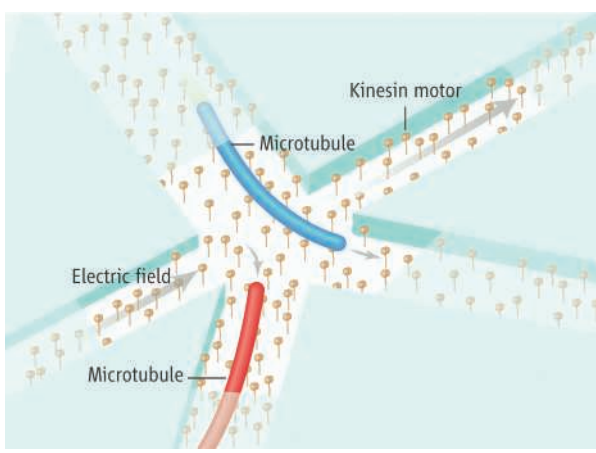
Biomolecular motors, such as the motor protein kinesin, convert chemical energy derived from the hydrolysis of individual adenosine triphosphate (ATP) molecules into directed, stepwise motion (*1*). This process enables them to actively transport designated cargo—such as vesicles, RNA, or viruses—to predetermined locations within cells. For engineers, active transport in biology inspires visions of nanofluidic systems for biosensing, of active materials that can rearrange their components, and of molecular conveyor belts and forklifts for nanometer-scale manufacturing.

Enhanced online at www.sciencemag.org/cgi/content/full/312/5775/860

Nanofluidic devices, which extend the lab-on-a-chip paradigm to systems with picoliter volumes and submicrometer channel diameters, present an immediate opportunity for the application of biomolecular motors. On page 910 of this issue, van den Heuvel *et al.* (*2*) show that kinesin motor proteins can drive the directed transport of microtubules (filamentous assemblies of thousands of tubulin proteins) in closed channels with submicrometer dimensions. Controlled application of an external electric field steers the microtubules into either one of two arms of a Y junction (see the figure).

The setup is an adaptation of the classic gliding motility assay (*3*), in which the kinesin motor proteins adhere to a surface via their rotationally flexible tails, bind to the leading ends of approaching microtubules with their two heads, and move the microtubules by stepping forward with alternating heads until they reach the trailing end and detach. In biological systems, the motors move and the microtubules are stationary. The key advantages of the inverted geometry used in the assay are that the microtubules are continuously bound to the surface over transport distances of more than a millimeter (*4*) and that the large microtubule allows the attachment of fluorescence tags for observation and of specific linkers for cargo binding (*5*).

Open or micrometer-scale closed channels have previously been fabricated to confine microtubule movements (*6*–*8*). Van den Heuvel *et al*. have now created closed channels with submicrometer dimensions. The channels not only provide better confinement, but they also mimic the dimensions of axons, in which motor–driven transport plays a central role. They may thus enable more realistic model studies at the system level of active transport in biology. Electric fields for active steering provide direct control over the paths of individual microtubules. By coupling fluorescence detec-



CREDIT: P. HUEY/*SCIENCE*

Nanofluidics with molecular motors. In van den Heuvel *et al.*'s work (*2*), an electric field is used to steer the microtubules into one of two arms of a Y junction; the microtubules move perpendicular to the field. The microtubules are transported by kinesin motor proteins.

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tion of microtubules with this control mechanism, van den Heuvel *et al*. have integrated optics, electronics, and molecular transport, thus introducing an element of real-time programmability.

This work is related to efforts by several teams of bioengineers to envision molecular motor–based technology and build proof-of-principle devices that radically depart from current engineering concepts (*9*). For example, minute volumes of biological samples can now be rapidly analyzed in credit-card–sized microfluidic devices connected to desktop-scale peripheral instruments. Downscaling of the lateral device dimensions by a factor of 100 would result in dust-particle–sized devices reminiscent of unicellular organisms. These devices would not necessarily be useful as as microscopic extensions of macroscopic peripheral devices, but would rather lend themselves to the application of the "smart dust" concept: smart dust biosensors would be immersed in the liquid sample of interest, independently perform an analysis, and be read out collectively to generate a statistically significant signal. Biomolecular motors that coat the inner surfaces of such devices and use dissolved ATP fuel as an energy source would drive the internal transport and remove the need for peripheral pumps and batteries (*10*).

In addition to fulfilling transport functions, biomolecular motors can exert localized forces on nanostructures. They can thus cause conformational changes, such as the stretching of coiled DNA molecules into a linear configuration (*11*) or the rupture of intermolecular bonds. Molecular motors could thus push supramolecular assembly and disassembly processes away from chemical equilibrium and generate dynamic, nonequilibrium structures (*12*). The force exerted by motor proteins could also be exploited in nanorobotics, where the sequential examination or manipulation of molecules by scanning probe microscopes and optical tweezers could be complemented by a parallel approach relying on arrays of microscopic, motor-driven actuators.

A key challenge in the field of molecular motors is to replicate the direct and efficient conversion of chemical energy into mechanical work by macroscopic arrays of biomolecular motors in muscles. This would pave the way toward a "molecular engine," creating an alternative to the prevailing heat engines (whose efficiency in converting chemical energy to mechanical work is limited according to Carnot) or to the two-step process of converting chemical energy into electricity via fuel cells and then into mechanical work via electrical motors. Building on insights from muscle physiology, we can pursue the engineering of either hybrid or fully synthetic molecular motor arrays of increasing size and explore a new avenue toward the design of artificial muscles (*13*).

Biomolecular motor–based hybrid devices face limitations with respect to environmental conditions (such as temperature) and lifetime (now typically on the order of hours to a few days) (*14*). Long-term storage of these devices in an inactivated state, which is reached by freezing or lyophilization technologies already used for protein pharmaceuticals, can be used to separate device fabrication and use by at least several months. However, limited lifetime and small power density are the principal disadvantages of biomolecular motors and motivate a transition to fully synthetic molecular motors in the long term.

