

On the Way to Rotaxane-Based Molecular Motors: Studies in Molecular Mobility and Topological Chirality[†]

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ABSTRACT

ATP synthase represents a machine at the molecular level which couples the rotation of an axle in a wheel with the endergonic production of ATP, the general source of chemical energy in the cell. The natural system prototypically bears all features of a macroscopic motor: a rotor within a stator held by a membrane and fueled by a difference in chemical potential in the form of a proton gradient combined with a machine for ATP production. The assembly of axle and wheel to a rotor device reminds one very much of a rotaxane. In this Account, we discuss some important features of motors and their (potential) realization in simpler artificial model systems, that is, the molecular mobility of mechanically bound molecules, the importance of chirality for unidirectional motion, the sources of energy for driving the rotation, and the potential of using membranes and surfaces for ordering a large number of devices to achieve macroscopic effects.

Introduction: The Natural Prototype

With F₀F₁-ATP synthase,¹ nature very elegantly demonstrates that devices can be constructed at a molecular scale which are not only close structural analogues of macroscopic world motors, but also represent *functional models*

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Kaweh Beizai, of Austrian origin, grew up in Cologne where he studied chemistry and received his diploma in 1998. Currently, he is working on his Ph.D. thesis in the area of rotaxane chemistry in the group of Fritz Vögtle and Christoph Schalley.

Fritz Vögtle studied chemistry in Freiburg and chemistry and medicine in Heidelberg, Germany. In 1965, he received his Ph.D. for studies of the valence isomerization of double Schiff bases with Heinz A. Staab. After his habilitation on steric interactions inside cyclic compounds, he was professor in Würzburg from 1969 to 1975. He then accepted a position as full professor and director of the Kekulé-Institut in Bonn. He is the author of *Supramolecular Chemistry*, a book which is internationally known through translations into several different languages. His research interests are supramolecular chemistry; deformed helical molecules and their chiroptical properties; and compounds with appealing architectures such as rotaxanes, catenanes, knots, and, last but not least, dendrimers. Recently, he was awarded an honorary degree from the University of Jyväskylä, Finland.

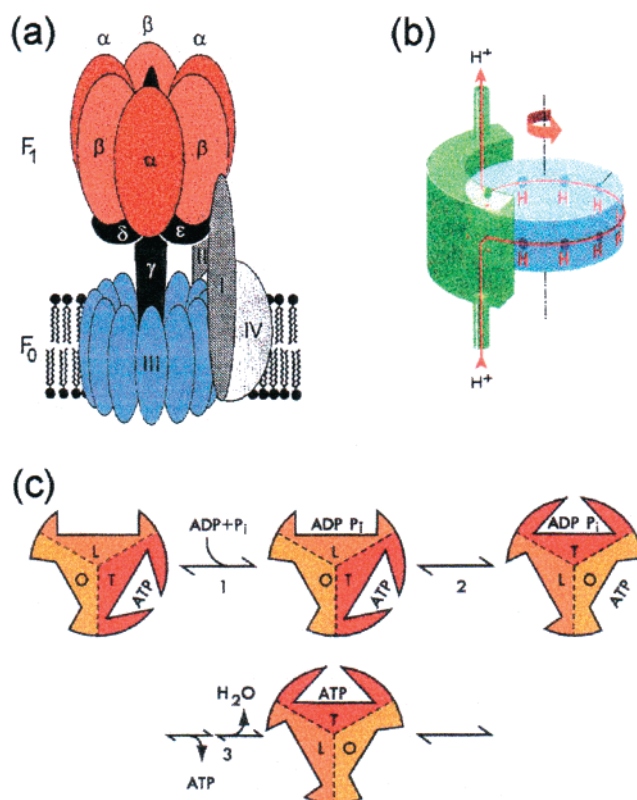
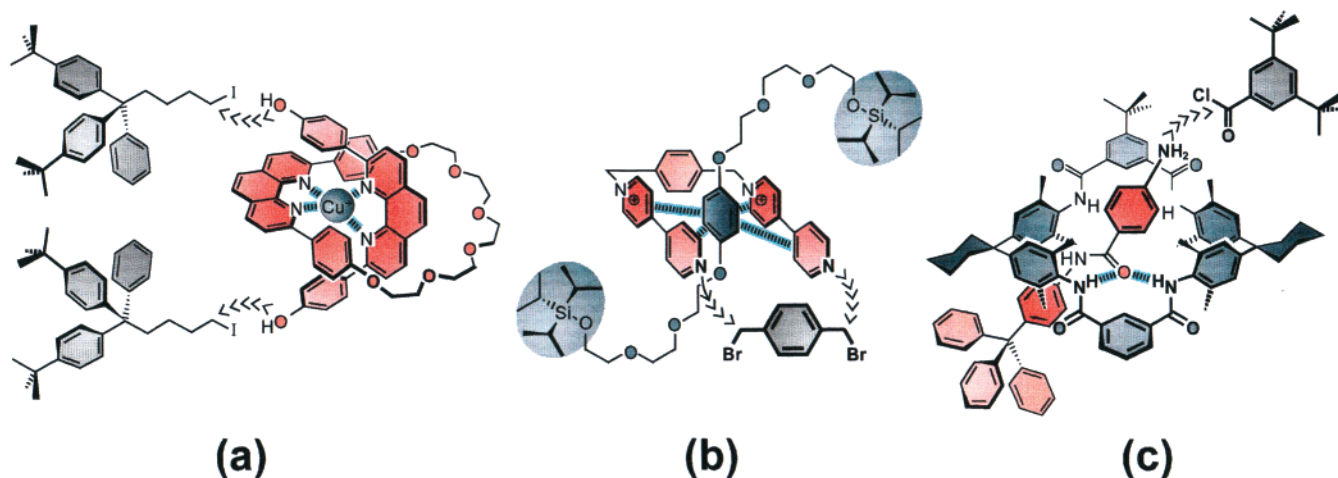


FIGURE 1. Schematic representations of (a) F₀F₁-ATP synthase, (b) the helical proton channel and proton transport mechanism, and (c) the ATP production cycle.

of their large-scale brothers. A macroscopic motor converts energy into work, and in every-day life, usually consists of an axle rotating inside a stator. The rotary motion can be utilized to drive a large variety of machines for an almost endless number of different purposes. Basic courses² in physics or physical chemistry already teach the students that according to the second law of thermodynamics, heat cannot be converted into work. Instead, a potential difference is required, for example, a temperature gradient or a difference in electric potential. It is the flow of heat or electricity from a higher level to a lower one that drives a motor.

