JOURNAL OF PHYSICAL ORGANIC CHEMISTRY
J. Phys. Org. Chem. 2002; **15:** 476–483
Published online in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/poc.481

Review Commentary

Towards molecular machines and motors based on transition metal complexes†

Benoît Xavier Colasson, Christiane Dietrich-Buchecker, Maria Consuelo Jimenez-Molero and Jean-Pierre Sauvage*

Laboratoire de Chimie Organo-Minérale, UMR 7513 du CNRS, Université Louis Pasteur, Faculté de Chimie, 4 rue Blaise Pascal, 67070 Strasbourg Cedex, France

Received 12 October 2001; revised 15 December 2001; accepted 18 December 2001

ABSTRACT: Biological motors and machines are multicomponent assemblies undergoing large-amplitude geometrical changes or leading to the locomotion of one of the components, under the action of either an external stimulus (pH change, redox process, light pulse, etc.) or a chemical gradient. Many examples are known of proteins which undergo important shape modifications (folding–defolding) after a signal has been sent to the protein. Threaded or interlocking rings are ideally suited to the construction of fully artificial molecular motors. If a ring is threaded onto a rod, it can either rotate around the axle or undergo a translation movement. Similarly, in catenanes (i.e. interlocking ring multicomponent systems), a ring can glide at will and spin within another ring. Several examples of such compounds have been elaborated and studied in recent years, using threaded and interlocking molecules. Our group has proposed several molecular assemblies acting as 'machines.' They are based on transition metal complexes and the systems are set in motion by sending an electrochemical or photochemical signal. A recent contribution from our team describes a doubly threaded compound which can be contracted or stretched at will. By sending a chemical signal to the molecule, one can readily convert the contracted compound [copper(I) complex] to the extended situation (zinc complex). The back reaction is also easily carried out and it is quantitative. Potentially, the system is ready to react to an electrochemical stimulus and lead to the same movement. The present molecular assembly is thus reminiscent of skeletal muscles.

KEYWORDS: molecular machines; molecular motors; transition metal complexes

INTRODUCTION

In biology, molecular machines and motors play an essential role.[1] Many examples are known of proteins which undergo important shape changes, such as folding–defolding, after a signal has been sent to the molecules.[2] Molecular motors consist of several components, among which some parts will be considered as motionless and some others will move continuously while energy is consumed (ATP hydrolysis or pH-gradient consumption). Biological motors can be classified as rotary or linear motors, ATP synthase being certainly the most important and best understood rotary motor.[3]

Artificial molecular machines and motors have appeared as one of the emerging fields of chemistry in the last decade.[4] Molecules or molecular assemblies for which a certain part can be set into motion deliberately have triggered great interest as 'machines' in the course of the last 7–8 years.[5] Several such systems have been designed and elaborated recently, many of them being based on electroactive compounds whose shape will be modified at will by a redox process. Threaded or interlocking rings[6] are ideally suited to the construction of machines or motors since large-amplitude motions can be envisaged with such architectures, without the risk of damaging the chemical structure of the system. If a ring is threaded onto a rod, it can either spin around the axle or undergo a translation movement. In a similar way, a ring can glide and spin within another ring in interlocking ring systems (catenanes).

Two representative examples of 'molecular machines' are depicted in Fig. 1. They are based on organic acceptor–donor and hydrogen-bonded complexes[5a] [Fig. 1(a)] or transition metal (copper) complexes[5b] [Fig. 1(b)].

This review article is focused on linear machines and motors, which are essential in many biological processes. Recently, several linear motors have been especially

**Correspondence to:* J.-P. Sauvage, Laboratoire de Chimie Organo-Minérale, UMR 7513 du CNRS, Université Louis Pasteur, Faculté de Chimie, 4 rue Blaise Pascal, 67070 Strasbourg Cedex, France.
†Presented at the 8th European Symposium on Organic Reactivity (ESOR-8), Cavtat (Dubrovnik), Croatia, September 2001.
Contract/grant sponsor: CNRS.
Contract/grant sponsor: European Commission.

