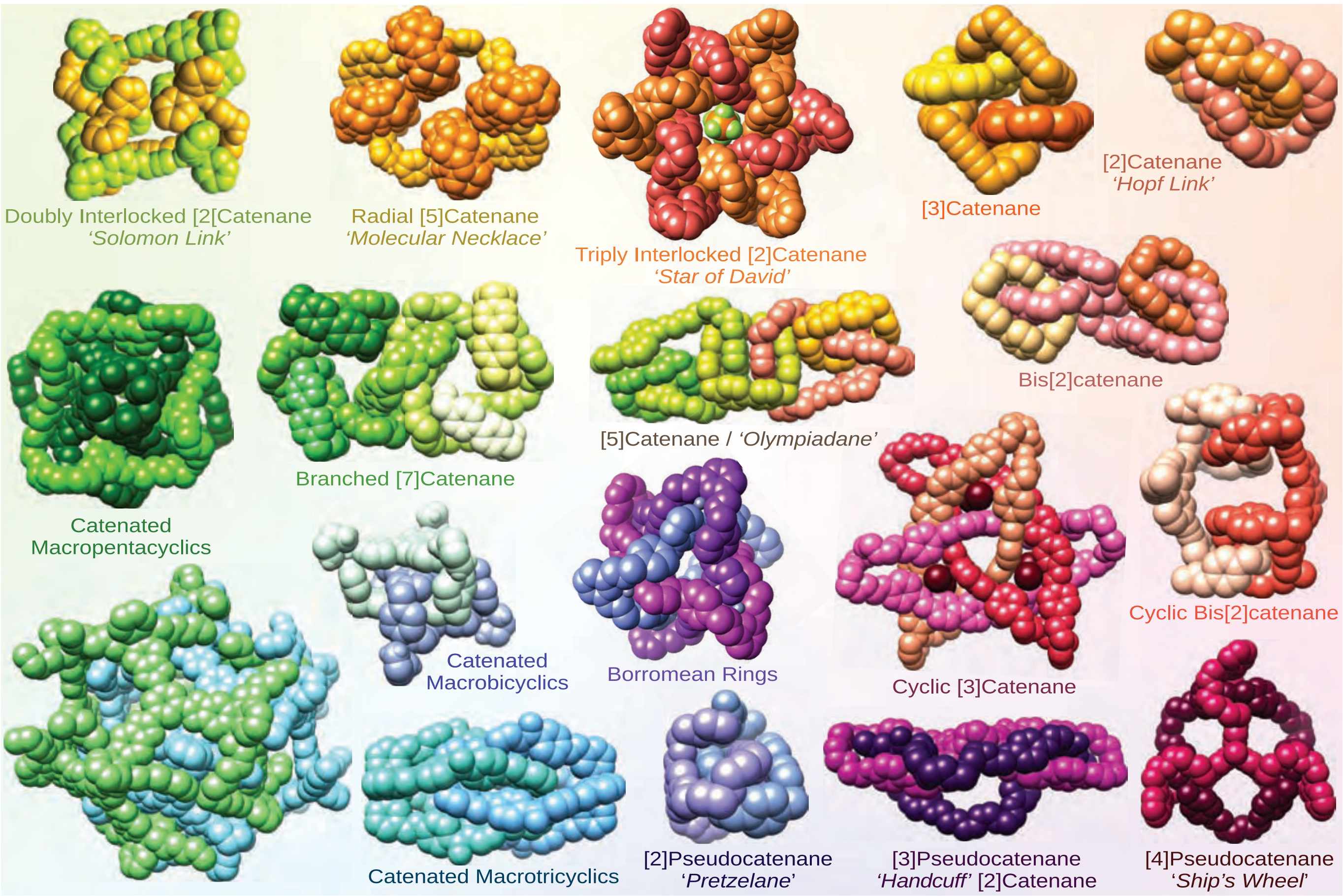


Figure 1.27 Space-filling representations of the solid-state structures of some beautiful MIM topologies: [2]catenane,[134] [3]catenane,[123] [5]catenane (Olympiadane),[133] [5]catenane 'molecular necklace',[184] branched [7]catenane,[135] eightfold interlocked multicatenane,[269] triply interlocked coordination cages,[248] quadruply interlocked coordination cages,[249,270] Solomon link,[266] Borromean Rings,[237] triply interlocked 'Star of David' [2]catenane,[236] cyclic [3]catenane,[238] pretzelane,[267] doubly threaded 'handcuff' [2]catenane or [3]pseudocatenane,[260] 'ship's wheel' [4]pseudocatenane,[262] bis[2]catenane,[268] cyclic bis[2]catenane.[265] Solvent molecules, counterions, and protons are omitted for the sake of clarity.

single bridge between two rings have also been called[293] handcuff rotaxanes, by analogy with handcuff catenanes. Cyclic [4]rotaxanes (**Figure 1.28c**) have been introduced[294] in which two bis-macrocycles are threaded by two dumbbells to give a ladder-like geometry. Sauvage[295] has obtained a crystal structure (**Figure 1.29i**) of a cyclic [4]rotaxane based on transition metal templates. Tris- and tetra-macrocyclic 'platforms', which are triply or quadruply interlocked with tripodal or tetrapodal 'rigs', respectively, have been described as mechanically interlocked 'bundles',[296] and 'molecular elevators',[178] the latter case pertaining to situations where a platform can be translocated under the influence of external stimuli—see **Section 6.13.1.3**. A triply interlocked bundle[296] is illustrated in **Figure 1.28g**, while the solid-state structure