Molecular motors, either of biological or synthetic origin, are central in the transition from passive to active nanostructures, because they enable coupling to a reservoir of chemical energy. In previous centuries, the use of human and animal power enabled the development of a wide range of technologies—including roads, carriages, and pumps—which were augmented after the invention of the steam engine and the internal combustion engine. Similarly, biomolecular motor nanotechnology, where van den Heuvel *et al*. have devised improved roads and the first traffic control system, and the on-going development of synthetic molecular motors (*15*) contribute to the same vision of fast, efficient, and controlled nanometer-scale transport systems.

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10.1126/science.1126399

NEUROSCIENCE

Regulating Energy Balance: The Substrate Strikes Back

Jeffrey S. Flier

Hormones and dietary nutrients control appetite and metabolism by acting on the brain, where the signals they elicit promote hunger or satiety. Neurons in the hypothalamus integrate these signals to regulate energy balance.

Appetite, energy expenditure, and metabolism are critically regulated by hypothalamic neural circuits, and a "wiring diagram" through which neurons and neurochemicals exert these effects is rapidly emerging. To achieve energy homeostasis, neuronal pathways in the central nervous system receive and integrate signals from the periphery that convey information about the status of energy fluxes and stores. These signals are of several types. Hormones, such as the fat-derived hormone leptin, act directly on a subset of neurons; a deficiency of leptin is interpreted by the brain as starvation. Leptin deficiency overrides other signals to produce ongoing hunger despite massive obesity, as in rare human cases and in rodent models. Other regulatory signals include gut-derived peptide hormones released with meals that promote feeding (ghrelin) or satiety (cholecystokinin and peptide YY) through actions on the same neuronal targets.

Although these endocrine effectors have received the most attention recently, metabolic fuels and substrates, the evolutionarily ancient regulators of cellular and organismic homeostasis, also affect the neurocircuitry to regulate energy balance. For example, a low glucose level sensed by this circuitry provokes hunger (*1*). More recently, free fatty acids have been shown to act on targets in the central nervous system to regulate metabolism (*2*). On page 927 in this issue, Cota *et al*. (*3*) establish a novel, and potentially important role for

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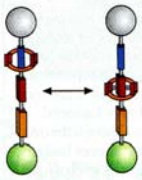
7. "Light drives molecular motor" Chemical&Engineering News, January 2006

SCIENCE & TECHNOLOGY

CONCENTRATES

Light drives molecular motor

A molecular motor powered by sunlight alone has been prepared by chemists in Italy and in the U.S. (*Proc. Natl. Acad. Sci. USA* **2006,** *103,* 1178). Vincenzo Balzani and Alberto Credi of the University of Bologna, J. Fraser Stoddart of the University of California, Los Angeles, and their coworkers believe their device is unique for several reasons. Because it's powered solely by visible light, the motor's movement—the shuttling of a crown ether back and forth between two points on the handle of a dumbbell-shaped structure (shown)—requires no additional chemicals and produces no waste products. Also, the shuttle's movement relies on intramolecular processes, so it could, in principle, be operated at the single-molecule level. The motor moves when a ruthenium complex (green sphere) at one end of the dumbbell absorbs a photon and transfers an electron to a 4,4′-bipyridinium moiety (blue bar) within the dumbbell's handle. This reduction prompts the crown ether (pink circle) to move 1.3 nm to a 3,3′-dimethyl-4,4′-bipyridinium unit (red bar) in the compound. The crown ether moves back to its original position via a back electron-transfer process.



subjected the protein to an approach called SIAFE (simultaneous incorporation and adjustment of functional elements) in conjunction with directed evolution (iterative modification and selection for desirable activity). The result was evMBL8, a designed enzyme with the ability to hydrolyze β-lactam amide bonds, a type of activity on which bacterial resistance to β-lactam antibiotics is based. Key to the change was the replacement of several of the enzyme's surface loop structures. The researchers say they hope the technique can be extended to convert other structures into enzymes that catalyze diverse reactions, including some not found in nature.

Down-to-earth NMR spectrometry

8. “Motore molecolare superveloce” Corriere de la Sierry, Milano, Italy, January 2006

SCIENZA

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UOMO, TECNOLOGIA, ECOLOGIA, NATURA

UNIVERSITÀ DI BOLOGNA

Motore molecolare superveloce

Si chiama Sunny il nanomotore inventato da un gruppo di scienziati del dipartimento di Chimica dell'Università di Bologna in collaborazione con l'Università della California di Los Angeles. È un minuscolo motore a 4 tempi che funziona con l'energia solare, non produce inquinanti e supera i 60.000 giri al minuto (è il più veloce del mondo della categoria). Il nuovo prototipo di motore molecolare (nell'illustrazione sopra), che verrà presentato nei «Proceedings of the National Academy of Sciences», è composto di due molecole: una filiforme, lunga circa 6 nanometri che funziona da asse di scorrimento (B), l'altra ad anello (A), infilata nella prima, con un diametro di 1,3 nanometri.

9. “Un nanomotore a benzina solare” Il sole-24 ore, Roma, Italy, January 2006

MADE IN ITALY IL PIÙ ECOLOGICO E VELOCE DEL MONDO

Un nanomotore a «benzina» solare

Chimici bolognesi hanno costruito una macchina microscopica azionata dalla luce, che non genera alcun prodotto di scarto

DI LARA RICCI

Un motore portentoso: funziona a energia solare, è velocissimo e pulito, non emette prodotti di scarto. «Sunny» è un macchinario al confine dell'altro mondo, quello invisibile, dell'ultrapiccolo, dove le leggi sono quelle della fisica quantistica. Ha quattro tempi come il motore a scoppio, ma è molto diverso, a partire dalle dimensioni: l'asse più lungo misura sei nanometri, impossibile da vedere, difficile da immaginare. Un nanometro, cioè un miliardesimo di metro, è circa 80mila volte più piccolo del diametro di un capello umano, o ancora, è uno spessore centomila volte minore di quello di un foglio di carta. La velocità di Sunny è sbalorditiva: un milione di volte maggiore dell'unico altro esempio al mondo di motore molecolare a energia pulita costruito dall'uomo.

