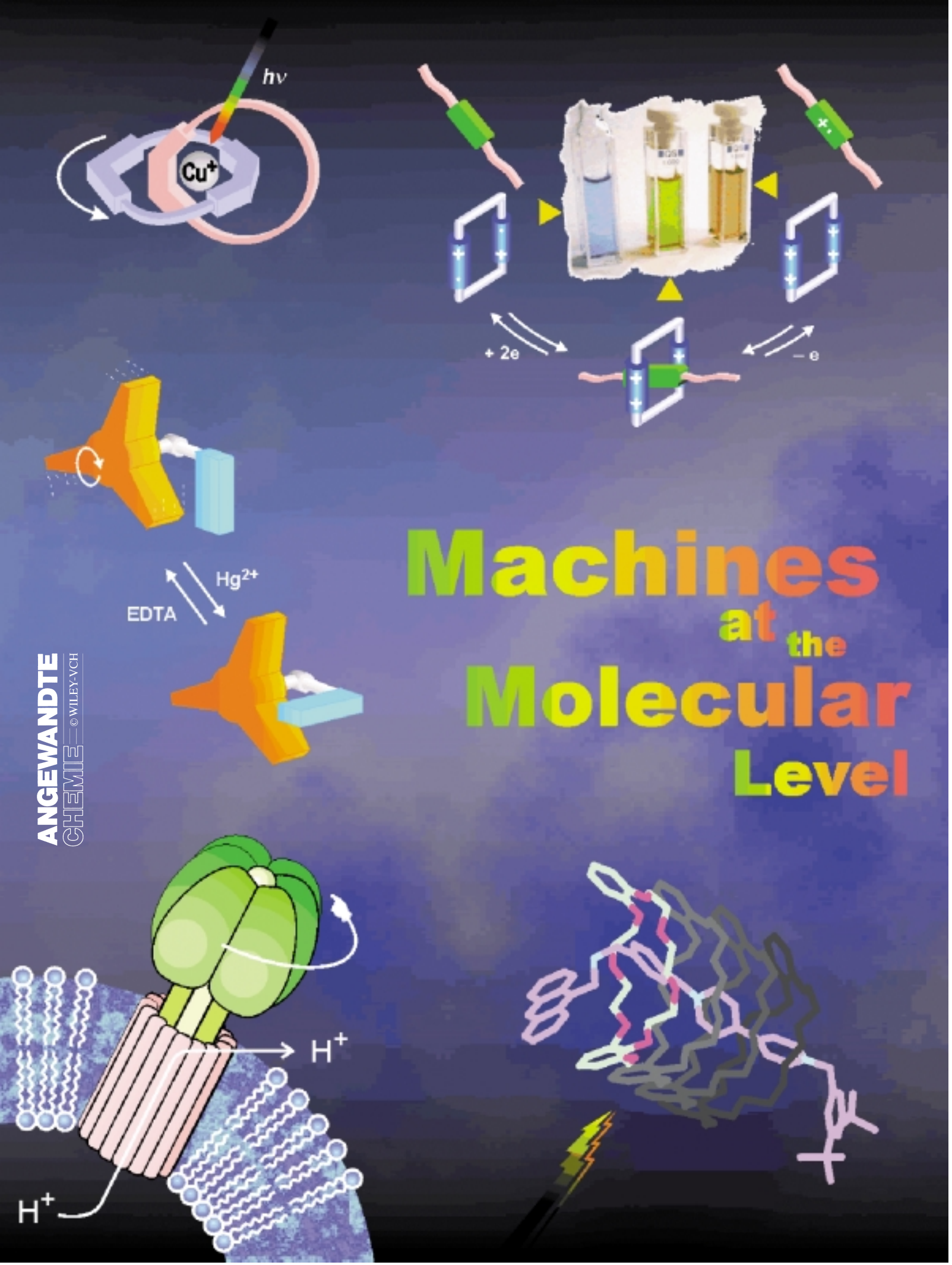


# Machines at the Molecular Level

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# Artificial Molecular Machines

**Vincenzo Balzani,* Alberto Credi, Françisco M. Raymo, and J. Fraser Stoddart***

The miniaturization of components used in the construction of working devices is being pursued currently by the large-downward (top-down) fabrication. This approach, however, which obliges solid-state physicists and electronic engineers to manipulate progressively smaller and smaller pieces of matter, has its intrinsic limitations. An alternative approach is a small-upward (bottom-up) one, starting from the smallest compositions of matter that have distinct shapes and unique properties—namely molecules. In the context of this particular challenge, chemists have been extending the concept of a macroscopic machine to the molecular level. A *molecular-level machine* can be defined as an assembly of a distinct number of molecular components that are designed to perform machinelike movements (output) as a result of an appropriate external stimulation (input). In common with their macroscopic counterparts, a molecular machine is characterized by 1) the kind of energy input supplied to make it work, 2) the nature of the movements of its component parts, 3) the way in which its operation can be monitored and controlled, 4) the ability to make it repeat its operation in a cyclic fashion, 5) the timescale needed to complete a full cycle of movements, and 6) the purpose of its operation. Undoubtedly, the best energy inputs to make molecular machines work are *photons* or *electrons*. Indeed, with appropriately chosen photochemically and electrochemically driven reactions, it is possible to design and synthesize molecular machines that do work. Moreover, the dramatic increase in our fundamental understanding of self-assembly and self-organizational processes in chemical synthesis has aided and abetted the construction of artificial molecular machines through the development of new methods of *noncovalent synthesis* and the emergence of *supramolecular assistance to covalent synthesis* as a uniquely powerful synthetic tool. The aim of this review is to present a unified view of the field of molecular machines by focusing on past achievements, present limitations, and future perspectives. After analyzing a few important examples of natural molecular machines, the most significant developments in the field of artificial molecular machines are highlighted. The systems reviewed include 1) chemical rotors, 2) photochemically and electrochemically induced molecular (conformational) rearrangements, and 3) chemically, photochemically, and electrochemically controllable (co-conformational) motions in interlocked molecules (catenanes and rotaxanes), as well as in coordination and supramolecular complexes, including pseudorotaxanes. Artificial molecular machines based on biomolecules and interfacing artificial molecular machines with surfaces and solid supports are amongst some of the cutting-edge topics featured in this review. The extension of the concept of a machine to the molecular level is of interest not only for the sake of basic research, but also for the growth of nanoscience and the subsequent development of nanotechnology.

**Keywords:** catenanes · molecular machines · nanodevices · photochemistry · rotaxanes · supramolecular chemistry

[*] Prof. V. Balzani, Dr. A. Credi
Dipartimento di Chimica "G. Ciamician"
Università di Bologna
via Selmi 2, 40126 Bologna (Italy)
Fax: (+39) 051-2099456
E-mail: vbalzani@ciam.unibo.it

Prof. J. F. Stoddart
Department of Chemistry and Biochemistry
University of California, Los Angeles
405 Hilgard Avenue, Los Angeles, CA 90095-1569 (USA)
Fax: (+1) 310-206-1843
E-mail: stoddart@chem.ucla.edu

Prof. F. M. Raymo
Center for Supramolecular Science
Department of Chemistry, University of Miami
1301 Memorial Drive, Coral Gables, FL 33146-0431 (USA)
E-mail: fraymo@miami.edu

## 1. Molecular-Scale Machines

> *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 arrangement of things on a molecular scale we will get an enormously greater range of possible properties that substances can have, and of the different things we can do.*
>
> Richard P. Feynman[1] (1959)

### 1.1. The Concept of a Machine at the Molecular Level

In everyday life we make extensive use of (macroscopic) machines. A machine is[2] "an apparatus for applying mechanical power, having several parts each with a definite function".

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V. Balzani


A. Credi


F. M. Raymo


J. F. Stoddart

*Vincenzo Balzani was born in Forlimpopoli (Italy) in 1936. He received his "Laurea" in Chemistry at the University of Bologna in 1960. After a few years as Assistant Professor at the University of Ferrara, he joined the Faculty of Science of the University of Bologna in 1969, where he has remained to this day. He was Director of the Photochemistry and Radiaton Chemistry Institute of the Italian National Research Council (1977–1988) and Chairman of the European Photochemistry Association (1988–1992). He has obtained several awards, including the Ziegler–Natta Lectureship of the Gesellschaft Deutscher Chemiker (1994), the Italgas European Prize for Research and Innovation (1994), the Centenary Lectureship of the Royal Chemical Society (1996), and the Porter Medal for Photochemistry (2000). He is the author of two monographs and of more than 400 scientific papers. His research interests include photochemistry, electron-transfer reactions, supramolecular chemistry, dendrimer chemistry, and molecular-level devices and machines.*

*Alberto Credi was born in Bologna (Italy) in 1970. After receiving a "Laurea" in Chemistry from the University of Bologna (1994), he spent one more year in the same University as a research fellow (Ciba-Geigy), and six months as a visiting scientist (NATO) at the University of Virginia with Professor F. S. Richardson. In early 1999 he obtained his Ph.D in Chemical Sciences from the University of Bologna under the supervision of Professor V. Balzani. He was selected, as a graduate student, to attend the meeting Scientia Europæa, and invited to illustrate his research at the University of Zurich, Switzerland. His dissertation, entitled "Molecular-level Machines and Logic Gates", received the annual award of the Italian Chemical Society and, very recently, the 2000 IUPAC Prize for young Chemists. After a short period as a research assistant, he is presently researcher at "G. Ciamician" Department of Chemistry of the University of Bologna. His research interests, which include photophysics, photochemistry and electrochemistry of metal complexes, supramolecular systems, and dendrimers, are mainly focused on the development of molecular-level devices and machines. He is the author of about 60 publications in the field of molecular and supramolecular photochemistry and electrochemistry.*

*Françisco M. Raymo was born (1969) and educated in Messina (Italy). He obtained a "Laurea in Chimica" (1992) from the University of Messina and a "Ph.D. in Chemistry" (1996) from the University of Birmingham. As a graduate student, he developed numerous approaches to the template-directed syntheses of catenanes and rotaxanes under the supervision of Professor J. F. Stoddart. Thereafter, he was a Postdoctoral Research Fellow at the University of Birmingham (1996–1997) and, later, at UCLA (1997–1999) working, in collaboration with Professors K. N. Houk and J. F. Stoddart, on the design, synthesis, and computational investigation of molecular machines incorporating interlocked components. Currently, he is an Assistant Professor in the Center for Supramolecular Science at the Department of Chemistry of the University of Miami. In 1998, he was selected as the "Marie Curie Success Story" for Chemistry by the European Commission and also received a "Chancellor's Award for Postdoctoral Research" at UCLA. His research interests range from the design and synthesis of artificial self-assembling systems, molecule-based materials, and mechanically interlocked molecules to crystal engineering, template-directed syntheses, and the computational investigation of recognition phenomena. He is the author of more than 90 publications in the areas of computational chemistry, chemical synthesis, materials science, and supramolecular chemistry.*

*J. Fraser Stoddart was born in Edinburgh, Scotland in 1942. He received all of his degrees (B.Sc., 1964; Ph.D., 1966; D.Sc., 1980) from the University of Edinburgh. He carried out postdoctoral work at Queen's University in Canada before joining the academic staff at the University of Sheffield in 1970. After a seven-year spell as the Professor of Organic Chemistry at the University of Birmingham, he moved, in 1997, to the Saul Winstein Chair of Organic Chemistry at UCLA. Much of his research effort over the last 15 years has been channeled into the design and construction of molecular machinery based on switchable catenanes and rotaxanes obtained by both noncovalent synthesis and supramolecular assistance to covalent synthesis. Present and future research goals include the interfacing of artificial molecular machines with the macroscopic world by applying self-assembly protocols to the fabrication of molecular devices.*

When a machine is working, at least some of its components display changes in their relative positions. A machine is characterized by 1) the kind of energy input supplied to make it work, 2) the type of movements performed by its components, 3) the manner in which its operation can be monitored and controlled, 4) the possibility to repeat the operation at will and establish a cyclic process, 5) the timescale needed to complete a cycle of operation, and 6) the function performed by the machine.

The concept of a machine can be extended to the molecular level. A *molecular-level machine* can be defined as an assembly of a discrete number of molecular components designed to perform mechanical-like movements (output) as a consequence of appropriate external stimuli (input). Although there are many chemical compounds whose constitutions and/or shapes can be modified by an external stimulus—for example, molecules capable of undergoing photoinduced *cis*/*trans* isomerizations of their C=C, C=N, or N=N bonds—the term molecular-level machine will only be used for systems whose component parts undergo movement with relatively large amplitudes. Furthermore, systems in which the molecular movements are not controlled by some easily identifiable and well-characterized external stimulus will not be considered to be molecular-level machines. The extension of the concept of a machine to the molecular level is of interest not only for the sake of basic research, but also for the growth of nanoscience and the subsequent development of nanotechnology.

The concept of a machine at the molecular level is not a new one. Our bodies can be viewed as very complex ensembles of molecular-level machines that power our physical motions in a multitude of different guises, repair tissue damage in a wide spectrum of situations and circumstances, as well as preside over our innermost worlds where we are preoccupied by our sensory perceptions, emotional states, and thought processes. The idea of constructing artificial molecular-level machines, however, is quite a recent one. The first time the topic was seriously contemplated was in 1959 by Richard Feynman,[1] Nobel Laureate in Physics, in his historic address "There is Plenty of Room at the Bottom" to the American Physical Society in December of that year. The earliest examples of synthetic molecular-level machines, based on the photoisomerization of azobenzene, were reported[3] in the early 1980s. In the last 15 years research in the field of artificial molecular-level machines has been stimulated by several major scientific breakthroughs and paradigm shifts: they include 1) the rapid development of probe microscopies[4] following the award of the Nobel Prize in Physics to Binnig and Rohrer in 1986; 2) a growing interest in supramolecular chemistry[5] after the award of the 1987 Nobel Prize in Chemistry to Pedersen, Cram, and Lehn; 3) the elucidation and unraveling of the working mechanisms of some key biological devices and machines,[6, 7] such as those involved in photosynthesis (Deisenhofer, Huber, and Michel recognized by the 1988 Nobel Prize in Chemistry) and in the ATP synthesis (leading to the 1997 Nobel Prize in Chemistry to Boyer, Skou, and Walker); 4) the great progress in understanding the mechanisms of the homogeneous and heterogeneous thermal and photoinduced electron-transfer reactions[8] provided by Marcus who was awarded the Nobel Prize in Chemistry in 1992; and 5) the realization that the (physical) top-down approach to miniaturization in the electronics industry, for example, has intrinsic limitations and the increasing confidence that it can be replaced profitably by a (chemical) bottom-up approach.[9]

In the past few years interest in artificial molecular machinery has grown exponentially and several short reviews covering specific aspects of the field are now available.[10] The aim of this article is to present a unified view of the field by focusing in on past achievements, present limitations, and future perspectives.

### 1.2. Defining Molecular-Level Machines

We have already identified the features and characteristics of macroscopic machines in Section 1.1, and have also established that one of the operational requirements of a molecular machine will be that the movement of its component parts will have relatively large amplitudes—a property which implies the occurrence of chemical reactions. In his 1959 address to the American Physical Society, Feynman[1] noted that "An internal combustion engine of molecular size is impossible. Other chemical reactions, liberating energy when cold, can be used instead." Even relatively "cold" chemical reactions, however, can destroy the molecules constituting a machine. Since such a machine works by repeating cycles (Point 4), an important requirement is that any chemical change or reaction taking place in the system has to be reversible. Within this constraint, any kind of chemical process that causes motions of a machine's component parts—for example, isomerizations, acid/base reactions, oxidation/reduction processes, complexation/decomplexation equilibria involving, for example, the making and breaking of hydrogen bonds—can be useful. Most chemical reactions occur as a result of thermal activation on mixing the reactants. If a molecular-level machine has to work by thermal activation it will need the addition of reagents at all steps in its working cycle, since the added reagents play the role (Point 1) of chemical energy inputs. Although such kinds of input can be useful, clearly the repeated addition of reagents will result in the accumulation of by-products that, after a relatively small number of cycles, will compromise the operation of the machine unless the products can be removed from the system, which is not an easy task to perform. In principle, the best energy inputs to make a molecular machine work (Point 1) are photons and electrons (or holes). Indeed, with appropriately chosen photochemically or electrochemically driven reactions, it is possible to design interesting and intriguing molecular machines.

The motions performed by the component parts of a molecular-level machine (Point 2) depend to some extent on whether the machine is molecular or supramolecular in nature.[11] Movements of component parts within classical molecules will necessarily involve changes in their conformations and/or configurations around covalent bonds that are formally single or double, respectively, in their orders, although these changes in molecular structure are accompanied by the making and breaking of *intramolecular noncovalent bonds*. Movements of the component parts within

supermolecules (complexes) may be accompanied by conformational and/or configurational changes within their covalently linked molecular components; however, it will be largely the reorganization of *intermolecular noncovalent bonds* between the molecules that will usually reflect and constitute the movements within these kinds of molecular-level machines. In nonclassical so-called interlocked molecules the mechanical bonds that link the component parts together offer the close to unique opportunity, within relatively small molecules at least, to effect movements with large amplitudes upon their components, mainly as a result of the making and breaking of *intercomponent noncovalent bonds.*

In order to monitor and control the operation (Point 3) of a molecular machine the motions of the component parts should bring about readable changes in some properties of the system. Any kind of chemical or physical probe can be useful in providing read-outs, particularly the various different types of spectroscopies that are currently available to us. In this regard, it should be pointed out that photochemistry and electrochemistry are often very useful since both photons and electrons can play the dual role of "writing", that is, causing the change in the system, and "reading", that is, reporting the resulting state of the system. The operating timescale (Point 5) of molecular machines is that of nuclear motions, which can range from nanoseconds to seconds depending on the nature of the components involved and the type of motions that are happening. We would like to point out that the description of a motion implies the definition of a fixed reference system. In the case of molecular machines, this matter is not so trivial (see Section 4.2). Finally, the functions that can be performed by exploiting the movements of the components in artificial machines (Point 6) are largely unpredictable. Some comments on this topic will be presented later on in Section 5.

## 1.3. Natural Molecular Machines

Before reviewing artificial molecular machines, we will discuss a few examples of natural molecular machines. Since the molecular machines produced by nature are extremely complicated systems, there is little hope of reproducing them artificially, at least in the short term. The functions of living organisms involve free energy differences caused by 1) changes in chemical potential, mechanical forces, temperature, extent of order, pressure, etc., or by 2) changes arising from absorption of light or other electromagnetic radiations. The task of biological molecular machines, which are assemblies of proteins, is to convert energy from one form or location into another.[12] When energy in one of the above forms is available to the correct protein construct, that is, a specific molecular machine, it can be converted or transduced by the appropriate protein into any one of the other forms of energy. Living organisms represent the synergistic integration of functionally diverse molecular machines.[13]

In the last few years the outstanding development of single molecule manipulation and observation, particularly by fluorescence spectroscopy,[14, 15] has thrown light on the operational mechanism of several biological machines.

### *1.3.1. A Rotary Motor: $F_1$-ATPase*

Mitochondria, bacteria, and chloroplasts use the free energy stored in transmembrane ion gradients to manufacture adenosine triphosphate (ATP) from adenosine diphosphate (ADP) and inorganic phosphate ($P_i$) by the action of ATP synthase. This enzyme consists[16] of two principal domains (Figure 1). The asymmetric membrane-spanning $F_0$ portion

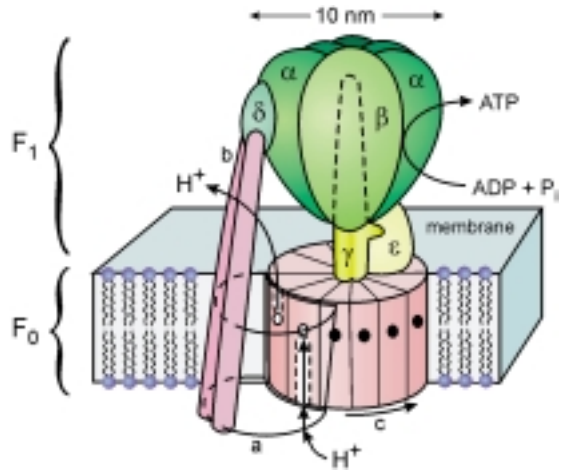



Figure 1. The structure of $F_0F_1$ATP synthase.[16] The catalytic region is composed of the subunits $\alpha-\varepsilon$. The proton channels lie at the interface between the subunits a and c (dashed lines indicate the putative inlet and outlet channels). Proton flow through the channels develops torque between the a and c subunits. This torque is transmitted to $F_1$ via the $\gamma$ shaft and the $\varepsilon$ subunit, where it is used to release ATP sequentially from the catalytic sites in $F_1$. The c subunit consists of 9–12 twin $\alpha$-helices arranged in a central membrane-spanning array. The a subunit consists of 5–7 membrane-spanning $\alpha$-helices and is connected to $F_1$ by the b and $\delta$ subunits. Reprinted by permission from ref. [16f] (Copyright© Macmillan Magazines Ltd 1998).

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 in the stoichiometry $\alpha:\beta:\gamma:\delta:\varepsilon = 3:3:1:1:1$ and approximates to a flattened sphere, 10 nm across and 8 nm high. The flow of protons through $F_0$ is thought to generate a torque which is transmitted to $F_1$ by an asymmetric shaft, the coiled-coil $\gamma$-subunit. This subunit acts as a rotating "cam" within $F_1$, sequentially releasing ATP molecules from the three active sites. The free-energy difference across the inner membrane of mitochondria and bacteria is sufficient to produce three ATP molecules per twelve protons that pass through the motor. The $F_0F_1$-ATP synthase is reversible, that is, the full enzyme can synthesize or hydrolyze ATP; $F_1$ in isolation, however, can only hydrolyze it. The spinning of $F_1$-ATPase, namely, the rotary motor nature of this enzyme, was first proposed by Boyer.[16b] Recently, the rotation of $F_1$-ATPase has been directly observed[17] during ATP hydrolysis by attaching a fluorescent actin filament as a marker to the $\gamma$ subunit. In other experiments[18] performed with actin filaments of variable length, discrete 120° rotations have been observed, as expected from the threefold rotational symmetry of $\gamma F_1$. A rather puzzling result is that $F_1$-ATPase is reported to convert chemical into mechanical energy with near 100% efficiency.

### *1.3.2. Linear Motor Proteins: Myosin*

Enzymes such as myosin, kinesin, dynein, and their relatives are linear motors which convert the energy of ATP hydrolysis into mechanical work along polymer substrates—myosin along actin filaments in muscle and other cells, and kinesin and dynein along microtubules.[13] Motion derives from a mechano-chemical cycle during which the motor protein binds to successive sites along the substrate in such a way as to move forward on average.

Myosin provides the power for all of our voluntary motions (running, walking, lifting, etc.) as well as for involuntary muscles (for example, beating heart). Myosin is composed of two large heads connected to a long, thin tail. In the muscle cells, many myosin molecules combine by aligning their tails, staggered one relative to the next. Muscle cells are also filled with cables of actin, which are used as a ladder on which myosin climbs. The head groups of myosin extend from the surface of the resulting filament like bristles in a bottle brush. The bristling head groups provide the power to contract muscles. They reach from the myosin filament to a neighboring actin filament and attach to it. Breakage of an ATP molecule then forces the myosin head into a radically different shape. It bends near the center and drags the myosin filament along the actin filament. This is the power stroke of muscle contraction. In a rapidly contracting muscle, each myosin head may stroke five times a second, each stroke moving the filament about 10 nm.

The term myosin refers to at least 14 classes of proteins, each containing actin-based motors. For myosin II (skeletal muscle myosin), the working stroke has been observed[19] by optical methods in the following way (Figure 2): An actin

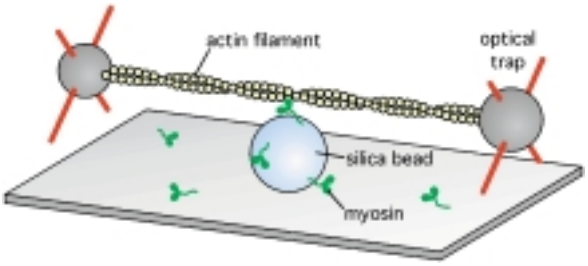


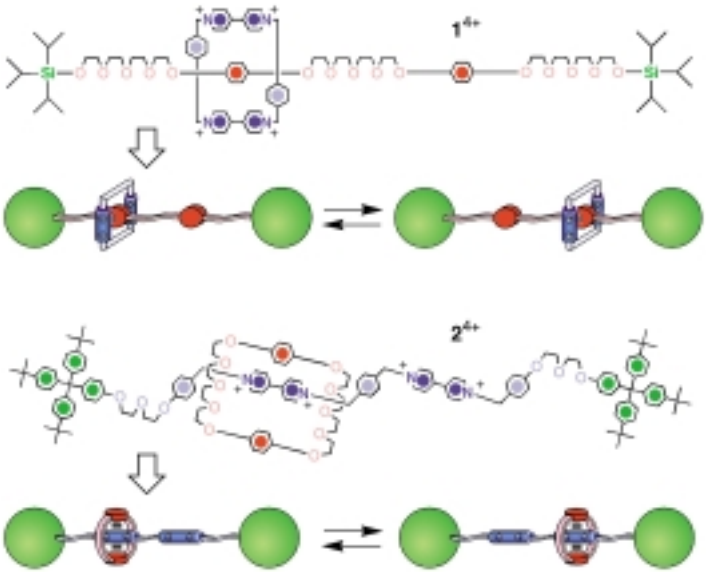

Figure 2. Experimental geometry used[19] to observe single myosin molecules binding and pulling an actin filament. The filament was attached at either end to a trapped bead. These beads were used to stretch the filament taut and move it near surface-bound silica beads that were decorated sparsely with myosin molecules. Adapted with permission from ref. [19] (Copyright© Macmillan Magazines Ltd 1994).

filament was bound at either end to a polystyrene bead to form a dumbbell structure. Both beads were then optically trapped, and the filament was pulled taut and moved near surface-bound silica spheres that were decorated sparsely with myosin molecules. Transient bead deflections parallel to the long filament axis were observed and interpreted as reflecting myosin binding and the pulling of the filament. These experiments, however, could not resolve a number of issues—such as the motor mechanism—which are still the subject of extensive investigation.[20] Several other biological processes are based on motions. For example, RNA polymerase moves along DNA while carrying out transcriptions, thus it acts as a molecular motor. The force and velocity of single molecules of RNA polymerase have recently been measured.[21] Evidence of concerted operation of kinesin and myosin motors has also been reported.[22]

## 1.4. Interlocked Molecules as Prototypes of Artificial Molecular Machines

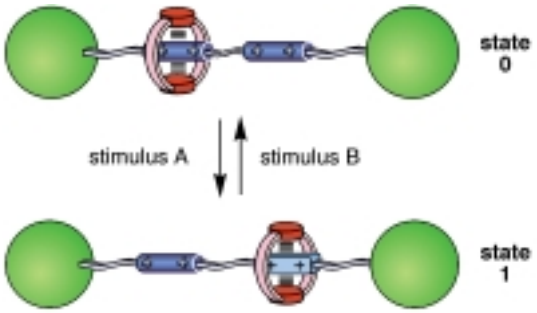
One of the goals of supramolecular chemistry[5, 11] is to create organized, functioning molecular-scale devices which are able to interpret, store, process, and dispatch information just like the sophisticated machines found in natural systems. Arguably, the most profound influence upon the art of chemical synthesis in recent times has been a supramolecular one, in which intermolecular noncovalent bonding interactions play a prominent role in templating reactions.[23, 24] While *supramolecular synthesis* has led to the creation of the so-called *rotaxanes*[25, 26] under thermodynamic control, *supramolecular assistance to molecular synthesis*, under both kinetic and thermodynamic control,[27] has led to the construction of the so-called *catenanes*,[25, 26] as well as of the rotaxanes. As observed in natural systems, *self-assembly*[28] in its strictest sense, and also with covalent modification, has provided the impetus for the development of *synthetic supramolecular chemistry*[29] to a point where synthesizing catenanes and rotaxanes is quite routine.