of a fourfold interlocked molecular elevator[297,298] is represented in **Figure 1.29d**. A suitane (**Section 4.3.5**) is a molecule that has been named[8,299] to reflect a molecular 'suit' which mechanically envelops a multi-limbed molecular 'body' (a suit[*n*]ane has *n* 'limbs'). A suit[2]ane (**Figure 1.29g**) thus involves a bulky molecular core bearing two appendages, all of which are encircled by a unibody macrotricyclic 'suit'.

There remain many architectures with mechanical bonds beyond simple two- or three-component rotaxanes that do not involve covalently bridged component parts. Polyrotaxanes, for example, are relatively commonplace in the literature—see **Section 4.2.1.1**. Recently, it has proven to be possible to control the secondary structure of oligorotaxanes, creating large, well-defined rigid-rods[138,300] (**Figure 1.28i**) and foldamers[301–303] (**Figure 1.28j**) based on the mechanical bond. Another type of multicomponent architecture is that of the rotacatenane (**Figure 1.28a**, **Section 4.3.1**), first introduced[7] in 1999, which comprises a [2]catenane threaded by a molecular dumbbell. More recently, the term rotacatenane has been expanded to describe[304] larger architectures possessing both rotaxane and catenane moieties. A similar concept involves two dumbbells encircled by a single ring—an architecture (**Figure 1.28e**, **Section 4.2.1.2**) first created by Anderson.[305] Sauvage[306] and Leigh[307] have also created examples of these doubly threaded architectures, the latter case, which was nicknamed a 'molecular sheaf', includes a crystal structure (**Figure 1.29c**) of the architecture. A larger

