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Artificial nanomachines based on interlocked molecules

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Abstract

The extension of the concept of machine to the molecular level is of great interest for the growth of nanoscience and the development of nanotechnology. A molecular machine can be defined as an assembly of a discrete number of molecular components (that is, a supramolecular structure) designed to perform a function through the mechanical movements of its components, which occur under appropriate external stimulation. Hence, molecular machines contain a motor part, that is a device capable of converting energy into mechanical work. Molecular motors and machines operate via nuclear rearrangements and, like their macroscopic counterparts, are characterized by the kind of energy input supplied to make them work, the manner in which their operation can be monitored, the possibility to repeat the operation at will, i.e., establishing a cyclic process, the timescale needed to complete a cycle of operation, and the performed function. Owing to the progresses made in several branches of chemistry, and to the better understanding of the operation mechanisms of molecular machines of the biological world, it has become possible to design and construct simple prototypes of artificial molecular motors and machines. Some examples based on rotaxanes, catenanes, and related interlocked molecules will be described.

(Some figures in this article are in colour only in the electronic version)

1. Basic principles

1.1. Introduction

Movement is one of life's central attributes. Nature provides living systems with complex molecules called motor proteins which work inside a cell like ordinary machines built for everyday needs. The development of civilization has always been strictly related to the design and construction of devices, from wheel to jet engine, capable of facilitating man movement and travelling. Nowadays the miniaturization race leads scientists to investigate the possibility of designing and constructing motors and machines at the nanometre scale.

The study of motion at the molecular level is a fascinating topic from the viewpoint of basic research and a promising field for novel applications. This paper is intended to illustrate some basic features and chemical design principles of molecular machines. A few recent examples of artificial systems based on rotaxanes, catenanes and related interlocked molecules, taken from research carried out at the University of Bologna, will be described.

1.2. The bottom-up (supramolecular) approach to nanodevices

In everyday life we make extensive use of devices. A *device* is something invented and constructed for a special purpose. More specifically, it is an assembly of components designed to achieve a specific *function*, resulting from the cooperation of the (simple) *acts* performed by each component. 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.

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 about 50 nm) [1]. Miniaturization, however, can be pushed further on since 'there is plenty of room at the bottom', as Richard 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 people [3, 4] did not convince chemists who are well aware of the high reactivity of most atomic species and of the subtle aspects of chemical bond. Atoms are not spheres that can be moved from a place to another place at will [5]. They do not stay isolated, but rather bind strongly to their neighbours, and it is difficult to imagine that individual atoms can be taken from a starting material and transferred to another material.

In the 1980s, in the frame of research on supramolecular chemistry [6, 7], the idea began to arise in a few laboratories [8–10] 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 [11–13].

In the following years it became clear that the bottom-up approach based on molecules opens virtually unlimited possibilities concerning design and construction of artificial molecular devices and machines. 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 [14, 15] and the various types of probe

microscopies [16], capable of visualizing or manipulating single molecules [17], and even to investigate bimolecular chemical reactions at the single molecule level [18].

Much of the inspiration to construct molecular devices and machines comes from the outstanding progress of molecular biology that has begun to reveal the secrets of the natural nanodevices which constitute the material base of life [19]. The bottom-up construction of devices as complex as those present in Nature is, of course, a prohibitive task. Therefore chemists have tried to construct much simpler systems, consisting of a few molecular components capable of moving in a controllable way, without mimicking the complexity of the biological structures, and to investigate the challenging problems posed by interfacing artificial molecular devices with the macroscopic world, particularly as far as energy supply and information exchange are concerned. In the last few years the development of powerful synthetic methodologies, combined with a device-driven ingenuity evolved from the attention to functions and reactivity, have led to remarkable achievements in this field [20–25].

1.3. Characteristics of molecular motors and machines

A *molecular motor* can be defined as an assembly of a discrete number of molecular components designed to perform mechanical-like movements under control of appropriate energy inputs. This definition excludes the molecular motions caused simply by thermal energy [26]. 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 motors and machines operate via electronic and/or nuclear rearrangements and make use of thermal fluctuations (Brownian motion) [27, 28]. Like the macroscopic couterparts, they 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 timescale 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.

The problem of the energy supply to make artificial molecular motors work (point (i)) is of the greatest importance [29]. The most obvious way to supply energy to a chemical system is through an exergonic chemical reaction. In the previously mentioned address [2] to the American Physical Society, Richard Feynman observed: *'An internal combustion engine of molecular size is impossible. Other chemical reactions, liberating energy when cold, can be used instead'*. This is exactly what happens in our body, where the chemical energy supplied by food is used in long series of slightly exergonic reactions to power the biological machines that sustain life.

If an artificial molecular motor has to work by inputs of chemical energy, it will need addition of fresh reactants ('fuel') at any step of its working cycle, with the concomitant formation of waste products. Accumulation of waste products, however, will compromise the operation of the device unless they are removed from the system, as it happens in our body as well as in macroscopic internal combustion engines. The need to remove waste products introduces noticeable limitations in the design and costruction of artificial molecular motors based on chemical fuel inputs.

Photochemical and electrochemical energy inputs can indeed cause the occurrence of *endergonic* and *reversible* reactions. In recent years, the progresses made by supramolecular photochemistry [30] and electrochemistry [31] has thus led to the design and construction of molecular machines powered by light or electrical energy, which work without formation of

waste products. In the case of photoexcitation, the commonly used endergonic and reversible reactions are isomerization and redox processes. In the case of electrochemical energy inputs, the induced endergonic and reversible reactions are, of course, heterogeneous electron transfer processes. Photochemical and electrochemical techniques offer further advantages, since lasers provide the opportunity of working in very small space and very short time domains, and electrodes represent one of the best way to interface molecular-level systems with the macroscopic world.

