The Rise and Promise of Molecular Nanotopology

Qing-Hui Guo1,2,3*, Yang Jiao1†, Yuanning Feng1† & J. Fraser Stoddart1,2,3,4*

1Department of Chemistry, Northwestern University, Evanston, IL 60208, 2Stoddart Institute of Molecular Science, Department of Chemistry, Zhejiang University, Hangzhou 310027, 3ZJU-Hangzhou Global Scientific and Technological Innovation Center, Hangzhou 311215, 4School of Chemistry, University of New South Wales, Sydney, NSW 2052

*Corresponding authors: qinghui.guo@northwestern.edu; stoddart@northwestern.edu; † Q.-H. Guo, Y. Jiao, and Y. Feng contributed equally to this work.

Cite this: CCS Chem. 2021, 3, 1542–1572

Molecular nanotopology—a term we coined recently—is a rapidly developing field of research that is emerging out of the confluence of chemical topology with the mechanical bond. When perusing the increased research activities in this field, it is clear that a new discipline is ready to receive recognition in its own right. In this Mini-Review, we address the historical development of chemical topology and describe how the rational design and practical synthesis of molecular links and knots with mechanical bonds, together with interwoven extended frameworks, have led to the rapid establishment of molecular nanotopology as a discipline. Representative examples are highlighted to offer the reader an extensive overview of ongoing research. We spotlight the major challenges facing chemists and materials scientists and provide some indications as to how molecular nanotopology is going to develop in the years ahead.

Keywords: chemical topology, helicates, interwoven grids, mechanical bonds, molecular knots, molecular links, nanoconfinement, networks, template synthesis, topological chirality

Introduction to Molecular Nanotopology

A skill set in our everyday lives is to endow strands of materials with either artistic or practical properties by incorporating topological features based on the age-old techniques of tying and weaving. Be they functional or decorative, examples can be found ranging from shoe-laces to fishing nets not to mention in traditional Chinese knots, which are decorative, handcrafted arts tied from pieces of red cord. Molecular architectures with topologies also exist in the microscopic world. Knotted strands that have been identified in DNA1–5 and proteins6–14 have been shown15–17 to form randomly in synthetic polymer chains. Molecules with topologies expressed on the nanoscale are beginning to attract greater attention in the chemical community. In an attempt to control molecular topology and understand its special features at the nanoscopic level, chemists have devoted substantial efforts to the rational design and synthesis of molecules with different kinds of topology during the past three decades. Thanks to the advent of the mechanical bond in chemistry,18 the emergence of mechanically interlocked molecules (MIMs),18–20 and a growing awareness of chemical topology,21 chemists have made significant progress in the syntheses of molecules exhibiting topology.

The mechanical bond18,22,23 is a relatively new class of chemical bond that exists in MIMs in which components are bound together by the simple act of mechanical...
interlocking. The chemistry of the mechanical bond is already well established and has been applied with remarkable success to the design and synthesis of catenanes, rotaxanes, molecular shuttles, and switches, as well as MIMs-based artificial molecular machines (AMMs), pioneered by Sauvage and one of us, who were awarded the 2016 Nobel Prize in Chemistry jointly with Feringa.

The concept of chemical topology was introduced by Frisch and Wasserman in 1961 to explain the phenomenon of topological isomerism in which two molecules have the same molecular formulas, yet their structures cannot be interconverted by any kind of deformation.

Chemical topology is of fundamental importance in distinguishing and describing the molecular structures of MIMs. For example, the intrinsic distinction between catenanes and rotaxanes is very clear when taking chemical topology into consideration. A catenane is topologically nontrivial since its molecular components cannot be separated by any continuous deformation without breaking at least one participating covalent bond. A rotaxane, on the one hand, is topologically trivial for the simple reason that its molecular components can be separated—indeed at least by the slippage of the ring off its dumbbell by its passing over one of the stoppers. In a catenane, on the other hand, the mechanical bond is also a topological bond, which is not the case in a rotaxane. For this reason, we have advocated the use of the term mechanical bond, first suggested by Frisch et al. in 1953.

In mathematical topology (Figure 1), a knot is defined as a closed loop embedded in three-dimensional (3D) Euclidean space, whereas a link is a collection of rings that are mechanically interlocked, one with another. Prime knots refer to those that cannot be represented as sums of other knots, in analogy with prime numbers, while combinations of prime knots generate composite knots. The definitions of prime and composite links can be expressed in similar ways.

The Alexander-Briggs notation has been used to classify different topologies. In this notation, a link or a knot is denoted in the form $x^n_y^z$, where $x$ is equal to the minimum number of crossings in the projection of a topology, $y$ is the number of components (in a knot $y = 1$ and is usually omitted), and $z$ represents the order of the given topology among its peers with the same $x$ and $y$ descriptors. (a) Topological isomerism in knots with 0, 3, 4, 5, 7, and 6 nodes or crossings, respectively. (b) Topological isomerism in links consisting of two or three mechanically interlocked rings with 2, 4, 6, 6, and 9 nodes/crossings, respectively. The graphics were prepared using KnotPlot.

Figure 1 | Graphical representations of several links and knots in mathematical topology. In the Alexander-Briggs notation, which is featured in red, a link or a knot is denoted in the form $x^n_y^z$, where $x$ is equal to the minimum number of crossings in the projection of a topology, $y$ is the number of components (in a knot $y = 1$ and is usually omitted), and $z$ represents the order of the given topology among its peers with the same $x$ and $y$ descriptors.

Aesthetically appealing topologies have encouraged chemists to express their counterparts in molecules. The foremost challenge in the synthesis of molecules with topologies lies in how to precisely control the entanglement of the closed loops and the generation of crossover points. Because of the innovative research on molecular knots and links, pioneered by Sauvage et al. and Leigh et al., a new and independent research field—one we have ventured to call molecular nanotopology—is emerging (Figure 2) out of the potpourri of chemical topology, mechanical bonds, and MIMs such as links (catenanes) and knots. In the case of molecular nanotopology involving links and knots, not to mention interwoven frameworks, a mechanical bond is a fundamental requirement for the formation of these topologically nontrivial molecules, keeping in mind that the existence of topology in links and knots does not lay claim to the exclusive use of mechanical bonding, which is also present, for examples, in rotaxanes and suitanes.

Given the recent developments and breakthroughs in molecular nanotopology, we believe that a sea change is afoot and that molecular nanotopology is waiting in the wings to be embraced by the wider community of chemists and other scientists. It is timely to...
review this rapidly emerging field to encourage more young scientists to promote molecular nanotopology by pursuing research into molecular links and knots, some of which will prove to be transformative in the years to come.

In this Mini-Review, following our brief discussion of the historical development of molecular nanotopology, we will present a blueprint and roadmap for its implementation by placing the emphasis on the rational design, practical syntheses, and potential applications of molecular links and knots, as well as interwoven molecular frameworks. Rather than trying to discuss numerous examples from the past, we will focus mainly on a few seminal contributions39,40,51–56 and some recent breakthroughs45–50,57–59 to offer readers a comprehensive overview of ongoing research in the field. Many more examples can be found in other informative perspectives and reviews21,42,43,60–66 We will start by summarizing the general design strategies for the efficient construction of molecules with increasingly sophisticated topologies. We will also illustrate the existence of nanotopology in naturally occurring macromolecules, including its presence in DNA and proteins. Thereafter, proof-of-concept demonstrations and applications of molecular nanotopology will be discussed in some depth. To conclude, we will venture to offer our opinions in the context of recent and current developments and provide suggestions as to what we think lies ahead in what we predict will become an increasingly rapid and evolving field of research in the coming years.

Figure 2 | A Venn diagram showing (1) a set of MIMs, including rotaxanes, daisy chains, suitanes, catenanes/links, and knots; (2) a set of molecules that exhibit molecular nanotopology, including rings, belts, Möbius strips, catenanes/links, knots, nets, and interwoven frameworks—interwoven supramolecular nets, woven fabrics, and COFs. As far as molecular nanotopology is concerned, a mechanical bond is a fundamental requirement of topologically nontrivial molecules, whereas molecules that are topologically trivial can also exhibit mechanical bonding.

The Design and Synthesis of Molecular Nanotopology

In this section, we will discuss one-by-one the design principles employed in the synthesis of molecular links and knots regarding four strategies—linear and circular helicates, interwoven grids, and all-in-one approaches—in addition to describing how to synthesize a variety of molecules with topology by applying these four strategies, with the emphasis placed on particular synthetic routes.

Since the statistical synthesis reported in 1960 by Wasserman67 of a [2]catenane—also described as a Hopf or 21 link—the template-directed synthesis68,69 of molecular links and knots—starting with the seminal work by Schill et al.,70,71 who employed covalent templation in the synthesis of catenanes and knots—exhibiting topological features has represented a significant advance18 in the realms of the mechanical bond. When designing routes to synthesize molecules exhibiting topology, three key factors need to be considered: (1) the generation of crossing points by loops, (2) the appropriate selection of connectivities between the loops, and (3) the formation of covalent bonds to complete the closure of the loops. Although loop closure is kinetically controlled, the all-in-one strategy employs dynamic covalent chemistry72–75 and is conducted under thermodynamic control.

Templates, often aided and abetted by noncovalent bonding interactions, can be employed to entice building
blocks to adopt entwined, preorganized co-conformations. Among all the known templates, transition metal ions are especially valuable and powerful in gathering and organizing organic strands into well-defined arrangements and crossings, largely on account of the specific coordination geometries dictated by these ions. Sauvage et al. described the first metal-templated synthesis in 1983 by employing the tetrahedral coordination between a Cu(I) ion and two bidentate phenanthroline ligands to produce, in their orthogonal disposition with respect to each other, the required crossing geometry for generating a catenane. Subsequently, metal templation, relying on coordination bonds and multifunctional ligands, has become a powerful and efficient approach to the rational synthesis of molecules with complex molecular topologies.

By invoking traditional metal templation, Leigh et al. pioneered the concept of active-metal template synthesis in 2006. In the first reported example of this approach, Cu-mediated alkyne-azide cycloaddition (CuAAC) was employed in the synthesis of a rotaxane. The Cu(I) ion was bound to a pyridine ligand embedded in the backbone of a macrocycle. The alkyne and azide moieties of two half-axle components, on opposite faces of the macrocycle, coordinated to the Cu(I) ion and were activated to undergo a 1,3-dipolar cycloaddition to afford the rotaxane. The yields of rotaxane, based on the macrocycle, are very high—namely, up to 94% with stoichiometric Cu(I) and 82% with 20 mol % of Cu(I). In addition, the experimental procedure involved in running the reaction is extremely simple because neither an inert atmosphere nor a dried solvent is required.

During the process of active-metal template synthesis, the metal ion plays a dual role, serving (1) as a template for entwining ligands and (2) as a catalyst for facilitating the formation of covalent bonds. The active-template process is driven kinetically simply because the bond formation occurring in the cavity of the macrocycle is faster than that taking place in bulk solution. The use of this approach has expanded rapidly and become a highly efficient strategy for the synthesis of a wide range of molecular links, that is, catenanes.

While Leigh et al. were reporting the use of the active-metal template approach to the synthesis of [2] rotaxanes, they were joined by Saito et al. who investigated the catalytic reactions of a macrocyclic copper complex to synthesize [2]rotaxanes. Saito et al. reported the synthesis of [2]catenanes by oxidative intramolecular diyne coupling mediated by macrocyclic copper(I) complexes in early 2009. Soon thereafter in 2009, Leigh et al. published the active-metal template synthesis of [2]catenanes by employing appropriately functionalized pyridine ether or bipyridine ligands and either the CuAAC click reaction of azides with terminal alkynes or the Cu(I)-mediated Cadiot-Chodkiewicz heterocoupling of an alkyne halide with a terminal alkyne. Subsequently in 2011, Leigh et al. extended the active-template CuAAC approach to the synthesis of a molecular knot by combining the passive and active templating portions. In this ingenious approach, the first Cu(I) ion assists in the formation of a looped intermediate, and the second Cu(I) ion mediates the CuAAC reaction to close the knotted structure. Notably, the resulting trefoil knot was the smallest one to have been reported at that time. The relatively good yield of this tight knot was ascribed to the kinetically controlled bond formation promoted by the active CuAAC template.

Linear helicates

In the linear helicate strategy (Figures 3a–3e), templates, often accompanied by noncovalent bonding interactions, initiate the twisting of two linear strands to generate crossings and eventually form a double helicate. The final topology of a link or knot is determined by the number of crossings in the double helicate. If the number of crossings is odd, a molecular knot—the trefoil knot 3 or the pentafoil knot 51—will be formed, otherwise a molecular link, for example, the [2]catenane 2, the Solomon link 42, or the Star of David [2]catenane 62, will be generated. Several examples (Figures 3f–3j) of molecular knots and links employing metal coordination, donor–acceptor interactions, hydrogen-bonding, [x–x] interactions, and hydrophobic effects to assemble linear strands have been accomplished by some of the pioneers in the field. In the following contents of this subsection, the rational synthesis of catenanes, trefoil knots, Solomon links, and figure-eight knots based on this linear helicate strategy will be introduced.

In 1989, Sauvage et al. reported his seminal investigation on the metal-templated synthesis of molecular trefoil knots and a molecular Solomon link based on double-stranded helicates (Figures 3f and 3g). In the presence of Cu(I) ions, a ligand comprising two 1,10-phenanthroline units connected by a tetramethylene linker, formed a double-stranded helicate with two crossings. The subsequent ring-closure step, involving alkylation of this double helicate with hexaethylene glycol chains under highly dilute conditions, afforded the molecular trefoil knot 1 (Figure 3f). By increasing the number of phenanthroline units to three, and extending the linkers to hexamethylenes, a double helicate with three crossings was generated, affording a molecular Solomon link 2 after cyclization with heptaethylene glycol chains (Figure 3g).

Donor–acceptor interactions have been employed by one of us as the driving force in the preparation of topological molecules (Figure 3h), including a trefoil knot 3 with six positive charges. A starting material with two electron-rich dioxybenzene units was threaded by another starting material containing three electron-poor bipyridinium units, forming a double helical

DOI: 10.31635/ccschem.021.202100975
Citation: CCS Chem. 2021, 3, 1542–1572
Citation denotes calendar and volume year of first online publication.
Issue Assignment: Volume 3 (2021), Issue 7
precursor that underwent alkylation under high-pressure to afford the molecular trefoil knot \( 3 \).

During his attempts to synthesize a macrocycle, Vögtle et al.\(^9\) discovered serendipitously that a hydrogen-bonded molecular trefoil knot \( 4 \) was formed during a one-pot reaction (Figure 3i). The structure of this knot was identified unambiguously by single-crystal X-ray diffraction analysis. Vögtle believed a network of hydrogen-bonding interactions was responsible for directing the assembly of \( 4 \) from no less than 12 precursors. The ease of the synthesis and the ready availability of hydrogen-bonded knots led to the preparation of other topologically complex compounds that were resolved and isolated as their enantiomers.\(^1\)

In 2012, Sanders et al.\(^5\) developed a strategy (Figure 3j) for directing the synthesis of entwined architectures from naphthalenediimide-based building blocks, employing a disulfide-based dynamic combinatorial library (DCL) in an aqueous buffer. The topologies of the assembled end-products depended to a considerable extent on the number of aromatic components—1,4,5,8-naphthalenediimide (NDI) units—connected by flexible hydrophilic amino acid linkers. The driving force for the formation of these topological molecules in water was most likely a hydrophobic effect, which ensured that the NDI units were buried in hydrophobic cavities, while hydrophilic carboxyl groups on the amino acids were exposed to the aqueous environment. A molecular trefoil knot was formed\(^5\) from the trimeric building block in nearly quantitative yield, whereas topological isomers, including a \([2]\)catenane, a Solomon link, and a figure-eight knot were generated\(^5\) starting from a dimeric building block.

Notably, in this DCL of molecular links and knots, the stereogenic centers present in the building blocks played an important role in governing the outcome of the reaction. The amino acids employed must be enantiopure, either singly or—as in the case of the knots—with two to
four stereogenic centers in one building block. Changing just one of these centers in the building block killed any production of links or knots. Self-sorting occurred during the synthesis of the molecular trefoil knot. A racemic mixture of enantiopure knots was generated when a mixture of enantiopure trimeric building blocks was employed, whereas a topologically achiral meso figure-eight knot was produced when starting with a mixture of enantiopure dimeric building blocks. These results demonstrate the idiosyncrasies associated with the thermodynamics that constitute dynamic covalent chemistry.

