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Towards artificial muscles at the nanometric level

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The authors describe their study of molecular systems suited to the fabrication of machines and (rotory or linear) motors at the molecular level. They indicate that a future application of these molecular 'muscles' could be in the area of information storage and processing.

Motility is an essential feature of many living organisms. For instance, bacteria are equipped with flagellae[1] able to drive the motions of the bacterium within its surrounding by spinning flagellae bundles in one direction or in the other, in a way reminiscent of a boat propeller. At a nanoscopic level, many biological processes involve complex motor proteins, whose motions are coupled to important chemical reactions or transport processes. Among the many biological motors known, two particularly significant examples are ATP synthase,[2] a rotary motor responsible for the synthesis of ATP from ADP and inorganic phosphate, and kinesin motor proteins.[3] This latter family of proteins fulfils many functions, but one is particularly relevant to the present discussion. Kinesin is able to travel along microtubules in a way reminiscent of linear motors. It can travel with control of directionality, to carry and transport various components of the cell, contained in an organelle, over large distances (micrometers).

The field of synthetic molecular machines and motors has recently experienced a remarkable development.[4] Many examples are based on catenanes and rotaxanes,[5] which are obviously ideally adapted to large-amplitude but non-destructive motions. Under the action of an external signal, one can set a given component—most of the time, a ring—in motion while the other components can be considered as motionless. In such a way, a ring will glide within another ring with which it is interlocked[6] or a ring will move along a rod on which it has been threaded[7] ('shuttle', travelling between two 'stations'). These two types of motion have been shown to occur in a controlled fashion by oxidising or reducing a given fragment of the compound and they represent prototypical examples of electrochemically driven movements in simple machines.

Very elegant systems based on non-interlocking molecules have also been reported. The most remarkable ones mimic the behaviour of a rotary motor,[8,9] with a stator (motionless part) and a rotor (mobile component).

Maria Consuelo Jiménez (LEFT) was born in Valencia, Spain, in 1967. She studied chemistry at the Universidad de Valencia and obtained her Ph.D. from the Universidad Politécnica de Valencia in 1997 with Professor Miguel A. Miranda on organic photochemistry. She spent two years in Strasbourg (1998–2000) as post-doctoral researcher in Professor Jean-Pierre Sauvage group. She currently holds a research and teaching position at the Chemistry Department of the Universidad Politécnica de Valencia.

Christiane Dietrich-Buchecker (CENTRE) earned her Ph.D from the Université Louis Pasteur in 1973 in Professor M. Frank-Neumann's laboratory where she studied small rings. Dr. Dietrich-Buchecker has been a member of the CNRS since 1970. She did post-doctoral work with Professor K. B. Sharpless (MIT) on the study of new organoselenium compounds. Her present research field is the synthesis rotaxanes, catenanes and molecular knots.

Jean-Pierre Sauvage (RIGHT) obtained his Ph.D from the University of Strasbourg under the supervision of Professor J.-M. Lehn. After Postdoctoral research in Oxford (U.K.) with Professor M. L. H. Green, he went back to Strasbourg. His current interests range from models of the photosynthetic reaction centre to topology and molecular machines and motors. He is a member of the French Academy of Science.

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The motivations for creating and studying artificial molecular machines are manifold. To mimic the motions taking place in biological motors is, of course, very challenging. Generally speaking, synthetic chemists have always been fascinated by natural molecular systems, be it from a structural viewpoint or in relation to the complex functions that these molecular assemblies can perform. Other motivations are certainly more applied. One of them, in particular, is related to information storage and processing at the molecular level and will be briefly discussed at the end of this article. Many other nanoscopic devices, including molecular level-electromechanical devices, are also of special interest.

Polymers have been used in the past to elaborate macroscopic devices whose behaviour is reminiscent of muscles.[10] A remarkable example of an electrochemically driven actuator is that of a polypyrrole film (redox active polymer) whose volume changes, resulting from oxidation or reduction of the polymer matrix, lead to large amplitude motions of the film once deposited onto another flexible but redox inactive organic film.[11]

Another strategy, which should in principle also lead to electromechanical devices, relies on annulenes and their polymers. By oxidising an [8]annulene, flattening of the ring should lead to significant increase of the overall length of the compound, opening the gate to new electromechanical actuators.[12]

For almost twenty years, our group has been much interested in catenanes and rotaxanes.[13] Clearly, these systems are ideally suited to the fabrication of machines and (rotary or linear) motors at the molecular level. In order to make a roughly rod-shaped compound whose overall length can be controlled and modified at will, a system whose topology is that of a rotaxane dimer (see Fig. 1) was envisaged.