A very important feature of molecular motors, related to energy supply (point (i)) and cyclic operation (point (iv)), is their capability to exhibit an *autonomous* behaviour; that is, to keep operating, in a constant environment, as long as the energy source is available. Natural motors are autonomous, but the vast majority of the artificial molecular motors reported so far are *not autonomous* since, after the mechanical movement induced by a given input, they need another, opposite input to reset. Obviously, the operation of a molecular machine is accompanied by partial conversion of free energy into heat, regardless of the chemical, photochemical, and electrochemical nature of the energy input. The motions performed by the component parts of a molecular motor (point (ii)) may imply rotations around covalent bonds or the making and breaking of intercomponent noncovalent bonds, as we shall see later on.

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). Luminescence spectroscopy, in particular, is a most valuable reading technique since it is easily accessible and offers good sensitivity and selectivity, along with the possibility of time-resolved studies.

The operation timescale of molecular machines (point (v)) can range from microseconds to seconds, depending on the type of rearrangement and the chemical 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 motors and machines are various and, to a large extent, still unpredictable. In natural systems the molecular motions are always aimed at obtaining specific functions, e.g., catalysis, transport, gating. As it will be described in the next sections, the mechanical movements taking place in molecular 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 [32, 33].

1.4. Natural molecular motors and machines

In the last few years, much progress has been made in elucidation of the moving mechanisms of motor biomolecules, owing to the fact that—in addition to the established physiological and biochemical methods—novel *in vitro* techniques have been developed which combine optical and mechanical methods to observe the behaviour of a single protein. The most important and best known natural molecular motors are ATP synthase, myosin and kinesin [34, 35].

ATP synthase is the ubiquitous enzyme that manufactures adenosine triphosphate (ATP) and is a rotary motor powered by a proton gradient. It consists of two rotary molecular motors attached to a common shaft, each attempting to rotate in the opposite direction (figure 1). The F_1 motor uses the free energy of ATP hydrolysis to rotate in one direction, while the F_0 motor

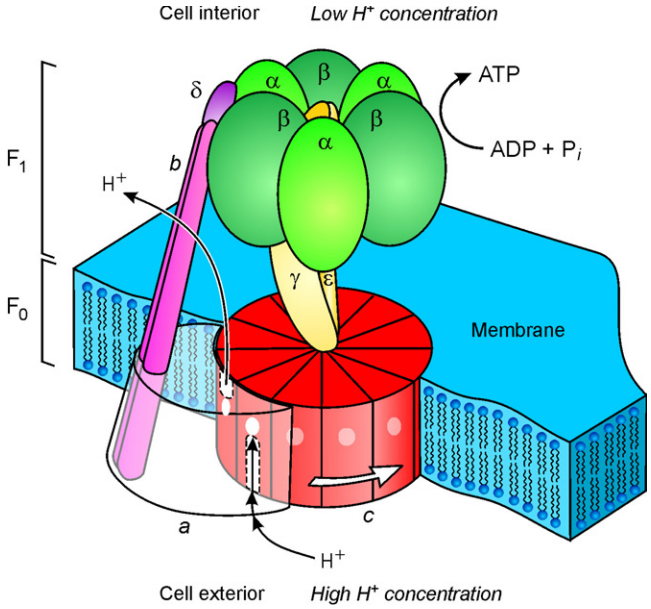

Figure 1. Schematic representation of the structure of F_0F_1-ATP synthase.

uses the energy stored in a transmembrane electrochemical gradient to turn in the opposite direction. Which motor 'wins' (i.e., develops more torque) depends on cellular conditions. When F_0 takes over, which is the normal situation, it drives the F_1 motor in reverse whereupon it synthesizes ATP from its constituents, adenosine diphosphate (ADP) and inorganic phosphate, P_i. When F_1 dominates, it hydrolyzes ATP and drives the F_0 motor in reverse, turning it into an ion pump that moves ions across the membrane against the electrochemical gradient. The mechanochemistry of ATP synthase has been studied in great detail [34–38] and new structural information continue to appear [39].

This enzyme consists of two principal domains (figure 1). The asymmetric membrane-spanning F_0 portion contains a proton channel, and the soluble F_1 portion contains three catalytic sites which cooperate in the synthetic reactions. The catalytic region is made up of nine protein subunits with the stoichiometry $3\alpha{:}3\beta{:}1\gamma{:}1\delta{:}1\varepsilon$, approximating to a flattened sphere, 10 nm across and 8 nm high. The flow of protons through F_0 generates a torque which is transmitted to F_1 by an asymmetric shaft, the γ-subunit. This subunit acts as a rotating 'cam' within F_1, sequentially releasing ATPs from the three active sites. The free energy difference across the inner membrane of mitochondria and bacteria is sufficient to produce three ATPs per twelve protons passing through the motor.

As mentioned above, the F_0F_1-ATP synthase is reversible, i.e., the full enzyme can synthesize or hydrolyze ATP; F_1 in isolation, however, can only hydrolyze it. The spinning of F_1-ATP synthase, i.e., the rotary motor nature of this enzyme was directly observed [40] by attaching a fluorescent actin filament to the γ subunit as a marker. Further data on motor rotation were obtained from other experiments carried out on single molecules of ATP synthase [39, 41].

The enzymes of the myosin and the kinesin families are linear motors that move along polymer substrates (actin filaments for myosin and microtubules for kinesin), converting the energy of ATP hydrolysis into mechanical work [42]. Motion derives from a mechanochemical

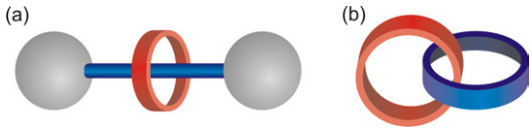

Figure 2. Schematic representation of a rotaxane (a) and a catenane (b).