In summary, this linear helicate strategy has resulted in the construction of a series of topological molecules, including catenanes, trefoil knots, Solomon links, and figure-eight knots. The attempted synthesis, however, of molecules exhibiting higher-order topologies—such as the pentafoil knots and Star of David [2]catenanes—has not been successful, most likely because of the long distances that exist between the two ends of the double helicate loops.

Circular helicates

The limitations of the linear helicate strategy, as exemplified by its failure in providing access to molecules with topological structures of high order, have stimulated researchers to use a circular helicate strategy. In this strategy, templates or noncovalent bonding interactions can braid and arrange short molecular strands in a circular fashion to enable the efficient synthesis of molecules with complex topologies. The number of strands and crossings determines the final topology of the molecules—including trefoil knots, Solomon links, pentafoil knots, and Star of David [2]catenanes. In the circular helicate precursors, distances between the reactive ends of the loops are relatively short in comparison with those involving linear helicates.

Figure 4 | Graphical representations of the circular helicate strategy for constructing links and knots. (a–d) In the case of this strategy, templates can braid and arrange short molecular strands in a circular fashion to enable the efficient synthesis of molecular links and knots, including trefoil knots, Solomon links, pentafoil knots, and Star of David [2] catenanes. The number of strands and crossings determines the topology of the molecule. (e) A braid diagram with three strands and the circular triple-helicate strategy used in the construction of an $8_{19}$ knot. (f) Synthesis of a molecular $8_{19}$ knot, employing the circular triple-helicate approach. The reaction of strand 5 with FeCl$_2$, followed by anion exchange with KPF$_6$, affords an intermediate circular triple-helicate. A subsequent ring-closing metathesis (RCM) links the ends of the ligands in the intermediate to afford a metal-coordinated molecular $8_{19}$ knot 6 that houses a chloride anion as a template in its central cavity as revealed by single-crystal X-ray diffraction. Demetallation by NaOH provides the wholly organic $8_{19}$ knot 7 that adopts a flexible conformation. (a–d) Adapted with permission from ref 42. Copyright 2013 Royal Society of Chemistry. (e and f) Adapted with permission from ref 50. Copyright 2017 American Association for the Advancement of Science.
helicates, thus promoting the formation of covalent bonds that lead to loop closure. Moreover, the high symmetry of the precursors with much fewer recognition motifs makes their synthesis somewhat easier. This strategy has been applied to the syntheses of molecules with topologies that are inaccessible using the linear helicate strategy.

In the 1990s, Lehn et al.\textsuperscript{109–111} serendipitously discovered circular helicates that form double helices woven around metal centers of Fe(II) or Ni(II) ions. With these well-established scaffolds available, Leigh et al.\textsuperscript{43,63} decided, quite ingeniously, to form molecular links and knots by modifying the ligand strands and judiciously selecting the appropriate connectivities. By employing the circular helicate strategy, a trefoil knot,\textsuperscript{105} a Solomon knot,\textsuperscript{106} (a doubly interlocked [2]catenane), a pentafoil knot,\textsuperscript{107} and a Star of David\textsuperscript{[2]catenane} (triplly interlocked [2]catenane) have all been synthesized from trimeric, tetramer, pentameric, and hexameric circular helicates, respectively. The coordination environments, defined by the geometries, shapes, bond lengths, angles, spacers, counterions, and substituents, associated with each strand play important roles in the assembly and creation of molecular topologies on the nanoscale level.

The rational synthesis of a metal-coordinated molecular 8\textsubscript{19} knot, based on the circular helicate strategy, is discussed in detail in the following paragraph.

In 2017, Leigh et al.\textsuperscript{50} extended the circular helicate strategy from double- to triple-helicates (Figure 4e) to synthesize molecules with higher-order topologies. An 8\textsubscript{19} molecular knot (Figure 4f) was prepared by braiding three strands with octahedrally coordinated Fe(II) ions. Reaction of ligand strand A with FeCl\textsubscript{3}, followed by anion exchange with KPF\textsubscript{6}, produced a circular triple-helicate. In this precursor, the relative positions of the three strands at each crossing point were controlled by Fe(II) ions, while the braiding connections were determined by structural constraints imposed on the ligands. The subsequent ring-closing metathesis (RCM) connected the ends of ligands, affording the metal-coordinated 8\textsubscript{19} knot B. The steric restraints in the preorganized scaffold maintain high selectivity at the reaction sites so that the closures can only occur between strands coordinated to neighboring iron centers. Hence, the tight molecular 8\textsubscript{19} knot C with loops containing 24 atoms per crossing was constructed with relatively high efficiency. The metal-free knot exhibits topological chirality, which is expressed in the circular dichroism (CD) spectra of the enantiomers.

This strategy holds considerable promise in the building of intricate topologies from some short and simple molecular strands. The principle for connecting strands selectively is expected to be applied to the synthesis of a range of topological molecules exhibiting higher-order complexity. For example, a composite molecular knot— which contains three trefoil tangles of the same handedness with a total of nine crossings—as well as a 9\textsubscript{3} link have been synthesized\textsuperscript{49} stereoselectively from a hexameric Fe(II) circular helicate by controlling the connectivity patterns associated with the ligands.

### Interwoven grids

In this subsection, the rational design and synthesis of an interwoven supramolecular net—a molecular endless 7\textsubscript{4} knot—a woven two-dimensional (2D) molecular fabric, and covalent organic frameworks (COFs) based on the interwoven grids strategy will be introduced following a discussion of supramolecular weaving.

To synthesize more complex molecular topologies, an interwoven grids strategy has been applied to facilitate the arrangement of molecular strands. In 1997, one of us\textsuperscript{12} introduced the concept of supramolecular weaving (Figure 5) and obtained an extended interwoven topology using a carboxylic acid dimer A as a supramolecular synthon, a term introduced by Desiraju et al.\textsuperscript{113,114} in 1995. The interwoven supramolecular net was produced (Figure 5a) by noncovalent synthesis, starting from the building blocks bis-p-phenylene[34]crown-10 (BPP34C10) and secondary dibenzylammonium ions. The self-assembly of two [3]pseudorotaxanes, formed by the double threading\textsuperscript{15} of two secondary dibenzylammonium ions through the center of BPP34C10, became aligned with each other to support two supramolecular synthons A. Using two pairs of secondary dibenzylammonium ions, each encircled by BPP34C10 and each containing one carboxylic acid function, a six-component superstructure comprised of two [3]pseudorotaxanes was obtained (Figure 5b). The arrangement of [3]pseudorotaxanes was stabilized by [N\textsuperscript{+}H\textsuperscript{–}O\textsuperscript{–}] and [C\textsuperscript{–}H\textsuperscript{–}O\textsuperscript{–}] interactions between the CH\textsubscript{2}NH\textsubscript{2}–CH\textsubscript{2} cationic centers and O atoms in the crown ether. Furthermore, two [3]pseudorotaxanes were linked by two supramolecular synthons A through pairs of strong [O–H–O] hydrogen bonds. In the case of secondary dibenzylammonium ions containing two carboxylic acid functions, an interwoven supramolecular cross-linked net was formed (Figures 5c and 5d). The [3]pseudorotaxanes, in which the doubly encircled pairs of secondary dibenzylammonium ions are orientated in an antiparallel manner, became interlinked through multiple [O–H–O] hydrogen bonds between carboxylic dimers A to form a 2D pseudopolyrotaxane sheet with a thickness of 12.5 Å.

By extending this approach, one of us\textsuperscript{18} also synthesized an interwoven supramolecular cage and polyknot,\textsuperscript{17} while Kim and Whang\textsuperscript{18} have constructed a 2D polyrotaxane net by threading cucurbit[6]urils onto Ag(I) coordinated polymers. In 2017, Wennemers et al.\textsuperscript{19} reported an extended triaxially woven superstructure by the self-assembly of oligoporphyrin-based building blocks, comprising two perylenemonoimide chromophores, separated at a distance of 18 Å. The organic strands
interlaced to form an interwoven network driven by $\pi-\pi$ and \(\text{C}-\text{H} \cdots \pi\) interactions.

In the wake of supramolecular weaving, an interwoven grid strategy (Figure 6a) has been employed\(^{120-122}\) to synthesize more complicated molecules with higher-

order topologies and infinitely entwined frameworks. In the case of the interwoven grid strategy, metal-ion chela-
tion can generate the required crossings to form inter-

woven grids with constrained geometries. Rather than twisting, folding, or threading molecular building blocks,
molecular grids feature interwoven ligand strands, form-
ing an over-under-over-under sequence. The extra strain
and stress imposed by the mechanical entanglement of
every strand constitutes one of the main hurdles
that need to be overcome to assemble strands with crisscrossed patterns. The interwoven grid strategy
(Figure 6a) is a fundamentally newfangled route to un-
precedented molecular topologies and interwoven poly-

meric materials.

Recently, Leigh et al.\(^{123,124}\) reported the syntheses of a molecular endless 7$_4$ knot (Figure 6b) and a 2D molecular
fabric (Figure 7a) by employing interwoven [3 x 3] grids. Thiazolo[5,4-d]thiazole (TTZ) was chosen\(^{125}\) as the coor-
dinating unit to minimize excessive strain by holding all
the metal ions within the same plane. The strand 8 was
designed to feature two outer coordination sites
involving benzimidazole and pyridine units as well as an inner site incorporating two TTZ moieties in combination with a 4-dimethylaminopyridine (DMAP) motif. The electron-donating 4-dimethylamino group is crucial to meet the stringent requirements for the formation of \([3 \times 3]\) grids. The metal-coordinated molecular grid \(9\) was obtained exclusively using either Zn(II) or Fe(II) ions to weave the strands. Notably, the tetrafluoroborate anions were essential to template the assembly by binding within the square cavities of the interwoven grid through multiple [anion--π] and [anion--metal] interactions. Subsequent RCM is then used to connect the ends of the strands in sequence and after demetallation affords the wholly organic \(7_4\) knot \(10\), accompanied by the formation of molecular grids. Subsequent ring-closing metathesis (RCM) connects the ends of appropriate strands. Demetallation affords the wholly organic \(7_4\) knot \(10\), starting from the molecular strand \(8\). The use of BF\(_4^-\) anions was found to be essential for the formation of molecular grids. Subsequent ring-closing metathesis (RCM) connects the ends of appropriate strands. Demetallation affords the wholly organic \(7_4\) knot \(10\), accompanied by the Solomon link \(11\) and the macrocycle \(12\) as side-products.

(b) Adapted with permission from ref 123. Copyright 2021 Springer Nature.

Figure 6 | Graphical representations of the interwoven grid strategy for constructing a \(7_4\) knot and an interwoven framework. (a) Grids featuring interwoven strands and forming over–under–over sequences. The \([3 \times 3]\) interwoven grid creates potential routes to unprecedented molecular topologies, such as a molecular \(7_4\) knot and molecularly woven fabrics. (b) Synthesis of an interwoven \([3 \times 3]\) molecular grid \(9\), which acts a precursor for the molecular \(7_4\) knot \(10\), starting from the molecular strand \(8\). The use of BF\(_4^-\) anions was found to be essential for the formation of molecular grids. Subsequent ring-closing metathesis (RCM) connects the ends of appropriate strands. Demetallation affords the wholly organic \(7_4\) knot \(10\), accompanied by the Solomon link \(11\) and the macrocycle \(12\) as side-products.
Figure 7 | Bottom-up syntheses of interwoven molecular frameworks. (a) Self-assembly of a layered 2D molecularly woven fabric. In the presence of Fe(BF₄)₂, both the anion (BF₄⁻) and the metal cation (Fe(II)) serve as templates to direct the weaving of strand 13, leading to the formation of the interwoven molecular tile 14, expressed as a [3 × 3] grid. When exposed to oxygen in the air, oxidation of the thiols to disulfides is accompanied by slow precipitation of 14, resulting in a woven fabric with both templates still in place. (b) A 3D covalent organic framework COF-505, classified as a dia net, and woven COF-505, classified as a dia-w net, have been synthesized from formyl-functionalized Cu(I)-bisphenanthroline complexes and benzidine (BZ) by reversible imine condensations. The process of demetallation and metalation is reversible without the breaking up of the COFs. (a) Adapted with permission from ref 123. Copyright 2020 Springer Nature. (b) Adapted with permission from ref 59. Copyright 2016 American Association for the Advancement of Science.
(Figure 7a). The strand 13 with thiol groups at each end contains three tridentate sites, separated by TTZ units for coordination with octahedral Fe(II) ions. In the presence of Fe(BF4)2, both the anion and metal ion serve as templates to weave the strand. The “woven tile” 14 is formed as a [3 × 3] interwoven grid. When exposed to air, slow precipitation of 14 out of solution promotes the connections between pre-woven grids because of the oxidative transformation of thiol groups to disulfide bonds. The removal of the ion templates provides a wholly organic molecular material, consisting of interwoven aliphatic and aromatic segmented polymer strands associated through periodic mechanical entanglements within discrete layers. The layered 2D woven material was demonstrated to have long-range order and acted as a net for slowing down the passage of large ions.

In 2016, Yaghi et al.59 reported the first example of a mutually interwoven framework at regular intervals in the form of a COF-505 belonging to a dia-w net (Figure 7b). By combining Sauvage’s seminal work24 on the Cu(I)-templated synthesis ofbisphenanthroline [2]catenanes with the principles of reticular chemistry,126,127 a 3D COF-505 in the form of a dia net was constructed from formyl-functionalized Cu(I)-bisphenanthroline complexes and benzidine (BZ) units through reversible imine condensations. The copper centers served as templates for braiding the threads. The process of demetallation and metatalation was reversible without breaking the patterns established by organic scaffolds. The high degree of movement on the part of the threads in COF-505 endowed the bulk material with tunable elasticity and mechanical properties. Applying a similar approach, more interwoven frameworks with characteristic topologies have been prepared by Yaghi et al.128-130

Leigh makes the point that the design principles for the construction of woven COFs and molecularly woven fabrics are different. In the discussion at the end of his recent article in Nature,24 Leigh et al. state that:

Three-dimensional woven covalent organic frameworks (COFs) have previously been formed89,127 from tetrahedral building blocks of stacked bidentate ligands with a single crossing, relying on reticular assembly to generate the entanglements necessary for a weave. However, reticular considerations are insufficient to ensure that a framework of coordination tetrahedra, that feature a single crossing, generate a lattice that is woven: a weave results only when all adjacent tetrahedra are internally oriented so that the correct ligand ends are connected.

In the case of Leigh’s molecularly woven fabrics, the “building blocks that are pre-woven are tessellated to extend an already established weave.”

Numerous crystal structures of inorganic salts,131 metal coordination networks,132,133 porous coordination polymers,134 and metal–organic frameworks135,136 (MOFs) reveal that interwoven structures can be formed spontaneously when long and flexible ligands are employed as the building blocks. This phenomenon has become known as interpenetration,137 wherein individual polymeric networks become catenated with each other in the lattices of metal ions or clusters linked by organic ligands. These interpenetrated motifs minimize empty space and enhance significantly framework stability. In some cases, the interpenetration can be helpful for gas storage, capture, and separation.135,136,138-143 The formation of interpenetrated structures is not predictable and is usually discovered serendipitously. Recently, however, the precise control144 and rational design of the geometry of periodic knots and polycatenanes in MOFs have been attracting145,146 more attention in reticular chemistry.137

All-in-one approaches

Most approaches to the syntheses of molecules exhibiting topology have been conducted in a stepwise fashion with the irreversible formation of covalent bonds leading to the final products. To simplify their construction and enable error-corrections, an all-in-one strategy (Figure 8) featuring the reversible formation of dynamic covalent bonds has been developed.72,147,148 In this strategy, the interconversion among all reactive species leads eventually to the generation of the more thermodynamically stable products. Furthermore, the introduction of templates can regulate the Gibbs free energies of specific products, offering additional stabilizing interactions that have proven useful in steering thermodynamic equilibria toward one topology rather than another. In the following portions of this subsection, the rational synthesis of Borromean rings, a Solomon link, a metal-peptide capsule, and metalla-knots based on the all-in-one approach will be reviewed.

One of us52,53 reported the selective synthesis of molecular Borromean rings and Solomon links utilizing this strategy (Figure 8a). By employing the powerful templation of transition metals and the reversibility of imine bond formation, molecular Borromean links have been synthesized from a set of 18 precursors including (1) six endo-tridentate 2,6-diformylpyridine (DFP) ligands, (2) six transition metals, and (3) six exo-bidentate diaminobipyridine (DAB) ligands. Using either Zn(II) or Cu(II) as the sole template, molecular Borromean rings BR-Zn124 or BR-Cu124 were formed in remarkably high yields. By harnessing the dynamic nature of this process, a molecular Solomon link has been constructed from the same ligand system.53 The utilization of equal amounts of Zn(II) and Cu(II) as the metal templates led to a DCL, containing molecular Borromean rings and Solomon links, from which the Solomon link SK-Zn/Cu14 crystals preferentially.

