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The Role of Dethreading Process in Pseudorotaxanes and Rotaxanes towards Advanced Applications: Recent Examples

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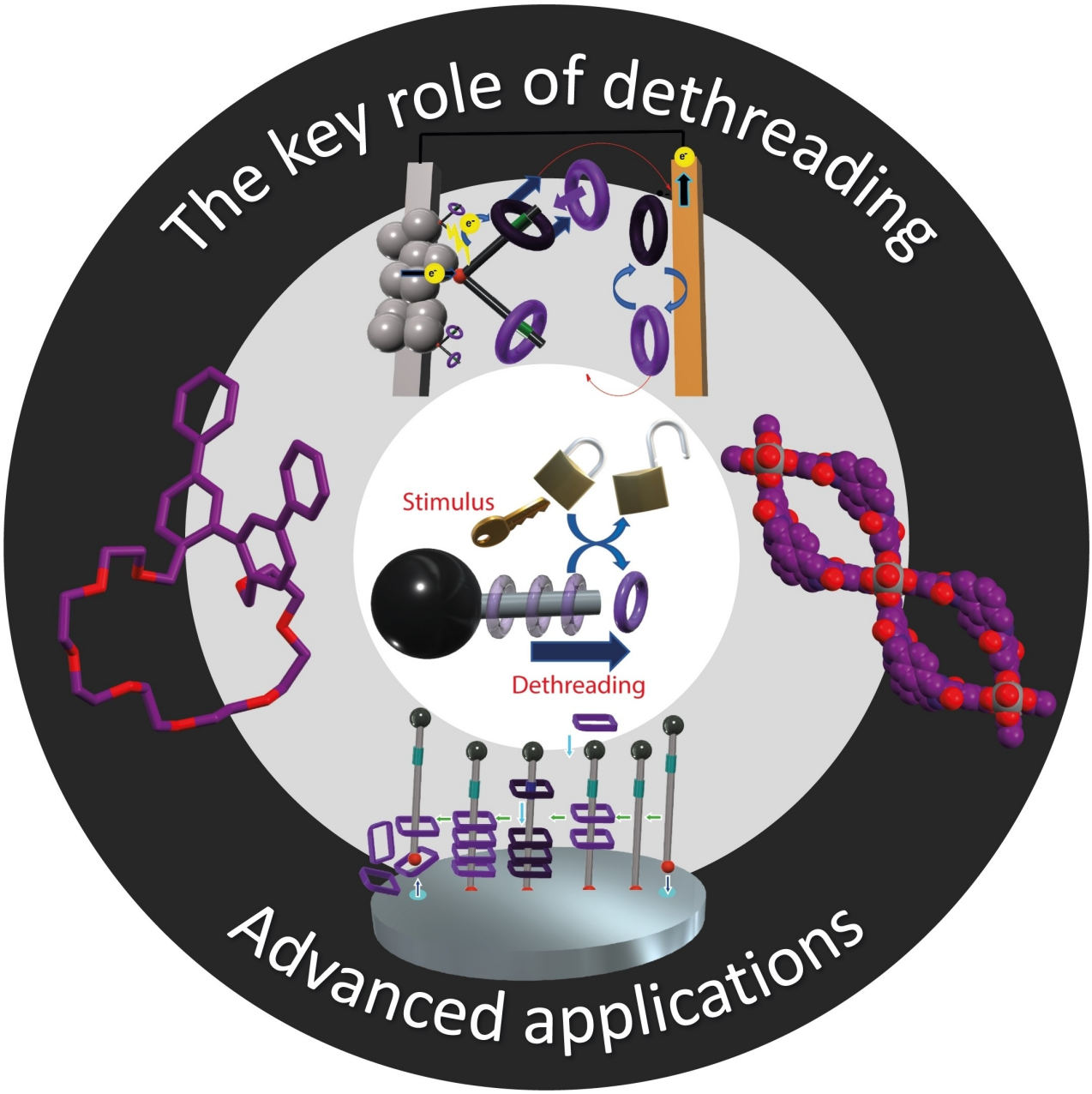
This review is dedicated to my mentors Alberto Martinez-Cuezva and Jose Berna for their promotion to Associate Professor and Full Professor, respectively.



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Rotaxanes are a type of mechanically interlocked molecules (MIMs), constituted by at least a thread surrounded by a wheel, which are widely employed in the research field of artificial molecular machines. Although applications retaining the integrity of the mechanical bond are usually reported, the dethreading of the components can be crucial to develop some advanced applications. Thus, different dethreading strategies have been reported, and advanced applications which require such a process have turned out to be suitable approaches towards machine-like operation. This review article covers recent examples of applications of pseudorotaxanes and rotaxanes in which dethreading processes have a key role to accomplish the desired function.

