The Burgeoning of Mechanically Interlocked Molecules in Chemistry

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Abstract

Mechanically interlocked molecules (MIMs), such as rotaxanes, catenanes, and molecular knots, have attracted significant interest because of their unique properties originating from their mechanically bonded components. Recently, MIMs have been employed in increasingly diverse architectures thanks to the tools of rational molecular design and the ability to incorporate functions in a precise manner. Here, we discuss advances in MIM synthesis, fundamental understanding of their working processes, and applications exploiting their singular behaviors. This Review covers some of the most recent studies demonstrating the widespread interest in MIMs by scientists pursuing the ultimate goal of designing functional molecular machines that surpass their natural analogs or exhibit unprecedented properties.

Keywords: mechanically interlocked molecules; MIMs; molecular machines; rotaxanes; catenanes; molecular knots

Conflict of interest

The authors declare no conflicts of interest.

The golden age of mechanically interlocked molecules

In the 1960s, several chemists [1-2] reported on the formation of molecules consisting of subcomponents connected together without being covalently linked. Compounds comprised of these molecules were isolated and described [2] as mechanically interlocked molecules (MIMs) (Box 1). Since then, these mere laboratory curiosities have been investigated intensively and many synthetic strategies have been devised to produce them with high complexity in their architectures and functionalities.

Over the past few years, MIM investigation has expanded from the sole domain of organic chemistry to invoke a much larger interest by the scientific community. Constituting more and more sophisticated architectures, these molecules still continue to fascinate (and sometimes frustrate) chemists from many different backgrounds. Supramolecular chemists have been joined by material chemists, physicists, and theoreticians in understanding the influence of the mechanical bond on the molecular **(co-)conformations** (see Glossary) of catenanes and rotaxanes, their physicochemical and mechanical properties, and emerging potential applications stemming from their unique properties. In 2016, the Royal Swedish Academy of Sciences awarded the Nobel Prize in Chemistry conjointly to Jean-Pierre Sauvage, Ben Feringa, and one of the present authors (J.F.S.) for the "*design and synthesis of molecular machines*" [3-5]. A large part of the work performed by Sauvage and J.F.S. in this area (and emphasized by this prize) is connected to design and development of MIMs. Some may claim that the golden age of MIMs is yet to come, only reachable with valuable and tangible applications, as contrasted with proof-of-concept examples. Here, we argue that the golden age of MIMs has arrived with the flourishing of these molecules in many domains of chemistry. Indeed, numerous examples of the use of MIMs have been described that exploit their unique properties arising from the presence of mechanical bonds.

In this Review, we discuss advances in the domain of MIMs over the past three years. Rather than attempting to cite all recently published studies, we focus only on several select examples to give the reader an overview of the impact of MIMs in numerous areas of chemistry. We first discuss synthetic protocols for constructing new MIM-based molecular

systems, showing increasingly sophisticated and functional architectures. Thereafter, we present an overview of the characterization techniques recently employed to understand MIM fundamentals, including: interactions maintaining the (co-)conformation, the switching ability, and the working processes of functional molecules. The last portion of the review focuses on recent proof-of-concept demonstrations and applications based on MIMs. This logical order will hopefully aid the reader in appreciating the widespread use of MIMs in modern chemistry. It is only with constant feedback between these three sectors (i.e., synthesis, fundamental understanding, and applications development) that MIMs will eventually show their extraordinary potential for the design of novel materials or molecular devices with emergent properties.

Building new MIM architectures

Rotaxanes

The synthesis of rotaxanes has evolved drastically since the discovery of MIMs, now turning toward the construction of atomically precise chemical structures [2,6]. Efforts aimed at the incremental development of MIM chemistry (e.g., increasing synthetic yields or formation of desired compound under less harsh conditions) should facilitate, over time, the design of functional molecules having ever greater complexity. Recently, Leigh and colleagues [7] reported on the synthesis of rotaxanes using a **transition-state stabilization** strategy. It was demonstrated that the stoppered axle of the molecule (referred to as the **dumbbell)** can be assembled in a **macrocycle** cavity to form a [2]rotaxane. The macrocycle used in their study contains a hydrogen-bond acceptor region connecting to the terminal amine of the first half-dumbbell and a hydrogen-bond donor unit binding to the cyclic sulfate of the other half-dumbbell. Both parts are pre-organized in the vicinity of the macrocycle which acts as a template and catalyst, stabilizing the reaction transition state. This reagent-free synthesis could be applied to additional reactions with polar transition states. Goldup and co-workers [8] presented a stereoselective approach for the synthesis of **mechanically planar chiral** (MPC) rotaxanes. Using the versatility of the active template Cu-mediated alkyne-azide cycloaddition (CuAAC), the possibility of delivering mechanically **epimeric** rotaxanes was demonstrated with a maximum diastereoisomeric ratio of 98:2. This approach could provide enantio-enriched MPC rotaxanes where the

mechanical bond provides the sole **stereogenic** unit.

