From Chemical Topology to Molecular Machines

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To a large extent, the field of "molecular machines" started after several groups were able to prepare reasonably easily interlocking ring compounds (named *catenanes* for compounds consisting of interlocking rings and *rotaxanes* for rings threaded by molecular filaments or axes). Important families of molecular machines not belonging to the interlocking world were also designed, prepared and studied but, for most of them, their elaboration was more recent than that of catenanes or rotaxanes. Since the creation of interlocking ring molecules is so important in relation to the molecular machinery area, we will start with this aspect of our work. The second part will naturally be devoted to the dynamic properties of such systems and to the compounds for which motions can be directed in a controlled manner from the outside, i.e., molecular machines. We will restrict our discussion to a very limited number of examples which we consider particularly representative of the field.

CHEMICAL TOPOLOGY

Generally speaking, chemical topology refers to molecules whose graph (i.e., their representation based on atoms and bonds) is non-planar [1–2]. A planar graph cannot be represented in a plane or on a sheet of paper without crossing points. In topology, the object can be distorted as much as one likes but its topological properties are not modified as long as no cleavage occurs [3]. In other

words, a circle and an ellipse are topologically identical. The most representative examples of topologically non-planar, and thus non-trivial, molecules are interlocking ring molecules or knotted cycles such as the trefoil knot. Interestingly, topology and chemistry were not at all connected till 1961 when two chemists working at Bell Telephone Laboratories, Frisch and Wasserman, published an important discussion simply entitled "Chemical Topology" [1]. For the first time, chemists were exposed to topology thanks to this seminal paper. It contains a very clear account of most of the ideas that constitute the background of chemical topology. For example, the idea of topological isomers (also named "stereoisomers") is introduced by comparing a [2]catenane (drawing III, two interlocked rings) to the set of the two separate cyclic molecules (object IV) as shown in Figure 1. Another example is provided by considering a single closed curve, which can be a normal cycle such as I (topologically trivial or planar) or the knotted cycle, the simplest example being the trefoil knot II. Hypothetic compounds I and II of Figure 1 are topological stereoisomers: although they may consist of exactly the same atoms in the same sequence, and the same chemical bonds between them, they cannot be interconverted by any type of continuous deformation in three-dimensional space.
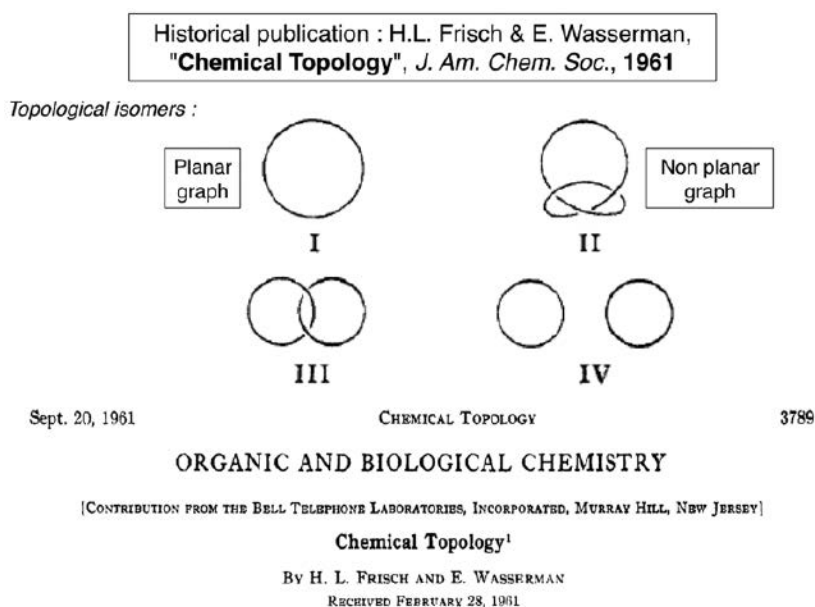

FIGURE 1. The historical publication introducing the notion of chemical topology in the chemical literature. Trefoil knot II and catenane III are topologically non-planar in the sense that their graphs, once projected on a plane, will always require crossings in order to be represented.

Schill's book *Catenanes, Rotaxanes and Knots*, written in 1971, is indispensable for the topologist [4]. In addition to interesting theoretical considerations regarding interlocked rings and knots, it contains much information on the experimental approaches used by Lüttringhaus, Schill and their co-workers to prepare such topologically novel systems. One of the first [2]catenanes to be reported in the literature was prepared by Schill and Lüttringhaus more than 50 years ago [5]. This remarkable piece of work was greeted by the scientific community due to the elegance of the procedure and also due to the impressive synthetic work it represented at the time. Unfortunately, the complete synthesis required a large number of steps and, as a consequence, the overall yield was limited. In spite of the novelty of the work, there were very few follow-up contributions from other organic chemists, mostly because of the extreme difficulty that a gram scale synthesis of such compounds would represent following a purely organic chemistry approach similar to that of Schill and Lüttringhaus.

Before our group started in the field of catenanes, we were interested in markedly different topics. We contributed to various research areas such as homogeneous catalysis of the water-gas shift reaction using iridium complexes [6], electrochemical reduction of carbon dioxide [7] and inorganic photochemistry [8] in relation to solar energy conversion to chemical energy. Like a relatively
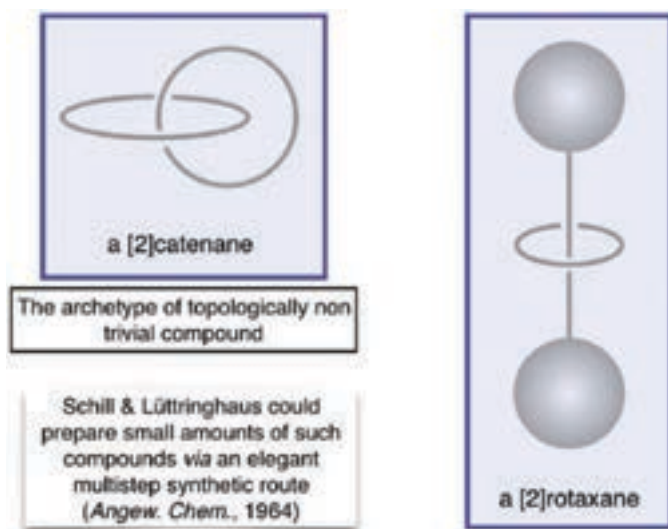

a [2]catenane

The archetype of topologically non trivial compound

Schill & Lüttringhaus could prepare small amounts of such compounds via an elegant multistep synthetic route (*Angew. Chem.*, 1964)

a [2]rotaxane

FIGURE 2. A [2]catenane and a [2]rotaxane. The number in square brackets (2 in this case) indicates the number of components incorporated in the interlocking structure. A [2]catenane is considered as the prototype of molecules having a non planar graph. In mathematics, the object consisting of two interlocking rings is called "Hopf link." Heinz Hopf was a German topologist.

large number of other research teams, we were fascinated by the "grand project" known by the community as "water splitting," i.e., photochemical splitting of the water molecule into oxygen and hydrogen, supposedly the ideal fuel for the future. Since the Nobel Foundation recommended that the laureates tell as honestly as possible "the story behind the discovery," I would like to explain how we moved from inorganic photosensitizers to catenanes and related species. At the end of the 70s, there was considerable interest for ruthenium complexes of the $Ru(bipy)_3^{2+}$ family (bipy : 2,2'-bipyridine) [9]. Several prestigious photochemistry groups had shown that this compound displays promising properties in terms of ability to transfer electrons, positive holes or electronic energy. Even more spectacular, several approaches to the "water splitting" reactions had already been reported [10]. A particularly interesting project was to replace the second raw ruthenium metal, notoriously know to be rare and expensive, by common first raw transition metals. Along this line of research, very few candidates appear as reasonable. The only one was copper(I) since this metal was known to form highly coloured complexes with aromatic diimine ligands of the bipy family. The absorption band responsible for the colour in the visible spectrum was shown long ago to be a Metal-to-Ligand Charge Transfer band. An American photochemist, David R. McMillin (Purdue University) had already published seminal work on the photochemical properties of copper(I) complexes in 1978 [11]. At the beginning of the 80s, our group prepared 2,9-diphenyl-1,10-phenanthroline (dpp) for various reasons, mostly in relation to sterically hindering ligands able to favour coordination unsaturation once complexed to rhodium or iridium centres [6]. David spent some time in Strasbourg when he was on sabbatical leave. He visited our group and, after several discussions, we embarked in a common project dealing with $Cu(dpp)_2^+$ and related complexes containing two intertwined ligands disposed more or less orthogonally to one another once coordinated to the central Cu(I). At that time $Cu(dpp)_2^+$ was unknown since dpp itself seemed to be a new compound. The beginning of this collaboration coincided with another major event which was the arrival of Christiane Dietrich-Buchecker in our team. Christiane had a superb organic chemistry background and we knew that she had all the necessary expertise for making novel ligands either by herself or associated to the PhD students she would co-supervise with me. Coming back to $Cu(dpp)_2^+$, by looking carefully at its three-dimensional representation [8] as shown on Figure 3, it was relatively easy to figure out that this compound, with its two intertwined ligands, was the ideal precursor to a [2]catenane.