The synthesis of a rotaxane dimer is a challenge in itself.[14, 15, 16] Two possible strategies can *a priori* be considered:

• the preparation of a rotaxane whose threaded fragment is end-functionalized by a stopper on one side and, on the opposite side, a chemical function ready to be used subsequently in a coupling reaction with a group attached to the ring

• the synthesis of a ring-and-string conjugate, expected to undergo the desired double threading reaction under certain circumstances, followed by the attachment of additional chemical groups, including stoppers, at the two ends of the threaded dimer.

These two strategies are depicted on Fig. 2.

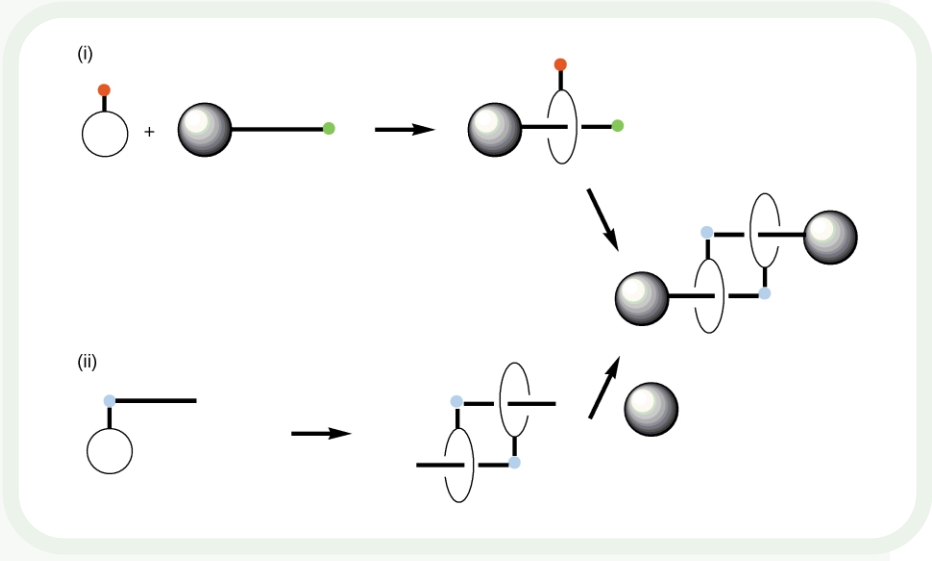

Fig. 2 A rotaxane dimer can be prepared either by single threading followed by cyclisation (i) or by double threading and stoppering (ii).

The second approach was preferred and after substantial synthetic work, the conjugate **1** of Fig. 3 was obtained and tested in the gathering and threading process. This ring-and-string conjugate incorporates a bidentate chelate (1,10-phenanthroline) in the macrocyclic unit and another analogous coordinating unit in the small filament attached to the ring. In view of the potential complexity and variety of complexation reactions which could be envisaged by mixing copper(I) and ligand **1** of Fig. 3, it was not certain that the doubly threaded topology of Fig. 1 be obtained. However, as represented in Fig. 3, the desired hermaphrodite-like complex was formed quantitatively.[15]

This complexation reaction represents an interesting assembly process in itself : immediately after mixing the two components **1** and Cu(I) in the stoichiometric proportion, a complex mixture of products is obtained—as shown by thin-layer chromatography and NMR—which probably consists of threaded and non threaded complexes with various nuclearities. After a few days at room temperature, the system finds its way to the thermodynamically most stable situation by a series of decoordination/recoordination reactions, so as to afford compound **2**. An X-ray structure of the complex was obtained.[15] It is shown in Fig. 4. Interestingly, the length of this incomplete "muscle" is already respectable, being of ~3.6 nm from one end to the other. The Cu···Cu intramolecular distance is also large (1.8 nm), precluding any electronic interaction between the two metal centres.

In order to make a muscle-like compound and thus to be able to modify the length of the molecule in a controlled fashion, additional functions have to be added. As easily visualised on the structure of Fig. 4, if the distance between the two copper centres is increased, the effect on the overall length will be opposite : the molecule will be shortened by moving away the two metals from one another. An

Fig. 1 The stretching/contraction motion of the rotaxane dimer is induced by gliding filaments along one another instead of using mechanical strain like in springs. This functioning principle is reminiscent of biological muscles, for which thick filaments (mostly myosin) glide along thins filaments (actin).