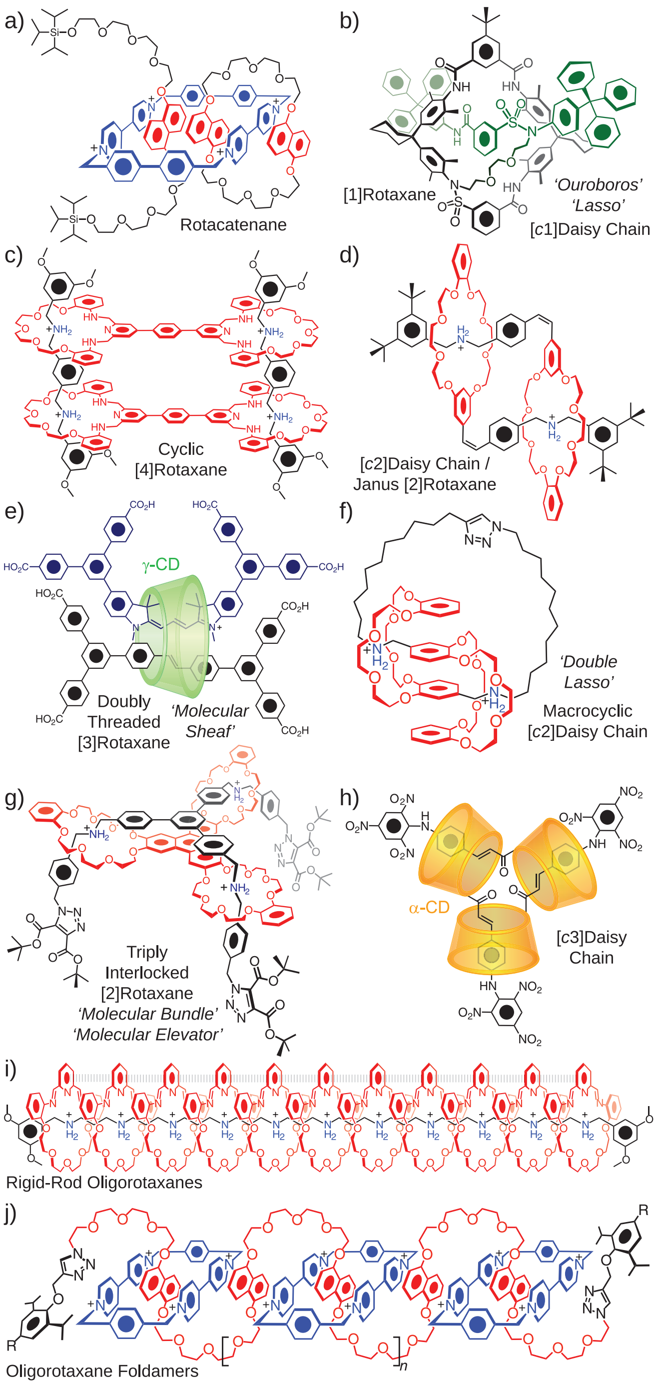


Figure 1.28 Seminal examples of MIM architectures. (a) Rotacatenane.[7] (b) [1]Rotaxane,[271] (c) Cyclic [4]rotaxane.[294] (d) [*c*2]-Daisy chain,[284] (e) Doubly threaded [3]rotaxane,[305] (f) Macrocyclic [*c*2]daisy chain double-lasso.[287] (g) Triply interlocked [2]rotaxane.[296] (h) [*c*3]Daisy chain.[286] (i) Rigid-rod oligorotaxanes.[138,300] (j) Oligorotaxane foldamers.[301,302]

molecular sheaf (**Figure 1.29h**) comprising two dumbbells, each encircled by two inorganic rings, has also been described by Leigh and Winpenny.[139]

The solid-state structures of two particularly unusual architectures are depicted in **Figure 1.29a–b**. Jiang and Huc[10] have produced a number of 'helix-rod' host-guest complexes, which resemble [2]rotaxanes wrapped (**Figure 1.29a**) in molecular helices instead of rings. The mechanical bond in this case lies in a grey area (see **Section 3.1.1**) since the rod and helix can dissociate, although the timescale of exchange is relatively slow, on the order of days, when the stoppers are sufficiently bulky. Stang and Chi[11] have reported the self-assembly of a rotaxane-like ring-in-ring architecture (**Figure 1.29b**) in which two bulky metallacycles are mechanically interlocked, yet not catenated.