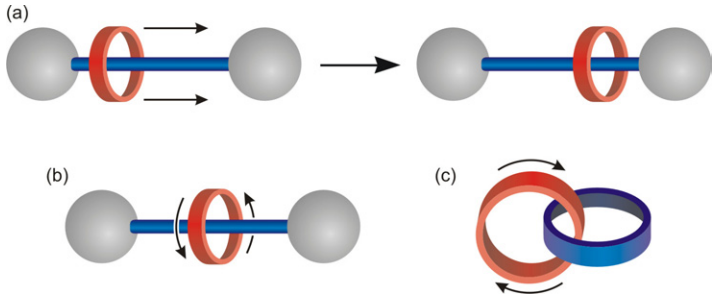

Figure 3. Some of the intercomponent motions that can be obtained with rotaxanes and catenanes: shuttling (a) and ring rotation ((b), (c)).

cycle, during which the motor protein binds to successive sites along the substrate in such a way as to move forward on average.

Several other biological processes are based on motions, including protein folding and unfolding. Another example is RNA polymerase, which moves along DNA while carrying out transcriptions, thus acting as a molecular motor. Suitable engineering of natural molecular motors and/or integration of motor proteins within artificial nanodevices has also been obtained [43–45], thereby opening up the possibility of building functional hybrid devices. For space reasons, the basic principles and operation mechanisms of these molecular motors cannot be discussed in detail here, and the reader should refer to the cited references.

1.5. Rotaxanes and catenanes as artificial molecular machines

In principle, molecular motors and machines can be designed starting from several kinds of molecular [46–48] and supramolecular [49–51] systems, including DNA [52–54]. However, most of the systems constructed so far are based on rotaxanes, catenanes, and related structures. Some relevant features of these multicomponent systems will therefore be summarized.

The names of these compounds derive from the Latin words *rota* and *axis* for wheel and axle, and *catena* for chain. Rotaxanes [55] are minimally composed (figure 2(a)) of a dumbbell-shaped molecule surrounded by a macrocyclic compound and terminated by bulky groups (stoppers) that prevent disassembly; catenanes [55] are made of (at least) two interlocked macrocycles or 'rings' (figure 2(b)). Rotaxanes and catenanes are appealing systems for the construction of molecular machines because of the peculiar mechanical bonds that keep the molecular components together; hence, relative motions of such molecular components can be easily imagined (figure 3).

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, include 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. The stability of a specific structure for rotaxanes and catenanes is determined by the intercomponent interactions that can take place. In general, in order to cause controllable mechanical movements, these interactions have to be modulated by means of external stimulation.

Among the most common types of rotaxanes and catenanes are those characterized by (i) charge-transfer (CT) intercomponent interactions between a π-electron acceptor (e.g. a 4,4′-bipyridinium derivative) and a π-electron donor (e.g. a dioxyaromatic unit or a tetrathiafulvalene derivative), and/or (ii) N^+–H$\cdots$O intercomponent hydrogen bonding between secondary ammonium functions (e.g. dibenzylammonium ion) and a suitable crown ether (e.g. dibenzo[24]crown-8,DB24C8). A leading group in the synthesis and characterization of these compounds is that of Professor Fraser Stoddart at the University of California, Los Angeles. All the examples described in this chapter are fruits of a long lasting collaboration between our group and the Stoddart team.

2. Prototypes

2.1. Linear motions in rotaxanes

Because of their peculiar structure, at least two interesting molecular motions can be envisaged in rotaxanes, namely (i) translation, i.e. shuttling [56], of the ring along the axle (figure 3(a)), and (ii) rotation of the macrocyclic ring around the axle (figure 3(b)). Hence, rotaxanes are good prototypes for the construction of both rotary and linear molecular motors. Systems of type (i), termed molecular shuttles, constitute indeed the most common implementation of the molecular motor concept with rotaxanes.

If two identical recognition sites for the ring, i.e., 'stations', are located within the dumbbell component, the result is a degenerate, conformational equilibrium state in which the ring spontaneously shuttles back and forth along the axle [56]. When the two recognition sites on the dumbbell component are different, a rotaxane can exist as two different equilibrating conformations, the population of which reflect their relative free energy as determined primarily by the strengths of the two different sets of noncovalent bonding interactions. In the schematic representation shown in figure 4, the molecular ring resides preferentially around station A (state 0), until a stimulus is applied that switches off this recognition site. The rotaxane then equilibrates according to the new potential energy landscape, and the molecular ring moves by Brownian motion to the second recognition site (station B, state 1). If station A is switched on again by an opposite stimulus, the original potential energy landscape is restored, and another conformational equilibration occurs through the shuttling of the ring back to station A by Brownian motion. In appropriately designed rotaxanes, the switching process can be controlled by reversible chemical reactions (protonation–deprotonation, reduction–oxidation, isomerization) caused by chemical, electrochemical, or photochemical stimulation.

2.2. An acid–base controlled molecular shuttle

The first example of a controllable molecular shuttle was reported in 1994 [57]. Since then, many molecular shuttles relying on chemical, electrochemical and photochemical stimulation have been described in the literature [20–25]. A chemically driven system with good performance in terms of switching and stability is compound $\mathbf{1}H^{3+}$ shown in figure 5 [58]. It is made of a dumbbell component containing an ammonium and an electron acceptor 4,4′-bipyridinium units that can establish hydrogen-bonding and CT interactions, respectively, with the ring component DB24C8, which is a crown ether with electron donor properties.