1. Introduction

Mechanically interlocked molecules (MIMs) are a type of compounds constituted by components which are bonded together through noncovalent interactions, forming a mechanical bond.[1–3] Within the range of intertwined compounds, rotaxanes are postulated as ideal candidates for the design of molecular machines, developing applications in a wide range of fields,[4–6] such as catalysis,[7–14] materials science[15–24] or medicinal chemistry.[25–27]

Usually, the design of these structures seeks the stability of the mechanical bond, thus preventing the dissociation of the different components in order to carry out a specific function. However, as it occurs in many biological processes, in which the mechanical bond is temporarily formed to undertake a precise function (such as the biological molecular machine processive catalysts), sometimes the design of these molecules requires the rational incorporation of certain functionalities which allow the dethreading of the counterparts by applying different stimuli.[28–30]

To contextualize the concept of dethreading in rotaxanes, a [2]rotaxane, which is the simplest example constituted by a macrocycle and a thread containing the binding site, is considered. The interlocked architecture of this molecule is stabilized by noncovalent interactions between both counterparts. If these supramolecular interactions are interrupted, the force that retains the bond between cyclic and linear components disappears. However, the dissociation of the counterparts could be avoided by bulky groups placed at the ends of the thread which prevent the dethreading to take place. In order to visualize this phenomenon, a [2]rotaxane could be considered as a dumbbell having a ring surrounding the bar. If this ring has a smaller diameter than that of the weights, the separation of ring and dumbbell is impossible unless the rupture of some components is carried out (covalent bonds in the case of the intertwined molecules).

As abovementioned, most of the synthetic strategies towards rotaxanated architecture pretend the formation of robust structures in which the interlocked assembly is not threatened, thus disrupting the dethreading process.[31–35] In stark contrast, certain design difficulties arise when systems in which a dethreading process can be induced by the application of external stimuli are required.

In this scenario, there are some requirements which must be fulfilled in order to design interlocked compounds experiencing a switchable dethreading: (i) the stoppers should be small enough to allow the dissociation of both counterparts or easily removable by an external input; (ii) the stability of the mechanical bond must be retained during storage; and (iii) the dethreading process must not occur under the application conditions until the exact moment in which such a process is needed.

Thus, different reversible and irreversible dethreading strategies have been reported,[36–43] operating through the application of different stimuli, such as light, pH and chemical inputs. Indeed, a number of applications in which such processes are mandatory have been carried out by different researchers in the area of molecular machines.

In order to highlight the importance of the dethreading process in the operation mode of different rotaxanes, this short review is focused on recent examples in which the application performed by these intertwined molecules requires a final dethreading step. Thus, the selected examples cover a wide range of applications, from the simple preparation of macrocyclic compounds to more sophisticated functionalities such as stereoselective syntheses, smart delivery of target compounds, active mechanisorption and improvement of the efficiency of solar cells. In addition to the tutorial analysis of the examples, a critical opinion of the state of the art and future research directions are provided.

2. Synthesis of Target Molecules

A priori, the assembly of a mechanical bond with the aim of disassembling it at a later step could be perceived as meaningless. However, the importance of this approach is clearly exemplified by the simplest example, the synthesis of tetralactam macrocycles.

The synthesis of these macrocycles was traditionally accomplished through a (2 + 2) condensation reaction of an aroyl dichloride and *p*-xylylenediamine derivatives.[44,45] But this synthetic strategy involves a series of difficulties when the macrocycle is the target compound. Indeed, a [2]catenane turns out to be the main product as a consequence of the hydrogen bonding interactions between reaction intermediates. Further-

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more, several oligomers are formed during the reaction, hindering the isolation of pure macrocycles. In this scenario, the research group of Leigh was pioneer in the preparation of such a macrocycle by a dethreading of a benzylic amide rotaxane induced by a transesterification reaction of the stoppers of the thread.[46] More recently, Berna and coworkers reported the preparation of tetralactam macrocycles through the thermally and photochemically induced dethreading of fumaramide-based pseudo[2]rotaxanes.[29,30] The advantage of these methodologies which operate *via* the formation of rotaxanes lies in the increase in yield and the facilitation of the purification step.

Through the thermally induced dethreading approach, a tetralactam macrocycle bearing methoxycarbonyl groups at the isophthalamide motifs (**1**) from a tetrabutylfumaramide-based pseudo[2]rotaxane (**2**) was accomplished (Figure 1a).[47] With this purpose, dimethylsulfoxide (DMSO) was employed as a solvent to disrupt the hydrogen bonding interactions between thread and macrocycle. The increase in temperature (110 °C) induced the final dethreading of both counterparts (**1** and **3**). The subsequent saponification reaction of the macrocycle provided a useful ligand which was employed in the preparation of metal-organic frameworks (MOFs) having copper or zinc as the metal source, which effectively encapsulated fullerene C_{60} (Figure 1b).

The discussed examples above are focused on the synthesis of macrocycles during the assembly of a mechanical bond, where dethreading helps to remove the templates, affording the target molecules. In contrast, molecular nanoreactors involve post-mechanical bond formation chemical transformations.

Before giving details of the importance of the dethreading of rotaxanes in molecular nanoreactors, there are two considerations which must be made in order to contextualize this concept. First, the term "molecular nanoreactor" employed in this article refers to a component of the interlocked structure that mediates the effective performance of a specific chemical process. Thus, the presence of the mechanical bond is necessary for the chemical reaction to take place. The second consideration refers to the dethreading process itself. Although this process is not strictly necessary for the reaction to be carried out successfully, this step turns out to be essential if it is intended to go beyond the academic curiosity generated by these elegant chemical processes operated by molecular machines. The dethreading process thus allows the application of the non-interlocked species after the chemical transformation.