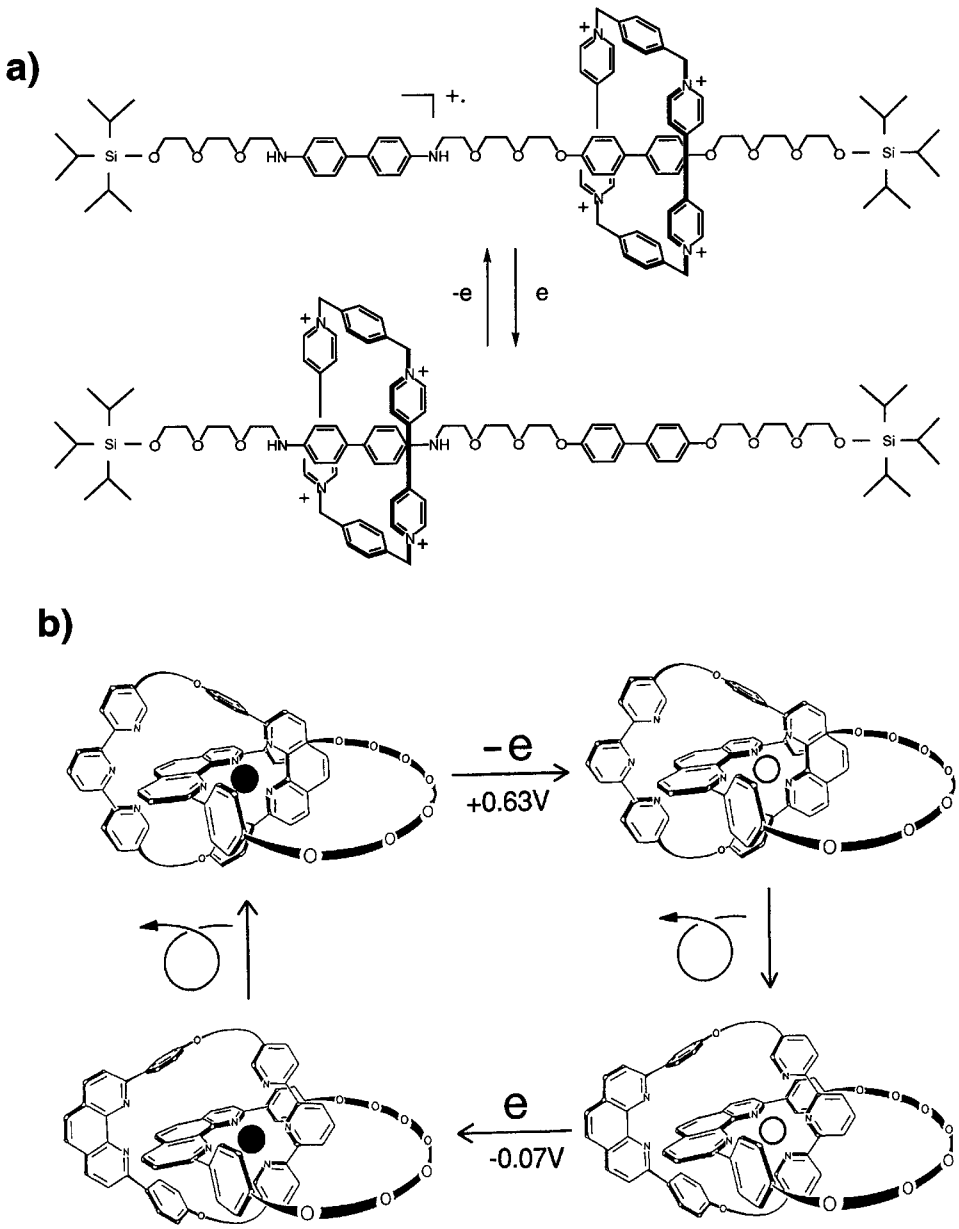

Figure 1. (a) The molecular 'shuttle' elaborated and studied by Stoddart, Kaifer and co-workers is based on electroactive organic functions (aromatic amine) and electron donor and acceptor groups. (b) A two-geometry [2]catenane constructed around copper(I); the gliding motion of one ring within the other is triggered by oxidizing or reducing the metal center (Cu^{I}/Cu^{II})

investigated, such as microtubule-associated ATPases. Kinesin and dyneine play an essential role in organelle transport along the microtubules in cells.[7] These proteins travel in a controlled fashion, in a way reminiscent of trains on rails.

Clearly, the functioning of skeletal muscles is the best understood linear motor.[8] The actin–myosin linear motor, which constitutes the most important part of muscles, has been extensively studied in the three last decades. There is obviously some analogy between the motion of actin filaments with respect to myosin-containing filaments (thick filament) and classical motors consisting of a piston moving in a cylinder (see Fig. 2).

In terms of molecular synthetic models, shuttles,[5a] consisting of rings gliding on the filaments (or rods) on which they have been threaded, also display functional analogy with the myosin–actin complex.

MOLECULAR MUSCLES

In order to obtain efficient machines, elaborated topol-

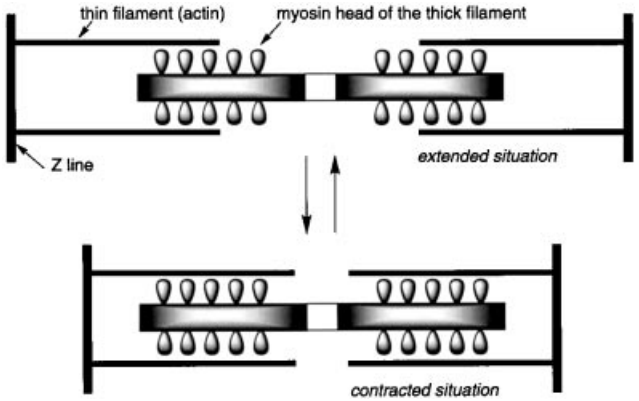

Figure 2. Schematic representation of a muscle in action. From the stretched situation, the contracted situation is obtained by a gliding process of the thick filament (myosin) along the thin filament (actin polymer)

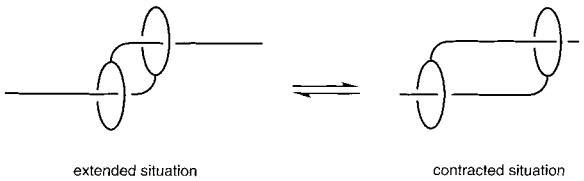

Figure 3. The topology and the shape of a linearly arranged pseudo-rotaxane dimer is adapted to a contraction/stretching motion

ogies are needed. In particular, one-dimensional molecular assemblies able to undergo stretching and contraction motions under the action of an external signal, similar to those observed in the real muscles, appeared as an exciting target.

