Review

Molecular Machines

ZOUHAIR ASFARI and JACQUES VICENS
E.C.P.M., Groupe de Chimie des Interactions Moléculaires Spécifiques, UMR 7512 du CNRS, 25, rue Becquerel, F-67080 Strasbourg, France

> *It is enough to create new names, estimations and probabilities in order to create in the long run 'things'.*
> F. Nietzche: *The Gay Science*

> *We commonly accept the feasibility of new devices without formal proof, where analogies to existing systems are close enough.*
> K. Eric Drexler: *Proc. Natl. Acad. Sci. USA* **78**, 5275 (1981)

> *The designer and the inventor, who bring elements together in new combinations, are each able to assemble and manipulate in their minds devices that as yet do not exist.*
> E. S. Ferguson: *Science* **197**, 827 (1977)

1. Introduction

One of the consequences of the research dealing with supramolecular systems and self-assembling architectures is the development of synthetic strategies for constructing artificial systems with a precise disposition of atoms and functional groups to obtain a desired behaviour [1]. Molecular manufacturing [2] and molecular engineering [3] are approaches to the development of general capabilities for molecular manipulation to produce new organic and biological materials manufactured 'atom by atom' [4] at the molecular level. For example such terms as 'Molecular-size Tinkertoy construction' [5], 'Molecular Lego' [2], and 'Molecular Meccano' [6], with an obvious reference to children's construction games, have been used in the literature to characterize this branch of organic chemistry. The ability to build single custom-designed molecules and assemble them into systems of defined size has been recently described by Kelly and co-workers [7] in terms of *molecular Vernier*. Three molecules of a dicarboxylate were combined with two molecules of a triguanidinium to give a pentamer of predetermined dimension.

Thus, molecular machines are in vogue but there is no definition of what they are, nor what they are directed towards [8]. Numerous examples have been given in the literature in the last few months of chemically-, electrochemically- and/or photochemically-active molecular switches or devices, sensors, logic gates etc. In most cases these molecular machines are using chemical or electrical energy or light to work [9–13].

In the present paper we will only describe molecular-sized systems (either molecular or supramolecular) exhibiting *mechanical* properties interpretable in terms of *classical mechanics*. That is they can be seen as an assemblage of parts designed to transmit or modify the application of power, forces, or motions to others in a predetermined manner [14–16]. Their mechanical properties are rather related to geometries, thermal rotation of single bonds, steric effects, transmission of forces through rigid architectures than to molecular devices working with an external energy different from natural thermal activation. A very recent example of such a molecular machine has been reported by Gimzewsky and co-workers [17]. This paper describes the rotation of a single molecule within a supramolecular bearing. The authors demonstrated the real-space realization of single-molecule rotors surrounded by like molecules that form a supramolecular *bearing*. Evidence of the high rotation of these rotors, driven by thermal energy at room temperature, was obtained by means of scanning tunneling microscopy (STM).

2. Propellers, Gears, Bevel Gears and Toothed Cogs

In 1976 Mislow [18] reported an account of the stereochemical consequences of correlated rotation in *molecular propellers*. When two or more aryl rings (Ar) are attached to a single atomic center (Z), rotation about the C—Z bond axis by one of the aryl rings in Ar_nZ is sensed by the other $n - 1$ rings (Figure 1 gives an Ar_3Z model). The motions of the aryl rings are coupled in the sense that none of the rings moves independently of the others. This behaviour was called *correlated rotation*.
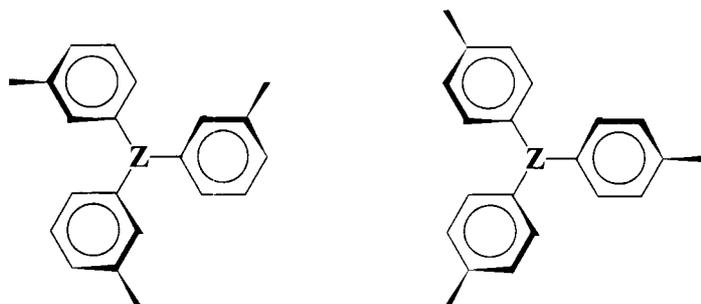

Figure 1. Ar_3Z molecular propellers.