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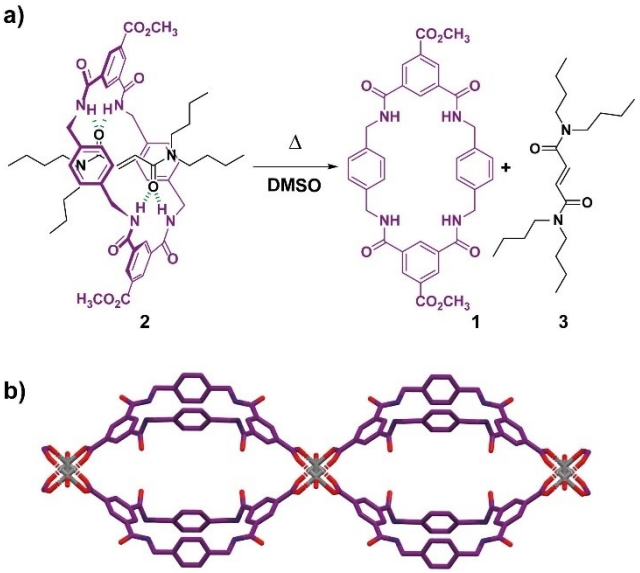

Figure 1. a) Thermally induced dethreading of pseudo[2]rotaxane **2**; and b) stick representation of the pocket of four macrocyclic ligands of the MOF along the *c* axis.[47] Grey = copper; purple = carbon and nitrogen; red = oxygen.

Once these considerations have been addressed, it is appropriate to establish the stark contrast that rotaxane-based nanoreactors represent in comparison with the properties that the mechanical bond usually provides. Indeed, the protective effect of the macrocycle towards the threaded linear component has been widely employed with the aim of stabilize unstable species or protect them from the reaction medium.[48–50]

A simplified division between two types of rotaxane-based nanoreactors could be carried out, molecular track synthesizers and confined space systems.

Molecular track synthesizers, which take inspiration from processive catalysts in nature, operate through the shuttling of the macrocycle along a thread. There are two subtypes within these interlocked systems. On one side, there are systems in which the macrocycle induces chemical transformations in groups placed at the thread during the shuttling motion, such as the processive catalytic epoxidation of polymeric polyalkene-based thread by a porphyrin-based macrocycle reported by Rowan, Nolte and coworkers.[51–53] On the other side, there are systems bearing a reactive unit placed at the macrocycle which react with different motifs grafted on the thread, such as the small peptide synthesizers developed by Leigh and colleagues.[54–56]

A recent representative example of a rotaxane-based molecular track is rotaxane **4** constituted by a thread having different phosphonium ylides motifs and a macrocycle bearing an aldehyde-ended chain (Figure 2).[57] This system worked through an iterative manner synthesizing an oligomer by

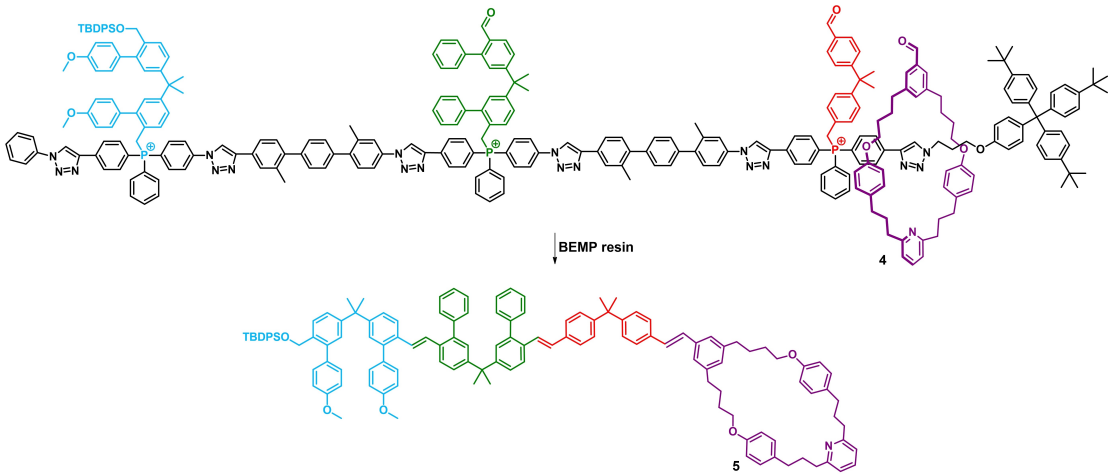

Figure 2. Schematic representation of molecular track **4** which provided the oligomer **5**.[57] The structure of the linear component is omitted for simplicity.

sequential Wittig reactions which occur during the shuttling of the macrocycle. The rational design of the system allowed to retain an inactive mode until a treatment with a basic BEMP resin was carried out. Then, the shuttling process began, incorporating units into the newly formed oligomer, until the end which lacks a stopper was reached. Thus, a final dethreading process afforded the target oligomer **5**. As above-mentioned, the relevance of the dethreading process lies in the obtention of the novel non-interlocked product, which can be used in different implementations.

The other type of rotaxane-based molecular nanoreactors are those working within the confined space provided by the cavity of the macrocycle. In these systems, the cyclic counterpart assists a chemical transformation of the directly surrounding functionality of the thread. Berna and colleagues have reported the stereocontrolled synthesis of β-lactams within [2]rotaxanes.[58–60] This reaction proceeds through the base-promoted cyclization of interlocked *N*-(arylmethyl)fumaramide threads by the assistance of the polyamide macrocycle. The tetralactam cyclic component plays a dual role, both as activating element and as the stereodifferenciating factor which led to diastereoselection over *trans*-β-lactams. Although the ring-activated reaction is interesting from a conceptual point of view, interlocked β-lactams are not relevant molecules regarding their biological activity. However, their non-interlocked analogous are well known for their biological properties.[61] Thus, a dibutylamido group was placed as one of the stoppers in the molecular design in order to accomplish a dethreading reaction in a final step, affording the target molecules of biological interest.