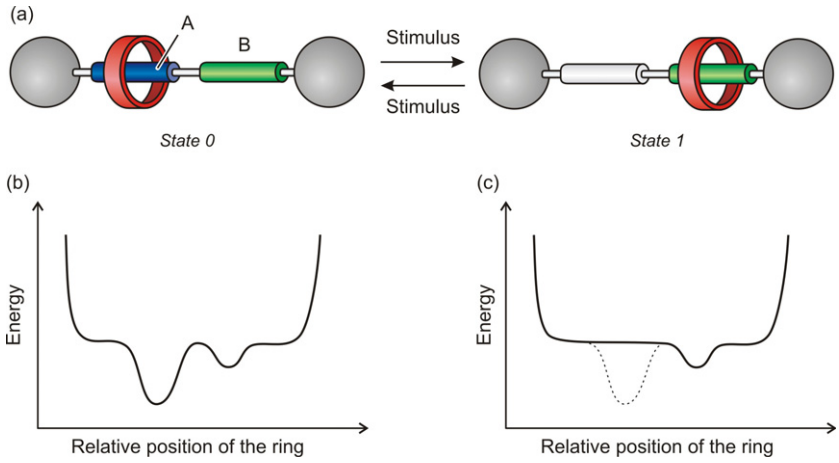

Figure 4. Schematic representation of a two-station rotaxane and its operation as a controllable molecular shuttle (a). The graphs are a simplified representation of the potential energy of the system as a function of the position of the ring relative to the axle before (b) and after (c) switching off station A. An alternative approach would be to modify station B through an external stimulus in order to make it a stronger recognition site compared to station A.

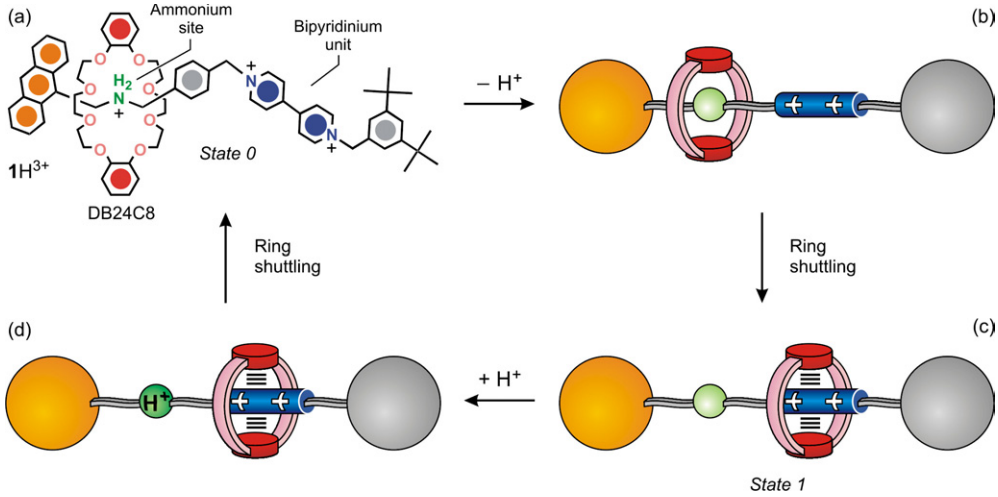

Figure 5. Schematic representation of the operation of the acid–base controllable molecular shuttle $\mathbf{1}H^{3+}$ in solution. It should be noted that the used cartoons, albeit giving a simple and convenient representation of the rotaxane architecture and of its operation, are somewhat misleading under a structural viewpoint because these systems possess a large degree of flexibility in solution. According to molecular models, a rotaxane molecule is approximately 2.5 nm long.

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$\cdots$O hydrogen bonding interactions between the macrocyclic ring and the ammonium centre are much stronger than the CT interactions of the ring with the bipyridinium unit, the rotaxane exists as only one of the two possible translational isomers (figure 5(a), state 0). Deprotonation of the ammonium centre of $\mathbf{1}H^{3+}$ with a base (figure 5(b)) weakens the hydrogen bonding interactions and causes the quantitative displacement of the DB24C8 ring by Brownian motion to the bipyridinium

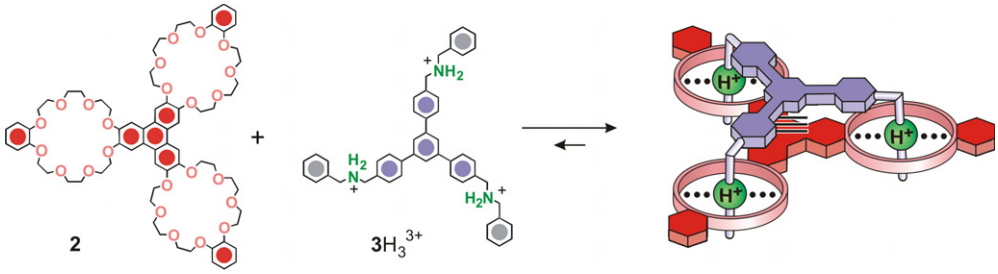

Figure 6. The self-assembly of the tritopic host **2** and tripod component $\mathbf{3}H_3^{3+}$ to afford a triply threaded supramolecular bundle. The adduct can be disassembled and reassembled in solution by addition of base and acid, respectively.

unit (figure 5(c), state 1). Reprotonation of $\mathbf{1}^{2+}$ with an acid (figure 5(d)) directs the ring back on the ammonium centre. Such a switching process was investigated in solution by ^{1}H nuclear magnetic resonance (NMR) spectroscopy and by electrochemical and photophysical measurements [58]. Very recently, the kinetics of ring shuttling were also studied in detail [59]. 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 rotaxane is a bistable system and in principle could be used to store binary information.