A *[2]rotaxane*[25, 26] is a molecule composed of a macrocyclic and a dumbbell-shaped component. The macrocycle encircles the linear rodlike portion of the dumbbell-shaped component and is trapped mechanically around it by two bulky stoppers. Thus, the two components cannot dissociate from one another, even although they are not linked covalently to each other. If it can be arranged, during the template-directed synthesis[23, 24] of a [2]rotaxane, to locate two identical recognition sites within its dumbbell component, then the result is a degenerate, co-conformational[30] equilibrium state in which the macrocyclic component can shuttle back and forth along the linear portion of the dumbbell. Such a molecule constitutes a *molecular shuttle*.[31, 32] Two examples[31, 33] of [2]rotaxanes that behave as degenerate molecular shuttles are shown in Scheme 1. When the two recognition sites in the dumbbell component differ in their constitutions, then the [2]rotaxane can exist as two different equilibrating co-conformations,[30] whose populations reflect their relative free energies as determined primarily by the strengths of the two different sets of noncovalent bonding interactions in the molecule. In the schematic representation shown in Scheme 2, it has been assumed that the molecular shuttle resides preferentially in "state 0" until a stimulus is applied that switches off the stronger of the two recognition sites, thus inducing the macrocycle to move to the second weaker recognition site, "state 1". In appropriately designed [2]rotaxanes, this nondegenerate process can be controlled[10p,q,t,v,y, 34] reversibly using stimuli that are either chemical, electrochemical, or photochemical. Protonation/deprotonation as well as oxidation/reduction processes can all be exploited to alter reversibly the stereoelectronic properties

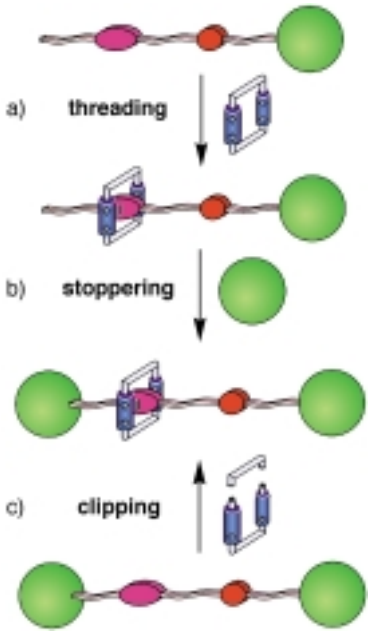



Scheme 1. In the [2]rotaxane $\mathbf{1}^{4+}$, the bipyridinium-based cyclophane shuttles[31] from one 1,4-dioxybenzene recognition site to the other at a rate of about 2000 $s^{-1}$ in $(CD_3)_2CO$ at ambient temperature. In the [2]rotaxane $\mathbf{2}^{4+}$, the 1,4-dioxybenzene-based macrocyclic polyether shuttles[33] from one bipyridinium recognition site to the other one at a rate of about 300 000 $s^{-1}$ under the same conditions.

of one of the two recognition sites, thus affecting their relative abilities to sustain noncovalent bonds. By switching the recognition properties of one of the two recognition sites off and on again, the relative proportions of the two species can be controlled reversibly. These kinds of controllable molecular shuttles can be self-assembled using one of a number of different template-directed synthetic strategies.[23, 24] In one instance, a linear half-dumbbell-shaped compound is threaded (Scheme 3; step a) through the cavity of a preformed macrocycle with the assistance of noncovalent bonding interactions and then the so-called *pseudorotaxane*[35] is stoppered (step b) by the covalent attachment of a bulky group. In another instance, the macrocycle is clipped (step c) around the preformed dumbbell, again with the help of noncovalent bonding interactions. Both the threading followed by stoppering and the clipping approaches to synthesizing controllable molecular shuttles are examples of supramolecular assistance to molecular synthesis. An alternative approach is provided by slippage,[36] which is an example of supramolecular (noncovalent) synthesis.[29] In this approach




Scheme 2. The two co-conformations associated with a [2]rotaxane incorporating two different recognitions sites within its dumbbell-shaped component[31] can be interchanged by appropriate stimuli.




Scheme 3. The a) threading followed by b) stoppering and the c) clipping strategies[28c] for the template-directed synthesis of a [2]rotaxane.

the macrocyclic and the dumbbell-shaped components are synthesized separately. When the two species are heated together in solution the macrocycle "slips" over the dumbbell's stoppers to form a molecular shuttle. Upon cooling the reaction mixture, the macrocycle is obliged to remain threaded on the dumbbell as a result of the thermodynamic trap (Figure 3) provided by the stabilizing noncovalent bonding interactions.

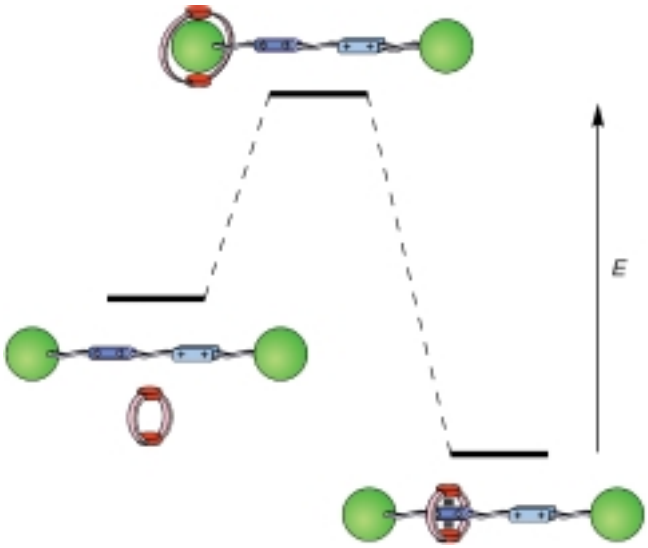
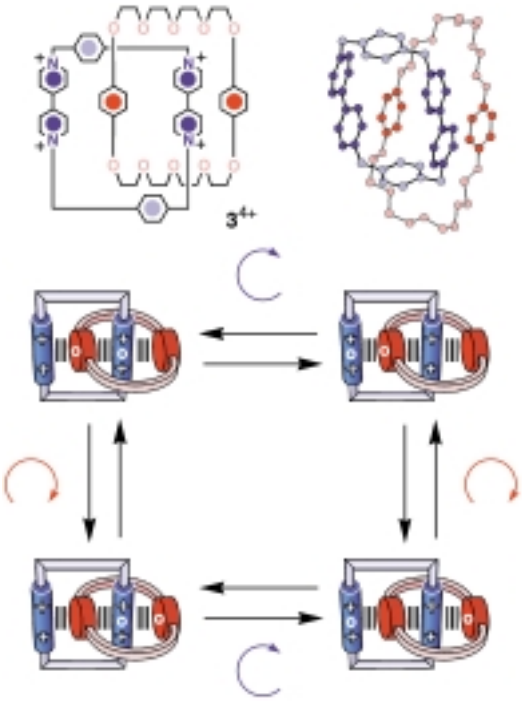



Figure 3. The change in energy associated with the slipping[36] of a macrocycle over one of the stoppers of a dumbbell-shaped compound.

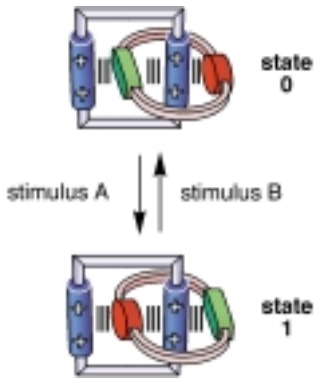
A *[2]catenane*[25, 26] is a molecule composed of two interlocked macrocyclic components. The two macrocycles are not linked covalently to each other: rather, a mechanical bond holds them together, and prevents their dissociation. If it is arranged during the template-directed synthesis[23, 24] to have

two identical recognition sites located within two different macrocycles, then the [2]catenane that results is one that undergoes a degenerate co-conformational[30] change when one of the macrocycles circumrotates[37] through the cavity of the other and vice versa. An example[38] of a degenerate [2]catenane is shown in Scheme 4 wherein the dynamic



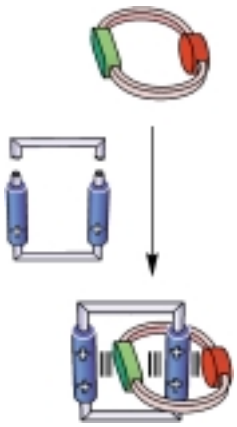

Scheme 4. The solid-state structure of the [2]catenane $\mathbf{3}^{4+}$ and the dynamic processes associated[38] with this molecule in solution which involve the circumrotations of the macrocyclic components through each other's cavities.[26h]

processes in solution are illustrated together with its solid-state structure. When one of the two macrocyclic rings carries two different recognition sites then the opportunity exists to control[10p,q,v,y, 39, 40] the dynamic processes in these switchable [2]catenanes (Scheme 5) in a manner reminiscent of the controllable molecular shuttles. In essence, the requirement for being able to switch between "state 0" and "state 1" in




Scheme 5. The two co-conformations associated with a [2]catenane that incorporates two different recognition sites within one of its two macrocyclic components can be interchanged by appropriate stimuli.

such a [2]catenane is that the "symmetric" macrocyclic component resides preferentially around one of the two different recognition sites incorporated within the "asymmetric" macrocycle. The two associated co-conformations[30] are stabilized by intercomponent noncovalent bonding interactions and their interconversion requires the circumrotation of the "asymmetric" macrocycle through the cavity of the "symmetric" one. In solution, the equilibrium between the two co-conformations is governed by the relative magnitudes of the intercomponent noncovalent bonding interactions. By switching off and on again the recognition properties of one of the two recognition sites of the "asymmetric" macrocycle, the relative populations of the two species can be controlled reversibly. Complexation/decomplexation of metal ions or of neutral organic molecules as well as protonation/deprotonation and oxidation/reduction processes can all be exploited to alter reversibly the stereoelectronic properties of one of the two recognition sites, thus affecting its ability to sustain noncovalent bonds. These kinds of switchable [2]catenanes can be prepared following the template-directed synthetic strategy[23, 24] illustrated in Scheme 6 wherein one of the two macrocyclic components is preformed and then the other one is clipped around it with the help of noncovalent bonding interactions in what amounts to supramolecular assistance to molecular synthesis.

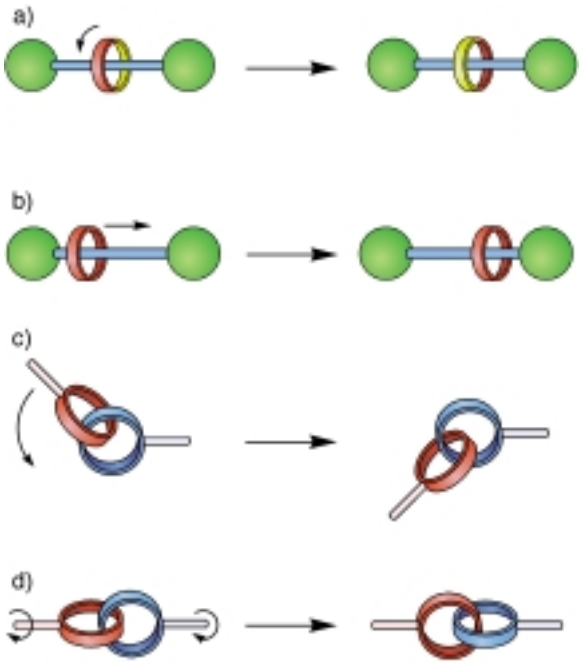


Scheme 6. The clipping strategy[28c] for the template-directed synthesis of a [2]catenane.

A large variety of recognition sites and noncovalent bonding interactions have been employed[25, 26] to assist in the covalent syntheses of rotaxanes and catenanes. For example, the ability of 1) cyclodextrins to bind organic molecules in aqueous solution, 2) crown ethers to bind metal cations or secondary dialkylammonium recognition sites, and 3) amide groups to sustain hydrogen-bonding interactions have all been exploited to template the formation of these interlocked molecules. However, rotaxanes and catenanes which are particularly attractive for the generation of molecular machines are those incorporating redox- and/or photo-active units in one or both or all of their interlocked components.[10p,q,t,v,y] Thus, the most promising synthetic strategies for the generation of molecular machines incorporating interlocked components are those relying on the use of transition metal templates or of complementary π-electron-rich and π-electron-deficient recognition sites. Indeed, the ability of transition metals to coordinate organic ligands with specific geometries has been exploited[25b, 26b–d] to template the formation of rotaxanes and catenanes incorporating phenanthroline ligands. The redox- and photo-active metal centers embedded in the resulting interlocked molecules provide the means to address them electrochemically and photochemically.[10q,r,x] Similarly, the ability of bipyridinium recognition sites to sustain π–π and C–H···O interactions with polyethers incorporating π-electron-rich recognition sites has been employed[25b, 26g,h,j–l,n,o] to

self-assemble, under kinetic or thermodynamic control,[27] rotaxanes and catenanes. The presence of the redox-active π-electron-rich and π-electron-deficient units makes these interlocked molecules perfect candidates for building molecular machines.[10a,b,h,i,p,y]

The co-conformational changes associated with rotaxanes and catenanes are reminiscent[10p,q] of the mechanical motions associated with some macroscopic machines. In a [2]rotaxane, the "wheel" component can rotate around or shuttle along (Scheme 7a and b, respectively) the "axis" component. The




Scheme 7. Some of the dynamic processes[10q] associated with (a and b) a [2]rotaxane and (c and d) a [2]catenane.

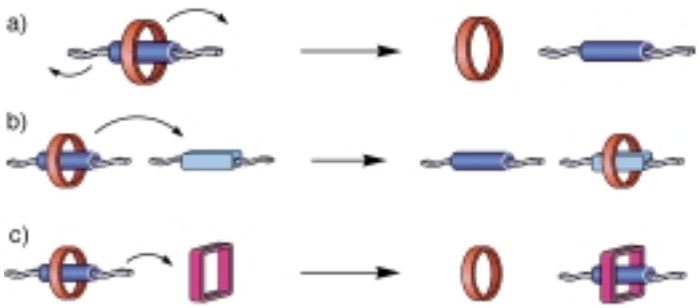
movement of one ring relative to the other in a [2]catenane is reminiscent of a "ball and socket joint", as illustrated in Scheme 7c. Similarly, the twisting of one ring around the main axis of the [2]catenane forces (Scheme 7d) the other ring to rotate in the same direction in a manner reminiscent of a "universal joint".[41]

### 1.5. Pseudorotaxanes as Prototypes of Artificial Molecular Machines

Supramolecular complexes are appealing systems for the construction of simple molecular-level machines since they can be obliged to undergo dissociation into their free molecular components and eventually assemble again upon appropriate counter-stimulations. They are an attractive proposition and of considerable interest because they can be prepared under thermodynamic control simply by mixing the molecular components in solution. The challenge for chemists engaged in this particular approach to building molecular-level machines resides in the "programming" of the system, that is, in the design and synthesis of components, which carry within their structures the pieces of information necessary for the construction of the desired supramolecular architecture.[5, 11]

From the viewpoint of molecular machines, the most interesting complexes are the pseudorotaxanes.[35] The reason is that they can be reversibly dissociated into a free ring-type host and a free thread-type guest, which gives rise to dethreading/rethreading motions. Some of the molecular motions that can be obtained with pseudorotaxanes are represented pictorially in Scheme 8. Starting from the simple dethreading/rethreading motion (Scheme 8a), more complex processes can be devised. In a chemical system composed of a macrocycle and two threadlike species one can select (Scheme 8b), by means of a suitable input, which thread enters the ring's cavity. Analogously, a suitable stimulus can be employed to choose which one of the two macrocycles surrounds (Scheme 8c) a particular threadlike species. The investigation of such systems is of interest not only for its own sake, but also for the design of more complex molecular machines based on rotaxanes and catenanes (see Section 3).

The external stimulus employed to operate such rudimentary molecular machines must be able to weaken the noncovalent bonding forces that stabilize the initial supramolecular complex. Therefore, the type of stimulus that is used depends on the nature of such forces. The majority of complexes studied so far rely on $^{+}N{-}H\cdots O$ and $C{-}H\cdots O$ hydrogen-bonding or on a combination of $C{-}H\cdots O$ hydrogen-bonding and π-electron donor/acceptor (charge-transfer) interactions.[10a,b,h,i,p,y] $^{+}N{-}H\cdots O$ Hydrogen-bonding interactions can be easily destroyed by addition of a base capable of deprotonating an ammonium center, and can be restored by addition of an acid capable of reprotonating an amine function. Thus, in supramolecular complexes based on hydrogen-bonding interactions, mechanical motions can be driven by means of chemical (acid/base) stimulation. When the interactions responsible for complexation are donor/acceptor in nature, they can be weakened by oxidation of the electron-donor unit or by reduction of the electron-acceptor one. The reduction of the electron-acceptor unit also weakens the $C{-}H\cdots O$ hydrogen bonds which accompany the donor/acceptor interactions in most of these supramolecular complexes. In most cases, the donor/acceptor interaction can be restored by means of the reverse redox process. The oxidation




Scheme 8. a) The dissociation of a pseudorotaxane and the interchange of b) a macrocycle between two threads and of c) a thread between two macrocycles.[10y]

and reduction processes needed to dissociate/associate a supramolecular complex can be achieved by means of chemical, photochemical, or electrochemical stimulation.

### 1.6. Types of Molecular Machines

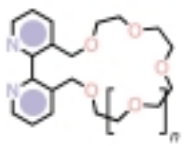
Some structure and order is required in any meaningful discussion. This task is never an easy one when discussing chemical systems. The reason relates to their complexity which, in turn, results from their multi-dimensional character. Artificial molecular machines are no exception. Nonetheless, one clear-cut distinction that can be made between different types of artificial molecular machines is according to 1) whether the component parts involved only rotate about covalent, usually single or partial double, bonds in conventional molecules or 2) whether the component parts are associated with topological or other geometrically related changes occurring within interlocked molecules, for example, catenanes and rotaxanes. The terms conformation and co-conformation are employed in this review in order to distinguish between these two types of fundamentally different motions that can take place within molecules. Some kind of mechanical bonding within a molecule is required, on top of the normal range of covalent and noncovalent bonds, to permit changes in the relative positionings of components that are co-conformational in nature. It is convenient to extend this terminology from the molecular world into the supramolecular domain, such that pseudorotaxanes, for example, may be considered to undergo co-conformational changes between their complexed and uncomplexed states. The other clear-cut distinction that can be made in discussing the abilities of molecules and supramolecules to behave as switches is how they are stimulated to perform their internal movements. In this review, it has been found convenient to discuss the addressing issue under the headings of chemical, electrochemical, and photochemical, depending on the nature of the fuel. In this ad hoc manner, we have been able to introduce some semblance of structure and order into our discussion of artificial molecular machines.

## 2. Artificial Molecular Machines Based on Conformational Motions

### 2.1. Chemically Induced Conformational Motion

#### *2.1.1. On/Off Switches Based on Allosteric Effects*

In enzymology, conformational changes induced by binding give rise to interactions between remote sites (allosteric effects) and provide a means by which the activity of enzymes can be regulated. Amongst the earliest examples of artificial chemically induced conformational motions are those[42] related to the construction of molecules, such as **4** and **5**, which are capable of allosteric behavior (Scheme 9). Such molecules are characterized by 1) an active site, 2) an allosteric or remote site, and 3) a conformational mechanism which transmits binding information from one site to the other. In the ditopic receptors **4** and **5**, the 2,2′-bipyridine and crown ether binding sites, although separated and electronically insulated, cannot behave independently. Chelation of metals with the 2,2′-bipyridine unit forces the aromatic rings toward coplanarity and brings the groups in the 3- and 3′-positions of the bipyridyl unit close together. This binding restricts the conformational freedom of the crown ether and thereby alters its receptivity toward metal ions. In the case of compound **4**, the change in selectively is small (a factor of four for $K^+$).[42b] However, in the case of compound **5**, which contains a larger crown ether macrocycle, it has been found[42c] that the capability of the macrocycle to coordinate $Hg(CF_3)_2$ in a pseudorotaxanelike manner is drastically affected by coordination of $Pd^{2+}$ at the bipyridyl site (on/off behavior).

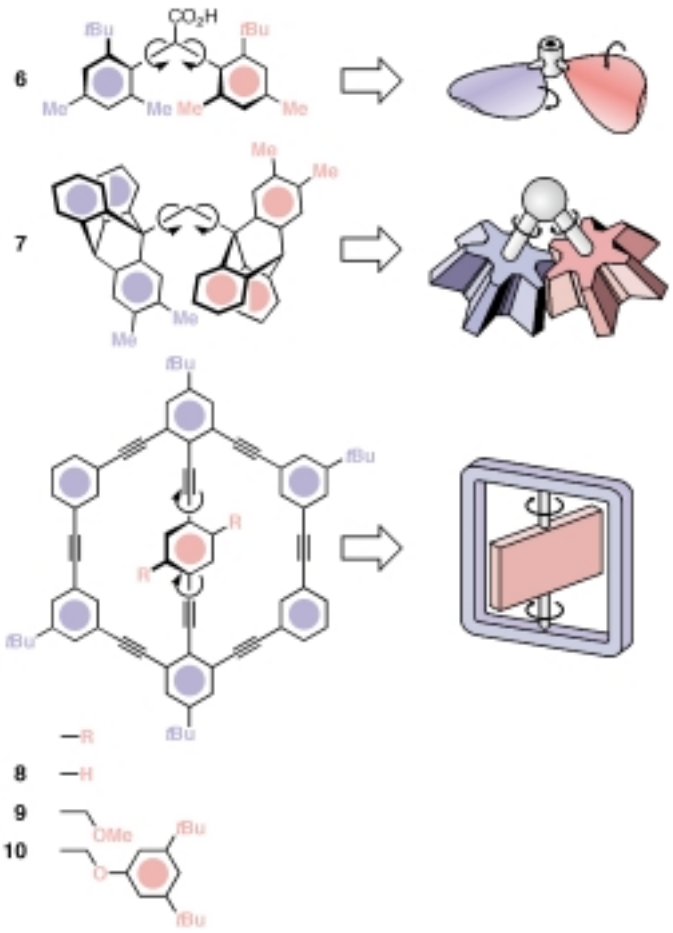


**4** $n = 1$
**5** $n = 2$

Scheme 9. The ditopic receptors **4** and **5**,[42] in which conformational changes induced by metal binding at one site alter the receptivity of a remote binding site.

#### *2.1.2. Chemical Rotors*

The correlated rotation of bulky groups in crowded molecules has presaged[43] the design of molecular-sized propellers and gears. A molecule composed of two bulky aryl rings attached to a "focal" atom can be regarded as the molecular equivalent of a macroscopic two-bladed propeller. The diarylacetic acid derivative **6** (Scheme 10) incorporates[44] two identical aryl rings linked to the same atom. Rotation of one ring in one direction about the single bond linking it to the "focal" methine carbon atom forces[44, 45] the other ring to rotate in the opposite direction. Thus, when one ring rotates clockwise, the other must rotate anticlockwise, and vice versa. The mechanism for this coupled conformational motion, which involves a concerted disrotation, has been termed "cogwheeling".[46] The coupled motions of two chemical rotors have also been exploited[47, 48] in the design of *molecular gears* incorporating triptycyl ring systems. For example, the molecular gear **7** (Scheme 10) incorporates[47c] two 9-triptycyl ring systems bridged by a methylene group. The aryl rings of the two 9-triptycyl ring systems interdigitate in a manner reminiscent of the notches of a pair of meshed bevel gears. As a result, the rotations of the two 9-triptycyl ring systems about the single bonds linking them to the "focal" methylene group are coupled. When one 9-triptycyl ring system rotates clockwise, the other one rotates anticlockwise, and vice versa. Another interesting class of chemical rotors are the macrobicyclic molecules[49] **8**–**10** illustrated in Scheme 10. The central phenyl ring of **8** can rotate about its axis. This conformational motion is reminiscent of the movement of the spindle of a turnstile[50] and, as a result, this compound has been called a *molecular turnstile*. The dynamic process associated with the molecular turnstile is affected considerably by the size of the R groups attached to the central *p*-phenylene ring. Indeed, two degenerate conformations can be identified in the case of **9** by low temperature $^1H$ NMR spectroscopy. At ambient temperature, however, the rotation about the axis of the central ring of **9** is fast on the $^1H$ NMR



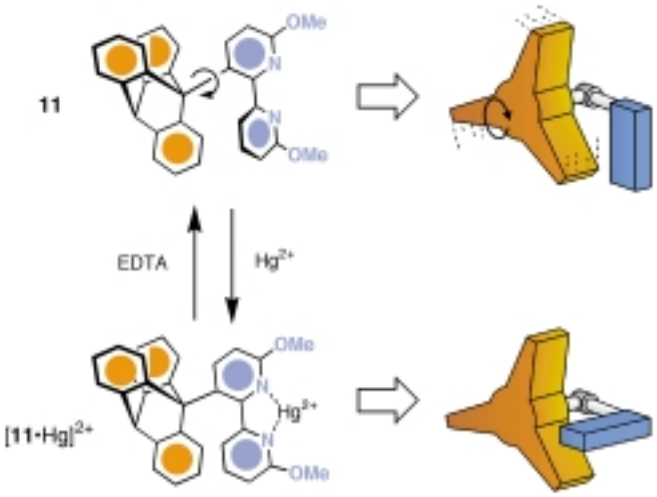

Scheme 10. The molecular propeller **6**,[44] the molecular gear **7**,[47c] and the molecular turnstiles **8**–**10**.[49]

timescale and a free energy barrier of 13.4 kcal mol$^{-1}$ is associated with this dynamic process. By contrast, this rotation does not occur in **10**, even when a solution of this compound is heated up to high temperatures. In this instance, the substituents attached to the central *p*-phenylene ring are far too bulky to be able to pass through the cavities of the macrobicyclic ring system.

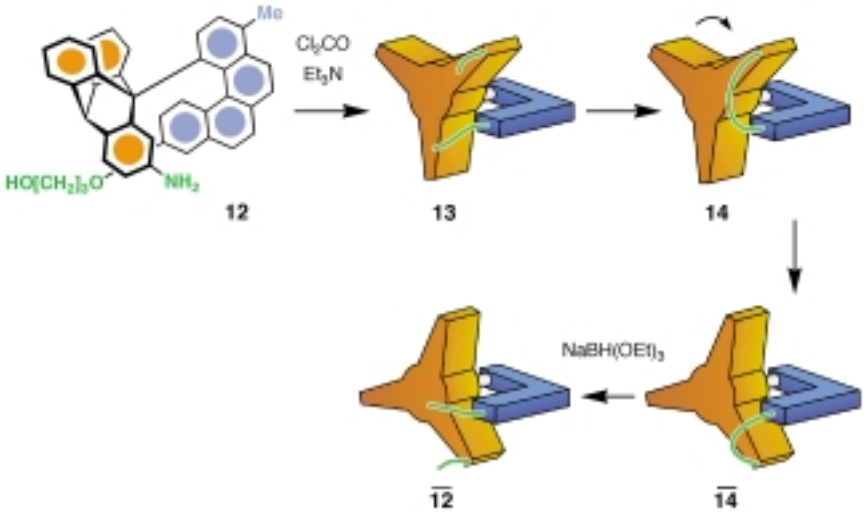
The rotations associated with the chemical rotors **6**–**9** are spontaneous, in common with the conformational motions observed in most organic molecules possessing single bonds.[51] By contrast, the large amplitude motion associated with a real molecular machine has to be controllable.

An example of a chemically controllable rotor[52] is the compound shown in Scheme 11 which incorporates a 9-triptycyl ring system attached to a 2,2′-bipyridine unit. The rotation about the single bond connecting these two units in $(CD_3)_2CO$ at 303 K is fast on the $^1$H NMR timescale. As a result, only four sets of resonances are observed in the $^1$H NMR spectrum for the aromatic protons of the 9-triptycyl ring system. The solution has to be cooled down to 193 K to slow down this dynamic process. Under these conditions the twelve aromatic protons of the 9-triptycyl unit became nonequivalent. Upon addition of $Hg(O_2CCF_3)_2$ to a solution of **11** in $(CD_3)_2CO$, the metal ion is coordinated by the 2,2′-bipyridine ligand. As a result, the conformation of this unit is locked and the $^1$H NMR spectra (303 K) recorded before and after the addition of the metal ion are markedly different. Upon chelation, the singlet associated with the protons of the methoxy group attached to the disubstituted pyridine ring is shifted downfield by +2.02 ppm. Furthermore, the resonances of the aromatic protons of the 9-triptycyl ring system broaden significantly. At 243 K, rotation about the single bond connecting the 9-triptycyl ring system to the 2,2′-bipyridine unit is already slow enough to render some of the aromatic protons of the 9-triptycyl ring system nonequivalent. These observations indicate that the locked conformation of the 2,2′-bipyridine unit brakes the rotation of the 9-triptycyl ring system. The *molecular brake* can be released by adding EDTA to the solution of $[\mathbf{11}\cdot Hg]^{2+}$ in $(CD_3)_2CO$. Indeed, removal of the coordinated metal unlocks the conformation of the 2,2′-bipyridine unit, thus disengaging the brake.

