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Design strategies and emerging applications for mechanically interlocked molecules

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Communications Chemistry is pleased to introduce a Collection of articles on the design and applications of mechanically interlocked molecules. Here, the Guest Editors introduce the topic, outline recent advances in the field, and provide their thoughts for future directions of research.

Mechanically interlocked molecules (MIMs), such as rotaxanes, catenanes, and molecular knots, represent a fascinating class of molecular architectures defined by their non-covalent mechanical bonds. Once studied primarily for their structural uniqueness, they are now recognized as key players in molecular machines, stimuli-responsive materials and catalytic systems. The growing understanding of how to control the dynamic behavior and functionalities of MIMs makes them highly attractive for applications that conventional covalent systems cannot easily achieve. Advances in synthetic strategies, including templated and kinetically controlled self-assembly as well as coordination-driven approaches, have expanded the structural diversity of interlocked molecules, allowing for precise control over molecular interactions. The integration of metal-based macrocycles, the development of increasingly intricate topologies, and the incorporation of stimuli-responsive elements have opened new avenues for designing molecular systems capable of motion, conformational switching and selective reactivity in response to external triggers such as light, redox conditions and pH variations.

This Collection brings together recent breakthroughs in MIM science, focusing on two key themes. The first explores innovations in molecular design, highlighting studies that push the boundaries of structural complexity while maintaining functional versatility. Novel synthetic methodologies enable the construction of interlocked systems with greater stability, tunability and dynamic adaptability. The second focus is on functional properties and applications, demonstrating how mechanical bonds influence

chemical reactivity, molecular recognition, and stability, with promising implications for catalysis, therapeutically relevant systems and advanced materials. As the role of MIMs expands across multiple disciplines, their integration into supramolecular chemistry, nanotechnology and biomedical research is poised to redefine their impact on both fundamental science and technological applications.

New directions in MIM design

The synthesis of mechanically interlocked molecules can be a challenging task, and the realization of intricate and often esthetically compelling structures is one of the appealing aspects of this field of research. Nevertheless, as properties are much related to structure, the implementation of novel building blocks and synthetic strategies enables the design and construction of ever more complex stimuli-responsive systems.

Rotaxanes, catenanes and knots. Knots are fascinating structures, which captured the interest of scientists mainly for their challenging preparation. Nowadays, synthesis of knots is becoming more accessible, and their properties can be finally explored. Within our Collection, Schaufelberger discusses the future directions in the field, asking open questions on how knotting, knot tightness, and topology can affect the mechanical properties and possible functions of this intriguing class of molecules (<https://doi.org/10.1038/s42004-020-00433-7>)¹.

Several hybrid organic–inorganic structures are reported in this Collection, wherein the coordination compounds play very different roles: structural units in metal–organic cages (MOCs); control elements to switch ring dimensions; functional elements to confer magnetic properties in micrometric objects.

The review by Marti-Rujas explores the development of MOC-based catenanes, from the first work by Fujita to the more recent results. The author discusses the possible driving forces that govern the formation of these intriguing structures. Applications in guest recognition (anions, cations and organic molecules) and photo-thermally responsive elastomers are illustrated (<https://doi.org/10.1038/s42004-025-01493-3>)².

Akine and coworkers show how non-covalent interactions can be exploited to produce assembled structures under kinetic control (<https://doi.org/10.1038/s42004-024-01246-8>)³.

A saloph-based macrocycle, which assembles with ammonium axle components, can be shrunk upon metallation: a non-threaded or threaded structure is formed depending on the order of the assembly and metallation reactions. Kinetic control with non-covalent interactions is an uncommon feature; moreover, the tunability of the coordination bonds could be further exploited to switch between the assemblies and enable or disable their interconversion.

Hybrid metal–organic structures are also reported by Winpenny and coworkers: polymer beads are decorated with up to 10¹⁴ polymetallic rotaxanes, to confer paramagnetic properties to the microparticles. As a matter of fact, each bead is formally a [10¹⁴] rotaxane (<https://doi.org/10.1038/s42004-022-00689-1>)⁴.