There is perhaps an important factor in the fact that we recognised the link between $Cu(dpp)_2^+$ and catenanes: the molecules were drawn manually using Indian ink since this period corresponded to the "pre-ChemDraw era." We thus
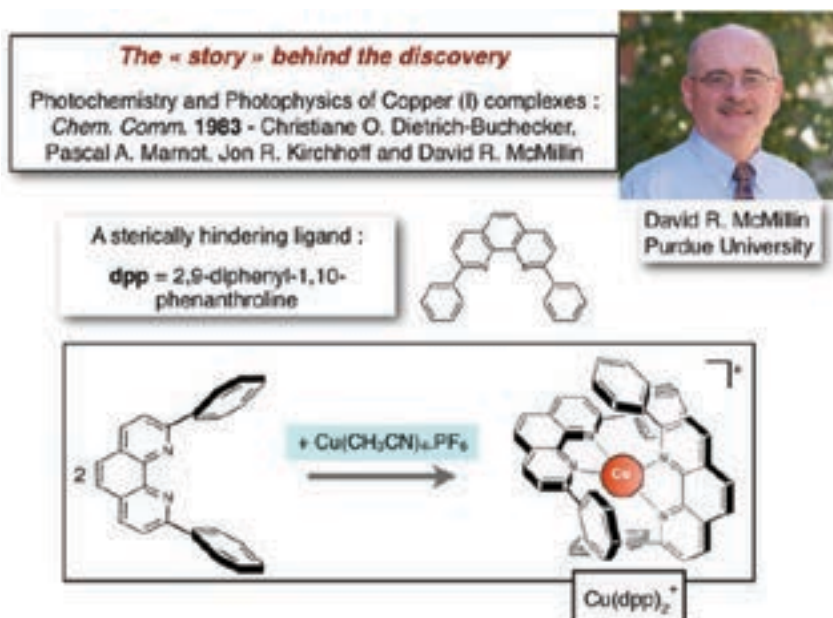
FIGURE 3. The simple coordination chemistry reaction leading to Cu(dpp)$_2^+$ and its 3-dimensional representation.

had time to completely "digest" the molecular structures of the compounds we were making and, first, that we had to draw. From the drawing of Figure 2, it is clear that by connecting the two para-positions of the phenyl nuclei attached to the same 1,10-phenanthroline group, one should obtain a ring. Furthermore, by doing this operation simultaneously on both dpp sub-units within the complex, formation of a [2]catenane appeared to be almost certain.

With Christiane, we thus embarked in the new field of catenanes. After a few months, we obtained the first positive results and about one year after the beginning of the project, the first communication on our new strategy for making interlocking rings was published [12] (Figure 4).

We described this new strategy as a *3-dimensional* template synthesis around a transition-metal centre by reference to classical template effects so efficiently used for making macrocycles by several groups such as Busch and his team in particular [13]. The work seemed to be the first practical synthesis of a [2]catenane in the sense that, for a good chemist, 500 milligrams could be obtained within a few weeks. After the preparative work performed by Christiane, what remained was to characterise the compound and convince ourselves that the molecule obtained was indeed a [2]catenane. ^{1}H NMR studies demonstrated
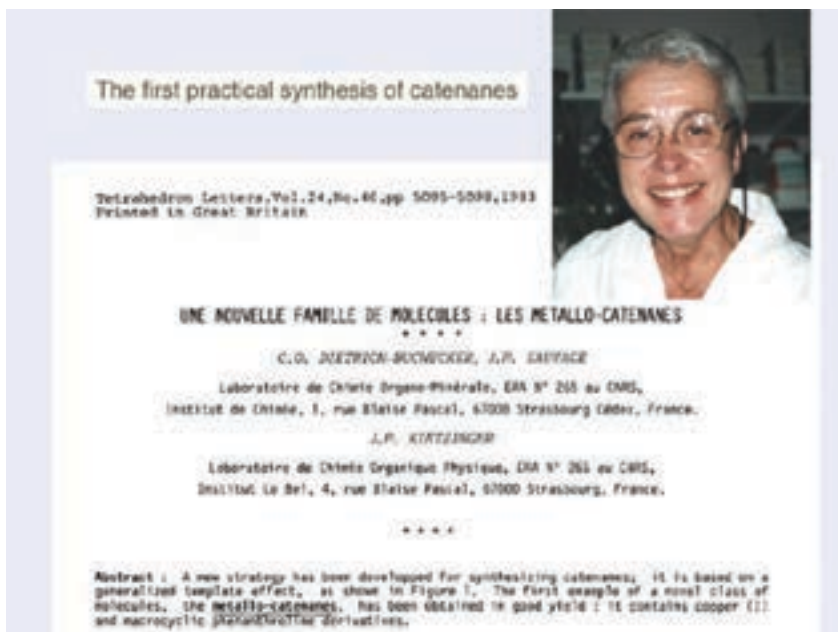
The first practical synthesis of catenanes

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UNE NOUVELLE FAMILLE DE MOLÉCULES : LES METALLO-CATENANES
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Abstract : A new strategy has been developed for synthesizing catenanes; it is based on a
generalized template effect, as shown in Figure 1. The first example of a novel class of
molecules, the metallo-catenanes, has been obtained in good yield : it contains copper (I)
and macrocyclic phenanthroline derivatives.

FIGURE 4. The title and the abstract of the first publication on catenanes from our group with the picture of the late Dr C.O. Dietrich-Buchecker (1942–2008).

that the two dpp coordinating fragments were intertwined, thus indicating that the rings were interlocking with one another. The general strategy is depicted in Figure 5.

Strategy **A** is both very general and simple. Both coordinating fragments have to bind to the metal centre so as to be mutually perpendicular. By an appropriate choice of metal, chelates, linkers (g-g), and functional groups (f and g), the system consisting of two intertwined organic fragments interacting with the central metal will react in the expected fashion with formation of two interlocked rings. The only apparent weakness of strategy **A** is that a total of eight reacting points have to find one another in the double-cyclisation reaction. The second approach, strategy B, reduces this problem since it involves only four reacting groups to be interconnected in a single cyclisation (twice g-f) leading to the catenane. The only requirement is that the starting macrocycle has to be pre-synthesised before the template reaction is performed. This ring contains a coordinating fragment (f-f) and a non-coordinating linker (g-g), and it is also likely to be formed as an intermediate in strategy **A**. It is noteworthy that, provided the threaded bis-chelate complex (bottom left) is stable enough, it must form *quantitatively* from a 1:1:1 mixture of the macrocycle, the metal ion, and the
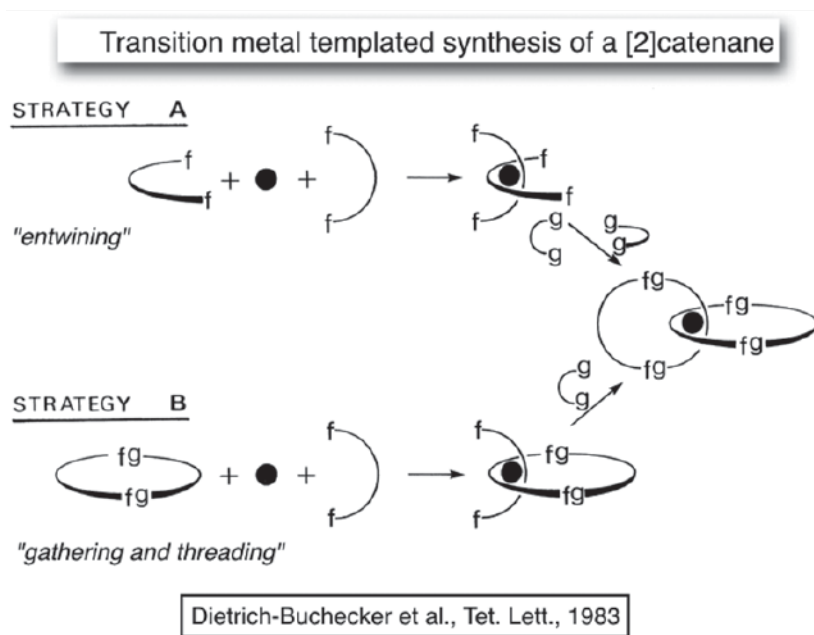
FIGURE 5. Synthesis of interlocking ring systems. The strategy is based on a 3D-template effect induced by a transition metal centre, copper(I) in the present case. The arcs of a circle and the rings contain coordinating fragments f-f able to interact with a transition metal centre (black disk). The f and g letters represent chemical functions able to react with one another and form an f-g chemical bond.