Synthetic advances in MIM chemistry are continually being made as a result of choosing different structures for the mechanically interlocked components, which aim to change the components' sizes or to include recognition sites exploiting different types of intramolecular interactions between the interlocked components, all in a bid to produce molecules whose internal motion can be mechanically controlled. In 2016, Flood and colleagues [9] reported the high-yield synthesis of anion-templated rotaxanes comprised of cyanostar macrocycles threaded onto a tetrabutylammonium dipropargyl phosphate and stoppered by a bulky aryl-azide. By changing the acid-base conditions, a reversible modification in the complex affinity was observed, providing a foundation for the development of molecular switches. A different type of noncovalent interaction was used by Stoddart and co-workers for the design of a molecular lasso [10]. There, the recent discovery of reversible radical-mediated recognition [11] was exploited to design **pseudorotaxanes** capable of mimicking the threading/unthreading motion of lasso peptides. Depending on the size of the linker joining the tail and loop segments, movement of the tail inside the loop could be observed under reducing conditions, favored by the formation of a trisradical-tricationic complex. Using a different strategy, von Delius and co-workers [12] investigated **π–π templates** for the synthesis of different rotaxanes with cycloparaphenylene-fullerene interactions. Other examples of similar carbon-rich molecules include carbon nanotube-based rotaxanes [13-15]. These carbon-rich rotaxanes are potentially useful in technologies based on molecular electronics, for example.

The aforementioned synthetic strategies also permit design of more complex rotaxanes integrating multiple rings or multiple threads. Adding more complexity into rotaxane-type molecular architectures potentially leads to the generation of multiple movements in a single molecule. For instance, Leigh and colleagues [16] reported use of an **active-metal template** strategy for the design of triply threaded [4]rotaxanes. This approach requires the proper balancing of macrocycle-cavity and stopper size. Recently, McGonigal [17] reviewed the synthesis and unique properties of multithreaded rotaxanes. Additionally, Coutrot and colleagues [18] reported on the synthesis of a **daisy chain** and a tetra-

interlocked molecule, consisting of a [*c*2]daisy chain connected to two [2]rotaxanes. The particular architecture of the hetero[4]rotaxane potentially serves as a model for the design of pH-responsive molecular muscles. Tian and Loeb [19-20] both designed rotaxanes with a single dumbbell bearing several macrocycles. Tian and colleagues [19] used a one-pot self-sorting process to obtain a hetero[6]rotaxane bearing three different types of ring, whereas Loeb and co-workers [20] synthesized a [3]rotaxane with two macrocycles of varying size. Interestingly, the macrocycles of the [3]rotaxane were free to slide along the chain by a ring-through-ring mechanism (Figure 1). This novel shuttling mechanism can potentially be used in the design of more complex polyrotaxanes or switches.

Catenanes

Catenanes are molecules containing two or more topologically linked macrocycles (Box 1) and are another molecular structure with mechanical bonds [2]. Originally starting from simple [2]catenanes without any particular functionality, organic chemists are now able to design rather elaborate architectures. Every newly synthesized molecule potentially exhibits some novelty based on chemical structure (e.g., recognition sites), (co-)conformation (or change in (co-)conformation under external stimulus), and/or mechanical properties arising from unique topology. In 2016, Stoddart and colleagues [21] reported on the synthesis of a neutral [2]catenane presenting the sliding of one ring in relation to the other upon reductive conditions. The tetracationic cyclobis(paraquat-*p*-phenylene) cyclophane units (also known as blue boxes) contained in the first macrocycle could either interact with electron-rich units of the second ring or be reduced to induce rotation. This behavior is controllable through reduction/oxidation reactions. Using Ca-templated ring-closing metathesis, Niemeyer and colleagues [22] showed the synthesis and characterization of a chiral [2]catenane. Early binding studies revealed their role as artificial receptors for dicationic guests, a major potential application for catenanes.

Another form of catenane, designed by Cong and colleagues [23], consists of two Möbius-conjugated **nanohoops**. Cong evidenced a rare solid-state stabilization of a Möbius twisted π-conjugated system via noncovalent interactions. The twisting of interlocked rings was also described by Leigh and co-workers [24] for the design of a six-crossing doubly

interlocked [2]catenane. Here, a ring-closing metathesis of an interwoven grid was employed as a synthetic strategy similar to that used in the synthesis of molecular knots (discussed below). This work evidences the advances in synthetic strategy, forming a toolbox for the design of MIMs with sophisticated architectures. In this regard, Maarseveen and co-workers [25] also reported the use of spiro compounds for the synthesis of quasi[1]catenanes and quasi[1]rotaxanes, molecules in which two components are mechanically interlocked but also covalently linked by a single atom.

For the design of larger catenanes consisting of more than two rings, other enabling synthetic strategies were required. Although challenging, syntheses of [*n*]catenanes have been recently reported [26]. For example, Yeung and colleagues [27] described a new strategy to synthesize one **topoisomer** of a [6]catenane, amongst other smaller [3]- and [4]catenanes. Their modular approach of employing both orthogonal supramolecular interactions and efficient bond formation, can potentially be extended to larger [*n*]catenanes. Recently, Stoddart and colleagues [28] described the design and synthesis of catenanes made of three or five repulsive rings, leading to densely positively charged [3]- and [5]catenanes. It was revealed that stable polycations can be confined in small spaces if connected by mechanical bonds, providing the possibility of storing a large quantity of positive charges in nano-spaces. The mechanical linkage of similar repulsive macrocycles was also reported for a homo[2]catenane [29], demonstrating the delicate balance between intramolecular π–π interactions and Coulombic repulsions. In 2017, Rowan and co-workers [30] reported on the synthesis of very long poly[*n*]catenanes using a metallosupramolecular polymer template. Following this strategy, they obtained a mixture of linear, branched, and cyclic poly[*n*]catenanes. This work paves the way for the design of longer polymers connected by mechanical bonds that may possibly reveal unique mechanical properties compared to their covalently linked analogs.