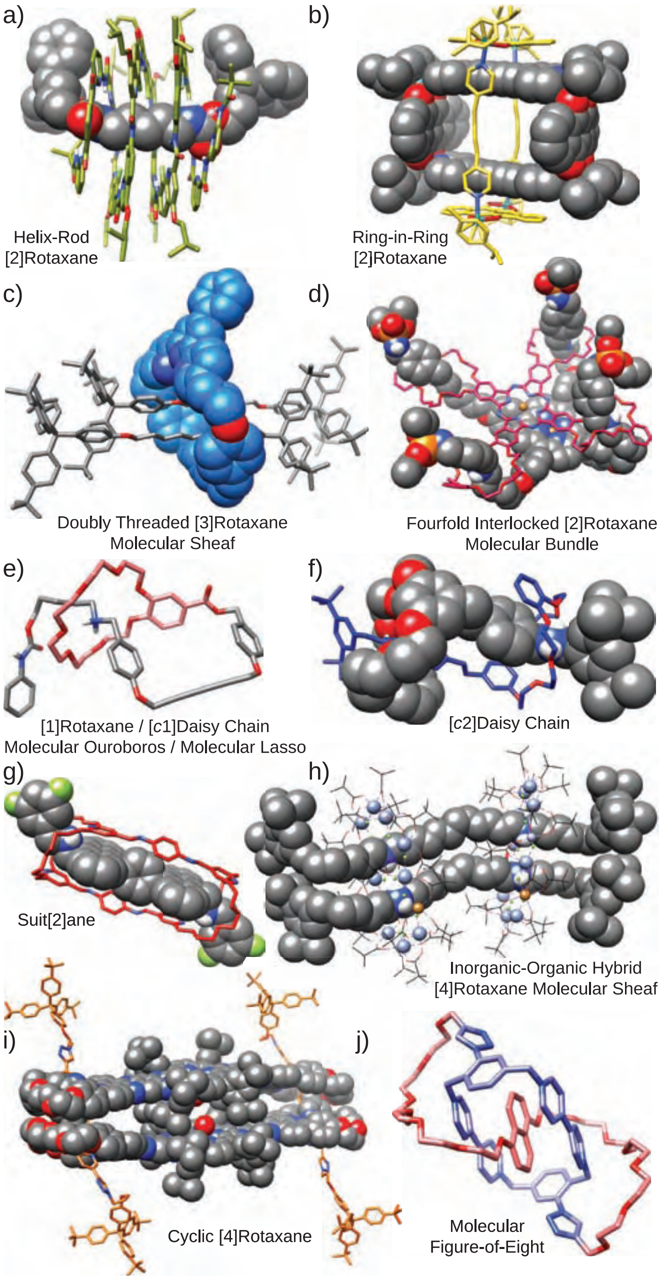


Figure 1.29 Solid-state structures of some beautiful MIM architectures. (a) Helix-rod rotaxane.[10] (b) Ring-in-ring rotaxane.[11] (c) Doubly-threaded [3]rotaxane.[307] (d) Fourfold interlocked [2]rotaxane.[298] (e) [1]Rotaxane.[272] (f) [*c*2]Daisy chain.[285] (g) Suit[2]ane.[8] (h) Organic-inorganic hybrid doubly threaded doubly encircled [4]rotaxane.[139] (i) Cyclic [4]rotaxane.[295] (j) Figure-of-eight.[281] Solvent/matrix molecules, counterions, and C–H protons are omitted for the sake of clarity.

Given all of the pleasure and beauty derived from creating new interlocked architectures, we have only scratched at the surface of what is possible. Many of the molecules shown in this Section were already framed in the context of beauty in the primary literature, and we expect that aesthetic considerations will continue to motivate new architectural developments.

1.3.4 Simplicity and Elegance

Simplicity is probably the least controversial trait that a molecule needs to be beautified in the minds of chemists, who have always been drawn to Platonic notions of beauty. Who could blame chemists for this kind of thinking? Simplicity is tied to the pleasing virtues of balance, symmetry, wholeness, and harmony. It is also tied to clarity and comprehension, which is tied to truth (**Section 1.2.4**), which is tied to beauty. When a chemist examines a simple molecule, a network of these related concepts inevitably leaves him or her with a sense of pleasure and satisfaction.