open-chain fragment. A statistical mixture of complexes, as would arise if two different open-chain ligands were reacted with a metal ion, cannot occur because it is impossible for two of the macrocyclic ligands to attach to the same metal ion.

Since it was less risky, we started with strategy B, which led to an interlocked system in good yield (1983) [12]. Later on, we used strategy A since it is slightly shorter than strategy B in terms of number of steps from commercially available compounds (1984) [14]. The actual reactions carried out are shown in Figures 6 and 7. It is noteworthy that strategy B is more general than strategy A since it opens the way to asymmetric [2]catenanes, i.e., compounds containing two different rings. In addition, the threaded intermediate is close to a [2]rotaxane: it suffices to end-functionalise the threaded fragment of the compound using bulky groups to generate such a [2]rotaxane. We have used this synthesis route extensively for making porphyrin-containing catenanes and rotaxanes as well as variously substituted compounds of the same family.

The copper-complexed catenane of Figure 7 could be quantitatively demeta-lated using a cyanide salt. The back reaction leading to the starting copper(I)
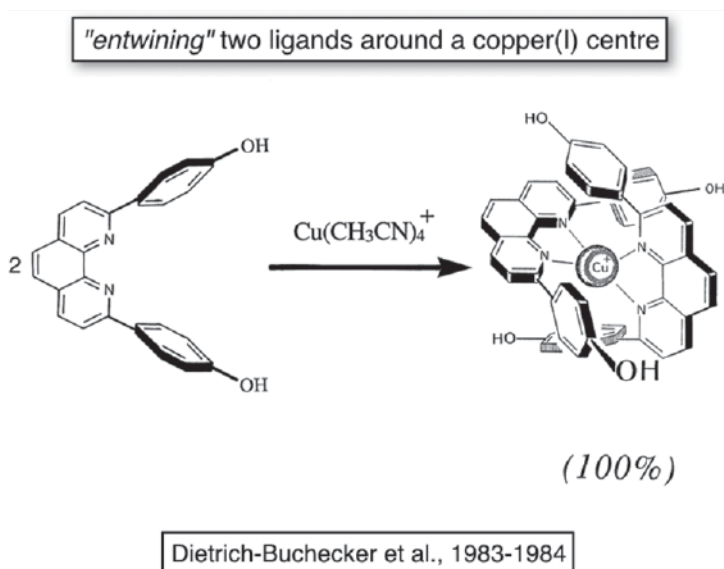
"entwining" two ligands around a copper(I) centre

Cu(CH₃CN)₄⁺

(100%)

Dietrich-Buchecker et al., 1983-1984

FIGURE 6. The starting compound represented on the left is formed from commercially available 1,10-phenanthroline in two steps. It can be made at the 10-gram scale within one or two weeks. In the presence of copper(I), the entwined compound represented on the right is formed quantitatively.
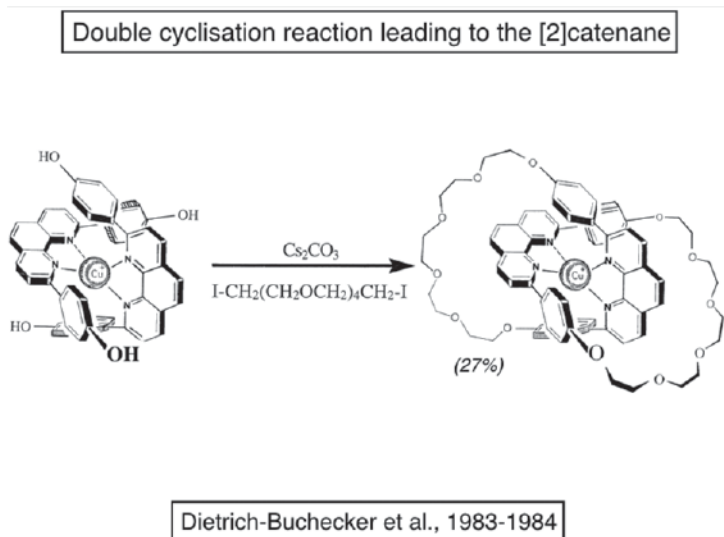

Double cyclisation reaction leading to the [2]catenane

Cs₂CO₃

I-CH₂(CH₂OCH₂)₄CH₂-I

(27%)

Dietrich-Buchecker et al., 1983-1984

FIGURE 7. The double cyclisation reaction leading to the catenane is relatively low-yielding. Nevertheless, it was possible to prepare batches of 0.5 g within a few weeks. By slightly modifying the structure of the starting molecules and by applying the ring-closing methodology brilliantly proposed by Grubbs, we substantially improved the yield (up to 92%) [15].
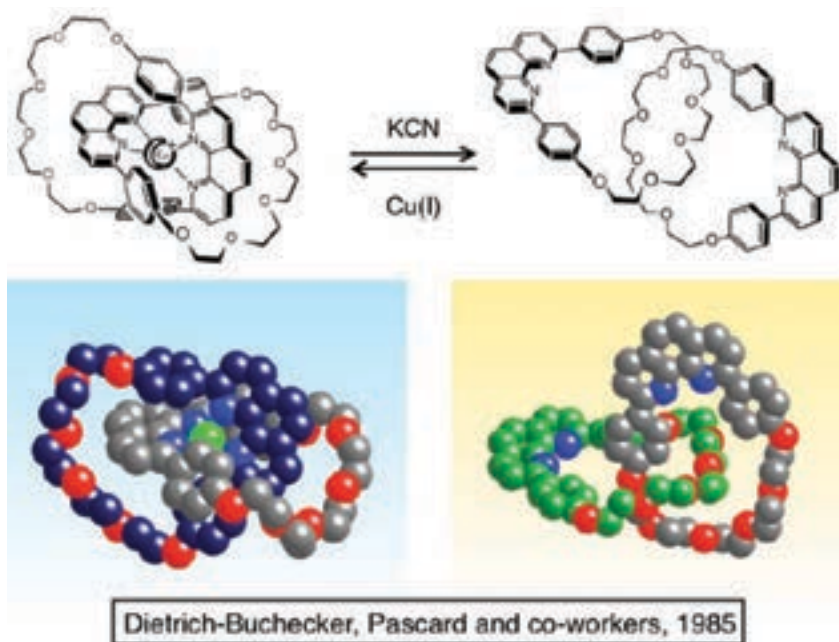
Dietrich-Buchecker, Pascard and co-workers, 1985

FIGURE 8. The demetalation-remetalation reaction and the X-rays structures of the copper(I) catenate and the catenand.

complex from the metal-free compound was perfectly reversible as shown on Figure 8. X-ray quality crystals of both forms could be grown and their crystallographic structures were obtained by Pascard and co-workers [16]. We coined the terms "catenates" and "catenands" for complexes whose ligands are interlocking rings and for the corresponding metal free-compounds, respectively.