Molecular knots

Knots are structural components found in biomolecules (e.g., some proteins and circular DNA) and are of interest to cellular and molecular biologists [31]. The design of such features in wholly synthetic molecules was introduced by Sauvage and colleagues [32],

who performed the first synthesis of a molecular trefoil knot in 1989. Advances in this domain over the past 20 years were recently reviewed by Leigh and co-workers [33] in 2017. The basic aspects of knots (e.g., classification, types, and chirality) were presented before reporting synthetic aspects and possible applications. Recent advances relating to the synthesis of molecular knots include: the synthesis of the first metalla-knot with the 8_{18} topology [34-35]; the use of the hydrophobic effect for the self-assembly of knots [36]; an increase in overall yield in molecular knot synthesis based on self-assembly of a trimeric circular helicate, followed by covalent linking using a ring-closing metathesis [37]; and synthesis of a 324-membered ring showing nine crossings [38]. Recently, the performance of a molecular knot as a mechanical blocker was also reported [39]. The tied knot was attached at one end of a rotaxane, as a bulky end-group (Figure 2). When the cation maintaining the knotted topology was removed, the end-group no longer constrained the macrocycle, which then unthreads from the rotaxane axle. The design of other knot topologies raises many synthetic challenges, but the examples discussed here clearly point toward prospects for molecular knots with novel properties and applications.

MIM characterization using a diverse array of techniques

Many fundamental aspects of MIMs must be better understood in order to become sensitized to their potential within the scientific community and beyond into the realm of technology. The second part of the Review focuses on a description of the analytical, physical, and theoretical tools used to characterize MIMs and elucidate their properties. Recent publications using ensemble (i.e., probing the average signal from many molecules) and single-molecule techniques are discussed.

Ensemble techniques are routinely employed to characterize the (co-)conformations of MIMs and their modes of operation in molecular machines and motors. Representative techniques include nuclear magnetic resonance (one or multi-dimensional), cyclic voltammetry, X-ray crystallography, and other fluorescence-based or spectroscopic techniques. These techniques are also very powerful in obtaining information about the solution or solid-state switching abilities of **non-degenerate** MIMs. Recently, Goldup and colleagues [40] explored the potential of mechanically interlocked ligands and assessed

their impact in catalysis. By combining electron paramagnetic resonance measurements with density functional theory (DFT) calculations, Schalley and co-workers [41] probed the pirouetting motions in a redox-active [3]rotaxane. The relative positions of both rings are governed by their oxidation states, allowing for controllable synchronization of their pirouetting motions. This illustrates the use of ensemble techniques to understand better fine processes occurring within MIMs. Imaging techniques have also been employed to characterize substrate-deposited MIMs, such as self-assembled monolayers of rotaxanes on gold substrates [42]. Techniques such as electron microscopy and atomic force microscopy (AFM) have revealed the potential of these synthetic molecules for surface modification and information processing at the nanoscale.

The importance of MIMs as a field of investigation is now apparent from the growing interest of scientists from different backgrounds working on them and employing different characterization techniques. For instance, De Pauw and co-workers [43] have characterized the controlled extension of foldamer-like MIMs in the gas phase using ion mobility mass spectrometry, demonstrating the presence of different (un)folded (co-)conformations depending on the charged state. Sonochemical mechanochemistry has also been employed for investigating the impact of mechanical bonds in relation to their strengths [44]. Craig and co-workers measured the mechanical strength of a multicatenane polymer as compared with covalently linked analogs, showing that mechanical bonds are at least as strong as covalent bonds. Similarly, De Bo and colleagues [45] exploited the mechanical activation of MIMs by high-intensity ultrasound to show the effect of a mechanical bond in the vicinity of a mechanophore, in particular the decrease of a retro-Diels-Alder reaction rate (under tension) when introducing a mechanical bond. These investigations highlight the possibility for adjusting the mechanical resistance of macromolecules by introducing mechanical bonds.

Single-molecule techniques employing atomic force microscopy or optical tweezers (OT) were also used to probe MIMs (co-)conformations and their force capacities. Duwez and co-workers [46-47] carried out the mechanical unfolding of oligorotaxanes and measured the refolding force of these wholly synthetic molecules. Using AFM-based single-molecule

force spectroscopy in solution, dynamic information was obtained concerning the (un)folding process revealing the potential of these MIMs to exceed the force performance of their natural counterparts. Similarly, Ibarra and co-workers [48] trapped individual rotaxane-based molecular shuttles (Figure 3) to measure their mechanics and dynamics in aqueous solution at the single-molecule level. This fundamental information is crucial for the design of novel MIMs and their integration into larger operating devices.

In parallel with the wide use of different experimental techniques, the development of theoretical studies is of huge importance, especially for the application of MIMs in molecular machines. In this regard, Williams and co-workers [49] used statistical mechanics to describe the size and shape fluctuations of a [3]rotaxane with and without recognition sites. They examined its inclusion area variations for hosting capabilities. Employing similar prediction tools, they also discussed [50] the case of a macroscopic phase transition (isotropic to nematic phase) based on a realistic extension of rotaxanes. The construction of switching diagrams will potentially help in designing MIMs that would be organized differently in solution, depending on their contraction state, and thus provide different macroscopic outcomes. In a recent review, Astumian and colleagues [51] discussed the basic principles supporting the design of mechanically bonded molecules intended to operate as molecular machines. The application of physical principles and a constant relation between theory and experiment are essential for the understanding of MIMs and their use in the design of new materials and in (nano)technological applications.