In order to generate a chemical rotor which undergoes unidirectional[53] motion, the design of the molecular brake **11** was modified. The 2,2′-bipyridine unit was replaced[54] by helicenes of appropriate lengths and the unidirectional, ratchet-type rotation about the single bond connecting the 9-triptycyl ring system to a [4]helicene has now been achieved.[55] The steric hindrance associated with the [4]helicene group of **12** (Scheme 12) inihibits the rotation about the single bond connecting this unit to the 9-triptycyl ring system. Treatment of **12** with $Cl_2CO$ and $Et_3N$ gives the isocyanate **13**. The intramolecular reaction of the hydroxyl and isocyanate groups affords the urethane **14** in a highly strained conformation. The strain is released by the clockwise rotation of the 9-triptycyl ring system about the single bond connecting it to the [4]helicene. Cleavage of the urethane linkage regenerates compound **12** in a conformation that is different from the original one. This new conformation is obtained as a result of a unidirectional 120° rotation induced by the formation of a covalent bond. The process can be followed by $^1$H NMR spectroscopy using the bridgehead proton of the 9-triptycyl ring system as a probe. The rapid transformation of **12** into **14** is accompanied by a shift of the singlet associated with the




Scheme 11. The molecular brake **11** is engaged[52] upon chelation of a $Hg^{II}$ ion by the 2,2′-bipyridine ligand and it is released upon addition of EDTA which captures the metal ion ($(CD_3)_2CO$, 303 K).

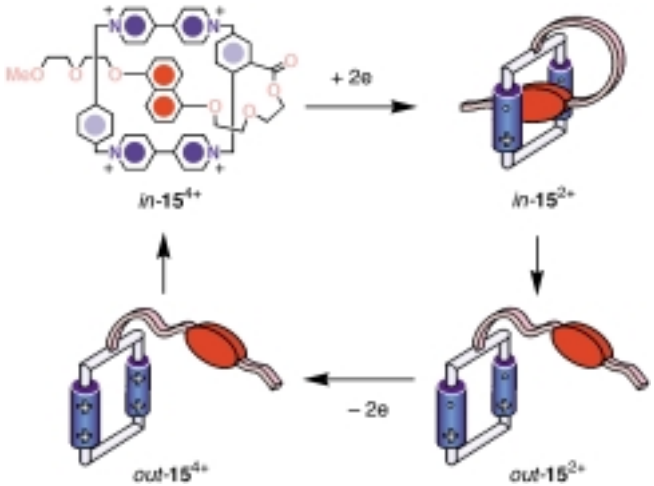



Scheme 12. The rotation about the single bond connecting the 9-triptycyl ring system to the [4]helicene group in chemical rotor **12** ($CDCl_3$, 295 K) is assisted[55] by the formation of a covalent bond and occurs in one direction only.

probe proton to low field and is followed by the unidirectional rotation which causes a decrease in the intensity of this signal and the concomitant growth of another singlet. After about 6 h, the conformational change is almost complete.

### 2.2. Electrochemically Induced Conformational Motion

Conformational changes can be induced electrochemically[56] in appropriately designed self-complexing molecules. An example is compound *in*-**15**$^{4+}$ (Scheme 13), which incorporates[57, 58] a π-electron-deficient head and a π-electron-rich




Scheme 13. The motion of the π-electron-rich tail of the self-complexing compound **15**$^{4+}$ can be induced[57] electrochemically in MeCN solution at 298 K by reducing/oxidizing the bipyridinium units of the π-electron-deficient head.

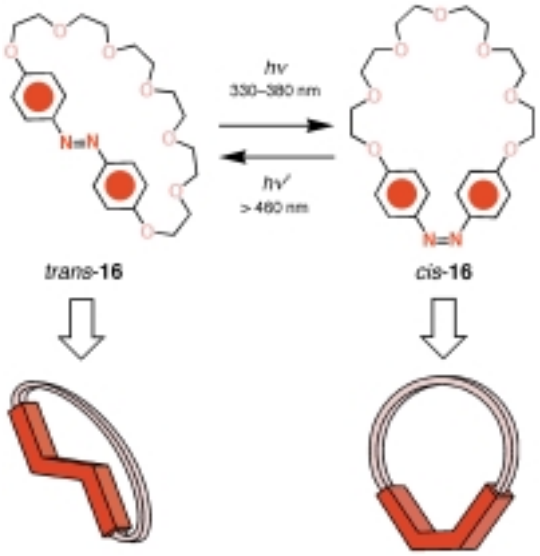
tail. The tail threads through the cavity of its own head in solution, which results in the positioning the 1,5-dioxynaphthalene ring system between the two bipyridinium units. This conformation is stabilized by π–π stacking interactions between the complementary π-electron-rich and π-electron-deficient aromatic units, as well as by C–H···O hydrogen bonds between the α-bipyridinium hydrogen atoms and the polyether oxygen atoms. Consistently, the absorption spectrum of *in*-**15**$^{4+}$ recorded in MeCN at 298 K shows a band in the visible region at 515 nm, which arises from charge-transfer interactions between the 1,5-dioxynaphthalene ring system and the sandwiching bipyridinium units. The absorbance of the charge-transfer band increases linearly with the concentration. This behavior is remarkably similar to that of a model self-complexed system[57] bearing a bulky stopper at the end of the tail. The stopper prevents dethreading of the tail and so this model compound can exist only in a self-complexed conformation. The similarities between the absorption spectra of *in*-**15**$^{4+}$ and of this model compound indicate that *in*-**15**$^{4+}$ also exists completely in its self-complexed conformation in solution. The cyclic voltammogram of *in*-**15**$^{4+}$ shows two reversible two-electron reduction waves. The first one (−0.35 V versus the saturated calomel electrode (SCE)) corresponds to the simultaneous addition of one electron to each of the two bipyridinium units. The second one (−0.71 V) corresponds to the simultaneous addition of a second electron to each of the two bipyridinium units. A model tetracationic cyclophane that does not incorporate the 1,5-dioxynaphthalene tail undergoes two consecutive two-electron reduction processes at −0.29 and −0.70 V. Thus, the first reduction process occurs at a more negative potential in the case of *in*-**15**$^{4+}$, while the second reduction process occurs at the same potential in both compounds. These observations indicate that the 1,5-dioxynaphthalene unit of *in*-**15**$^{4+}$ is sandwiched (Scheme 13) initially between the two bipyridinium units, which makes their first reduction more difficult. However, after the addition of one electron to each of the two bipyridinium units, the 1,5-dioxynaphthalene unit is expelled from the cavity of the tetracationic cyclophane[59] and the second reduction process is not affected by the presence of the π-electron-rich unit. Subsequent removal of the electrons previously added to the bipyridinium units leads back to the insertion of the tail into the cyclophane. This is an example of an artificial molecular machine where both the input and the output are electrochemical.

### 2.3. Photochemically Induced Conformational Motion

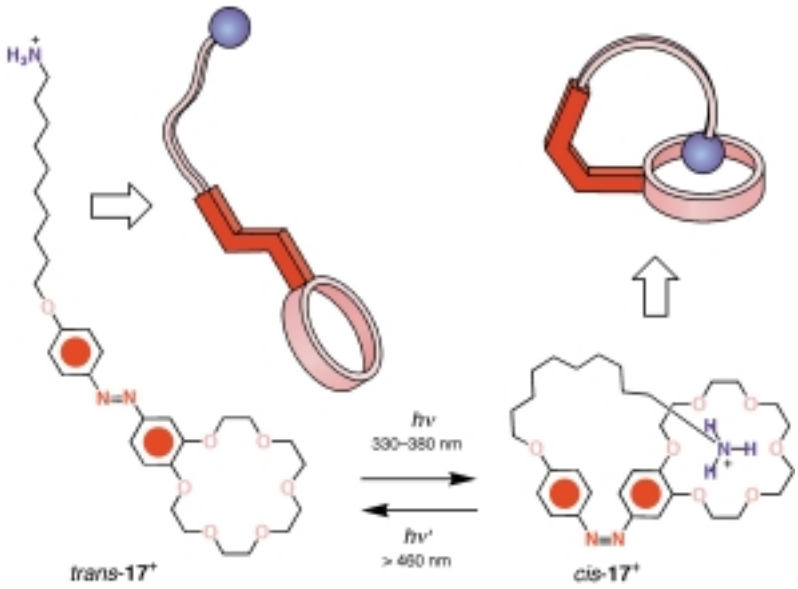
Suitable donor-bridge-acceptor compounds have been shown[60] to undergo conformational folding in nonpolar solvents upon excitation with light. Excitation of such compounds with light leads to the formation of an excited state, localized on the acceptor subunit, which then decays to a charge-separated state. In this state, the donor and the acceptor subunits carry a positive and a negative charge,

respectively, and are well separated in space. However, electrostatic attractions bring the subunits close together, thereby making the molecule fold over on itself. Crucial for the observation of this "harpooning" motion is the fact that both the extended and folded charge-separated states show a characteristic fluorescence. This is an excellent example of a system in which photons are employed as both a stimulation and a read-out signal.

The N=N bond of azobenzene (1,2-diphenyldiazene) can adopt *cis* and *trans* configurations. Their interconversion can be induced by irradiation at appropriate wavelengths. Thus, the geometries of molecules incorporating one or more azobenzene units can be altered reversibly by the controlled isomerization of these photoactive sites. In turn, these structural changes can be exploited to modulate the physico-chemical properties of such molecules and/or of their surrounding environment. Indeed, this strategy has been employed extensively to control the geometries and functions of biomolecules,[61] of organic materials,[62] and of supramolecular complexes.[3, 63, 64] For example, the photoresponsive crown ether *trans*-**16** (Scheme 14) incorporates a *trans*-azobenzene unit.[65, 66] Upon irradiation of a solution of *trans*-**16** in *o*-dichlorobenzene at 330–380 nm a *trans* → *cis* isomerization of the photoactive unit occurs. The photoinduced configurational change about the N=N bond is accompanied by pronounced conformational changes of the polyether linkages. The overall effect is an expansion of the macrocyclic cavity upon *trans* → *cis* isomerization. The *cis* → *trans* reisomerization can be induced by irradiating at a different wavelength (> 460 nm). Thus, the macrocyclic cavity associated with **16** can be expanded and contracted reversibly by irradiating this compound at appropriate wavelengths. In turn, these controlled configurational and conformational changes affect the binding ability of **16**. Thus, while the "expanded" macrocycle *cis*-**16** binds alkali metal cations, the "contracted" one *trans*-**16** does not. In a similar fashion, the photoinduced *cis*/*trans* isomerization of azobenzene was exploited to shrink and enlarge the cavities of cyclophanes,[67] to shorten and elongate the distance between the recognition sites of ditopic receptors,[64, 68, 69] and to induce (Scheme 15) intramolecular complexation in self-complementary molecules[70, 71] such as **17**$^+$. This compound incorporates a macrocyclic polyether head bridged by a photoactive azobenzene unit to a linear tail bearing a terminal ammonium group. The ammonium recognition site in the *trans* isomer is positioned away from the complementary macrocyclic head. Upon irradiation (*o*-dichlorobenzene, 330–380 nm), however, *trans* → *cis* isomerization occurs, which brings the ammonium recognition site in closer to the crown ether head and allows their intramolecular association. Thus, while the *trans* isomer of **17**$^+$ has a strong affinity for metal cations, the binding ability of the *cis* isomer toward metal cations is almost completely suppressed by the photoinduced self-complexation.

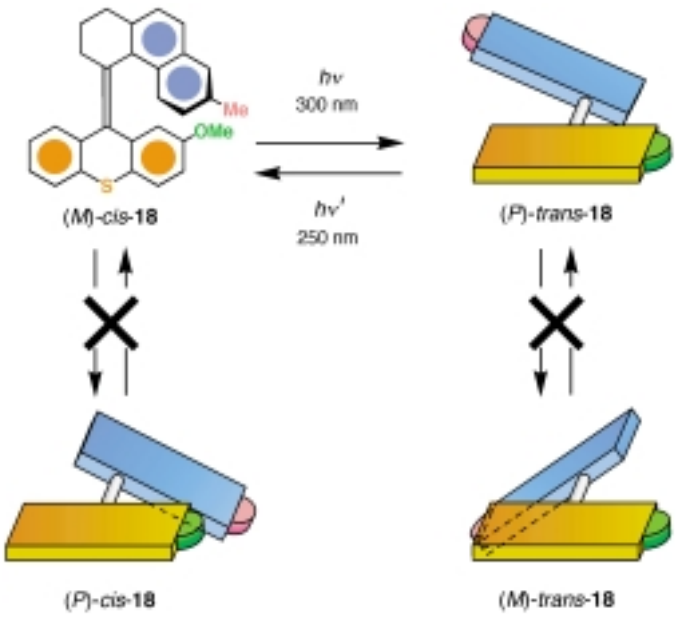



Scheme 14. The photoinduced *cis*/*trans* isomerization of the azobenzene unit of **16** (*o*-dichlorobenzene, 303 K) is accompanied[65] by the expansion/contraction of the macrocyclic cavity of this molecule.



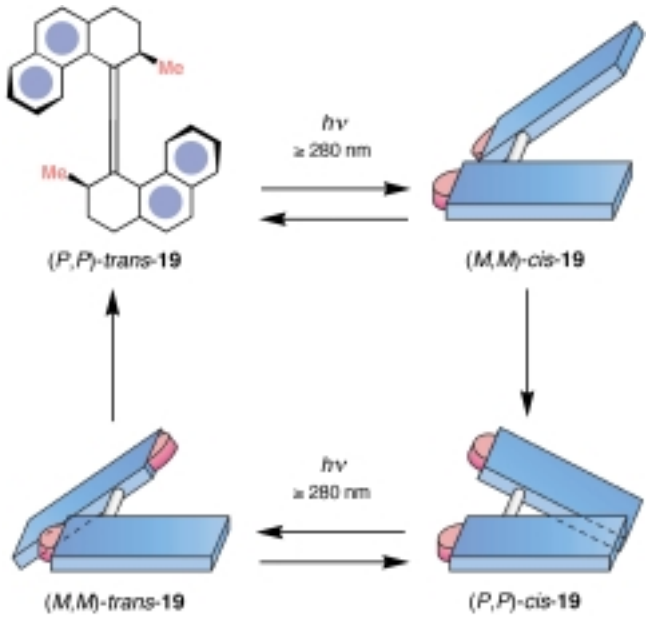

Scheme 15. The photoinduced *cis*/*trans* isomerization of the azobenzene unit of **17**$^+$ (*o*-dichlorobenzene, 303 K) is accompanied[70] by the motion of the cationic tail which can only interact with its macrocyclic head in the *cis* isomer.

Two pairs of enantiomers (Scheme 16) are associated[72, 73] with the helical compound **18**. Polarimetry, $^1$H NMR spectroscopy, and high performance liquid chromatography (HPLC) revealed that no racemization and no *cis*/*trans* isomerization occur under ambient conditions. The bulky and flexible tetrahydrophenanthrene unit prevents racemization without producing an excessive distortion of the central double bond. Upon continuous irradiation of a solution of pure (*M*)-*cis*-**18** at either 250 or 300 nm, *cis*/*trans* isomerization occurs to afford mixtures of (*M*)-*cis*-**18** and (*P*)-*trans*-**18** in ratios of 68:32 or 64:36, respectively. The same results were obtained when (*P*)-*trans*-**18** was irradiated. In all instances, however, no racemization occurred. Interconversion between the two photostationary states associated with this chiroptical molec-




Scheme 16. The photoinduced *cis*/*trans* isomerization of the chiroptical molecular switch **18** (*n*-hexane/*i*PrOH 9/1, 298 K) is not accompanied[72] by any racemization.

ular switch can be achieved by the consecutive irradiation at 250 and 300 nm. The periodical change in the ratio of the isomers (*M*)-*cis*-**18** and (*P*)-*trans*-**18** produced by the alternating irradiation can be followed by monitoring the intensities of the absorption bands at 232 and 262 nm in the circular dichroism (CD) trace. In order to generate a light-driven unidirectional molecular rotor, the design of this molecular switch was modified[74] (Scheme 17) by replacing the thioxanthylidene ring system with another tetrahydrophenanthrene unit. Each of the two helical subunits of the resulting compound **19** can adopt a right-handed (*P*) or a left-handed




Scheme 17. The light-fueled rotary motor **19** undergoes[74] unidirectional rotation in *n*-hexane at 333 K upon irradiation at appropriate wavelengths.

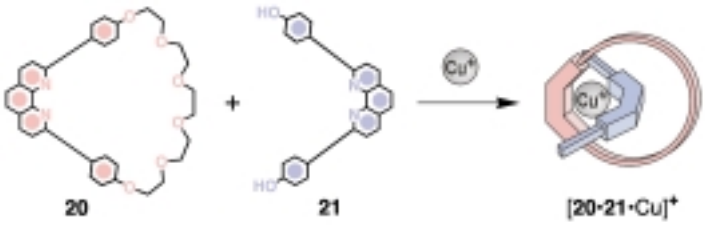
(*M*) helicity. As a result, a total of four stereoisomers (Scheme 17) are possible for this compound. However, the *cis*/*trans* isomerizations are reversible and occur upon irradiation at appropriate wavelengths. By contrast, the inversions of helicities, while maintaining a *cis* or a *trans* configuration, occur irreversibly under the influence of thermal energy. Upon irradiation ($\geq$280 nm, 218 K) of a solution of (*P*,*P*)-*trans*-**19**, a mixture of (*P*,*P*)-*trans*-**19** and (*M*,*M*)-*cis*-**19** is obtained in a ratio of 5:95. By warming the solution up to 293 K, (*M*,*M*)-*cis*-**19** interconverts irreversibly to (*P*,*P*)-*cis*-**19**. Subsequent irradiation ($\geq$280 nm) of the solution produces a mixture of (*P*,*P*)-*cis*-**19** and (*M*,*M*)-*trans*-**19** in a ratio of 10:90. Upon increasing the temperature further (333 K), (*M*,*M*)-*trans*-**19** interconverts irreversibly to the original isomer (*P*,*P*)-*trans*-**19**. Thus, a sequence of light- and temperature-induced isomerizations can be exploited to move this molecular rotor in one direction only. Indeed, when (*P*,*P*)-*trans*-**19** is irradiated ($\geq$280 nm) at a high temperature (293 K), a clockwise 360° rotation occurs spontaneously. The overall process can be followed by monitoring the change in the intensity of the absorption band at 217 nm in the CD trace. The unidirectional motion in this system is dictated by the stereogenic centers associated with the two methyl substituents. As a result of a *trans* $\rightarrow$*cis* isomerization, the axial methyl substituents of (*P*,*P*)-*trans*-**19** are forced to adopt a less favorable equatorial orientation in (*M*,*M*)-*cis*-**19**. However, the strain associated with the equatorial methyl substituents is released upon thermal interconversion of (*M*,*M*)-*cis*-**19** to the more stable isomer (*P*,*P*)-*cis*-**19**. The subsequent *cis* $\rightarrow$trans isomerization forces the methyl groups to adopt, once again, equatorial orientations in the isomer (*M*,*M*)-*trans*-**19**. Finally, the thermal interconversion of (*M*,*M*)-*trans*-**19** to the original isomer (*P*,*P*)-*trans*-**19** is accompanied by a change from the equatorial to the more stable axial orientations for the methyl substituents.

## 3. Artificial Molecular Machines Based on Co-Conformational Motions

### 3.1. Supramolecular Complexes

#### *3.1.1. Chemically Controllable Complexes*

Coordination around a metal center was the first kind of interaction exploited[75] in order to organize molecular components in a pseudorotaxane fashion.[35] Suitably designed macrocyclic and threadlike species containing phenanthroline ligands, such as **20** and **21**, self-assemble (Scheme 18) upon addition of $Cu^{I}$ ions to yield a pseudorotaxane. Such a complex was used as an intermediate in the template-directed synthesis of metal-containing catenanes[25b, 26b–d] and could therefore also be called a precatenane.[25a] The formation of this complex can be followed easily by $^{1}H$ NMR spectroscopy as well as visually, since it is accompanied by a change in the color of the solution.[75] $Cu^{I}$-containing pseudorotaxane complexes are very stable and therefore difficult to dethread: the copper ion can only be removed[76] upon treatment of the complexes with an excess of highly nucleophilic ligands, such



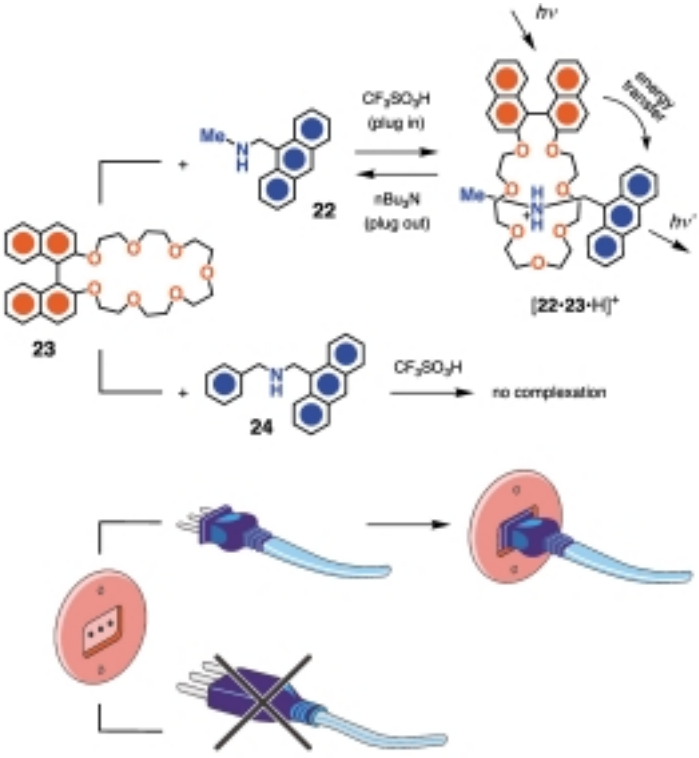

Scheme 18. The gathering ability of a $Cu^{I}$ ion induces[75] the threading of the phenanthroline-based macrocycle **20** onto the phenanthroline-based ligand **21** (MeCN, ambient temperature).

as cyanide ions. For this reason, metal complexation has not been used to develop prototypes of molecular machines based on chemically stimulated threading/dethreading movements. Nonetheless, it is a very convenient way[25b, 26b–d, 75, 76] to promote the threading of pseudorotaxanes using suitably designed threadlike and macrocyclic ligands. The versatility and the properties of metal complexes have been exploited to design and construct elegant examples of catenane- and rotaxane-based molecular machines (see Sections 3.2 and 3.3).

An interesting example[77] of redox-induced ion translocation[78] is that which occurs in triple-stranded helical ligands that contain internal, "hard" hydroxamate and external, "soft" bipyridyl binding sites. When the metal ion is $Fe^{III}$, it is accommodated in the hard coordination environment. The metal ion translocates to the external soft bipyridyl sites upon chemical reduction to the $Fe^{II}$ state. The translocation is reversible and takes place with a change in color.

Complexes which are good candidates for chemical switching include those that rely upon hydrogen-bonding interactions between ammonium ions and crown ethers. It has long been known that organic ammonium ions can form adducts with crown ethers.[25b, 26h,j,l,n] More recently, it has been found[79] that suitable threadlike dialkylammonium ions, for example, the dibenzylammonium cation, can interpenetrate suitably sized crown ethers, for example, dibenzo[24]crown-8, in nonpolar solvents to form pseudorotaxanes.[35] These complexes, whose formation can be demonstrated by $^1$H NMR spectroscopy in solution and by X-ray crystallography in the solid state, are stabilized by $^+N{-}H\cdots O$ and, to a lesser extent, by $C{-}H\cdots O$ hydrogen bonds and sometimes also by $\pi-\pi$ stacking interactions. Once the pseudorotaxane has been obtained, it can be easily dethreaded[80] by adding a base that is able to destroy the hydrogen bonds by deprotonating the $^+NH_2$ center. Suitable bases are bulky, nonnucleophilic amines such as $i$Pr$_2$NEt and $n$Bu$_3$N. The pseudorotaxanes can also be prepared from a mixture of the crown ether and a threadlike dialkylamine by addition of an acid (typically, $CF_3SO_3H$ or $CF_3CO_2H$) which protonates the amine function: the threading process can again be reversed upon addition of a base.[81] The acid has to be selected so that it does not give insoluble ammonium salts and such that its anion does promote ion-pairing.[82]

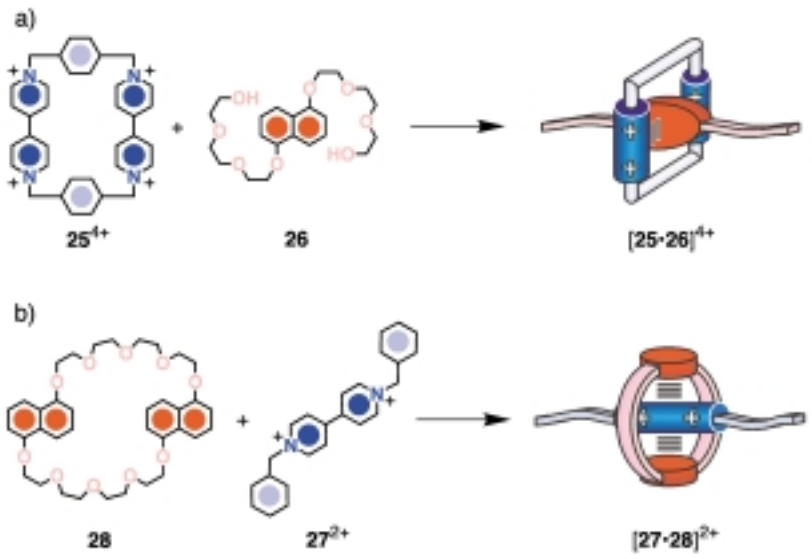
Recently, chromophoric and/or luminescent units such as dioxybenzene,[83] dioxynaphthalene,[83b,c] binaphthyl,[84] anthracene,[83a,b] as well as fullerenes,[85] have been incorporated into crown ethers or ammonium ions in order to study the photoinduced processes that take place within pseudorotaxanes. In all these cases, the goal is to design chemically (acid/base) controllable molecular machines that are able to give a light signal as a readout. For instance, the absorption and fluorescence spectra of a solution of amine **22** and crown ether **23** in $CH_2Cl_2$ (Scheme 19) indicate[84a] the absence of any interaction between the two compounds. Addition of a stoichiometric amount of acid with respect to the amine causes profound changes in the fluorescence spectrum of the solution. These changes arise particularly from the result of the quenching of the luminescence of **23** and the sensitization of the luminescence of **22** upon excitation with light that is absorbed exclusively by the crown ether. These observations are consistent with the formation of a pseudorotaxane-type adduct wherein very efficient energy transfer takes place from the binaphthyl unit of the crown ether to the anthracenyl group incorporated within the dialkylammonium ion. Such a pseudorotaxane can be disassembled by the subsequent addition of a stoichiometric amount of base, thereby interrupting the photoinduced energy flow, as indicated by the fact that the initial absorption and fluorescence spectra are restored. Besides the machine aspect, such systems can be viewed (Scheme 19) as molecular-level plug-in-socket devices since they are characterized by 1) chemically controlled, reversible "plug in"/"plug out" behavior and 2) photoinduced energy transfer in the "plug in" state. Interestingly, the "plug in" process does not take place when a plug component that is




Scheme 19. A molecular-level plug/socket system based[84a] on the reversible acid/base-driven threading/dethreading motions in the hydrogen-bonded pseudorotaxane $[\mathbf{22}\cdot\mathbf{23}\cdot H]^+$ ($CH_2Cl_2$, 298 K). The acid-driven threading of the compound **24**, which incorporates a bulky benzyl group, through the macrocyclic cavity of **23** does not occur.

incompatible with the size of the socket, such as the benzyl-substituted amine **24**, is employed.