Several interesting artificial systems have been described which aim at reproducing some essential properties of skeletal muscles. Polypyrrole-based devices are particularly promising, allowing one to bend a solid polymer film in one direction or another depending on the sign of an electric current applied to the film.[9] Another recent approach relies on single-walled nanotube sheets.[10] However, unimolecular linear arrays capable of undergoing contraction or stretching have so far not been made.

Design and motion principle

We designed and studied a multicomponent system able to contract or stretch under the action of an external chemical signal. Our system, based on a symmetrical doubly threaded topology and represented in a very schematic fashion in Fig. 3, was originally assumed to fulfil the requirements to mimic the behavior of a muscle at the molecular level.

Double-threaded topologies were obtained by Stoddart and co-workers in the solid state by dimerization of a self-complementary monomer, whereas in solution single-threading processes led to the formation of various pseudo-oligomeric rotaxane topologies.[11a,b] By analogy with real muscles, a molecular assembly in which two filaments can glide along one another was designed. This is the very process taking place in the sarcomere, in which the thick filament (containing myosin) moves along the thin filament (actin polymer) in one direction or

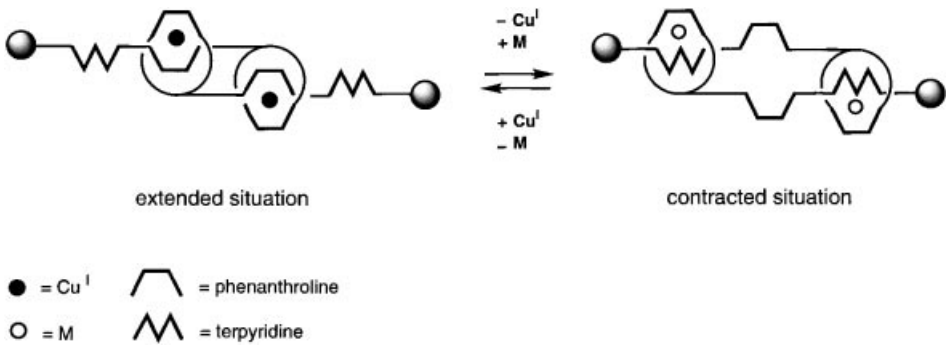

Figure 4. Functioning principle of the unimolecular synthetic 'muscle' discussed. The two-component rotaxane dimer contains identical ring-and-string conjugates. Each component consists of a bidentate chelate (U-shaped symbol) embedded in a ring, the ring being covalently attached to a filament-like part. This string contains another bidentate ligand, a terdentate coordinating unit (schematically represented by a W-shaped symbol) and a bulky stopper (sphere on the drawings) whose function is to prevent dethreading of the filaments from the rings through which they are threaded. The four-coordinate situation (left-hand side) is such that the metal (black disk) is coordinated to two bidentate chelates. If the bidentate chelate belonging to the string is replaced by a terdentate fragment, a five-coordinate situation is reached, which corresponds to an overall contracted situation (right-hand side). The contracted situation is obtained by replacing the four-coordinate metal of the compound represented on the left [copper(I) in the present work] by a five-coordinate center [white disk; zinc(II) in the present work]

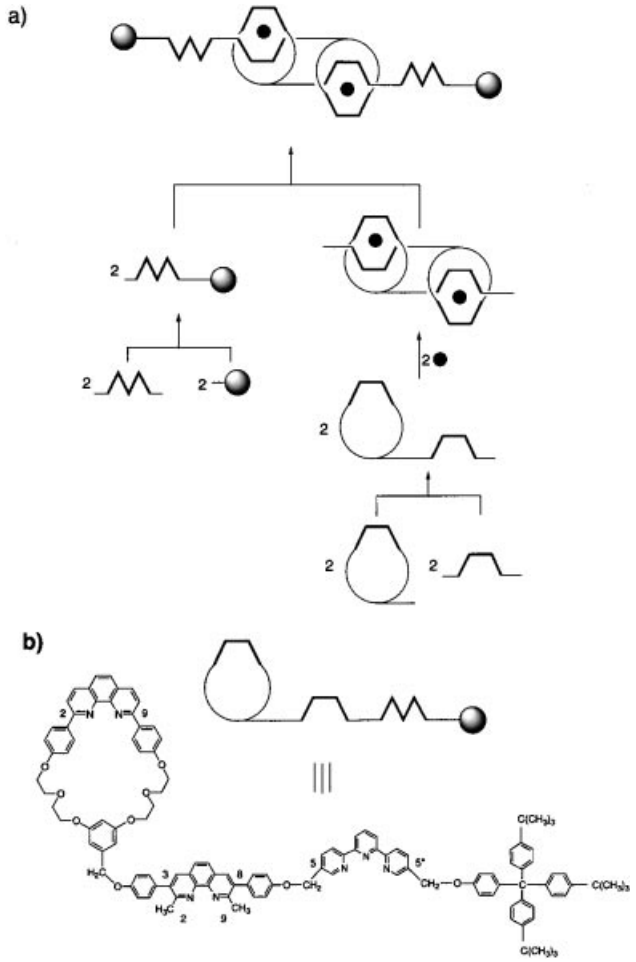

Figure 5. (a) Synthetic strategy used for the building up of the rotaxane dimer. (b) Chemical content of each subunit contained in the double-threaded assembly