MIM-based applications

The ultimate goal of MIM science is to design rationally functional molecules for defined purposes. The work performed by such molecules can be related to their (co-)conformations or induced by an external stimulus. Examples of transformative chemistry are flourishing in the literature, showing the transition from the sole synthetic aspect of MIMs as laboratory curiosities to the actual use of those structures in demonstrating proof-of-concept or real applications [6]. Different areas of research are discussed below including: catalysis; bio-related or bio-inspired processes; molecular machines; gels; and integrated functional MIMs.

In 2016, Leigh and co-workers [52] showed the impact of a molecular knot in catalysis. The conformational restriction induced by the knot architecture (a pentafoil knot) initiated and regulated a catalyzed reaction **allosterically**. The reduction of the degrees of freedom in knots enables them to adopt other conformations and perform tasks not accessible by their untied counterparts, comparable to the biological role of knotted proteins. Another MIM design with possible catalysis or metal sequestration properties was reported by Loeb and co-workers [53]. Here, a [2]rotaxane made of a dumbbell presenting a chelate site and a crown ether macrocycle with a specific chemical structure was constructed. Rotation of the macrocycle was observed depending on the metal ion complexed in its vicinity. Such rotationally active macrocycles can be chemically tuned and used in coordination chemistry for the encapsulation of specific ions or ligands. Mechanical bonds have also been used to stabilize the helical conformation of an oligomer (*m*-ethynylpyridine), increasing its resistance to hydrogen-bonding inhibitors [54]. In 2017, Niemeyer and co-workers [55] reported on the use of catenanes for asymmetric organocatalysis. These mechanically interlocked catalysts supported high stereoselectivities compared to their non-interlocked counterparts, demonstrating the relevance of mechanical bonds in the design of novel catalyst systems.

Because of their incomparable structures, MIMs also have potential for use in biological applications. For instance, Huang and co-workers [56] designed a pillar[5]arene-based [2]rotaxane stoppered by tetraphenylethene (TPE) and triphenylphosphonium (TPP) groups, exhibiting enhanced aggregation-induced emission characteristics and specificity, respectively, in mitochondria. Owing to its particular architecture, this molecule exhibits targeting, imaging, and therapeutic properties. Recently, Beer and co-workers [57] synthesized an unprecedented MIM-based host system as a sensor for dicarboxylates, a large class of anions with biological importance. Using a chiral [3]rotaxane incorporating a fluorophore component, they demonstrated the possibility of discriminating host molecules and show the efficient use of mechanically bonded architectures for molecular sensing. Xu and co-workers [58] took advantage of the translational motion of rotaxanes in their design of a movable proton carrier. They assembled a rotaxane-based polymer and

demonstrated its thermally triggered fast proton transfer. This example also supports the potential use of such architectures in energy-conversion devices. Following the idea of mimicking biomolecular systems, Tian and co-workers [59] designed a [2]rotaxane-based molecular shuttle that can transport ions across lipid bilayers. The macrocycle, encircling an amphiphilic dumbbell, is covalently connected to an ion-carrier ring (Figure 4). This second ring can therefore move in either direction, following the movement of the main macrocycle which interacts with different stations along the dumbbell.

Molecular machines comprising MIMs are of considerable interest nowadays, especially since the announcement of the 2016 Nobel Prize in Chemistry. Advances in this domain are crucial [60] for the development of applications at the nanoscale and for the bottom-up building of larger motors. Using similar approaches developed recently for an artificial molecular pump [61-62], Leigh and co-workers [63-64] designed chemically driven rotary and linear molecular motors. The rings of the [2]- and [3]catenanes can be continuously moved directionally by an **energy-ratchet mechanism**. The same group also synthesized a rotaxane-based peptide synthesizer [65]. This molecular machine has the ability to attach ß-amino-acids sequentially, an important step towards the design of an artificial ribosome. A similar approach was used to access the synthesis of a polymer chain [66], where each monomer is transferred to the growing polymer during the movement of the polymer-bearing ring along the monomer-bearing track (Figure 5).

In 2018, Boulatov and coworkers [67] designed a rotaxane-like molecular machine based on a photoisomerizable stilbene which induces the translation of a pillar[5]arene macrocycle along the dumbbell. The stilbene acts here as the chromophore to trigger nanometer-scale motion but is also present as a bulky group to constrain the macrocycle around the dumbbell.

The utilization of MIMs in macroscopic objects has been expressed in the design of a wide range of gel materials. In 2016, Harada and co-workers [68] reported on the incorporation of [*c*2]daisy chains into hydrogels and xerogels. Upon ultraviolet irradiation, the mechanically interlocked structures present a contracted form, causing a macroscopic and

visible bending of the gel, and producing work on the environment. Similarly, cyclodextrin-based artificial muscles were prepared for examination of their photoresponsive actuation in hydrogels and dry gels [69]. Additionally, Giuseppone and co-workers [70-71] designed daisy chain-based molecular systems to amplify the mechanical actuation from the nanoscale up to a macroscopic response in a bulk material. On one hand, they designed a pH-responsive supramolecular polymer that can induce a controllable sol-gel transition at the macroscopic level [70]. On the other hand, they described a method for the branched polymerization of a similar pH-sensitive [*c*2]daisy chain giving rise to a macroscopic chemical gel [71]. The authors observed a large expansion/contraction of this gel upon (de)protonation, corresponding to the muscle-like contraction-extension movements of the mechanically interlocked structure. Similar behaviors were also observed recently in other hydrogels with MIM components [72-73].