Mislow and co-workers [19, 20] and Iwamura and co-workers [21, 22] invoked correlated or geared rotation in Tp_2Z systems presenting two triptycenes (Tp)
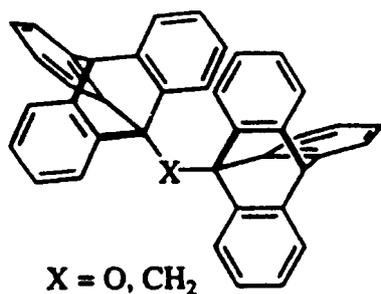
Figure 2. **Tp₂Z** bevel gears.

linked by one oxygen or by a methylene bridge (Z=O or CH$_2$) (See Figure 2). Un-expectedly fast internal rotation observed in such apparently sterically-congested molecules led to the idea of a molecule acting as *a bevel gear*. ^{1}H- and ^{13}C-NMR showed that C—O rotation in bis(1-triptycyl) ether Tp$_2$O occurred even at −94 °C, the barrier height being not greater than 8 kcal mol^{-1} [20]. The bevel gears were labelled by a chlorine at the 4-position of the triptycene of Tp$_2$O and by two methyl groups on the 3- and 4-positions in Tp$_2$CH$_2$ to definitively demonstrate by stereoisomerism considerations that there is a real gear and not just a slippage of the triptycene three-toothed gears [21].

Rotors such as Tp$_2$Z are limited by the presence of only *three cog teeth*. In order to increase the number of cog teeth, Stevens and Richards [23] designed a *metallocene molecular gear* combining an acetylene substituted triptycene and a tetraphenylcyclobutadiene linked through a cobaltocene unit (see Figure 3).
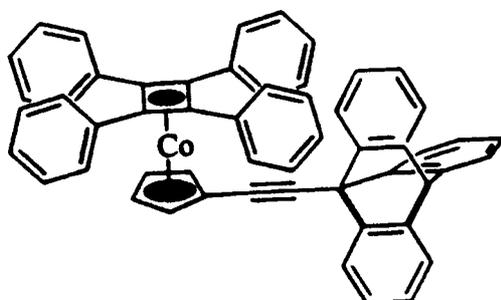

Figure 3. A metallocene molecular gear.

The tetraphenylcyclobutadiene represents a four-toothed cog. Variable temper-ature ^{1}H-NMR indicated that the rotation of the triptycene is still rapid even at 203 K on the NMR timescale. The simplicity of the peaks from the four phenyl groups revealed that rotation about the metal and about the phenyl-butadiene bonds is also rapid at 203 K.
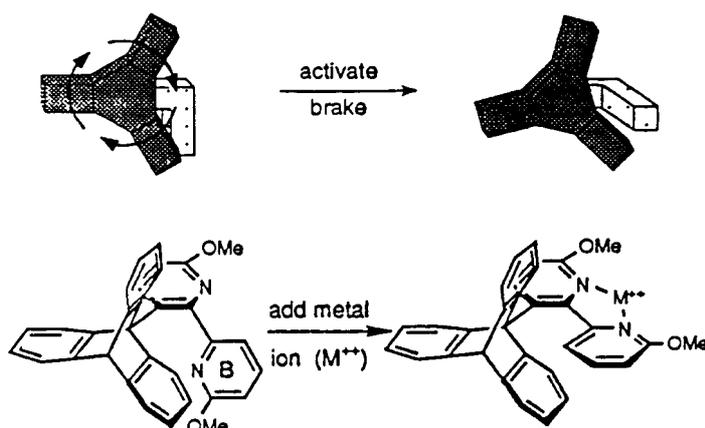
Figure 4. Conceptual and molecular depiction of a molecular brake.

3. Brakes, Ratchets and Turnstiles

The preceding examples describe free rotation around single bonds. This motion is due to natural thermal activation. In order to arrest free rotation, Kelly and co-workers [24] reported *a reversible molecular brake* as a molecular analog of mechanical brakes. Figure 4 presents the conceptual and molecular depiction of a molecular brake.

When the brake is disengaged, the wheel represented by a triptycene spins rapidly around the C—C bond between the triptycene and the bipyridyl unit. Addition of Hg^{2+} ion resulted in the formation of a complex which rigidified the bipyridyl unit and activated the brake. The effect was shown by ^{1}H-NMR. A simple, well-resolved ^{1}H-NMR spectrum was observed for the pure ligand at 30 °C. Addition of $Hg(O_2CCF_3)$ resulted in a coalescence pattern attributable to a strong coordination with the nitrogen atoms rigidifying the bipyridyl. At −30 °C the three aromatic rings of the triptycene were no longer equivalent because of the arrest of the rotation on the NMR time-scale. Treatment of the Hg^{2+} complex with EDTA removed the Hg^{2+} and released the brake restoring the free ligand. This was the first example of a molecular brake which operates by coordination of a metal at a *remote* site to bring about a conformational change that reversibly halts rotation of a molecular-scale gear. This communication has been highlighted by Constable and Smith [25].