The X-ray structures are represented below the corresponding chemical drawings of the copper-complexed and metal-free [2]catenanes. As far as the copper complex is concerned, the similarity between the drawing and the X-ray structure is striking. By contrast, the shape of the solid state free catenane is significantly different from the drawing. In any case, demetalation of the complex or complexation of the free form results in a complete rearrangement of the organic backbone. This metamorphosis can clearly be connected to the molecular machinery field although it is still relatively far from movements taking place in real molecular machines.

The Strasbourg approach to catenanes represented significant progress in the catenane and rotaxane field. All of a sudden, the transition metal templated approach developed by our team opened the way to novel topologies and to rotaxanes. In fact, the potential of transition metal in relation to catenanes,

rotaxanes and even knotted rings appeared to be limitless. Although the contribution of Lüttringhaus and Schill was conceptually important, the template approach completely modified the way molecular chemists looked at catenanes. Within a few years, they changed status from very exotic and almost impossible-to-make species, at least at a macroscopic scale, to normal and reasonably accessible compounds. A few pioneering contributions based on organic templates were successfully explored by other groups. In 1989 Stoddart and his group reported a particularly efficient and attractive synthesis of a [2]catenane [17]. They took advantage of acceptor-donor interactions between an electron deficient 4,4'-bipyridinium derivative and an aromatic electron donor, combined to favourable hydrogen bonds, to predispose the various groups implied in a very favourable situation before a cyclisation reaction leading to the desired [2]catenane. This seminal piece of work was followed by two reports based on hydrogen bonding only, published in 1994 by Hunter and his group [18] and Voegtle and co-workers [19]. Both teams reported almost simultaneously very similar data although they were working far away from one another. These two pioneering hydrogen bonding-based approaches were followed by remarkable work performed by Fujita and co-workers [20]. It was based on kinetically labile Pd-N bonds and hydrophobic interactions. Fujita introduced the concept of "magic rings" since the [2]catenane could be reversibly dissociated to the set of two non-interlocking rings by just changing the nature of the medium in which the catenane was dissolved or the concentration of its constitutive components.

As far as rotaxanes are concerned, cyclodextrins turned out to be particularly interesting. These natural rings were used as the cyclic components of a large variety of rotaxanes. In the presence of appropriate string-like organic fragments, threading through the cyclodextrin was shown to take place thanks to hydrophobic forces. The first convincing example of a cyclodextrin-based [2]rotaxane was reported by Ogino in 1981 [21]. This pioneering publication was followed by remarkable work from various groups and, in particular, from Harada and co-workers [22].

Figure 9 gathers a few remarkable topologies which could be obtained at the molecular level by our group using a generalised transition metal-based strategy, i.e., by assembling two or more transition metal centres and molecular threads containing two or more coordinating fragments: a [3]catenane [23], the trefoil knot [24] and a doubly interlocking [2]catenane also known as the Solomon rings [25]. Other groups have also been interested in chemical topology. Impressive topologies at the molecular level have been reported by the research teams of Stoddart, Leigh and Siegel, just to cite a few [26, 27, 28].
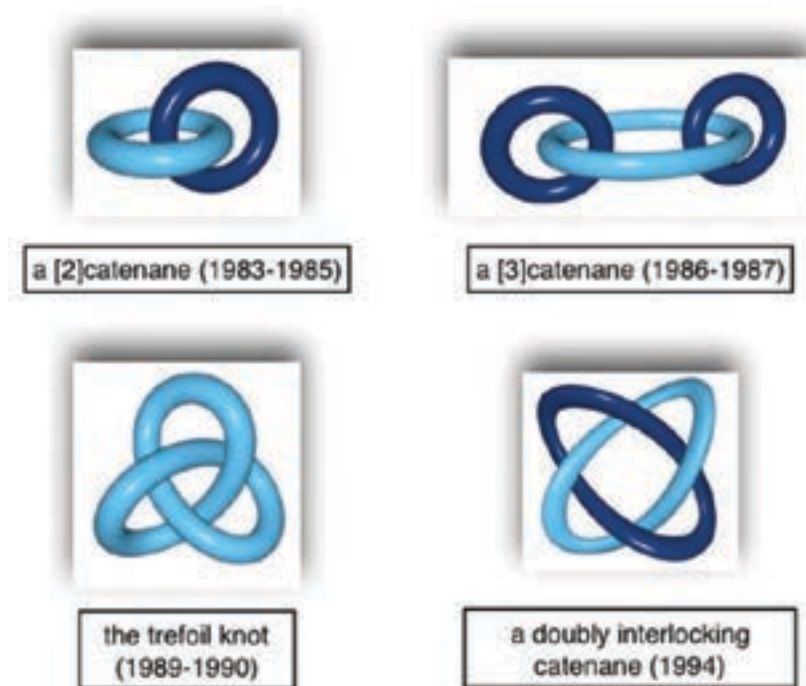
a [2]catenane (1983-1985)

a [3]catenane (1986-1987)

the trefoil knot
(1989-1990)

a doubly interlocking
catenane (1994)

FIGURE 9. From a simple [2]catenane to more complex topologies. The examples represented on Figure 9 are those made in Strasbourg.

MOLECULAR MACHINES

The field of molecular machines, mostly initiated by Stoddart, Balzani and their co-workers [29–30], was to a large extent an extension of that of interlocking ring molecules, at least at the beginning. The structures of catenanes and rotaxanes seem to be ideally suited to the making of molecular switches and machines, i.e., compounds which can undergo large amplitude motions in a controlled and reversible way.

Electrochemically-driven swinging motion of a copper-complexed catenane

The very first system made by our group for which a large amplitude motion can deliberately be triggered by an external signal was reported in 1994 [31]. A ring could be forced to rotate inside the other ring by playing with the copper(I)/copper(II) redox couple which led us to name the compound a "swinging catenane." Since that time, molecular machinery has blown up in a very impressive

Catenanes and Rotaxanes are very well adapted to large amplitude motions : a ring can glide along the axis on which it is threaded (linear motor); it can also «pirouette» around the axis or within another ring
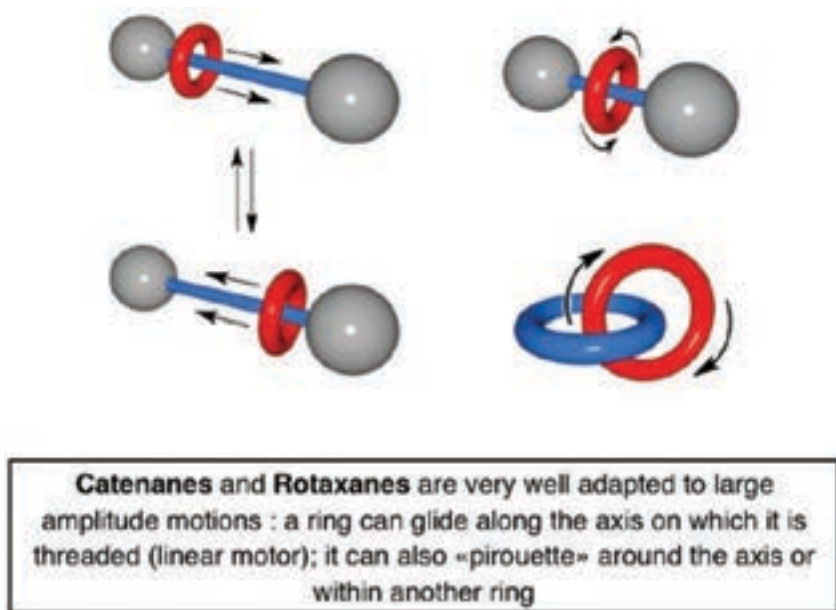
FIGURE 10. Catenanes and rotaxanes in motion: towards molecular machines.

way thanks to the great contributions of various groups, either working with catenanes or rotaxanes, or using non-interlocking compounds. Stoddart, Kaifer and co-workers reported their first molecular "shuttle" in the same year [30]. The compound made and studied in Strasbourg is a copper-complexed [2]catenane, displaying two very distinct coordination modes corresponding to two extremely different geometries. Having taken advantage of the roughly tetrahedral arrangement of the copper(I) centre in bis-diimide complexes to construct catenanes and molecular knots, the electrochemical properties of related copper complexes have later been used in our group to design and prepare a large variety of catenanes and rotaxanes and for investigating their controlled dynamic properties, playing on the two classical oxidation states of copper, +1 and +2. As far as the first "swinging catenane" is concerned, the interconversion between both forms of the complex is electrochemically triggered and corresponds to the sliding motion of one ring within the other. It leads to a profound rearrangement of the compound and can thus be regarded as a complete metamorphosis of the molecule. The principle of the process is explained in Figure 11.