Even if most MIMs to date have been investigated in solution, their deposition onto substrates can be controlled; the effect of such thin films on molecular behavior must be understood properly for on-surface applications. In this regard, Schalley and co-workers [74] synthesized a photoswitchable rotaxane and examined its switching behavior after deposition on glass and silicon substrates. They showed a change of orientation in the rotaxane monolayer after irradiation. By extension of the same strategy, they envisioned the possibility of designing multi-responsive multi-layer surfaces, leading to a potentially controllable macroscopic change in the surface structure. In 2017, Choi and co-workers [75] reported on the impact of mechanical bonds in term of elasticity when integrated in a polymer network. Indeed, the addition of sliding-ring polyrotaxanes in polyacrylic acid modified the mechanical properties of this polymer. This approach is highly valuable in the design of lithium-ion battery electrodes that are subjected to large volume changes during cycling, polyrotaxanes being essential for the increase of their cycle lifetime. Recently, Weder and colleagues [76] also reported on the synthesis of a rotaxane-based fluorescent mechanophore that can be turned on when subjected to an external force. This new concept will potentially be useful for the detection of small mechanical forces, for instance in polymers and living cells.

Concluding remarks and future perspectives

Since the report of their first efficient synthesis, MIMs have attracted the attention of chemists because of the unique properties arising from the mechanical bonds that connect their components. Over the past 35 years, interest in MIMs has blossomed and pervaded all the sub-disciplines of chemistry and into materials science. Here, we have highlighted some of the most recent MIM investigations including synthesis, (co-)conformational properties and machine-like behavior, and MIM-based applications. The constant exchange among scientists from these fields and beyond is crucial for reaching tangible applications (see Outstanding Questions) where mechanically interlocked molecules can be expected to surpass the performance of their covalently bonded counterparts and biological analogs. Now that the fundamental characteristics of simple MIMs are understood, the possibilities are infinite and are only limited by our imagination and creativity. We hope that the overview presented here will provide a starting point for collaborations between scientists from different backgrounds and disciplines in order to push the envelope as far as possible into the exploration of the unknown.

Box 1: MIMs and the Mechanical Bond

In between molecular entities presenting variable topologies and supramolecular assemblies, mechanically interlocked molecules (MIMs) emerged (Figure I) as a group of entangled molecules gathering rotaxanes, catenanes, and molecular knots. Unlike other molecules directly constructed using chemical bonds, MIMs are made of component parts connected by mechanical bonds. A mechanical bond is defined [2] as "*an entanglement in space between two or more molecular entities (component parts) such that they cannot be separated without breaking or distorting chemical bonds between atoms*". In other words, the component parts of MIMs are mechanically connected. The simplest rotaxane —a [2]rotaxane, the term in brackets representing the number of interlocked components— comprises a macrocycle threaded around a molecular axle stoppered by bulky end-groups. A [2]catenane is defined similarly as two mechanically interlocked rings. Considering the additional degrees of freedom originating from their mechanically bonded architectures, MIMs are perfect candidates for the study and control of molecular motions. The

translation of one ring along a molecular dumbbell (in rotaxanes) or the rotation of one ring in relation to another (in catenanes) are examples of molecular motions taking place as a result of stochastic Brownian motions or in response to various external stimuli and leading to (co-)conformational changes. By rationally modifying the MIMs' chemical structure and therefore their intramolecular interactions, it has become possible to control their molecular motions with high precision and to observe unique properties arising from their mechanically interlocked architectures.

Glossary

Active-metal template: use of a metal ion as a template and a catalyst for a reaction

Allosteric regulation: modification (increase or decrease) of a second site binding-activity depending on the binding of an effector molecule at a first binding site of a molecule (commonly employed in biochemistry)

(Co-)conformation: spatial arrangement of interlocked components in a mechanomolecule, (co-)conformational changes appear through translation or pirouetting motions and potentially lead to important changes in molecules shapes and properties

Conformation: spatial arrangement of atoms in a molecule, conformational changes appear through rotations about single bonds

Daisy chain: doubly-interlocked rotaxane, leading to cyclic or acyclic architectures

Dumbbell: component part of a rotaxane consisting of a stoppered axle

Energy-ratchet mechanism: mechanism involving the raising and lowering of thermodynamic wells, possibly leading to a directed motion in molecular machines

Epimer: molecule that only differs from another stereoisomer by the configuration of only one stereogenic center

Macrocycle: a cyclic molecule; the term is mainly used here to describe the component part of a rotaxane or catenane (also mentioned as the ring)

Mechanically planar chiral rotaxane: molecule presenting chirality arising from the relative orientation of its mechanically interlocked components (even with component parts devoid of covalent chirality)

Nanohoops: connected aromatic rings

Non-degenerate molecules: molecules that exhibit distinct behaviors upon measurement

Pseudorotaxane: complex of two molecular components (an axle and a macrocycle) held together by noncovalent bonding interactions instead of mechanical bonds (no stoppering of the axle)

Stereogenic element: element of a molecule bearing ligands or groups such that the interchange of two of these ligands leads to a stereoisomer

Topoisomers (or topological isomers): molecules presenting identical chemical formula but differences in molecular topology

Transition-state stabilization: lowering of the transition state of a reaction using a catalyst

π-π template: arrangement of atoms ordered by face-to-face stabilizing interactions between aromatic moieties

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Figures

[Figure I is included in Box 1]