Altra particolarità: per ora il motore non

LUCE SOLARE

A B C D

MOTORE MOLECOLARE

STEFANO TARTAGLIA

Il Sole-24 Ore
26 Gennaio 2006

10. “Il nanomotore é meglio di uns formula 1” La Stampa, Roma, Italy, February 2006

TECNOLOGIA

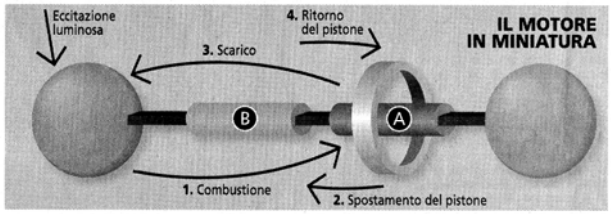
Il nanomotore è meglio di una Formula 1

DUE MOLECOLE CON IL SOLE COME CARBURANTE. TANTE APPLICAZIONI, DALLA MEDICINA ALL'INFORMATICA

UN motore di Formula 1 arriva a 20 mila giri al minuto. Questo supera i 60 mila. Piacerebbe di sicuro a Schumacher, se non fosse piccolissimo: è un nanomotore formato da due molecole. Invisibile a occhio nudo. Ha però un vantaggio straordinario: non richiede benzina, lo fa girare la luce del sole. Per questo i ricercatori dell'Università di Bologna, che l'hanno realizzato con l'Università della California, lo chiamano «Sunny». La notizia è su «Pnas», la rivista dell'Accademia americana delle Scienze. Il gruppo italiano fa capo a Vincenzo Balzani, uno dei 50 chimici più citati nelle riviste scientifiche. Il laboratorio Nanofaber della Regione Emilia sta esplorandone le future applicazioni.

L'unità di misura delle nanotecnologie è il nanometro, il miliardesimo di metro o - se preferite - il milionesimo di millimetro. Il motore «Sunny» è formato da una molecola sottile, lunga 6 nanometri, che funziona da asse di scorrimento, e da una molecola ad anello dal diametro di 1,3 nanometri, infilata nella prima. Sotto l'azione della luce l'anello scorre lungo la molecola mille volte al secondo. In sostanza, l'anello si muove come un pistone che trasforma l'energia dei fotoni solari in lavoro utilizzabile. Esiste un altro motore molecolare concettualmente simile costruito all'Università di Groningen nei Paesi Bassi, ma impiega un'ora a completare un ciclo: quello bolognese è quasi 4 milioni di volte più veloce.

Tipica delle nanotecnologie è la trasversalità. Sono utilizzabili nei settori più diversi: farmacia, elettronica, meccanica, chimica, fisica. Una possibile applicazione riguarda la salute: l'anello mobile funziona come un nastro trasportatore e, quindi, può far passare un farmaco attraverso la membrana delle cellule. Un altro uso potenziale riguarda l'informatica: si pensa a un computer chimico che sfrutti la logica binaria del nanomotore, fa-



11. La mia auto, Roma, Italy, March 2006

la mia auto

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SOMMARIO

12. “Lighting up nanomachines” Nature, London, UK, March 2006

PHOTOCHEMISTRY

Lighting up nanomachines

Euan R. Kay and David A. Leigh

A cleverly engineered molecule uses light to generate a charge-separated state and so cause one of its components to move. It's the latest study of a molecular machine that exploits nature's most plentiful energy source.

Nature runs the nanomachinery that makes life possible using the last word in clean, free and readily available power sources — sunlight. In photosynthetic bacteria and green plants, photon absorption by chlorophyll generates a charge-separated state, from which the electron is quickly passed down a cascade of electron carriers, ultimately generating energy in a convenient chemical form. Can similar capabilities be engineered? An exemplary effort to do just this is given by Balzani *et al.* who, writing in *Proceedings of the National Academy of Sciences*[1], describe photochemical experiments on an artificial machine that uses light to displace a fragment of its unimolecular structure.

Those who seek to harness the Sun's energy for synthetic molecular machines find that chemistry is always throwing up obstacles. In particular, charge recombination typically occurs thousands or millions of times faster than the nuclear movements on which such machines rely, making charge-separated states difficult to exploit. This problem can be overcome using bimolecular systems: here, the charged partners quickly diffuse apart so their energy can be used, for example, to achieve switching in a rotaxane[2]. This class of molecule, consisting of a ring that shuttles randomly and incessantly along a string, stopped only by bulky groups at the string's termini, is also that used by Balzani and colleagues[1].

Their rotaxane[1] (Fig. 1) incorporates two structurally different bipyridinium sites — 'stations' 1 and 2 — that slow the shuttling ring's motion through strong short-range electrostatic interactions. The ring thus divides its time between station 1, station 2 and the rest of the string in the ratio of around 95:5:<1. At room temperature, the ring shuttles between the stations tens of thousands of times per second, but the net flux is zero. So no work can be done, or useful task performed, by the shuttling action (the 'principle of detailed balance'[3]).

One of the bulky end-groups of the rotaxane's string is a ruthenium trisbipyridine complex. This can absorb a photon of visible light and so form a reactive, excited state that donates an electron to the more easily reduced of the two bipyridinium sites — station 1, the ring's preferred binding site. One would normally expect the resulting charge imbalance to be corrected by back-transfer of an electron on

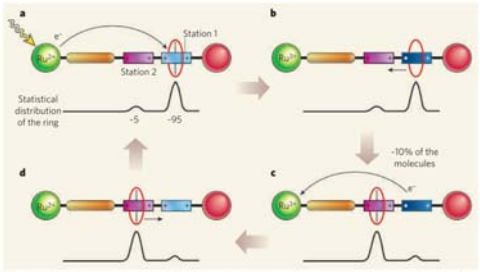
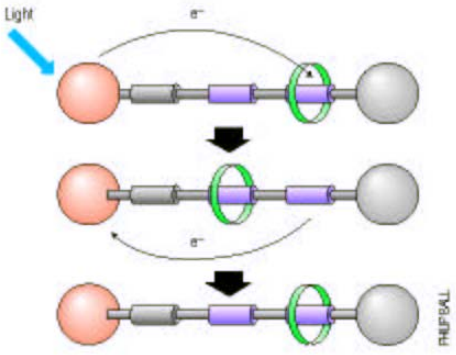


Figure 1 | Light-driven molecular shuttle. Balzani and colleagues' rotaxane[1,2] consists of a molecular ring free to move along a molecular string. **a**, At equilibrium in the ground state, the ring spends most of the time over station 1, as a result of attractive, non-covalent interactions. But irradiation of the ruthenium complex (green) at one end of the string generates a highly reducing excited state, resulting in electron transfer to station 1, and the weakening of this station's electrostatic interactions with the ring. **b**, Normally, charge recombination is fast in comparison with nuclear motions, but here a delay allows approximately 10% of the molecules to undergo significant brownian motion, shifting the distribution of these rings to favour station 2. **c**, When charge recombination eventually does take place, the higher binding affinity of station 1 is restored, and **d**, the system relaxes to restore the original statistical distribution of rings.