A similar system has been reported[86] where the chemical stimuli provided by counterions are employed to achieve switching. In keeping with detailed results from previous investigations,[83a,b] the (9-anthrylmethyl)methylammonium cation $[\mathbf{22}\cdot H]^+$ dissolves in $CH_2Cl_2$ as its hexafluorophosphate salt and threads through the cavity of dibenzo[24]crown-8 to form a pseudorotaxane. Such a pseudorotaxane can be dethreaded by the addition of one equivalent of $n$Bu$_4$NCl as a result of the formation of an ion pair between the chloride ions and the $^+NH_2$ center incorporated in $[\mathbf{22}\cdot H]^+$. Rethreading of the molecular components can be performed by the further addition of one equivalent of $n$Bu$_3$NH$^+$ ions (as the hexafluorophosphate salt) which compete with $[\mathbf{22}\cdot H]^+$ for the binding of chloride ions. All the processes can be followed by changes in the luminescence properties of the solution and the cycle can be repeated several times on the same system, as tertiary and quaternary ammonium ions do not compete with $[\mathbf{22}\cdot H]^+$ in its association with dibenzo[24]crown-8. Such a chemical system can also be viewed as a fluorescent chemosensor[10k] for species as different as protons, amines, and chloride ions. These kinds of multimode molecular devices,[10y] which can be operated by either acid/base or anionic stimuli, are expected to prove useful for information processing, for example, for the construction of molecular-level logic gates (see below and Section 3.1.2).

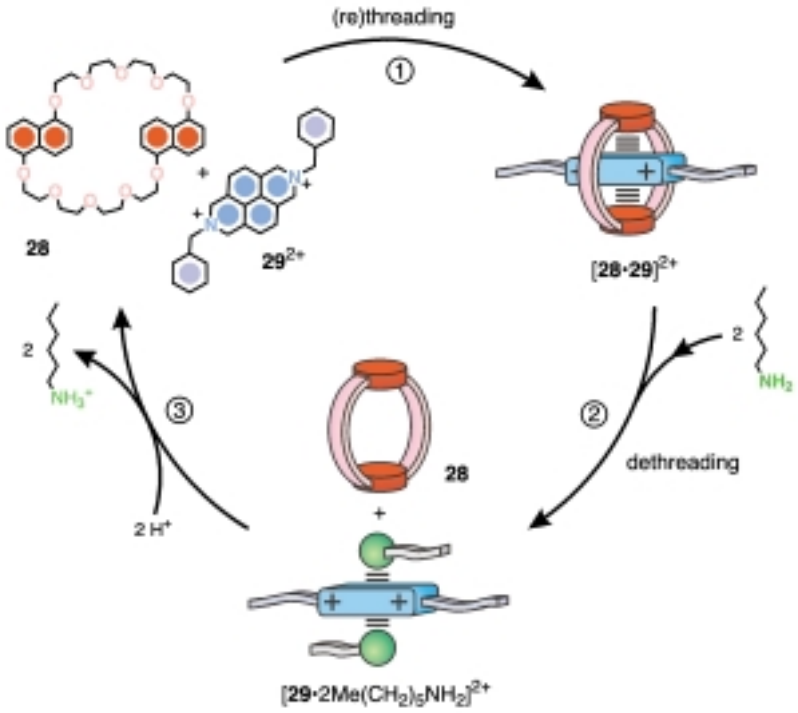



Scheme 20. The formation of the pseudorotaxanes $[\mathbf{25}\cdot\mathbf{26}]^{4+}$ and $[\mathbf{27}\cdot\mathbf{28}]^{2+}$ incorporating π-electron-rich and π-electron-deficient components.[26h]

Threadlike dimeric pyridylpyridinium dications, in which the aromatic units are linked by a long alkyl chain, have been used[87] as guests for α-cyclodextrin. In this system the formation of a pseudorotaxane in aqueous solution is driven by hydrophobic interactions between the aliphatic chain and the lipophilic cavity of α-cyclodextrin. It has been shown that the pseudorotaxane can be partially dethreaded by protonating the two basic nitrogen atoms of the terminal pyridyl units of the thread. This response can be explained by the decrease in the hydrophobic character associated with the alkyl chain in the protonated guest.

As an alternative to metal coordination and $^+N{-}H\cdots O$ hydrogen-bonding interactions, the stabilization that exists between π-electron-donor and π-electron-acceptor species, aided and abetted often by $C{-}H\cdots O$ hydrogen-bonding interactions, is a means of template direction which has been used[25b, 26g,h,j–l,n,o] extensively to produce threaded superstructures. In the last few years, a number of complexes with pseudorotaxane geometries have been prepared from the self-assembly (Scheme 20a) of a π-electron-rich threadlike component, such as **26**, and a π-electron-deficient macrocycle,[25b, 26g,h,j–l,n,o] such as the tetracationic cyclophane cyclobis(paraquat-*p*-phenylene) ($\mathbf{25}^{4+}$). Similarly, pseudorotaxanes, in which a linear π-electron-deficient species, such as the 1,1′-dibenzyl-4,4′-bipyridinium dication $\mathbf{27}^{2+}$, threads (Scheme 20b) through the cavity of a π-electron-rich macrocycle such as 1,5-dinaphtho[38]crown-10 (**28**), have been characterized.[25b, 26g,h,j–l,n,o] These complexes[88] are stabilized by a combination of electrostatic and dispersive forces, in particular 1) π–π stacking[89] (including charge-transfer) interactions, 2) $C{-}H\cdots O$ hydrogen bonds[90] between the hydrogen atoms located in the α-positions, with respect to the nitrogen atoms, of the bipyridinium unit and some of the polyether oxygen atoms, and 3) $C{-}H\cdots\pi$ interactions.[91] For instance, the 2,7-dibenzyldiazapyrenium dication $\mathbf{29}^{2+}$ self-assembles (Scheme 21) in solution with crown ethers, such as **28**, to give pseudorotaxanes (process 1), as shown by a variety of techniques, including absorption, luminescence, and $^1$H NMR spectroscopies.[92] The dication $\mathbf{29}^{2+}$ forms[92] adducts with aliphatic amines, presumably as a result of charge-transfer interactions and, possibly, also because of hydrogen bonding to the acidic α-protons of the dication. Such an affinity has been exploited chemically to drive the dethreading of its pseudorotaxane with **28**. In fact, upon addition of 20 molar excess of *n*-hexylamine to a solution of the pseudorotaxane in MeCN, profound absorption and luminescence spectral changes are observed, which indicates that the free crown ether and the adduct between $\mathbf{29}^{2+}$ and the amine are formed (process 2). The dethreading can be reversed quantitatively (process 3) by the addition of a stoichiometric amount of $CF_3CO_2H$ (with respect to the added amine) to the solution. Despite its structural similarity to the dication $\mathbf{29}^{2+}$, the 1,1′-dibenzyl-4,4′-bipyridinium dication $\mathbf{27}^{2+}$ (Scheme 20b) does not interact with amines. This observation has led[93] to the above system being extended to one in which the amine/acid chemical inputs select which one of two threadlike species enters the cavity of the macrocycle, which can cause a reversible interchange to occur between the threads.

The ability of pseudorotaxanes composed of $\mathbf{29}^{2+}$ and aromatic crown ethers to be disassembled by aliphatic amines has been coupled with the possibility of dethreading the same systems by protonation of the crown ether in nonpolar solvents. It has been shown[94] that the pseudorotaxane formed




Scheme 21. Schematic representation of the amine/acid-controlled dethreading/rethreading cycle[92] of the pseudorotaxane $[\mathbf{28}\cdot\mathbf{29}]^{2+}$ (MeCN, 298 K).

by $\mathbf{29}^{2+}$ and 2,3-dinaphtho[30]crown-10 in $CH_2Cl_2$ can be dethreaded upon addition of $n$Bu$_3$N and assembled again by adding protons. The same result can be obtained by reversing the order of the two chemical inputs, that is, dethreading can be achieved by the protonation of the crown ether's cavity and rethreading can be obtained by the addition of $n$Bu$_3$N. All these processes are accompanied by on/off switching of easily monitorable changes in the absorption and luminescence spectra, particularly of an intense fluorescence band, characteristic of the aromatic crown ether, with a maximum at 343 nm. It is worth emphasizing that these results contrast with the usual behavior of chemical systems that either remain unchanged or undergo very different changes upon addition of reactants of opposite chemical types such as amines and acids. An important consequence of this behavior is that the input/output relationships of the system correspond to those of the XOR (eXclusive OR) logic operation.[95] This development shows[10y] that carefully designed dual-mode chemically driven molecular machines are potentially useful for information processing.

The assembly of complexes based on electron donor/acceptor interactions can be controlled by means of redox stimuli, which can be provided by the addition of oxidants and reductants. The inclusion complex[96] formed between the electron-acceptor cyclophane $\mathbf{25}^{4+}$ and the well-known electron donor tetrathiafulvalene (TTF, **30**), as well as pseudorotaxanes[97] composed of $\mathbf{25}^{4+}$ and threadlike species containing a tetrathiafulvalene unit, can be disassembled[93, 97] into their free components by oxidation of the tetrathiafulvalene unit to its radical cation with one equivalent of $Fe(ClO_4)_3$ in MeCN or aqueous solution. The one-electron-oxidized form of the TTF unit is stable in such conditions and can be reduced back to its neutral form by adding a stoichiometric amount of ascorbic acid. The reduction results in the insertion of the tetrathiafulvalene unit into the tetracationic cyclophane. Dethreading can also be achieved by adding *o*-chloroanil, which forms an adduct with the TTF unit. The addition of $Na_2S_2O_5$ in the presence of water results in the reduction of *o*-choroanil and the generation of the original pseudorotaxane.[97c] Such dethreading/rethreading processes can be easily monitored by UV/Vis absorption spectroscopy, since 1) the complex shows a broad absorption band with a maximum around 850 nm, which is ascribed to the charge-transfer interaction between the electron-rich tetrathiafulvalene unit and the electron-poor bipyridinium units of $\mathbf{25}^{4+}$, and 2) the neutral and cationic forms of the tetrathiafulvalene unit exhibit very different absorption features. Moreover, a system of this kind can serve as a basis for the construction of a supramolecular device in which it is possible—by means of chemical stimuli—to select which one of two guests enters (Figure 4) a macrocycle's cavity and to interchange reversibly the two guests.[93] Addition of the threadlike compound **26**, which contains a π-electron-rich

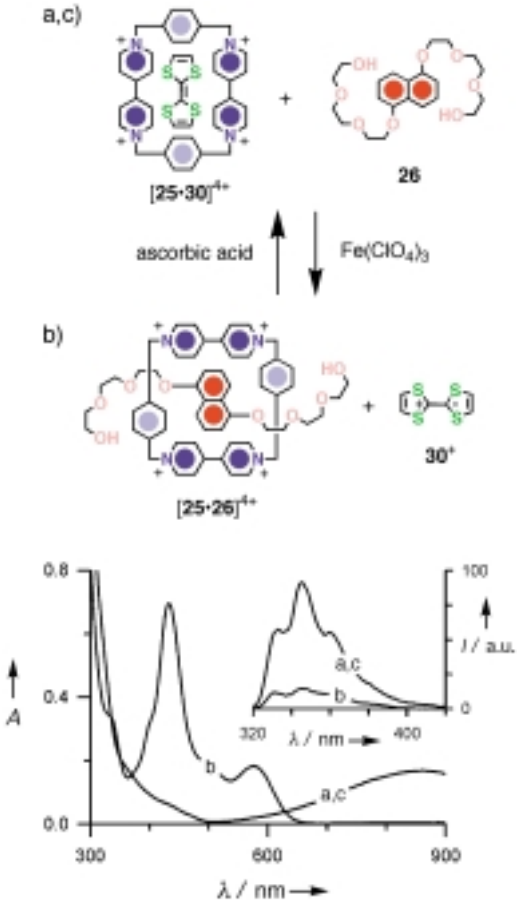
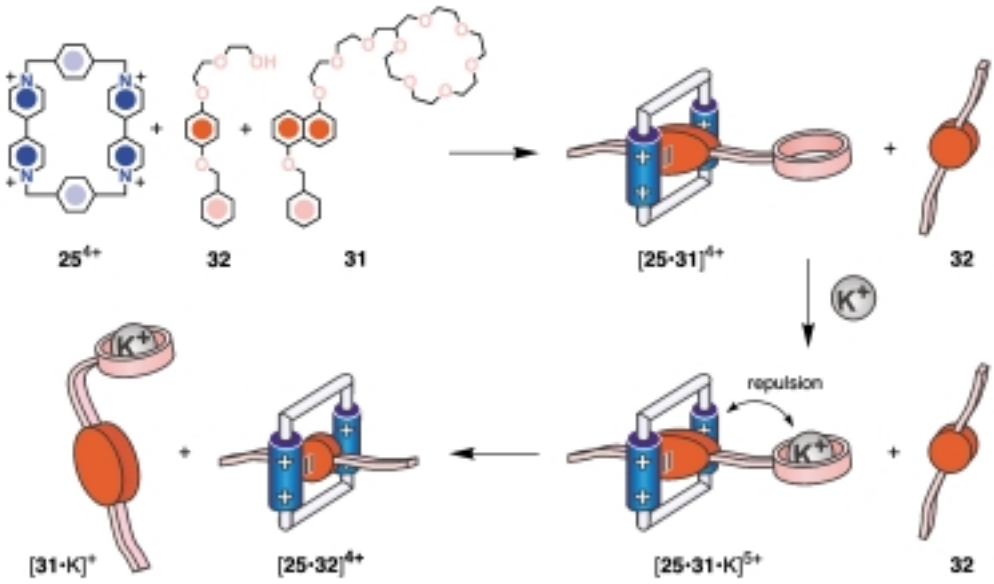



Figure 4. Top: the chemically induced interchange of guests **26** and **30** into the cavity of cyclophane $\mathbf{25}^{4+}$.[93] Bottom: absorption and (inset) fluorescence ($\lambda_{exc} = 295$ nm) spectra of a) a $5 \times 10^{-5}$ M aqueous solution (298 K) of $[\mathbf{25}\cdot\mathbf{30}]^{4+}$ and **26;** b) the same solution after addition of one equivalent of $Fe(ClO_4)_3$; c) solution b) after addition of one equivalent of ascorbic acid.

dioxynaphthalene unit, to an aqueous solution of the $[\mathbf{25}\cdot\mathbf{30}]^{4+}$ complex affects neither the charge-transfer absorption band characteristic of the complex nor the strong fluorescence band of the dioxynaphthalene-based thread (Figure 4, curves a), which indicate that this thread does not displace **30** from inside the macrocyclic host. On addition of a stoichiometric amount of $Fe(ClO_4)_3$ (with respect to **30**), the absorption bands of the radical cation $\mathbf{30}^{+}$ are formed, and the charge-transfer band of $[\mathbf{25}\cdot\mathbf{30}]^{4+}$ disappears, while the fluorescence band of the dioxynaphthalene-based species is substantially quenched (curves b). These results show that oxidation causes expulsion of $\mathbf{30}^{+}$ from $\mathbf{25}^{4+}$ and its replacement by the dioxynaphthalene-based thread. On subsequent addition of ascorbic acid, the system returns to its initial state (curves c).

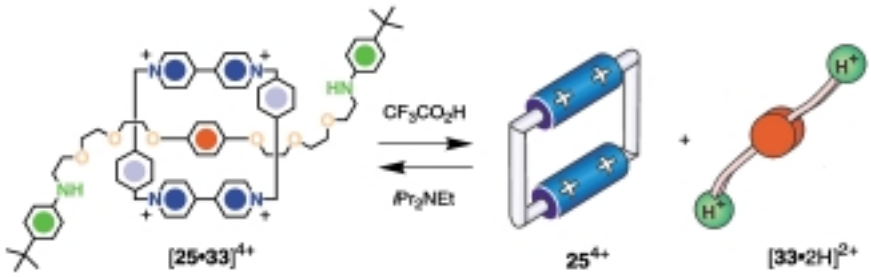



Scheme 22. The chemically controlled competition[99] in MeCN at 298 K between the two threadlike species **31** and **32** for the cavity of a tetracationic cyclophane $\mathbf{25}^{4+}$.

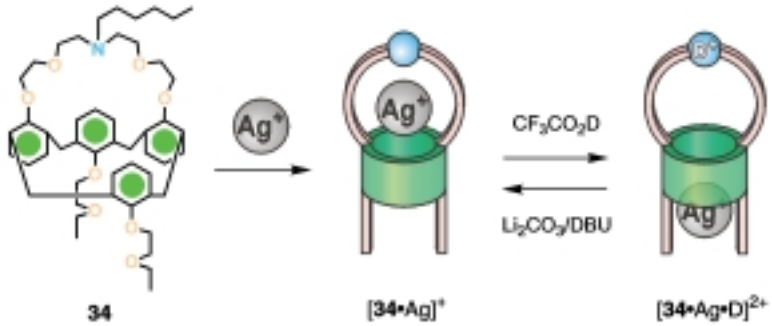
Recently, threadlike species containing both π-electron-acceptor and hydrogen-bonding recognition sites have been prepared and employed to generate[83c] multicomponent pseudorotaxanes of various stoichiometries that, in their turn, can be used to construct acid/base-controlled molecular machines that exhibit a complex pattern of dethreading/rethreading motions. Another way of controlling the association between the $\mathbf{25}^{4+}$ cyclophane and threadlike guests containing electron-donor units takes advantage of allosteric effects, that is, of the electrostatic repulsion that arises when a positive charge is created in the vicinity of the tetracationic cyclophane. For example, the pseudorotaxane composed of $\mathbf{25}^{4+}$ and a molecular thread which incorporates a dioxybenzene unit in its middle and is terminated at each end by [12]crown-4 rings is dethreaded[98] readily in MeCN upon addition of an excess of alkali metal salts, such as $NaPF_6$ or $LiPF_6$. These changes are a response to the electrostatic repulsion between the alkali metal cation within the [12]crown-4 macrocycles and the tetracationic cyclophane. The dethreading of the pseudorotaxane can be followed visually by the decrease in the intensity of the characteristic charge-transfer absorption band of the pseudorotaxane.

Such a strategy can be employed to design even more complex devices, where, not only the dethreading of the system, but also the replacement of a thread with another one can be controlled by chemical stimuli provided in the form of alkali metal cations. The [18]crown-6 derivative **31**, which carries a 1,5-dioxynaphthalene moiety, is a ditopic compound that can act (Scheme 22) as a host for alkali metal cations and as a guest for $\mathbf{25}^{4+}$, in this latter case, with the formation of a pseudorotaxane.[99] In MeCN, the $[\mathbf{25}\cdot\mathbf{31}]^{4+}$ species is not affected by the presence of the 1,4-dioxybenzene-containing thread **32**, while it dethreads upon addition of $K^+$ ions because of the electrostatic repulsions between the bound potassium cation and the $\mathbf{25}^{4+}$ tetracation and is then free to host the neutral thread **32** within its cavity, thus forming the pseudorotaxane $[\mathbf{25}\cdot\mathbf{32}]^{4+}$. Since the exchange of guests causes the color of the solution to change from purple to red-orange, this molecular machine can also be regarded as a metal-controlled chromophoric molecular switch. The exchange processes occurring in these supramolecular systems can also be monitored by $^1$H NMR spectroscopy.

Although the exploitation of electrostatic repulsion exerted by positive charges to dethread pseudorotaxanes is a promising strategy, if metal cations are used to provide such positive charges, then problems can be anticipated as far as the reversibility of the system is concerned because of the difficulty of removing the bound metal cations to achieve rethreading. For this reason, acid/base reactions are preferred because of their reversibility and simplicity. Quite recently,[100] the pseudorotaxane $[\mathbf{25}\cdot\mathbf{33}]^{4+}$, which comprises a dioxybenzene-containing thread **33** terminated by *tert*-butylaniline groups, has been self-assembled (Scheme 23) in solution. In this supramolecular system, protonation of the nitrogen atoms of the thread with $CF_3CO_2H$ results in the complete dethreading of the pseudorotaxane, as evidenced in both the absorption and $^1$H NMR spectra. Addition of $i\mathrm{Pr}_2\mathrm{NEt}$, which acts as a base, restores (Scheme 23) the original equilibrium and regenerates the pseudorotaxane. The acid-driven dethreading and base-induced rethreading processes can be repeated on the same solution without risk of degrading the participating species. Other intriguing acid/base switchable systems have been described in the recent literature. An interesting example[101] is the ingenuously designed prototype of the so-called "molecular syringe" **34** (Scheme 24), which uses a 1,3-alternate calix[4]arene as a π-basic tube that carries a nitrogen-containing crown cap on one side of the calixarene and two ethoxyethoxy groups on the other side. An $Ag^I$ ion,




Scheme 23. The base/acid-controlled dethreading/rethreading motions[100] of the pseudorotaxane $[\mathbf{25}\cdot\mathbf{33}]^{4+}$ in MeCN at 298 K.



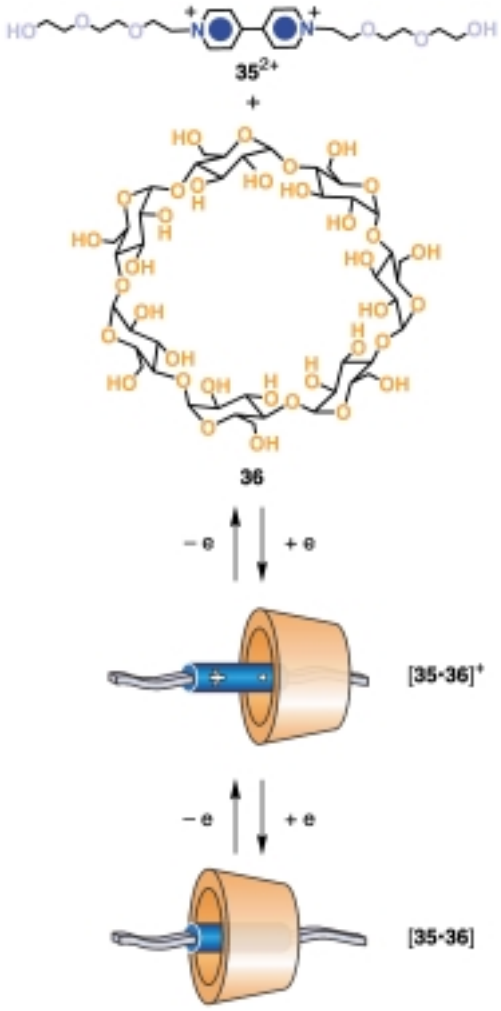

Scheme 24. The reversible acid/base-controlled metal pumping in a "molecular syringe" **34**,[101] designed from a 1,3-alternate calix[4]arene ($CD_2Cl_2/CD_3OD$ 4/1, 303 K). Conditions: protonation with $CF_3CO_2D$; deprotonation with $Li_2CO_3$/1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).

which is coordinated to the azacrown ether, is pushed through the tube to the side carrying the twin ethoxyethoxy groups when the nitrogen atom in the azacrown ether is protonated. On deprotonation of the nitrogen atom, the $Ag^I$ ion is sucked back through the middle of the calixarene once again.

### 3.1.2. Electrochemically Controllable Complexes

Redox processes have been used extensively to control molecular recognition.[10s,t, 11f,g, 102] Indeed, electrochemical stimulation represents a valuable tool for triggering host–guest interactions. Electrochemical techniques can be employed, not only to induce chemical or (co-)conformational changes in supramolecular systems, but also to probe their superstructures and organization. In other words, electrochemistry gives us a handle on both the input stimuli and the readout signals that are necessary for the operation of molecular machines.

A large number of inclusion complexes in which the association/dissociation of the components can be triggered by changing the oxidation state of the guest or the host have been investigated.[10s,t, 11f,g, 102] Some of the key features of such systems are 1) the presence of an electroactive unit in one component which exhibits reversible redox processes and 2) the effect of the other component on the electrochemical behavior of the component containing the electroactive unit. This second property allows the investigation of the complexation/decomplexation process by, for example, voltammetric techniques. Cyclodextrins are a class of hosts that are inactive electrochemically yet can form stable inclusion complexes with a variety of electroactive guests.[103] For example, it has been found[104] that, while bipyridinium-containing compounds in the dicationic forms (for example, $\mathbf{35}^{2+}$; Scheme 25) are not bound by $\beta$-cyclodextrin (**36**), they interact weakly with the cavity of this host when reduced to their monocationic forms, and give fairly stable pseudorotaxane complexes with **36** when they are finally reduced to their uncharged forms. Similar results have been found[105] for cobaltocenium derivatives, that do not

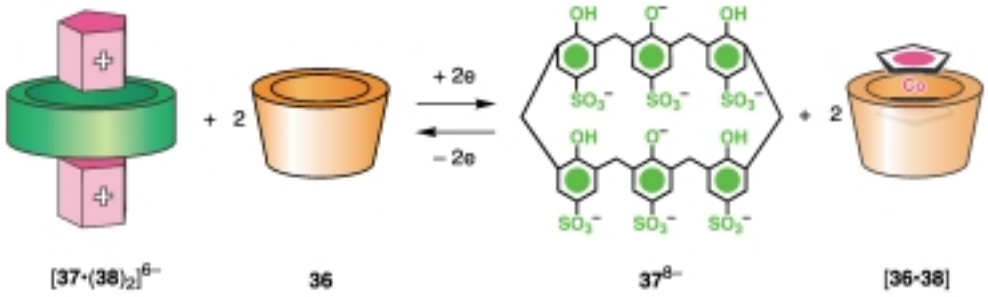



Scheme 25. The electrochemically induced threading/dethreading processes ($H_2O$, pH 7, 298 K)[104a] associated with the pseudorotaxane $[\mathbf{35}\cdot\mathbf{36}]^{2+}$.

interact with cyclodextrins, yet become good guests for inclusion in **36** upon one-electron reduction to yield the neutral cobaltocene. Ferrocene and its derivatives exhibit[106] the opposite behavior, that is, they are strongly bound in their most stable oxidation states, which correspond to uncharged species. When they are oxidized, they are not bound. These features have been exploited recently to construct dendrimers that display redox-controllable multisite complexation of **36**, since the dendrimers contain up to 16 ferrocene units[107] or up to 32 cobaltocenium units[108] on their peripheries. Such

dendrimers form very large supramolecular architectures that can be either broken apart or assembled upon oxidation of the ferrocene units[107] or upon reduction of the cobaltocenium units,[108] respectively.

Similar investigations have been carried out on calixarenes, another important class of redox-inactive receptors. It has been found[109] that the water-soluble calixarene hexasulfonate $\mathbf{37}^{8-}$ forms (Scheme 26) stable complexes with ferrocene




Scheme 26. Redox switching ($H_2O$, pH 7, 298 K)[109] between the complexes $[\mathbf{37}\cdot(\mathbf{38})_2]^{6-}$, which incorporate two cobaltocenium cations ($\mathbf{38}^+$) and one octaanionic calixarene $\mathbf{37}^{8-}$, and $[\mathbf{36}\cdot\mathbf{38}]$, which is composed of cobaltocene (**38**) and $\beta$-cyclodextrin (**36**).

and cobaltocene derivatives,[110] as well as with bipyridinium-based compounds.[111] However, in contrast with cyclodextrins, the binding to calixarenes such as $\mathbf{37}^{8-}$ becomes stronger on increasing the charge on the guest. This result has been exploited[110] to design a three-component supramolecular system where an electroactive guest can choose reversibly between two macrocyclic hosts, depending on its oxidation state.[112] The cobaltocenium cation ($\mathbf{38}^+$) gives a strong 2:1 complex with $\mathbf{37}^{8-}$, even in the presence of an excess of **36**. However, reduction of the cobaltocenium guests leads (Scheme 26) to their inclusion in **36** and subsequent oxidation back to the monocation affords the initial complex.