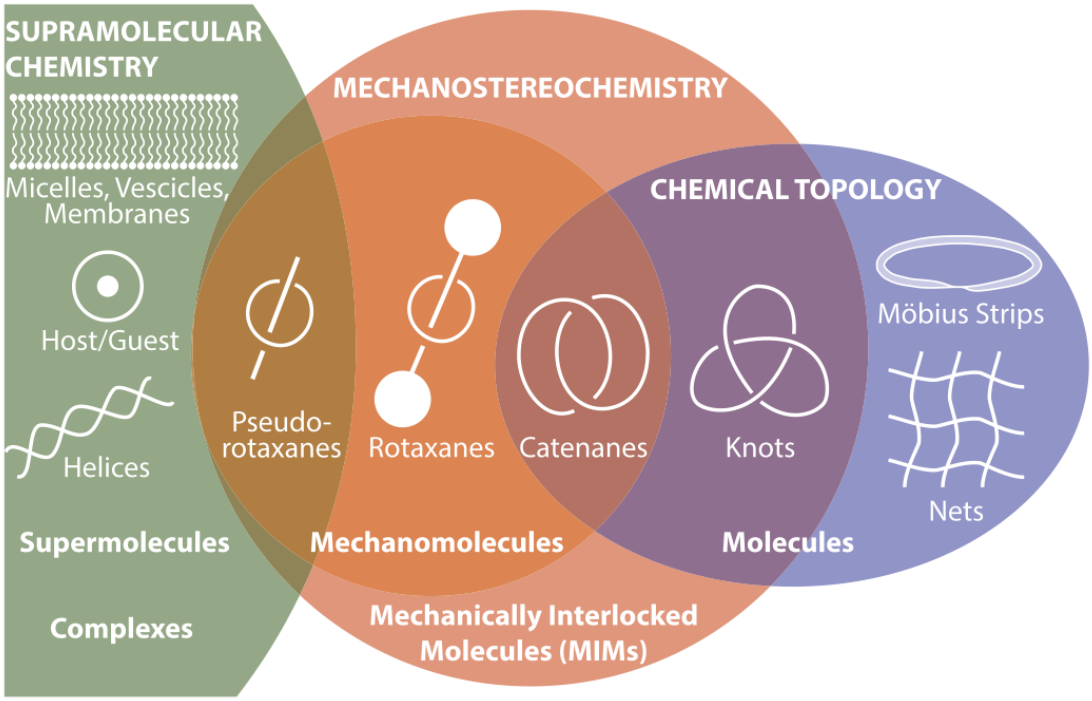

Figure I. MIMs, gathering molecules from different fields.
A Venn diagram showing the grouping of mechanically interlocked molecules (rotaxanes, catenanes and knots) from supramolecular chemistry, mechanostereochemistry, and chemical topology [2]. Reprinted by permission from John Wiley & Sons, Inc, © 2016.

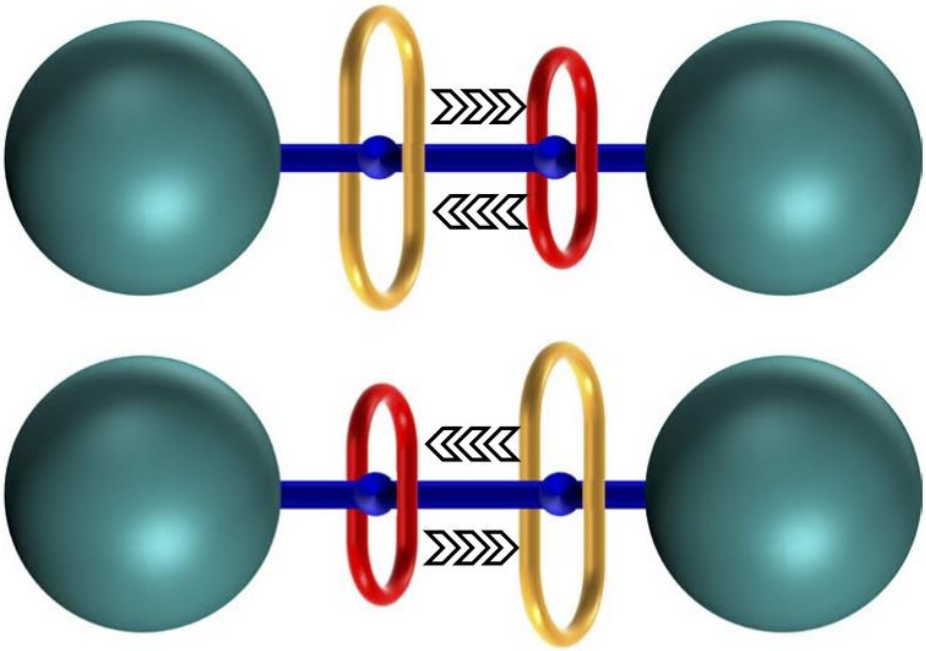

Figure 1. Ring-through-ring shuttling of a [3]rotaxane.

As part of novel original MIM architecture, this [3]rotaxane is composed of two rings of different sizes threaded along a dumbbell component. The exchange between the rings' positions involves a ring-through-ring shuttling mechanism [20]. Reprinted by permission from Springer: Nature Chemistry © 2018.