13. “Making light work of it” Nature Materials, London, UK, March 2006

Making light work of it

In contrast to motors in nature, artificial ones generally require one input to cause motion, followed by another to reset the motor. Often these inputs are chemical fuels, and therefore generate waste products, as well as requiring intervention at each stage. Now Balzani *et al.* report an autonomous motor powered simply with light (*Proc. Natl Acad. Sci.* **103**, 1178–1183; 2006). The motor consists of a rotaxane — a ring threaded around a dumbbell-shaped component of two electron-acceptor sites, or ‘stations’, for the ring to move between, with a bulky stopper group on each end. Absorption of a photon at a stopper group initiates electron transfer to the station where the ring rests, causing displacement to the second station. An electron can then transfer back to the stopper group from the now-free first station, and the ring can return to its original position. The motor works analogously to a four-stroke engine, with fuel injection and combustion, piston displacement, exhaust removal and piston-replacement steps. The motors of Balzani *et al.* rely exclusively on intramolecular processes and light absorption, and therefore do not consume chemical fuel or produce waste.



14. “Nanomotor powered by solar energy” Small, Weiheim, Germany, April 2006

Synthetic procedures

Nano Motor Powered by Solar Energy

Chemists at the University of Bologna (Italy), UCLA, and the California NanoSystems Institute (both USA) have designed and constructed a rotaxane-based molecular motor of nanometer size that is powered only by sunlight. The system is built up from a dumbbell-shaped component, which is more than 6 nm long, and a ring component of a diameter of approximately 1.3 nm. The ring component is trapped on the rod portion by two bulky stoppers, which are attached to the ends of the rod so that the ring cannot slip off. The rod portion of the dumbbell contains two “stations” that can be called “A” and “B”. The absorption of sunlight by one of the two stoppers, a light-harvesting species, causes the transfer of one electron to station A, which is deactivated as far as wanting

15. **Two broadcasting emissions in the German introduced to the research work of M. Ruben, 3Sat and MDR, June/October 2005**

See under www.3sat.de/3sat.php?http://www.3sat.de/nano/cstuecke/76580/index.html

Vorstoß in die unbekannte Welt des unsagbar Winzigen

Chemiker Mario Ruben sucht in Karlsruhe nach neuen Wegen der Nanotechnologie

"Für mich persönlich liegt der Reiz der Nanotechnologie darin: Es ist fast jeder Quadratmeter unserer Erde erforscht worden, aber an dieser Grenze gibt es noch viel Raum. Es ist noch viel Raum nach unten, wo jeder neue Schritt ein Schritt ins Unbekannte ist." Der Chemiker Mario Ruben vom Forschungszentrum Karlsruhe befasst sich zusammen mit den Forschern seiner Arbeitsgruppe mit molekularen Systemen, die sich auf Oberflächen selbst organisieren.

Section 3 – Publishable results

The full content version of the publications and press releases can be down-loaded and printed under www.biomach.org

MOLECULAR NANOTECHNOLOGY. TOWARDS ARTIFICIAL MOLECULAR MACHINES AND MOTORS

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Abstract

Miniaturization is an essential ingredient of modern technology. In this context, concepts such as that of (macroscopic) device and machine have been extended to the molecular level. A *molecular machine* can be defined as an assembly of a discrete number of molecular components – that is, a supramolecular system – in which the component parts can display changes in their relative positions as a result of some external stimulus. While nature provides living organisms with a wealth of molecular machines and motors of high structural and functional complexity, chemists are interested in the development of simpler, fully artificial systems. Interlocked chemical compounds like rotaxanes and catenanes are promising candidates for the construction of artificial molecular machines. The design, synthesis and investigation of chemical systems able to function as molecular machines and motors is of interest not only for basic research, but also for the growth of nanoscience and the subsequent development of nanotechnology. A few examples of molecular machines taken from our own research will be illustrated.

1. INTRODUCTION

A *device* is something invented and constructed for a special purpose, and a *machine* is a particular type of device in which the component parts display changes in their relative positions as a result of some external stimulus. Progress of mankind has always been related to the construction of novel devices. Depending on the purpose of its use, a device can be very big or very small. In the last fifty years, progressive miniaturization of the components employed for the construction of devices and machines has resulted in outstanding technological achievements, particularly in the field of information processing. A common prediction is that further progress in miniaturization will not only decrease the size and increase the power of computers, but could also open the way to new technologies in the fields of medicine, environment, energy, and materials.

Until now miniaturization has been pursued by a large-downward (top-down) approach, which is reaching practical and fundamental limits (presumably ca. 50 nanometers).[1] Miniaturization, however, can be pushed further on since "there is plenty of room at the bottom", as Richard P. Feynman stated in a famous talk to the American Physical Society in 1959.[2]

The key sentence of Feynman's talk was the following: *"The principle of physics do not speak against the possibility of manoeuvring things atom by atom"*. The idea of the "atom-by-atom" bottom-up approach to the construction of nanoscale devices and machines, however, which was so much appealing to some physicists[3] did not convince chemists who are well aware of the high reactivity of most atomic species and of the subtle aspects of chemical bond. Chemists know[4] that atoms are not simple spheres that can be moved from a place to another place at will. Atoms do not stay isolated; they bond strongly to their neighbours and it is difficult to imagine that the atoms can be taken from a starting material and transferred to another material.