In the past, metals have been employed as templates to gather and direct the entwining of building blocks to

DOI: 10.31635/ccschem.021.2021000975
Citation: CCS Chem. 2021, 3, 1542-1572
Citation denotes calendar and volume year of first online publication.
Issue Assignment: Volume 3 (2021), Issue 7
make molecular links and knots. Recently, however, metal centers have been integrated increasingly within the backbones of topological molecules, forming organometal complexes. In the past couple of years, Fujita et al. have described some spectacular research involving the synthesis of metal-peptide complexes, for example, capsule with highly entangled polypeptide chains, are prepared from short peptides by coordinating them with Ag(I) cations. (c) A molecular Borromean ring and a molecular metalla-knot have been isolated, starting from the nonlinear dipyridyl ligand and Cp*Rh. (a) Adapted with permission from ref. Copyright 2004 American Association for the Advancement of Science and from ref. Copyright 2007 VCH Verlagsgesellschaft mbH, Germany. (c) Adapted with permission from ref. Copyright 2021 American Chemical Society.

**Figure 8** | Graphical representations of the all-in-one strategy for synthesizing molecular links and knots. In the case of this strategy, the dynamic processes and interconversions among all the reactive species leads eventually to the most thermodynamically stable compounds. (a) Using Zn(II) or Cu(II) as the sole templates, the molecular Borromean rings or BR-Cu are formed in close to quantitative yields. Employing equal amounts of Zn(II) and Cu(II) as the metal templates leads to the formation of a dynamic combinatorial library (DCL), from which the Solomon link crystallizes out preferentially. (b) Peptide-based organometallic-knots, such as the metal-peptide capsule with highly entangled polypeptide chains, are prepared from short peptides by coordinating them with Ag(I) cations. (c) A molecular Borromean ring and a molecular metalla-knot have been isolated, starting from the nonlinear dipyridyl ligand and Cp*Rh. (a) Adapted with permission from ref. Copyright 2004 American Association for the Advancement of Science and from ref. Copyright 2007 VCH Verlagsgesellschaft mbH, Germany. (c) Adapted with permission from ref. Copyright 2021 American Chemical Society.

**The Occurrence of Molecular Nanotopology in Natural Macromolecules**

Examples of molecular nanotopology exist in nature. Naturally occurring macromolecules, such as DNA and proteins, are formed from their monomers—nucleotides in the case of DNA and amino acids in the case of proteins —and linked by covalent bonds in a linear sequence, to give the so-called primary structure. These monomers contain functional groups with heteroatoms, resulting in...
the formation of intramolecular hydrogen bonding and dynamic covalent bonds. The maze-like entanglements in DNA and proteins create a variety of 3D tertiary structures, which have caught the imaginations of structural biologists. Some researchers have been claiming for several decades that the nanotopology of these complex natural macromolecules is important. With the help of technologically advanced microscopy and crystallography, the presence of knots and links in nature has been observed. Furthermore, chemists have developed techniques for the design and synthesis of large molecules using DNA and protein fragments.

The occurrence of molecular nanotopology in nature

DNA is well-known for its double-helical superstructure, which can be viewed as two very long, intertwined chains coiling around the same axis. The chains bearing base pairs have a radius of 10 Å and each helical twist is repeated every 34 Å, a length corresponding to 10 nucleotides. Although the size of a nucleotide is small, a DNA macromolecule contains hundreds of millions of these monomers, thereby forming a one-dimensional line hundreds of nanometers in length. As a result of the flexibility of their backbones, DNA supermolecules can easily twist and fold to form loopy superstructures such as circular DNA. This flexibility allowed researchers to discover DNA catenanes. The observation of DNA catenanes goes back to the 1930s when Navashin commented, “in one case, the two daughter strands, composing a normal chromosome failed to separate” and McClintock noticed that the “lack of uniformity in the splitting plane could give rise to a double sized ring with two insertion regions or cause split halves of the ring to become interlocked”.

It was the discovery of natural DNA catenanes by Vinograd et al. in 1967 that caught the attention of biologists and other scientists. Thereafter, researchers have found DNA molecules exhibiting topology in mammalian mitochondria, human leukocytes, SV40-infected monkey cells, and trypanosomes. One of the most noteworthy examples (Figure 9a) is the kinetoplast DNA (kDNA) network that exists in the mitochondria of Crithidia fasciculata. According to the researchers involved in solving the topological structure of isolated kDNA by electron microscopy, the structure consists of approximately 5000 DNA minicircles (2.5 kb) and 25 DNA maxicircles (37 kb) that are mechanically interlocked in a gigantic planar network. Each minicircle is closed covalently and catenated with, on the average, three neighbors (a valence of 3) as well as being stretched out and aligned side-by-side approximately perpendicular to the planar network. Researchers have advanced many hypotheses to explain why kDNA is a polycatenane network. In contrast with a combinatorial linear chromosome, one of the advantages of this complex structure is that such a mechanically interlocked network provides an orderly mechanism of replication and segregation, as well as a more efficient process for exchanging genes.

As a result of the formation of disulfide bonds and metal coordination, pseudolinks and pseudoknots are formed in protein structures. Takusagawa and Kimitori reported the first example of a linear protein-based knot in the structure of (S)-adenosylmethionine synthetase (MAT) in 1996, and later, in 2000, Johnson et al. discovered the first protein-based catenane in the bacteriophage HK97 capsid. Nowadays, approximately 6% of the total structures in the Protein Data Bank (PDB) contain knots and links. After the synthesis of the first catenane in 1960, Wasserman pointed out the rich potential for making topologically complex structures that contain mechanical bonds. If life knows how to make molecules exhibiting topology in cells, what about synthesizing artificial counterparts in the laboratory?

Synthesis of natural macromolecules exhibiting molecular nanotopology

The first synthetic DNA catenanes were described in 1967 by Wang and Schwartz, who reproduced Wasserman’s statistical protocol for the synthesis of a catenated compound through cyclization of linear precursors. The phage 186 DNA from Escherichia coli W3550 (186p) was isolated and the 5-bromouracil (5-Bu) labeled λcat (λ DNA) from the lambda bacteriophage was prepared. Both 186 and 5-Bu λ DNA molecules were divided in half in an apparatus with a high-pressure gas system, and then mixed together in a variety of predetermined concentration ratios. The statistical synthesis was completed while the mixture of two DNAs underwent cyclization. The homology in base sequences between the cohesive ends of two DNAs was tested, showing weak cohesion, making it possible to demonstrate the formation of a [2] catenane between the two cyclic DNA rings. The buoyant densities of 186 DNA and 5-Bu λ DNA in CsCl solutions were identical and distinguishable from an intermediate band that corresponded to a dimeric species formed by those two DNAs. A higher concentration of 186 DNA present during the cyclization of 5-Bu λ DNA resulted in a higher yield of the [2] catenane, which was isolated by centrifugation. Like Wasserman’s statistical procedure, the isolation of the synthetic DNA [2] catenane was demanding. Wang and Schwartz commented that the formation of catenanes can be processed in a bacterium if it is infected with a bacteriophage of high multiplicity.

An active template-directed and autonomous cellular synthesis has opened promising and versatile methods for engineering synthetic mechanically interlocked proteins. A well-established catalytic center, employed in the synthesis of MIMs, has been
introduced to encourage the entwinement of polypeptide chains. In 2019, Zhang et al. developed (Figure 9b) a biologically compatible, active-template approach to the synthesis of proteinaceous heterocatenanes. The SpyTag–SpyCatcher complex derived from the CnaB2 domain in Streptococcus pyogenes can be split into three fragments. One of them, SpyStapler, acts as a powerful catalyst, facilitating isopeptide bond formation between the other two—that is, BDTag and SpyTag—both in vitro and in vivo. To form the first ring component, an elastin-like polypeptide (ELP) with an inserted SpyStapler fragment was cyclized by split-intein chemistry, producing a cyclic protein, c-SpyStapler-ELP1 (c-S-E1). Thereafter, the second component, BDTag-ELP2-SpyTag (BD-E2-A), which contains BDTag and SpyTag fragments at each terminus of the ELP chain, was mixed with c-S-E1, reconstituting an intermediate of the SpyStapler-catalytic ligation. According to the 2D 1H–15N HSQC (heteronuclear single quantum coherence) NMR spectroscopic analysis, the clustered signals in the spectra of both 15N-labeled BD-E2-A and c-S-E1 revealed a disordered structure, suggesting that the catalytic center was located in the internal space between two ring components. The SpyStapler-catalytic ligation was then carried out to connect two termini of the BD-E2-A to form a cyclic protein, resulting in the formation of the [2]catenane, cat-ELP. The creation of cat-ELP has been proved by SDS-PAGE (sodium dodecyl sulphate-polyacrylamide gel electrophoresis), size exclusion chromatography, and mass spectrometry. This protocol has also been applied to the catenation between the fluorescent proteins (1) mCherry and EGFP (enhanced green fluorescent protein) and (2) GFPim (less stable green fluorescent protein variant) and DHFR (dihydrofolate reductase), respectively, demonstrating its precision, generality, and programmability. Furthermore, the [2]catenane, consisting of the

Figure 9 | (a) Left: Electron micrograph of a segment of a kDNA network from Crithidia fasciculata. The small rings in the electron micrograph are minicircles and big rings are maxicircles. Right: Graphical representations of the kDNA network that has been isolated in the laboratory (top) compared with the kDNA network present in vivo (bottom). (b) Schematic representation of the formation of the protein heterocatenane, cat-ELP, using a biologically enabled, active-template approach.
two fluorescent proteins, exhibits identical absorption and emission profiles to its components. Comparing the catenate with its open-ended topological isomer, the former has a higher thermal stability as a result of entropy restriction by chain cyclization and mechanical interlockening as a consequence of the catenation. In addition, cat-GFPPrm-DHFR has been demonstrated to possess a higher kinetic stability and proteolysis resistance than its precursors.

**Isolation and Characterization of Molecules with Topology**

Due to the growing development of efficient strategies for the synthesis of molecular links and knots, the formation of mixtures of topological isomers is an almost inevitable occurrence during a chemical reaction. Reliable separation methods, which are necessary to isolate pure topological isomers, play a key role in molecular nanotechnology. Although traditional column chromatography can be employed in the isolation of small molecules with different topologies, in the case of the construction of complex molecular links and knots, more efficient separation methods, such as high-performance liquid chromatography (HPLC) and preparative gel permeation chromatography (GPC), are indispensable to distinguish the subtle differences between a mixture of topological isomers that might be present in a DCL.

Sanders et al. used HPLC to isolate and identify several topological isomers (Figure 3) from a DCL composed of bis-NDI monomers, in which a Solomon link (60% yield) and a figure-eight knot (18% yield) turned out to be the major products, with a trefoil knot being the minor one. Despite having the same molecular formulas, the different topologies of these isomers have a significant influence on their physical properties—including compactness, rigidity, and hydrophobicity—resulting in the efficient retention-time-dependent separation by HPLC. Moreover, the success in identifying each topological isomer encouraged the authors to explore the competing kinetic pathways leading to their formation, knowledge of which is further used to control product selectivities and create new topological structures.

In addition to the isolation of topological isomers, the separation of the topological enantiomers of molecular links and knots becomes of paramount importance for probing their chiroptical properties. The assignment of absolute configuration to a topologically chiral molecule can be realized by (1) solving the single-crystal structures of each enantiomer and (2) comparing their calculated and experimental CD spectra.

In 1989, Sauvage and Dietrich-Buchecker studied the chirality of a molecular trefoil knot by mixing 1 with a chiral shift reagent, Pirkle’s alcohol (Figure 10a). Large chemical shifts in the signal for this mixture were observed in the $^1$H NMR spectrum. The chirality of the molecular trefoil knot 1 was revealed unambiguously from its single-crystal structure. Moreover, the compound underwent spontaneous resolution during crystallization, an observation verified by the fact that only one of the two topological enantiomers exists in each single crystal. On mixing the racemic molecular knot 1 with (S)-(−)-1,1′-binaphthyl-2,2′-diyl phosphate (BNP) diastereoisomers (Figure 10a) were isolated by flash chromatography on alumina. Their subsequent crystallization enhanced their chiral resolution. The CD spectra of the diastereoisomers appeared as mirror images since the CD signal of the chiral anion was silent in the region where $\lambda > 280$ nm. The optically pure knot expressed its chiral bias on quenching the luminescence of racemic Ln(III) complexes in an enantioselective manner.

Vögtle et al. achieved the racemic resolution of the amide-based molecular trefoil knot 4 by using HPLC (Figure 10b). He employed a procedure developed by Okamoto. The separation of two enantiomers, P-4 and M-4, was achieved on a column wherein a chiral stationary phase was linked covalently to a silica-gel support. The separation factor was 2.14 and both enantiomers were obtained as pure compounds, allowing the chiroptical properties of the topologically chiral knot to be probed by CD spectroscopy.

More recently, Leigh et al. have developed a strategy for the stereoselective synthesis of a molecular overhand knot displaying single-handedness, starting from an enantiopure strand. In this procedure, the topological chirality is influenced and determined by the stereogenic centers in the molecular strand. Thus, a molecule with a single-handed topology can be produced and there is no need for chiral resolution. Leigh et al. have also accomplished the selective synthesis of three topological isomers—an unknot $0_1$ macrocycle, a trefoil $3_1$, and a three-twist $5_2$ knot—from one molecular strand 18 (Figure 10c). Under the guidance of transition-metal and lanthanide ions, the strand can fold into the specific geometries and topologies. These approaches, which rely on selective synthesis, can render the separation of isomers and enantiomers much easier.

Single-crystal X-ray diffraction analysis is the most reliable method to verify the structures of topologically nontrivial molecules, in conjunction with supporting evidence from NMR spectroscopy and mass spectrometry. In some cases, single crystals of metal-coordinated links or knots can be obtained and used for characterization, particularly when the metal-free forms of these MIMs do not produce single crystals as a result of their structural flexibility. Variable-temperature $^1$H NMR spectroscopy is also a powerful tool for gaining insights into the co-conformational dynamics of molecules that are topologically flexible. For example, the energy barriers associated with different kinds of intercomponent motions, such as translation, circumrotation, pirouetting,
and rocking, can be estimated\textsuperscript{25} by dynamic NMR line-shape analysis.

Ion-mobility mass spectrometry (IM-MS) has proven\textsuperscript{206} useful in determining the topology of molecules in the gas phase, usually by comparing the experimental data and the calculated values for the molecular collision cross section. Nitschke et al.\textsuperscript{207} have combined the IM-MS technique with tandem mass spectrometry to assign the

---

**Figure 10** | Separation of topologically chiral molecules and stereoselective synthesis of molecular knots. (a) A pair of diastereoisomers can be isolated by flash chromatography on alumina by mixing the racemic molecular knot 1 with \((\text{S})\text{-}(\text{S})\text{-}1,1'\text{-binaphthyl-2,2'-diyl phosphate BNP}\). (b) The racemic resolution of amide-based molecular trefoil knot 4 can be achieved by using chiral HPLC. (c) A strategy for the stereoselective synthesis of molecular knots of single handedness. The topological chirality is influenced and determined by the stereogenic centers in molecular strand 18. Under the guidance of transition-metal and lanthanide ions, specific geometries and chiral topologies can be acquired.

(a) Adapted with permission from ref 201. Copyright 1996 American Chemical Society. (c) Adapted with permission from ref 45. Copyright 2020 Springer Nature.
topologies to molecular links and knots. Through the characterization of structure-indicative fragments generated by collision-induced dissociation, as well as the definition of a floppiness parameter based on parent- and fragment-ion arrival times, this simple and rapid method is not only free of the computational modelling of chemical structures but also applicable to the analysis of complicated mixtures or DCLs that contain different topologies.

Characterizing the properties of molecular links and knots on the single-molecule level is fundamentally important for understanding the effect of topology on their dynamic behavior. In this context, commonly used single-molecule techniques are based mainly on the use of atomic force microscopy (AFM) and optical tweezers, that are capable of (1) probing the mobility of component rings in catenanes, (2) monitoring the folding and unfolding processes of molecular knots, and (3) estimating the strength of intercomponent interactions within molecules exhibiting different topologies. Besides the observation of nanomechanical characteristics, there is a lot of room for assessing other properties of molecular knots and links at the single-molecule level. For example, single-molecule measurements of electrical or magnetic performance have rarely been performed, although experiments might well lead to the discovery of new topology-dependent features.