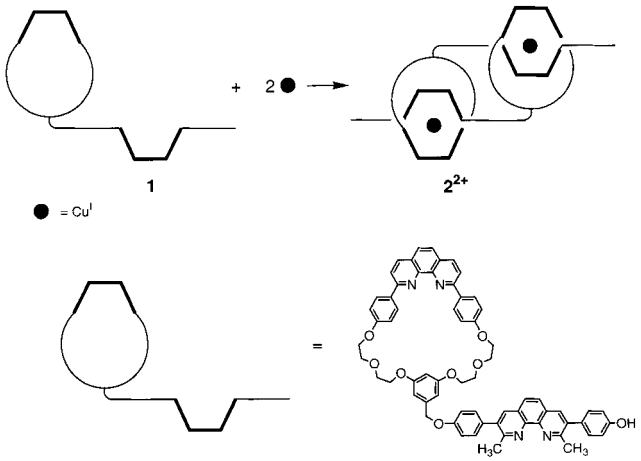

Figure 6. Schematic representation of the double-threading process induced by copper(I) (black dots) between two hermaphrodite ligands each containing a chelating ring and a coordinating stick and chemical structure of the target ligand **1**

the other so as to induce contraction or stretching. In the double-threaded object in Fig. 3, the motion is easy to visualize. Both strings (mimicking the muscle filaments) move along one another but stay together thanks to the rotaxane nature of the system.

So far, the machine-like compounds elaborated and studied in our group were mostly copper complexes, the motion being triggered by an electrochemical reaction (Cu^{I}/Cu^{II}),[5b,12] although photochemically driven processes based on ruthenium(II) compounds also seem to be promising.[13] The present system contains copper(I) as the assembling and templating metal, but the movement is induced by a chemical reaction, corresponding to metal exchange. As shown in Fig. 4 the doubly-threaded compound reported here can bind simultaneously two metal centers, in either a four or a five-coordinate geometry. The four-coordinate situation results from the coordination of a copper(I) ion with two phenanthroline units and corresponds to an extended geometry (left part of Fig. 4), whereas the pentacoordinated situation resulting from the coordination of a divalent ion M with one phenanthroline and one terpyridine leads to a contracted geometry (right part of Fig. 4).

To reach such a rotaxane dimer we envisaged the general synthetic strategy represented schematically in Fig. 5(a).

A macrocycle containing a 2,9-diaryl-1,10-phenanthroline was covalently linked to a linear 3–8-substituted 1,10-phenanthroline, ended by a phenolic function which will allow the final stoppering process. Synthesis of the dinuclear doubly threaded central core was performed using copper(I) as gathering and threading actuator between two of the latter bis-bidentate ligands. After separate synthesis of a functionalized 2,2′,6′,2″-terpyridine bearing a bulky stopper, we reacted two such terdentate coordinating units with the phenolic functions of the doubly threaded dicopper(I) complex. This last reaction not only allowed us to introduce terdentate sites into the molecular assembly, but gave also access to a real rotaxane structure in which any dethreading process is prohibited owing to the presence of the two bulky stoppers. Once both principles (motion principle and construction principle) were defined, CPK models were very helpful in deciding what should be the precise chemical structure of each symbolic fragment used in Figs 4 and 5(a). Indeed, CPK models suggested us that a 31-membered macrocycle should have the optimum size. It appeared large enough to allow the threading of a phenanthroline belonging to an opposite rod, but also small enough so that an intramolecular copper(I) complexation between the two phenanthrolines of the same unit will be avoided. In fact, such a kind of intramolecular complexation could occur with a large, flexible macrocycle able to fold up easily. For the rod we chose a tetrasubstituted phenanthroline. Substitution at the 2- and 9-positions was necessary for the formation of

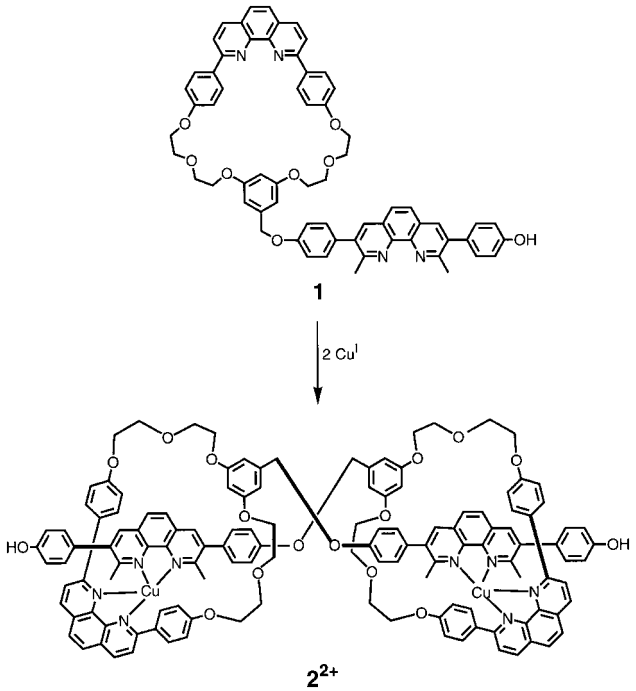

Figure 7. The copper(I)-induced threading process leading to the dimer $\mathbf{2}^{2+}$

a stable diphenanthroline–copper(I) complex, but here again the size was critical: even if necessary, these substituents should not be too bulky so that the threading process will not be inhibited for steric reasons. Methyl groups fulfil such a requirement. Finally, the 3- and 8-positions were substituted by aromatic groups so that the rod would be as linear as possible, avoiding the formation of an intramolecular copper(I) complex between the two adjacent phenanthrolines of the same subunit. A 5,5″-dimethylterpyridine able to be connected to the other fragments after functionalization of the methyl groups was chosen as terdentate site. The large bulky tris(terbutylphenyl)methane derivative stoppers should avoid any dethreading. After all the connections between the various fragments had been achieved, the precise chemical nature of the monomeric multisite ligand used in the present work is as given in Fig. 5(b).