An illustrative example of this molecular nanoreactor is the ring-to-thread chirality transfer of the fumaramide-based rotaxanes **6** bearing a single stereogenic center in the tetralactam macrocycle towards the preparation of the enantioenriched lactams **7** (Figure 3).[62] Rotaxanes **6** are orientational mechanostereoisomers which are constituted by nonsymmetric *N*-(arylmethyl)fumaramides as threads and a tetralactam polyamide macrocycle having an α-methyl group with *R* configuration. The cesium hydroxide-induced cyclization followed by a thermally promoted dethreading yielded majorly the same *trans*-β-lactam enantiomer from each intertwined mechanical epimer. Thus, the covalent stereogenic center placed at the cyclic counterpart turned out to be the unit controlling the enantioselectivity of such mechanical bond-activated process. The mere presence of the small methyl group of the macrocycle broke the symmetry of the intertwined system, affording high levels of enantioselectivities over the formation of lactams and aminoacids as the transfer of chiral information from the macrocycle to the thread through the mechanical bond was accomplished. In this example, since the target products are the noninterlocked derivatives, the dethreading reaction was sequentially performed without additional purification steps after the intramolecular cyclization reaction took place.

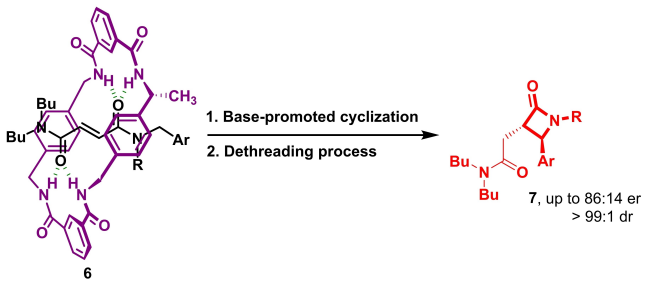

Figure 3. Synthesis of β-lactams **7** from orientational mechanostereoisomers **6**.[62] The structure of the macrocyclic compound is omitted for simplicity.

These highlighted molecular systems reveal the importance of disassembling a mechanical bond once it has fulfilled its function by activating an individual chemical transformation.

3. Controlled Release Systems

Beyond the synthetic protocols which proceed through the prior formation of a mechanical bond, the dethreading process

of rotaxanated architecture is also useful for the controlled release of target molecules. Different controlled release systems have been designed to accomplish this advanced implementation. Stimuli-cleavable polyrotaxanes have been successfully employed as platforms for therapeutic applications through the delivery of target drugs upon an external input.[63] Papot and colleagues also developed a therapeutic application in which the cleavage of an ester bond of a [2]rotaxane-based prodrug by an esterase released a potent anticancer drug within tumor cells.[64] Enzyme-responsive interlocked profragrances, which act as molecular logic gates, turned out to be ideal scaffolds for the controlled release of scents.[65] Cucurbit[6]uril (CB6) rotaxane probes for protease detection were prepared by the research group of Francis, in which an enzyme-triggered dethreading process released CB6 allowing interactions between this macrocycle and ^{129}Xe, thus leading to a protease-responsive hyperpolarization exchange saturation transfer.[66] The abovementioned systems, which operate through the dethreading induced by enzymes, take inspiration from the biological nanomachines working within living organisms. In addition to the systems at the molecular level, solid state rotaxane-based materials have been implemented in order to accomplish a controlled release of target molecules through a dethreading process, such as the pH-responsive pseudorotaxane-based mesoporous silica nanoparticles employed as rhodamine B delivery nanovalves by Stoddart, Zink and coworkers.[67]

A recent representative work described the employment of rotaxanes as cages to control DNA binding, cytotoxicity and cellular uptake of Pt^{II}-salphen complex.[68] Rotaxanes **8** are constituted by a bipyridine based macrocycle which encircles a thread bearing a Pt^{II}-salphen motif and an ester-ended stopper (Figure 4). The platinum-based compound selectively targets G-quadruplex (G4) DNA, thus acting as a potential anti-cancer drug. In an initial state, the macrocycle prevented the G4 DNA binding of this metallic complex. The controlled release interlocked systems operated in a sequential manner following a two-stage cleavage mechanism which involved two inputs. The modification of the cleavable stopper afforded two different dethreading operations: (i) when esterase-responsive pivalic (Pv) ester scaffolds were employed as part of the aryl ester-based stopper (rotaxane **8a**), the release of the target complex **9** operated through the sequential esterase-assisted hydrolysis of the ester bond of the pivalic motif and the subsequent hydrolysis of the aryl ester; (ii) when photoresponsive nitroveratryl (Nv) motifs were included as part of the aryl ester-based stopper in the molecular design (rotaxane **8b**), a light input followed by the enzyme-triggered hydrolysis led to the release of the target compound. Interestingly, these intertwined systems were tested *in vitro* by cell viability assays with osteosarcoma cells, observing a better cell permeability compared to that of the non-interlocked analogous. Noteworthy, the photo-triggered dethreading strategy has turned out to be a suitable approach to afford an enhanced growth inhibition of the cancer cells, resulting in a fine-tunable spatiotemporal control of the cytotoxicity and cellular localization of Pt^{II}-salphen complex **9**. This example nicely illustrates how a rational design of the stoppers can lead to different dethreading operation modes.