The same principles hold true for ATP synthase (Figure 1a). A rodlike central protein rotates within a stator held in a membrane usually by 12 intermembrane proteins. This so-called F₀ subunit is coupled to the F₁ part located outside the membrane through the rod and through some smaller proteins. The F₁ building block itself is a circular assembly of three α - and three β -domains in an alternating pattern. In an endergonic process, the β subunits generate ATP from ADP and inorganic phosphate by binding the reactants in an enzyme pocket (Figure 1c). Upon rotation of the axle by 120°, the pocket changes its conformation so that ATP is formed.³ The next 120° step again leads to conformational changes of the pocket, and ATP is released. The use of more than one active subunit has the advantage of catalytic cooperativity and allows,

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Scheme 1. Some Commonly Employed Template Effects: (a) Coordination to Cu(I), (b) π -Donor– π -Acceptor Interactions, and (c) Hydrogen Bonding in Amide Rotaxanes

for example, the binding energy of ADP and phosphate gained in one pocket to support the energy consuming processes in another one. If ATP production is an endergonic process, then what is the energy source coupled to it which makes the overall process exergonic? The F_0 subunit employs a chemical potential difference in the form of a proton gradient just like the electric potential gradient of macroscopic world motors. According to a widely accepted hypothesis, protons flow along the gradient from one side of the membrane to the other through a transmembrane proton channel in the intermembrane proteins of the F_0 subunit. The channel describes a circular loop with an entrance on one side and an exit on the other side of the membrane, thus providing a helical path for the protons along which the protons are connected to the central rod and drive its rotation (Figure 1b). The helicity of the channel can well be considered an element of chirality which turns out to be an important feature of any molecular motor capable of unidirectional rotation (see below). In summary, the most important features of this fascinating natural motor are (i) the presence of a membrane which forms compartments allowing the build up of a proton gradient, (ii) the proton gradient as driving force, (iii) an element of chirality providing the basis for unidirectional rotation, (iv) appropriately located rotor and stator units which self-assemble from a number of separate protein subunits, and finally, (v) a device coupled to the rotor which uses the rotation to produce chemical energy in the form of ATP.

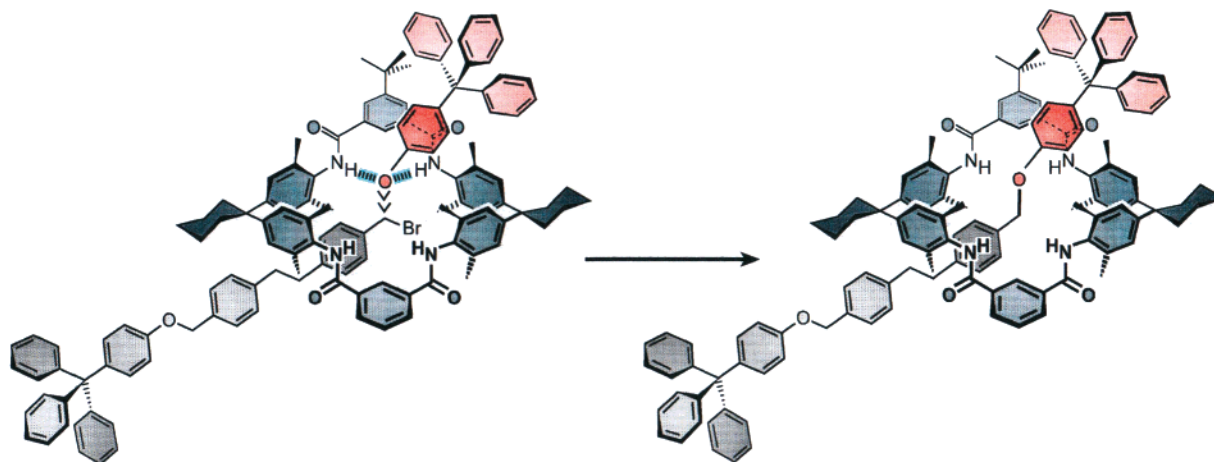
The structure of ATP synthase, in particular the rotating rod inside a static wheel, suggests rotaxanes⁴ as potential—although extremely simplified—artificial models for such natural molecular motors.^{5,6} In the following sections, we will discuss the above requirements for a working artificial motor at the molecular scale and the progress made toward their implementation in synthetic rotaxanes. This Account does not intend to be comprehensive, but tries to focus on more recent work that illustrates the different aspects of molecular motors under discussion. We will start with a brief introduction into rotaxane synthesis.

Templated Synthesis: Assembling the Parts of a Rotaxane

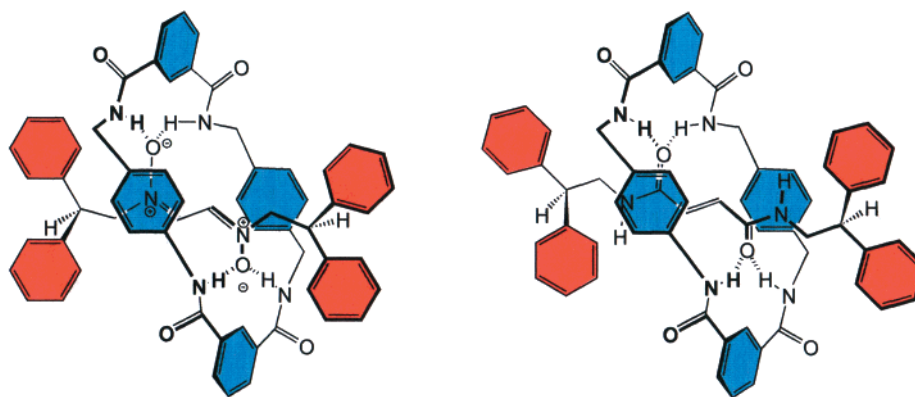
The use of mechanically bound molecules as the basis for functional devices requires efficient strategies for their preparation. The statistical synthesis of rotaxanes usually is a low-yield process and thus is not suited for their production on a large scale. Necessarily, template effects⁷ have to be used to direct threading of the axle through the rotaxane's wheel. Meanwhile, a large arsenal of such effects exists which allows synthesis of a large number of structurally different rotaxanes with high yields. Rotaxane synthesis is becoming more and more routine.

In view of earlier reviews, we will restrict the following section to a detailed discussion of only one anion template effect recently discovered in our laboratory and give only a brief introduction to the others. The tetrahedral coordination geometry of a Cu(I) ion provides the basis for a correct alignment of the axle within a macrocycle (Scheme 1a).⁶ Two phenanthroline moieties, one of which is part of the wheel, are positioned vertical to each other so that the other one just needs to be stoppered to obtain a rotaxane after removal of the copper ion. Incorporation of a hydroquinone derivative within a wheel bearing two paraquat units employs π -donor– π -acceptor interactions for templating the synthesis of rotaxanes (Scheme 1b).⁸ In aqueous media, the hydrophobic effect may be utilized to thread a lipophilic axle through a cyclodextrin.⁹ Finally, hydrogen bonding is the templating force for rotaxanes with secondary ammonium ions threaded through a crown ether macrocycle⁸ as well as for the synthesis of rotaxanes containing amide groups in the axle (Scheme 1c).¹⁰ In noncompetitive solvents, the tetralactam macrocycle utilized in the synthesis of the amide rotaxanes in Scheme 1c strongly binds anions such as chloride, bromide, or phenolate. Phenolate stoppers (Scheme 2) bound to the macrocycle can act as “wheeled” nucleophiles and react through the wheel with centerpieces such as dibromo xylene to yield ether rotaxanes in yields of 57–95%.¹¹ Thus, the macrocycle not only acts as a receptor for anions, but at the same time orients the guest