There is no lack of beautifully simple MIMs. The quintessential example is the all-hydrocarbon [2]catenane (**Figure 1.30**) prepared by Schill,[308] in which the simplest non-trivial topology is constituted only by methylene units. Other beautifully simple MIMs comprise highly symmetrical structures that make them “easy on the brain”, such as many of the compounds in **Sections 1.3.2** and **1.3.3**. Although these molecules look relatively simple, it is clear that an IUPAC name would be far from simple, a testament to the growing importance of images and graphical representation in chemistry.

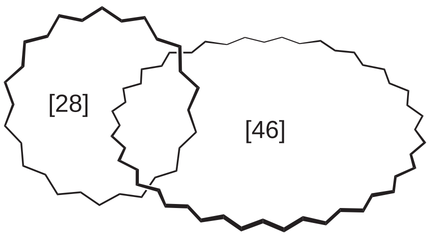


Figure 1.30 Stereoformula of an all-hydrocarbon [2]catenane introduced by Schill.[307] Bracketed numbers denote the number of carbon atoms constituting each ring.

Although we are, no doubt, aesthetically drawn to simple molecules—recall the Platonic solids from the introduction—experiments are where the beauty of simplicity truly shines. While we have chosen the word ‘beauty’ to describe the aesthetic value of structural representations, ‘elegance’ is a term that has been employed[61] to describe the aesthetic value of experiments. Here, we present some selected examples of experimental milestones that embody elegance in mechanostereochemistry. This case is our only foray into experimental beauty and the list is by no means exhaustive.

1. Templated Synthesis: Sauvage[120] revived an all but forsaken discipline by introducing (**Figure 1.31**) transition metal templates for synthesizing MIMs. His raison d’être for using coordination chemistry to position organic precursors appropriately to interlock them in subsequent reactions, which dramatically reduces the number of steps and increases the yield by orders of magnitude over those obtained for previous MIMs, was supremely elegant. **Figure 1.31** portrays his shorthand drawing of the original template strategies[120] for catenane synthesis. Sauvage’s templated synthesis set the stage for the plethora of novel molecular recognition motifs (see **Figure 1.22** and **Section 2.3**) employed today in the making of mechanical bonds.

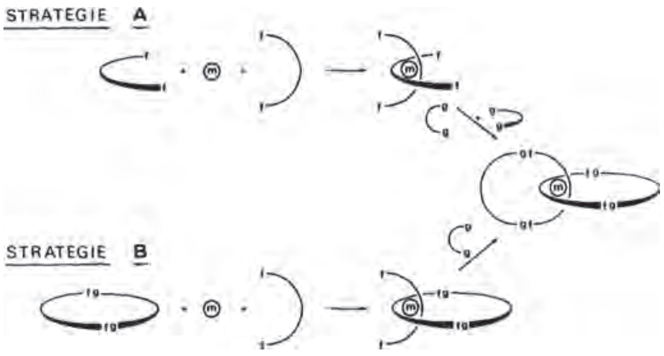


Figure 1.31 Sauvage’s scheme depicting his seminal template-directed strategies for synthesizing MIMs. A tetrahedral center orients U-shaped species appropriately for subsequent ring-closure, resulting in a catenate. Reprinted with permission from ref. 120 (copyright 1983 Elsevier).