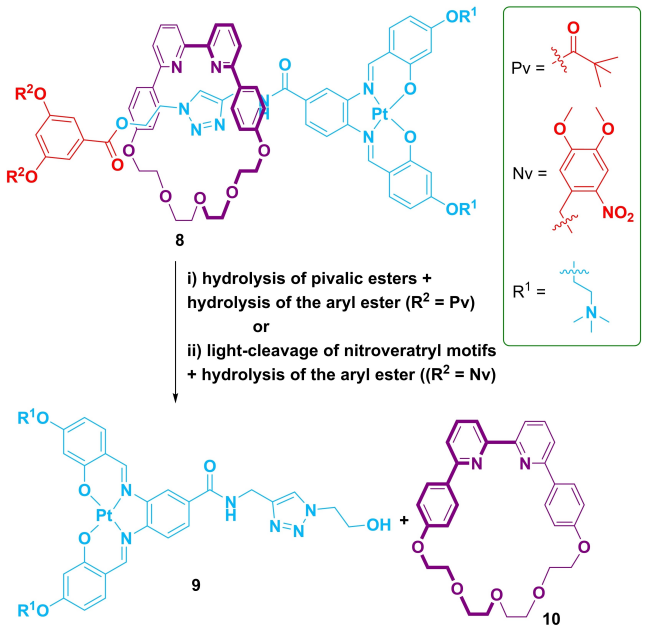

Figure 4. Controlled release of platinum complex **9** from rotaxanes **8** showing two different dethreading modes.[68] The structure of the carboxylic acid byproducts, as well as the byproduct of the photocleavage reaction are omitted for clarity. R^2 represents pivalic (Pv) or nitroveratryl (Nv) motifs.

4. Molecular Pumps

Rotaxane-based molecular pumps are artificial molecular machines which operate through the transport of macrocycles from bulk solution to a linear component upon the application of external stimuli and the other way around, thus pumping macrocycles in an out-of-equilibrium manner.[69–73]

An early example of a pseudorotaxane operating as a molecular pump was reported by Credi and colleagues in 2014, working through the application of light stimuli.[74] In the initial state, dinaphthocrown ether macrocycle **11** threaded a linear component having an azobenzene unit with *E*-configuration and an ammonium binding site (*E*-**12**) in a directional manner, affording pseudorotaxane **13** (Figure 5). Irradiation at 365 nm led to *E* to *Z* isomerization of the azobenzene motif, thus leading to the unidirectionally dethreading of the macrocycle **11** and *Z*-**12**. Interestingly, the reversible formation of pseudorotaxane is possible by simply photoirradiating or heating. This example, which clearly illustrates the working of a molecular pump, paved the way to accomplish a unidirectional motion of a macrocycle towards a thread by using light energy in a repetitive manner out-of-equilibrium.

The examples discussed up to this section could be classified as systems in which something tangible is achieved, such as certain product which is generated after a series of chemical transformations. However, molecular machines can also have other purposes, such as reading information from

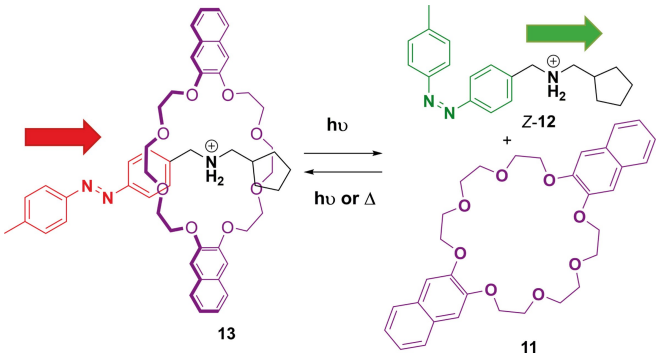

Figure 5. Operation mode of the light-driven rotaxane-based molecular pump constituted by **11** and **12**.[74] The red arrow indicates the direction of the threading process and the green one, the direction of the dethreading.

other molecules. Indeed, this type of process occurs dynamically within living organisms, such as the nucleotide sequence transported by mRNA from the nucleus to the cytoplasm.