Scheme 2. Rotaxane Synthesis via a "Wheeled" Nucleophile (Note That the Phenolate Is Held within the Macrocycle by Hydrogen Bonds)



Scheme 3. Tetralactam Rotaxanes in Which the Rotation of the Wheel around the Axle Can Be Influenced by an Oscillating Electric Field



appropriately for threading the axle through the wheel. We therefore coin the term "threading receptor" for it. In similar reactions, we were also able to synthesize rotaxanes with acetal, ester, or carbonate groups in the axle by this method,¹² and even the Michael addition of thiophenolate stoppers to the triple bonds of propiolic acid Michael acceptors has led to the synthesis of rotaxanes through the anion template effect and thus provides quite a broad variety of structural motifs.¹³

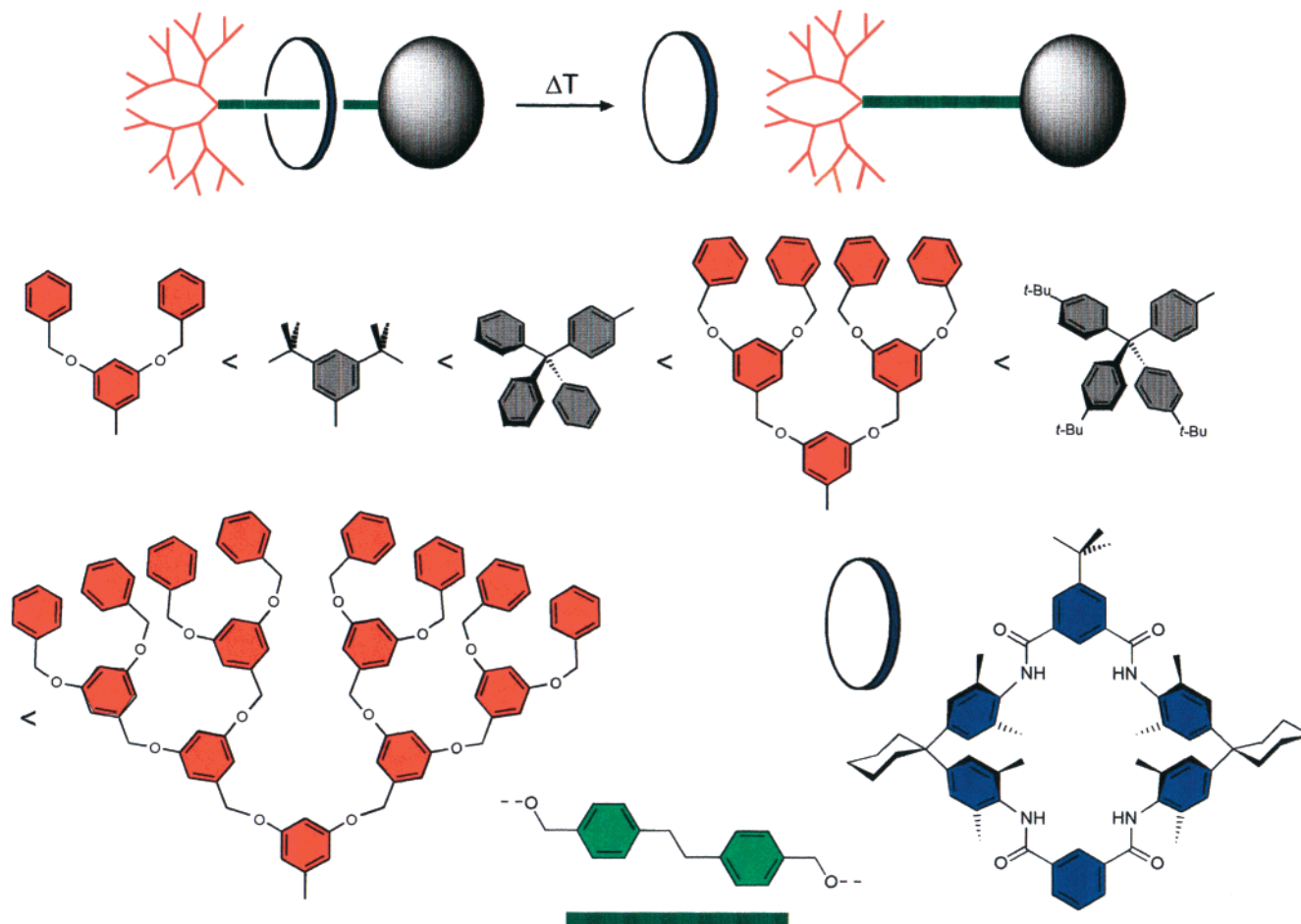
Molecular Mobility: Guiding Rotary Motion

Originally, the bulky stopper groups were intended to prevent the rotaxane's axle from dethreading by steric demand. However, for the construction of molecular motors, they may be important as means for guiding the axle's rotation and restricting its degrees of freedom to the desired rotary motion. Several types of motion are feasible for a rotaxane. The axle can, of course, rotate within the wheel, but the wheel can also shuttle along the axle in what can be regarded as a unidimensional diffusion process. Further, a pivoting motion changing the angle between the axle and the plane of the macrocycle is possible. The shuttling motion has been studied in great detail experimentally and theoretically.¹⁴ A similar approach investigates the circumrotation of catenanes. Depending on the point of view, this process can either be regarded as "shuttling" of a wheel along a circular axle

or as rotation of a circular axle within a wheel, that is, both motions become identical in catenanes. We will come back to these studies below when discussing potential driving forces for the motors. Here, we focus on the possibility to induce the rotation of the rotaxane wheel around the axle by an external electric field. In a recent report,¹⁵ it has been shown that an alternating-current electric field as an external stimulus induces the rotation of the wheels of the rotaxanes depicted in Scheme 3 around their axles. The rotation can also be monitored by variable-temperature NMR experiments, which coincide well with the results from Kerr-effect measurements and molecular dynamics studies. While one of the rotaxanes (Scheme 3, left) shows only rotary motion, the other (Scheme 3, right) displays a more complex picture with a superposition of rotation and pivoting motion. In the two rotaxanes in Scheme 3, hydrogen bonding of the wheel and axle provides some guiding of the axle; one may speculate that differences in hydrogen-bond strengths may be the reason for the differences in behavior.

Molecular dynamics calculations are a valuable tool for the theoretical investigation of the *intracomplex* mobility of mechanically bound species. Studies of the shuttling of rotaxanes¹⁶ and the circumrotation of catenanes¹⁷ resulted in a detailed description of these motions by the minima and transition structures involved. They further show the "large-scale" motions within mechanically in-

Scheme 4. Schematic Representation of the Deslipping Process and the Parts of Rotaxanes with Dendritic Stoppers of Different Sizes (The Different Stoppers Are Ranked According to Their Effective Sizes)



terlocked species to be coupled to other low-frequency motions which are needed to minimize the energy along the circumrotational pathway.