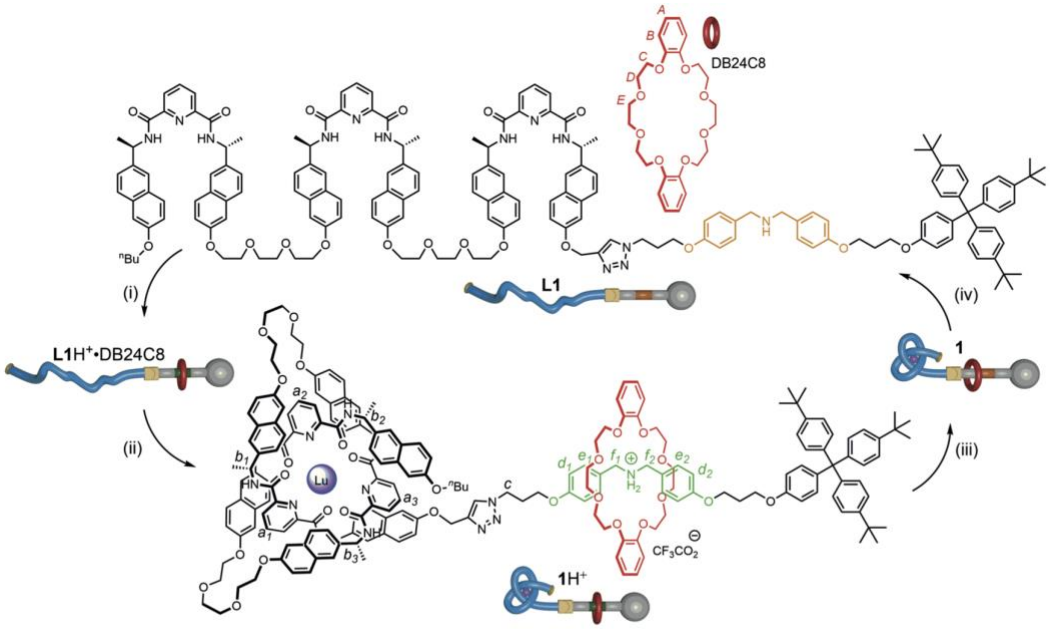

Figure 2. A rotaxane-like architecture stoppered by a molecular knot.

By tying and untying a molecular knot, Leigh and coworkers [39] were able to secure and release, respectively, a macrocycle from the molecular thread of a [2]rotaxane. The reversible aspect of tying/untying a knot reveals considerable potential for molecular knots integrated in molecules with unprecedented functionalities. Reproduced from [39].

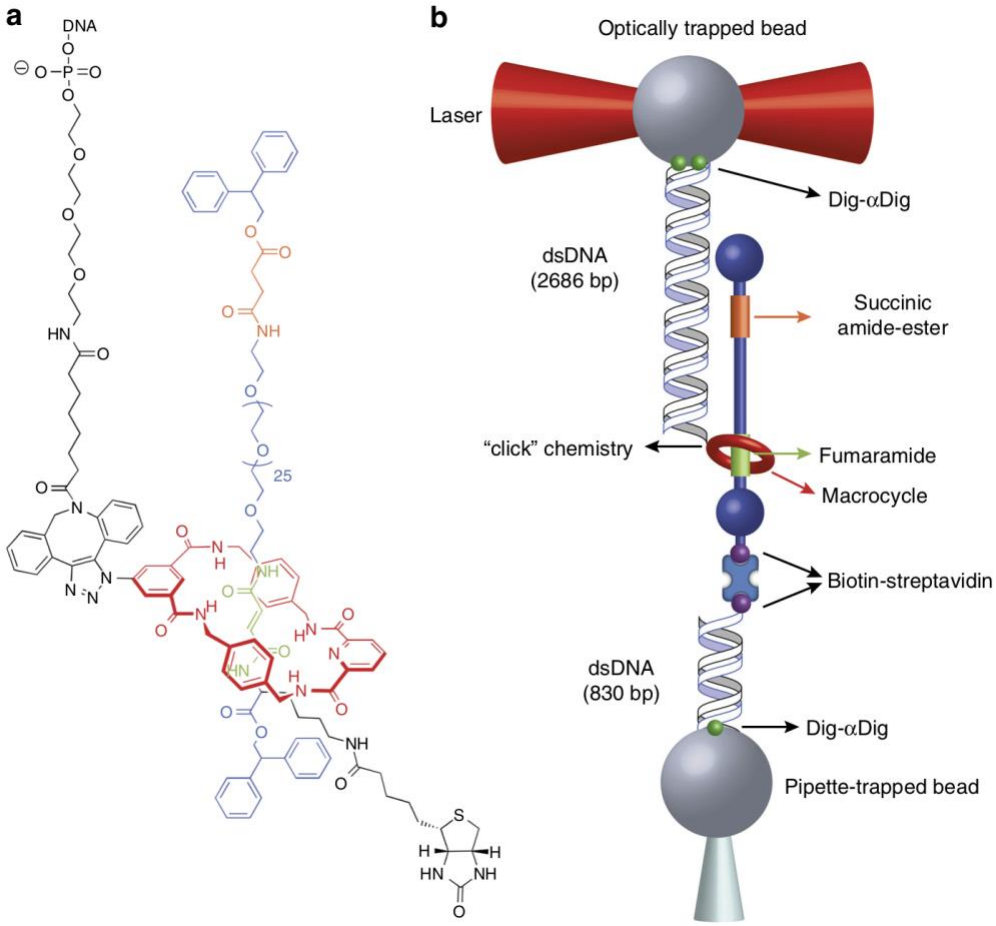

Figure 3. Force-induced shuttling of a single rotaxane.

Molecular structure of a [2]rotaxane (left) and experimental design of the single-molecule investigation in aqueous solution (right). Ibarra and coworkers [48] attached a single molecular shuttle between two optically-trapped beads and probed the force-induced movement of a ring along the rotaxane's axle. Crucial information on the mechanics and dynamics of the movement can be obtained from single-molecule investigations. Reproduced from [48].