Compared with single-molecule studies, ensemble properties of molecular knots and links can be characterized using more diverse technologies, including but not limited to CD spectroscopy, fluorescence spectroscopy, cyclic voltammetry, differential scanning calorimetry, dynamic mechanical analysis, and rheological measurements. To establish a topology–property relationship, a joint use of several characterization methods, together with theoretical calculations or simulations, is often required. For example, by combining $^1$H NMR diffusion-ordered spectroscopy, CD spectroscopy, collision-induced dissociation mass spectrometry, and molecular dynamics simulation, Leigh et al. have revealed how the tightness of a series of molecular $\text{8}_{\text{19}}$ knots affects their conformation, topological chirality, and reactivity. These insights offer valuable blueprints and roadmaps for the development of the applications of molecular nanotopology.

### Applications in materials science

Molecular links and knots in proteins have been recognized to impact significantly their mechanical strength and stability, as revealed by both theoretical simulations and single-molecule force spectroscopy. To harness these features in smart new materials, mechanical bonds are usually incorporated into synthetic polymers and their influence on the properties of the polymers evaluated. For example, Fustin et al. have demonstrated that improving the mobility of the component rings of a [2]catenane—by removing the Pd$^{2+}$ ion from the crossing point—results in a decreased glass-transition temperature and accelerated crystallization of [2]catenate-embedded polymers. Yan et al. have constructed interwoven polymer networks by ring-opening metathesis polymerization of a [2]catenane and shown that this topologically linked network has emergent mechanical performance, including high modulus and thermomechanical stability.

To develop a new type of mechanical protecting group for mechanophores, De Bo and Zhang have introduced one [2]catenane junction into a poly(methyl acrylate) chain and evaluated the influence of this topological link on the transduction of mechanical forces. The system bore two mechanically active Diels–Alder (D–A) cycloadducts. One of them—an intracyclic D–A cycloadduct—was embedded in the [2]catenane and the other one—an extracyclic D–A cycloadduct—was in the linear segment of the polymer chain. When subjected to high-intensity ultrasound, the polymer chain underwent selective breakage at the site of the extracyclic D–A cycloadduct, indicating that the intracyclic D–A cycloadduct was protected in the presence of the catenane. The protecting role of the [2]catenane is ascribed to the mobility of its two component rings. Upon application of mechanical force, the component rings within the [2]catenane can circumrotate with respect to each other until the tension equalizes over the entirety of the catenated framework. This relative motion diverts mechanical forces effectively away from the intracyclic D–A cycloadduct, reducing its mechanical susceptibility. Although rotaxanes have also been reported to affect the responsiveness of mechanophores, the topologically trivial structures themselves are susceptible to force-induced degradation. In contrast, catenanes are free of this weakness, rendering them more practical to tame the activity of mechanophores without impairing the mechanical integrity of the polymer chains.
Collecting and amplifying the single-molecule behavior of MIMs has proven to be a critical step for their real use in new materials. A recent study by Huang et al. have showcased (Figure 11a) how to establish the mechanistic correlation between the single-molecule properties of a poly[2]catenane and the macroscopic performance of the corresponding polymer gels. The poly[2]catenane, which was synthesized by the olefin-metathesis polymerization of a benzylic amide [2]catenane, involves strong intercomponent hydrogen bonding (IHB) between the component rings. AFM-based single-molecule force spectroscopy was used to probe the reversible dissociation and rebinding of IHB under the stretching and relaxation, respectively, of a single-chain poly[2]catenane. The molecular-level behavior of this topologically linked polymer was switchable by manipulating the IHB with either acids or bases. Furthermore, a polymer gel was prepared by the thiol–ene reaction between the poly[2]catenane and a cross-linker. Since the IHB can be preserved during gelation, the resulting polymer gel was...
tough and rigid as a result of the constrained mobility provided by the catenated rings. Once incubated at high temperature (80 °C) or low pH (2.5), the gel became flexible and soft because of the destruction of IHB, as indicated by a significant decrease in the Young’s modulus from 86.8 to 2.96 MPa. By altering the temperature or pH, the polymer gel can be switched reversibly between two states at least three times. In this research, the mechanical adaptability of the poly[2]catenane-based bulk gel correlates well with the dynamic and robust features of the single-chain poly[2]catenane, demonstrating the effectiveness of constructing materials rationally by polymerizing topologically nontrivial building blocks in a linear tandem manner.

The nanocoﬁnement effect,229,230 present in molecular links and knots, enables the controlled assembly of molecular components that are difﬁcult to combine using traditional pathways, thereby resulting in the emergence of unprecedented properties. For example, corolling a large number of like charges in a small-sized molecule was previously considered to be destined for failure because of strong Coulombic repulsions. This goal, however, has been realized by one of us231 in 2013 using mechanical bonding. We employed radical-pairing interactions232–234 between bipyridinium radical cations to template the formation of a homo[2]catenane (HC), in which two rigid and positively charged cyclobis(paraquat-p-phenylene) (CBPQT) rings were forced into proximity with each other (Figure 11b). Consequently, as many as eight positive charges were gathered within a conﬁned space of just over 1 nm. Sequential reductions observed by differential pulse voltammetry (DPV) measurements identiﬁed six (electro)chemically accessible redox states for the HC, wherein only the HC⁷⁺ was paramagnetic while the others—HC⁴⁺, HC⁵⁺, HC⁶⁺, HC⁷⁺, and HC⁸⁺—were all diamagnetic. Density functional theory (DFT) calculations on the homo[2]catenane were performed in both gas and solution phases, revealing the different binding energies between two CBPQT⁺⁺ rings in the six redox states as a combined result of radical-pairing attractive interactions and Coulombic repulsive interactions. Notably, from the highly energetic nature of the fully oxidized state, this molecule resisted complete oxidation to HC⁷⁺ in air, but instead existed as an HC⁷⁺/HC⁶⁺ equilibrium mixture under ambient conditions. Consequently, HC⁷⁺ exhibited remarkable air-stability and was isolated as a persistent organic radical. This topologically linked molecule has potential for incorporation into organic radical frameworks, electronic memory devices, semiconductors, and energy storage devices. More recently, we have extended this approach to build up air-stable organic bisradicals,235 as well as densely charged dodecacaticatic [3]catenane and tetraascaticatic [5]catenane,236 thereby enriching this class of molecular links for potential applications in electronic materials.

Applications in catalysis

Molecular knots can serve as good receptors214,237 to recognize guest molecules or ions. This property is capable of advancing efﬁcient catalysis by stabilizing intermediates or transition states during chemical reactions. Leigh et al.238 have exploited catalytic properties of molecular knots. Because a Zn(II)-pentafoil knot can accommodate chloride or bromide anions within its central cavity, this molecular knot can promote (Figure 12a) the hydrolysis of bromodiphenylmethane (Ph₂CHBr) to form Ph₂CHOH by facilitating the cleavage of carbon-halogen bonds and the generation of Ph₂CH⁺ carboxations. Moreover, the Zn(II)-pentafoil knot can also be used for the in situ generation (Figure 12b) of Lewis acidic trityl carboxations, which play the role of a catalyst for Michael additions. The well-deﬁned conformation of the Zn(II)-pentafoil knot proves to be necessary in sustaining this catalytic process. Upon removal of Zn²⁺ ions from the molecular knot, its ability to bind halide ions is switched off, leading to a sharp decline in the catalytic effect, whereas treating the metal-free pentafoil knot with Zn²⁺ ions brings about the recovery of the anion-binding-initiated catalysis. It follows that allosteric regulation, a central part in the feedback loops of enzymatic catalysis, has been reproduced in a synthetic molecular knot. In a similar fashion, Trabolsi et al.239 have also realized C–Br bond activation using a self-assembled trefoil knot.

In an attempt to highlight the advantages of using molecular nanotopology in catalysis, Au-Yeung et al.240 have proposed the strategic use of a [2]catenane ligand in the promotion of highly efﬁcient copper catalysis. The topologically linked ligand enjoys the dual characteristic of robustness and dynamics, favoring the different stages of catalysis. In contrast, the strong mechanical bond between two mechanically interlocked phenanthroline-derived macrocycles within the [2]catenane leads to a coordinatively saturated, stable Cu(I) complex in the resting state. On the other hand, when subjected to reactions, the ﬂexibility of the mechanical bond induces a co-conformational change in the [2]catenane, revealing a transiently open coordination site surrounding the copper center for substrate transformation. Consequently, the responsive and dynamic coordination sphere has endowed the copper catalyst with both high catalytic activity and prolonged lifetime. The catalytic effect of this system has been tested in the cross-dehydrogenative C(sp³)–O coupling between phenols and bromodicarboxyls, which is not only efﬁcient for a wide scope of substrates but also applicable for gram-scale transformations without a signiﬁcant loss in catalytic activity.

The promise of molecular links and knots in asymmetric catalysis is being increasingly recognized, given their propensity for nanocoﬁnement in addition to topological chirality. Leigh et al.241 have reported the synthesis of a left-handed trefoil knot (Figure 12c) using a chiral tris
(2,6-pyridinedicarboxamide) oligomer as the starting material and an Eu$^{3+}$ ion as the template. The Eu(III)-trefoil knot of single-handedness is an effective catalyst for asymmetric Mukaiyama aldol reactions between aromatic aldehydes and silyl enol ethers, leading to an enantiomeric excess (ee) of 66%. Besides the transition metal catalysis, Niemeyer et al.\textsuperscript{241} have extended the use of molecular nanotopology to asymmetric organocatalysis, by constructing a catenated Brønsted acid catalyst (Figure 12d) featuring two chiral 1,1'$'$-binaphthyl-phosphoric acids. Compared with the non-interlocked macrocyclic and acyclic analogues, this [2]catenane catalyst exhibits excellent stereoselectivity—up to 98% ee—in the transfer hydrogenation of a variety of 2-substituted quinolines in the presence of Hantzsch esters. Mechanistic studies by DFT calculations reveal that the topological link associated with the [2]catenane not only ensures a high local concentration of catalytically active phosphoric acid groups but also allows their suitable relative orientation, facilitating the formation of a compact sandwich-type transition state in a stereoselective manner.

Biomedical applications

Although the topological entanglements existing in DNA and proteins are believed to play important roles in their physiological functions, the development of synthetic molecular links and knots for biomedical applications remains rare. A recent investigation by Leigh et al.\textsuperscript{57} have probed (Figure 13a) the use of a Fe(II)-coordinated Star of David [2]catenane and a Fe(II)-pentafol knot for transporting anions across phospholipid bilayers. Various factors that influence the ion-transport efficacy have been investigated by conducting comparative studies.
Firstly, the constitution of the molecular link and knot has a large influence on this process. For example, the Fe(II)-coordinated Star of David [2]catenane, formed by a hexameric cyclic precursor, acts as a much better ion channel than the Fe(II)-pentafoil knot and the conformational restrictions relative to the metal-free Star of David [2]catenane and the non-interlocked cyclic hexameric Fe(II)-helicate. This dramatic difference in properties, resulting from subtle structural changes, highlights the
necessity of the conformational restrictions imposed by the nanotopology that graces molecular links and knots.

The application of MIMs in chemotherapeutics has been explored by Trabolsi et al., who have used five kinds of metal-templated trefoil knots (M-TKs) as vesicles (Figure 13b) to deliver different metal ions—including Zn\(^{2+}\), Cd\(^{2+}\), Cu\(^{2+}\), Fe\(^{3+}\), and Mn\(^{2+}\)—to cancer cells, resulting in selective in vitro and in vivo antiproliferative effects. These MIMs, which are stable under physiological conditions and well-tolerated by normal cells, exhibit potent cytotoxicities against both zebrafish embryos and human cancer cells. The half-maximum lethal doses (LD\(_{50}\)) of M-TKs (4–8 \(\mu\)M) have been found to be an order of magnitude lower than that of cisplatin (250 \(\mu\)M), a commercial antitumor drug of long-standing. Detailed mechanistic studies indicate that energy-demanding endocytosis, rather than passive diffusion, serves as the main pathway for the cellular uptake of these MIMs. This kind of internalization is more active in cancer cells than in normal cells, providing a good explanation for the cancer-selective toxicity and minimal side effects. After entering the cells, the M-TKs undergo rapid hydrolysis in the acidic environment of lysosomes and release their metal ions for the generation of reactive oxygen species, thereby leading to damage to the mitochondria and initiating cell apoptosis. This elegant piece of research has demonstrated the utility of topologically nontrivial molecules as yet another class of antitumor agents.

**Outlook**

The past three decades have witnessed rapid growth in the rational design of ways to make MIMs. A wealth of prime and composite knots and links, as well as interwoven frameworks, have been synthesized and fully characterized during the past few years. The initial investigations of these topological molecules bode well for them having a promising future in contemporary chemistry and as precursors for making smart new materials. We expect molecular nanotopology to evolve even more rapidly and establish state-of-the-art frontiers in chemistry, as well as in medical and materials sciences. Looking to the future, these advances will change the scientific landscape and motivate forward-thinking molecular topologists to develop interdisciplinary research, both in relation to the fundamental science, and in forging advanced applications.

Reflecting on the examples of molecular links and knots in nature, we expect to learn how and why life has evolved to code for complex (supra)molecular structures in living cells. During the replication of the kDNA network, for example, a catenane is formed after the daughter rings become segregated from one another, while covalent closure occurs only after all the rings have been replicated from their progenitorial rings. The organization that leads to a network makes it possible for essential rings to be present in low numbers of copies without placing them at risk of rapid loss. Chemists should focus on mimicking nature’s mechanisms, honed by evolution, to design and create yet more topologically complex molecules.

With the advent of up-to-the-minute synthetic strategies, the directed synthesis of molecular links and knots is now available. To expand the reach of molecular nanotopology, uncovering easier ways of introducing more complexity into the topologies of molecules is needed. Only a very few of the six billion prime knots tabulated by mathematicians to date have been synthesized by chemists from easily accessible molecular building blocks. There is a vast area of molecular space remaining to be explored. Advanced methods of templation and innovative strategies for the synthesis of molecules with intricate topologies need to be invented and developed. Largely unexplored noncovalent bonding interactions, such as radical-templation, would certainly be worthy of planned and careful scouting. The divergent knotting strategy that was introduced recently by Leigh et al., is undoubtedly not only useful but also highly efficient for constructing selectively different topologies from single-molecule strands.

Beyond the synthetic challenges lies the study of the functions of those molecules that are topologically well-defined. We have arrived at the point where their properties can be investigated in much more detail. It is well-recognized that the particular topologies associated with links and knots have assumed important functions in the macroscopic world. A similar situation must surely exist at the molecular level. Identifying topological isomers should be helpful in linking particular topologies to specific properties and functions. Tying strands, which will result in an increase in local bulk, while introducing topological chirality into molecules will become center-stage in chemistry. Recently, empirical investigations have been conducted to unravel how tightness and chiral expression can be influenced by the topology of a molecule. Leigh et al. have shown that the chiral expression in a nanoscale knot can invert reversibly the chiral organization of cholesteric liquid crystals on the centimeter scale, that is, chiral amplification can span over seven orders of scalar magnitude. Chemical topology has attracted the interest of chemists like Itami et al., who have observed the phenomenon of conformational dynamics—a snake-like reptation in a spectacular all-benzene trefoil knot. It is now reasonable to believe molecular nanotopology will deliver more and more surprises in the years ahead.

In relation to the topologies present in DNA and proteins, the answer to the question “what are topologies in biological systems really used for?” remains obscure. Tying DNA strands and proteins into links and knots is obviously a way to reduce the degrees of freedom enjoyed by their chains. As a result, specific
conformations are accessible to perform useful tasks that would otherwise be inaccessible by their counterparts without topological constraints. During the process of exploring the roles played by topological DNA and proteins, more nature-mimicking functions will be discovered.

Nanoconfinement and robust dynamics within the context of molecular nanotopology in aqueous solution offer many opportunities to elevate research on synthetic enzymes to much higher levels with improved performances in terms of substrate specificities, reaction rates, and product selectivities—including enantioselectivities—than what have been the outcome when studying enzyme analogues in the past.

The high selectivities expressed in natural macromolecules provide infinite possibilities for creating transformative examples that exhibit molecular nanotopology. Recently, Zhang et al. have developed additional programmable, autonomous, and high-yielding ligation tools, making it possible to access a wide variety of protein topologies. Topologically isomeric proteins show little influence on their 3D structure and function, but their stability and resistance can be increased dramatically. With this newfound control over functional macromolecules, the door to a brand-new era of chemical biology is opening to researchers.