2.3. A molecular elevator

In pursuit of a better fundamental understanding of the intercomponent electronic interactions that occur in complex supramolecular species, we have investigated [60] the acid–base controlled (figure 6) assembly and disassembly of a triply threaded two-component superbundle. This 1:1 adduct consists of a tritopic host **2**, in which three DB24C8 rings are fused together within a triphenylene core, and a trifurcated guest $\mathbf{3}H_3^{3+}$ wherein three dibenzylammonium ions are linked to a central benzenoid core. Fluorescence titration experiments, as well as electrochemical and ^{1}H NMR spectroscopic data in solution, have established the remarkable strength of the superbundle encompassing the triply cooperative binding motif revealed by x-ray crystallography in the solid state. In acetonitrile solution, the dethreading-rethreading of the 1:1 adduct can be controlled by addition of base and acid.

By using an incrementally staged strategy, we incorporated the architectural features of the acid–base switchable rotaxane $\mathbf{1}H^{3+}/\mathbf{1}^{2+}$ (figure 5) into those of the trifurcated trication $\mathbf{3}H_3^{3+}$ (figure 6) and we came up with the design and construction of a two-component molecular device, $\mathbf{4}H_3^{9+}$ (figure 7(a)), that behaves like a nanometre-scale elevator [61]. This nanomachine, which is about 2.5 nm in height and has a diameter of about 3.5 nm, consists of a tripod component containing two different notches—one ammonium centre and one 4,4′-bipyridinium unit—at different levels in each of its three legs. The latter are interlocked by the tritopic host **2**, which plays the role of a platform that can be made to stop at the two different levels. The three legs of the tripod carry bulky feet that prevent the loss of the platform. Initially, the platform resides exclusively on the 'upper' level[1], i.e., with the three rings surrounding the ammonium centres (figure 7(b), state 0). This preference results from strong N^+–H $\cdots$ O hydrogen bonding and weak stabilizing π–π stacking forces between the aromatic cores of

[1] The molecular elevator operates in solution, i.e. with no control of the orientation of the molecules relative to a fixed reference system. Therefore, in the present context the words 'upper' and 'lower' are used only for descriptive purposes.

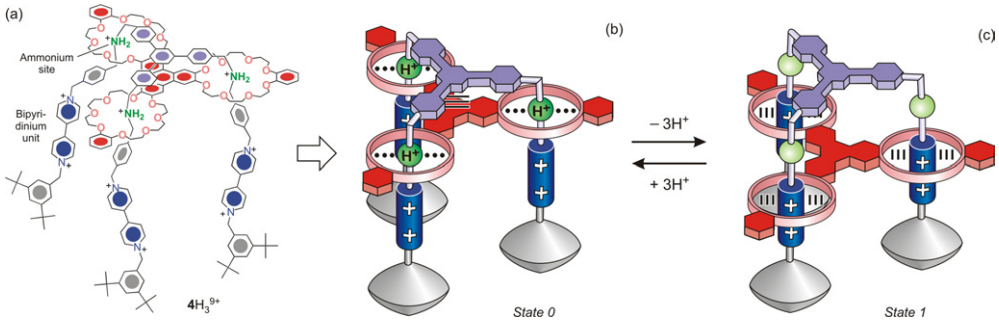

Figure 7. Chemical formula (a) and operation scheme in solution ((b), (c)) of the molecular elevator $\mathbf{4}H_3^{9+}$. The molecule is approximately 2.5 nm high and 3.5 nm wide.

the platform and tripod components. Upon addition of a strong, non-nucleophilic phosphazene base to an acetonitrile solution of $\mathbf{4}H_3^{9+}$, deprotonation of the ammonium centre occurs and, as a result, the platform moves to the 'lower' level, that is, with the three DB24C8 rings surrounding the bipyridinium units (figure 7(c), state 1). This structure is stabilized mainly by CT interactions between the electron rich aromatic units of the platform and the electron deficient bipyridinium units of the tripod component. Subsequent addition of acid to $\mathbf{4}^{6+}$ restores the ammonium centres, and the platform moves back to the upper level. The 'up and down' elevator-like motion, which corresponds to a quantitative switching and can be repeated many times, can be monitored by ^{1}H NMR spectroscopy, electrochemistry, and absorption and fluorescence spectroscopy [62].

From thermodynamic considerations on the electrochemical and NMR data, the amount of free energy released in the motion of the platform was estimated to be 87 kJ mol^{-1} for the base-driven motion and >17 kJ mol^{-1} for the acid-driven motion [61]. Since molecular models show that the distance travelled by the platform is about 0.7 nm, and in the assumption that all the free energy change associated to the motion can be used to do mechanical work, one can speculate that the elevator movement from the upper to lower level could in principle generate a force of up to 200 pN—one order of magnitude higher than that developed by myosin and kinesin [34].

It should be noted that the acid–base controlled mechanical motion in $\mathbf{4}H_3^{9+}$ is associated to interesting structural modifications, such as the opening and closing of a large cavity and the control of the positions and properties of the bipyridinium legs. This behaviour can in principle be used to control the uptake and release of a guest molecule, a function of interest for the development of drug delivery systems.

2.4. An autonomous nanomotor powered by sunlight

The chemically powered artificial motors described in the previous sections are *not autonomous* since, after the mechanical movement induced by a chemical input, they need another, opposite chemical input to reset, which also implies generation of waste products. However, addition of a reactant (fuel) is not the only means by which energy can be supplied to a chemical system. In fact, Nature shows that, in green plants, the energy needed to sustain the machinery of life is ultimately provided by sunlight. Energy inputs in the form of photons can indeed cause mechanical movements by reversible chemical reactions without formation of waste products. Only a few examples of light driven artificial molecular motors exhibiting autonomous behaviour have been reported so far [20–25, 47, 63].