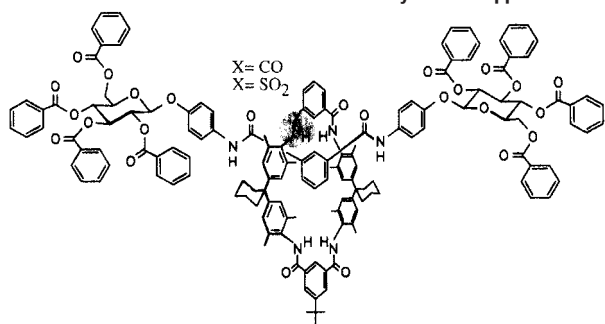
An approach to restricting the degrees of freedom for the axle to the desired rotation is the use of sterically demanding stoppers together with short-axle centerpieces. This would reduce the pivotal and shuttling motions to a minimum. Several studies have been devoted to the examination of the deslipping process (Scheme 4) that give insight into the size complementarity¹⁸ of stoppers and the macrocyclic cavity of the corresponding wheel and thus allow the estimation of the minimum size demand for stoppers that prevent deslipping. The transition from pseudorotaxanes to stable rotaxanes with increasing stopper size¹⁹ has been studied, and we have used the deslipping kinetics as a means to compare and rank dendritic and tritylphenol stoppers with respect to their effective sizes.²⁰ Further insight into the slippage²¹ of a crown ether macrocycle over several different alkyl-substituted trityl stoppers was gained from molecular dynamics calculations, which provided evidence for a two-step process.²² First, one phenyl ring of the trityl stopper slips through the wheel. Then, passing an intermediate local minimum, the other two phenyl rings follow in the rate-determining step. In our laboratory, the effects of small structural variations on the deslipping kinetics of

rotaxanes with intermediate stoppers have been examined. It turned out that even intramolecular hydrogen bonding within the wheel can have large effects on the kinetic behavior with lifetimes for the rotaxanes increasing by a factor of more than 10^4 as compared to a non-hydrogen-bonded analogue.²³ This also indicates that hydrogen bonds may well offer an appropriate means to control and guide the rotation.

Unidirectional Rotation: The Importance of Chirality

An important question for successful construction of a molecular motor is how to achieve unidirectional rotation. A system in which the direction of rotation is not well defined will not be productive because the motors rotating clockwise will consume in the reverse process the work done by the motors running counterclockwise and vice versa. Considering that a clockwise sense of rotation is enantiomeric to a counterclockwise rotation, it becomes immediately clear that an additional chiral element will render the two directionalities diastereomeric in nature; one can expect one of them to be more favorable than the other one. Consequently, chirality is an important, if not necessary, prerequisite for defining unidirectionality. As discussed above, nature makes use of this principle in

Scheme 5. A Rotaxane with Carbohydrate Stoppers

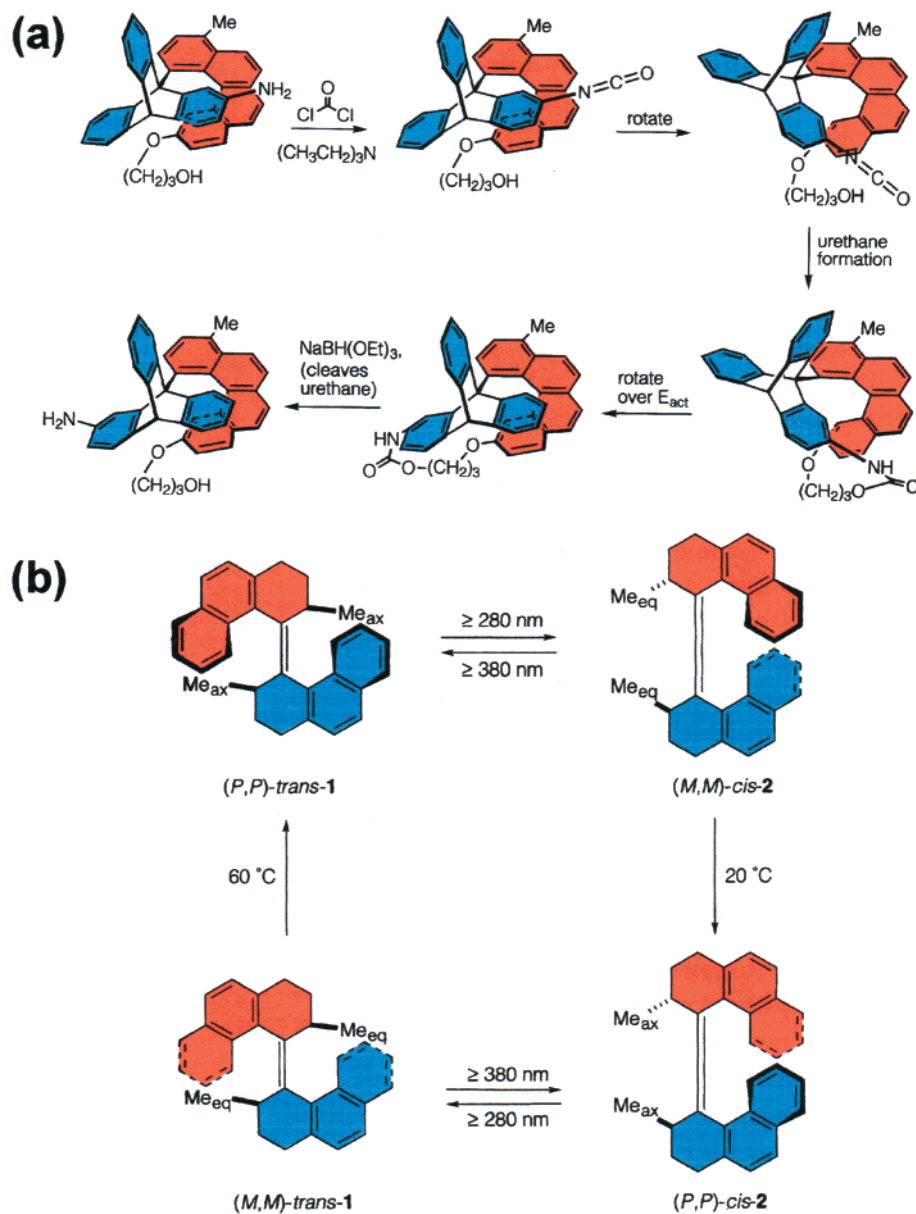


defining the sense of the spinning axle in ATP synthase by using a helical proton channel as an element of chirality.