Unlike cyclodextrins and calixarenes, the cyclophane $\mathbf{39}^{2-}$ is electroactive[113] and was one of the early examples (Scheme 27) of redox-switchable macrocyclic receptors. In-


Scheme 27. Redox switching ($H_2O$, pH 10, 298 K)[113] between the complexes $[\mathbf{39}\cdot\mathbf{40}]^{2-}$ and $[\mathbf{39}\cdot\mathbf{40}]^{3-}$ in which the naphthalene ring system (**40**) is located "alongside" the macrocyclic cavity of $\mathbf{39}^{2-}$ and "inside" that of $\mathbf{39}^{3-}$, respectively.

terestingly, this host in its oxidized form interacts with naphthalene (**40**) in an "alongside" fashion: however, upon two-electron reduction of its isoalloxazine moiety, the binding mode of naphthalene changes and an inclusion complex is formed.

Inorganic systems capable of exhibiting a redox-driven linkage isomerism resulting in molecular hysteresis are known.[114] Electrochemically driven cation[115] and anion[116] translocations have also been reported. Translocation of $Cl^-$ or $NCO^-$ ions has been achieved[116a] in a system consisting of a tripodal tetramine subunit (tris(2-aminoethyl)amine, tren) and a tetramine macrocyclic ring (1,4,8,11-tetraazacyclotetradecane, cyclam), covalently linked by a 1,4-xylyl spacer. When $Cu^{II}$ occupies the tren center and $Ni^{II}$ the cyclam ring, the $X^-$ anion is coordinated to the $Cu^{II}$ center. However, upon oxidation of $Ni^{II}$ to $Ni^{III}$, the $X^-$ anion moves to the $Ni^{III}$ coordinating center. This redox-driven anion translocation, which is intramolecular in nature, is fast and fully reversible.

One of the most extensively studied receptors in recent years has been the cyclophane $\mathbf{25}^{4+}$. It constitutes[26h] a very efficient host for a wide variety of $\pi$-electron-donating guests. Since it is redox active,[117] its binding ability can be subjected to electrochemical control. The tetracationic cyclophane $\mathbf{25}^{4+}$ shows two bielectronic reduction processes, the first one corresponding to the uptake of the first electron by each of the equivalent bipyridinium units and the second one to the subsequent reduction of radical cations to neutral units. In general, when an electron-donor unit is located inside the cavity of the cyclophane, the half-wave potential associated with the first reduction process is shifted to more negative values, as a consequence of the charge-transfer interactions with the two bipyridinium groups of $\mathbf{25}^{4+}$ which stabilize[11g, 97, 117, 118] the complex. The fact that this cyclophane exhibits another reduction process at more negative potentials is very important since it can be used to monitor the occurrence of decomplexation induced[10t, 11g] by the first two-electron reduction. For example, in the presence of an excess of a threadlike compound composed of a polyether chain containing one 1,4-dioxybenzene ring the potential value for the first bielectronic reduction of $\mathbf{25}^{4+}$ is shifted cathodically, while the second reduction process is practically unaffected.[117] This observation is consistent with 1) formation of a [2]pseudorotaxane between the cyclophane and the thread and 2) dethreading of the [2]pseudorotaxane upon two-electron reduction of the $\mathbf{25}^{4+}$ host, so that the second two-electron reduction process reflects that of the free host. The occurrence of the dethreading process is not surprising because reduction of the electron-acceptor component weakens the charge-transfer interaction that helps to hold the components of the supramolecular architecture together. Since all these processes are reversible, oxidation of **25** back to the tetracationic form affords the original [2]pseudorotaxane. In principle, it should be possible to obtain useful information on the occurrence of dethreading/

rethreading processes from the electrochemical behavior of the guest; however, the poor reversibility of the oxidation process associated with a 1,4-dioxybenzene ring prevents the use of this type of control. More interesting are [2]pseudorotaxanes wherein both the cyclophane and thread components exhibit chemically reversible redox processes, as in the case of the complex $[\mathbf{25}\cdot\mathbf{30}]^{4+}$ of tetrathiafulvalene (**30**) with $\mathbf{25}^{4+}$ [97a, 118b] and related [2]pseudorotaxanes.[97] This improvement in design not only permits the monitoring of the formation of the supramolecular species, by studying both the reduction of the electron-acceptor component and the oxidation of the electron-donor one, but it also provides a dual mode (reductive and oxidative) of control on the dethreading/rethreading process. The molecular thread **41**, obtained by adorning a tetrathiafulvalene unit with two polyether chains (Figure 5), forms[97a] a very stable ($K_a = 5 \times 10^5\,\text{M}^{-1}$ in MeCN) [2]pseudorotaxane with $\mathbf{25}^{4+}$. Although the TTF unit in **41** retains the same electron-donor power of free tetrathiafulvalene, as revealed by comparing their voltammograms, the $K_a$ value for the complex $[\mathbf{25}\cdot\mathbf{41}]^{4+}$ is 50 times higher than that for the complex $[\mathbf{25}\cdot\mathbf{30}]^{4+}$, which indicates that the presence of the polyether chains strengthens the association because of the hydrogen bonding between the oxygen atoms in the chain and the hydrogen atoms in the $\alpha$-positions with respect to the nitrogen atoms of the bipyridinium units. This cooperative interaction is extremely important in improving the on/off switching. It has been shown[97a] that reversible dethreading/rethreading cycles of the complex $[\mathbf{25}\cdot\mathbf{41}]^{4+}$ (as well as of $[\mathbf{25}\cdot\mathbf{30}]^{4+}$) can be performed either 1) by oxidation and successive reduction of the electron-donating thread or 2) by reduction and successive oxidation of the electron-accepting cyclophane. Such processes are accompanied by pronounced spectral differences (Figure 5) that can be followed easily by the naked eye since the solution changes color from the emerald green typical of the pseudorotaxane to either brown or deep blue upon oxidative or reductive dethreading, respectively. This unique behavior makes this system appealing for the construction of electrochromic display devices and, since its input(electrochemical)/output(color) characteristics correspond to those of the XNOR (eXclusive NOR) logic operation,[97a] for the design of molecular-level logic gates.[94, 95] Moreover, the voltammetric behavior on oxidation of this system is scan-rate dependent,[119] which indicates that the dethreading/rethreading processes (Figure 5) associated with the redox steps take place on the timescale of the electrochemical experiment.[120]

The supramolecular complex composed (Scheme 28) of the enlarged tetracationic cyclophane $\mathbf{42}^{4+}$ and the ferrocene-based thread **43** has been studied[121] recently with the aim of developing new dual-mode switchable systems. This tetracation is an electron-acceptor cyclophane related to $\mathbf{25}^{4+}$; however, while the cavity of $\mathbf{25}^{4+}$ is ideal for accommodating aromatic rings, that of $\mathbf{42}^{4+}$ is perfect[122] for hosting ferrocene as a guest. It has been found[121] by means of absorption and electrochemical experiments that the $[\mathbf{42}\cdot\mathbf{43}]^{4+}$ complex, which interestingly does not adopt a pseudorotaxane geometry, can be dethreaded reversibly (Scheme 28) either by oxidation/reduction of the ferrocene unit of **43** or by reduction/oxidation of the bipyridinium units of $\mathbf{42}^{4+}$.

Very recently, a three-component supramolecular system composed (Scheme 29) of tetrathiafulvalene (**30**), which can exist in three stable forms—namely, **30**, $\mathbf{30}^{+}$, and $\mathbf{30}^{2+}$—and two hosts, specifically the π-electron-accepting cyclophane ($\mathbf{25}^{4+}$) and the π-electron-donating crown ether **28**, has been investigated.[123] In its role as an electron donor, **30** forms a 1:1 inclusion complex with $\mathbf{25}^{4+}$ which can be dissociated/reasso-

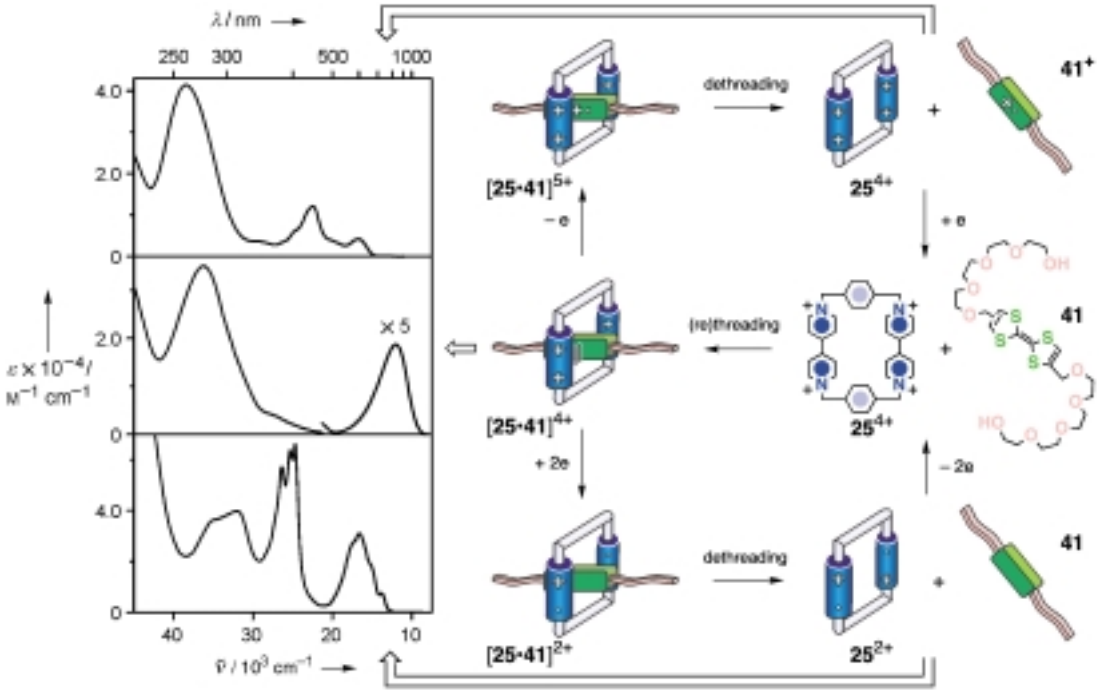
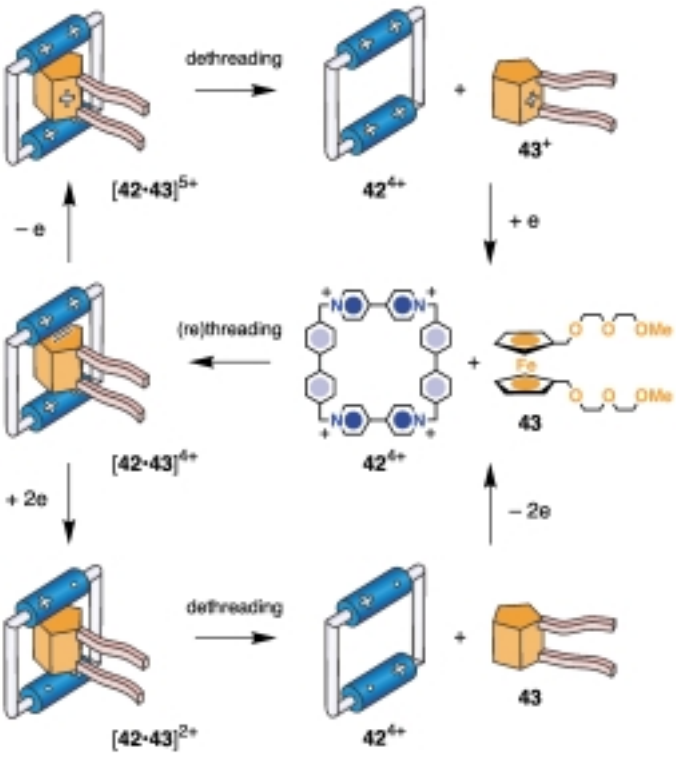
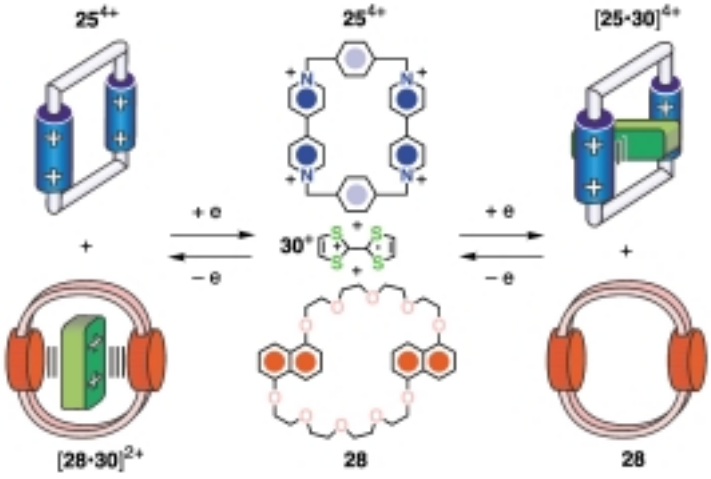



Figure 5. The electrochemically induced dethreading/rethreading processes[97a] associated with the pseudorotaxane $[\mathbf{25}\cdot\mathbf{41}]^{4+}$ and the absorption spectra recorded (MeCN, 298 K) before (center) and after oxidation (top) or reduction (bottom).




Scheme 28. The decomplexation/recomplexation of the inclusion complex $[\mathbf{42}\cdot\mathbf{43}]^{4+}$ upon electrochemical reduction or oxidation (MeCN, 298 K).[121]

ciated reversibly by cyclic oxidation/reduction of **30**,[97a, 118b] while $\mathbf{30}^{2+}$ acts[123] as a π-electron acceptor to give a 1:1 inclusion complex ($K_a = 4 \times 10^3\,\text{M}^{-1}$ in MeCN at 298 K) with **28**. By contrast, $\mathbf{30}^{+}$ is not bound by either of the two hosts. When the electrochemical potential applied to the solution becomes more positive than about +0.4 V versus SCE **30** is oxidized to the radical cation and the $[\mathbf{25}\cdot\mathbf{30}]^{5+}$ complex disassembles, to give three essentially noninteracting species. Further one-electron oxidation of $\mathbf{30}^{+}$ to $\mathbf{30}^{2+}$ at potentials more positive than about +0.7 V versus SCE leads to the insertion of the dication into the cavity of **28**. Since both

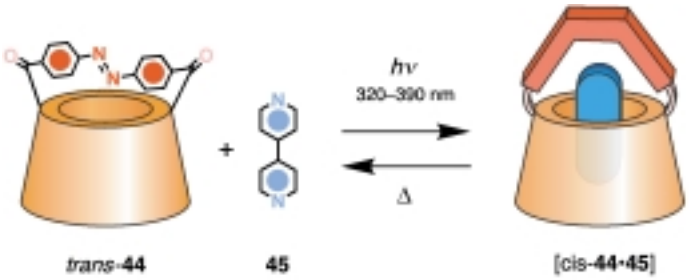



Scheme 29. Redox switching (MeCN, 298 K)[123] between the complexes $[\mathbf{28}\cdot\mathbf{30}]^{2+}$, which incorporates the macrocyclic polyether **28** and the dication $\mathbf{30}^{2+}$, and $[\mathbf{25}\cdot\mathbf{30}]^{4+}$, which is composed of the tetracationic cyclophane $\mathbf{25}^{4+}$ and tetrathiafulvalene (**30**).

oxidized forms of **30** are stable, the initial state can be restored by subsequent reduction. This system can therefore be switched[124] reversibly between three distinct states by exercizing electrochemical control over the guest behavior of **30**. The fact that the three states have different colors, coupled with the ease of their electrochemical interconversion, renders this supramolecular system suitable for electrochromic applications; moreover, the system could form the basis for the construction of molecular devices in which energy- or electron-transfer processes between selected components can be controlled.[123] This investigation, along with others discussed in this review, suggests that carefully designed molecular machines could be employed to perform[10y] a variety of valuable functions that go far beyond the molecular motions they display.

### 3.1.3. Photochemically Controllable Complexes

Stimulation by light is arguably the most interesting and promising way to control the formation/disruption of supramolecular complexes in a machinelike fashion. Photons, like electrons, can be exploited,[11d,e] both for causing the changes ("writing") in chemical systems and for monitoring ("reading") their states. In general, the systems of this type that have been reported so far can be subdivided into those based on photoisomerizations, and those relying on photoinduced electron-transfer processes.




Scheme 30. The photoinduced inclusion[128] of 4,4′-bipyridine (**45**) inside the cavity of the azobenzene-capped β-cyclodextrin derivative **44** ($H_2O$, pH 7.2, 298 K). The 4,4′-dicarbonylazobenzene unit is attached to two of the primary oxygen atoms of the β-cyclodextrin derivative.

Photoisomerizations, particularly the well-known[125] reversible *cis*/*trans* photoisomerization of the azobenzene group, have long been used[3, 62–74, 126, 127] to exert photocontrol on chemical systems. The azobenzene-capped β-cyclodextrin **44** (Scheme 30) cannot bind[128] 4,4′-bipyridine (**45**) at all when the azobenzene group is in the *trans* form: its conversion to the *cis* isomer, upon irradiation with UV light, leads to the inclusion ($K_a \approx 500\,\text{M}^{-1}$ in aqueous solution at 298 K) of **45** into the expanded cavity of *cis*-**44**, as indicated by circular dichroism studies. The reversion to the *trans* isomer, with subsequent ejection of the guest, takes place (Scheme 30) in the dark. Azobenzene-containing compounds can also act as photocontrollable guests. For example, the *trans* form of *p*-(phenylazo)benzoate is bound[129] by β-cyclodextrin (**36**) more strongly than the *cis* isomer in aqueous solution. The different affinity has been ascribed to the fact that the "stretched",

threadlike structure of the *trans*-azobenzene group fits the cavity of **36** better than the elbow-shaped *cis* isomer. This observation has been exploited to trigger the catalytic activity of **36** in ester hydrolysis, since the cavity of **36** can be made available to the substrate upon light-driven expulsion of the azobenzene guest.

Threadlike species containing a π-electron-rich azobiphenoxy unit have been used[130] (Figure 6), in conjunction with electron-accepting hosts such as $\mathbf{25}^{4+}$ or $\mathbf{46}^{4+}$, to obtain charge-

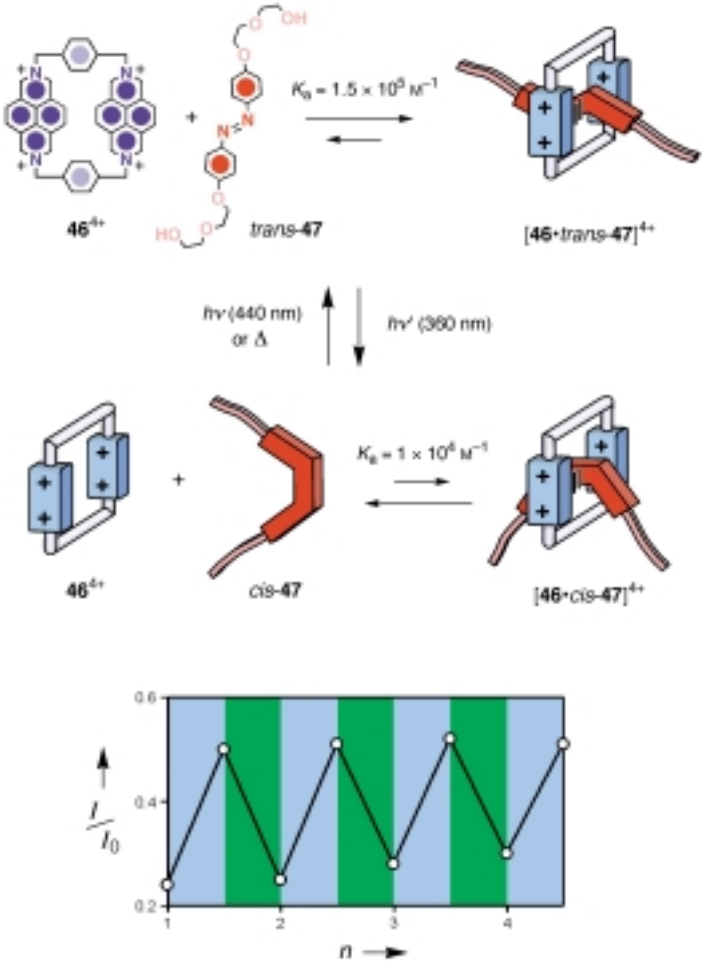
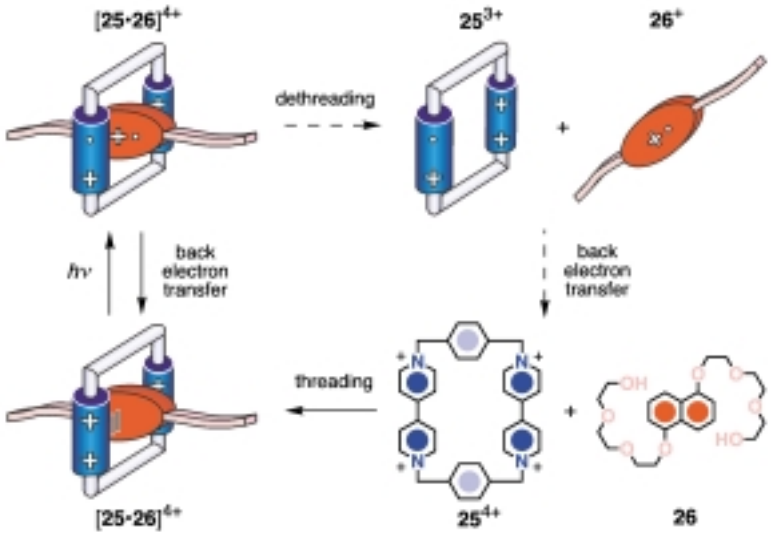



Figure 6. The change in intensity of the luminescence ($\lambda_{exc} = 411$ nm) associated[133] with the tetracationic cyclophane $\mathbf{46}^{4+}$ for an equimolar solution ($1 \times 10^{-4}$ M, MeCN, 298 K) of $\mathbf{46}^{4+}$ and **47** upon consecutive *trans* → *cis* (irradiation at 365 nm, cyan areas) and *cis* → *trans* (irradiation at 436 nm and rest in the dark, green areas) isomerization cycles. $I_0$ is the luminescence intensity of the tetracationic cyclophane $\mathbf{46}^{4+}$ in the absence of the guest under otherwise identical experimental conditions.

transfer complexes with pseudorotaxane geometries. Indeed, the compound *trans*-**47** self-assembles with $\mathbf{25}^{4+}$ to give[130] a pseudorotaxane ($K_a = 470$ M$^{-1}$ in MeCN at 298 K) both in solution and in the solid state, as shown by $^1$H NMR spectroscopy and X-ray crystallography, respectively. On irradiation at 360 nm of an equimolar MeCN solution of $\mathbf{25}^{4+}$ and *trans*-**47**, which are in part associated to give a pseudorotaxane superstructure, the N=N bond isomerizes to the *cis* form and the pseudorotaxane dethreads. The *trans* isomer of the guest can be reformed and, as a result, rethreads inside the cyclophane either on irradiation at 440 nm or by warming the solution in the dark. These photoinduced dethreading/rethreading motions have been monitored by $^1$H NMR spectroscopy and by careful photochemical studies, which have also shown that the photoisomerization efficiency of *trans*-**47** is reduced considerably when it is encircled by the tetracationic cyclophane. It is not clear[131] whether such a decreased photoreactivity, as well as the lower affinity of *cis*-**47** for $\mathbf{25}^{4+}$, is a consequence of steric or electronic effects. Because of its excellent reversibility, a system of this type is of considerable potential interest for the development of molecular machines featuring photoinduced dethreading/rethreading motions. However, the efficiency of the self-assembly of the molecular components needs to be improved. For this purpose, the cyclophane $\mathbf{46}^{4+}$, in which the bipyridinium units have been replaced (Figure 6) by the more effective[93, 94, 132] π-electron-accepting 2,7-diazapyrenium units, has been used instead of $\mathbf{25}^{4+}$ as a host for *trans*-**47**. Moreover, since the 2,7-diazapyrenium unit shows highly characteristic absorption and luminescence bands, $\mathbf{46}^{4+}$ provides additional readout signals for the system. In fact, $\mathbf{46}^{4+}$ self-assembles[133] very efficiently ($K_a = 1.5 \times 10^5$ M$^{-1}$ in MeCN at 298 K) with the *trans* isomer of **47**, but it also interacts with the *cis* form ($K_a = 1 \times 10^4$ M$^{-1}$ under the same conditions). The photochemical and chemical processes occurring in this system are schematized in Figure 6. Although it is clear that irradiation with light does not lead to 100% dethreading, these photocontrolled dethreading/rethreading motions can be followed easily by absorption and luminescence spectroscopy: the diagram in Figure 6 shows the changes in the fluorescence intensity characteristic of the uncomplexed macrocycle $\mathbf{46}^{4+}$ upon repeated *trans* → *cis* and *cis* → *trans* isomerization cycles of the thread **47**.

We now focus on complexes, such as $[\mathbf{25} \cdot \mathbf{26}]^{4+}$ (Scheme 31), which are primarily stabilized by π-electron-donor/acceptor interactions. In most cases, these interactions introduce new energy levels that cause[57, 92–94, 97–100, 117a, 123] the appearance of charge-transfer absorption bands, often in the visible region of the spectrum. Excitation in these bands leads formally to the transfer of an electron from the donor to the acceptor component and is therefore expected to destabilize the charge-transfer interaction responsible for self-assembly. Furthermore, in some cases, the photoinduced electron transfer leads to the formation of charges of the same sign that repel each other and so contribute to forcing the molecular components apart. This simple approach, however, is precluded by the fact that the back electron transfer, that is, the deactivation of the charge-transfer excited state to the ground state, is much faster than the separation of the molecular components, a process which requires[134] extended nuclear motions and solvation processes. In some particular cases,[135] laser flash photolysis experiments have been interpreted as indicating the dissociation of a small fraction of the irradiated complex.