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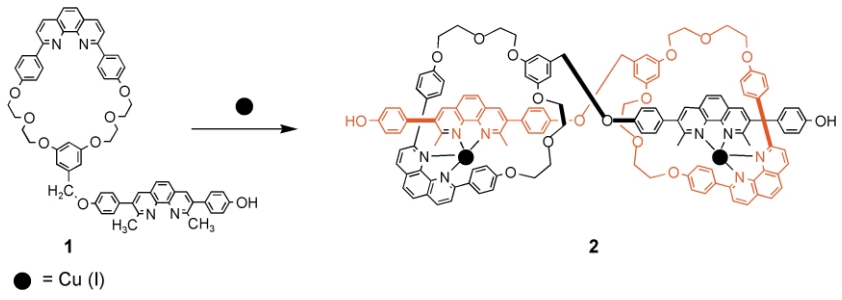

Fig. 3 Copper(I)-directed formation of the rotaxane dimer **2**, precursor to the muscle.

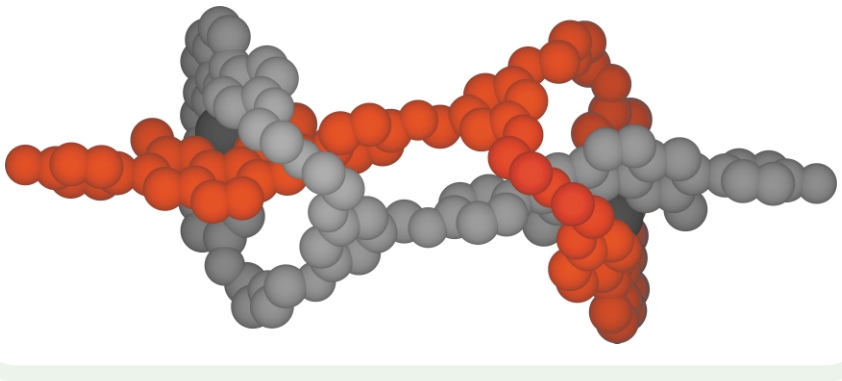

Fig. 4 X-ray structure of **2**.

attractive way to induce lengthening of the metal···metal distance is to attach other coordinating units at both ends of compound **2** and, subsequently, send an external signal to the compound, which will trigger ligand exchange so as to force the newly attached ligands to replace the 1,10-phenanthroline units in the metal coordination sphere. 2,2′:6′,2″-terpyridine (terpy) was selected because it is a *tri*dentate ligand, expected to form 5-coordinate complexes when used in conjunction with the *bi*dentate 1,10-phenanthroline ligand inscribed in the ring. The principle of the motion is explained in the cartoon of Fig. 5.

Two triggering signals can be envisioned to set the molecule in motion:

• an electrochemical signal, converting copper(I) to copper(II) and thus favouring 5-coordinate situations [Cu(II)] over tetrahedral situations [Cu(I)]. The reversible nature of metal-localised redox processes makes electrochemical signals particularly appealing.

• a chemical reaction, leading to reversible metal exchange allowing to convert the 4-coordinate situation to the 5-coordinate binding mode and *vice versa*.

The first approach did not reveal successful since the 4-coordinate copper(II) complex, although formed very readily by electrochemical oxidation of the monovalent copper(I) complex, was kinetically too stable and did not lead to the thermodynamically more stable 5-coordinate species. Fortunately, metal exchange takes place easily and quantitatively at room temperature, allowing to interconvert both forms, the 4- and the 5-coordinate species. Copper(I) is expelled from its coordination sites by CN^- and addition of Zn^{2+} leads instantaneously to the 5-coordinate complex. In order to regenerate the 4-coordinate species, excess copper(I) is added to the bis-zinc complex, the metal exchange reaction being again very fast. The two forms of the complete rotaxane dimer are depicted in Fig. 6.[17] Clearly, the 4-coordinate situation corresponds to the 'stretched' geometry, with a Cu···Cu distance of 1.8 nm (from the X-ray structure of **2**; see Fig. 4) whereas the pentacoordinated species is significantly contracted compared to the bis-copper(I) complex. Paradoxically, the Zn···Zn distance is larger than the Cu···Cu distance of the stretched form. It can be estimated on CPK models as ~4 nm.

However, a chemical signal does not seem to be the best means to set molecular systems in motion, although most of the biological motors are chemically driven (ATP hydrolysis). Electrochemical or, better, photochemical signals are certainly more promising in terms of potential applications. It is reasonable to assume that systems derived from that of Fig. 6 will soon afford light-driven muscle-like machines or electrochemically addressable molecules. Interestingly, reactive functional groups will replace the chemically inert stoppers, allowing to attach the 'muscle' to a large variety of substrates including molecular species (chromophores, biological systems, tags, *etc.*), organic beads, inorganic and metal surfaces (electrodes). It will also be of particular interest to incorporate stretchable/contractible molecules in polymers and thus to fabricate real muscle-like fibres.