Kelly and co-workers [26] have also reported a *molecular rachet*. Figure 5 shows the mechanical ratchet composed of (a) a toothed ratchet wheel, (b) a pawl that prevents unintended rotation of the ratchet wheel, and (c) a spring that holds the pawl against the wheel. Both tension and the contours of the ratchet wheel and the pawl impose the ease and the direction of rotation. The molecular ratchet is composed of a triptycene as ratchet wheel and [*n*]helicenes as pawls and springs. Two molecular ratchets were synthesized with *n* = 3 and 4. Unexpectedly, the ratchet
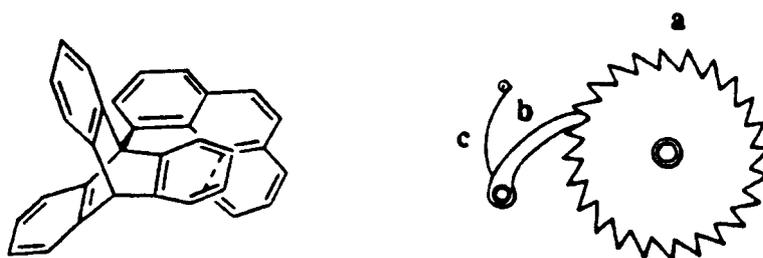
Figure 5. Conceptual and molecular depiction of a molecular ratchet.

with *n* = 3 presented a greater barrier to the triptycene/helicene bond. Because of the helicity of the [4]helicene the rotation of the triptycene is favored in one direction. This was shown by a calculated energy diagram, fortunately in agreement with spin polarized transfer data. The main interest resides in the possibility of preparing a molecule in which one bond rotates in one direction.

The communication of Kelly and co-workers [26] has been highlighted twice. First, Bradley [27] in a paper entitled 'What a ratchet' concluded that the ability to modulate the barrier to free rotation should make these molecules useful components of more complex systems such as *molecular motors*. Second, from a thermodynamic point of view and with reference to *Maxwell's demon* [28], Davis [29] entitled his paper 'Tilting at Windmills? The Second Law Survives' expressing some doubts because such a process may not occur because of the Second Law of Thermodynamics and reporting of theoretical arguments against molecular ratchets and *trapdoors* [30]. The later controversial communication has recently been answered by Kelly and co-workers [31], indicating that in fact rotation in one direction (if any) was rather difficult to evidence.

Bedard and Moore [32] reported the design and synthesis of a molecular *turnstile*. The turnstile architecture consists of a hexa(phenylacetylene) macrocyclic frame and a diethynylarene bridge (see Figure 6).

The bridging unit acted as the *spindle* of a turnstile with rotational motion around its own axis. The architecture should present conformational bistability corresponding to two stable positions in which the aromatic moiety in the spindle is perpendicular to the hexa(phenylacetylene) macrocyclic frame. Hindrance to rotation about the spindle occurred with steric interactions between R groups attached to the spindle and the macrocycle framework. This provided two achiral derivatives which provided homomeric rotamers. Combination of chirality and dipolar order may have important implications in designing electroattractive materials.

4. Pendulums and Hour Glasses

The conformational characteristics of macrocyclic cyclophanes, especially those of calixarenes, have been widely demonstrated. Calixarenes are made of phenolic units ordered in well-shaped cyclic arrays due to strong intramolecular hydrogen
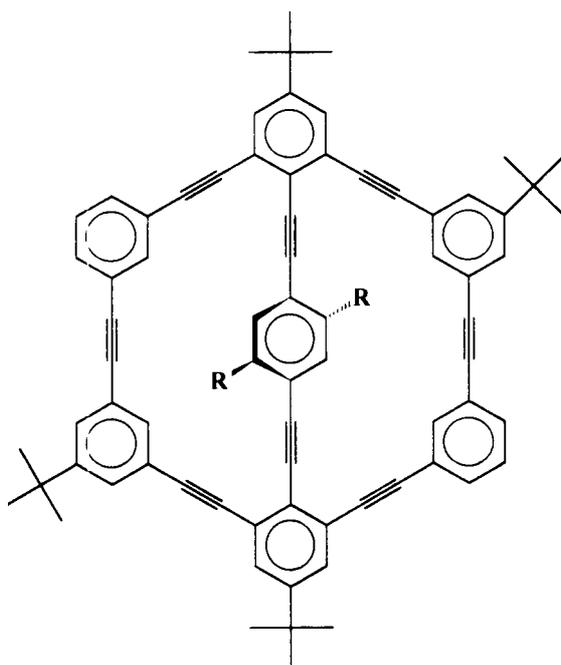
Figure 6. Chemical structure of a molecular turnstile.

bonds. The phenolic units can pass through the macrocyclic ring to interconvert from one conformation to another. Yamato and co-workers [33] have prepared a hydroxy[3.l.l]metacyclophane which can be regarded as an unsymmetric or incomplete homocalixarene bearing a propane bridge (see Figure 7)

The dimethoxy derivative is fixed in an asymmetric partial cone conformation at room temperature. The two methoxy groups point up and down with one enclosed within the π-cavity formed by two benzene rings. By increasing the temperature the methoxy groups flipped from one side to the other by ring inversion acting like a *molecular pendulum*. Hydrogen bonding between the OH and the flipping methoxy was considered to be the force maintaining both the stable positions of the pendulum. The free energy of activation of conformational inversion was estimated to be 16.7 kcal/mol.