Stimuli-responsive MIMs. Berna, Martinez-Cuezva and colleagues propose conjugated bis(enaminones) as novel and efficient templates for the construction of amide-based rotaxanes through a clipping reaction (<https://doi.org/10.1038/s42004-024-01258-4>)⁵. They also developed a synthetic route to obtain a three-station rotaxane by a double stopper-exchange reaction. A chemical-input can be used to reversibly disable the central enaminone unit thus compartmentalizing the macrocycle in one of the peripheral stations.

Controlled and reversible shuttling of a macrocycle along an axle of a rotaxane can also be used to enable/disable particular units. For instance, the mechanically interlocked structures can be designed to incorporate and protect reactive sites. Schalley and colleagues report on the design of a multi-stimuli responsive electrochemically switchable squaraine-rotaxane: the oxidation state of the squaraine dye controls the position of a macrocycle, which in turn protects or exposes the dye itself (<https://doi.org/10.1038/s42004-024-01312-1>)⁶.

Alternatively, shuttling of a macrocycle can be exploited to bring two sites closer or further apart. In this context, Niemeyer, Grimme and colleagues designed and constructed a switchable

system for singlet oxygen production (<https://doi.org/10.1038/s42004-024-01247-7>)⁷. The photosensitizer, which is attached to the macrocycle, can approach or depart from a quencher upon acid-base driven shuttling. Interestingly, this system operates in the opposite way to what was intended, because of folding. This paper indeed evidences also the subtle and sometimes unpredictable factors that govern the physico-chemical processes in MIMs.

The integration of MIMs into larger, organized structures, such as liposomes, opens new opportunities for potential applications in biology or medicine. For instance, perturbing the membrane in predetermined regions could induce different effects on the structure. As a first step towards this goal, a team led by Smith, Smith and García-López inserted a photoresponsive macrocycle into a rotaxane to modulate the interaction of the MIM with a lipid bilayer (<https://doi.org/10.1038/s42004-024-01343-8>)⁸.

Functional systems and applications

Beyond new methods for their synthesis, a major research frontier for MIMs is the investigation into their function and application. The Collection includes several recent excellent studies where the mechanical bond is used for introducing function and to modify the reactivity, stability or selectivity of the individual components that make it up. The synthetic inaccessibility of MIMs has long hindered their more widespread application, but with improved synthesis methods, MIMs can much more routinely be used in fields such as catalysis, materials and biomedicine, where they often display major functional advantages.

Catalysis and reactivity. The ability of MIMs to fine-tune catalytic environments gives them great potential in, for example, green chemistry or asymmetric synthesis. In this Collection, several examples of catalytically active MIMs are reported.

Mezzina, Silvi, Lucarini and co-workers demonstrate rotaxanes as catalysts for the oxidation of primary alcohols (<https://doi.org/10.1038/s42004-024-01375-0>)⁹. They synthesized small rotaxane scaffolds using nitroxide-radical containing crown ether macrocycles, and then demonstrated that the rotaxane formation did not impair the catalytic ability of the nitroxide functional group in TEMPO-type radical oxidations. This study demonstrates that mechanical bond formation is an efficient conjugation method by which catalysts can be anchored to support without loss in activity.

In a similar manner, Perez and co-workers make use of their mechanically interlocked

nanotube technology to attach organocatalysts to carbon nanotubes¹⁰. They then demonstrated that not only did these supported catalysts retain their activity in a model Knoevenagel reaction, but the mechanical bond also enabled the catalysts to be continuously recycled in a way that could not be reproduced with other catalysis modes.

Beyond using the mechanical bond to anchor catalytic functionality to other molecules, mechanical linkages can also tailor catalytic reactivity, selectivity or function of the system. For example, restrictions in co-conformational freedom or space can strongly alter the physical or chemical properties of a system. These aspects of the mechanical bond are highlighted in the Review article on mechanical bond-enhanced basicity by Di Stefano and co-workers (<https://doi.org/10.1038/s42004-024-01205-3>)¹¹. The authors chronicle the now well-known effect of conformationally induced basicity within MIMs from the first spurious observations to recent results where researchers have systematically and predictably been able to tune basicity of rotaxane superbases via introduction of different macrocycles. Furthermore, Wang highlights how the mechanical bond influences catalytic activity in a recent report by Leigh and co-workers where macrocycle movement in a catenane organocatalyst enables co-conformational adaptation of the catalyst to selectively accelerate different steps in a catalytic cycle (<https://doi.org/10.1038/s42004-023-01088-w>)^{12,13}.