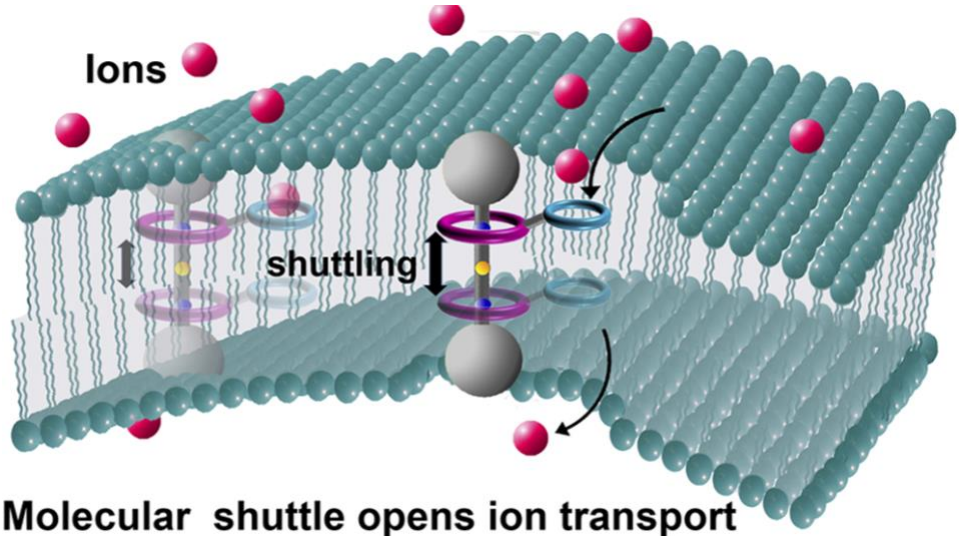

Figure 4. Artificial ion-transporter across lipid bilayers.

A [2]rotaxane mimicking the function of channel proteins was synthesized for its integration into lipid bilayers. The threaded ring is able to shuttle stochastically along the dumbbell, directly followed by another covalently bonded ring. The use of the second ring as an ion carrier allows the transport of potassium ions within the bilayer. Reprinted with permission from [59]. Copyright 2018 American Chemical Society.

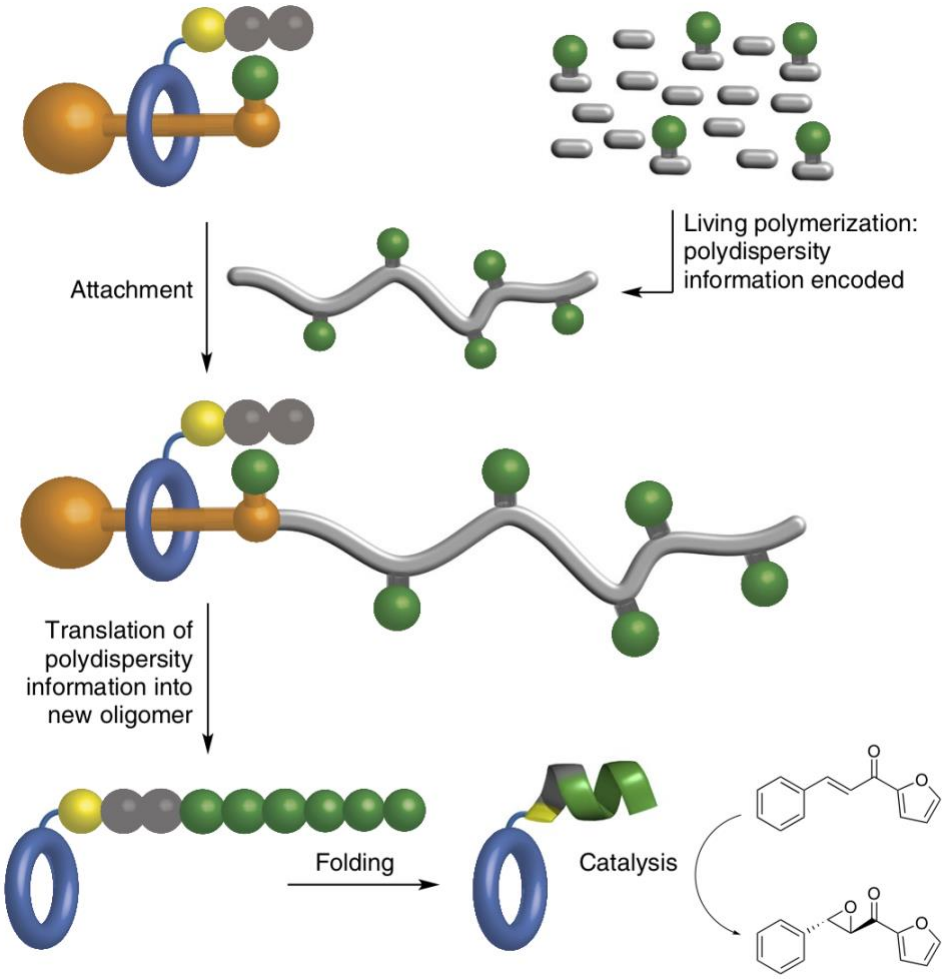

Figure 5. Synthesis of a catalyst by an artificial molecular machine [66]. An original rotaxane-based molecular machine was synthesized to add sequentially monomers attached along its track to a ring-bearing growing oligomer. The polydispersity information is transferred from the living polymerization into the oligomer synthesized by the artificial machine. In this example, the oligomer obtained can adopt a specific conformation and act as a catalyst for an epoxidation. Reprinted by permission from Springer: Nature Nanotechnology © 2018.