The key feature of the transformation is the difference in preferred coordination number (CN) for the two different redox states of the metal: $CN = 4$ for copper(I) and $CN = 5$ (or 6) for copper(II). The organic backbone of the
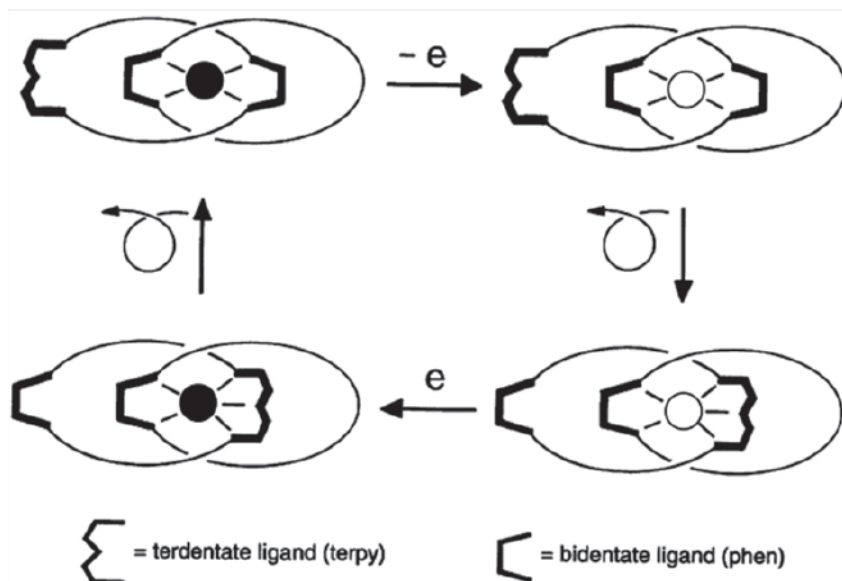
FIGURE 11. Principle of electrochemically induced molecular motions in a copper-complexed [2]catenane. The stable 4-coordinate monovalent complex (*top left*, the black circle represents Cu(I)) is oxidised to an intermediate tetrahedral divalent species (*top right*, the white circle represents Cu(II)). This compound undergoes a complete reorganisation process to afford the stable 5-coordinate Cu(II) complex (*bottom right*). Upon reduction, the 5-coordinate monovalent state is formed as a transient (*bottom left*). Finally, the latter undergoes the conformational change that regenerates the starting complex. The bidentate coordinating fragment is phen (1,10-phenanthroline), part of the dpp ligand, and the tridentate ligand is terpy (2,2':6,2"-terpyridine).

asymmetric catenate consists of a dpp bidentate chelate included in one cycle and, interlocked to it, a ring containing two different subunits: a dpp moiety and a terpy ligand. Depending upon the mutual arrangement of both interlocking rings, the central metal copper can be tetrahedrally complexed (two dpp units) or 5-coordinate (dpp + terpy). Interconversion between these two complexing modes results from a complete pirouetting of the two-site ring in one given direction or the other. It can easily be induced electrochemically, by means of a chemical reductant or oxidant or even photochemically [32]. From the stable tetrahedral monovalent complex, oxidation leads to a 4-coordinate Cu(II) state, which rearranges to the more stable 5-coordinate compound. The process can be reversed by reducing the divalent state to the 5-coordinate Cu(I) complex, obtained as a transient species before a changeover process takes place to afford back the starting tetrahedral monovalent state.
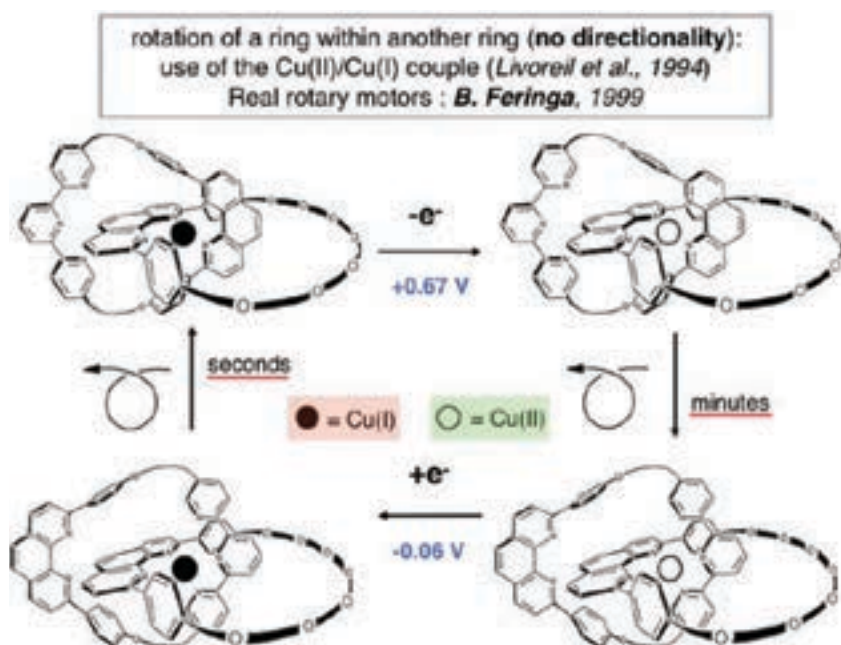
FIGURE 12. Square scheme corresponding to the process whose principle is depicted in Figure 11, with the chemical structures of the compounds. The dpp-containing cycle is a 30-membered ring whereas the dpp+terpy incorporating one is a 31-membered ring. It could be shown that the 5-coordinate Cu(II) complex has a square pyramidal geometry and not a trigonal bipyramid one. [33]

The real molecules are represented in Figure 12 as well as the square scheme interconverting the 4-and the 5-coordinate species.

Interestingly, the transformations of Figure 11 and Figure 12 is accompanied by a change in the electrochemical properties of the complex as well as spectroscopic changes. As expected, the tetrahedral copper complex has a relatively high redox potential: $Eo = +0.63$ V vs. SCE in CH_3CN, whereas the 5-coordinate species has a slightly negative potential, pointing to greater stabilisation of the divalent copper than in the 4-coordinate species: $Eo = -0.07$ V.

The obvious weak point of the swinging catenane of Figures 11 and 12 is its kinetic inertness. It should be noted that this first system was dramatically improved by modifying structural parameters of the compounds and, in particular in replacing the [2]catenane organic backbone by a [2]rotaxane, either acting as a pirouetting species or as a two- or three-station molecular shuttle. The rearrangement process was also markedly sped up by modifying the structure of the bidentate chelate incorporated in the rings. By replacing the highly sterically

hindering dpp fragment by an endocyclic but non-sterically hindering chelating group of the 8,8'-diaryl-3,3'-biisoquinoline family, fast moving rotaxanes were obtained [34–35]. Finally, it should be noted that the motion taking place in the swinging [2]catenane is by no means a rotation motion. The ring that incorporates both a bidentate and a tridentate chelating group undergoes a "pirouetting" motion corresponding to a 180° rotation in a given direction or in the other. Real rotary machines were reported much later. Feringa's contribution to the field of rotary motions was indeed crucial [36].