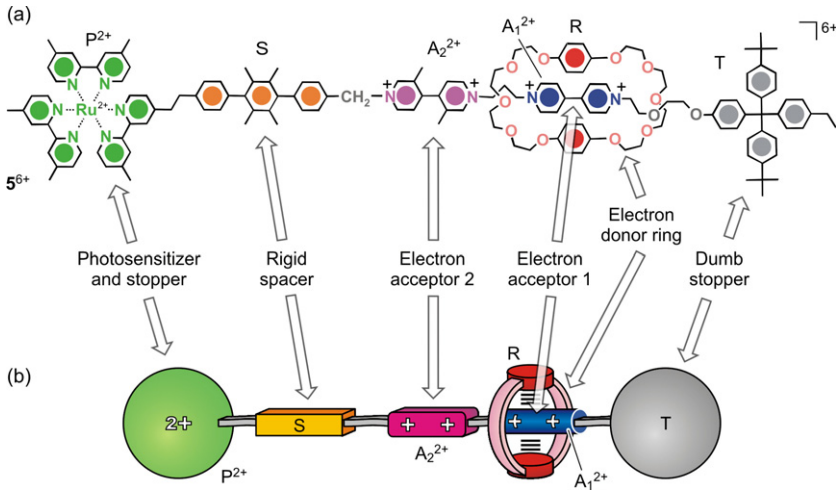

Figure 8. Chemical formula (a) and cartoon representation (b) of the rotaxane $\mathbf{5}^{6+}$, showing its modular structure. Molecular models show that a rotaxane molecule is approximately 5 nm long, and the diameter of the ring is about 1.3 nm.

The design and construction of molecular shuttles powered exclusively by light energy is therefore a fascinating yet challenging subject. On the basis of the experience gained with previous studies on pseudorotaxane model systems [64–66], the rotaxane $\mathbf{5}^{6+}$ (figure 8) was specifically designed to achieve photoinduced ring shuttling in solution [67]. This compound is made of the electron donor ring R, and a dumbbell component which contains several units: a ruthenium(II) polypyridine complex (P^{2+}) that plays the dual role of a light-fueled motor [68] and a stopper, a *p*-terphenyl-type rigid spacer (S), a 4,4′-bipyridinium unit (A_1^{2+}) and a 3,3′-dimethyl-4,4′-bipyridinium unit (A_2^{2+}) as electron accepting stations, and a tetraarylmethane group as the second stopper (T). The stable translational isomer of rotaxane $\mathbf{5}^{6+}$ is the one in which the R component encircles the A_1^{2+} unit, in keeping with the fact that this station is a better electron acceptor than the other one.

The strategy devised in order to obtain the photoinduced abacus-like movement of the R macrocycle between the two stations A_1^{2+} and A_2^{2+}, illustrated in figure 9, is based on the following four operations:

(a) *Destabilization of the stable translational isomer.* Light excitation of the photoactive unit P^{2+} (process 1) is followed by the transfer of an electron from the excited state to the A_1^{2+} station, which is encircled by the ring R (process 2), with the consequent 'deactivation' of this station; such a photoinduced electron-transfer process has to compete with the intrinsic decay of the P^{2+} excited state (process 3).
(b) *Ring displacement.* The ring moves by Brownian motion (process 4) for 1.3 nm from the reduced station A_1^{+} to A_2^{2+}, a step that has to compete with the back electron-transfer process from A_1^{+} (still encircled by R) to the oxidized unit P^{3+} (process 5).
(c) *Electronic reset.* A back electron-transfer process from the 'free' reduced station A_1^{+} to the oxidized unit P^{3+} (process 6) restores the electron acceptor power to the A_1^{2+} station.
(d) *Nuclear reset.* As a consequence of the electronic reset, back movement of the ring by Brownian motion from A_2^{2+} to A_1^{2+} takes place (process 7).

The crucial point for such a mechanism is indeed the favourable competition between ring displacement (process 4) and back electron transfer (process 5). The rate constants of

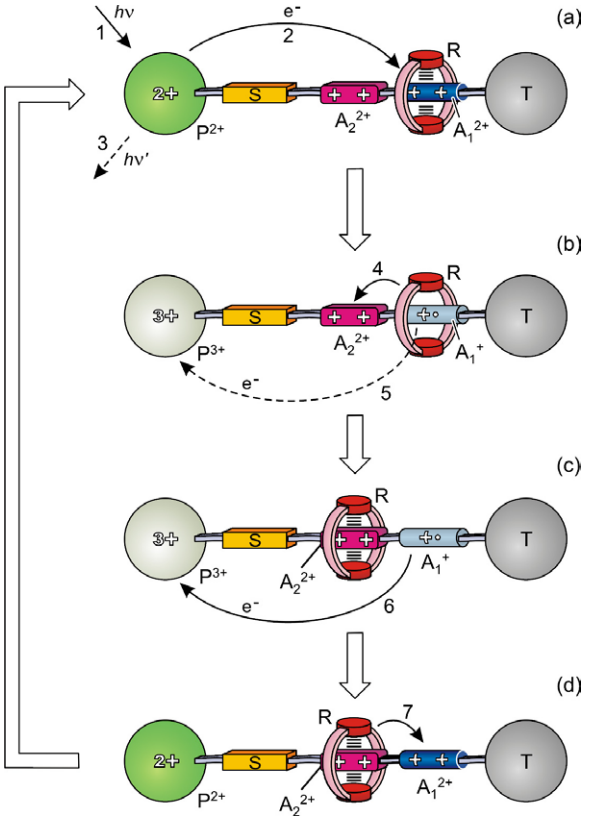

Figure 9. Operation scheme of rotaxane $\mathbf{5}^{6+}$ as an autonomous 'four stroke' linear nanomotor powered by light.

the relevant electron-transfer processes were measured in acetonitrile solution by laser flash photolysis [67]; however, direct time-resolved observation of the ring displacement proved to be quite elusive. Very recently, we performed laser flash photolysis experiments in the presence of an electron relay in order to slow down the back electron-transfer process and facilitate the observation of ring displacement [69]. We observed that the transient absorption spectrum of the photogenerated one-electron reduced unit A_1^+ in the rotaxane changes slightly with time, while it does not change at all for the dumbbell-shaped component. Such changes have been attributed to the motion of the ring R, which immediately after light excitation surrounds the reduced unit A_1^+ and subsequently moves away from it to encircle the A_2^{2+} station.