Any artificial rotaxane-based motor must also bear a chiral element. Chirality can, of course, be implemented in such molecules by adding chiral groups as the stoppers or the wheel. Rotaxanes with cyclodextrins⁹ as the wheels

have been described, and we described rotaxanes with glucose-containing stoppers²⁴ (Scheme 5). Also, rotaxanes with elements of planar chirality have been realized.²⁵ More challenging, however, is the preparation of cycloenantiomeric rotaxanes²⁶ and the resolution of their two enantiomers, which has been a major research topic in our laboratory during the past few years.²⁷ Neither the axle nor the wheel is itself chiral, but both together give a cycloenantiomeric species (Figure 2). Such molecules can be accomplished if both the axle and the wheel bear groups with a certain directionality. For example, the sulfonamide group in the wheel in Figure 2 defines such a directionality. Any rotaxane built from an axle with two different stoppers and a sulfonamide wheel exists in two enantiomeric forms as shown in the figure.²⁸ On the basis of the same idea, even a cyclodiastereomeric [3]rotaxane has been synthesized that exists as a pair of enantiomers plus an additional *meso* form (Figure 3).²⁹ Separation into

Scheme 6. Unidirectionality Realized through Chirality in (a) Kelly's Trypticenylic Helicene and (b) Feringa's Overcrowded Double-Bond System



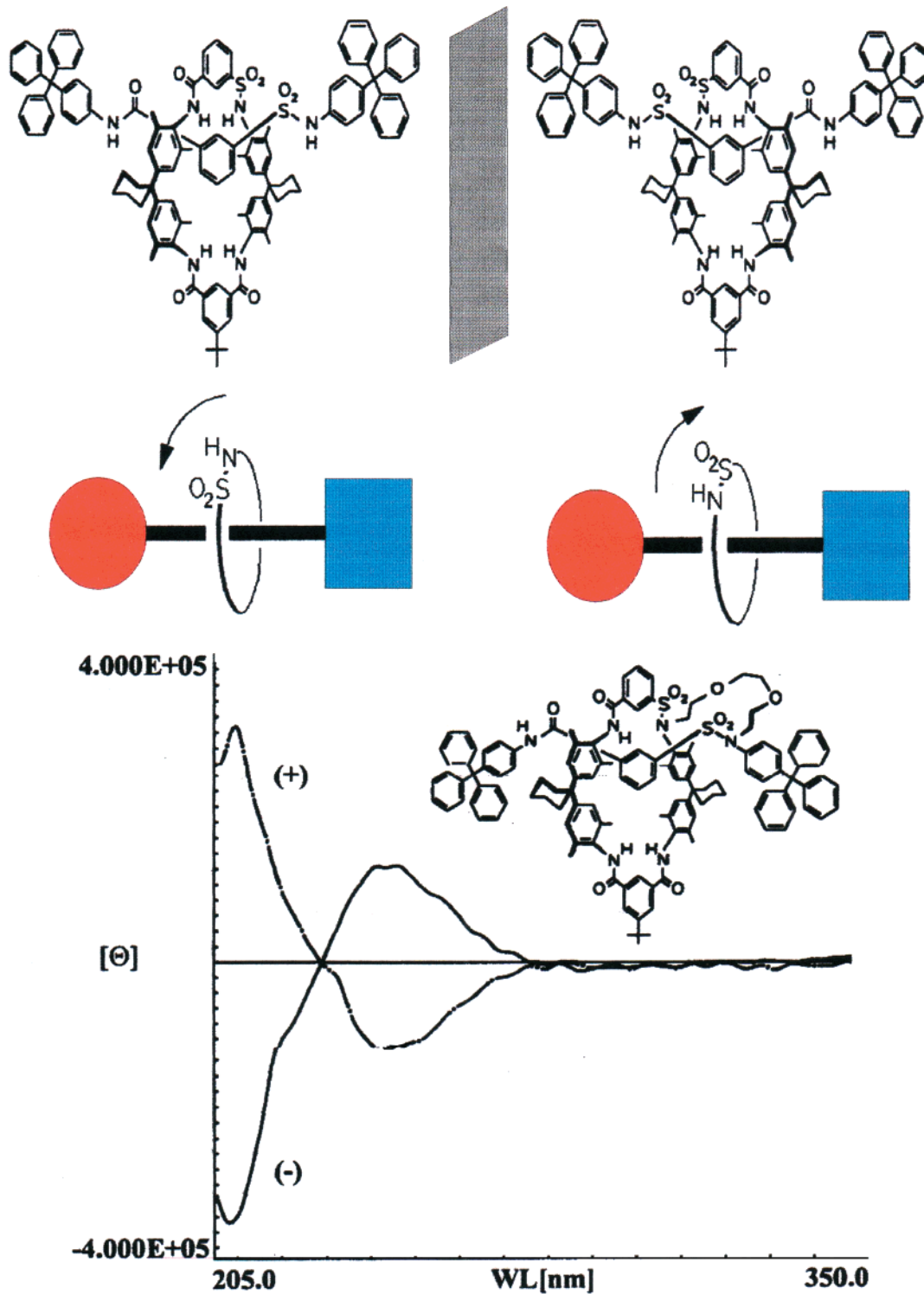


FIGURE 2. Cycloenantiomeric [2]rotaxanes and the CD spectra of analogues bridged between the axle and wheel by an oligoether chain.

the stereoisomers by HPLC on a chiral stationary phase is often possible, and the CD spectra have been recorded for many of them.

In artificial minimal systems, two groups have invented systems that work in a unidirectional manner. Kelly and co-workers³⁰ synthesized a trypticene with a helicene as the chiral element attached to one of the bridgehead carbon atoms (Scheme 6a). Unidirectionality is realized

by connecting one of the aromatic rings of the trypticene to the helicene by a covalent bond which introduces strain. The strain is released if the trypticene rotates by 120° and flips with one of the aromatic rings along the helicene like a ratchet. The covalent bond is subsequently cleaved and the system is ready for the next cycle. A similar approach has been chosen by Feringa et al.³¹ (Scheme 6b) who prepared an overcrowded double-bond