TOWARDS SYNTHETIC MOLECULAR MUSCLES: CONTRACTION AND STRETCHING OF A LINEAR ROTAXANE DIMER

The topic of this paragraph is dealing with a special type of molecular machine related to contraction and extension of switchable species reminiscent of muscles [37–38]. Rotaxane dimers as represented in Figure 13, can be regarded as synthetic analogues of natural muscles. Since real muscles mostly consist of filaments able to glide along one another, a molecular assembly in which two string-like molecular fragments can glide along one another was designed. This is the process taking place in the sarcomere, in which the thick filament (containing
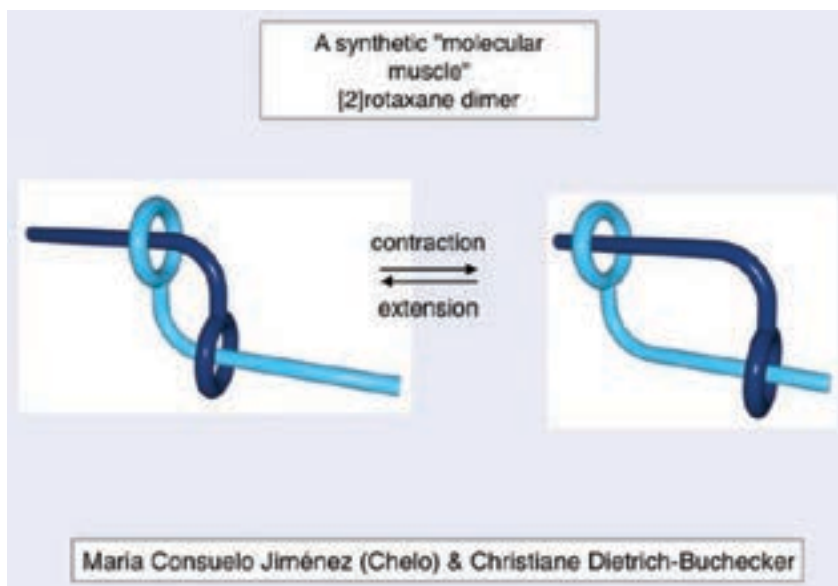

FIGURE 13. The molecular structure of a rotaxane dimer or pseudo-[2]rotaxane dimer (i.e., without bulky stoppers at the ends of the threaded filaments) is adapted to the contraction/extension motion mimicking the dynamic properties of a muscle.

myosin) moves along the thin filament (actin polymer) in one direction or the other so as to induce contraction or elongation. The actin-myosin complex as well as other motor proteins are fascinating biological systems which represent an inexhaustible source of inspiration for synthetic chemists.

After careful design mostly based on space-filling model, we started the synthesis work. It turned out to be particularly delicate and time consuming. In the present discussion, we will skip the preparation of the ring-and-lateral thread conjugate although the synthesis of this compound was far from trivial.

A 31-membered ring incorporating a dap fragment (dap: 2,9-diaryl-1,10-phenanthroline), prepared in several steps from commercially available compounds, was covalently linked to a linear fragment incorporating a 2,9-dimethyl-3,8-bis-(p-hydroxyphenyl)-1,10-phenanthroline so as to afford the bis-chelating target consisting of a coordinating ring attached to a lateral arm containing another bidentate chelating group. The reaction of the ring-and-string conjugate with a stoichiometric amount of $[Cu(CH_3CN)_4]PF_6$ in CH_3CN/CH_2Cl_2 at room temperature led to the doubly threaded species whose structure is represented in Figure 15. The success of this latter reaction was certainly far from being certain, considering the number of Cu(I) complexes which could be formed by coordinating the two different chelating fragments (endocyclic and
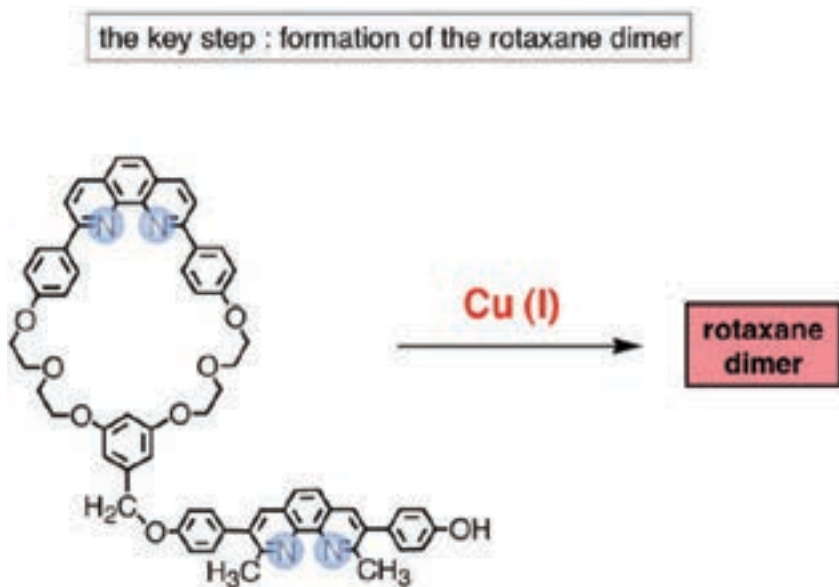

FIGURE 14. Cu(I)-induced double threading process leading to a dicopper(I) rotaxane dimer. The reaction is quantitative. The structure of the doubly threaded compound obtained is shown in Figure 15.

lateral coordination sites) of the ligand to metal centres. Nevertheless, we were happy to observe that formation of the doubly threaded complex was quantitative. In fact, the complexity of the reaction leading to the doubly threaded species is reflected by the slowness of the reaction leading to the desired product (several days at room temperature). Many coordination/de-coordination steps have to occur before the system finds its thermodynamic well. The desired [2] pseudorotaxane was formed under thermodynamic equilibrium and thus it was obtained pure as a deep red crystalline solid without further purification. X-ray quality crystals were grown from acetone/diethyl ether by diffusion. The crystallographic structure of the dicopper(I) [2]rotaxane dimer is represented in Figure 15. The most striking feature of the structure is its linear extended arrangement, which results in a distance between the two terminal phenolic oxygen atoms of 36.3 Å. The two copper atoms are 18.3 Å apart and occupy similar environments. The coordination tetrahedron around both copper(I) atom are strongly distorted.

In order to complete the synthesis of the switchable dimer rotaxane we had to introduce additional function. In particular, the project involved two potential
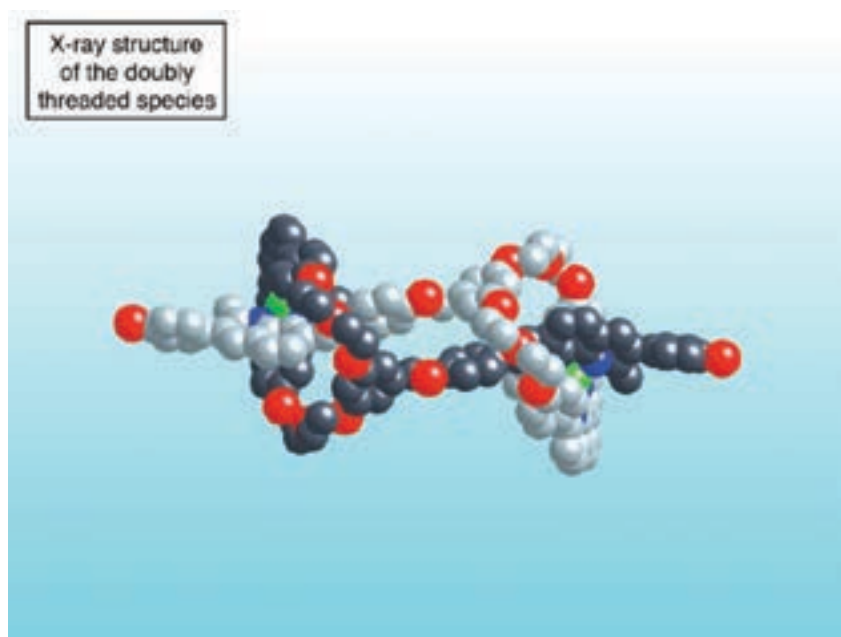

FIGURE 15. X-ray structure of the dicopper(I) rotaxane dimer. The pale grey ring-and-string component and the black subunit are identical. The carbon atoms are pale grey or black. The two copper(I) centres are green. The nitrogen and oxygen atoms are deep blue and red, respectively.
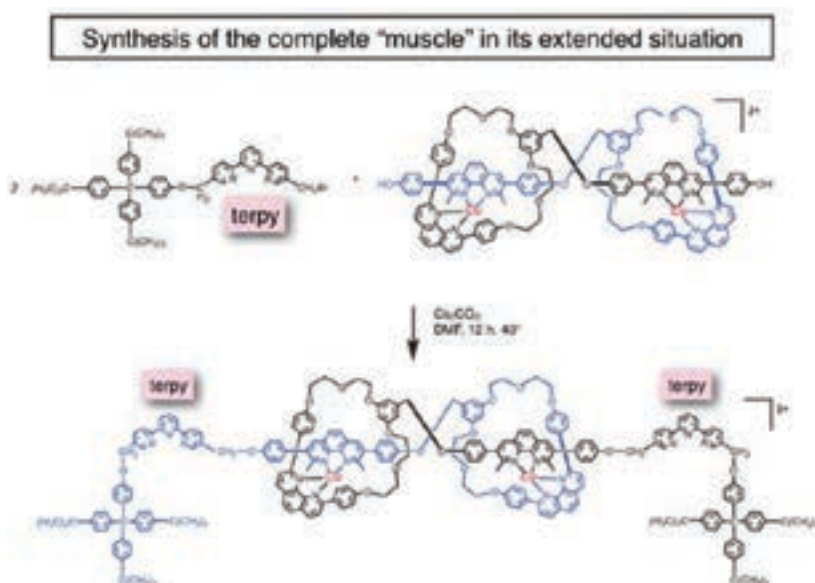
FIGURE 16. Functionalisation of the [2]pseudorotaxane dimer, precursor to the "muscle," by attaching a terpy-bulky stopper conjugate to its both ends. The "muscle" represented at the bottom of the figure is in its extended situation.