Reflecting on the historical trajectory that brought mechanical bonds, chemical topology, and MIMs into the reach of chemists, more rapid progress in the production of molecular links and knots can be anticipated over the next few years. The much wider range of stereochemical options—for example, axial, planar, and helical chirality, that becomes possible in MIMs—and can be enhanced by the introduction of topology—will eventually be applied in the design of smart new materials and molecular devices with emergent properties. When scientists discover how topology can be as useful at the molecular and nanoscale levels as it has been, and continues to be, in our daily lives in the macroscopic world, we believe that more fundamental science and potential applications will begin to emerge in the not-too-distant future. We are witnessing the dawning of a brand-new era in chemistry where, more than ever, invention and innovation will be limited only by the extent of our imaginations and a burning desire to be creative in the practice of chemistry.

Additions and Corrections

The authors would like add two important references that were published following online publication of this Mini Review.

a. Carpenter, J. P.; Mcternan, C. T.; Greenfield, J. L.; Lavendomme, R.; Ronson, T. K.; and Nitschke, J. R. Controlling the Shape and Chirality of an Eight-Crossing Molecular Knot. *Chem.*, 2021, 7, 1534–1543.

b. Zhang, L. New Synthetic Strategies Hold Promise for the Future of Molecular Nanotopology. *Chem.*, 2021, 7, 1407–1409.

These additions were made post publication on Jul. 5, 2021. All authors on the article are aware of and agree with the changes.

Conflicts of Interest

The authors declare no competing interests.

Acknowledgments

The authors thank Northwestern University for financial support. The authors would also like to thank Professors Jon Buees, David Leigh, Jeremy Sanders, and Jean-Pierre Sauvage for providing us with their additions to and comments on the manuscript during the final stages of its production.

References

1. Seeman, N. C. DNA Nanotechnology: Novel DNA Constructions. *Annu. Rev. Biophys. Biomol. Struct.* 1998, 27, 225–248.
2. Seeman, N. C. Nucleic Acid Nanostructures and Topology. *Angew. Chem. Int. Ed.* 1998, 37, 3220–3238.
3. Summers, D. W. DNA Knots: Theory and Experiments. *Progr. Theor. Phys. Suppl.* 2011, 191, 1–19.
4. Summers, D. W. DNA, Knots and Tangles. In *The Mathematics of Knots: Theory and Application*; Banagl, M., Vogel, D., Eds.; Springer: Berlin, Heidelberg, 2011; pp 327–353.
5. Bucka, A.; Stasiak, A. Construction and Electrophoretic Migration of Single-Stranded DNA Knots and Catenanes. *Nucleic Acids Res.* 2002, 30, e24.
6. Sulkowska, J. I.; Rawdon, E. J.; Millett, K. C.; Onuchic, J. N.; Stasiak, A. Conservation of Complex Knotting and Slipknotting Patterns in Proteins. *Proc. Natl. Acad. Sci. U. S. A.* 2012, 109, E1715–E1723.
7. Taylor, W. R. A Deeply Knotted Protein Structure and How It Might Fold. *Nature* 2000, 406, 916–919.
8. Taylor, W. R.; Lin, K. Protein Knots: A Tangled Problem. *Nature* 2003, 421, 25.
9. Cao, Z.; Roszak, A. W.; Gourlay, L. J.; Lindsay, J. G.; Isaacs, N. W. Bovine Mitochondrial Peroxiredoxin III Forms a Two-Ring Catenane. *Structure* 2005, 13, 1661–1664.
10. Dabrowski-Tumanski, P.; Sulkowska, J. I. Topological Knots and Links in Proteins. *Proc. Natl. Acad. Sci. U. S. A.* 2017, 114, 3415–3420.
11. Wang, X.-W.; Zhang, W.-B. Chemical Topology and Complexity of Protein Architectures. *Trends Biochem. Sci.* 2018, 43, 806–817.
12. Flapan, E.; He, A.; Wong, H. Topological Descriptions of Protein Folding. *Proc. Natl. Acad. Sci. U. S. A.* 2019, 116, 9360–9369.
13. Jaromilcinska, A. I.; Perlinska, A. P.; Runkel, R.; Trefz, B.; Ginn, H. M.; Virlau, P.; Sukowska, J. I. Proteins’ Knotty Problems. J. Mol. Biol. 2019, 431, 244–257.
14. Wikoff, W. R.; Liljas, L.; Duda, R. L.; Tsuruta, H.; Hendrix, R. W.; Johnson, J. E. Topologically Linked Protein Rings in the Bacteriophage HK97 Capsid. Science 2000, 289, 2129–2133.
15. Schappacher, M.; Defieux, A. Imaging of Catenated, Figure-of-Eight, and Trefoil Knot Polymer Rings. Angew. Chem. Int. Ed. 2009, 48, 5930–5933.
16. Frank-Kamenetskii, M. D.; Lukashin, A. V.; Vologodskii, A. V. Statistical Mechanics and Topology of Polymer Chains. Nature 1975, 258, 398–402.
17. Saltia, A. M.; Soper, P. D.; Wasserman, E.; Klein, M. L. Influence of a Knot on the Strength of a Polymer Strand. Nature 1999, 399, 46–48.
18. Bruns, C. J.; Stoddart, J. F. The Nature of the Mechanical Bond: From Molecules to Machines. Wiley: Hoboken, NJ, 2016.
19. Stoddart, J. F. Mechanically Interlocked Molecules (MIMs)—Molecular Shuttles, Switches, and Machines (Nobel Lecture). Angew. Chem. Int. Ed. 2017, 56, 11094–11125.
20. Sluymans, D.; Stoddart, J. F. The Burgeoning of Mechanically Interlocked Molecules in Chemistry. Trends Chem. 2019, 1, 185–197.
21. Forgan, R. S.; Sauvage, J.-P.; Stoddart, J. F. Chemical Topology: Complex Molecular Knots, Links, and Entanglements. Chem. Rev. 2011, 111, 5434–5464.
22. Stoddart, J. F. The Chemistry of the Mechanical Bond. Chem. Soc. Rev. 2009, 38, 1802–1820.
23. Stoddart, J. F.; Colquhoun, H. M. Big and Little Meccano. Tetrahedron 2008, 64, 8231–8263.
24. Dietrich-Buchecker, C. O.; Sauvage, J.-P.; Kintzinger, J.-P. Une Nouvelle Famille de Molecules: Les Metallo-Catennanes. Tetrahedron Lett. 1983, 24, 5095–5098.
25. Ashton, P. R.; Goodnow, T. T.; Kaifer, A. E.; Reddington, M. V.; Slawin, A. M. Z.; Spencer, N.; Stoddart, J. F.; Vicent, C.; Williams, D. J. A [2]Catenane Made to Order. Angew. Chem. Int. Ed. Engl. 1989, 28, 1396–1399.
26. Stoddart, J. F.; Dietrich-Buchecker, C. O.; Sauvage, J.-P. A Synthetic Molecular Trefoil Knot. Angew. Chem. Int. Ed. 2000, 39, 1083–1088.
27. Fielden, S. D. P.; Leigh, D. A.; Woltering, S. L. Molecular Knots. Angew. Chem. Int. Ed. 2017, 56, 11166–11194.
28. Stoddart, J. F. Dawning of the Age of Molecular Nano-topology. Nano Lett. 2020, 20, 5597–5600.
29. Leigh, D. A.; Schaufelberger, F.; Pirvu, L.; Stenlid, J. H.; August, D. P.; Segard, J. Tying Different Knots in a Molecular Strand. Nature 2020, 584, 562–568.
30. Katsonis, N.; Lancia, F.; Leigh, D. A.; Pirvu, L.; Ryabchun, A.; Schaufelberger, F. Knotting a Molecular Strand Can Invert Macroscopic Effects of Chirality. Nat. Chem. 2020, 12, 939–944.
31. Inomata, Y.; Sawada, T.; Fujita, M. Metal-Peptide Torus Knots from Flexible Short Peptides. Chem 2020, 6, 294–303.
32. Sawada, T.; Inomata, Y.; Shimokawa, K.; Fujita, M. A Metal-Peptide Capsule by Multiple Ring Threading. Nat. Commun. 2019, 10, 5687.
33. Zhang, L.; Stephens, A. J.; Nussbaumer, A. L.; Lemonnier, J. F.; Jurček, P.; Vitorica-Yzpeabal, I. J.; Leigh, D. A. Stereoselective Synthesis of a Composite Knot with Nine Crossings. Nat. Chem. 2018, 10, 1083–1088.
34. Harrison, I. T. The Effect of Ring Size on Threading Reactions of Macrocycles. J. Chem. Soc. Chem. Commun. 1972, 231–232.
35. Raymo, F. M.; Houk, K. N.; Stoddart, J. F. The Mechanism of the Slippage Approach to Rotaxanes. Origin of the “Allor-Nothing” Substituent Effect. J. Am. Chem. Soc. 1998, 120, 9318–9322.
36. Ashton, P. R.; Belohradsky, M.; Philip, D.; Stoddart, J. F. Slippage—An Alternative Method for Assembling [2] Rotaxanes. J. Chem. Soc. Chem. Commun. 1993, 1269–1274.
37. Frisch, H.; Martin, I.; Mark, H. Zur Struktur der Polysiloxene. I. Monatsh. Chem 1953, 84, 250–256.
38. Alexander, J. W.; Briggs, G. B. On Types of Knotted Curves. Ann. Math. 1926, 28, 562–586.
39. Nierengarten, J. F.; Dietrich-Buchecker, C. O.; Sauvage, J.-P. Synthesis of a Doubly Interlocked [2]Catenane. J. Am. Chem. Soc. 1994, 116, 375–376.
40. Dietrich-Buchecker, C. O.; Sauvage, J.-P. A Synthetic Molecular Trefoil Knot. Angew. Chem. Int. Ed. Engl. 1989, 28, 189–192.
41. Stoddart, J. F. The Master of Chemical Topology. Chem. Rev. 2009, 38, 1521–1529.
42. Ayme, J. F.; Beves, J. E.; Campbell, C. J.; Leigh, D. A. Template Synthesis of Molecular Knots. Chem. Soc. Rev. 2013, 42, 1700–1712.
43. Frisch, H.; Martin, I.; Mark, H. Zur Struktur der Polysiloxene. II. Ann. Math. 1927, 29, 232–239.
44. Stoddart, J. F. Dawning of the Age of Molecular Nano-topology. Nano Lett. 2020, 20, 5597–5600.
45. Leigh, D. A.; Schaufelberger, F.; Pirvu, L.; Stenlid, J. H.; August, D. P.; Segard, J. Tying Different Knots in a Molecular Strand. Nature 2020, 584, 562–568.
46. Katsonis, N.; Lancia, F.; Leigh, D. A.; Pirvu, L.; Ryabchun, A.; Schaufelberger, F. Knotting a Molecular Strand Can Invert Macroscopic Effects of Chirality. Nat. Chem. 2020, 12, 939–944.
47. Inomata, Y.; Sawada, T.; Fujita, M. Metal-Peptide Torus Knots from Flexible Short Peptides. Chem 2020, 6, 294–303.
48. Sawada, T.; Inomata, Y.; Shimokawa, K.; Fujita, M. A Metal-Peptide Capsule by Multiple Ring Threading. Nat. Commun. 2019, 10, 5687.
49. Zhang, L.; Stephens, A. J.; Nussbaumer, A. L.; Lemonnier, J. F.; Jurček, P.; Vitorica-Yzpeabal, I. J.; Leigh, D. A. Stereoselective Synthesis of a Composite Knot with Nine Crossings. Nat. Chem. 2018, 10, 1083–1088.
50. Danon, J. J.; Kruger, A.; Leigh, D. A.; Lemonnier, J. F.; Stephens, A. J.; Vitorica-Yzpeabal, I. J.; Woltering, S. L. Braiding a Molecular Knot with Eight Crossings. Science 2017, 355, 159–162.
53. Pentecost, C. D.; Chichak, K. S.; Peters, A. J.; Cave, G. W.; Cantrill, S. J.; Stoddart, J. F. A Molecular Solomon Link. Angew. Chem. Int. Ed. 2007, 46, 218–222.
54. Ayme, J. F.; Beves, J. E.; Leigh, D. A.; McBurney, R. T.; Rissanen, K.; Schultz, D. A. Synthetic Molecular Pentafoil Knot. Nat. Chem. 2011, 4, 15–20.
55. Ponnuswamy, N.; Cougnon, F. B.; Clough, J. M.; Pantos, G. D.; Sanders, J. K. M. Discovery of an Organic Trefoil Knot. Science 2012, 338, 783–785.
56. Ponnuswamy, N.; Cougnon, F. B.; Pantos, G. D.; Sanders, J. K. M. Homochiral and meso Figure Eight Knots and a Solomon Link. J. Am. Chem. Soc. 2014, 136, 8243–8251.
57. August, D. P.; Borsley, S.; Cockroft, S. L.; Della Sala, F.; Leigh, D. A.; Webb, S. J. Transmembrane Ion Channels Formed by a Star of David [2]Catenane and a Molecular Pentafoil Knot. J. Am. Chem. Soc. 2020, 142, 18859–18865.
58. Benyettou, F.; Prakasam, T.; Ramdas Nair, A.; Witzel, II; Alhashimi, M.; Skorjanc, T.; Olsen, J.-C.; Sadler, K. C.; Trabolsi, A. Potent and Selective in vitro and in vivo Antiproliferative Effects of Metal–Organic Trefoil Knots. Chem. Sci. 2019, 10, 5884–5892.
59. Liu, Y.; Ma, Y.; Zhao, Y.; Sun, X.; Gandara, F.; Furukawa, H.; Liu, Z.; Zhu, H.; Zhu, C.; Suena, K.; Oleynikov, P.; Alshammari, A. S.; Zhang, X.; Terasaki, O.; Yaghi, O. M. Weaving of Organic Threads into a Crystalline Covalent Organic Framework. Science 2016, 351, 365–369.
60. Horner, K. E.; Miller, M. A.; Steed, J. W.; Sutcliffe, P. M. Knot Theory in Modern Chemistry. Chem. Soc. Rev. 2016, 45, 6432–6448.
61. Fenlon, E. E. Open Problems in Chemical Topology. Eur. J. Org. Chem. 2008, 2008, 5023–5035.
62. Beves, J. E.; Blight, B. A.; Campbell, C. J.; Leigh, D. A.; McBurney, R. T. Strategies and Tactics for the Metal-Directed Synthesis of Rotaxanes, Knots, Catenanes, and Higher Order Links. Angew. Chem. Int. Ed. 2011, 50, 9260–9327.
63. Gil-Ramirez, G.; Leigh, D. A.; Stephens, A. J. Catenanes: Fifty Years of Molecular Links. Angew. Chem. Int. Ed. 2015, 54, 6110–6150.
64. Schaufelberger, F. Open Questions in Functional Molecular Topology. Commun. Chem. 2020, 3, 182.
65. Amabilino, D. B.; Pérez-García, L. Topology in Molecules Inspired, Seen and Represented. Chem. Soc. Rev. 2009, 38, 1562–1571.
66. Sauvage, J.-P.; Amabilino, D. B. The Beauty of Knots at the Molecular Level. In Beauty in Chemistry: Artistry in the Creation of New Molecules; Fabbriazi, L., Ed.; Springer: Berlin, Heidelberg, 2012; pp 107–125.
67. Wasserman, E. The Preparation of Interlocking Rings: A Catenane. J. Am. Chem. Soc. 1960, 82, 4433–4434.
68. Dietrich-Buchecker, C. O.; Sauvage, J.-P. Interlocking of Molecular Threads: From the Statistical Approach to the Template Synthesis of Catenands. Chem. Rev. 1987, 87, 795–810.
69. Meyer, C. D.; Joiner, C. S.; Stoddart, J. F. Template-Directed Synthesis Employing Reversible Imine Bond Formation. Chem. Soc. Rev. 2007, 36, 1705–1723.
70. Schill, G. Catenanes, Rotaxanes, and Knots; Academic Press: New York, 1971.
71. Schill, G.; Lüttringhaus, A. The Preparation of Catenane Compounds by Directed Synthesis. Angew. Chem. Int. Ed. Engl. 1964, 3, 546–547.
72. Rowan, S. J.; Cantrill, S. J.; Cousins, G. R.; Sanders, J. K. M.; Stoddart, J. F. Dynamic Covalent Chemistry. Angew. Chem. Int. Ed. 2002, 41, 898–952.
73. Furlan, R. L. E.; Otto, S.; Sanders, J. K. M. Supramolecular Templating in Thermodynamically Controlled Synthesis. Proc. Natl. Acad. Sci. U. S. A. 2002, 99, 4801–4804.
74. Corbett, P. T.; Leclaire, J.; Vial, L.; West, K. R.; Wietor, J.-L.; Sanders, J. K. M.; Otto, S. Dynamic Combinatorial Chemistry. Rev. 2006, 106, 3652–3711.
75. Lehn, J.-M. From Supramolecular Chemistry towards Constitutional Dynamic Chemistry and Adaptive Chemistry. Chem. Soc. Rev. 2007, 36, 151–160.
76. Fyfe, M. C. T.; Glink, P. T.; Menzer, S.; Stoddart, J. F.; White, A. J. P.; Williams, D. J. Anion-Assisted Self-Assembly. Angew. Chem. Int. Ed. Engl. 1997, 36, 2068–2070.
77. Chambron, J.-C.; Sauvage, J.-P. Topologically Complex Molecules Obtained by Transition Metal Templation: It Is the Presentation that Determines the Synthesis Strategy. New J. Chem. 2013, 37, 49–57.
78. Aucagne, V.; Hänni, K. D.; Leigh, D. A.; Lusby, P. J.; Walker, D. B. Catalytic “Click” Rotaxanes: A Substoichiometric Metal-Template Pathway to Mechanically Interlocked Architectures. J. Am. Chem. Soc. 2006, 128, 2186–2187.
79. Crowley, J. D.; Goldup, S. M.; Lee, A.-L.; Leigh, D. A.; McBurney, R. T. Active Metal Template Synthesis of Rotaxanes, Catenanes and Molecular Shuttles. Chem. Soc. Rev. 2009, 38, 1530–1541.
80. Denis, M.; Goldup, S. M. The Active Template Approach to Interlocked Molecules. Nat. Rev. Chem. 2017, 1, 0061.
81. Goldup, S. M.; Leigh, D. A.; Lusby, P. J.; McBurney, R. T.; Slawin, A. M. Z. Active Template Synthesis of Rotaxanes and Molecular Shuttles with Switchable Dynamics by Four-Component Pd⁰-Promoted Michael Additions. Angew. Chem. Int. Ed. 2008, 47, 3381–3384.
82. Crowley, J. D.; Hänni, K. D.; Lee, A.-L.; Leigh, D. A. [2]Rotaxanes through Palladium Active-Template Oxidative Heck Cross-Couplings. J. Am. Chem. Soc. 2007, 129, 12092–12093.
83. Berná, J.; Crowley, J. D.; Goldup, S. M.; Hänni, K. D.; Lee, A.-L.; Leigh, D. A. A Catalytic Palladium Active-Metal Template Pathway to [2]Rotaxanes. Angew. Chem. Int. Ed. 2007, 46, 5709–5713.
84. Aucagne, V.; Berná, J.; Crowley, J. D.; Goldup, S. M.; Hänni, K. D.; Lee, A.-L.; Leigh, D. A. A Catalytic Palladium Active-Metal Template Pathway to [2]Rotaxanes. Angew. Chem. Int. Ed. 2007, 46, 5709–5713.
85. Yamazaki, R.; Saito, S. Synthesis of [2]Catenanes by Oxidative Intramolecular Diyne Coupling Mediated
by Macrocyclic Copper(!) Complexes. *Angew. Chem. Int. Ed.* 2009, 48, 504–507.
87. Goldup, S. M.; Leigh, D. A.; Long, T.; McGonigal, P. R.; Symes, M. D.; Wu, J. Active Metal Template Synthesis of Catenanes. *J. Am. Chem. Soc.* 2009, 131, 15924–15929.
88. Barran, P. E.; Cole, H. L.; Goldup, S. M.; Leigh, D. A.; McGonigal, P. R.; Symes, M. D.; Wu, J.; Zengerle, M. Active-Metal Template Synthesis of a Molecular Trefoil Knot. *Angew. Chem. Int. Ed.* 2011, 50, 12280–12284.
89. Dietrich-Buchecker, C. O.; Guilhem, J.; Pascard, C.; Sauvage, J.-P. Structure of a Synthetic Trefoil Knot Coordinated to Two Copper(I) Centers. *Angew. Chem. Int. Ed. Engl.* 1990, 29, 1154–11561.
90. Amabilino, D. B.; Ashton, P. R.; Reder, A. S.; Spencer, N.; Stoddart, J. F. Olympiadane. *Angew. Chem. Int. Ed. Engl.* 1994, 33, 1286–1290.
91. Amabilino, D. B.; Ashton, P. R.; Boyd, S. E.; Lee, J. Y.; Menzer, S.; Stoddart, J. F.; Williams, D. J. The Five-Stage Self-Assembly of a Branched Heptacatenane. *Angew. Chem. Int. Ed. Engl.* 1997, 36, 2070–2072.
92. Safarowsky, O.; Nieg, M.; Fröhlich, R.; Vögtle, F. A Molecular Knot with Twelve Amide Groups—One-Step Synthesis. *Crystal Structure, Chirality*. *Angew. Chem. Int. Ed.* 2000, 39, 1616–1618.
93. Hunter, C. A. Synthesis and Structure Elucidation of a New [2]Catenane. *J. Am. Chem. Soc.* 1992, 114, 5303–5311.
94. Vögtle, F.; Meier, S.; Hoss, R. One-Step Synthesis of a Fourfold Functionalized Catenane. *Angew. Chem. Int. Ed. Engl.* 1992, 31, 1619–1622.
95. Johnston, A. G.; Leigh, D. A.; Pritchard, R. J.; Deegan, M. D. Facile Synthesis and Solid-State Structure of a Benzyllic Amide [2]Catenane. *Angew. Chem. Int. Ed. Engl.* 1995, 34, 1209–1212.
96. Cougnon, F. B. L.; Caprice, K.; Pupier, M.; Bauza, A.; Frontera, A. A Strategy to Synthesize Molecular Knots and Links Using the Hydrophobic Effect. *J. Am. Chem. Soc.* 2018, 140, 12442–12450.
97. Zhu, Z.; Bruns, C. J.; Li, H.; Lei, J.; Ke, C.; Liu, Z.; Shafaie, S.; Colquhoun, H. M.; Stoddart, J. F. Synthesis and Solution-State Dynamics of Donor–Acceptor Oligorotaxane Foldamers. *Chem. Sci.* 2013, 4, 1470–1483.
98. Zhu, Z.; Li, H.; Liu, Z.; Lei, J.; Zhang, H.; Botros, Y. Y.; Stern, C. L.; Sarjeant, A. A.; Stoddart, J. F.; Colquhoun, H. M. Oligomeric Pseudorotaxanes Adopting Infinite-Chain Lattice Superstructures. *Angew. Chem. Int. Ed.* 2012, 51, 7231–7235.
99. Boyle, M. M.; Forgan, R. S.; Friedman, D. C.; Gassensmith, J. J.; Smaldone, R. A.; Stoddart, J. F.; Sauvage, J.-P. Donor–Acceptor Molecular Figures-of-Eight. *Chem. Commun.* 2011, 47, 11870–11872.
100. Basu, S.; Coskun, A.; Friedman, D. C.; Olson, M. A.; Benitez, D.; Tkatchouk, E.; Barin, G.; Yang, J.; Fahrenheit, A. C.; Goddard, W. A., III; Stoddart, J. F. Donor–Acceptor Oligorotaxanes Made to Order. *Chem. Eur. J.* 2011, 17, 2017–2019.
101. Lukin, O.; Recker, J.; Böhrer, A.; Müller, W. M.; Kubota, T.; Okamoto, Y.; Nieger, M.; Fröhlich, R.; Vögtle, F. A Topologically Chiral Molecular Dumbbell. *Angew. Chem. Int. Ed.* 2003, 42, 442–445.
102. Guo, J.; Mayers, P. C.; Braeult, G. A.; Hunter, C. A. Synthesis of a Molecular Trefoil Knot by Folding and Closing on an Octahedral Coordination Template. *Nat. Chem.* 2010, 2, 218–222.
103. Adams, H.; Ashworth, E.; Braeult, G. A.; Guo, J.; Hunter, C. A.; Mayers, P. C. Knot Tied around an Octahedral Metal Centre. *Nature 2001*, 411, 763–763.
104. Zhang, G.; Gil-Ramírez, G.; Markevicius, A.; Browne, C.; Vitorica-Yrezabal, I. J.; Leigh, D. A. Lanthanide Template Synthesis of Trefoil Knots of Single Handedness. *J. Am. Chem. Sci.* 2015, 137, 10437–10442.
105. Zhang, L.; August, D. P.; Zhong, J.; Whitehead, G. F. S.; Vitorica-Yrezabal, I. J.; Leigh, D. A. Molecular Trefoil Knot from a Trimeric Circular Helicate. *J. Am. Chem. Sci.* 2018, 140, 4982–4985.
106. Beves, J. E.; Campbell, C. J.; Leigh, D. A.; Pritchard, R. G. Tetrameric Cyclic Double Helicates as a Scaffold for a Molecular Solomon Link. *Angew. Chem. Int. Ed.* 2013, 52, 6464–6467.
107. Ayme, J.-F.; Beves, J. E.; Leigh, D. A.; McBurney, R. T.; Rissanen, K.; Schultz, D. A Synthetic Molecular Pentafoil Knot. *Nat. Chem.* 2012, 4, 15–20.
108. Leigh, D. A.; Pritchard, R. G.; Stephens, A. J. A Star of David Catenane. *Nat. Chem.* 2014, 6, 978–982.
109. Hasenkopf, B.; Lehn, J.-M.; Kneisel, B. O.; Baum, G.; Fenske, D. Self-Assembly of a Circular Double Helicate. *Angew. Chem. Int. Ed.* 1996, 35, 1838–1840.
110. Hasenkopf, B.; Lehn, J.-M.; Boumediene, N.; Dupont-Gervais, A.; Van Dorselaer, A.; Kneisel, B.; Fenske, D. Self-Assembly of Tetra- and Hexanuclear Circular Helicates. *J. Am. Chem. Soc.* 1997, 119, 10956–10962.
111. Hasenkopf, B.; Lehn, J.-M.; Boumediene, N.; Leize, E.; Van Dorselaer, A. Kinetic and Thermodynamic Control in Self-Assembly: Sequential Formation of Linear and Circular Helicates. *Angew. Chem. Int. Ed.* 1998, 37, 3265–3268.
112. Ashton, P. R.; Collins, A. N.; Frye, M. C. T.; Menzer, S.; Stoddart, J. F.; Williams, D. J. Supramolecular Weaving. *Angew. Chem. Int. Ed.* 1997, 36, 735–739.
113. Desiraju, G. R. Supramolecular Synthons in Crystal Engineering—A New Organic Synthesis. *Angew. Chem. Int. Ed. Engl.* 1995, 34, 2311–2327.
114. Nangia, A.; Desiraju, G. R. Supramolecular Synthesis and Pattern Recognition. In |Design of Organic Solids|; Weber, E., Aoyama, Y., Caira, M. R., Desiraju, G. R., Glusker, J. P., Hamilton, A. D., Meléndez, R. E., Nangia, A., Eds.; Springer: Berlin, Heidelberg, 1998, pp 57–95.
115. Ashton, P. R.; Glink, P. T.; Schiavo, C.; Stoddart, J. F.; Chrystal, E. J. T.; Menzer, S.; Williams, D. J.; Tasker, P. A. Doubly Encircled and Double-Stranded Pseudorotaxanes. *Angew. Chem. Int. Ed. Engl.* 1995, 34, 1869–1871.
116. Ashton, P. R.; Collins, A. N.; Frye, M. C. T.; Glink, P. T.; Menzer, S.; Stoddart, J. F.; Williams, D. J. An Interwoven Supramolecular Cage. *Angew. Chem. Int. Ed. Engl.* 1997, 36, 59–62.
117. Li, P.; Chen, Z.; Ryder, M. R.; Stern, C. L.; Guo, Q.-H.; Wang, X.; Farha, O. K.; Stoddart, J. F. Assembly of a Porous Supramolecular Polynknot from Rigid Trigonal
Prismatic Building Blocks. *J. Am. Chem. Soc.* 2019, *141*, 12998–13002.