Synthesis of the dinuclear doubly threaded central core

Using copper(I) as a gathering and threading center, it was possible to generate the doubly threaded species shown schematically in Fig. 6, both in solution and in the solid state. In this dinuclear dimer each organic ligand is a self-complementary monomer of a chelating ring attached to a coordinating stick. Owing to the structural features of the ring-and-stick ligand **1**, the complexation reaction that affords the doubly threaded copper(I) complex $\mathbf{2}^{2+}$ can be regarded as a double plugging-in process between the female (ring) and the male (coordinating stick) components; thus the organic ligand has a hermaphrodite character.

As expected, **1** was not able to form an intramolecular tail-bitten complex. The rigid rod consisting of 3,8-diaryl-1,10-phenanthroline is too rigid and connected to the ring via a too short linker for **1** to fold up so as to allow a self-threading process, comparable to what was observed in previously reported organic systems.[14] In fact, the dimerization reaction represented in Fig. 6 occured quantitavely in solution upon addition of a stoichiometric amount of $Cu(CH_3CN)_4^+PF_{6^-}$ to **1**. ^{1}H NMR and mass spectrometry (MS) turned out to be particularly useful to demonstrate the quantitative formation of the dimer $\mathbf{2}^{2+}$ at room temperature[15] (see Fig. 7)

Interestingly, ^{1}H NMR and thin-layer chromatography clearly showed that the initial mixture of the kinetic copper(I) complexes obtained immediately after addition of the copper(I) salt to ligand **1** re-equilibrates. The various cyclic or linear oligomers initially present in the reaction mixture besides $\mathbf{2}^{2+}$ are spontaneously converted to the thermodynamically more stable dimer $\mathbf{2}^{2+}$

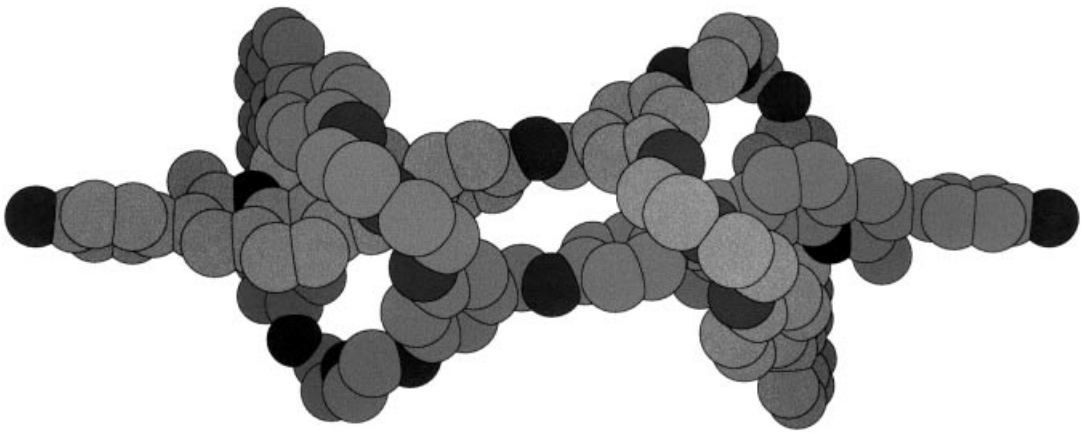

Figure 8. Crystal structure of the dicopper(I) dimer $\mathbf{2}^{2+}$. Space filling representation