In the late 1970s a new branch of chemistry, called *supramolecular chemistry*, emerged and expanded very rapidly, consecrated by the award of the Nobel Prize in Chemistry to C.J. Pedersen,[5] D.J. Cram,[6] and J.-M. Lehn[7] in 1987. In the frame of research on supramolecular chemistry, the idea began to arise in a few laboratories[8,9,10] that molecules are much more convenient building blocks than atoms to construct nanoscale devices and machines. The main reasons at the basis of this idea are: (i) molecules are stable species, whereas atoms are difficult to handle; (ii) Nature starts from molecules, not from atoms, to construct the great number and variety of nanodevices and nanomachines that sustain life; (iii) most of the laboratory chemical processes deal with molecules, not with atoms; (iv) molecules are objects that exhibit distinct shapes and carry device-related properties (e.g., properties

that can be manipulated by photochemical and electrochemical inputs); (v) molecules can self-assemble or can be connected to make larger structures. In the same period, research on molecular electronic devices began to flourish.[11]

In the following years supramolecular chemistry grew very rapidly[12] and it became clear that the "bottom-up" approach based on molecules opens virtually unlimited possibilities concerning design and construction of artificial molecular-level devices and machines. Recently the concept of molecules as nanoscale objects exhibiting their own shape, size and properties has been confirmed by new, very powerful techniques, such as single-molecule fluorescence spectroscopy and the various types of probe microscopies, capable of "seeing"[13] or "manipulating"[14] single molecules, and even to investigate bimolecular chemical reactions at the single molecule level.[15]

Much of the inspiration to construct molecular-level devices and machines comes from the outstanding progress of molecular biology that has begun to reveal the secrets of the natural molecular-level devices and machines which constitute the material base of life. Bottom-up construction of devices and machines as complex as those present in Nature is, of course, an impossible task.[16] Therefore chemists have tried to construct much simpler systems, without mimicking the complexity of the biological structures. In the last few years, synthetic talent, that has always been the most distinctive feature of chemists, combined with a device-driven ingenuity evolved from chemists' attention to functions and reactivity, have led to outstanding achievements in this field.[17,18,19,20]

2. CHARACTERISTICS OF MOLECULAR MACHINES AND MOTORS

The words *motor* and *machine* are often used interchangeably when referred to molecular systems. It should be recalled, however, that a motor converts energy into mechanical work, while a machine is a device, usually containing a motor component, designed to accomplish a function. Molecular machines and motors operate via electronic and/or nuclear rearrangements and, like the macroscopic ones, are characterized by *(i)* the kind of energy input supplied to make them work, *(ii)* the type of motion (linear, rotatory, oscillatory, ...) performed by their components, *(iii)* the way in which their operation can be monitored, *(iv)* the possibility to repeat the operation at will (cyclic process), and *(v)* the time scale needed to complete a cycle. According to the view described above, an additional and very important distinctive feature of a molecular machine with respect to a molecular motor is *(vi)* the function performed.[18]

As far as point *(i)* is concerned, a chemical reaction can be used, at least in principle, as an energy input. In such a case, however, if the machine has to work cyclically [point *(iv)*], it will need addition of reactants at any step of the working cycle, and the accumulation of by–products resulting from the repeated addition of matter can compromise the operation of the device. On the basis of this consideration, the best energy inputs to make a molecular device work are photons[21] and electrons.[22] It is indeed possible to design very interesting molecular devices based on appropriately chosen photochemically and electrochemically driven reactions.[20]

In order to control and monitor the device operation [point *(iii)*], the electronic and/or nuclear rearrangements of the component parts should cause readable changes in some chemical or physical property of the system. In this regard, photochemical and electrochemical techniques are very useful since both photons and electrons can play the dual role of "writing" (i. e., causing a change in the system) and "reading" (i.e., reporting the state of the system).

The operation time scale of molecular machines [point *(v)*] can range from microseconds to seconds, depending on the type of rearrangement and the nature of the components involved.

Finally, as far as point *(vi)* is concerned, the functions that can be performed by exploiting the movements of the component parts in molecular machines are various and, to a large extent, still unpredictable. It is worth to note that the mechanical movements taking place in molecular-level

machines, and the related changes in the spectroscopic and electrochemical properties, usually obey binary logic and can thus be taken as a basis for information processing at the molecular level. Artificial molecular machines capable of performing logic operations have been reported.[23]

3. ROTAXANES AND CATENANES AS ARTIFICIAL MOLECULAR MACHINES

Most of the recently designed artificial molecular machines and motors are based[20] on interlocked chemical compounds named rotaxanes and catenanes. The names of these compounds derive from the Latin words *rota* and *axis* for wheel and axle, and *catena* for chain. Rotaxanes[24] are minimally composed (Figure 1a) of an axle-like molecule surrounded by a macrocyclic compound and terminated by bulky groups (stopper) that prevent disassembly; catenanes[24] are made of (at least) two interlocked macrocycles or "rings" (Figure 1b). Rotaxanes and catenanes are appealing systems for the construction of molecular machines because motions of their molecular components can be easily imagined (Figure 2).

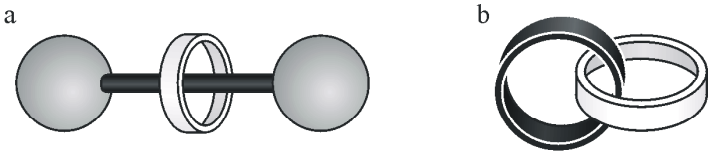

FIG. 1. Schematic representation of a rotaxane (a) and a catenane (b).

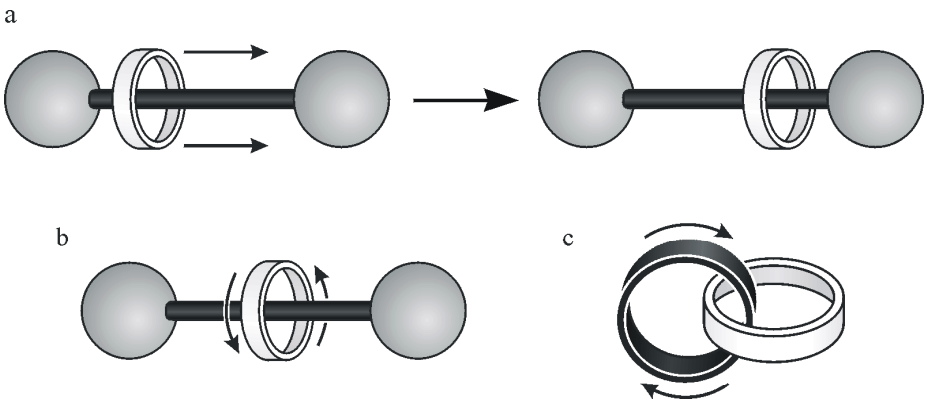

FIG. 2. Schematic representation of some of the intercomponent motions that can be obtained with rotaxanes and catenanes: shuttling (a) and ring rotation (b, c).