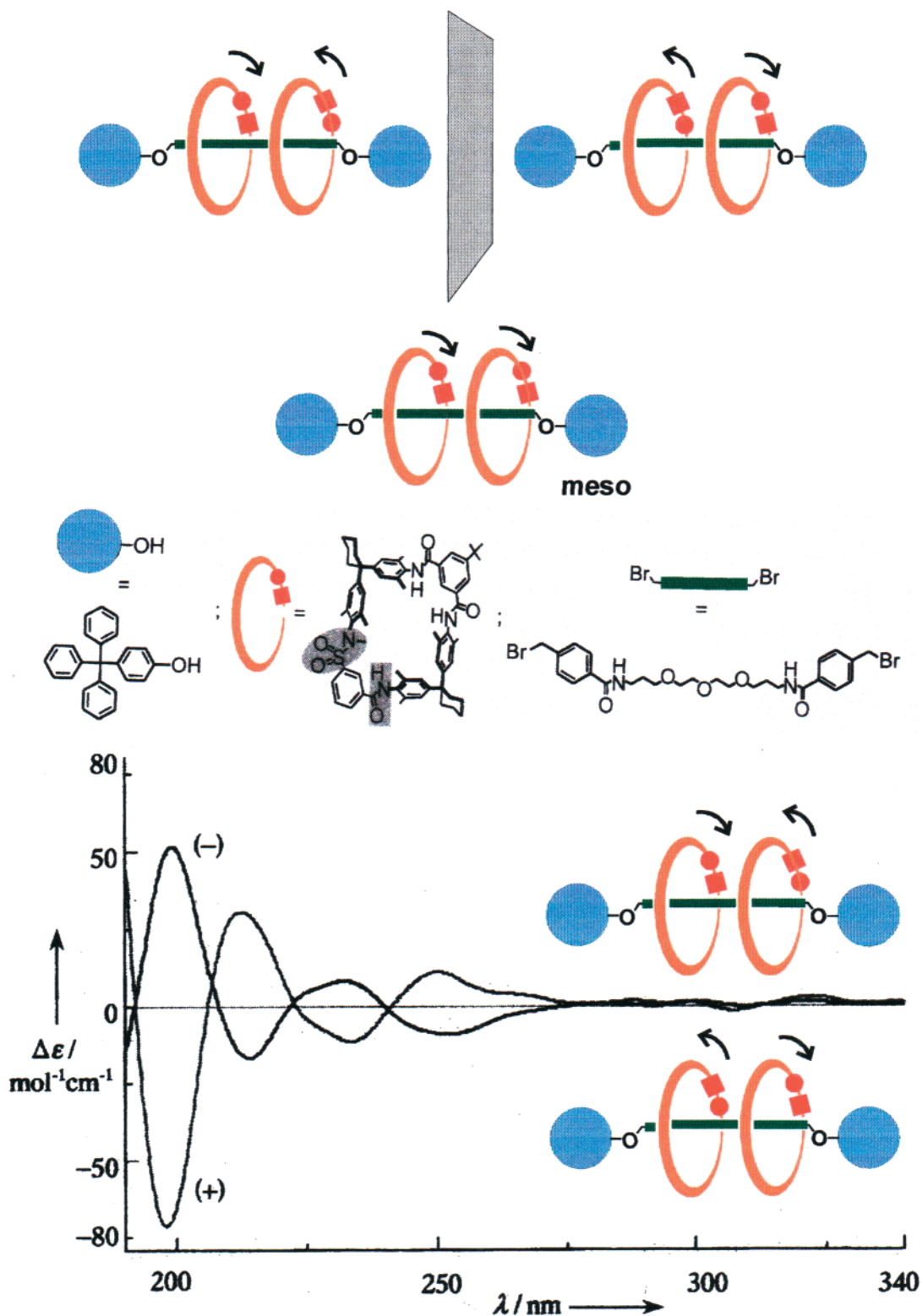
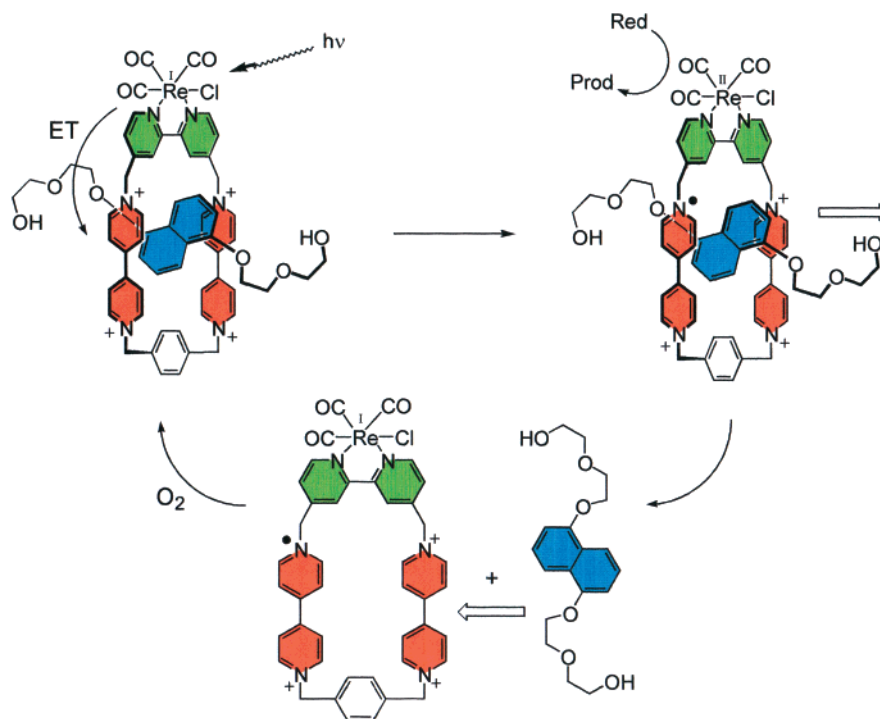


FIGURE 3. Cycloenantiomeric [3]rotaxanes and their CD spectra.

with chiral substituents. Photochemical *E*–*Z* isomerization produces a sterically strained state in which the methyl substituents are positioned in close proximity. The strain is released when the methyl groups switch their positions. This second step is followed by back-isomerization from the *Z* to the *E* form of the double-bond and again steric hindrance provides an energetically unfavorable state

which can reach an energetically more favorable state by a second flip of the substituents. These two systems are driven by the chemical energy that is released upon bond formation and cleavage in Kelly's rotor and by light inducing the isomerizations of Feringa's molecule. This brings us directly to the next point: How to fuel a molecular motor?

Scheme 7. A Molecular-Scale Piston Cylinder Machine Driven by Light



Light, Electrons, and Chemical Energy: Fueling the Motor

As discussed above, a molecular motor must be driven by a potential gradient, not merely background heat. There are at least three different sources of energy for driving rotaxane-based molecular motors:³² light, which is the driving source for proton translocation in photosynthetic systems; the reaction energy of any appropriate chemical transformation; and the electric energy that is applied to the motor by means of electrochemical methods. All these approaches have been used in recent studies, and in the following section, we present a small selection from these. It should be noted that most of these studies^{5,6,14} involve the shuttling motion of rotaxanes or the circumrotation of catenanes, and the threading/dethreading of pseudorotaxanes has been controlled by external stimuli. Since these movements are closely related, we will discuss examples for each of them.

Driven by light, the dethreading of a rodlike molecule from a pseudorotaxane can be realized, followed by rethreading after oxidation by air (Scheme 7).³³ In the resting form, the (electron-rich) axle of this “piston cylinder” machine is held inside the (electron-poor) bis-paraquat cyclophane as the wheel by π -donor π -acceptor interactions. Upon irradiation, a photosensitizer built into a pseudorotaxane structure transfers an electron to one of the paraquat units in the wheel. In its reduced form, the noncovalent forces between the axle and the wheel are reduced, and the axle dethreads if the back electron transfer is suppressed by reducing the photosensitizer with a sacrificial reductant such as sodium oxalate. Addition of oxygen to the solution reoxidizes the cyclophane wheel, and rethreading occurs.