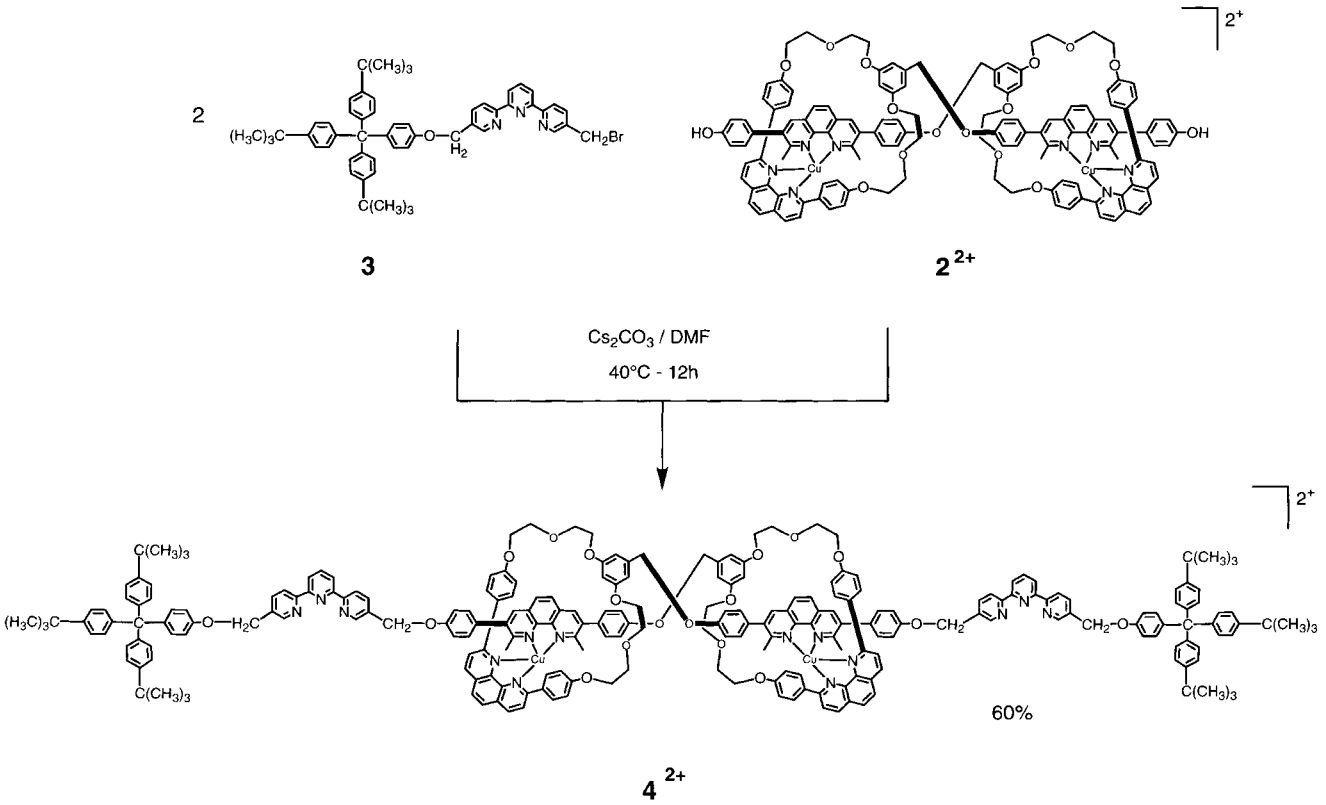

Figure 9. Synthesis of the 'muscle' $\mathbf{4}^{2+}$ in its extended situation

in quantitative yield over a period of 48 h at room temperature.

The dimer $\mathbf{2}^{2+}$ was isolated as deep red crystals of its PF_6^- salt, which allowed the determination of its actual molecular structure by x-ray diffraction. The molecular structure of the dinuclear dimer $\mathbf{2}^{2+}$ which possesses only a single C_2 axis is shown in Fig. 8.

The complex $\mathbf{2}^{2+}$ contains two identical symmetry-related subunits each consisting of one macrocycle, one linear 3,8-diaryl-1, 10-phenanthroline rod and one copper ion. The most striking feature of this structure is its linear well extended anti-parallel arrangement which locates the two terminal phenolic oxygen at a distance as large as 36.3 Å. The two copper atoms are 18.3 Å apart and have identical environments.

Synthesis of a linear rotaxane dimer

The interesting topology of the complex $\mathbf{2}^{2+}$ prompted us to react its phenolic functions in DMF and Cs_2CO_3 at 40 °C with two equivalents of bromide **3** (a stopper-bearing disymmetrical 2,2′,6′,2″-terpyridine which was obtained in a multi-step synthesis). The latter coupling reaction led to the molecular 'muscle' $\mathbf{4}^{2+}$ in 60% yield as represented in Fig. 9.

2D-ROESY NMR experiments and high-resolution fast atom bombardment (FAB) MS showed clearly that the stoppering procedure leading to $\mathbf{4}^{2+}$ occured without significant dethreading, as evidenced by large interfragment interactions in its NMR spectrum and the expected molecular ion peak at *m/z* 3834.2 (calculated, 3834.3).

Chemically triggered stretching and contracting motions

The free ligand **5** obtained in quantitative yield by reacting $\mathbf{4}^{2+}$ with a large excess of KCN (in CH_2Cl_2–H_2O at room temperature) was subsequently remetalated with $Zn(NO_3)_2$ (in CH_2Cl_2–MeOH) affording $\mathbf{6}^{4+}$ quantitatively as a colorless solid, in the contracted situation (Fig. 10). The reverse motion, leading back to the extended situation, i.e. back to $\mathbf{4}^{2+}$, could be easily induced upon addition of excess $Cu(CH_3CN)_4 \cdot PF_6$ in CH_2Cl_2-CH_3CN at room temperature. If the dimeric nature of $\mathbf{4}^{2+}$, **5** and $\mathbf{6}^{4+}$ could be easily evidenced by MS [FAB or electrospray(ES)], the contraction/stretching phenomenon accompanying the metal exchange (Cu^I/Zn^{II}) required to be demonstrated by extensive NMR studies. The latter were mainly based on the unambiguous chemical shifts of some aromatic protons (belonging to either the phenanthroline or the terpyridine moieties), which turned