Important features of these systems derive from noncovalent interactions between components that contain complementary recognition sites. Such interactions, that are also responsible for the efficient template-directed syntheses of rotaxanes and catenanes, involve electron-donor/acceptor ability, hydrogen bonding, hydrophobic/hydrophylic character, π-π stacking, coulombic forces and, on the side of the strong interaction limit, metal-ligand bonding.

In the next sections, a few examples of artificial molecular machines based on rotaxanes and catenanes taken from our research will be illustrated.

4. AN ACID-BASE CONTROLLED MOLECULAR SHUTTLE

In rotaxanes containing two different recognition sites in the dumbbell-shaped component, it is possible to switch the position of the ring between the two 'stations' by an external stimulus. A system which behaves as a chemically controllable molecular shuttle is compound $\mathbf{1}^{3+}$ shown in Figure 3.[25] It is made of a dibenzo[24]crown-8 (DB24C8) macrocycle and a dumbbell-shaped component containing a dialkylammonium center and a 4,4'-bipyridinium unit. An anthracene moiety is used as a stopper because its absorption, luminescence, and redox properties are useful to monitor the state of the system. Since the N^+–H···O hydrogen bonding interactions between the DB24C8 macrocycle and the ammonium center are much stronger than the electron donor-acceptor interactions of the macrocycle with the bipyridinium unit, the rotaxane exists as only one of the two possible translational isomers. Deprotonation of the ammonium center with a base (a tertiary amine) causes 100% displacement of the macrocycle to the bipyridinium unit; reprotonation directs the macrocycle back onto the ammonium center (Figure 3). Such a switching process has been investigated in solution by ^{1}H NMR spectroscopy and by electrochemical and photophysical measurements.[25] The full chemical reversibility of the energy supplying acid/base reactions guarantees the reversibility of the mechanical movement, in spite of the formation of waste products. Notice that this system could be useful for information processing since it exhibits a binary logic behavior. It should also be noted that, in the deprotonated rotaxane, it is possible to displace the crown ring from the bipyridinium station by destroying the donor-acceptor interaction through reduction of the bipyridinium station or oxidation of the dioxybenzene units of the macrocyclic ring. Therefore, in this system, mechanical movements can be induced by two different types of stimuli (acid-base and electron-hole).

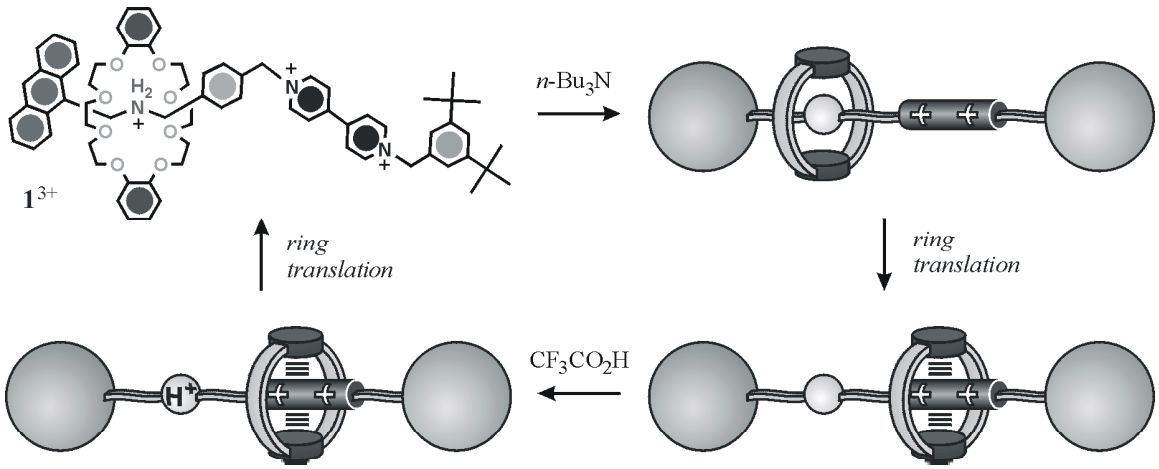

FIG. 3. A chemically controllable molecular shuttle. The macrocyclic ring can be switched between the two stations of the dumbbell-shaped component by acid-base inputs

5. A LIGHT-DRIVEN MOLECULAR SHUTTLE

For a number of reasons, light is the most convenient form of energy to make artificial molecular machines work.[21] In order to achieve photoinduced ring shuttling in rotaxanes containing two different recognition sites in the dumbbell-shaped component, the thoroughly designed compound $\mathbf{2}^{6+}$ (Figure 4) was synthesized.[26] This compound is made of the electron-donor macrocycle R, and a dumbbell-shaped component which contains (i) $[Ru(bpy)_3]^{2+}$ (P) as one of its stoppers, (ii) a 4,4'-bipyridinium unit (A_1) and a 3,3'-dimethyl-4,4'-bipyridinium unit (A_2) as electron accepting stations, (iii) a *p*-terphenyl-type ring system as a rigid spacer (S), and (iv) a tetraarylmethane group as the second stopper (T). The structure of rotaxane $\mathbf{2}^{6+}$ was characterized by mass spectrometry and ^{1}H

NMR spectroscopy, which also established, along with cyclic voltammetry, that the stable translational isomer is the one in which the R component encircles the A_1 unit, in keeping with the fact that this station is a better electron acceptor than the other one. The electrochemical, photophysical and photochemical (under continuous and pulsed excitation) properties of the rotaxane, its dumbbell-shaped component, and some model compounds have then been investigated and two strategies have been devised in order to obtain the photoinduced abacus-like movement of the R macrocycle between the two stations A_1 and A_2: one was based on processes involving only the rotaxane components (intramolecular mechanism), while the other one required the help of external reactants (sacrificial mechanism).