Vicens and co-workers [34] have observed very similar behaviour in a multi-functional calix[4]arene-derived phosphinite in the 1,2-alternate conformation and bearing two phosphinites and two methoxy groups arranged in a $2 + 2'$ manner. In this molecular arrangement, the two methoxy groups are pointing up and down and *rocking* from one position to the other topologically equivalent one.

Shinkai, Vicens and co-workers [35] have also reported the synthesis and metal cation complexing properties of 1,3-calix[4]-*bis*-crown-5 (Figure 8). The molecule combines one calix[4]arene unit in the 1,3-alternate conformation and two tetra-
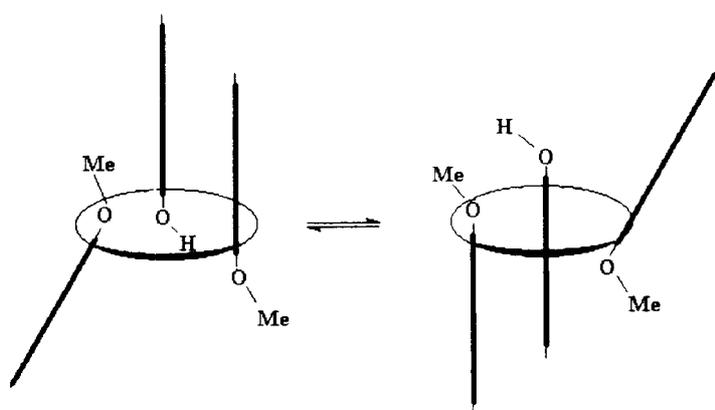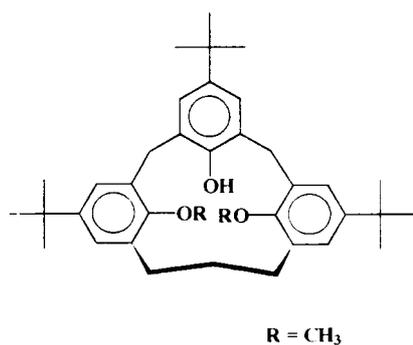
R = CH₃

Figure 7. The dimethoxy derivative of the hydroxy[3.1.1]metacyclophane acting as a pendulum.
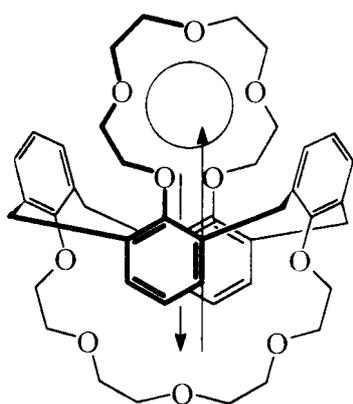

Figure 8. 1,3-calix[4]-*bis*-crown-5 acting as an hour-glass.

ethylene glycol ethers attached to the calixarene through O-linkages. In this geo-
metry the molecular receptor presents two equivalent binding sites delineated by
the oxygens of the polyether loops and two phenyl rings. These two metal-binding
sites are at the two edges of a tubular π-basic cavity providing an ideal architecture
to estimate metal oscillation occurring across a π-basic tube. The whole geometry
of the molecule resembles an *hour glass* in which the sand is represented by a
cation. Cation tunneling across the calix[4]arene cavity was detectable by [1]H-
NMR spectroscopy even at room temperature. The phenomenon was observed to
be *independent of the concentration* of the investigated sample.