Bio-applications. The use of interlocked molecules for therapeutics or diagnostics has been underdeveloped compared to other MIM application avenues. However, this has recently started to change with more interlocked molecules and materials being used in biomedicine. Here, Holland and d'Orchymont explore the use of rotaxanes as platforms for dual-modality imaging agents with applications in diagnostic medicine (<https://doi.org/10.1038/s42004-023-00906-5>)¹⁴. They incorporate both radio-imaging and optical imaging modalities into the same rotaxane, and demonstrate how the rotaxane architecture can be used for selective cancer cell imaging. Their findings underscore how MIMs can carry advanced biologically relevant functionality, paving the way for future theranostic systems. It should be mentioned that the work by Niemeyer and Grimme highlighted above also holds great potential for future smart photodynamic therapy⁷.

Functional polymers and materials.

Mechanically interlocked materials have been a flourishing research topic for several decades,

and there are even commercial polymer products on the market incorporating mechanical bonds. The Review article on γ -cyclodextrin-based hydrogels from Michieletto and Sapsford highlights these products and many more applications of interlocked materials (<https://doi.org/10.1038/s42004-025-01469-3>)¹⁵. Their discussion focuses on the use of 2:1 γ -CD/polymer host/guest binding motifs to construct interlocked gels, and they pedagogically go through both the different ways that these materials are synthesized and how they are characterized. MachLachlan and co-workers report an elegant approach to supramolecular polymer synthesis based on disassembly rather than assembly of an interlocked molecule (<https://doi.org/10.1038/s42004-022-00774-5>)¹⁶. In their work, the interlocked molecule acts as a “storage pot” for the crosslinking ingredients, and by user-triggered disassembly via thermal or pH stimuli, supramolecular polymerization of a connected network could be initiated on demand. Finally, the article by Pensack and co-workers describes the use of the mechanical bond to obtain an unusual oblique packing pattern between two squaraine chromophores, which gives unusual and interesting optical properties (<https://doi.org/10.1038/s42004-021-00456-8>)¹⁷. The authors use a DNA nanotechnology approach to promote proximity between the two dye-based rotaxanes, and demonstrate that the mechanical bond is directly necessary for obtaining the observed oblique rather than more standard H-aggregate packing pattern. All these works demonstrate the versatility of MIMs in materials science, particularly in developing self-healing and adaptive materials, to promote unusual reactivity or interactions, and to explore new frontiers in biopolymer conjugation chemistry.

Conclusions and outlook

The articles in this Collection underscore how mechanical bonds can be harnessed to construct molecular architectures that integrate structural design with functional performance. Advances in synthesis and molecular engineering are broadening the scope of MIMs, not only in terms of their complexity but also in their practical utility. Looking ahead, their role in energy storage, particularly through redox-active systems for batteries, is likely to become increasingly relevant, as is their contribution to more sustainable catalytic processes aimed at improving resource efficiency and greener chemical transformations. In parallel, the development of molecular machines capable of performing tasks such as cargo transport and signal transduction will continue to be an exciting frontier, with applications in targeted

drug delivery, dynamic sensing, and programmable motion^{18–20}.

The future of MIM research will depend on interdisciplinary collaboration, where expertise from chemists, materials scientists, physicists and engineers converges to translate these molecular designs into functional technologies. The ability of MIMs to integrate with nanoscale devices, self-assembled materials, and biologically relevant systems will shape the next generation of molecular tools and applications. As this Collection highlights, mechanically interlocked molecules are no longer just a structural curiosity—they represent a powerful platform for innovation in chemistry and materials science, offering new strategies for designing functional, adaptive, and interactive molecular systems.

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