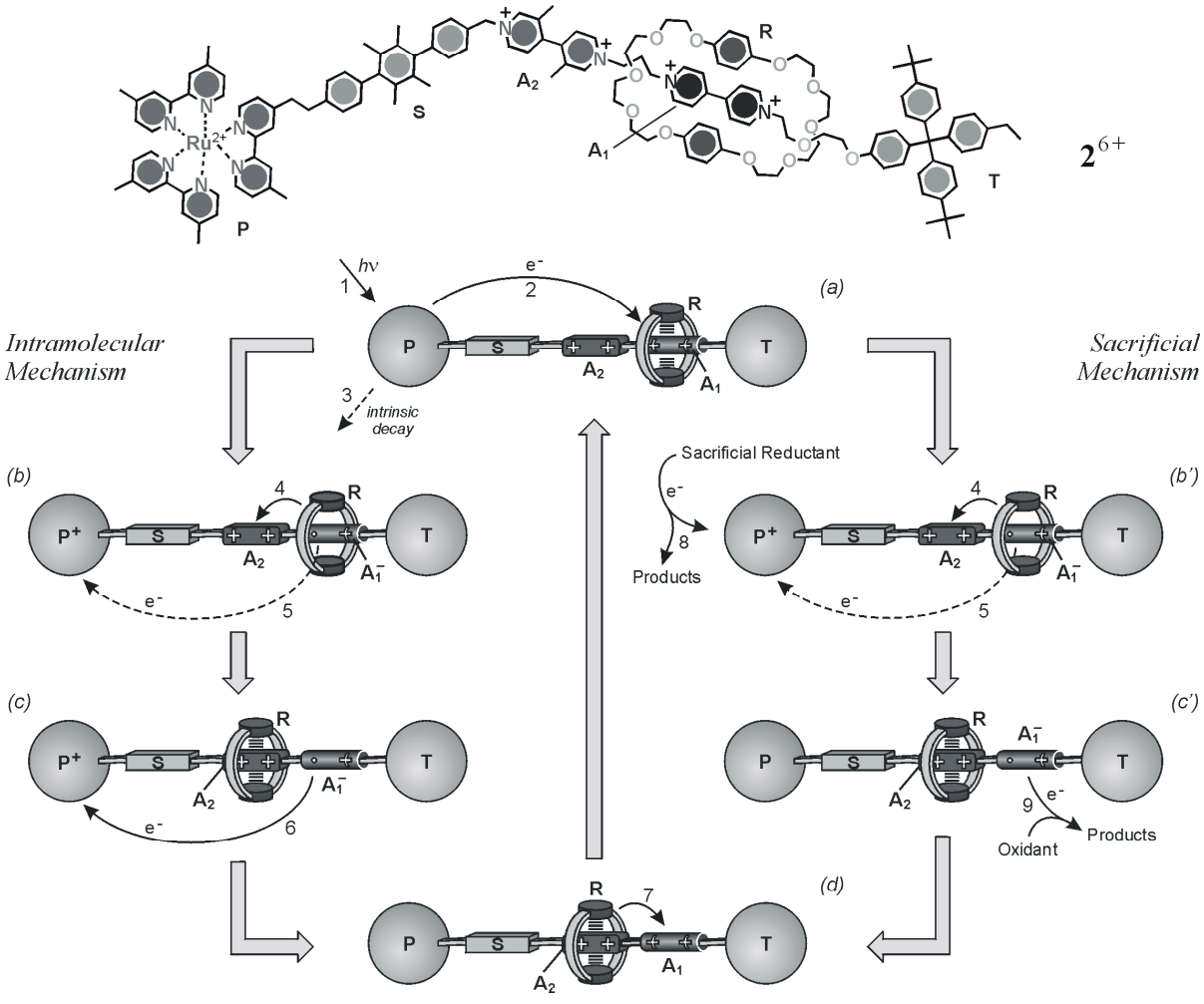

FIG. 4. Structural formula of the rotaxane $\mathbf{2}^{6+}$ *and schematic representation of the intramolecular (left) and sacrificial (right) mechanisms for the photoinduced shuttling movement of macrocycle R between the two stations* A_1 *and* A_2.

The intramolecular mechanism, illustrated in the left part of Figure 4, is based on the following four operations:[26]

(a) *Destabilization of the stable translational isomer*: light excitation of the photoactive unit P (Step 1) is followed by the transfer of an electron from the excited state to the A_1 station, which is

encircled by the ring R (Step 2), with the consequent "deactivation" of this station; such a photoinduced electron-transfer process has to compete with the intrinsic decay of P* (Step 3).

(b) *Ring displacement*: the ring moves from the reduced station A_1^- to A_2 (Step 4), a step that has to compete with the back electron-transfer process from A_1^- (still encircled by R) to the oxidized photoactive unit P^+ (Step 5). This is the most difficult requirement to meet in the intramolecular mechanism.

(c) *Electronic reset*: a back electron-transfer process from the "free" reduced station A_1^- to P^+ (Step 6) restores the electron-acceptor power to the A_1 station.

(d) *Nuclear reset*: as a consequence of the electronic reset, back movement of the ring from A_2 to A_1 takes place (Step 7).

The results obtained[26] do not indicate cleary whether the ring displacement (Step 4) is faster than the electronic reset of the system after light excitation (Step 5; $k = 2.4\times10^5$ s^{-1}). More detailed laser flash photolysis studies suggest that these two processes could occur on the same time scale.[27]

It is worthwhile noticing that in a system which behaves according to the intramolecular mechanism shown in Figure 4 (left) each light input causes the occurrence of a forward and back ring movement (i.e., a full cycle) without generation of any waste product. In some way, it can be considered as a "four-stroke" cyclic linear motor powered by light.

A less demanding mechanism is based on the use of external sacrificial reactants (a reductant like triethanolamine and an oxidant like dioxygen) that operate as illustrated in the right part of Figure 4:

(a) *Destabilization of the stable translational isomer*, as in the previous mechanism.

(b') *Ring displacement after scavenging of the oxidized photoactive unit*: since the solution contains a suitable sacrificial reductant, a fast reaction of such species with P^+ (Step 8) competes successfully with the back electron-tranfer reaction (Step 5); therefore, the originally occupied station remains in its reduced state A_1^-, and the displacement of the ring R to A_2 (Step 4), even if it is slow, does take place.