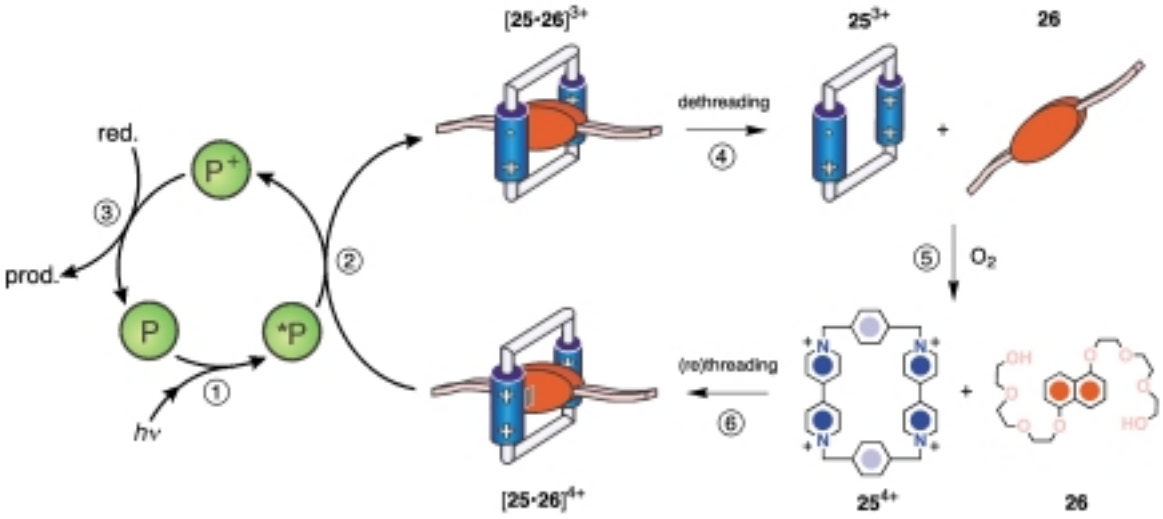
In order to achieve light-induced dethreading of the $[\mathbf{25} \cdot \mathbf{26}]^{4+}$ complex, a different approach was devised[57, 134a] which was based on the use (Scheme 32) of an external electron-transfer photosensitizer (P) and a reductant scavenger (red.) species. The photosensitizer must be able to 1) absorb light



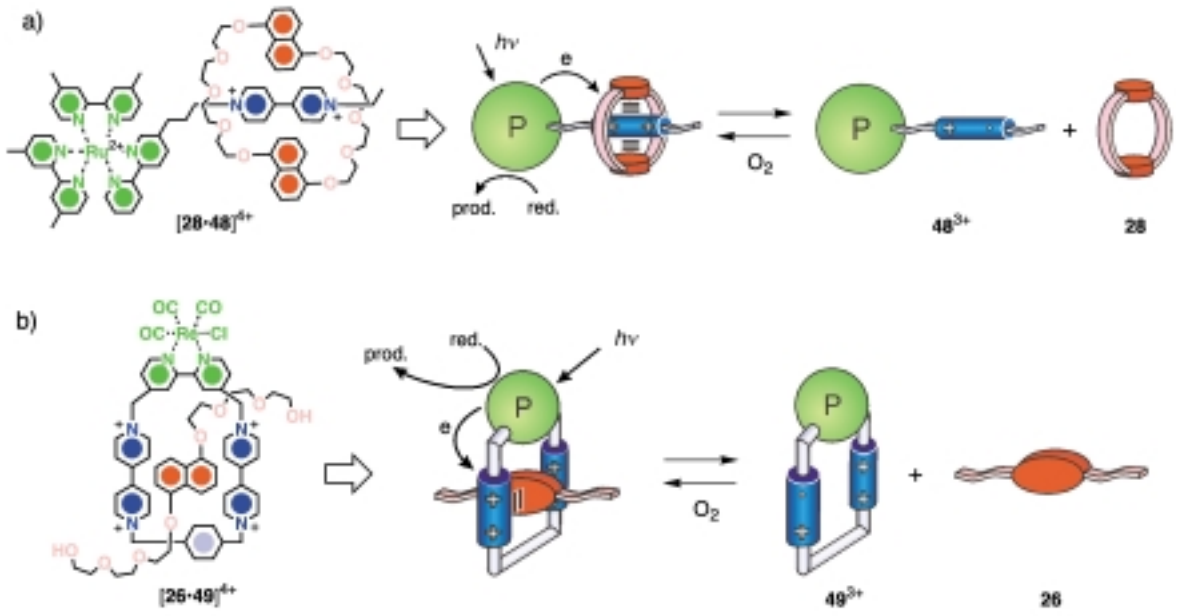

Scheme 31. The photochemical processes associated with the pseudorotaxane $[\mathbf{25}\cdot\mathbf{26}]^{4+}$ upon excitation in its charge-transfer absorption band.[57, 134a] The processes indicated by dashed arrows are unlikely to occur (see text).

efficiently and 2) have a sufficiently long-lived and reductant excited state so that its irradiation by light (process 1) in the presence of the pseudorotaxane will lead (process 2) to the transfer of an electron to a bipyridinium unit of the cyclophane. The relatively fast back electron transfer from the reduced cyclophane component to the oxidized photosensitizer is prevented by the reductant which, if present in a sufficient amount ($>10^{-2}$ M), intercepts the oxidized photosensitizer and regenerates (process 3) the original photosensitizer. Good candidates for the role of photosensitizer are 9-anthracenecarboxylic acid[136] and metal complexes[137] such as $[Ru(bpy)_3]^{2+}$ (bpy = 2,2′-bipyridine), while efficient reductant scavengers are triethanolamine and polycarboxylate anions (for example, oxalate).[138] Under these conditions, the persistent reduction of a bipyridinium unit of $\mathbf{25}^{4+}$ is achieved and the pseudorotaxane dethreads (process 4), as evidenced by absorption spectral changes and, more importantly, by the increase in the intensity of the 1,5-dioxynaphthalene fluorescence, which can only originate from free **26**. Oxygenation of the solution—from which $O_2$ was initially removed—reoxidizes the cyclophane back (process 5) to the tetracationic form, thereby promoting rethreading (process 6) with **26** as shown by the absorption and luminescence spectra.

This strategy has been extended recently to second-generation pseudorotaxanes in which the metal-complex photosensitizer, which can also be called a "light-fueled" motor, has been incorporated (Scheme 33) either into the thread[139] or into the ring[140] component.[141] The construction of these "integrated" pseudorotaxanes is not an easy task and so careful design is of paramount importance before embarking on sometimes time-consuming and demanding synthetic work. The successful operation of such a molecular machine is the result of 1) the appropriate choice of the functional units and 2) their covalent linking into the thread and ring components in order to achieve the correct integration of functions—for example, receptor ability, redox features, photophysical properties—and sequence of processes—for example, electron-transfer processes—as well as the lack of interference between the units. As in the case of the molecular machine shown in Scheme 32, the dethreading and rethreading motions of the pseudorotaxanes represented in Scheme 33 can be triggered by irradiation with visible light and oxygenation of the solution, respectively. The motions can also be easily monitored by means of UV/Vis absorption and luminescence spectroscopy. Once again, the most important readout signal is the intensity of the 1,5-dioxynaphthalene fluorescence associated with the free ring **28** (Scheme 33a) or




Scheme 32. The photochemically induced dethreading (MeCN or $H_2O$, room temperature) of the pseudorotaxane $[\mathbf{25}\cdot\mathbf{26}]^{4+}$, based on the use of the external photosensitizer P (9-anthracenecarboxylic acid) and the reductant scavenger (red. = triethanolamine). Rethreading occurs upon oxygenation of the solution.[57, 134a]



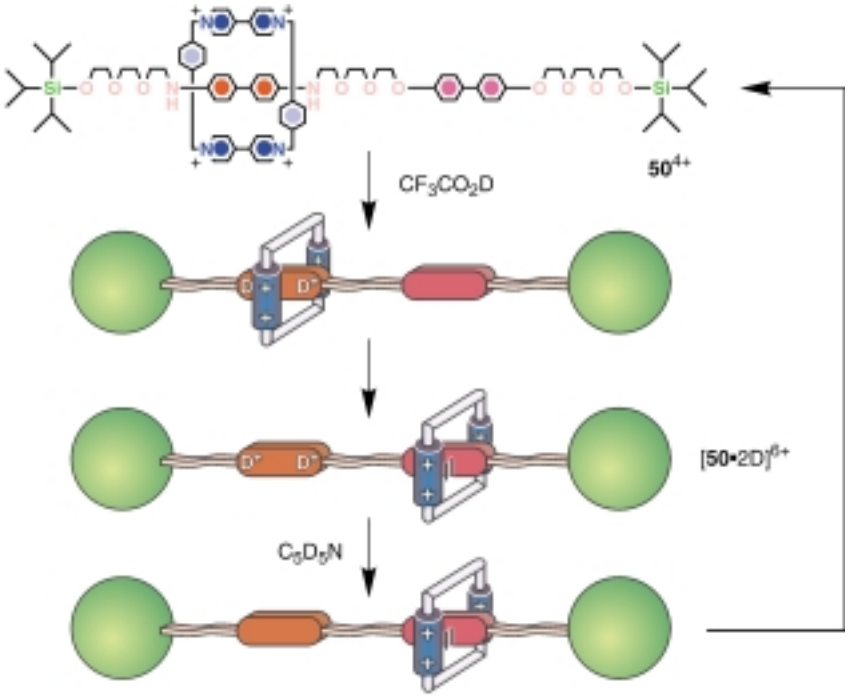

Scheme 33. Photocontrollable molecular machines based on pseudorotaxanes.[139, 140] In these second-generation systems the "light-fueled" motor (namely, the photosensitizer) is part of the acyclic and of the macrocyclic components of $[\mathbf{28}\cdot\mathbf{48}]^{4+}$ and $[\mathbf{26}\cdot\mathbf{49}]^{4+}$, respectively. Triethanolamine (red.) is the reductant scavenger. Conditions: a) EtOH, 298 K; b) $H_2O$, 298 K.

free thread **26** (Scheme 33b) components. It is worth noting that through a repeated sequence of deoxygenation and irradiation followed by oxygenation many dethreading/rethreading cycles can be performed on the same solution without any appreciable loss of signal until most of the reductant scavenger is consumed. It should also be stressed that systems which rely on this photosensitizer-scavenger strategy produce "waste" species from the decomposition of the reductant scavenger. In this regard, the search for efficient molecular machines exploiting "clean", reversible photochemical reactions—in other words, machines which use only light as an energy supply—is of fundamental importance.

## 3.2. Molecular Shuttles

### *3.2.1. Chemically Controllable Molecular Shuttles*

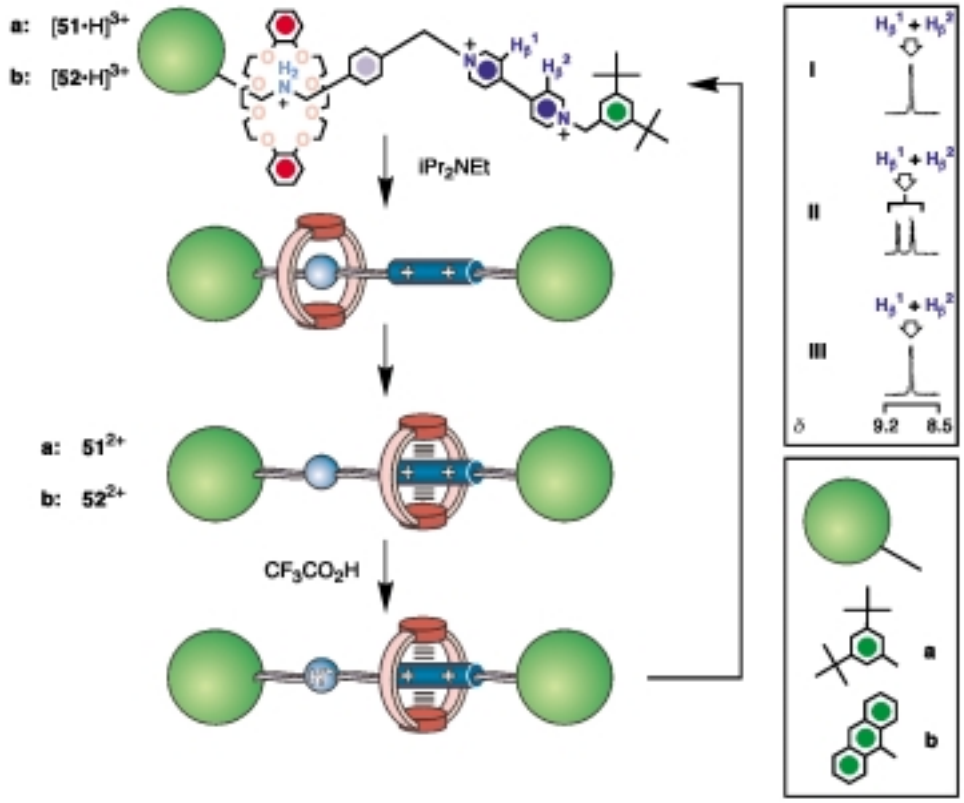
The [2]rotaxane $\mathbf{50}^{4+}$ incorporates (Scheme 34) a π-electron-deficient macrocycle and a π-electron-rich dumbbell.[142] In solution the macrocycle resides around the benzidine or the biphenol recognition site. The two co-conformations are stabilized by π–π stacking interactions between the bipyridium units of the macrocycle and the sandwiched π-electron-rich recognition site of the dumbbell, as a well as by C–H···O interactions between the α-bipyridinium hydrogen atoms and the polyether oxygen atoms. The $^1$H NMR spectrum ($CD_3CN$, 229 K) of this [2]rotaxane shows distinct signals for the two co-conformations. The ratio between them is 84:16 in favor of the isomer having the benzidine unit inside the cavity of the macrocycle. This selectivity is a result of the relative binding affinity[118a] of the tetracationic cyclophane for the two π-electron-rich recognition sites. The association constant for a complex formed between the tetracationic cyclophane and a model benzidine guest is one order of magnitude higher than




Scheme 34. The shuttling of the macrocyclic component of $\mathbf{50}^{4+}$ along its dumbbell-shaped component can be controlled[142] chemically or electrochemically in $CD_3CN$ at 229 K by protonating/deprotonating or oxidizing/reducing the benzidine unit.

that for an equivalent complex incorporating a biphenol guest. The addition (Scheme 34) of $CF_3CO_2D$ to a solution of the [2]rotaxane in $CD_3CN$ results in protonation of the benzidine unit. As a result, the tetracationic cyclophane shuttles away from the newly formed dicationic unit to encircle exclusively the biphenol recognition site in $[\mathbf{50}\cdot 2D]^{6+}$. Consistently, the $^1H$ NMR spectrum shows only the signals of the isomer having the biphenol recognition site inside the cavity of the tetracationic cyclophane. Upon addition of $C_5D_5N$, the benzidine recognition is deprotonated and the original equilibrium between the two co-conformations is restored.

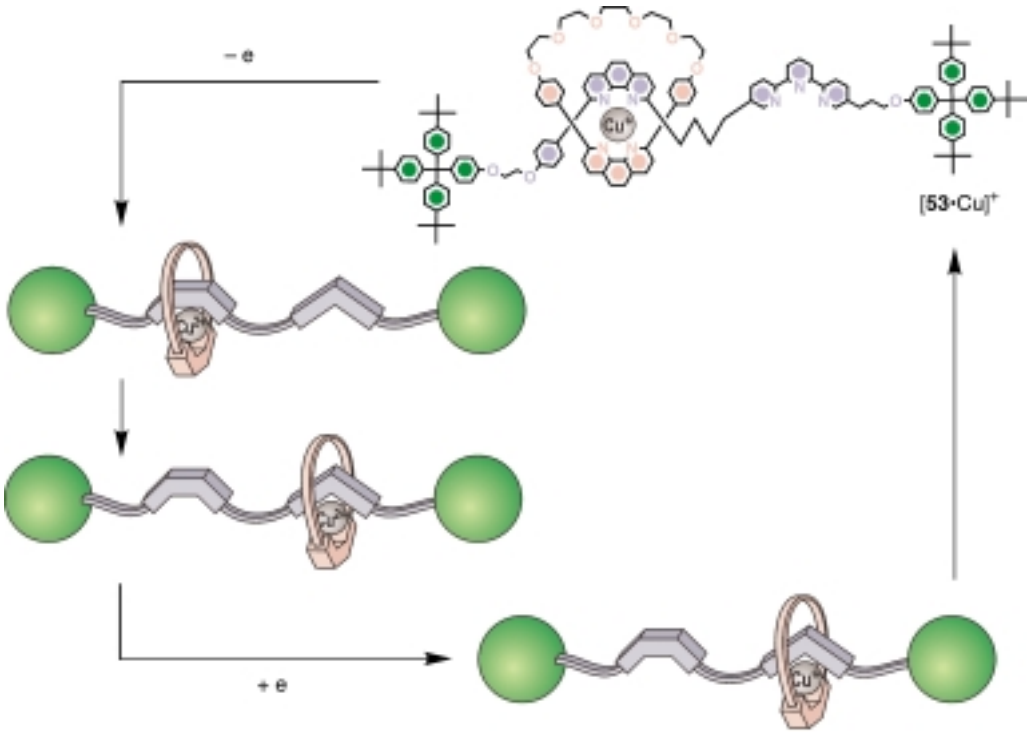
The [2]rotaxanes $[\mathbf{51}\cdot H]^{3+}$ and $[\mathbf{52}\cdot H]^{3+}$ incorporate (Scheme 35) a dialkylammonium and a bipyridinium recognition site in their dumbbell-shaped components.[143] Gradient-enhanced NOE spectroscopy demonstrated that the macrocycle resides exclusively around the ammonium recognition site in $(CD_3)_2CO$ at 298 K. Indeed, irradiation of the *p*-phenylene protons adjacent to the ammonium recognition site showed NOEs for some of the $CH_2O$ protons of the macrocycle. Similar effects were observed when the protons of the stopper adjacent to the ammonium recognition site were irradiated. The preference of the macrocycle for the ammonium recognition site is a result of a combination of $^+N-H\cdots O$ and $C-H\cdots O$ interactions between the $CH_2NH_2^+$ hydrogen atoms of the dumbbell and the oxygen atoms of the macrocycle. Upon addition (Scheme 35) of an excess of *i*$Pr_2NEt$ to a solution of one of these [2]rotaxanes in $(CD_3)_2CO$, deprotonation of the ammonium recognition site occurs. As a result, the intercomponent hydrogen bonds are destroyed and the macrocycle shuttles to the bipyridinium recognition site in $\mathbf{51}^{2+}$ and $\mathbf{52}^{2+}$. However, the original co-conformation is restored after the addition of $CF_3CO_2H$, since the protonation of the ammonium recognition site is followed by the shuttling of the macrocycle back to encircle the $NH_2^+$ center. The shuttling process can be followed by $^1H$ NMR spectroscopy by employing the bipyridinium protons $H_\beta^1$ and $H_\beta^2$ as probes. The $^1H$ NMR spectrum ($(CD_3)_2CO$, 298 K) of $[\mathbf{51}\cdot H]^{3+}$ shows (signal I in Scheme 35) a single resonance for the protons $H_\beta^1$ and $H_\beta^2$. After deprotonation of the ammonium recognition site, the macrocycle shuttles to the bipyridinium recognition site and two distinct resonances can be observed (signal II) for the protons $H_\beta^1$ and $H_\beta^2$. Once the ammonium group is regenerated after protonation, the macrocycle shuttles back to encircle this recognition site and the original signal for the protons $H_\beta^1$ and $H_\beta^2$. is restored (signal III). The movement of the ring can be also monitored by electrochemical techniques.




Scheme 35. The chemically controllable[143] molecular shuttles $[\mathbf{51}\cdot H]^{3+}$ and $[\mathbf{52}\cdot H]^{3+}$ and the $^1H$ NMR spectra ($(CD_3)_2CO$, 298 K) of $[\mathbf{51}\cdot H]^{3+}$ recorded before (I) and after the addition of *i*$Pr_2NEt$ (II), and after the addition of $CF_3CO_2H$ (III).

### *3.2.2. Electrochemically Controllable Molecular Shuttles*

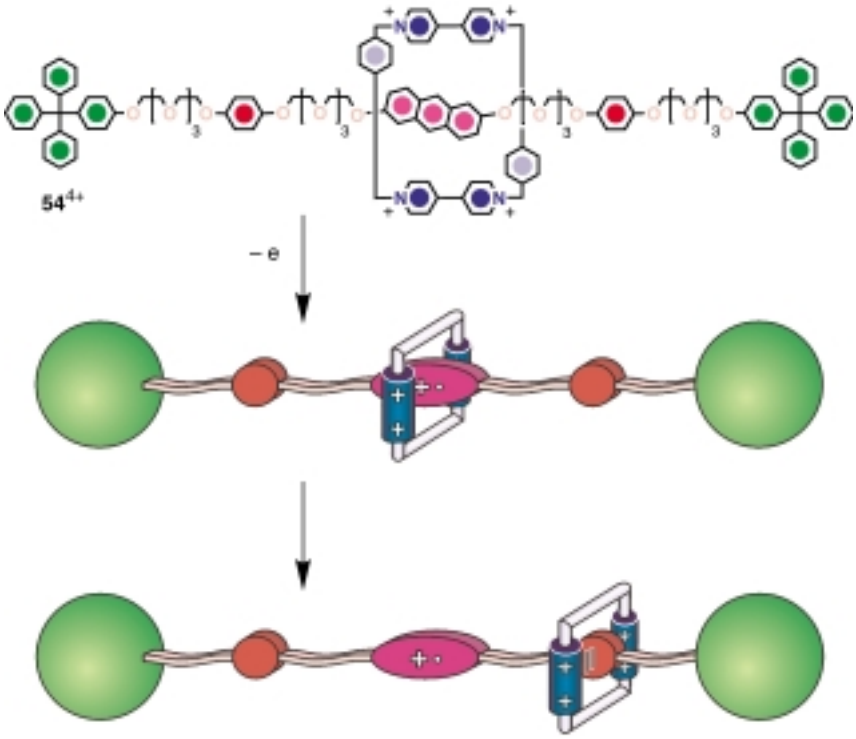
The shuttling of the macrocyclic component of [2]rotaxane $\mathbf{50}^{4+}$ along the linear portion of its dumbbell-shaped component can be also controlled[142, 144] (Scheme 34) electrochemically. Indeed, the benzidine recognition site undergoes two consecutive one-electron oxidations.[118a] Comparison of the half-wave potentials of the [2]rotaxane with those of a model compound incorporating a benzidine unit not encircled by the tetracationic cyclophane shows that the potential for the first oxidation is more positive in the [2]rotaxane while that for the second oxidation is the same in both compounds. These observations indicate that the tetracationic cyclophane makes the first one-electron oxidation of the encircled benzidine unit more difficult. However, once this unit is oxidized to the corresponding radical cation, the tetracationic cyclophane moves away from it to encircle the biphenol unit and so does not influence the second one-electron oxidation. Upon reduction of the benzidine unit back to its neutral state, the original equilibrium between the two co-conformations associated with the [2]rotaxane is restored.




Scheme 36. The shuttling of the macrocyclic component of [**53**·Cu]$^+$ along its dumbbell-shaped component can be controlled[145] electrochemically by oxidizing/reducing the metal center (MeCN, 298 K).

The [2]rotaxane [**53**·Cu]$^+$ has (Scheme 36) a phenanthroline and a terpyridine unit in its dumbbell-shaped component.[145] It also incorporates a $Cu^I$ center coordinated tetrahedrally by the phenanthroline ligand of the dumbbell together with the phenanthroline ligand of the macrocycle. Oxidation of the tetracoordinated $Cu^I$ center of [**53**·Cu]$^+$ to a tetracoordinated $Cu^{II}$ ion occurs[145b, 146] upon electrolysis (+1.0 V versus SCE) of a solution of the [2]rotaxane in MeCN. In response to the preference of $Cu^{II}$ for a pentacoordination geometry, the macrocycle shuttles away from the bidentate phenanthroline ligand of the dumbbell and encircles the terdentate terpyridine ligand instead. In this co-conformation, the $Cu^{II}$ center adopts a pentacoordination geometry that is significantly more stable than the tetracoordination one associated with the original co-conformation. Consistently, the cyclic voltammogram shows the disappearance of the reversible wave (+0.68 V) associated with the tetracoordinated $Cu^{II}/Cu^I$ redox couple and the concomitant appearance of a reversible wave (−0.03 V) corresponding to the pentacoordinated $Cu^{II}/Cu^I$ redox couple. A second electrolysis (−0.03 V) of the solution of the [2]rotaxane in MeCN reduces the pentacoordinated $Cu^{II}$ center back to a pentacoordinated $Cu^I$ ion. In response to the preference of $Cu^I$ for a tetracoordination geometry, the macrocycle moves away from the terdentate terpyridine ligand and encircles the bidentate phenanthroline ligand. The cyclic voltammogram recorded after the second electrolysis shows the original redox wave (+0.68 V) corresponding to the tetracoordinated $Cu^{II}/Cu^I$ redox couple.

The [2]rotaxane **54**$^{4+}$ incorporates (Scheme 37) a π-electron-deficient macrocycle and a π-electron-rich dumbbell.[147] The macrocycle resides around the 2,6-dioxyanthracene recognition site in solution. This co-conformation is stabilized by π–π stacking interactions between the bipyridium units of the macrocycle and the sandwiched 2,6-dioxyanthracene recognition site of the dumbbell, as well as by C–H···O interactions between the α-bipyridinium hydrogen atoms and the polyether oxygen atoms. The $^1$H NMR spectrum ($(CD_3)_2CO$, 298 K) of this [2]rotaxane shows a singlet at $\delta =$ 4.30 for the protons in positions 9 and 10 of the 2,6-dioxyanthracene ring system. By contrast, these protons resonate at $\delta = 8.16$ in the $^1$H NMR spectrum of the "free" dumbbell. The dramatic chemical shift change ($\Delta\delta = -3.86$) experienced by the resonances associated with these protons is a result of shielding effects exerted on them by the sandwiching bipyridinium units. The cyclic voltammogram of a solution of this [2]rotaxane in MeCN shows a first oxidation wave (+1.03 V versus SCE) that corresponds to the oxidation of the 2,6-dioxyanthracene recognition site. This oxidation occurs at a potential that is more positive than that of a model compound incorporating this unit. As far as the oxidation of the two 1,4-dioxybenzene rings is concerned, two waves (+1.29 and +1.59 V versus SCE) are observed. The oxidation of the first 1,4-dioxybenzene ring of the [2]rotaxane occurs at a potential that is almost identical to that of a model compound incorporating this unit. The oxidation of the second 1,4-dioxybenzene ring of the [2]rotaxane occurs at a potential that is almost identical to that of a model [2]rotaxane incorporating this unit that is encircled by the tetracationic cyclophane. These observations suggest that the tetracationic cyclophane resides (Scheme 37) initially around the 2,6-dioxyanthracene recognition site making its oxidation more difficult. However, once this recognition site is oxidized, the tetracationic cyclophane moves away from it and encircles one of the two 1,4-dioxybenzene rings.



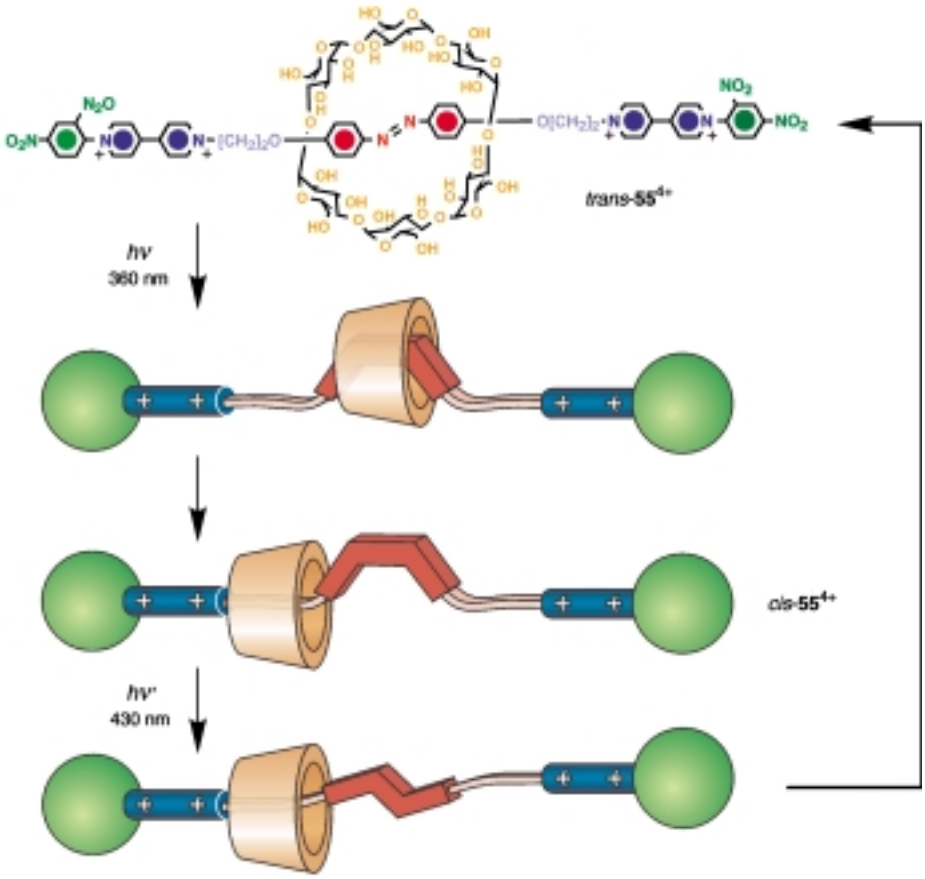

Scheme 37. The shuttling of the macrocyclic component of $\mathbf{54}^{4+}$ along its dumbbell-shaped component can be induced[147] by oxidizing electrochemically the anthracene ring system (MeCN, 298 K).

macrocycle moves away from the terdentate terpyridine ligand and encircles the bidentate penanthroline ligand to restore the original co-conformation.