2. Thermodynamic Control: MIMs can now be synthesized routinely in near-quantitative yields—a convenience that can be attributed in large part to the advent of thermodynamically controlled protocols, although a number kinetically controlled reactions are also high yielding. See **Chapter 3** for a review of MIM synthesis under thermodynamic control. Seminal examples[129,202,309–314] of elegant thermodynamically controlled protocols for making mechanical bonds are illustrated in **Figure 1.32**. They include (in order of appearance) (i) slippage[309] (**Section 3.1**), which involves the passage of a ring over a size-complementary stopper that is sufficiently bulky to prevent deslipping, (ii) olefin metathesis[310] (**Section 3.4**), which involves a catalyst—typically Grubbs’ Ru alkylidene catalysts—scrambling the constituents of double bonds, (iii) disulfide exchange (**Section 3.5.1**), which involves the oxidative coupling of thiols and reductive cleavage of disulfides, (iv) kinetically labile metal-ligand bonds (**Section 3.2**)—a revolution led by Makoto Fujita,[202] (v) reversible nucleophilic substitutions (**Section 3.5.2**), such competing S_N2 processes[312] in dynamic equilibrium, (vi) imine bonds[129,315] (**Section 3.3.1**) whose reversible nature facilitates the self-assembly of MIMs, (vii) boronic esters[313] (**Section 3.3.3**) formed reversibly from boronic acids and diols, and (viii) self-assembled monolayers[314] (SAMs) (**Section 3.6**).

We emphasize here that thermodynamically controlled reactions—especially olefin metathesis, metal coordination, and imine bonding—have been indispensible in orchestrating the self-assembly of many of the most exotic,

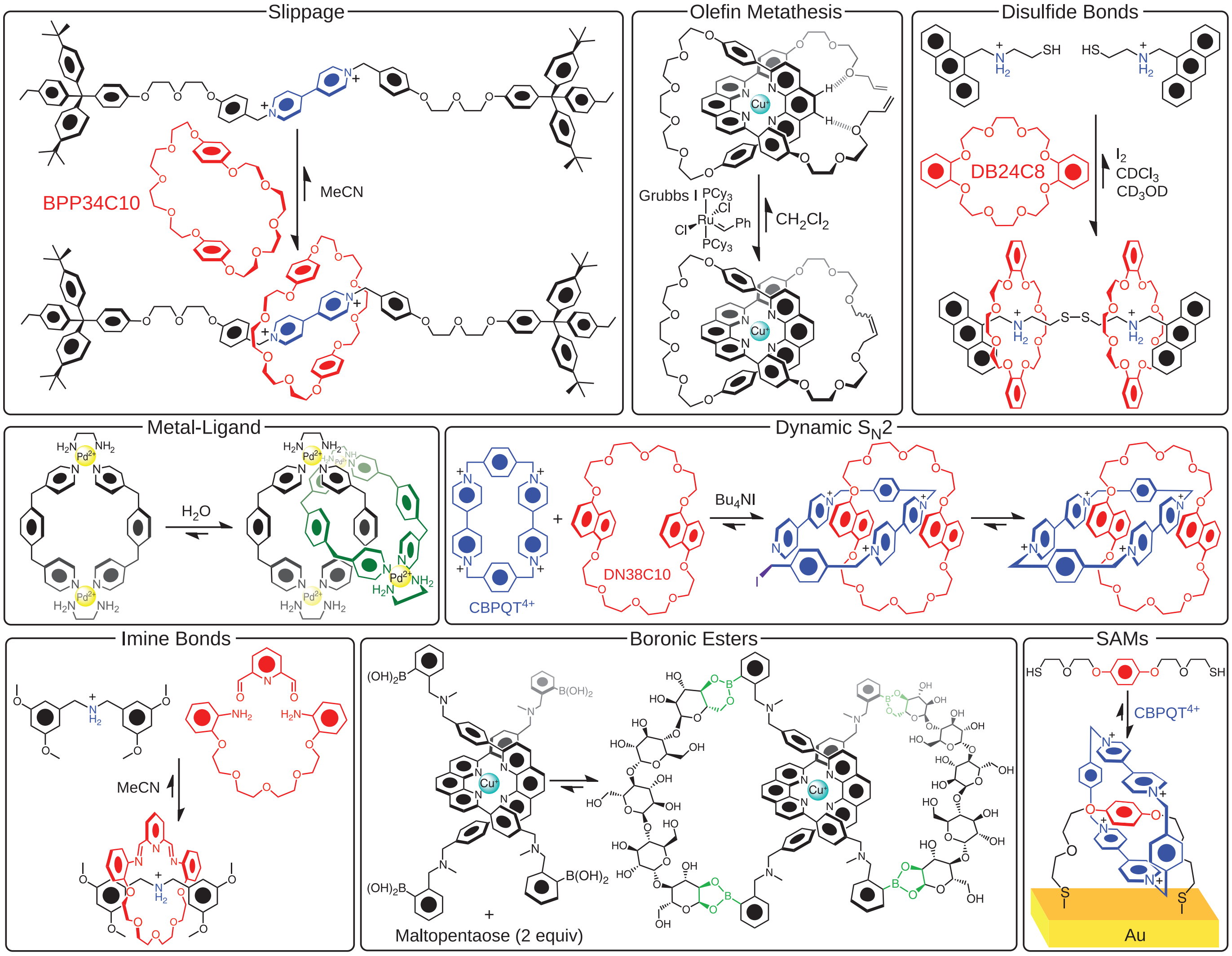
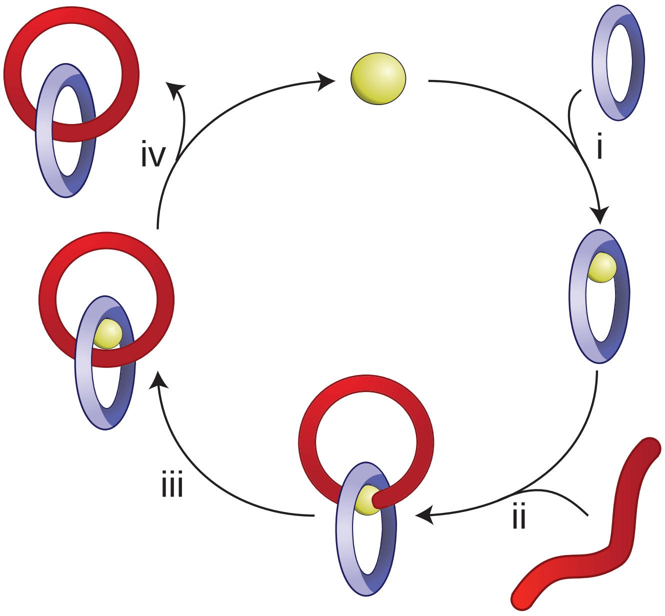