(c') *Electronic reset*: after an appropriate time, restoration of the electron-acceptor power of the A_1 station is obtained by oxidizing A_1^- with a suitable oxidant, such as O_2 (Step 9).

(d) *Nuclear reset*, as in the previous mechanism (Step 7).

The results obtained[26] show that such a sacrificial mechanism is fully successful. Of course, this mechanism is less appealing than the intramolecular one because it causes the formation of waste products. An alternative strategy is to use a non-sacrificial (reversible) reductant species that is regenerated after the back electron-transfer process.[28]

6. CONTROLLED RING ROTATION IN CATENANES

In a catenane, structural changes caused by rotation of one ring with respect to the other can be clearly evidenced when one of the two rings contains two non-equivalent units. In the catenane $\mathbf{3}^{4+}$ shown in Figure 5, the electron-acceptor tetracationic cyclophane is "symmetric", whereas the other ring contains two different electron–donor units, namely, a tetrathiafulvalene (TTF) and a 1,5-dioxynaphthalene (DON) unit.[29]

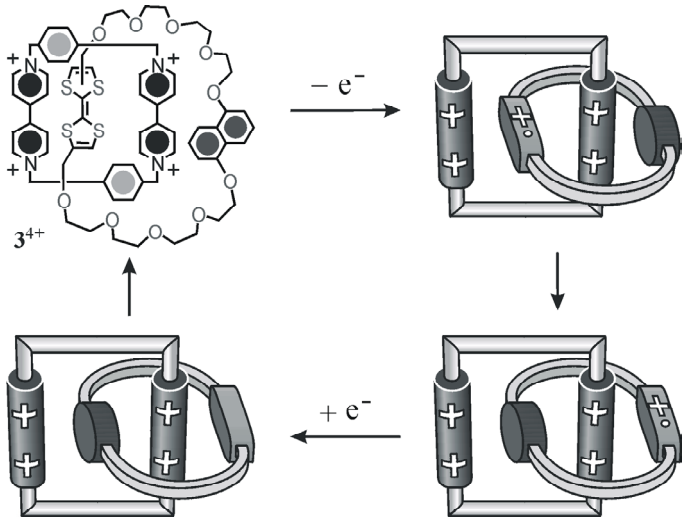

FIG. 5. Redox controlled ring rotation in a catenane containing a non-symmetric ring

In a catenane structure, the electron donor located inside the cavity of the electron-acceptor ring experiences the effect of two electron-acceptor units, whereas the alongside electron donor experiences the effect of only one electron acceptor. Therefore, the better electron donor (i. e., TTF) enters the acceptor ring and the less good one (i.e., DON) remains alongside. On electrochemical oxidation, the first observed process concerns TTF, which thus loses its electron donating properties. Furthermore, an electrostatic repulsion arises between TTF^+ and the tetracationic macrocycle. These effects cause rotation of one ring to yield the translational isomer with the DON moiety positioned inside the acceptor ring. Upon reduction of TTF^+, the initial configuration is restored. However, this may happen without the occurrence of a *full* rotation, because it is equally probable that the reset caused by reduction of TTF^+ occurs by a reverse rotation compared to that occurred in the forward switching caused by TTF oxidation. In order to obtain a full rotation, i.e., a molecular-level rotary motor, the direction of each switching movement should be controllable. This goal can likely be reached by introducing appropriate functions in one of the two macrocycles.[20,21] When this goal is reached, it will be possible to convert alternate electrical potential energy into a molecular-level mechanical rotation.

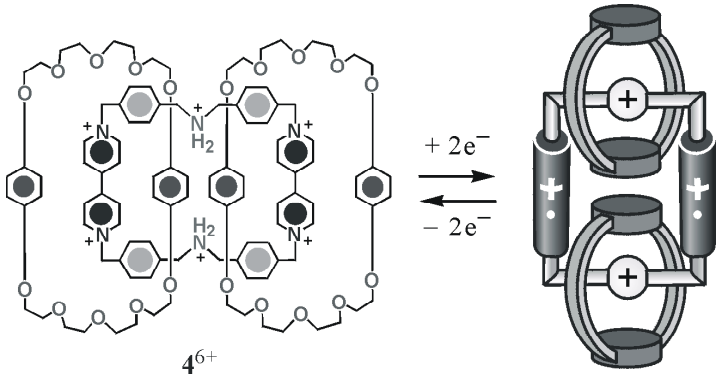

FIG. 6. Redox controlled movements of the ring components upon reduction-oxidation of the bipyridinium units in a catenane composed of three interlocked macrocycles

Controlled rotation of the molecular rings has been achieved also in a catenane composed of three interlocked macrocycles (**4**$^{6+}$, Figure 6).[30] Upon addition of one electron in each of the bipyridinium units, the two macrocycles move on the ammonium stations, and move back to the original position when the bipyridinium units are reoxidized. Unidirectional ring rotation has recently been obtained[31] in a peptide-based catenane having the same topology as **4**$^{6+}$.

7. CONCLUSIONS AND PERSPECTIVES

In the last few years, several examples of molecular machines and motors have been designed and constructed.[17–20] It should be noted, however, that the molecular-level machines described in this chapter operate in solution, that is, in an incoherent fashion. Although the solution studies of chemical systems as complex as molecular machines are of fundamental importance, it seems reasonable that, before functional supramolecular assemblies can find applications as machines at the molecular level, they have to be interfaced with the macroscopic world by ordering them in some way. The next generation of molecular machines and motors will need to be organized at interfaces,[32] deposited on surfaces,[33] or immobilized into membranes[16a,34] or porous materials[35] so that they can behave coherently. Indeed, the preparation of modified electrodes[22,36] represent one of the most promising ways to achieve this goal. Solid-state electronic devices based on functional rotaxanes and catenanes have already been developed.[37] Furthermore, addressing a single molecular-scale device[38] by instruments working at the nanometer level is no longer a dream.[13–15]

Apart from more or less futuristic applications, the extension of the concept of a machine to the molecular level is of interest not only for the development of nanotechnology, but also for the growth of basic research. Looking at supramolecular chemistry from the viewpoint of functions with references to devices of the macroscopic world is indeed a very interesting exercise which introduces novel concepts into Chemistry as a scientific discipline.

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