The [2]rotaxane $\mathbf{55}^{4+}$ incorporates (Scheme 38) an $\alpha$-cyclodextrin torus and a *trans*-azobiphenoxy-containing dumbbell.[149] Comparison of the $^1$H NMR spectra ($D_2O$, 303 K) of the [2]rotaxane and of its "free" dumbbell-shaped component indicates that the cyclodextrin resides exclusively around the *trans*-azobiphenoxy recognition site. While only two sets of signals are observed for the *trans*-azobiphenoxy protons of the "free" dumbbell, four sets of resonances are associated with the same protons in the [2]rotaxane. In the [2]rotaxane, the local $C_2$ symmetry of the *trans*-azobiphenoxy unit is lost, as a result of the toroidal shape of the $\alpha$-cyclodextrin component, and the two *p*-phenylene rings are no longer equivalent. Also, the circular dichroism spectrum ($H_2O$, 278 K) of the [2]rotaxane shows a positive band (360 nm) corresponding to $\pi-\pi^*$ transitions of the azobiphenoxy unit. This observation indicates that this unit is encircled by the $\alpha$-

### *3.2.3. Photochemically Controllable Molecular Shuttles*

The shuttling of the macrocyclic component of the [2]rotaxane [**53**·Cu]$^+$ (Scheme 36) along the linear portion of its dumbbell-shaped component can also be induced photochemically.[145b, 148] Upon irradiation (464 nm) of a solution of the [2]rotaxane in MeCN, in the presence of *p*-nitrobenzylbromide, the $Cu^I$-based chromophoric unit is excited to a metal-to-ligand charge-transfer excited state. Electron transfer from the photoexcited [2]rotaxane to *p*-nitrobenzylbromide follows, which generates a tetracoordinated $Cu^{II}$ center. In response to the preference of the $Cu^{II}$ ion for a pentacoordination geometry, the macrocycle shuttles away from the bidentate phenanthroline ligand of the dumbbell and encircles the terdentate terpyridine ligand instead. Upon addition of ascorbic acid, the pentacoordinated $Cu^{II}$ center is reduced to a pentacoordinated $Cu^I$ ion. In response to the preference of $Cu^I$ for a tetracoordination geometry, the




Scheme 38. The shuttling of the macrocyclic component of $\mathbf{55}^{4+}$ along its dumbbell-shaped component can be controlled[149] reversibly by photoisomerizing the azobenzene unit ($H_2O$, 278 K).

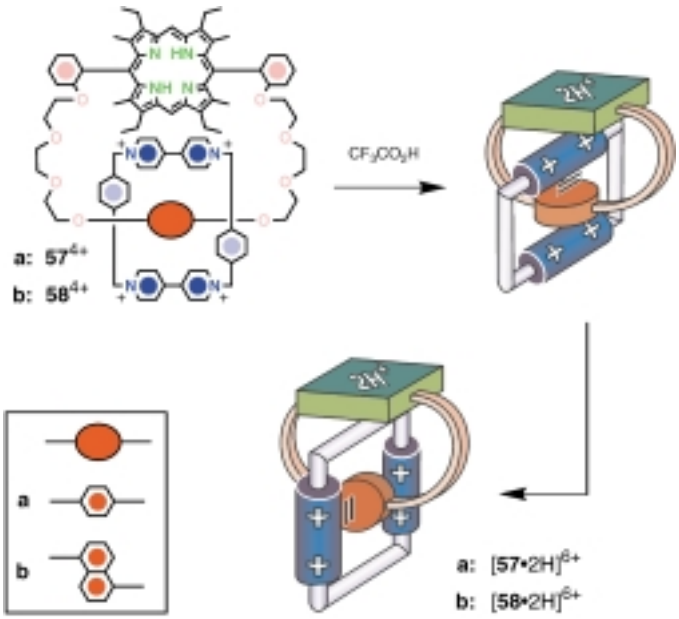
cyclodetxrin component, since long-axis-polarized transitions of aromatic guests inserted through the cavity of $\alpha$-cyclodextrin hosts produce positive bands. Upon irradiation (360 nm), the azobiphenoxy unit isomerizes[150] (Scheme 38) from *trans* to *cis* "pushing" the $\alpha$-cyclodextrin component away to encircle one of the $(CH_2)_2O$ chains. As a result, the intensity of the positive band decreases. Upon further irradiation (430 nm), the azobiphenoxy unit isomerizes from *cis* back to *trans*. This process is accompanied by the shuttling of the $\alpha$-cyclodextrin component back to encircle the *trans*-azobiphenoxy recognition site and, consequently, by an increase in intensity of the positive band at 360 nm.

### 3.3. Catenanes

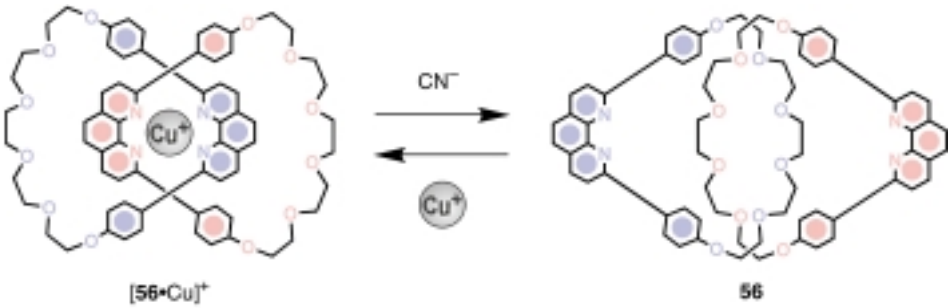
#### *3.3.1. Chemically Controllable Catenanes*

The [2]catenate $[\mathbf{56}\cdot Cu]^+$ incorporates (Scheme 39) two identical macrocyclic components.[75, 151] They possess a phenanthroline unit and a polyether chain connected by two *p*-phenylene rings. The X-ray crystallographic analysis of $[\mathbf{56}\cdot Cu]^+$ revealed[152] that the two phenanthroline ligands embrace the "central" $Cu^+$ ion, while the two polyether chains are located away from each other. However, a co-conformational change, which involves the circumrotation of both macrocycles through the cavity of each other, occurs (Scheme 39) upon demetalation. Indeed, the [2]catenand **56** is obtained[151, 153] quantitatively upon treating a solution of the [2]catenate $[\mathbf{56}\cdot Cu]^+$ with KCN. The X-ray analysis of **56** revealed[152] a co-conformation that is markedly different from the one adopted by $[\mathbf{56}\cdot Cu]^+$. In the [2]catenand **56**, the phenanthroline ligands are positioned away from each other, while the entangled polyether chains are located at the "center" of the molecule. Complete rearrangment of **56** occurs[154, 155] when $[Cu(MeCN)_4]BF_4$ is added to a solution of this [2]catenand. The two macrocyclic components circumrotate through the cavity of each other to allow the coordination of the $Cu^+$ ion by the two phenanthroline ligands and yield back the [2]catenate $[\mathbf{56}\cdot Cu]^+$. A similar co-conformational change was observed[156, 157] upon metalation of the [2]catenand with a variety of metal ions or upon protonation of one of the phenanthroline nitrogen atoms.

The [2]catenanes $\mathbf{57}^{4+}$ and $\mathbf{58}^{4+}$ incorporate (Scheme 40) a bipyridinium-based tetracationic cyclophane and a $\pi$-electron-rich macrocyclic polyether comprising a porphyrin ring system and either a 1,4-dioxybenzene or a 1,5-dioxynaphthalene unit.[158] The tetracationic cyclophane encircles exclusively the dioxyarene unit as a result of $\pi-\pi$ stacking interactions between this recognition site and the sandwiching bipyridinium units. The protons of the 1,4-dioxybenzene ring of the [2]catenane of $\mathbf{57}^{4+}$ resonate at $\delta = 2.62$ in the $^1H$ NMR spectrum ($CD_3CN$, 343 K). Similarly, the protons in positions 4 and 8 of the 1,5-dioxynaphthalene ring system in the [2]catenane $\mathbf{58}^{4+}$ resonate at $\delta = 1.47$ in the $^1H$ NMR spectrum ($(CD_3)_2SO$, 378 K). These "unusual" chemical shift values for the dioxyarene protons are a result of shielding effects exerted upon them by the sandwiching bipyridinium units. The porphyrin ring system is also engaged in $\pi-\pi$ stacking interactions with the bipyridinium unit located inside the cavity of the macrocyclic polyether. However, the tetracationic cyclophane circumrotates through the cavity of the macrocyclic polyether exchanging the "inside" and "alongside" bipyridinium units and, in the case of $\mathbf{57}^{4+}$, the rate of circumrotation is about 1500 times per second ($CD_3CN$, 298 K). This dynamic process is slow on the $^1H$ NMR timescale at 238 K in $(CD_3)_2CO$ and signals for the "inside" and "alongside" bipyridinium units can be distinguished. Upon addition (Scheme 40) of $CF_3CO_2H$, the porphyrin ring system is protonated.[159] As a result of electrostatic repulsion, the tetracationic cyclophane circumrotates to move the "inside" dicationic bipyridinium unit away from the now dicationic porphyrin ring system. As a consequence, the



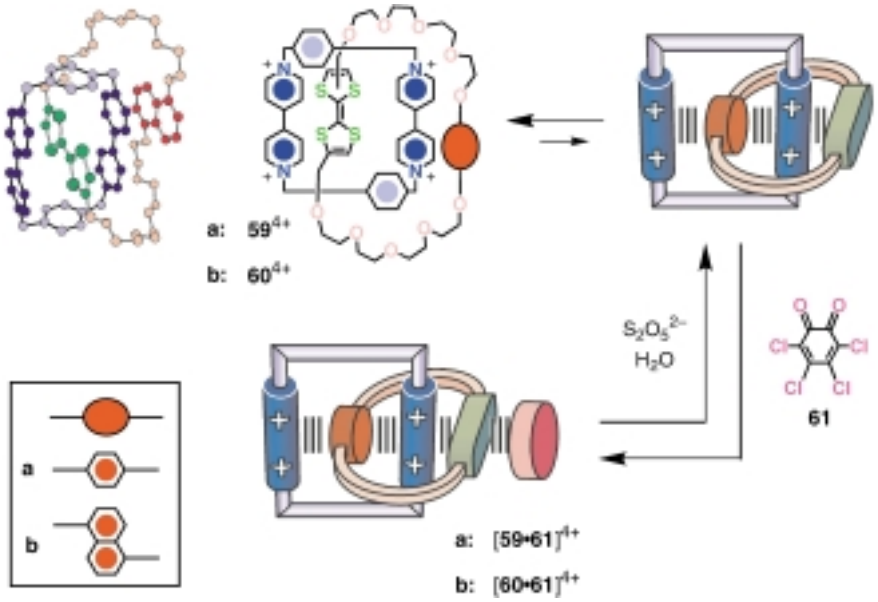

Scheme 40. The circumrotation of the tetracationic cyclophane component of the [2]catenanes $\mathbf{57}^{4+}$ and $\mathbf{58}^{4+}$ occurs[159] upon protonation of the porphyrin unit ($(CD_3)_2CO$, 238 K).




Scheme 39. Demetalation of the [2]catenate $[\mathbf{56}\cdot Cu]^+$ and the reverse reaction, metalation of catenand **56**, is accompanied[151] by co-conformational changes involving the circumrotation of the macrocyclic components through each other's cavity. Conditions: demetalation: $KCN/H_2O$, $MeCN/CH_2Cl_2$, 298 K; metalation: $[Cu(MeCN)_4]BF_4/MeCN/CH_2Cl_2$, $H_2O$, 298 K.

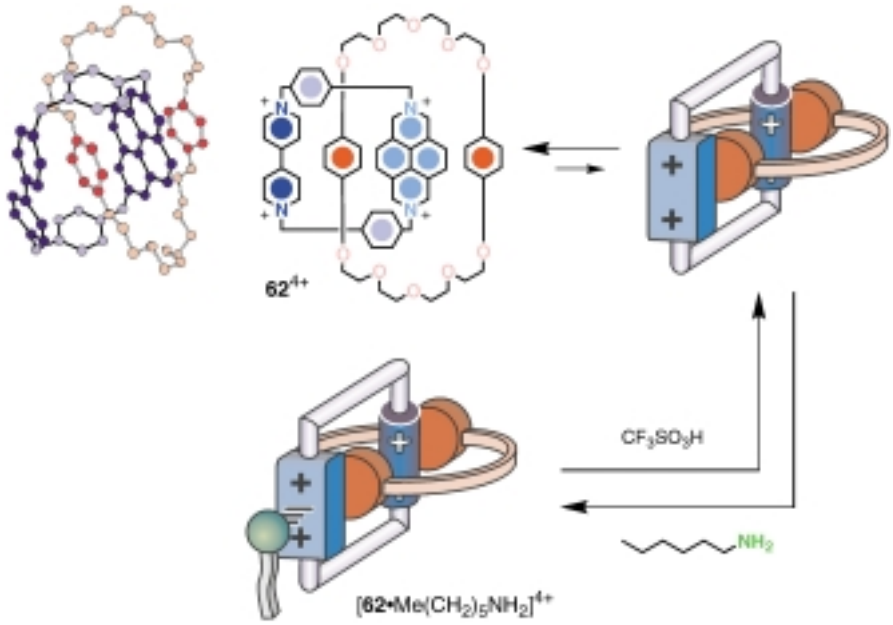
$^1$H NMR spectra ($(CD_3)_2CO$, 238 K) of the protonated [2]catenanes $[\mathbf{57}\cdot 2H]^{6+}$ and $[\mathbf{58}\cdot 2H]^{6+}$ show two distinct environments for the two *p*-phenylene rings of the tetracationic cyclophane. In the co-conformation obtained after protonation, one of the *p*-phenylene rings is located inside the cavity of the macrocyclic polyether, while the other is positioned alongside. Chemical-shift differences of $\Delta\delta = -0.39$ and $-0.50$ are observed between the resonances for the protons of the "inside" and "alongside" *p*-phenylene rings of $[\mathbf{57}\cdot 2H]^{6+}$ and $[\mathbf{58}\cdot 2H]^{6+}$, respectively.

The [2]catenanes $\mathbf{59}^{4+}$ and $\mathbf{60}^{4+}$ incorporate (Scheme 41) a bipyridinium-based tetracationic cyclophane and a π-electron-rich macrocyclic polyether comprising a tetrathiafulvalene ring system and either a 1,4-dioxybenzene or a 1,5-dioxynaphthalene unit.[97c, 160] The X-ray crystallographic analysis of the [2]catenane $\mathbf{60}^{4+}$ revealed (Scheme 41) that the tetracationic cyclophane encircles exclusively the tetrathiafulvalene ring system in the solid state. Also, the $^1$H NMR spectra ($CD_3CN$, 298 K) of $\mathbf{59}^{4+}$ and $\mathbf{60}^{4+}$ indicate that the tetrathiafulvalene unit resides preferentially inside the cavity of the tetracationic cyclophane in solution, while the dioxyarene unit is positioned alongside. For example, the characteristic[117a, 161] upfield shifts for resonances associated with protons in the dioxyarene units that are encircled by the tetracationic cyclophane are not observed in these [2]catenanes. The 1,4-dioxybenzene protons of $\mathbf{59}^{4+}$ and the 1,5-dioxynaphthalene protons of $\mathbf{60}^{4+}$ resonate at chemical shift values downfield from $\delta = 6.4$. Thus, if the co-conformation having a dioxyarene ring inside the cavity of the tetracationic cyclophane is present at all in solution, its concentration must be below the limit of detection by $^1$H NMR spectroscopy. Nonetheless, the ability of *o*-chloroanil (**61**) to stack (Scheme 41) against a tetrathiafulvalene ring system can be exploited[97c, 160] to "lock" this unit alongside the cavity of the tetracationic cyclophane. Indeed, comparison of the $^1$H NMR spectra, recorded at 298 K before and after the addition of **61** to a $CD_3CN$ solution of either $\mathbf{59}^{4+}$ or $\mathbf{60}^{4+}$, shows significant upfield chemical shifts for the resonances associated with the 1,4-dioxybenzene protons of $\mathbf{59}^{4+}$ ($\Delta\delta \approx -3$) and the protons in positions 4 and 8 of the 1,5-dioxynaphthalene ring system of $\mathbf{60}^{4+}$ ($\Delta\delta \approx -5$). These observations indicate that, after the addition of **61**, the dioxyarene rings become encircled by the tetracationic cyclophane and their protons suffer pronounced shielding effects from the sandwiching bipyridinium units. Upon addition of a mixture of $Na_2S_2O_5$ and $NH_4PF_6$ in $H_2O$, the adduct formed between the tetrathiafulvalene ring system and *o*-chloroanil is destroyed, and the original co-conformation with the tetrathiafulvalene unit inside the cavity of the tetracationic cyclophane is restored. Consistently, the original resonances for the protons of the "alongside" dioxyarene rings are observed again in the $^1$H NMR spectra of both [2]catenanes.




Scheme 41. The circumrotation of the macrocyclic polyether component of the [2]catenanes $\mathbf{59}^{4+}$ and $\mathbf{60}^{4+}$ can be controlled[97c, 160] reversibly in MeCN at 298 K by adding *o*-chloroanil (**61**), which forms a charge-transfer adduct with the tetrathiafulvalene unit of these [2]catenanes. The adduct can be disrupted by reducing *o*-chloroanil with $S_2O_5^{2-}$ ions. The geometry adopted in the solid state by $\mathbf{60}^{4+}$ is also shown.

The [2]catenane $\mathbf{62}^{4+}$ incorporates (Scheme 42) a 1,4-dioxybenzene-based macrocyclic polyether and a tetracationic cyclophane comprising a bipyridinium and a diazapyrenium unit.[132] Its X-ray crystallographic analysis revealed that the macrocyclic polyether encircles exclusively the diazapyrenium ring system in the solid state. The $^1$H NMR spectrum ($(CD_3)_2CO$, 193 K) of $\mathbf{62}^{4+}$ shows the signals for two distinct co-conformations in a ratio of 96:4. In the major isomer, the diazapyrenium ring system is located inside the cavity of the macrocyclic polyether and the bipyridinium unit is positioned "alongside". In the minor isomer, the bipyridinium unit is located inside the cavity of the macrocyclic polyether and the diazapyrenium ring system is positioned "alongside". The ability of *n*-hexylamine to form[92–94] adducts with diazapyrenium ring systems can be exploited[162] to displace the equilibrium between the two co-conformations in favor of the isomer having the diazapyrenium ring system alongside the cavity of the macrocyclic polyether. The differential pulse voltammogram (MeCN, 298 K) of $\mathbf{62}^{4+}$ shows two peaks at $-0.31$ and $-0.57$ V versus SCE for the monoelectronic reductions of the "alongside" bipyridinium unit and of the "inside" diazapyrenium ring system, respectively. After the addition of *n*-hexylamine, the first peak shifts by $-60$ mV to a potential that corresponds to the monoelectronic reduction of a bipyridinium unit encircled by the 1,4-dioxybenzene macrocyclic polyether. Similarly, the second peak shifts by $-20$ mV to a potential that is associated with the monoelectronic reduction of a diazapyrenium ring system interacting with *n*-hexylamine. Protonation of *n*-hexylamine occurs upon addition of $CF_3SO_2H$. As a result the adduct formed between *n*-hexylamine and the diazapyrenium unit of the [2]catenane is destroyed and the original equilibrium



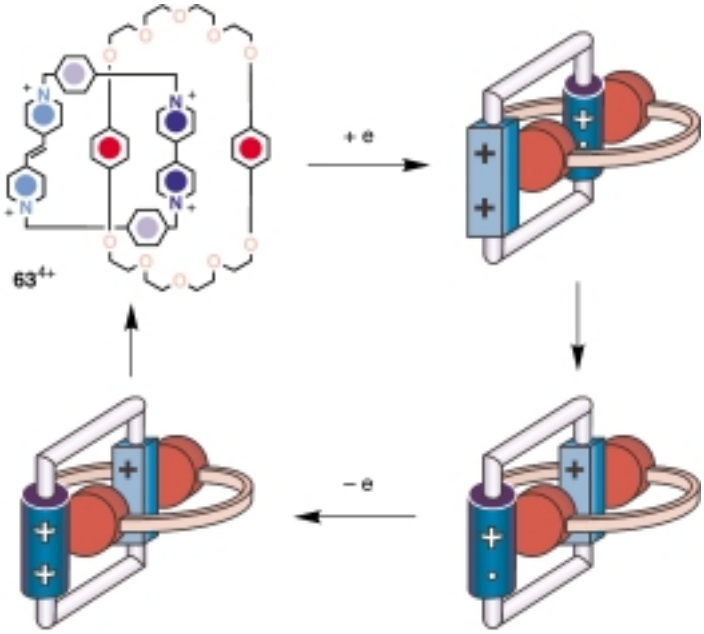

Scheme 42. The circumrotation of the tetracationic cyclophane component of the [2]catenane $\mathbf{62}^{4+}$ can be controlled[162] reversibly in MeCN at 298 K by adding *n*-hexylamine, which forms a charge-transfer adduct with the diazapyrenium unit of this [2]catenane. The adduct can be disrupted by protonating *n*-hexylamine with $CF_3SO_2H$. The geometry adopted in the solid state by the [2]catenane $\mathbf{62}^{4+}$ is also shown.

between the two co-conformations associated with $\mathbf{62}^{4+}$ is restored. The differential pulse voltammogram recorded after the addition of $CF_3SO_2H$ is identical with that recorded before the addition of *n*-hexylamine.

### 3.3.2. Electrochemically Controllable Catenanes

The co-conformational motion associated with the [2]catenanes $\mathbf{59}^{4+}$ and $\mathbf{60}^{4+}$ (Scheme 41) can also be controlled[160, 163, 164] electrochemically by the reversible oxidation/reduction of the tetrathiafulvalene ring system. The cyclic voltammograms of the "free" macrocyclic polyethers show a reversible wave (ca. +0.3 V versus SCE) for the monoelectronic oxidation of the tetrathiafulvalene unit. In the [2]catenanes, the tetrathiafulvalene ring system is located inside the cavity of the tetracationic cyclophane and its monoelectronic oxidation occurs at more positive potentials. Furthermore, a large separation between the anodic and cathodic peaks associated with this process is observed. This separation varies as the scan rate is changed. Upon increasing the scan rate, the anodic peak moves to more positive potentials, while the cathodic one shifts to less positive values. These observations indicate that the oxidation/reduction of the tetrathiafulvalene unit is accompanied by the circumrotation of the macrocyclic polyether through the cavity of the tetracationic cyclophane and that this co-conformational change is occurring on the timescale of the electrochemical experiment. Indeed, after oxidation, the newly formed monocationic tetrathiafulvalene unit is expelled from the cavity of the tetracationic cyclophane and is replaced by the neutral dioxyarene unit. After reduction, the original co-conformation is restored as the neutral tetrathiafulvalene unit replaces the dioxyarene unit inside the cavity of the tetracationic cyclophane.

The [2]catenane $\mathbf{63}^{4+}$ incorporates (Scheme 43) a 1,4-dioxybenzene-based macrocyclic polyether and a tetracationic cyclophane comprising a bipyridinium and a *trans*-bis(pyridinium)ethylene unit.[165] The $^1$H NMR spectrum ($(CD_3)_2CO$, 213 K) of $\mathbf{63}^{4+}$ shows the signals for two distinct co-conformations in a ratio of 92:8. In the major isomer, the bipyridinium unit is located inside the cavity of the macrocyclic polyether and the *trans*-bis(pyridinium)ethylene unit is positioned "alongside". The first two reduction waves in the cyclic voltammogram (MeCN, 298 K) of the "free" tetracationic cyclophane occur at −0.31 and −0.43 V versus SCE. They correspond to the first monoelectronic reductions of the bipyridinium and of the *trans*-bis(pyridinium)ethylene unit, respectively. In the case of the [2]catenane, these two waves are shifted to more negative potentials and occur at −0.39 and



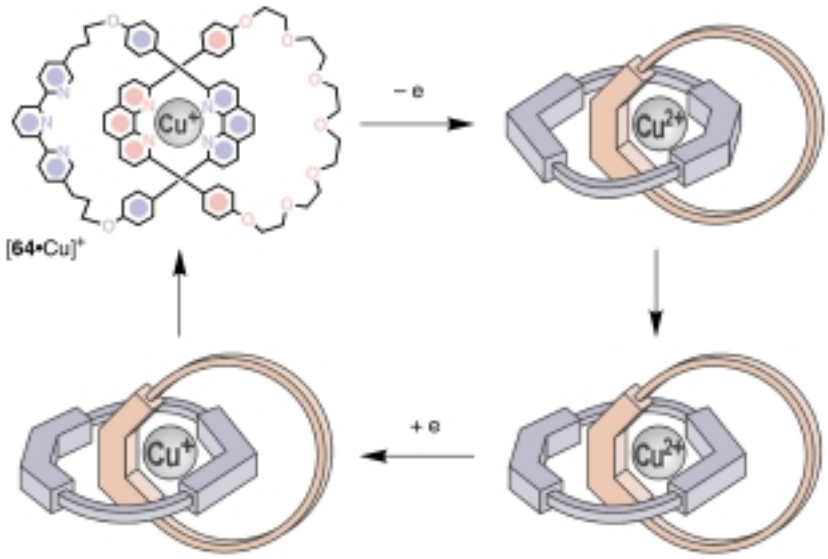

Scheme 43. The circumrotation of the tetracationic cyclophane component of the [2]catenane $\mathbf{63}^{4+}$ can be controlled[165] reversibly in MeCN at 298 K by oxidizing/reducing electrochemically its bipyridinium unit.

−0.49 V. These observations indicate that the bipyridinium unit is preferentially located (Scheme 43) "inside" the cavity of the macrocyclic polyether and its reduction is more difficult than in the case of the "free" tetracationic cyclophane. However, once this unit is reduced, the tetracationic cyclophane circumrotates through the cavity of the macrocyclic polyether moving the *trans*-bis(pyridinium)ethylene unit "inside", as shown by comparison of its reduction potential with that of a catenane model compound.[165b] The original

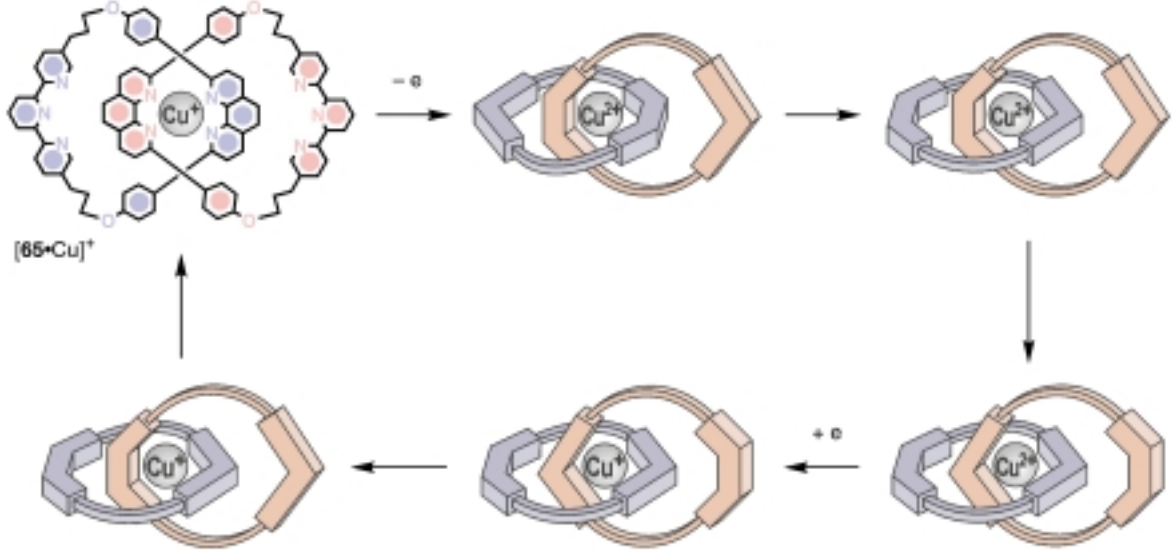
equilibrium between the two co-conformations associated with the [2]catenane $\mathbf{63}^{4+}$ is restored upon oxidation of both units back to their dicationic states.