Figure 1.32 Examples of elegant thermodynamically-controlled reactions employed in the near-quantitative synthesis of MIMs. Slippage[309] involves the passage of a ring over a size-complimentary stopper that is sufficiently bulky to prevent deslipping. Grubbs' catalysts impart olefin-containing MIMs with dynamic properties by scrambling the constituents of double bonds via olefin metathesis.[310] Reversible disulfide bonds establish thermodynamic control by disulfide exchange.[311] Labile coordinative bonds are employed in the self-assembly of MIMs.[202] A weakly nucleophilic leaving group (I^-) competes with a nucleophilic macrocylization/catenation event in a reversible S_N2 reaction.[312] Reversible imine bonds facilitate the selection of MIMs from dynamic combinatorial libraries.[129] MIMs can be self-assembled from boronic acids and diols via the reversible formation of boronic esters.[313] Self-assembled monolayers (SAMs) provide a means to mount rotaxanes on surfaces under thermodynamic control.[314] See **Chapter 3**.

beautiful, and challenging topologies and architectures including molecular necklaces,[184,186,190,247,316,317] handcuff catenanes,[259,260,318] mechanically interlocked cages,[230,248,249,270,319] molecular trefoil knots,[320–323] pentafoil knots,[241,242] Solomon knots,[324–326] Borromean rings,[89,237,327,328] the Star of David catenane,[236] the cyclic [3]catenane,[238] daisy chains,[329,330] molecular bundles,[331] and very large discrete rigid-rod oligorotaxanes.[138,300]