5. Globes, Gyroscopes, Rotors and Mills

Asfari and coworkers [36] have reported the synthesis of *molecular mappemondes*
or *gyroscopes* [8] (Figure 9). They are constructed from a globular 1,3-calix[4]-*bis-*
crown-6 held in the arms of a polyether loop. The presence of only well-resolved
singlets for the Ar—CH$_2$O methylene protons in the ^{1}H-NMR indicated that the
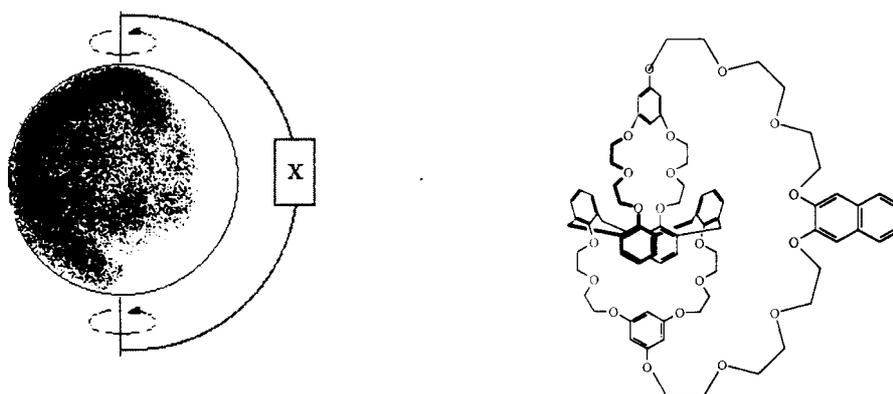calixcrown top spins.

Figure 9. Molecular mappemondes.

Depending on the length of the polyether arm, Asfari and co-workers [37] isol-
ated the corresponding 2 + 2 dimer in addition to the 1 + 1 condensation molecular
globe.

This molecule can be seen as a *molecular mill* (Figure 9) in which the two
rotors are maintained by two polyether loops. Similarly, a well-resolved singlet
for ArCH$_2$O protons indicated the free rotation of the calix rotors. In the presence
of an excess of ammonium picrate, molecular mappemondes and the molecular
mill formed multi-nuclear complexes with coalescence of the ^{1}H-NMR spectra,
indicating that the spinning of the globes had stopped.

Very similar systems in which the calix globes have been replaced by trypticene
units have been reported. Trypticenocrown ethers were described to perform *rope-*
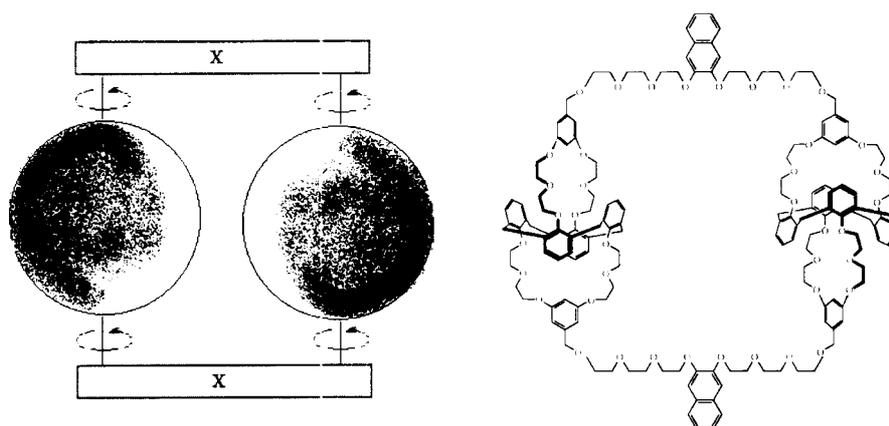
Figure 10. A molecular mill.

skipping in which the the trypticene rotation was slowed down by coordination of thallium by a crown ether loop [38]. *Bis*-trypticenecrown ethers in which two trypticene gears are connected by two polyoxyethylene links at their axles showed correlated rotation [39].

6. Shuttles, Stations, Rotaxanes

The name *rotaxanes* was coined by Schill and Zollenkopf [40] for *mechanically interlocked* molecules consisting of a macrocycle and a chain with bulky end groups. They can be seen as a *ring* (the macrocycle) threaded along a *string* (the chain) and trapped there by *stoppers* (the bulky groups) at both ends of the string
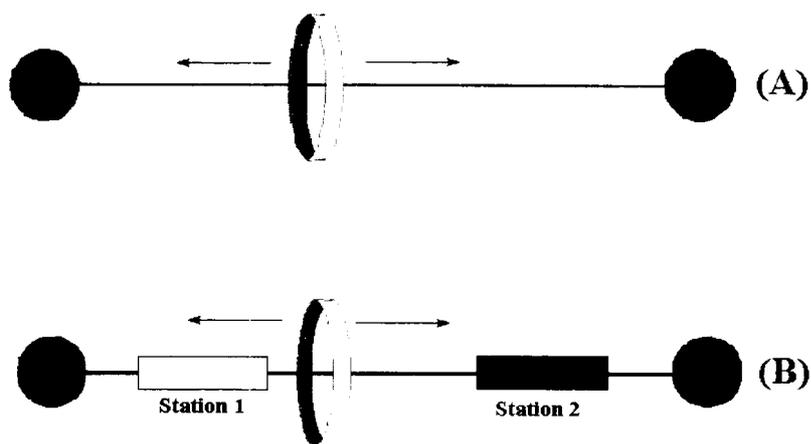