118. Whang, D.; Kim, K. Polycatenated Two-Dimensional Polyrotaxane. *Nat. J. Am. Chem. Soc.* 1997, *119*, 451–452.

119. Lewandowska, U.; Zajaczkowski, W.; Corra, S.; Tanabe, J.; Borrman, R.; Benetti, E. M.; Stappert, S.; Watanabe, K.; Ochs, N. A. K.; Schaebelin, R.; Li, C.; Yashima, E.; Pisula, W.; Mülken, K.; Wennemers, H. A Triaxial Supramolecular Weave. *Nat. Chem.* 2017, *9*, 1068–1072.

120. Dawe, L. N.; Abedin, T. S. M.; Thompson, L. K. Ligand Directed Self-Assembly of Polymeric [n x n] Grids: Racional Routes to Large Functional Molecular Subunits? *Dalton Trans.* 2008, *13*, 1661–1675.

121. Ruben, M.; Rojo, J.; Romero-Salgueiro, F. J.; Uppadine, L. H.; Lhein, J.-M. Grid-Type Metal Ion Architectures: Functional Metallosupramolecular Arrays. *Angew. Chem. Int. Ed.* 2004, *43*, 3644–3662.

122. Hubin, T. J.; Busch, D. H. Template Routes to Interlocked Molecular Structures and Orderly Molecular Entanglements. *Coord. Chem. Rev.* 2000, *200–202*, 5–52.

123. Leigh, D. A.; Danon, J. J.; Fielden, S. D. P.; Lemonnier, J. F.; Whitehead, G. F. S.; Woltering, S. L. A Molecular Endless (7+)* Knot. *Nat. Chem.* 2021, *13*, 117–122.

124. August, D. P.; Dryfe, R. A. W.; Haigh, S. J.; Kent, P. R. C.; Leigh, D. A.; Lemonnier, J.-F.; Li, Z.; Muryn, C. A.; Palmer, L. I.; Song, Y.; Whitehead, G. F. S.; Young, R. J. Self-Assembly of a Layered Two-Dimensional Molecularly Woven Fabric. *Nature* 2020, *588*, 429–435.

125. Beves, J. E.; Danon, J. J.; Leigh, D. A.; Lemonnier, J. F.; Vitorica-Yrezabal, I. A. Solomon Link through an Interwoven Molecular Grid. *Angew. Chem. Int. Ed.* 2015, *54*, 7555–7559.

126. Yaghi, O. M. Reticular Chemistry in All Dimensions. *ACS Cent. Sci.* 2019, *5*, 1295–1300.

127. Yaghi, O. M.; Kalmutzki, M. J.; Diercks, C. S. Introduction to Reticular Chemistry: Metal-Organic Frameworks and Cooperative Organic Frameworks. *Wiley: Weinheim*, 2019.

128. Zhao, Y.; Guo, L.; Gandara, F.; Ma, Y.; Liu, Z.; Zhu, C.; Lyu, H.; Trickett, C. A.; Kapustin, E. A.; Terasaki, O.; Yaghi, O. M. A Synthetic Route for Crystals of Woven Structures, Uniform Nanocrystals, and Thin Films of Imine Covalent Organic Frameworks. *J. Am. Chem. Soc.* 2017, *139*, 13166–13172.

129. Liu, Y.; Diercks, C. S.; Ma, Y.; Lyu, H.; Zhu, C.; Alshimiri, S. A.; Alshihri, S.; Yaghi, O. M. 3D Covalent Organic Frameworks of Interlocking 3D Square Ribbons. *J. Am. Chem. Soc.* 2019, *141*, 677–683.

130. Liu, Y.; Ma, Y.; Yang, J.; Diercks, C. S.; Tamura, N.; Jin, F.; Yaghi, O. M. Molecular Weaving of Covalent Organic Frameworks for Adaptive Guest Inclusion. *J. Am. Chem. Soc.* 2018, *140*, 16015–16019.

131. Konnert, J.; Britton, D. The Crystal Structure of AgC(CN)2. *Inorg. Chem. 1966*, 5, 1193–1196.

132. Biradha, K.; Fujita, M. A Springlike 3D-Coordination Network That Shrinks or Swells in a Crystal-to-Crystal Manner Upon Guest Removal or Readsorption. *Angew. Chem. Int. Ed.* 2002, *41*, 3392–3395.