A similar approach has been realized recently with a rotaxane structure (Scheme 8).³⁴ Again irradiation of a photosensitizer, which simultaneously serves as one of the stoppers, provokes electron transfer to one of the two different bipyridinium units incorporated in the axle, thereby reducing this “station” and inducing ring motion to the second bipyridinium unit. Again, a sacrificial reductant is necessary to efficiently suppress back electron transfer. Reoxidizing the bipyridinium cation-radical to the dication induces back shift of the wheel.

The rotaxane depicted in Scheme 9 bears a cyclophane wheel with two paraquat building blocks.³⁵ Two different “stations” are incorporated in the axle, and the preferred location of the wheel is in proximity to the benzidine part. Ring shuttling to the biphenol part can be induced chemically by protonation of the benzidine nitrogen atoms or by oxidation of the benzidine part to its cation-radical. In both cases, charge repulsion with the four-fold positively charged wheel induces ring migration to the biphenol station. Both processes are reversible, and either addition of a base or reduction of the benzidine cation-radical, respectively, leads back to the resting state.

An analogous process can be implemented in a catenane structure (Scheme 10).³⁶ One- or two-electron oxidation of the tetrathiafulvalene moiety to the corresponding cation-radical or dication provokes circumrotation of the catenane rings leading to a structure where the cyclophane wheel with its two paraquat units is located in proximity to the 1,5-dioxynaphthalene part of the crown ether ring. The switching process can easily be monitored by the color change from dark green to maroon. Again, the process is reversible and reduction of the tetrathiafulvalene to its neutral form shifts back the ring to its resting state. The two latter examples illustrate

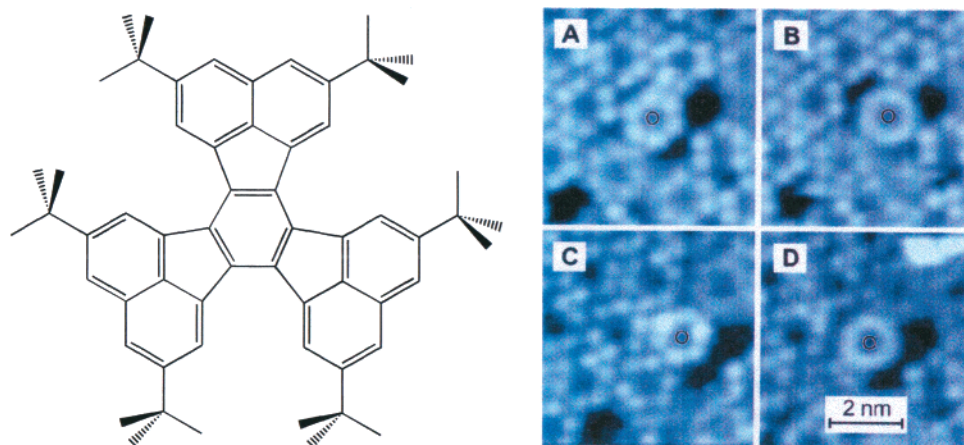
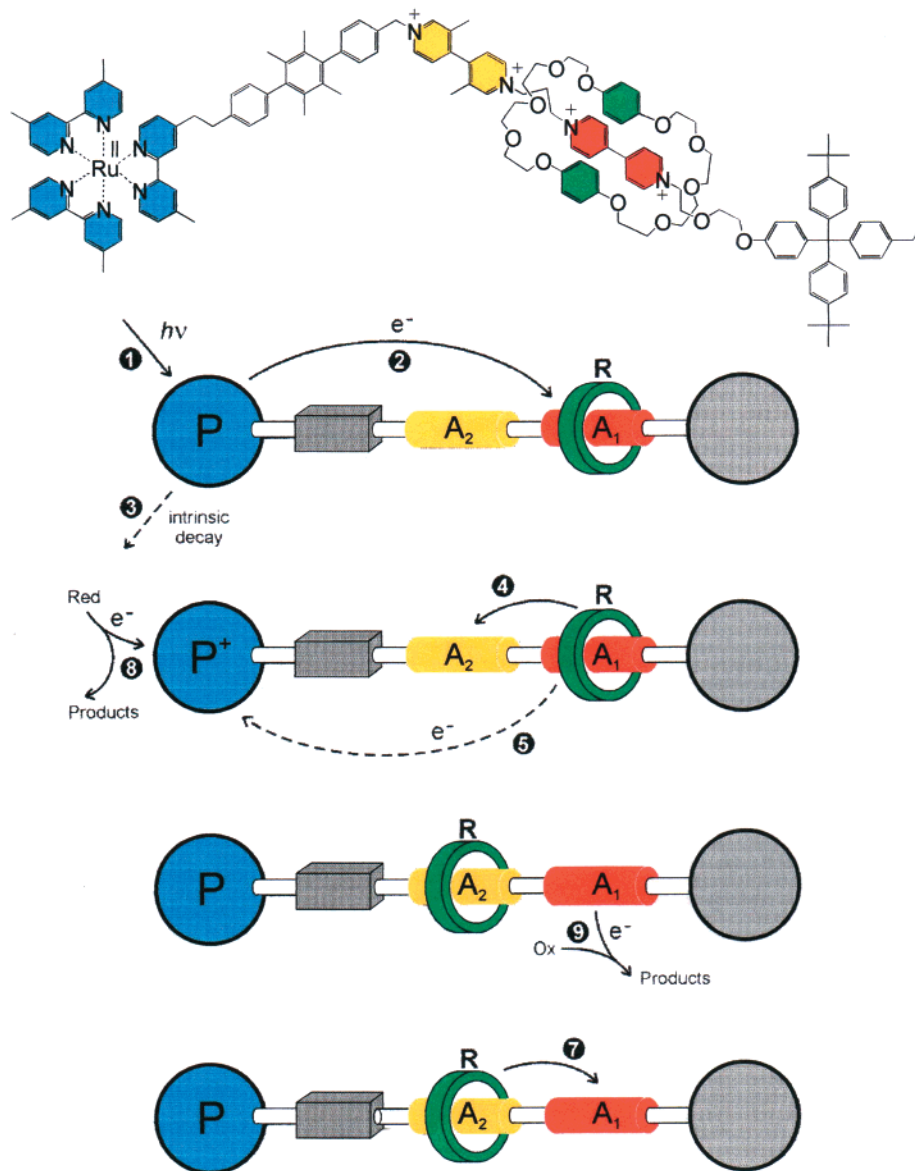
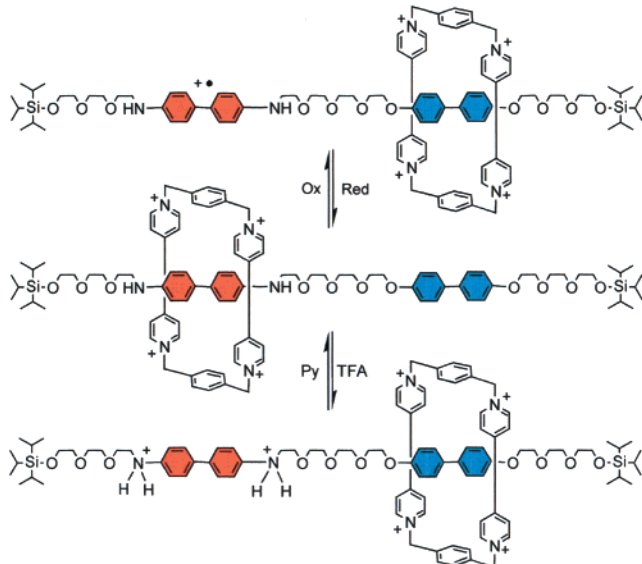