In a simpler molecular version, a tape-reading molecular ratchet-based rotaxane, which operated through an initial threading, switchable shuttling and final dethreading, has been recently reported by Leigh and coworkers.[75] The system consisted of a crown ether macrocycle bearing a biaryl unit (**14**, the "reading head") which can adopt different conformations as a consequence of the established interactions with the different three compartments of a thread (**15**, the "molecular tape") (Figure 6). These compartments of the molecular tape are well separated by removable hydrazone and disulfide motifs which act as barriers. The authors selected as compartments an achiral *N*-methyltriazolium station and two protonated asymmetric *N*-benzyl-α-methylbenzylamine motifs with a defined chirality (*R* or *S*). The molecular barriers grafted on the molecular tape can be reversibly removed by changes in pH (pulses of CCl_3CO_2H). While basic conditions led to the opening of the disulfide barriers, acidic conditions removed the hydrazone barrier. Thus, through pH variations, the macrocyclic reading head could shuttle unidirectionally from one compartment of the molecular tape to another until the dethreading process took place through a ratchet-type mechanism. Interestingly, if a molecular tape containing a (*S*)-compartment, a neutral one and a final (*R*)-compartment is employed, this information can be read by using circular dichroism (CD) because of the twisting of the biaryl group as a consequence of the binding of the macrocycle with the different asymmetric units along the molecular tape. Thus, when the crown ether reading head **14** surrounds the (*R*)-*N*-benzyl-α-methylbenzylamine compartment a +1 CD signal is read, a 0 signal when the macrocycle binds to the achiral *N*-methyltriazolium compartment (no CD response) and a −1 CD signal in the case of the (*S*)-*N*-benzyl-α-methylbenzylamine compartment. The final dethreading afforded the starting reading head **14** and molecular tape **15**, thus operating by a non-destructive operation mode which allow to read out the sequence of stereochemical information. This system paves the way to the development of artificial machines operating in a similar way to that of ribosomal transcription by transcribing information as it is read from the molecular tape for different implementations, such as modifying the stereochemical outcome of a catalyzed chemical transformation.

All the highlighted examples above are focused on the importance of the dethreading reactions in processes which occur in solution. This section goes one step further, including systems which operate in the solid state by grafting the

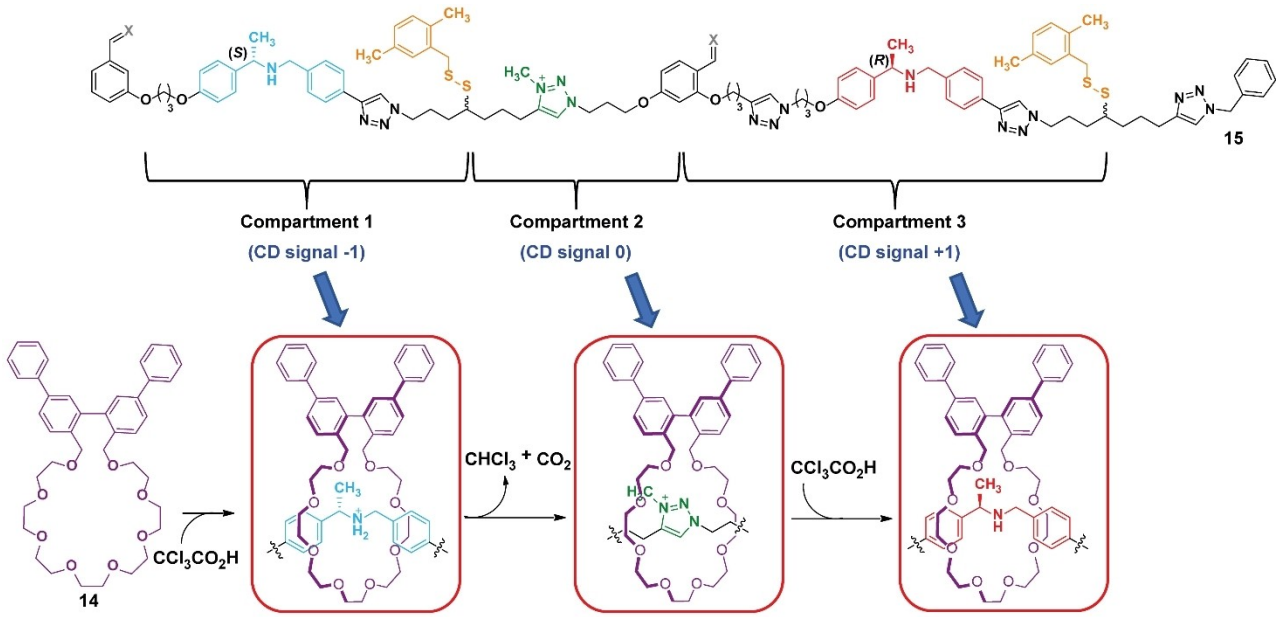

Figure 6. Chemical structures of reading head **14** and molecular tape **15**, and schematic representation of the operation mode of the tape reading molecular ratchet.[75] Since the dethreading step led to the starting products, it has been omitted from the figure. X represents oxygen or hydrazone depending on the pH.

interlocked architecture onto the surface of materials. Indeed, this strategy has allowed to transfer the inherent dynamic of the counterparts of rotaxanes from solution to the solid state, leading to macroscopic implementations. In this scenario, metal-organic frameworks (MOFs) and polymers have turned out to be ideal and tailorable scaffolds in order to integrate rotaxanated compounds in solid-state ordered materials.[76–82]