binding modes to a transition metal centre for the organic backbone: 4-coordinate or 5-coordinate. Tridentate ligands of the terpy family were thus introduced simultaneously to the stoppers, whose function was simply to prevent unthreading of the molecular filament from the rings they were threaded through. The last organic reaction of the synthesis sequence is shown in Figure 16. The functionalised terpy represented on the upper part of Figure 16 incorporates a tridentate chelating group and is attached to a bulky stopper. It was prepared separately and subsequently it was attached to both ends of the dicopper(I) precursor of Figure 15. This last reaction afforded the muscle-like compound depicted on Figure 16 (bottom) as a dark red solid in 60% yield. The last coupling step not only allowed the introduction of terdentate sites on both sides of the molecular assembly but also afforded a real rotaxane which cannot undergo any unthreading reaction.

    As usual in our group, Cu(I) was used as a gathering and templating metal. The movement was induced by a chemical reaction, namely a metal exchange. As shown in Figure 17 in a very schematic fashion, the doubly threaded compound can interact simultaneously with two metal centres, either in a four- or in a five-coordinate geometry each.

    Due to the synthesis procedure, each Cu(I) centre was coordinated to two 1,10-phenanthroline units, resulting in a four-coordinate situation. This binding
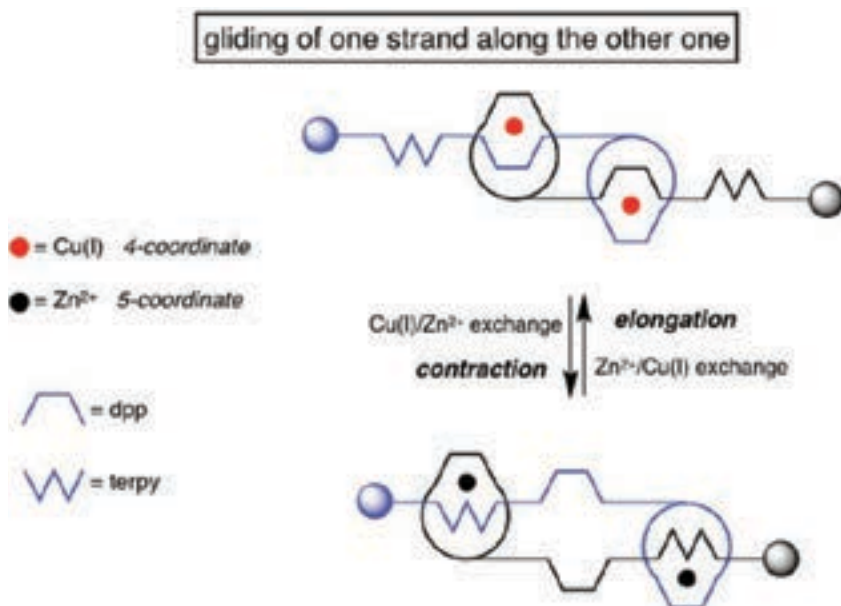
FIGURE 17. Principle—Contraction/extension of a [2]rotaxane dimer by gliding one strand along the other one. The W-shaped fragment represents a terdentate chelating group such as terpy whereas the U-shaped species is a bidentate ligands of the dpp type.

mode corresponds to an extended geometry (upper part of Figure 17), whereas coordination of a divalent metal ion such as Zn^{2+} affords a five coordinate situation corresponding to interaction of each metal centre with one 1,10-phenanthroline or dpp unit and one terpy. It corresponds to a contracted geometry (bottom of Figure 17).

As shown on Figure 18, by treating the dicopper(I) pseudorotaxane dimer with KCN, the metal-free ligand was obtained in quantitative yield (not shown on the figure). After remetalation using $Zn(NO_3)_2$, the colourless di-zinc complex (bottom) was obtained quantitatively. It is now in the contracted form. The extended dicopper(I) dimer could be regenerated by the reaction of the di-zinc complex with an excess of $[Cu(CH_3CN)_4]PF_6$ at room temperature. Using a metal exchange reaction, the muscle-like compound is thus set in motion. The Cu(I) complex corresponds to the extended form and the Zn(II)-complexed species is the contracted state. A metal exchange reaction was utilised to set the muscle in motion due to the fact that the electrochemical method turned out to be inefficient. The copper(I) complex was oxidised with the purpose of contracting the system to a dicopper(II) complex with two 5-coordinate Cu(II) centres but the motion was very slow which led us to use a chemical signal. The kinetic barrier

to the rearrangement is very large due to the fact that the gliding motion of a given thread is strongly coupled to that of the other thread. The tight connection between the two subunits makes it impossible for the [2]rotaxane dimer to move in a stepwise manner.

The two rotaxane dimers of Figure 18 represent one of the first examples of a unimolecular linear array able to elongate and contract at will under the action of a given stimulus. From Corey–Pauling–Koltun (CPK) model, one can estimate that the length of the compound changes from 83 to 65 Å between both situations (Figure 18). This corresponds roughly to the same relative amount as what is found in natural muscles (~27 %).

It is noteworthy that several muscle-like compounds have been proposed in recent years. In most cases, they were set in motion using principles which were somewhat different from ours. It is not the place in this article to review in detail
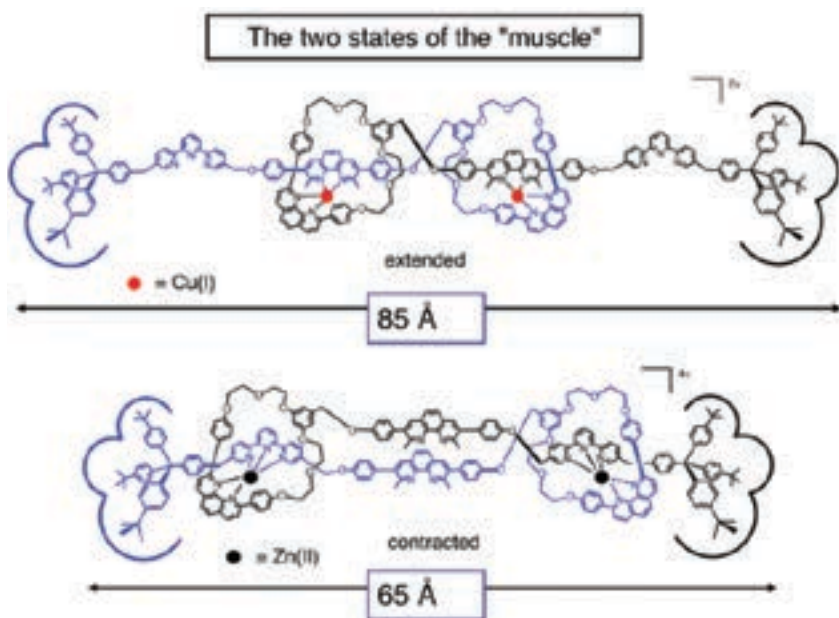

FIGURE 18. The two forms of the muscle-like [2]rotaxane dimer. Whereas the interconversion between both forms is easily induced by metal exchange, oxidation of copper(I) to copper(II) (upper form of the figure) was unfortunately not followed by rearrangement of the complex to the extended situation, at least on a reasonable timescale. Due to the rigid structure of the molecule, the gliding motions of both threads along one another have to take place simultaneously and in a concerted manner. The kinetic barrier to the global motion is thus very high which explains why the motion is so slow when no demetalation step is involved.

the work done by other groups in this area but we would like to mention some of the most significant contributions. Several groups prepared dynamic [2]rotaxane dimers based on cyclodextrins which, under the action of a given signal, could be contracted or elongated [39–40]. Reversible molecular motions mimicking natural muscles proceed through hydrophobic forces, size constraints, solvents polarity changes or photochemical isomerization of azobenzene or stilbene derivatives.