These investigations revealed that in acetonitrile at room temperature the ring shuttling rate is one order of magnitude slower than the back electron transfer. Hence, the absorption of a visible photon can cause the occurrence of a forward and back ring movement (i.e. a full cycle) without generation of waste products, but with a low (around 2%) quantum efficiency. The low efficiency is compensated by the fact that the operation of the system relies *exclusively* on intramolecular processes. Therefore, this artificial molecular motor does not need the assistance of external species and, in principle, it can work at the single-molecule level. In other words, $\mathbf{5}^{6+}$, performs as a 'four stroke' autonomous artificial linear motor working by an *intramolecular* mechanism powered by *visible* light (i.e., sunlight). It was estimated [69] that the fraction of the excited state energy used for the motion of the ring amounts to ∼10%, and the motor can generate a mechanical power of about 3×10^{-17} W per molecule.

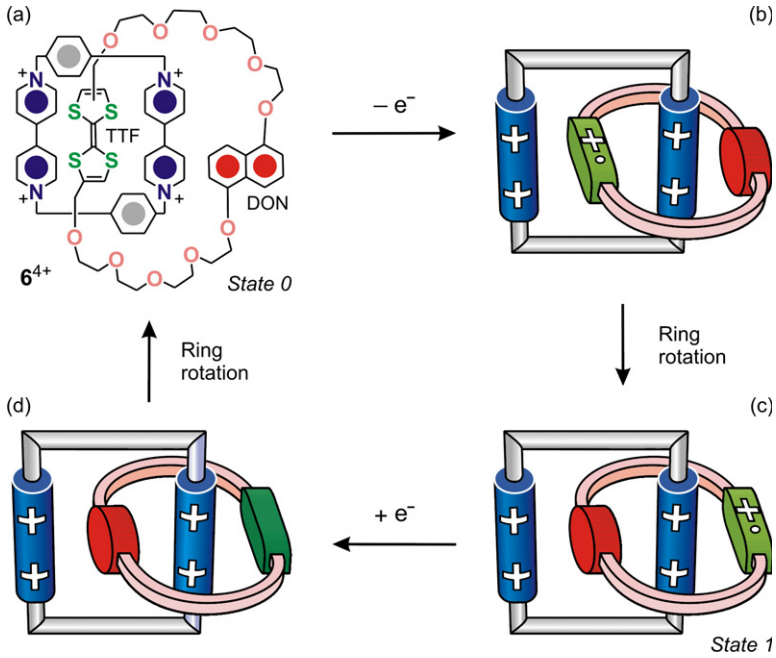

Figure 10. Redox controlled ring rotation in solution for catenane $\mathbf{6}^{4+}$, which contains a non-symmetric ring based on tetrathiafulvalene (TTF) and dioxynaphthalene (DON) electron donor units.

2.5. Systems based on catenanes

Catenanes are chemical compounds consisting minimally of two interlocked macrocycles [55]. When one of the two rings carries two different recognition sites, then the opportunity exists to control the dynamic processes in a manner reminiscent of the controllable molecular shuttles. By switching *off* and *on* again the recognition properties of one of the two recognition sites of the non-symmetric ring by means of external energy stimuli, it is indeed possible to induce conformational changes that can be viewed as the rotation of the non-symmetric ring.

An example of such a behaviour is offered by the catenane $\mathbf{6}^{4+}$ shown in figure 10 [70]. This compounds is made of a symmetric tetracationic ring containing two electron acceptor 4,4′-bipyridinium units and a non-symmetric ring comprising two different electron donor units, namely a tetrathiafulvalene (TTF) group and a 1,5-dioxynaphthalene (DON) unit. Since the TTF unit is a better electron donor than the DON one, as witnessed by the potentials values for their oxidation, the thermodynamically stable conformation of the catenane is that in which the symmetric ring encircles the TTF unit of the non-symmetric one (figure 10(a), state 0). On electrochemical oxidation in solution, the TTF unit loses its electron donor power and acquires a positive charge (figure 10(b)). As a consequence it is expelled from the cavity of the tetracationic ring and is replaced by the neutral DON unit (figure 10(c), state 1). At this stage, subsequent reduction of the oxidized TTF unit restores its electron donor ability and the system goes back to its original conformation. A variety of techniques, including cyclic voltammetry, were employed to characterize the system. The catenane $\mathbf{6}^{4+}$ was also incorporated in a solid state device that could be used for random access memory (RAM) storage [71]. Additionally, this compound could be employed for the construction of electrochromic systems, because its various redox states are characterized by different colours [72].