133. Blatov, V. A.; Carlucci, L.; Ciani, G.; Proserpio, D. M. Intercalating Metal-Organic and Inorganic 3D Networks: A Computer-Aided Systematic Investigation. Part I. Analysis of the Cambridge Structural Database. *CrystEngComm* 2004, *6*, 377–395.

134. Kitaura, R.; Seki, K.; Akiyama, G.; Kitagawa, S. Porous Coordination-Polymer Crystals with Gated Channels Specif- ic for Supercritical Gases. *Angew. Chem. Int. Ed.* 2003, *42*, 428–431.

135. Kesanli, B.; Cui, Y.; Smith, M. R.; Bittner, E. W.; Bockrath, B. C.; Lin, W. B. Highly Interpenetrated Metal-Organic Frameworks for Hydrogen Storage. *Angew. Chem. Int. Ed.* 2005, *44*, 72–75.

136. Sun, D.; Ma, S.; Ke, Y.; Collins, D. J.; Zhou, H.-C. An Interweaving MOF with High Hydrogen Uptake. *J. Am. Chem. Soc.* 2006, *128*, 3896–3897.

137. Batten, S. R.; Robson, R. Intercrinating Nets: Ordered, Periodic Entanglement. *Angew. Chem. Int. Ed. Engl.* 1998, *37*, 1460–1494.

138. Sikdar, N.; Bonakala, S.; Haldar, R.; Balasubramanian, S.; Maji, T. K. Dynamic Entangled Porous Framework for Hydro- carbon (C2–C3) Storage, CO2 Capture, and Separation. *Chem. Eur. J.* 2016, *22*, 6059–6070.

139. Nugent, P.; Belmbakhout, Y.; Burd, S. D.; Cairns, A. J.; Luebbe, R.; Forrest, K.; Pham, T.; Ma, S.; Space, B.; Wojtas, L. Porous Materials with Optimal Adsorption Thermodynamics and Kinetics for CO2 Separation. *Nature* 2013, *495*, 80–84.

140. Kim, H.; Das, S.; Kim, M. G.; Dbytsev, D. N.; Kim, Y.; Kim, K. Synthesis of Phase-Pure Interpenetrated MOF-5 and its Gas Sorption Properties. *Inorg. Chem.* 2011, *50*, 3691–3696.

141. Mulford, K. L.; Farha, O. K.; Malikas, C. D.; Kanatzidis, M. G.; Hupp, J. T. An Interpenetrated Framework Material with Hysteretic CO2 Uptake. *Chem. Eur. J.* 2010, *16*, 276–281.

142. Thallapally, P. K.; Tian, J.; Radha Kishan, M.; Hernandez, C. A.; Dalgarno, S. J.; Mcgrail, P. B.; Warren, J. E.; Atwood, J. L. Flexible (Breathing) Intercalating Metal–Organic Frameworks for CO2 Separation Applications. *J. Am. Chem. Soc.* 2008, *130*, 16842–16843.

143. Ma, S.; Sun, D.; Ambrogio, M.; Filling, J. A.; Parkin, S.; Zhou, H.-C. Framework-Catenation Isomerism in Metal–Organic Frameworks and Its Impact on Hydrogen Uptake. *J. Am. Chem. Soc.* 2007, *129*, 1858–1859.

144. Shekhab, O.; Wang, H.; Paradinas, M.; Ocal, C.; Schüpbach, B.; Terfort, A.; Zacher, D.; Fischer, R. A.; Wöll, C. Controlling Intercalation in Metal–Organic Frameworks by Liquid-Phase Epitaxy. *Nat. Mater.* 2009, *8*, 481–484.

145. Jiang, H.-L.; Makal, T. A.; Zhou, H.-C. Intercalation Control in Metal–Organic Frameworks for Functional Applications. *Coord. Chem. Rev.* 2013, *257*, 2232–2249.

146. Liu, Y.; O’Keeffe, M.; Treacy, M. M. J.; Yaghi, O. M. The Geometry of Periodic Knots, Polycatenanes and Weaving from a Chemical Perspective: A Library for Reticular Chem- istry. *Chem. Soc. Rev.* 2018, *47*, 4642–4646.

147. Prakasam, T.; Lusi, M.; Elhabiri, M.; Platas-Iglesias, C.; Olsen, J.-C.; Asfari, Z.; Cianférani-Sanglier, S.; Debaene, F.; Charbonnière, L. J.; Forrest, S. E.; Trabolsi, A. Simultaneous Self-Assembly of a [2]Catenane, a Trefoil Knot, and a Solomon Link from a Simple Pair of Ligands. *Angew. Chem. Int. Ed.* 2013, *52*, 9956–9960.

148. Meyer, C. D.; Forgan, R. S.; Chichak, K. S.; Peters, A. J.; Tangchaivang, N.; Cave, G. W.; Khan, S. I.; Cantrill, S. J.;
Stoddart, J. F. The Dynamic Chemistry of Molecular Borromean Rings and Solomon Knots. *Chem. Eur. J.* 2010, 16, 12570–12581.

149. Thorp-Greenwood, F. L.; Kulak, A. N.; Hardie, M. J. An Infinite Chainmail of M2L4 Metallacycles Featuring Multiple Borromean Links. *Nat. Chem.* 2015, 7, 526–531.

150. Huang, S. L.; Lin, Y. J.; Li, Z. H.; Jin, G. X. Self-Assembly of Molecular Borromean Rings from Bimetallic Coordination Rectangles. *Angew. Chem. Int. Ed.* 2014, 53, 11218–11222.

151. Huang, S.-L.; Lin, Y.-J.; Hor, T. A.; Jin, G.-X. Cp*Rh-Based Heterometallic Metallarectangles: Size-Dependent Borromean Link Structures and Catalytic Acyl Transfer. *J. Am. Chem. Soc.* 2013, 135, 8125–8128.

152. Loren, J. C.; Yoshizawa, M.; Haldimann, R. F.; Linden, A.; Siegel, J. S. Synthetic Approaches to a Molecular Borromean Link: Two-Ring Threading with Polypyridine Templates. *Angew. Chem. Int. Ed.Engl.* 2003, 42, 5702–5705.

153. Dolomanov, O. V.; Blake, A. J.; Chynapse, N. R.; Schröder, M.; Wilson, C. A Novel Synthetic Strategy for Hexanuclear Supramolecular Architectures. *Chem. Commun.* 2003, 682–683.

154. Schouwes, C.; Holstein, J. J.; Scopelliti, R.; Zhurov, K. O.; Nagornov, K. O.; Tsybin, Y. O.; Smart, O. S.; Briekigie, G.; Severin, K. Self-Assembly of a Giant Molecular Soliton Link from 30 Subcomponents. *Angew. Chem. Int. Ed.* 2014, 53, 11261–11265.

155. Peinador, C.; Blaco, V.; Quintela, J. M. A New Doubly Interlocked [2]Catenane. *J. Am. Chem. Soc.* 2009, 131, 920–921.

156. Fujita, M.; Tomina, M.; Hori, A.; Therrien, B. Coordination Assemblies from a Pd(II)-Cornered Square Complex. *Acc. Chem. Res.* 2005, 38, 369–378.

157. McCrudi, C. P.; Vittal, J. J.; Pudpehaff, R. J. Molecular Topology: Easy Self-Assembly of an Organometallic Doubly Braided [2]Catenane. *Angew. Chem. Int. Ed.* 2000, 39, 3819–3822.

158. Fujita, M.; Ibusuku, F.; Hagihiara, H.; Ogura, K. Quantitative Self-Assembly of a [2]Catenane from Two Preformed Molecular Rings. *Nature* 1994, 367, 720–723.

159. Sawada, T.; Saito, A.; Tamiya, K.; Shimokawa, K.; Hisada, Y.; Fujita, M. Metal–Peptide Rings Form Highly Entangled Topologically Inequivalent Frameworks with the Same Ring- and Crossing-Numbers. *Nat. Commun.* 2019, 10, 921.

160. Gao, W.-X.; Feng, H.-J.; Guo, B.-B.; Lu, Y.; Jin, G.-X. Coordination-Directed Construction of Molecular Links. *Chem. Rev. 2020, 120, 6288–6325.

161. Lu, Y.; Liu, D.; Lin, Y.-J.; Li, Z.-H.; Jin, G.-X. Self-Assembly of Metalla[3]Catenanes, Borromean Rings and Ring-in-Ring Complexes Using a Simple α-Donor Unit. *Nat. Sci. Rev.* 2020, 7, 1548–1556.

162. Dang, L.-L.; Feng, H.-J.; Lin, Y.-J.; Jin, G.-X. Self-Assembly of Molecular Figure-Eight Knots Induced by Quadruple Stacking Interactions. *J. Am. Chem. Soc.* 2020, 142, 18946–18954.

163. Cui, P.-F.; Lin, Y.-J.; Li, Z.-H.; Jin, G.-X. Dihydrogen Bond Interaction Induced Separation of Hexane Isomers by Self-Assembled Carbaborane Metallacycles. *J. Am. Chem. Soc.* 2020, 142, 8532–8538.

164. Zhang, H.-N.; Lin, Y.-J.; Jin, G.-X. Selective Construction of Very Large Stacking-Interaction-Induced Molecular 818 Metalla-Knots and Borromean Ring Using Curved Dipyridyl Ligands. *J. Am. Chem. Soc.* 2021, 143, 1119–1125.

165. Rizzuto, F. J.; Trinh, T.; Sleiman, H. F. Molecular Printing with DNA Nanotechnology. *Chem. 2020, 6, 1560–1574.

166. Platnich, C. M.; Rizzuto, F. J.; Rosa, G.; Sleiman, H. F. Single-Molecule Methods in Structural DNA Nanotechnology. *Chem. Soc. Rev.* 2020, 49, 4220–4233.

167. Seeman, N. C.; Sleiman, H. F. DNA Nanotechnology. *Nat. Rev. Mater.* 2017, 3, 17068.

168. Mao, C.; Sun, W.; Seeman, N. C. Assembly of Borromean Rings from DNA. *Nature 1997, 386, 137–138.

169. Ciengshin, T.; Sha, R.; Seeman, N. C. Automatic Molecular Weaving Prototyped by Using Single-Stranded DNA. *Angew. Chem. Int. Ed. 2011, 50, 4419–4422.

170. Watson, J. D.; Crick, F. H. C. Molecular Structure of Nucleic Acids: A Structure for Deoxyribosie Nucleic Acid. *Nature 1953, 171, 737–738.

171. Navashin, M. S. *Unbalanced Somatic Chromosomal Variation in Crepis;* University of California Press: Berkeley, CA, 1930; Vol. P6(3).

172. McClintock, B. A. Correlation of Ring-Shaped Chromosomes with Variegation in Zea Mays. *Proc. Natl. Acad. Sci. U. S. A.* 1932, 18, 677–681.

173. Radloff, R.; Bauer, W.; Vinograd, J. A. Dye-Buoyant-Density Method for the Detection and Isolation of Closed Circular Duplex DNA: The Closed Circular DNA in Hela Cells. *Proc. Natl. Acad. Sci. U. S. A.* 1957, 57, 1514–1521.

174. Hudson, B.; Vinograd, J. Catenated Circular DNA Molecules in Hela Cell Mitochondria. *Nature 1967, 216, 647–652.

175. Clayton, D. A.; Vinograd, J. Circular Dimer and Catenate Forms of Mitochondrial DNA in Human Leukaemic Leucocytes. *Nature 1967, 216, 652–657.

176. Sundin, O.; Varshavsky, A. Terminal Stages of SV40 DNA Replication Proceed via Multiply Intertwined Catenated Dimers. *Cell 1980, 21, 103–114.

177. Englund, P. T.; Hajduk, S. L.; Mari, J. C. The Molecular Biology of Trypanosomases. *Annu. Rev. Biochem.* 1982, 51, 695–726.

178. Englund, P. T. The Replication of Kinetoplast DNA Network in *Crithidia fasciculata*. *Cell 1978, 14, 157–168.

179. Lukaš, J.; Jys Guibride, D.; Votyčka, J.; Ziková, A.; Benne, R.; Englund, P. T. Kinetoplast DNA Network: Evolution of an Improbable Structure. *Eukaryot. Cell 2002, 1, 495–502.

180. Klingbeil, M. M.; Drew, M. E.; Liu, Y.; Morris, J. C.; Motyk, S. A.; Saxowsky, T. T.; Wang, Z.; Englund, P. T. Unlocking the Secrets of Trypanosomse Kinetoplast DNA Network Replication. *Protist 2001, 152, 255–262.

181. Shapiro, T. A.; Englund, P. T. The Structure and Replication of Kinetoplast DNA. *Annu. Rev. Microbiol.* 1995, 49, 117–143.

182. Chen, J.; Rauchen, C. A.; White, J. H.; Englund, P. T.; Cozzarelli, N. R. The Topology of the Kinetoplast DNA Network. *Cell 1995, 80, 61–69.

183. Klingbeil, M. M.; Englund, P. T. Closing the Gaps in Kinetoplast DNA Network Replication. *Proc. Natl. Acad. Sci. U. S. A.* 2004, 101, 4333–4334.
MINI REVIEW

184. Liang, C.; Mislow, K. Topological Features of Protein Structures: Knots and Links. J. Am. Chem. Soc. 1995, 117, 4201-4213.

185. Mansfield, M. L. Are There Knots in Proteins? Nat. Struct. Biol. 1994, 1, 213-214.

186. Liang, C.; Mislow, K. Knots in Proteins. J. Am. Chem. Soc. 1994, 116, 11895-1190.

187. Takusagawa, F.; Kamitori, S. A Real Knot in Protein. J. Am. Chem. Soc. 1996, 118, 8945-8946.

188. Dabrowski-Tumanski, P.; Sulkowska, J. I. To Tie or Not to Tie? That Is the Question. Polymers 2017, 9, 454.

189. Wang, J. C.; Schwartz, H. Noncomplementarity in Base Sequences between the Cohesive Ends of Coliphages 186 and λ and the Formation of Interlocked Rings between the Two DNA’s. Biopolymers 1967, 5, 953-966.

190. Liu, Y.; Wu, W.-H.; Hong, S.; Fang, J.; Zhang, F.; Liu, G.-X.; Seo, J.; Zhang, W.-B. Lasso Proteins: Modular Design, Cellular Synthesis, and Topological Transformation. Angew. Chem. Int. Ed. 2020, 59, 19153-19161.

191. Liu, Y.; Duan, Z.; Fang, J.; Zhang, F.; Xiao, J.; Zhang, W.-B. Cellular Synthesis and X-ray Crystal Structure of a Designed Protein Heterocatenane. Angew. Chem. Int. Ed. 2020, 59, 16122-16127.

192. Da, X.-D.; Zhang, W.-B. Active Template Synthesis of Protein Heterocatenanes. Angew. Chem. Int. Ed. 2019, 58, 11097-11104.

193. Wu, X.-L.; Liu, Y.; Liu, D.; Sun, F.; Zhang, W.-B. An Intrinsically Disordered Peptide–Peptide Stapler for Highly Efficient Protein Ligation Both in Vivo and in Vitro. J. Am. Chem. Soc. 2018, 140, 17474-17483.

194. Zhou, H.-X. Loops, Linkages, Rings, Catenanes, Cages, and Crowders: Entropy-Based Strategies for Stabilizing Proteins. Acc. Chem. Res. 2004, 37, 123-130.

195. Zhou, H.-X. Effect of Catenation on Protein Folding Stability. J. Am. Chem. Soc. 2003, 125, 9280-9281.

196. Wu, Q.; Rauscher, P. M.; Lang, X.; Wojtecki, R. J.; de Pablo, J. J.; Hore, M. J. A.; Rowan, S. J. Poly[n]:catenanes: Synthesis of Molecular Interlocked Chains. Science 2017, 358, 1434-1435.

197. Pirkl, W. H.; Hoekstra, M. S. Chiral Nuclear Magnetic Resonance Solvating Agents. Resolution, Determination of Enantiomeric Purity, and Assignment of Absolute Configuration of Cyclic and Acyclic Sulfinate Esters. J. Am. Chem. Soc. 1976, 98, 1832-1839.

198. Dietrich-Buchecker, C.; Rapenne, G.; Sauvage, J.-P.; De Cian, A.; Fischer, J. A. Dickopfer() Trefoil Knot with m-Phenylene Bridges between the Ligand Subunits: Synthesis, Resolution, and Absolute Configuration. Chem. Eur. J. 1999, 5, 1432-1439.