Another family of muscle-like compounds was developed based on other types of interlocking architectures. These systems contain two types of recognitions sites, one of them being based on hydrogen bonding (and thus pH sensitive) and the other one operating via acceptor-donor interactions. A few years ago, Stoddart and co-workers showed that a contraction and expansion motion was triggered by changing the pH of the solution containing the rotaxane [41]. They described a new bistable rotaxane dimer architecture in 2008, namely a two-component [c2]daisy chain topology. This system consists of two self-complementary interlocking molecular fragments in which a secondary ammonium ion-containing lateral arm is attached to a crown ether. The end of each arm is connected to a bulky stopper. Each crown ether glides between the two specific binding sites incorporated in the thread, the motion being triggered by modifying the pH. The gliding motions result in contracting or elongating the rotaxane dimer.

Simultaneously with the former piece of work, Coutrot et al. published another example of pH-switchable molecular muscle [42] based on a related principle. The system incorporates a cyclic rotaxane dimer consisting of two interlocking monomers. Again, each monomer incorporates a crown ether attached to a linear fragment. This fragment contains two different stations and the system can be switched from a contracted state to an elongated situation by modifying the pH. A remarkable extension of Coutrot's work was published in 2012 [43]. Giuseppone and co-workers designed and synthetised a pH-driven muscle-like system similar to Coutrot's "muscle" in which [2]rotaxane dimers are linked together linearly by taking advantage of a very efficient coordination chemistry-based polymerisation process. A remarkably high degree of polymerisation was obtained (~3,000 units) for both the contracted and extended forms. As in Coutrot's work, at low pH, a doubly-threaded dimer adopts an extended geometry. At basic pH, the compound adopts a contracted form. These two states were very convincingly characterized by dynamic light-scattering and small angle neutron scattering experiments. This remarkable piece of work is probably one the first examples of molecular muscle operating at a microscopic scale and thus functioning as a real device.

CONCLUSION

The main field of research of our group since the beginning of the 80s has clearly been that of transition metal chemistry. In relation to the molecular machine area, it should be stressed that the metals had a dual function:

1. Interlocking and knotted ring compounds were obtained by using transition metals such as Cu(I) in particular for gathering and disposing in a precisely defined geometry various organic fragments before they were incorporated in the target molecule.
2. The presence of transition metals provided the molecular systems with *electrochemical* or *photochemical* properties which allowed to set given fragments of the molecule in motion and thus to obtain molecular machines.

Generally speaking, motivation for doing research in the field of controlled dynamic systems of the muscle-like family is manifold. The most important one is related to the scientific challenge that the synthesis and the study of complex and functional molecular systems that can be set in motion in a controlled way represents. Making contractile and extensible molecules of the rotaxane dimer type was probably not even envisioned a few decades ago due to expected synthetic and analytical difficulties. Preparing and studying linear or rotary motors or artificial muscles is related to the fascination that biology exerts on chemists and engineers. It is very challenging for a synthetic chemist to make a molecule or molecular system whose function and mode of action are reminiscent of those of biological systems. The few examples discussed in the present chapter are certainly very remote from natural muscles and they are undoubtedly very primitive compared to their natural analogues. Nevertheless, it was a great challenge to elaborate these compounds and to show that they can be set in motion in a well-controlled fashion.

The field of molecular machines in general, still a basic science area of research, has been acknowledged by the Royal Swedish Academy of Science and the Nobel Committee. I would like to thank these prestigious organisations for this recognition. This field is nowadays more than 20 years old and it is certainly time to address the question of applications, either in a general fashion for machine-like compounds or more precisely for contractile and extensible molecular species. In which field of application will the area of molecular muscles be the most important in the future? It is today very risky to give an answer to this question. Presently, one of the most impressive extension of molecular machines towards applications is concerned with "molecular computing" and

the molecular approach to electronic memory devices. The Stoddart and Heath groups reported promising work in this area [44].

Many types of nanodevices and nanomachines can be envisaged in relation to chemical applications (for example, sorting and transport of molecules in solution or through membranes) but also to purely mechanical applications. In the future, nano- and microrobots able to fulfil a large variety of functions (from medicine to everyday life) will have to be articulated. The use of molecular components to control their movements is certainly a promising possibility. In a relatively long term prospective, artificial muscles of various length (from microns to millimetres or even centimetres) might be needed for various applications such as humanoid robots, actuators for microfluidic science and technology or prosthetic organs. However, in spite of all the possibilities offered by molecular machines in terms of potential applications for the future, it should be stressed that basic research is still of utmost importance and is or has been at the origin of the many technologies which are nowadays part of our daily life.

Finally, I would like to stress that the recent book written by Bruns and Stoddart represents a monumental piece of work which, today, gathers all the important data obtained by hundreds if not thousands of researchers since the beginning of catenanes, rotaxanes and molecular machines. Any interested reader must of course have a copy of this book.

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Nathalie Solladié, Jean-Luc Weidmann, Gwénaël Rapenne, Myriam Linke, Laurence
Raehm, Isabelle Dixon, Anne Chantal Laemmel-Gouget, Didier Pommeranc, Christine
Hamann-Schaffner, Etienne Baranoff, Pierre Mobian, Benoit Colasson, Damien Jouvenot,
Nicolas Belfrekh, Sylvestre Bonnet, Benoit Champin, Christian Tock, Julien Frey, Fabien Durola,
Jacques Lux, Julie Voignier, Yann Trolez, Maryline Beyler, Cécile Roche

FIGURE 19. 1. Permanent researchers of the "Laboratoire de Chimie Organo-Minérale" (LCOM): University members and CNRS researchers including the late Dr Christiane Dietrich-Buchecker (1942–2008) and the late Prof. Jean-Marc Kern (1944–2004). 2. PhD students listed by chronological order. The two first students, Pascal Marnot and Romain Ruppert, started their PhD work in 1980.

Many researchers have been associated to the work of our team, "Laboratoire de Chimie Organo-Minérale." In spite of the expected and unexpected difficulties they frequently had to face in the course of their work, these researchers have always been very enthusiastic and efficient. I owe them the success of our research team. The names of our CNRS researchers or University members (from assistant to full professors), of our PhD students and post-doctoral researchers as well as those of other visitors who contributed to our research are listed in Figure 19 and 20.

Laboratoire de Chimie Organo-Minérale

Post-doctoral researchers and other visitors

David Amabilino, Audrey Auffrant, Christine Beemelmanns, Martial Billon, Maria-Jesus
Blanco-Pillado, James I. Bruce, Diego J. Cardenas, Ricardo Carina, John D. Crane,
Christian S. Diercks, Vincent Duplan, Jonathan A. Faiz, Yoshio Furusho, Pablo
Gaviña, Christine Goze, David Hanss, Neri Geum Hwang, Akiko Hori, Elisabetta
Iengo, Fumiaki Ibukuro, Stuart James, Maria Consuelo Jimenez, Antoine Joosten,
Robert Kayhanian, Jérome Kieffer, Abdel Khemiss, Masatoshi Koizumi, Tomáš Kraus,
Ulla Létinois-Halbes, Jacques Lux, Alexander G. Martynov, Dennis Mitchell, Bernhard
Mohr, Cécile Moucheron, Frédéric Niess, Laure-Emmanuelle Perret-Aebi, Ingo
Poleschak, Alexander I. Prikhod'ko, Felipe Reviriego, Zeinab Saad, Efstathia G.
Sakellariou, Xavier J. Salom-Roig, Emma Schofield, Hideki Sugihara, Pierre Louis
Vidal, Michael D. Ward, Noémie Weber, Oliver Wenger, J. A. Gareth Williams

FIGURE 20. Post-doctoral researchers and other visitors.

Finally, I thank my parents, my wife, Carmen, and my son, Julien, for their continuous support and for their forgiveness regarding my pace of work and travel.

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