The [2]catenate $[\mathbf{64}\cdot Cu]^{+}$ incorporates (Scheme 44) a terpyridine ligand in one of its two macrocyclic components and a phenanthroline ligand in both.[166] Oxidation of the tetracoordinated $Cu^{I}$ center of $[\mathbf{64}\cdot Cu]^{+}$ to a tetracoordinated $Cu^{II}$ ion occurs[166, 167] upon electrolysis (+0.8 V versus SCE) of a solution of the [2]catenate in MeCN. In response to the preference of $Cu^{II}$ for a pentacoordination geometry, the terpyridine-containing macrocycle circumrotates through the cavity of the other one. In the resulting co-conformation, the $Cu^{II}$ center adopts a pentacoordination geometry that is significantly more stable than the original tetracoordinated one. The cyclic voltammogram shows the disappearance of the reversible wave (+0.63 V) associated with the tetracoordinated $Cu^{II}/Cu^{I}$ redox couple and the concomitant appearance of a reversible wave (−0.07 V) corresponding to the pentacoordinated $Cu^{II}/Cu^{I}$ redox couple. A second electrolysis (−0.4 V) of the solution of the [2]catenane in MeCN reduces the pentacoordinated $Cu^{II}$ center back to a pentacoordinated $Cu^{I}$ ion. In response to the preference of $Cu^{I}$ for a tetracoordination geometry, the terpyridine-containing macrocycle circumrotates through the cavity of the other one affording back the original co-conformation. The cyclic voltammogram recorded after the second electrolysis shows the original redox wave (+0.63 V) corresponding to the tetracoordinated $Cu^{II}/Cu^{I}$ redox couple.

The [2]catenate $[\mathbf{65}\cdot Cu]^{+}$ incorporates (Scheme 45) two identical macrocyclic components comprising a terpyridine and a phenanthroline ligand.[168] The $Cu^{I}$ ion is coordinated tetrahedrally by the two phenanthroline ligands, while the two terpyridine ligands are located well away from each other. The cyclic voltammogram of $[\mathbf{65}\cdot Cu]^{+}$ shows a reversible wave at +0.63 V versus SCE which is associated with the tetracoordinated $Cu^{II}/Cu^{I}$ redox couple. The visible absorption spectrum of the [2]catenate reveals a metal-to-ligand charge-transfer band at 439 nm for the tetracoordinated $Cu^{I}$ chromophore. Upon electrochemical oxidation of $[\mathbf{65}\cdot Cu]^{+}$ or upon treatment with $NOBF_4$, the tetracoordinated $Cu^{I}$ center is converted into a tetracoordinated $Cu^{II}$ ion. As a result, the visible absorption spectrum reveals a band at 670 nm for the tetracoordinated $Cu^{II}$ chromophore. However, the intensity of this band decreases with time. Indeed, in response to the preference of the $Cu^{II}$ ion for a coordination number higher than four, one of the two macrocycles circumrotates through the cavity of the other




Scheme 44. The circumrotation of the terpyridine-containing macrocyclic component of the [2]catenate $[\mathbf{64}\cdot Cu]^{+}$ can be controlled[166] reversibly in MeCN at 298 K by oxidizing/reducing the metal center.




Scheme 45. The circumrotation of the macrocyclic components of the [2]catenate $[\mathbf{65}\cdot Cu]^{+}$ can be controlled[168] reversibly in MeCN at 298 K by oxidizing/reducing the metal center.

to afford a pentacoordinated $Cu^{II}$ ion. Subsequently, the other macrocycle undergoes a similar circumrotational process to yield a hexacoordinated $Cu^{II}$ ion which shows instead a weak absorption band at 687 nm. Electrolysis (−1.0 V) of the solution of the [2]catenane in MeCN reduces the hexacoordinated $Cu^{II}$ center back to a hexacoordinated $Cu^{I}$ ion. In response to the preference of $Cu^{I}$ for a tetracoordination geometry, the two macrocycles circumrotate through the cavity of each other in turn to afford the original co-conformation quantitatively.

#### *3.3.3. Photochemically Controllable Catenanes*

The co-conformational motion associated with the [2]catenate $[\mathbf{64}\cdot Cu]^{+}$ (Scheme 44) can be also induced photochemically.[166b, 169] Upon irradiation (464 nm) of a solution of the [2]catenate in MeCN, in the presence of *p*-nitrobenzylbromide, the $Cu^{I}$-based chromophoric unit is excited to a metal-to-ligand charge-transfer excited state. Electron transfer from the photoexcited [2]catenate to *p*-nitrobenzylbromide follows, which generates a tetracoordinated $Cu^{II}$ center. In response to the preference of the $Cu^{II}$ ion for a pentacoordination geometry, the terpyridine-containing macrocycle circumrotates through the cavity of the other affording a pentacoordinated $Cu^{II}$ center. Upon addition of ascorbic acid, the pentacoordinated $Cu^{II}$ center is reduced to a pentacoordinated $Cu^{I}$ ion. In response to the preference of $Cu^{I}$ for a tetracoordination geometry, the terpyridine-containing macrocycle circumrotates through the cavity of the other, which restores the original co-conformation.

## 4. Perspectives

With an eye to the future, there are two prominent emerging perspectives concerning molecular machines, namely, the development of artificial molecular machines based on biomolecules and the interfacing of artificial molecular machines with solid supports, which we would now like to highlight.

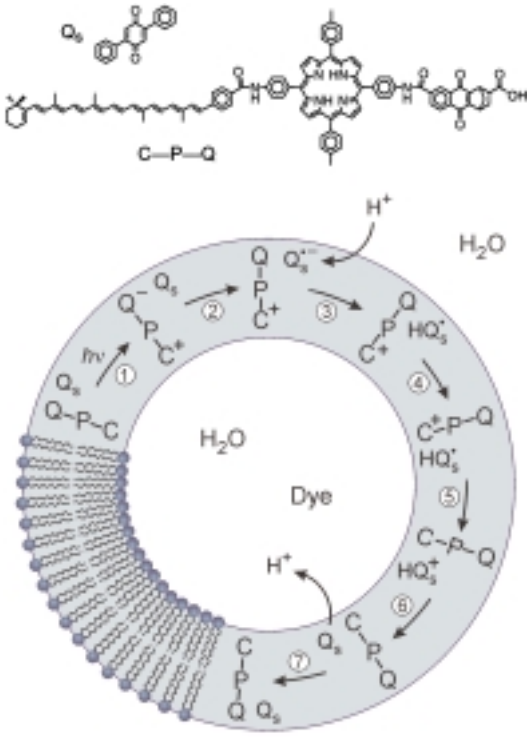
### 4.1. Artificial Molecular Machines Based on Biomolecules

#### *4.1.1. A Power Plant and Motor*

Recent scientific advances in both molecular biology and nanofabrication technology have opened up the possibility of building functional hybrid organic and inorganic devices on a nanometer scale. One long-term objective is to utilize the finest attributes associated with the worlds of both organic and inorganic materials for the creation of nanomechanical systems that are powered by biological motors.

At present, the best characterized biological motor is ATP synthase. The synthesis of ATP by this enzyme is based (see Section 1.3.1) on a proton pump across a membrane. Perhaps, the most spectacular molecular-scale machine constructed in recent years is a biomimetic, photon-driven proton pump which is able to power ATP synthase to produce ATP.

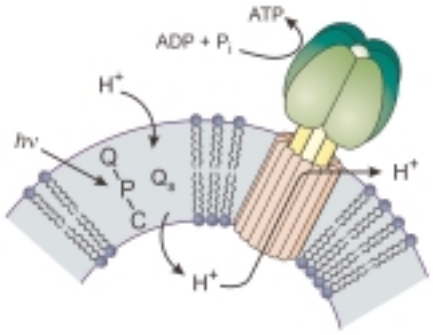
The first step in this research was the design of multicomponent systems capable of performing photoinduced charge-separation reactions.[170] Later on, a so-called C-P-Q triad for photoinduced charge separation that was composed of a naphthoquinone Q as the electron acceptor, free-base porphyrin P as the primary electron donor, and carotene C as the final electron donor[171] was implanted (Scheme 46) into




Scheme 46. Schematic representation of the liposome-based proton pump powered by a photoinduced charge-separation process.[172]

the lipid bilayer of a reconstituted liposome.[172] Photoinduced electron transfer in the triad molecule spanning the wall of the vesicle sets up an electrochemical potential difference between the interior and the exterior of the liposome and leads to directional proton transfer. The preference for the orientation of the triad within the layer is in part thermodynamic (the bulky porphyrin and quinone remain in the less densely packed outer layer) and in part kinetic (the activation barrier for the insertion of lipophilic carotenoid into the bilayer is much lower than those for the polar quinone and carboxylic group). Photoexcitation of the porphyrin moiety of C-P-Q with visible light generates, with a quantum yield of 0.1, the $C^{+}$-P-$Q^{-}$ charge-separated state (Scheme 46, step 1), which can be detected by monitoring the transient absorbance of the carotenoid radical. Electron transfer from $Q^{-}$ to the lipid-soluble 2,5-diphenylbenzoquinone ($Q_s$), with a reduction potential 0.6 V more positive than that of Q, results (step 2) in the formation of the radical anion $Q_S^{\bullet-}$. The reduced form of $Q_s$ accepts a proton from the external aqueous solution to form the corresponding uncharged semiquinone $HQ_S^{\bullet}$, which diffuses through the membrane and performs the crucial

function of a proton shuttle (steps 3 and 4). Upon reaching the interior layer of the membrane, $HQ_S^{\cdot}$ encounters the carotenoid radical cation, undergoes (step 5) oxidation to $HQ_S^+$, and releases (step 6) the proton into the aqueous medium inside the vesicle. Random diffusion of the regenerated $Q_s$ closes (step 7) the cycle. The pH-dependent fluorescent excitation spectrum of a water-soluble dye was used to monitor changes in the proton concentration inside liposomes. The efficiency of the system can be increased if an ionophore, such as valinomycin, is added in order to relax the membrane potential. The pH gradient thus established across the bilayer membrane gives rise to a proton-motive force, that is, the biological analogue of the electromotive force. In principle, such a force can be utilized to perfom work.[173] $F_0F_1$-ATP Synthase has been incorporated (Scheme 47) into liposomes

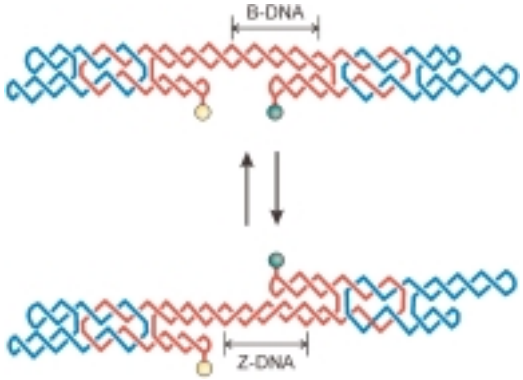



Scheme 47. Schematic representation of a liposome-based artificial photosynthetic membrane.[173]

containing the components of the proton-pumping photocycle. Irradiation of this artificial membrane with visible light leads to the charge-separation process that causes proton translocation and generation of a proton-motive force. When sufficient proton-motive force has accumulated protons flow through the $F_0F_1$-ATP synthase, with the concomitent formation of ATP from ADP and $P_i$. The functioning of the system was monitored by the luciferin–luciferase fluorescence assay. The results show that the synthesis of ATP occurs against an ATP chemical potential of approximately 12 kcal mol$^{-1}$ and with a quantum yield of more than 7%. One molecule of ATP is synthesized per 14 absorbed photons of light with a wavelength of 633 nm, an observation which means that up to 4% of the initial energy incident on the sample is stored by the system. The photocyclic system operates efficiently over a timescale of hours with a turnover number of seven ATP molecules per $F_0F_1$ per second. This system is the first complete biomimetic one which effectively couples electrical potential, derived from photoinduced electron transfer, to the chemical potential associated with the ADP-ATP conversion, thereby mimicking the entire process of bacterial photosynthesis. It constitutes a synthetic biological motor that, in principle, can be used to power anything which requires a proton grandient or ATP to work, for example, enzymatic systems that catalyze important reactions or even future nanomachines. Recently, a recombinant expression system has been established for the large-scale production of $F_1$-ATPase that has been modified to contain chemically active "handles".[174] Further performance data on motor rotation have also been obtained through the attachment of fluorescent microspheres to the tip of the $\gamma$ subunit.[174] Hybrid systems exploiting the motor protein kinesin[175] and dynein[176] to transport nonbiological molecules are under investigation. It is clear that this field is going to be an expansionary one in the near future.

### 4.1.2. A DNA-Based Mechanical Device

An interesting DNA-based artificial machine has recently been reported.[177] In DNA double-crossover (DX) molecules, two DNA double helices are joined to each other twice to yield rigid molecules. By attaching two DX molecules to one end of a longer DNA strand, a structure (Scheme 48)




Scheme 48. Schematic representation of a DNA-based mechanical device.[177] The two circles represent dyes whose separation distance changes upon the change in conformation of the middle DNA segment. The change in distance is measured by the change in resonance-energy transfer. Adapted by permission of the authors from ref. [199].

consisting of two short double helices anchored to a longer double helix has been obtained. The segment separating the two DX units consists of a special sequence which can switch conformation. Depending on the solution conditions, this segment can assume either the B conformation, in which DNA twists to the right, or the Z conformation, which has a left-handed twist. The two DX molecules lie on the same side of the longer DNA strand when the middle segment is in the B form and on opposite sides when that segment assumes the Z form. The B–Z transition results in a rotary displacement of up to 6 nm as well as a 0.6-nm lengthening of the segment. The motion (Scheme 48) is monitored through changes in the fluorescence of dyes attached to the free ends of the DX molecules. When the segment is in the B form, the two dyes are on the same side and closer to each other than when the segment is in the Z form. Thus, energy transfer is higher in the B form than in the Z form.

### 4.1.3. Machines Based on Protein Folding/Unfolding

The specific function of a protein is determined by its three-dimensional structure and the ability of this tertiary structure to evolve with time. The functional conformation of a protein is determined by its amino acid sequence, and understanding

how the one-dimensional primary sequence folds into the functional three-dimensional tertiary structure is a central problem in structural biology.[178] The folding of a protein is a complex molecular motion which results from a sequence of simple processes and starts from rotations about single bonds. In the search for kinetic methods of experimental investigation, ways of triggering the folding and unfolding processes have been developed. One particular approach consists of the reduction or oxidation of a component of the protein so as to shift the folded/unfolded equilibrium. Examples of proteins in which large-amplitude motions can be controlled by light, through a photoinduced electron-transfer reaction on the heme group of cytochrome c,[179] or by redox stimulation of methionine units[180] in the amino acid chain, have been reported. Such systems could serve as a basis for the construction of controllable nanomechanical motors based on proteins.

### 4.2. Interfacing Artificial Molecular Machines with Surfaces and Solid Supports

The investigation of supramolecular systems in solution is not only of fundamental importance to an understanding of their complex behavior, it also represents a starting point for the construction of molecular-level machines. A solution, however, contains a huge number of molecules which behave incoherently since they cannot be addressed individually and hence controlled.[181] It seems reasonable therefore that before functional supramolecular assemblies can be employed in a machinelike manner they have to be interfaced with the macroscopic world by ordering them in some way. The next generation of molecular machines will need to be organized at interfaces[182] or deposited on surfaces[183] so that they can behave coherently—either in parallel or in series—and can also be addressed on the nanometer scale.[184] We will now discuss an experiment in which the rotation of single molecules on a surface has been observed by scanning tunneling microscopy (STM), and some recent examples of interlocked molecular systems supported on solid electrodes.

#### *4.2.1. Rotation of a Single Molecule within a Supramolecular Bearing on a Solid Surface*

Nowadays experimental techniques involving various kinds of probe microscopies allow[4, 14, 15] the visualization and manipulation of single molecules. Single molecule rotors surrounded by like molecules that form a supramolecular bearing on a surface have been studied[185] recently by STM in ultrahigh vacuum. The molecular rotors are propeller-shaped hexa-*tert*-butyldecacyclene molecules of approximately 1.5 nm diameter, which were deposited onto an atomically clean Cu(100) surface. At surface coverages of just less than one monolayer, a close-packed supramolecular layer with nanometer-sized holes is formed by the molecules. As a result of robust intermolecular interactions, the packed molecules cannot rotate on the Cu(100) surface and they appear in the STM images (Figure 7a) as six-lobed objects. However, some

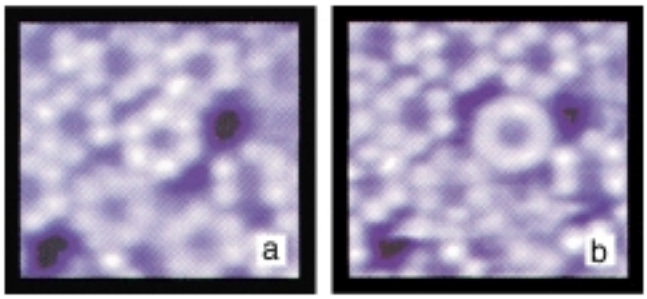
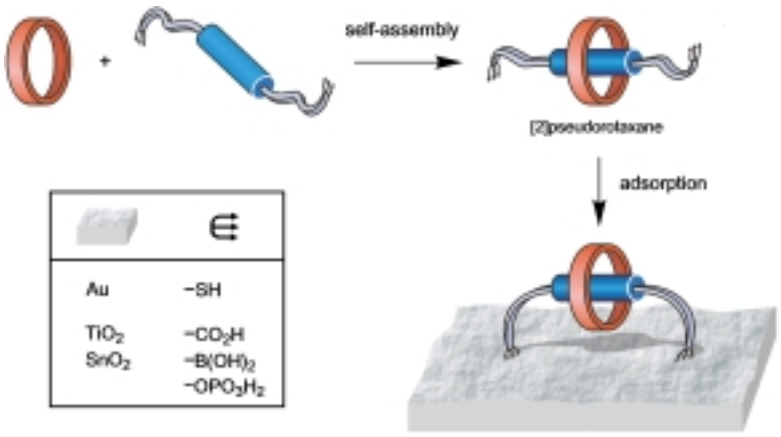



Figure 7. Ultrahigh-vacuum STM images of an atomically clean Cu(100) surface covered with hexa-*tert*-butyldecacyclene molecules.[185] In a) the molecule appears as a six-lobed object since it is immobilized by the surrounding molecules. In b) the same molecule rotates rapidly on the metal surface and it appears as a torus. Reprinted by permission from ref. [185].

of these molecules can dissociate from the supramolecular assembly to enter one of the nanometer-sized voids in which they are free to rotate. The rate of rotation is greater than the scan rate of imaging at ambient temperature and, as a result, the molecules in motion appear (Figure 7b) as toroidal objects. Interestingly, a single rotating molecule can be translated, with the aid of the STM tip, to a position where it is immobilized by the surrounding molecular layer. Although this system represents an impressive example of real-space observation of molecular motions, it should be noted that molecular machines powered by ambient (thermal) energy cannot be used to do work, unless they are driven by some kind of "asymmetric" stimulus.[53–55, 74, 186]

#### *4.2.2. Modified Electrodes*

With the aim of constructing electrochemical sensors, the affinity of thiol groups for gold surfaces has been exploited to develop electrodes modified with self-assembled monolayers containing receptors[187, 188] derived from both **25**$^{4+}$ and **36**. The self-assembly of molecular components in solution can be coupled (Scheme 49) to deposition techniques for obtaining surface-attached supramolecular and interlocked molecular systems. Amongst the most interesting examples are a monolayer constituted of macrocycles **25**$^{4+}$ or **20** catenated onto a gold surface by means of a molecular thread bearing thiol groups at both ends[189] and a polyrotaxane deposited as a film onto an electrode by electropolymerization.[190] In the latter case, the rotation of the ring component around the polymer-derivatized thread, confined to the film, can be electrochemically triggered. Another interesting approach is provided by the emerging field of heterosupramolecular chemistry.[191] Heterosupermolecules, that is, supramolecular systems in which one or more components are in the condensed phase (for example, nanocrystals), are expected to offer considerable advantages from the viewpoints of molecular organization and addressability. Following the strategy outlined in Scheme 49, hetero[2]catenanes in which nanosized particles of $TiO_2$ or $SnO_2$ are incorporated as a part of one of the ring components have been prepared and are currently the subject of photochemical and electrochemical investigations.[192]




Scheme 49. Pictorial representation of the preparation of a surface-attached catenane by coupling self-assembly in solution with chemisorption onto a solid support.[189, 192]

## 5. Reflections

Miniaturization of the components for the construction of useful devices is currently pursued by the large-downward (top-down) approach. This approach, however, which leads solid-state physicists and electronic engineers to manipulate progressively smaller pieces of matter, has intrinsic limitations. An alternative approach to the construction of nanoscale-sized components and devices is the small-upward (bottom-up) approach. Chemists, by the nature of their discipline, are in an ideal position to develop bottom-up strategies since they are able to manipulate molecules, that is, the smallest entities of matter that have distinct shapes and properties. Although the first steps have been taken along the path to constructing simple artificial molecular machines, it is very early days yet and much progress remains to be made at a fundamental level before the knowledge base reaches that critical threshold which will allow it to be exploited to the full in a technological context. The majority of the systems discussed in this review relate to investigations carried out in solution where incoherence remains a major impediment when it comes to designing and realizing molecular-level devices with machinelike characteristics that perform useful functions. To date, however, the research that has been conducted on artificial molecular machines reveals a number of positive features, a few of which we would like to highlight 40 years since Feynman[1] laid down the gauntlet. Let us reflect, for example, on the fact that:

- chemical synthesis is a massive parallel manufacturing process: for example, 100 milligrams of a machinelike compound with a molecular weight of 1000 Daltons correspond to $6 \times 10^{19}$ molecular-level machines;
- for some applications such as drug delivery, artificial molecular machines need to be able to work in solution;[126c]
- the use of molecular machines for the homogeneous catalysis of chemical reactions has already been demonstrated;[64, 129]
- natural molecular machines work in solution with the help of membranes and artificial analogues working under very similar conditions have already been constructed; [172–174]
- with the aim of achieving interfacing with the macroscopic world, artificial molecular machines can be organized in the form of monolayers and as Langmuir–Blodgett films[182] or congregated on surfaces[183] on and between electrodes;[184, 187–192]
- artificial molecular machines are able to perform logic operations[94, 97a] and, as such, constitute the forerunners of chemical computers;[184, 193–196]
- "when we have some control of the arrangement of things on a molecular scale, we will get an enormously greater range of possible properties that substances can have",[1] and that these new properties will lead most certainly to a wide variety of applications which we cannot even begin to envisage today;[197]
- last, but by no means least, the current high level of research activity surrounding artificial molecular machines demonstrates how new concepts continue to instill new life into Chemistry as a scientific discipline.[198]

## 6. Addendum

Since this review article was accepted for publication—aside from references to communications, papers, and reviews that could be inserted within the original bibliography—some announcements in the literature have been sufficiently important and novel to merit special mention in an addendum. In the area of programmed chemical systems, Lehn[199] has published an interesting article on multiple processing and expression of molecular information. Intriguing examples[200,201] of molecular machines based on metal-induced conformational changes have been described. Bermudez et al.[202] have shown that the hydrogen-bonded components of amide-based rotaxanes can be induced to move under the influence of oscillating electric fields. In a process which is reminiscent of those operating in natural muscles, a linear rotaxane-like dimer capable of undergoing contraction and stretching motions under the action of a chemical stimulus has been described by Sauvage et al.[203] The very important achievement of STM-controlled reversible shuttling of $\alpha$-cyclodextrin beads within a polyrotaxane has been reported.[204] Research on multiwalled carbon nanotubes has led[205] to the construction of low-friction nanoscale linear bearings. A DNA-fueled molecular machine has been described[206] and interest in the development of molecular computers has been highlighted yet again[207] and again.[208]

*We thank our many colleagues and co-workers, whose names appear beside ours in some of the references, with whom we had the distinct pleasure, in Sheffield, Birmingham, Bologna, and Los Angeles, to develop many of the concepts highlighted in this review. Their intellectual inputs and practical outputs gave the science done in our own research laboratories its direction and its substance. The research was supported in Birmingham by the University of Birmingham and the Engineering and Physical Sciences Research Council, in*

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[193] Recently, a solid-state, electronically addressable, bi-stable [2]catenane-based molecular switching device has been fabricated from a single monolayer of the [2]catenane $\mathbf{60}^{4+}$ (see Scheme 41), anchored with phospholipid counterions, and sandwiched between an n-type polysilicon bottom electrode with a titanium/aluminum top electrode. The device exhibits hysteretic current/voltage characteristics. The switch can be opened at $+2$ V, closed at $-2$ V, read at $\sim 0.2$ V, and may be recycled many times under ambient conditions. A mechanism for the action of the switch, which is molecular and mechanical in nature, has been presented. The mechanism is consistent with temperature-dependent measurements, which indicate that the overall cycling of the switches has at least one thermally activated stage and another thermally and voltage-activated stage and is quenched at about 200 K. The devices are robust under ambient conditions and could be cycled many times. The change in the junction resistance between the closed and open states of the device is approximately a factor of 1.8, which implies that they may be useful as memory devices, but are unlikely to be important for logic. For more details, see C. P. Collier, G. Mattersteig, E. W. Wong, K. Beverly, J. Sampaio, F. M. Raymo, J. F. Stoddart, J. R. Heath, *Science* **2000**, *289*, 1172 – 1175.

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[196] The term "molecular computer" is still an emotive one among chemists in spite of the continuous advances in the field of molecular electronics (see ref. [9] and *Acc. Chem. Res.* **1999**, *32*, 191 – 275 (special issue on molecular materials in electronic and optoelectronic devices)) and the forecast contained in the Pimentel report (*Opportunities in Chemistry*, National Academy of Sciences, National Academy Press, Washington, DC, **1985**), which stated some 15 years ago now that "There are those who dismiss as far-fetched the idea of man-made molecular scale computers. Only a few decades ago, however, these same individuals might have classified as science fiction a proposal that someday there would be a man on the Moon, that fertility could be controlled by taking a pill, or that we could learn the structure of DNA. But since we know that molecular computers are routine accessories of all animals from ants to zebras, it would be prudent to change the question from whether there will be man-made counterparts to questions concerning when they will come into existence and who will be leading in their development. The when question will be answered on the basis of fundamental research in chemistry; the who question will depend on which countries commit the required resource and creativity to the search".

[197] Some people have envisaged that nanoscale devices will be used for repairing and manufacturing—thereby remodeling engineering, chemistry, and medicine, as well as computer technology. See, for example: a) K. E. Drexler, *Nanosystems: Molecular Machinery, Manufacturing, and Computation*, Wiley, New York, **1992**; b) T. D. Schneider, *Nanotechnology* **1994**, *5*, 1 – 18; c) R. C. Merkle, *Nanotechnology* **1997**, *8*, 23 – 28; d) S. Becker, K. Müllen in *Stimulating Concepts in Chemistry* (Eds.: M. Shibasaki, J. F. Stoddart, F. Vögtle), Wiley-VCH, Weinheim, **2000**, pp. 317 – 337.

[198] In a recent editorial (A. J. Bard, *Chem. Eng. News* **1999**, 77(36), 5) stigmatizing hype in chemistry, the use of terms employed in the macroscopic world to discuss the behavior of chemical systems has also been criticized. While we would agree wholeheartedly that the properties of chemical systems at the molecular and supramolecular levels should not be described in inappropriate ways, we do believe that looking at interwoven supramolecular and interlocked molecular systems from the viewpoint of their functions and with some judicious mentioning of devices in the macroscopic world is a highly stimulating exercise that helps the development of Chemistry as a scientific discipline by introducing new concepts onto the scene. There are some people who share our philosophy: aside from another editorial (R. M. Baum, *Chem. Eng. News* **1999**, *77*(31), 3) entitled "In Defense of Hype" (!), in the final chapter of a monograph (P. M. S. Monk, *The Viologens: Physicochemical Properties, Synthesis and Applications of the Salts of 4,4′-Bipyridine*, Wiley-VCH, New York, **1998**, chap. 14) devoted to the viologens, the author seems to dispair that "so much jargon is introduced", yet refers to the fact that "an almost infectious enthusiasm permeates the reports of viologen self-assembly" at the beginning of the chapter and then concludes, at the end of the chapter, that "an understanding of physicochemical properties of the viologens allows for the construction of chemical species which are novel and exciting, but which can also show great beauty." We would not disagree—and would add that fresh fields of science have always generated their own vocabulary.[11b,c]

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