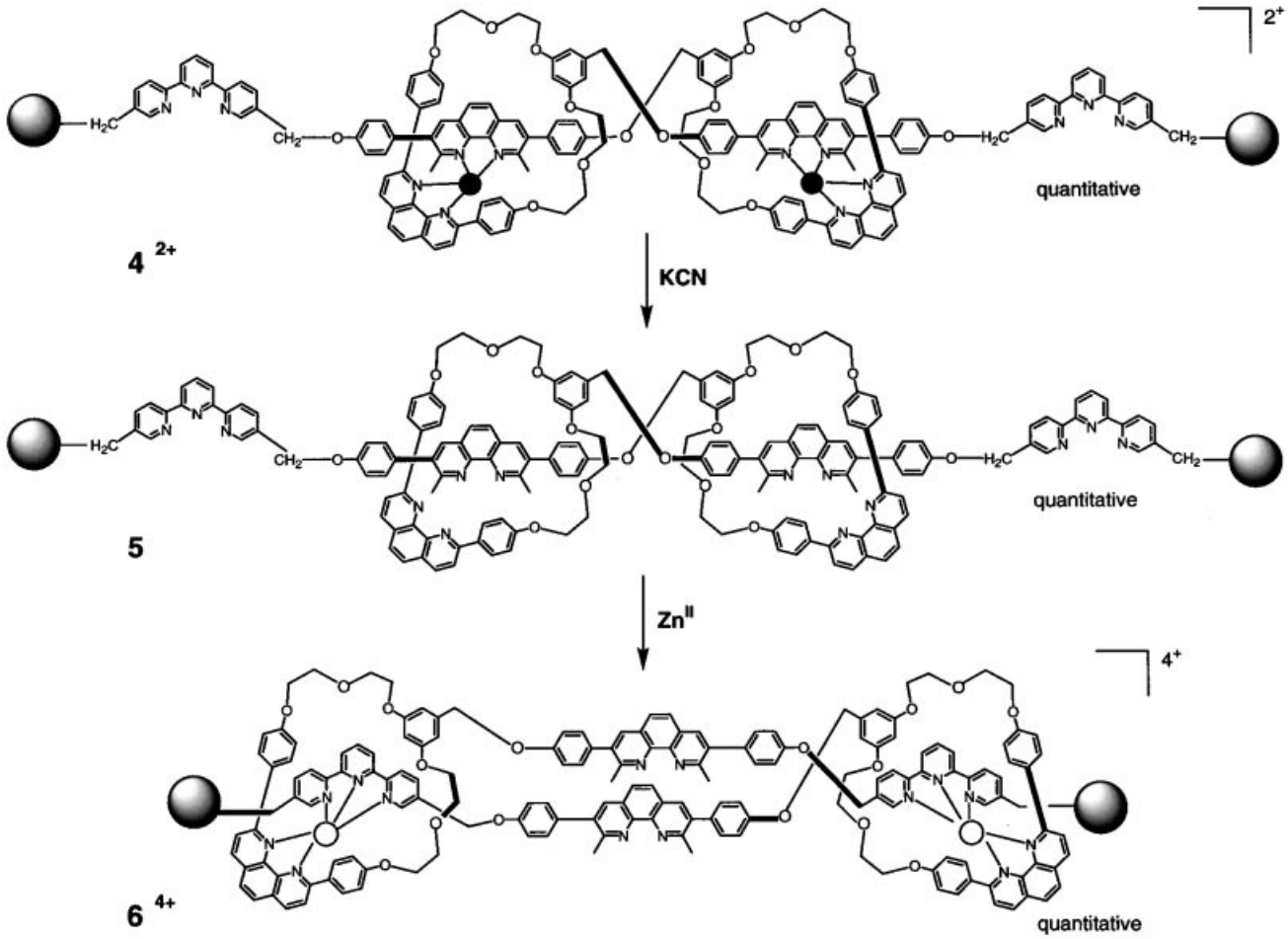

Figure 10. Reversible chemically induced motions between extended $\mathbf{4}^{2+}$ and contracted $\mathbf{6}^{2+}$. Black disk = copper(I); white circles = zinc(II)

out to be excellent probes in one- and two-dimensional ^{1}H NMR.[16]

The present rotaxane dimer represents the first example of a unimolecular linear array able to stretch and contract at will under the action of a chemical stimulus. From CPK model estimations, the length of the compound changes from 83 to 65 Å between the two situations, i.e. roughly of the same relative amount as natural muscles (~27%).

CONCLUSION

The field of molecules in motion, for which movements and shape changes are triggered and controlled from the outside, has indisputably been one of the most rapidly developing areas of the last decade. Transition metal-containing rotaxanes and catenanes represent an interesting class of such compounds, owing to the evident non-destructive nature of the redox processes taking place on the metal, as opposed to the involvement of organic radicals. Electrochemical signaling is attractive but photonic processes are likely to be more important if future applications are to be found. Here again, transition metal complexes will play an important role since many of them display rich and clean photochemistry. In this review, we have discussed a rotaxane dimer whose behavior is reminiscent of a muscle. The stretching/contraction process is triggered by a chemical reaction (metal exchange), but it is obviously hoped that electrochemical or photochemical reactions will also lead to the same mechanical effect in the future. Most of the work carried out in our group has been inspired by biology, and this is of course the case for the compounds described here. Nowadays, applications of transition metal-based synthetic muscles seem to be relatively far away, but other systems may turn out to be practically important much sooner.

Recent work[17] has demonstrated that molecular computers are perhaps not out of reach and could be proposed within one or two decades. In addition, the motion of a ring shuttling between two or several stations could easily be related to the transport of various chemical species, the ring playing the role of a cargo in

a way reminiscent of kinesin or dyneine moving along microtubules in cells.[18] Another important step will be to transpose what has been performed on large collections of molecules in solution to ordered 2D- and 3D-arrays and single molecules on a surface.

Acknowledgements

We thank all the researchers who participated in the work described here and whose names appear in the references. We are also grateful to the CNRS and to the European Commission for financial support.