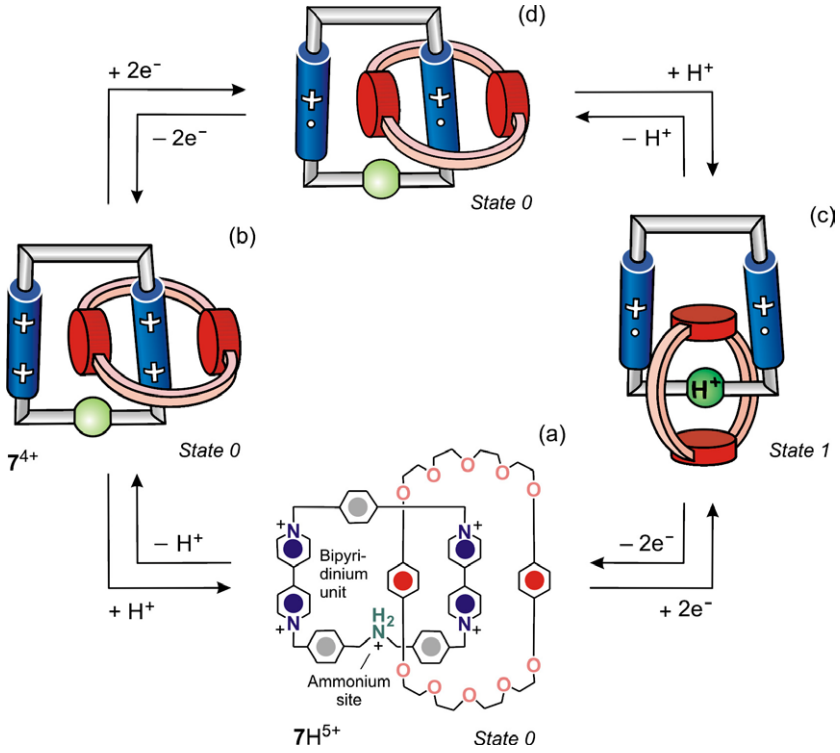

Figure 11. Switching processes of catenane $\mathbf{7}H^{5+}$ in solution. Starting from the deprotonated catenane $\mathbf{7}^{4+}$, the position of the crown ether ring switches under acid–base and redox inputs according to AND logic.

It should be pointed out that in the catenane system described above, repeated switching between the two states does not need to occur through a full rotation. In fact, because of the intrinsic symmetry of the system, both the movement from state 0 to state 1 and that from state 1 to state 0 can take place, with equal probabilities, along a clockwise or anticlockwise direction. A full (360°) rotation movement, which would be much more interesting from a mechanical viewpoint, can only occur in ratchet-type systems, i.e. in the presence of asymmetry elements which can be structural or functional in nature [23, 29]. This idea was recently implemented with a carefully designed catenane by relying on a sequence of photochemical, chemical and thermally activated processes [73] and employing ^{1}H NMR spectroscopy to characterize the system.

By an appropriate choice of the functional units that are incorporated in the catenane components, more complex functions can be obtained. An example is represented by catenane $\mathbf{7}H^{5+}$ (figure 11), composed of a symmetric crown ether ring and a cyclophane ring containing two 4,4′-bipyridinium and one ammonium recognition sites [74]. The absorption spectra and electrochemical properties show that the crown ether ring surrounds a bipyridinium unit of the other ring both in $\mathbf{7}H^{5+}$ (figure 11(a)) and in its deprotonated form $\mathbf{7}^{4+}$ (figure 11(b)), indicating that deprotonation-protonation of the ammonium-amine unit does not cause any displacement of the crown ether ring (state 0). Electrochemical measurements show that, after one-electron reduction of both the bipyridinium units of $\mathbf{7}H^{5+}$, the crown ether ring is displaced on the ammonium site (figure 11(c), state 1), which means that an electrochemically induced

conformational switching does occur. Furthermore, upon deprotonation of the two-electron reduced form $\mathbf{7}H^{3+}$ (figure 11(d)), the macrocyclic polyether moves to one of the monoreduced bipyridinium units (state 0). Therefore, in order to achieve the motion of the crown ether ring in the deprotonated catenane $\mathbf{7}^{4+}$, it is necessary *both* to reduce (switch off) the bipyridinium units *and* protonate (switch on) the amine site. The mechanical motion in such a catenane takes place according to an AND logic [32], a function associated with two energy inputs of different nature. Other examples of molecular motors based on catenanes can be found in the literature [20–25, 75, 76].

3. Summary and outlook

The results described here show that, by taking advantage of careful incremental design strategies, of the tools of modern synthetic chemistry, of the paradigms of supramolecular chemistry, as well as of inspiration by natural systems, it is possible to produce compounds capable of performing non-trivial mechanical movements and exercising a variety of different functions upon external stimulation.

In the previously mentioned address to the American Physical Society [2], Feynman concluded his reflection on the idea of constructing molecular machines as follows: *'What would be the utility of such machines? Who knows? I cannot see exactly what would happen, but I can hardly doubt that when we have some control of the rearrangement of things on a molecular scale we will get an enormously greater range of possible properties that substances can have, and of different things we can do'*. This sentence, pronounced in 1959, is still an appropriate comment to the work described here. The results achieved enable to devise future developments, which are under investigation in our laboratory: (i) the design and construction of more sophisticated artificial molecular motors and machines; (ii) the use of such systems to do tasks such as molecular-level transportation, catalysis, and mechanical gating of molecular channels; and (iii) the possibility of exploiting their logic behaviour for information processing at the molecular level and, in the long run, for the construction of chemical computers.

It should also be noted that the majority of the artificial molecular motors developed so far operate in solution, that is, in an incoherent fashion and without control of spatial positioning. The studies in solution of complicated chemical systems such as molecular motors and machines are indeed of fundamental importance to understand their operation mechanisms; moreover, for some use (e.g., drug delivery) molecular machines will have to work in liquid solution. In this regard, it should be recalled that motor proteins operate in—or at least in contact with—an aqueous solution. However, it seems reasonable that, before artificial molecular motors and machines can find applications in many fields of technology, 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 [77], deposited on surfaces [71, 72, 78, 79], or immobilized into membranes [80] or porous materials [81, 82] so that they can behave coherently and can be addressed in space. Indeed, the preparation of modified electrodes represent one of the most promising ways to achieve this goal [83]. Very recently, it has been shown that the collective operation of artificial nanomotors in carefully engineered surface-deposited monolayers can indeed develop mechanical work at a larger scale, that has been exploited for bending up and down microcantilevers [84] or to drive the movement of a microliter liquid droplet [85].

Apart from more or less futuristic applications, the extension of the concept of motor and 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 molecular and supramolecular species 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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