FIGURE 4. Hexa-*tert*-butyl decacyclene behaves as a molecular rotor in the voids of a Cu(100) surface covered with somewhat less than a monolayer (B and D). In those areas where the molecules are surrounded by an appropriate number of neighbors, rotation is stopped at room temperature (A and C). The white lobes correspond to the *tert*-butyl groups. Reproduced with permission from ref 41. Copyright 1998 American Association for the Advancement of Science).

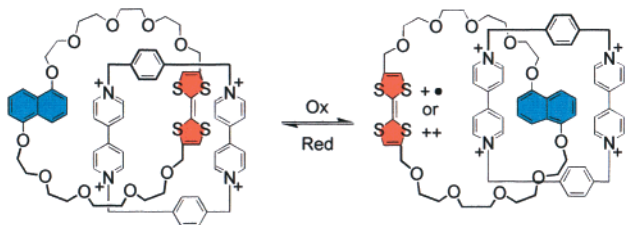
Scheme 8. A Molecular Abacus Controlled by Photochemistry



Scheme 9. The Position of the Cyclophane Ring on the Rotaxane's Axle Can Be Controlled Either Chemically or Electrochemically



Scheme 10. Triggering the Circumrotation of a Catenane by Chemical or Electrochemical Signals



that ring motion can be induced either chemically or electrochemically.

Another approach to electrochemically driven catenanes (or rather catenates) is realized in the copper-

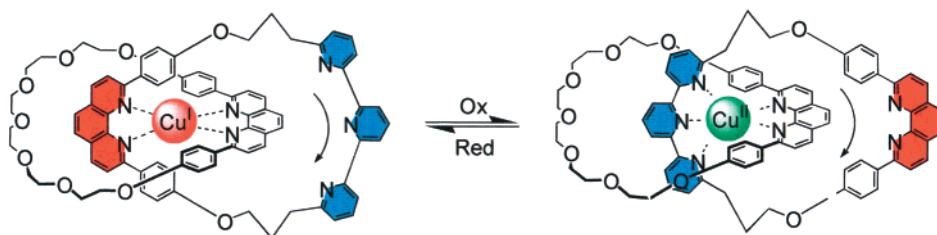
containing catenate in Scheme 11.³⁷ One of its rings bears a phenanthroline and a terpyridine unit, while the second cycle is equipped with a phenanthroline only. Depending on the oxidation state of the copper ion binding the two rings in its coordination sphere, either one is preferred. While Cu(I) is surrounded by a tetrahedral array of ligating nitrogens, Cu(II) favors trigonal-bipyridal coordination. Starting with Cu(I), the two phenanthroline moieties are complexed to the copper ion. Upon oxidation to Cu(II), a metastable state is generated and the catenate stabilizes itself by switching to coordination of the terpyridine instead of the former phenanthroline. Reduction to Cu(I) reverses the process. Finally, Scheme 12 shows the same basic principle realized in a rotaxane structure.³⁸

Membranes and Surfaces: Macroscopic Effects through Order?

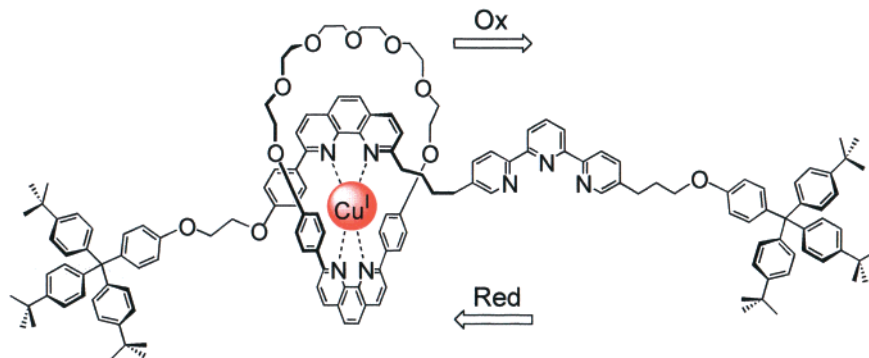
The last question which we would like to address is the following: Can macroscopic effects be achieved by ordering a large number of devices in a controlled way? The examples of natural ATP synthase and the photosynthetic reaction center (and artificial mimics of it)³⁹ provide evidence that this is indeed possible. Proton translocation through the thylakoid membrane leads to measurable pH differences on both sides.

Not only membranes may organize mechanical devices in such a manner. Attachment, for example, to a metal surface, also has been used to orient large numbers of species in a precisely defined way.⁴⁰ In the context of artificial motors, we would like to address only one particularly interesting study⁴¹ in which the rotation of a planar aromatic molecule hexa-*tert*-butyl decacyclene (Figure 4) on a surface has been examined by atomic force microscopy. Depending on the proximity of its neighbors, rotation can be hindered. With six neighboring molecules

Scheme 11. A Copper Catenate That Is Electrochemically Switchable between Two States Involving a Controlled Ring Motion



Scheme 12. An Electrochemically Driven Molecular Shuttle



on a surface covered with a complete monolayer, no rotation is possible under the conditions of the experiments. If, however, the surface is covered by an incomplete layer, those molecules located in an open "hole" can freely rotate at a frequency of more than 30 kHz. Although the rotation is clearly due to thermal motion, this example nicely shows how subtle effects can be addressed by ordering the molecule of interest on surfaces.

Conclusions: The Long Way to Artificial Molecular Motors

A critical view of the developments achieved on the way to artificial molecular motors makes clear that most of the important questions involved in the design of artificial motors have been addressed more or less separately so far. Unidirectional rotation has been realized for molecules that do not rotate continuously; experiments using light or chemical energy as fuel for nanoworld motors have not been carried out with molecules capable of rotating in one direction only. The problem of how to attach a machine that is driven by the motor, that is, the question how the motor could do useful work, has not been solved so far. In conclusion, there is still a long way to go. Nevertheless, the area of chemistry devoted to the design and generation of artificial molecular motors has developed quickly during the past few years. Many fine results from different systems await their integration into one rotaxane, which then may indeed act as a rotary device. With the natural ATP synthase as a prototype in mind, it is comforting to know that the generation of such a motor is at least in principle possible, and we trust that the goal to build an artificial analogue will be reached within the next decade or so.

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