Catenanes and rotaxanes are not the only families of molecules which can be considered in order to fabricate molecular systems with a controllable length. They are especially attractive if one wants to induce the gliding motions of a filament along another one, but molecular 'springs' can also be envisioned for elaborating stretchable/contractible molecular ensembles. Recent examples of such systems, based on transition metal complexes, have been reported.[18,19]

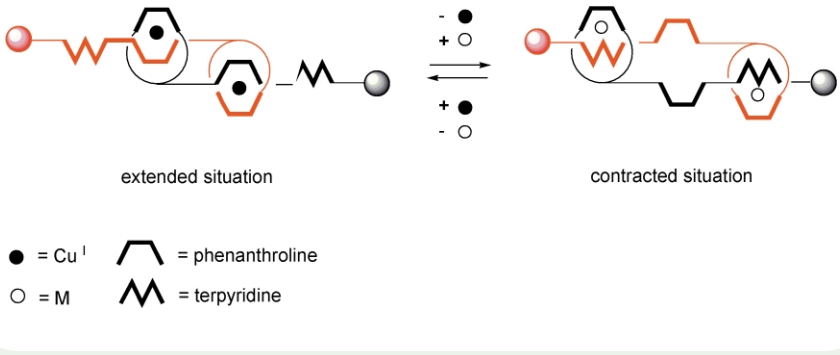

Fig. 5 Contraction and stretching of the muscle-like doubly threaded species obtained by anchoring a terpy unit and a stopper at both ends of **2**.

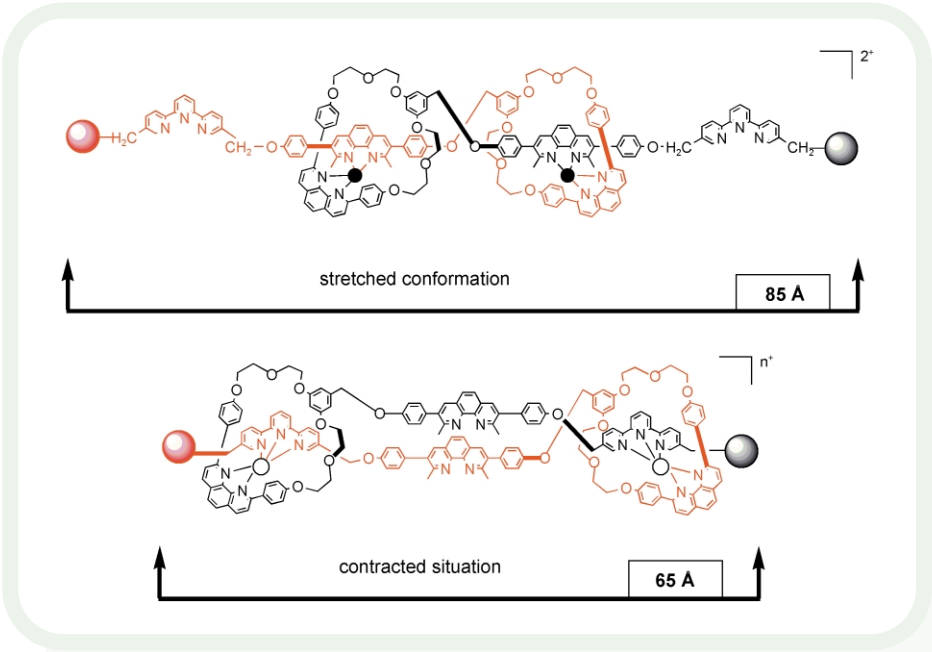

Fig. 6 The two states of the muscle. The bis-zinc species is approximately 2 nm shorter than the bis-copper(I) complex, these lengths being estimated on CPK models.

It is difficult to foresee today in which field of application the area of molecular machines and, in particular molecular 'muscles' will be the most important in the future. One of the most popular practical outcome, but still hypothetical, among the chemists community, is that of information storage and processing. Interesting examples of electronic devices reminiscent of very primitive computers have recently been reported by Heath, Stoddart and their co-workers.[20] The molecular components of these devices are catenanes or rotaxanes able to undergo intramolecular motions by oxidising or reducing a chemical group, the motions permitting the molecules to act as electronic switches. However, one should not restrict the future of the field to electronics and regard molecular machines and their assemblies as potential alternatives to silicon-based transistors only. Many types of nanodevices and nanomachines can be envisaged, in relation to chemical applications (for example, selection and transport of molecules in solution or through membranes) but also to purely mechanical applications. Nano- and microrobots, able to fulfil a large variety of functions (from medicine to everyday life) will be articulated and the use of molecular components to control their movements is a promising possibility.

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