199. Rapenne, G.; Dietrich-Buchecker, C.; Sauvage, J.-P. Resolution of a Molecular Trefoil Knot. J. Am. Chem. Soc. 1996, 118, 10932-10933.

200. Meskers, S. C. J.; Dekkers, H. P. J. M.; Rapenne, G.; Sauvage, J.-P. Chiroptical Properties of an Optically Pure Dickopfer() Trefoil Knot and Its Enantioselectivity in Luminescence Quenching Reactions. Chem. Eur. J. 2000, 6, 2129-2134.

201. Vögtle, F.; Hönten, A.; Vogel, E.; Buschbeck, S.; Safarowsky, O.; Recker, J.; Parham, A.-H.; Knott, M.; Müller, W. M.; Müller, U.; Okamoto, Y.; Kubota, T.; Lindner, W.; Francotte, E.; Grimm, S. Novel Amide-Based Molecular Knots: Complete Enantioseparation, Chirooptical Properties, and Absolute Configuration. Angew. Chem. Int. Ed. 2001, 40, 2468-2471.

202. Lukin, O.; Vögtle, F. Knotting and Threading of Molecules: Chemistry and Chirality of Molecular Knots and Their Assemblies. Angew. Chem. Int. Ed. 2005, 44, 1456-1477.

203. Enomoto, N.; Furukawa, S.; Ogawa, Y.; Akano, H.; Kawamura, Y.; Yashima, E.; Okamoto, Y. Preparation of Silica Gel-Bonded Amylose through Enzyme-Catalyzed Polymerization and Chiral Recognition Ability of Its Phenylcarbamate Derivative in HPLC. Anal. Chem. 1996, 68, 2798-2804.

204. Gils-Ramírez, G.; Hoekman, S.; Kitching, M. O.; Leigh, D. A.; Vitorica-Yrezabal, I. J.; Zhang, G. Tying a Molecular Overhand Knot of Single Handedness and Asymmetric Catalysis with the Corresponding Pseudo-D2-Symmetric Trefoil Knot. J. Am. Chem. Soc. 2016, 138, 13159-13162.

205. Cougnon, F. B.; Ponnuswamy, N.; Pantos, G. D.; Sanders, J. K. M. Molecular Motion of Donor-Acceptor Catenanes in Water. Org. Biomol. Chem. 2015, 13, 2927-2930.

206. Hanzon, E.; Migolet, B.; Martens, J.; Berden, G.; Sluysmans, D.; Duwez, A.-S.; Stoddart, J. F.; Eppe, G.; Oomens, J.; De Pauw, E.; Morsa, D. Radical-Pairing Interactions in a Molecular Switch Evidenced by Ion Mobility Spectrometry and Infrared Ion Spectroscopy. Angew. Chem. Int. Ed. 2021, 60, 10049-10055. doi: https://doi.org/10.1002/anie.202014728

207. Kruve, A.; Caprice, K.; Lavendomme, R.; Wollschläger, J. M.; Schoder, S.; Schröder, H. V.; Nitschke, J. R.; Cougnon, F. B. L.; Schalley, C. A. Ion-Mobility Mass Spectrometry for the Rapid Determination of the Topology of Interlocked and Knot-Molecules. Angew. Chem. Int. Ed. 2019, 58, 11324-11328.

208. Van Quaethem, A.; Lussis, P.; Leigh, D. A.; Duwez, A.-S.; Fustin, C.-A. Probing the Mobility of Catenane Rings in Single Molecules. Chem. Sci. 2014, 5, 1449-1452.

209. He, C.; Lamoure, G.; Xiao, A.; Gsponer, J.; Li, H. Mechanically Tightening a Protein Slipknot into a Trefoil Knot. J. Am. Chem. Soc. 2014, 136, 11946-11955.

210. Wang, H.; Li, H. Mechanically Tightening, Unsticking and Retying a Protein Trefoil Knot by Single-Molecule Force Spectroscopy. Chem. Sci. 2020, 11, 12512-12521.

211. Janke, M.; Rudzевич, Y.; Molokanova, O.; Metzroth, T.; Mey, I.; Diezemann, G.; Marszalek, P. E.; Gauss, J.; Böhm, V.; Janshoff, A. Mechanically Interlocked Calix[4](4)Arene Dimers Display Reversible Bond Breakage under Force. Nat. Nanotechnol. 2009, 4, 225-229.

212. Scott, G. D.; Chichak, K. S.; Peters, A. J.; Cantrill, S. J.; Stoddart, J. F.; Jiang, H. W. Mechanism of Enhanced Rectification in Unimolecular Borromean Ring Devices. Phys. Rev. B 2006, 74, 113404.

213. Zhang, L.; Leman, J. F.; Accella, A.; Calvaresi, M.; Zerbetto, F.; Leigh, D. A. Effects of Knot Tightness at the Molecular Level. Proc. Natl. Acad. Sci. U. S. A. 2019, 116, 2452-2457.

214. Ayme, J.-F.; Beves, J. E.; Campbell, C. J.; Gil-Ramírez, G.; Leigh, D. A.; Stephens, A. J. Strong and Selective Anion Binding within the Central Cavity of Molecular Knots and Links. J. Am. Chem. Soc. 2015, 137, 9812-9815.
215. De Bo, G. Mechanochemistry of the Mechanical Bond. Chem. Sci. 2018, 9, 15–21.
216. Garci, A.; Beldjoudi, Y.; Kodaimati, M. S.; Hornick, J. E.; Nguyen, M. T.; Cetin, M. M.; Stern, C. L.; Roy, I.; Weiss, E. A.; Stoddart, J. F. Mechanical-Bond-Induced Exciplex Fluorescence in an Anthracene-Based Homo[2]Catenane. J. Am. Chem. Soc. 2020, 142, 7956–7967.
217. Hanozin, E.; Mignolet, B.; Morsa, D.; Sluysmans, D.; Duwez, A.-S.; Stoddart, J. F.; Remacle, F.; De Pauw, E. Where Ion Mobility and Molecular Dynamics Meet to Unravel the (Un)Folding Mechanisms of an Oligorotaxane Molecular Switch. ACS Nano 2017, 11, 10253–10263.
218. Caraglio, M.; Micheletti, C.; Orlandini, E. Stretching Response of Knotted and Unknotted Polymer Chains. Phys. Rev. Lett. 2015, 115, 188301.
219. Sulkowska, J. I.; Sulkowski, P.; Szymczak, P.; Cieplak, M. Stabilizing Effect of Knots on Proteins. Proc. Natl. Acad. Sci. U. S. A. 2006, 105, 19714-19719.
220. Sluysmans, D.; Hubert, S.; Bruns, C. J.; Zhu, Z.; Stoddart, J. F.; Duwez, A.-S. Synthetic Oligorotaxanes Exert High Forcible Stabilization. J. Am. Chem. Soc. 2012, 134, 7190–7197.
221. Sluysmans, D.; Devaux, F.; Bruns, C. J.; Stoddart, J. F.; Duwez, A.-S. Dynamic Force Spectroscopy of Synthetic Oligorotaxane Foldamers. Proc. Natl. Acad. Sci. U. S. A. 2018, 115, 9362–9366.
222. Sluysmans, D.; Zhang, L.; Li, X.; Garci, A.; Stoddart, J. F.; Duwez, A.-S. Viologen Tweezers to Probe the Force of Individual Donor–Acceptor x-Interactions. J. Am. Chem. Soc. 2020, 142, 21153–21159.
223. Hart, L. F.; Hertzog, J. E.; Rauscher, P. M.; Rawe, B. W. Tranquilli, M. M.; Rowan, S. J. Material Properties and Applications of Mechanically Interlocked Polymers. Nat. Rev. Mater. 2021. doi:https://doi.org/10.1038/s41578-021-00278-z
224. Ahamed, B. N.; Van Velthem, P.; Robeyns, K.; Fustin, C.-A. Influence of a Single Catenane on the Solid-State Properties of Mechanically Linked Polymers. ACS Macro Lett. 2017, 6, 468–472.
225. Li, G.; Wang, L.; Wu, L.; Guo, Z.; Zhao, J.; Liu, Y.; Bai, R.; Yan, X. Woven Polymer Networks via the Topological Transformation of a [2]Catenane. J. Am. Chem. Soc. 2020, 142, 14343–14349.
226. Zhang, M.; De Bo, G. A Catenane as a Mechanical Protecting Group. J. Am. Chem. Soc. 2020, 142, 5029–5033.
227. Zhang, M.; De Bo, G. Impact of a Mechanical Bond on the Activation of a Manochromophore. J. Am. Chem. Soc. 2018, 140, 12724–12727.
228. Xing, H.; Li, Z.; Wang, W.; Liu, P.; Liu, J.; Song, Y.; Wu, Z. L.; Zhang, W.; Huang, F. Mechanochemistry of an Interlocked Poly[2]Catenane: From Single Molecule to Bulk Gel. CCS Chem. 2020, 2, 513–523.
229. Frasconi, M.; Kikuchi, T.; Cao, D.; Wu, Y.; Liu, W. G.; Dyar, S. M.; Barin, G.; Sarjeant, A. A.; Stern, C. L.; Carielli, R.; Wang, C.; Wasielewski, M. R.; Goddard, W. A., III; Stoddart, J. F. Mechanical Bonds and Topological Effects in Radical Dimer Stabilization. J. Am. Chem. Soc. 2014, 136, 11011–11026.
230. Barnes, J. C.; Frasconi, M.; Young, R. M.; Khdary, N. H.; Liu, W.-G.; Dyar, S. M.; McGonigal, P. R.; Gibbs-Hall, I. C.; Diercks, C. S.; Sarjeant, A. A.; Stern, C. L.; Goddard, W. A., III; Wasielewski, M. R.; Stoddart, J. F. Solid-State Characterization and Photoinduced Intramolecular Electron Transfer in a Nanoconfined Octacationic Homo[2]Catenane. J. Am. Chem. Soc. 2014, 136, 10569–10572.
231. Barnes, J. C.; Fahrenbach, A. C.; Cao, D.; Dyar, S. M.; Frasconi, M.; Giesener, M. A.; Benitez, D.; Tkatchouk, E.; Chernyashkevsky, O.; Shin, W. H.; Li, H.; Sampath, S.; Stern, C. L.; Sarjeant, A. A.; Hartlieb, K. J.; Liu, Z.; Carielli, R.; Botros, Y. Y.; Choi, J. W.; Slawin, A. M. Z.; Ketterson, J. B.; Wasielewski, M. R.; Goddard, W. A., III; Stoddart, J. F. A Radically Configurable Six-State Compound. Science 2013, 339, 429–433.
232. Wang, Y.; Frasconi, M.; Liu, W.-G.; Liu, Z.; Sarjeant, A. A.; Nassar, M. S.; Botros, Y. Y.; Goddard, W. A., III; Stoddart, J. F. Folding of Oligoviologens Induced by Radical–Radical Interactions. J. Am. Chem. Soc. 2015, 137, 876–885.
233. Trabolsi, A.; Khashab, N.; Fahrenbach, A. C.; Friedman, D. C.; Colvin, M. T.; Cotí, K. J.; Benitez, D.; Tkatchouk, E.; Olsen, J.-C.; Belowich, M. E.; Carielli, R.; Khatib, H. A.; Goddard, W. A., III; Wasielewski, M. R.; Stoddart, J. F. Radically Enhanced Molecular Recognition. Nat. Chem. 2010, 2, 42–49.
234. Fahrenbach, A. C.; Zhu, Z.; Cao, D.; Liu, W.-G.; Li, H.; Dey, S. K.; Basu, S.; Trabolsi, A.; Botros, Y. Y.; Goddard, W. A., III; Stoddart, J. F. Radically Enhanced Molecular Switches. J. Am. Chem. Soc. 2012, 134, 16275–16288.
235. Cai, K.; Mao, H.; Liu, W.-G.; Qiu, Y.; Shi, Y.; Zhang, L.; Shen, D.; Chen, H.; Jiao, Y.; Wu, H.; Liu, Z.; Feng, Y.; Stern, C. L.; Wasielewski, M. R.; Goddard, W. A., III; Stoddart, J. F. Highly Stable Organic Bisradicals Protected by Mechanical Bonds. J. Am. Chem. Soc. 2020, 142, 7190–7197.
236. Nguyen, M. T.; Ferris, D. P.; Pezzato, C.; Wang, Y.; Stoddart, J. F. Densely Charged Dodecacationic [3]- and Tetracacationic Radical [5]Catenanes. Chem. 2018, 4, 2329–2344.
237. Langton, M. J.; Beer, P. D. Rotaxane and Catenane Host Structures for Sensing Charged Guest Species. Acc. Chem. Res. 2014, 47, 1935–1949.
238. Marcos, V.; Stephens, A. J.; Jaramillo-Garcia, J.; Nussbaumer, A. L.; Woltering, S. L.; Valero, A.; Lemonnier, J. F.; Vitorica-Yrezabal, I. J.; Leigh, D. A. Allosteric Initiation and Regulation of Catalysis with a Molecular Knot. Science 2016, 352, 1555–1559.
239. Prakash, T.; Devaraj, A.; Saha, R.; Lusi, M.; Brandel, J.; Esteban-Gomez, D.; Platas-Iglesias, C.; Olson, M. A.; Mukherjee, P. S.; Trabolsi, A. Metal-Organic Self-Assembled Trefoil Knots for C-Br Bond Activation. ACS Catal. 2019, 9, 1907–1914.
240. Zhu, L.; Li, J.; Yang, J.; Au-Yeung, H. Y. Cross Dehydrogenative C-O Coupling Catalysed by a Catenane-Coordinated Copper(I). Chem. Sci. 2020, 11, 13008–13014.
241. Mitra, R.; Zhu, H.; Grimme, S.; Niemeyer, J. Functional Mechanically Interlocked Molecules: Asymmetric Organocatalysis with a Catenated Biphenyl Bristen Acid. Angew. Chem. Int. Ed. 2017, 56, 11456–11459.
242. Menasco, W.; Thistlethwaite, M. Handbook of Knot Theory; Elsevier Science: Amsterdam, 2005.
243. Marend, M.; Orlandini, E.; Micheletti, C. Discovering Privileged Topologies of Molecular Knots with Self-Assembling Models. Nat. Commun. 2018, 9, 3051.
244. Caprice, K.; Aster, A.; Coughon, F. B. L.; Kumpulainen, T. Untying the Photophysics of Quinolinium-Based Molecular Knots and Links. *Chem. Eur. J.* 2020, 26, 1576–1587.

245. Segawa, Y.; Kuwayama, M.; Hijikata, Y.; Fushimi, M.; Nishihara, T.; Pirillo, J.; Shirasaki, J.; Kubota, N.; Itami, K. Topological Molecular Nanocarbons: All-Benzene Catenane and Trefoil Knot. *Science* 2019, 365, 272–276.

246. Grommet, A. B.; Feller, M.; Klajn, R. Chemical Reactivity under Nanoconfinement. *Nat. Nanotechnol.* 2020, 15, 256–271.

247. Deng, H.; Olson, M. A.; Stoddart, J. F.; Yaghi, O. M. Robust Dynamics. *Nat. Chem.* 2010, 2, 439–443.

248. Bilbeisi, R. A.; Prakasam, T.; Lusi, M.; El Khoury, R.; Platas-Iglesias, C.; Charbonniere, L. J.; Olsen, J. C.; Elhabiri, M.; Trabolsi, A. [C–H···Anion] Interactions Mediate the Templantation and Anion Binding Properties of Topologically Non-Trivial Metal–Organic Structures in Aqueous Solutions. *Chem. Sci.* 2016, 7, 2524–2531.

249. Zhang, F.; Nangreave, J.; Liu, Y.; Yan, H. Structural DNA Nanotechnology: State of the Art and Future Perspective. *J. Am. Chem. Soc.* 2014, 136, 11198–11211.

250. Seeman, N. C. An Overview of Structural DNA Nanotechnology. *Mol. Biotechnol.* 2007, 37, 246–257.

251. Denis, M.; Lewis, J. E. M.; Modicom, F.; Goldup, S. M. An Auxiliary Approach for the Stereoselective Synthesis of Topologically Chiral Catenanes. *Chem* 2019, 5, 1512–1520.

252. Heard, A. W.; Goldup, S. M. Synthesis of a Mechanically Planar Chiral Rotaxane Ligand for Enantioselective Catalysis. *Chem* 2020, 6, 994–1006.

253. Maynard, J. R. J.; Goldup, S. M. Strategies for the Synthesis of Enantiopure Mechanically Chiral Molecules. *Chem* 2020, 6, 1914–1932.