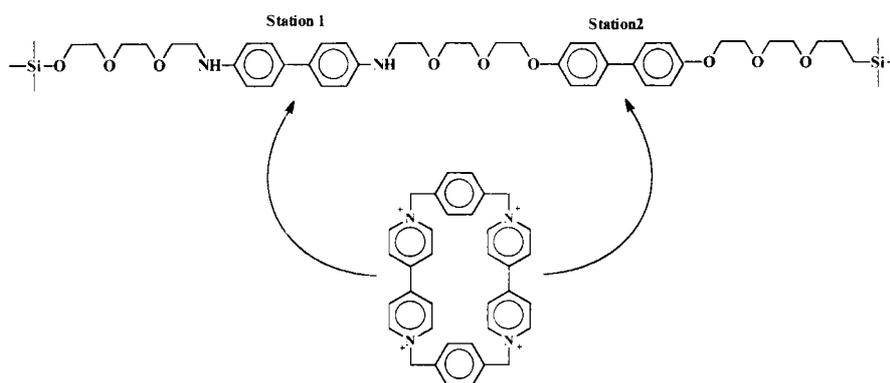*Figure 11.* Rotaxanes (A) acting as shuttles with stations (B).

Figure 12. Bipyridium shuttle with benzidine (station 1) and diphenol (station 2) stations.

(Figure 11A). Due to thermal agitation, the ring glides along the string, acting as a *shuttle*. The inherent restrictions in rotational and translation freedom in rotaxanes have permitted the precise *control* of the *positioning* of the ring along the string at so-called *stations* (Figure 11B). The stop of the shuttle at a given station is controllable by usual intermolecular forces.

Stoddart and co-workers [41] described a rotaxane combining a π-electron-accepting tetracationic cyclophane comprising two bipyridinium units bridged by two *p*-xylyl spacers as the ring (Figure 12). The two stations were biphenol and benzidine units (as electron donors). At room temperature the ring moved back and forth along the string at a rate comparable to the NMR timescale. This led to a broadening of many NMR signals for the rotaxane. By cooling the solution to 229 K, two dimensional NMR revealed that the shuttle stopped at the two stations. Preferential occupation of the benzidine *station 1* (84%) over the diphenol *station 2* (16%) was observed. The average position of the shuttle could be switched over to the diphenol station either by protonation of the basic nitrogens of the benzidine residue or by electrochemical oxidation of this station.

Sauvage and co-workers [42] have reported a rotaxane whose ring incorporates a ddp (ddp = 2,9-diphenyl-1,10-phenanthroline or shuttle) and whose open-chain molecular string consists of a bidentate coordinating unit (2-alkyl-9-phenyl-1,10-phenanthroline *station 1*) covalently attached to a terdentate ligand (terpy = 2,2′,6,2″-terpyridine *station 2*) (Figure 13). Copper(I) was used to construct the rotaxane by enforcing the string to thread through the ring while generating a *bis* chelate complex between copper(I) and the two 2,9-disubstituted-1,10-phenanthrolines. The system could be switched from a 4-coordinate to a 5-coordinate situation and vice versa by taking advantage of the different geometrical requirements of the two redox states of the copper(I)/copper(II) couple. The positioning of the ring at station 1 or 2 depended on the redox states of the copper.