The intermittent energy ratchet operation mode afforded by successive threading and dethreading processes in molecular pumps inspired Stoddart and colleagues to envision the concept of active mechanisorption by using a pioneering approach to incorporate rotaxane-based molecular pumps into MOF nanosheets. In this example, a series of pumping cassettes (MPCG) were embedded into the surface of MOF nanosheets, promoting the out-of-equilibrium integration of macrocycles on their collecting threads.[83] The introduction of functionalized MPCG, having an analogous structure to a previously reported example,[84] provided mechanisorption arrangements showing high storage capacity, in which several cyclic components could be stowed in each molecular pump. In order to accomplish this advanced machine-like operation mode, a rational design was carried out, thus incorporating the molecular pumps **16**$^{3+}$ bearing a carboxylate group at one of the ends, a redox-switchable bipyridinium ($BiPy^{2+}$) binding site and 2,6-dimethylpyridinium ($DiMePy^{+}$) as Coulombic barrier (Figure 7a). These systems were grafted into nanosheets of a zirconium-organic frameworks by forming coordination bonds between the carboxylate groups of the pumps and the metal clusters. The conversion of the binding sites into the radical cation $BiPy^{\cdot+}$ by applying a reduction potential led to the threading of cyclobis(paraquat-*p*-phenylene) macrocycles (**17**$^{2(+)}$) which are capable of straightforwardly overcoming the DiMePy Coulombic barrier (Figure 7b). This threading process is mediated by the establishment of strong radical-radical interactions between macrocycles and the newly formed $BiPy^{\cdot+}$ affinity scaffold. The redox-triggered oxidation of the macrocycles affording **17**$^{4+}$ led to the shuttling of these macrocycles to the collecting chain of the pumps, thus forming oligorotaxanes. Noteworthy, different examples varying in the number of collected macrocycles were prepared. A final acid-triggered cleavage of the coordination bonds afforded the dethreading of the interlocked systems, leading to the desorption of the collected macrocycles without causing any damage to the structural integrity of the MOF nanosheets. This dethreading on demand of molecules along a molecular pump allows the storage of energy as chemical gradients, leading to envision advanced applications in the development of enhanced molecular capacitors.

A related work was reported by Leigh and colleagues in which this out-of-equilibrium adsorption of wheels followed by the subsequent dethreading process was accomplished by grafting molecular pumps systems, whose structure is related to previously reported examples,[85] into polymer beads.[86]

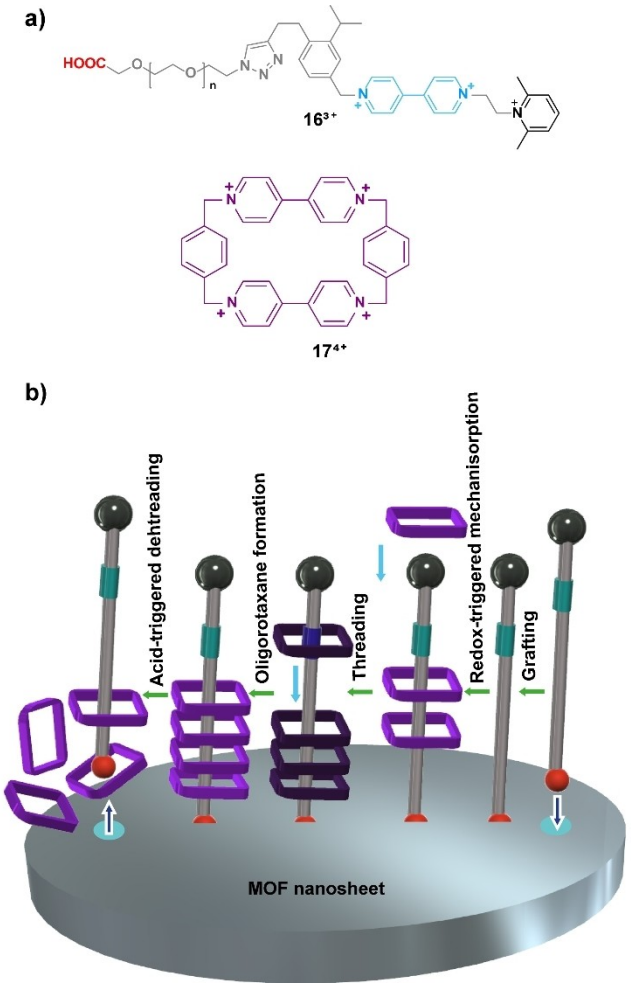

Figure 7. a) Chemical structures of **16**$^{3+}$ and **17**$^{4+}$; and (b) cartoon representation of the mechanisorption operation mode involving a final dethreading process.[83] The key colour of the cartoon representation is analogous to that of the chemical structures.

5. Solar Cells

The importance of dethreading of rotaxanes in solution and in molecular materials has been made clear in the examples included in the previous sections, but it is also relevant in the operation of certain devices. In this context, the incorporation of rotaxanes in different electronical devices, such as molecular electronic memory devices,[87–89] paves the way to advanced implementations. This further expands the possibilities of employing rotaxanes in the solid state in different fields.

One of these areas of application is the development of photoelectrochemical devices. Indeed, the employment of pseudorotaxanes has turned out to be an effective strategy to reduce recombination events in p-type dye-sensitized solar cells (DSSC) in which the macrocycles act as redox mediators.[90]