REFERENCES

1. (a) Kitamura K, Tokunaga M, Iwane AH. *Nature (London)* 1999; **397**: 129–134; (b) Howard J. *Nature (London)* 1997; **389**: 561–567; (c) Elston T, Wang H, Oster G. *Nature (London)* 1998; **391**: 510–513.
2. Pascher T, Chesick JP, Winkler JR, Gray HB. *Science* 1996; **271**: 1558–1560.
3. (a) Noji H, Yasuda R, Yoshida M, Kinosita K. *Nature (London)* 1997; **386**: 299–302; (b) Walker JE. *Angew. Chem., Int. Ed. Engl.* 1998; **37**: 2308–2319.
4. (a) Balzani V, Gómez-López M, Stoddart JF. *Acc. Chem. Res.* 1998; **31**: 405–414; (b) Sauvage J-P. *Acc. Chem. Res.* 1998; **31**: 611–619; (c) Fabbrizzi L, Licchelli M, Pallavicini P. *Acc. Chem. Res.* 1999; **32**: 846–853; (d) Kelly TR, De Silva H, Silva RA. *Nature (London)* 1999; **401**: 150–152; (e) Koumura N, Zijlstra WJ, Van Delden RA, Harada N, Feringa BL. *Nature (London)* 1999; **401**: 152–155.
5. (a) Bissell RA, Córdova E, Kaifer AE, Stoddart JF. *Nature (London)* 1994; **369**: 133–137; (b) Livoreil A, Dietrich-Buchecker CO, Sauvage J-P. *J. Am. Chem. Soc.* 1994; **116**: 9399–9400; (c) Zelikovich L, Libman J, Shanzer A. *Nature (London)* 1995; **374**: 790–792.
6. (a) Schill G. In *Catenanes, Rotaxanes and Knots*. Academic Press: New York, 1971; (b) Dietrich-Buchecker CO, Sauvage J-P. *Chem. Rev.* 1987; **87**: 795–810; (c) Amabilino DB, Stoddart JF. *Chem. Rev.* 1995; **95**: 2725–2828; (d) Jäger R, Vögtle F. *Angew. Chem., Int. Ed. Engl.* 1997; **36**: 930–944; (e) Fujita M. *Chem. Soc. Rev.* 1998; **27**: 417–426; (f) Sauvage J-P, Dietrich-Buchecker C, Rapenne G. In *Molecular Catenanes, Rotaxanes and Knots*, Sauvage J-P, Dietrich-Buchecker C (eds). Wiley-VCH: Weinheim, 1999; (g) Chambron J-C. In *Transition Metals in Supramolecular Chemistry*, Sauvage J-P (ed). John Wiley & Sons: Chichester, 1999; chapt. 6.
7. Hirokawa N. *Science* 1998; **279**: 519–526.
8. Rayment I, Holden HM, Whittaker M, Yohn CB, Lorenz M, Holmes KC, Milligan RA. *Science* 1993; **261**: 58–65.
9. Otero T, Sansiñena JM. *Adv. Mater.* 1998; **10**: 491–494.
10. Baughman RH, Cui C, Zakhidov AA, Iqbal Z, Barisci JN, Spinks GM, Wallace GG, Mazzoldi A, De Rossi D, Rinzler AG, Jaschinski O, Roth S, Kertesz M. *Science* 1999; **284**: 1340–1344.
11. (a) Ashton PR, Baxter I, Cantrill SJ, Fyfe MCT, Glink PT, Stoddart JF, White AJP, Williams DJ. *Angew. Chem., Int. Ed. Engl.* 1998; **37**: 1294–1297; (b) Ashton PR, Parsons IW, Raymo FM, Stoddart JF, White AJP, Williams DJ, Wolf R. *Angew. Chem., Int. Ed. Engl.* 1998; **37**: 1913–1916; (c) Yamaguchi N, Nagvekar DS, Gibson HW. *Angew. Chem., Int. Ed. Engl.* 1998; **37**: 2361–2354.
12. (a) Collin J-P, Gaviña P, Sauvage J-P. *Chem. Commun.* 1996; 2005–2006; (b) Collin J-P, Gaviña P, Sauvage J-P. *New J. Chem.* 1997; **21**: 525–528.
13. Laemmel A-C, Collin J-P, Sauvage J-P. *Eur. J. Inorg. Chem.* 1999; 383–386.
14. Ashton PR, Ballardini R, Balzani V, Boyd SE, Credi A, Gandolfi MT, Gómez-López M, Iqbal S, Philp D, Preece JA, Prodi L, Ricketts HG, Stoddart JF, Tolley MS, Venturi M, White AJP, Williams DJ. *Chem. Eur. J.* 1997; **3**: 152–170.
15. Jiménez MC, Dietrich-Buchecker C, Sauvage J-P, De Cian A. *Angew. Chem., Int. Ed. Engl.* 2000; **39**: 1295–1298.
16. Jiménez MC, Dietrich-Buchecker C, Sauvage J-P. *Angew. Chem., Int. Ed. Engl.* 2000; **39**: 3284–3287.
17. Collier CP, Mattersteig G, Wong EW, Luo Y, Beverly K, Sampaio J, Raymo FM, Stoddart JF, Heath JR. *Science* 2000; **289**: 1172–1175.
18. Hirokawa N. *Trends Cell Biol.* 1996; **6**: 135–141.