Leigh and co-workers [43] have prepared a peptide rotaxane containing an iso-phthaloyl benzamide macrocycle as ring and a string consisting of a polyether chain
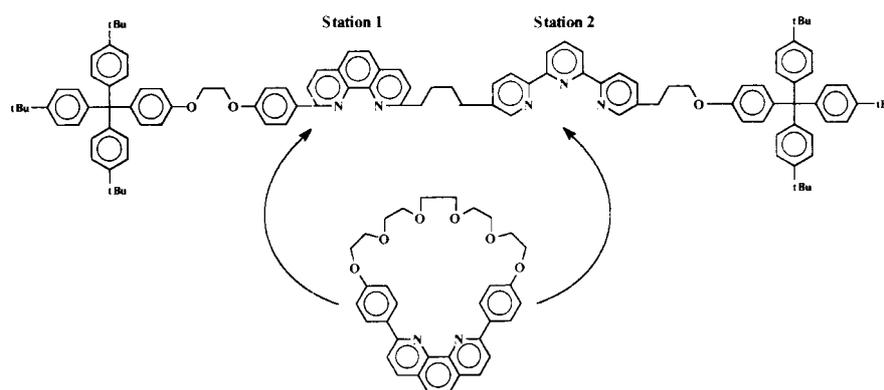
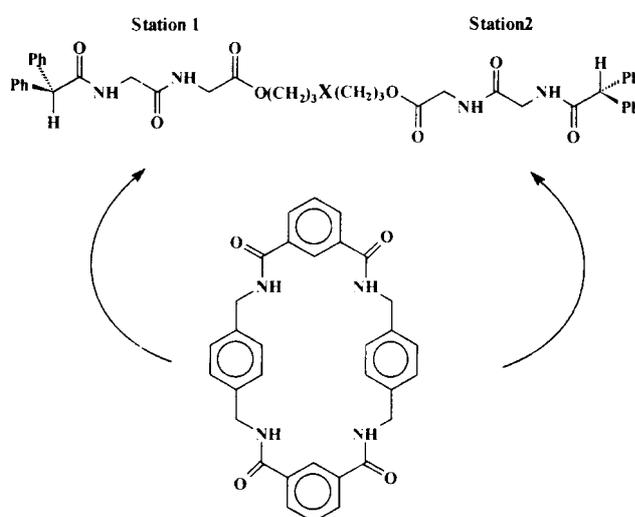*Figure 13.* Shuttle moving with the redox state of copper.

Figure 14. Peptide-based molecular shuttle.

terminated by two glycylglycine units as peptide stations 1 and 2 (see Figure 14). In CDCl$_3$ the ring was observed to shuttle from station 1 to station 2 due to the formation of hydrogen bonds between the ring and the peptide residues of the string. Cooling below the coalescence temperature for the shuttling process froze the ring at a single peptide station. In the presence of DMSO-d_6 hydrogen bonding disappeared and the ring stopped shuttling between the stations 1 and 2 to spend nearly all of its time on the lipophilic middle-part of the string.

7. Transmission of Forces and Energy. Allosteric Molecules

In the preceeding sections we presented molecular systems in motion and/or with modified motion. We now present a molecular model transmitting applied forces
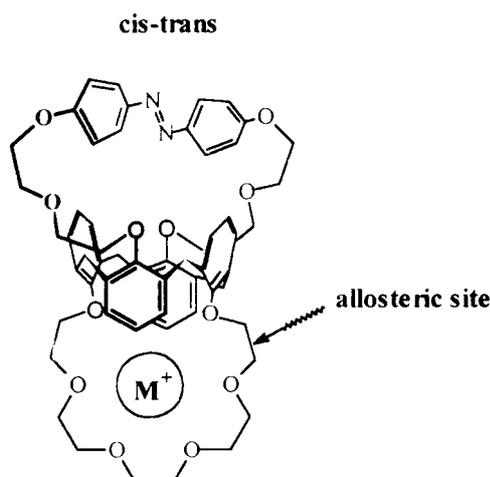
Figure 15. Allosteric receptor.

or energy. This behaviour is known in biology as *allostery*. In order to mimic *allosteric enzymes* [44], supramolecular chemists have developed artificial allosteric systems in which the allosteric site communicates with another part of the molecule via several bonds [1]. Saadioui and coworkers [45] have reported an azobenzene modified 1,3-calix[4]-*bis*-crown as an artificial potentially allosteric system. The receptor is shown in Figure 15.

The receptor combines a calix[4]arene unit in the 1,3-alternate conformation and two crown ether elements. One crown ether contains an azobenzene function existing in *cis* and *trans* forms in a *trans/cis* ratio equal to 70/30 for the free ligand. The *trans/cis* ratio changed from 70/30 to 80/20, 80/20, and 85/15 when the 1 : 1 complexes in chloroform with K^+, Rb^+, Cs^+, and NH_4^+ respectively were formed in chloroform. The largest changes probably occurred in the strongest complex. The transformation of the energy of complexation into conformational changes is mainly due to the transmission of this energy through the rigid molecular frame of the calix unit which acts as a *lever*. It will be of interest to evaluate the energy of complexation and to compare it to the energy needed for the conformational changes of the *trans-cis* forms.