The formation of pseudorotaxanes in DSSC was also employed by Reek and coworkers as a method to improve their efficiency.[91] The pseudorotaxanes were constituted by the p-type dye-based thread **18** bearing 1,5-dioxynaphthalene bind-

ing sites and a carboxylic acid group which anchored the intertwined species to the solar cell device, and the macrocycle **19** having a naphthalenediimide unit and a perylene diimide one (Figure 8a). The mechanical bond formation engendered the prearrangement and release of reduced redox mediators in DSSCs. Electron-hole recombination, which is a process hampering solar cells, was reduced by the fast reduction-induced dethreading of the macrocycles which also facilitated the threading of new neutral macrocycles. This process started with the photoexcitation of the dye-based thread **18** (Figure 8b, i) and the hole injection into NiO supported onto fluorine-dopped tin oxide (Figure 8b, ii). Thus, the macrocycle **19** was reduced (**19**$^{+}$) (Figure 8b, iii), leading to its dethreading and the subsequent replacement by a neutral wheel (Figure 8b, iv). This sequential dethreading followed by threading of macrocycles effectively removed the charged wheel from the NIO-dye thread interface, thus avoiding the electron-hole recombination. The counter electrode allowed the regeneration of the macrocyclic electron acceptor (Figure 8b, v), leading to neutral macrocycles which could then thread the binding sites of the dye derivatives (Figure 8b, vi). This molecular machinery formation approach has led to the improvement of all photovoltaic parameters compared to those obtained by using noninterlocked analogous devices, paving the way to the integration of molecular machinery within photoelectrochemical devices for supramolecular charge transfer rectification. In this scenario, the dethreading process is essential in order to launch the macrocycles to induce this electron-hole recombination rectification mechanism.

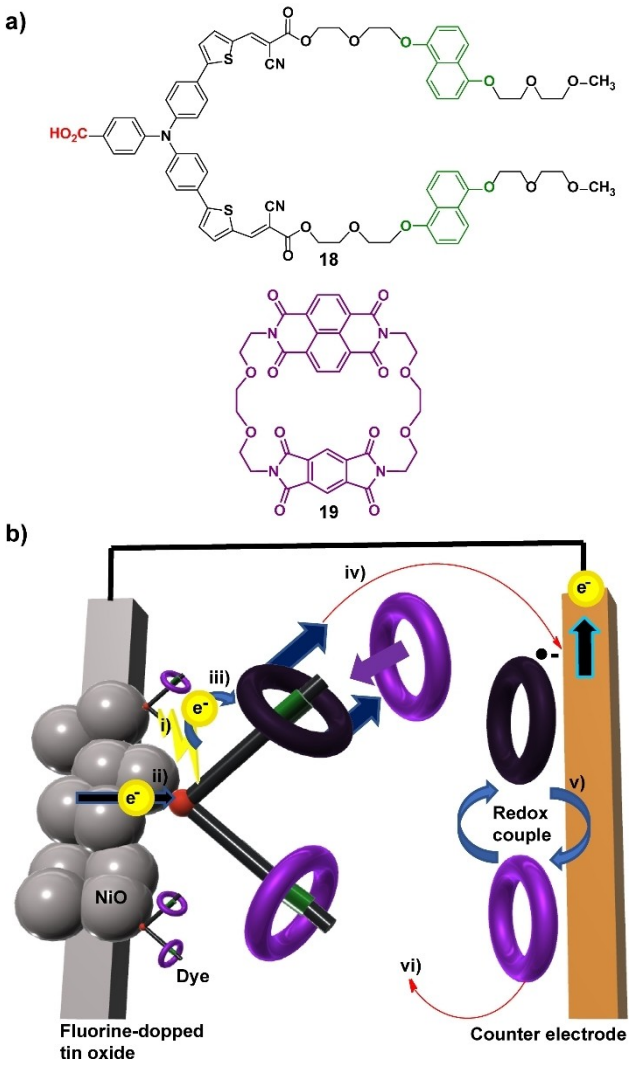

Figure 8. a) Chemical structures of dye-based thread **18** and macrocycle **19**; and b) cartoon representation of the operation of the pseudorotaxane-based DSSC.[91] The key colour of the cartoon representation is analogous to that of the chemical structures.

6. Summary and Outlook

In this short review, the role of the dethreading process in pseudorotaxanes and rotaxanes in order to accomplish different advanced implementations has been revised. The selected examples have covered a representative pool of applications of rotaxanated architecture in which a dethreading step turns out to be essential.

The dethreading process has been effectively used to obtain target molecules, to mimic the ribosome operation mode, to develop controlled release systems, to obtain new properties such as the mechanisorption and also to induce supramolecular charge transfer rectification processes. Additionally, such a process has been widely reported in studies of the stability of the entangled arrangement and in some dynamic processes which operate through the stimuli-driven exchange between interlocked and non-interlocked isomers or even between diverse intertwined arrangements having different structural order.

In order to develop rotaxane-based systems performing a specific function which requires a dethreading step, a rational design turns out to be mandatory. Thus, the incorporation of different substituents placed at any of the counterparts to obtain a slow release of macrocycles or to avoid the disassembly of the mechanical bond until the proper external stimulus is applied allows numerous possibilities which lead to envision the future development of improved systems. Thereby, future research should be focused on taking advantage of the dethreading process of rotaxanes in smart materials and devices, as well as on the development of intertwined architecture which emulate the sophistication of natural systems.

The complete understanding of the physicochemical properties of the dethreading process in rotaxanes should be one of the central topics of study, since this will lead to the development of more advanced operation modes which will allow applications beyond the laboratory and concept proofs. Thus, some machine-like mechanisms working far-from-equilibrium are expected to allow the preparation of improved molecular systems, such as chemical capacitors or energy ratchet-based stereoselective catalysts, among others.

The dethreading process in rotaxanes is just not a mere feature to be avoided in order to increase the robustness of

intertwined compounds, but also has turned out to be of particular relevance in numerous applications. Thus, an encouragement from the chemical community to turn the view towards this significant process is anticipated.

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Conflict of Interest

The authors declare no conflict of interest.

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