8. Conclusion

Biology is a *never ending source* of molecular machines [30, 46–49]. Schneider [15, 16] has proposed a *theory of molecular machines* presenting some of their features and characteristics. Although his papers mainly deal with thermodynamics applied to biological events, the definitions and concepts given for biological molecular machines can be used for chemical ones:

- A molecular machine is a *single molecule* (propellers, gears, cogs, ratchets, turnstiles, etc.), *interlocked molecules* (shuttles), or *a supramolecular complex* (molecular brake, time-glass).
- Each molecular machine acts as *an individual*.
- The *source of energy* of a molecular machine is the natural thermal agitation.
- A molecular machine performs *a specific operation*. It performs precise logical *operations* as for instance propellers, gears and cogs precisely constructed to provide a unique operation.
- An operation can occur because the machine has the possibility to occupy two geometrically and thermodynamically *equivalent positions* as, for example, the pendulum and the hour glass which are comparable to molecular clocks or molecular pacemakers.
- An operation can occur in systems presenting *bis-stability*, as the turnstile and the rachets. The isolation of both separate asymmetric systems is of interest for thermodynamical purposes.
- The operation can also be defined by *two limiting states*. For example, in the molecular brake, the first step is *before* operation when the trypticene turns around the C—C bond and the second step corresponds to *after* operation when the spinning is stopped.
- The operation can be *transmission* of power or forces.
- The operation performed by a single molecular machine gives *information* which can be used for further investigation.

The story of molecular machines is just at its beginning, and in order to develop as a separate field it is necessary to give birth to a large variety of simple molecular systems providing a *mechanical alphabet* [50], to associate individual molecular machines and design new devices, even if they look like useless.

Leonardo da Vinci is as famous for his paintings as for his scientific works. He is credited to be the inventor of mechanics and machinery. From 1490 and 1495 he developed his habit of recording his studies in illustrated notebooks. In 1493, he sketched a series of plates of weapons, loads, flying machines, geometry, and *machinery* known as the 'Tratado de Estetica y Mechanica en Italiano' as part of the *Codex of Madrid*. From his *mechanical* sketches, he drew a machine made of 13 like cogs in order to maintain a constant ratio of ten to one in each of them, seemingly with no use. In fact, he was designing the precursor of a so-called *device for calculation*, without knowing it.

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Jacques Vicens was born in Marseille (France) in 1945. He gained his Doctorat d'Etat (Ph.D.) in 1978 at the Université Louis Pasteur de Strasbourg (France) under the direction of Doctor Jean-François Biellmann. During his Ph.D., he developed the chemistry of carbanions α to sulfur atom in relationshipo to ion-pairing effects. He spent a first post-doctoral position, in the year 1979, with Professor Alain Krief from the Université de Namur (Belgium) working on selenium compounds as intermediates to epoxydes and aziridines. Then, in 1980, he joined Professors Leslie Leiserowitz and Meir Lahav at the Weizmann Institute of Science (Israel) where he was acquainted with organic solid state chemistry, mainly on photo-chemical reactions of sulfoxydes in asymmetric matrices. In 1981, he obtained a position at the Centre National de la Recherche Scientifique, at the Université Claude Bernard de Lyon (France) to develop a research on reactions of organic molecules and supermolecules in the solid state, involving photo-chemical reactions, gaseous hydrolysis, and gaseous chlorinations. During the year 1986, he began his research on calixarenes. In 1989, he went back to Strasbourg at the Ecole Europénne de Chimie, Polymères et Matériaux focusing his research on host-guest chemistry of calixarenes.

His is the author and co-author of nearly 170 scientific publications including reviews and 2 special issues of the *New Journal of Chemistry* and *Anales de Quimica* and 2 books as an Editor.

He is Associate Editor to the *Journal of Inclusion Phenomena and Molecular Recognition in Chemistry*.

He is the correspondent for France to *the Global Supramolecular Chemistry Network*.

Zouhair Asfari was born in Syria in 1954. He received his BSc degree in chemistry form the University of Alep in Syria in 1981. He then moved, in 1985, to the University of Besançon in France where he worked in the Organic Chemistry Laboratory with Professor B. Laude investigating lipid-protein interactions. In 1986, he obtained his DEA degree on that topic and then moved to the Université Claude Bernard (Lyon I). There he worked in Professor R. Perrin's Laboratory of Industrial Chemistry where he took up the study of supramolecular chemistry, particularly calixarene chemistry, under the supervision of Dr J. Vicens and obtained a PhD degree in 1989. After his PhD, he moved to the University of Twente in Enschede, Netherlands, for a one year-postdoctoral appointment in the group of Professor D. N. Reinhoudt, where he pursued his research on host-guest chemistry by synthesizing new calixarene compounds and investigating complexation by designed macrocyclic receptors in the liquid phase. In 1990, he returned to France, at the Ecole Européenne des Hautes Etudes des Industries Chimiques of Strasbourg of the Louis Pasteur University to work in the group of Professor M. Leroy again in association with Dr J. Vicens. His research interests have been documented in approximately 120 research papers. In May 1999, he obtained a position of research chemist within the CNRS in Strasbourg.