3. Active Template Synthesis: A step beyond the template is the 'active template,' introduced in 2006 independently by the groups of Saito[332] and Leigh.[333] An active template is a moiety acting simultaneously as a template and a catalyst. It relies on the use of a macrocycle that is capable of immobilizing a template/catalyst within its cavity, such that it promotes an endotopic ring-closing reaction (for catenanes) or coupling (for rotaxanes), resulting in a mechanical bond. A cartoon depicting the concept of an active metal template is shown in **Scheme 1.1**. The elegant dual role of the template means that the metal ion can be used in sub-stoichiometric amounts without compromising yield, and permanent coordination sites need not be built into every component part of the corresponding MIM. Although they are relatively new to the scene, active templates have already been employed[334] in the synthesis of rotaxanes, catenanes, trefoil knots, shuttles, and switches, making use of copper-catalyzed Huisgen terminal azide-alkyne 1,3-cycloadditions,[333] Glaser terminal alkyne homo-couplings,[332] Ullmann-type



Scheme 1.1 Generalized mechanism of active template synthesis,[334] exemplified by the case of a [2]catenane. (i) A metal catalyst (gold) is bound within the cavity of a macrocycle (blue). (ii) A reagent (red) coordinates the metal within the macrocycle. (iii) A covalent bond is formed catalytically, resulting also in the topological and mechanical bond of a catenane. (iv) The catalyst is regenerated and the catenane is expelled. See **Section 2.4**.

C–S couplings,[332] Cadiot-Chodkiewicz alkyne heterocouplings,[335] as well as Pd- and Ni-mediated homocouplings,[336,337] Ni-catalyzed sp^3–sp^3 homocoupling of unactivated alkyl bromides,[307,338] oxidative Heck cross-couplings,[339] Michael additions,[340] Diels-Alder reactions,[341] and Goldberg amidations.[342] See **Section 2.4** for a review of active template strategies. This new method of making mechanical bonds is undeniably versatile and elegant.

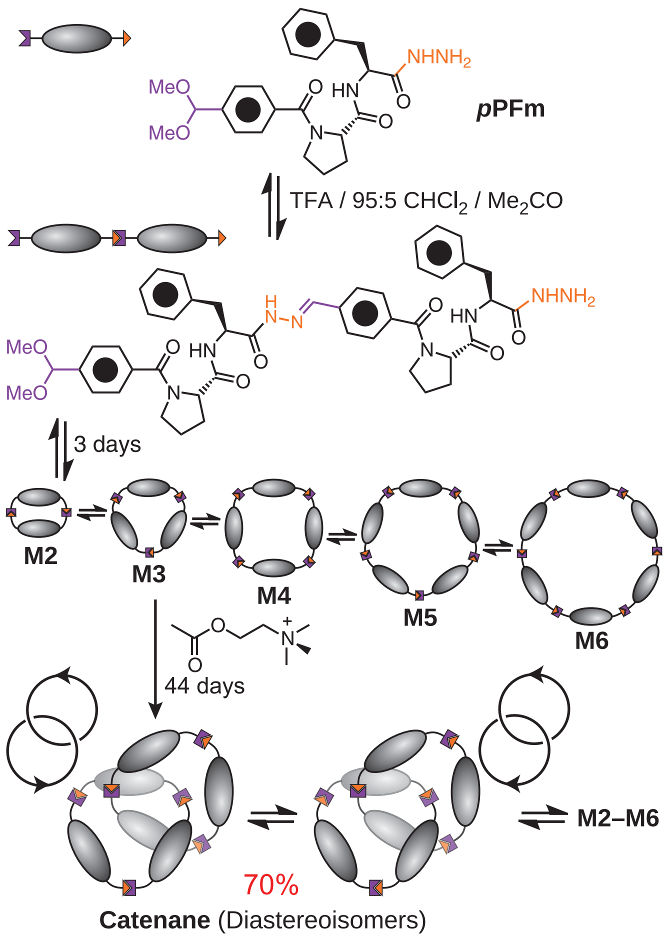
1.3.5 Complexity and Emergence

Opposite the pleasure of comprehension, harmony, and tidiness that goes with the topics of simplicity and elegance is the pleasure of surprise and learning that accompanies the related concepts of complexity[343,344] and emergence.[345–348] Since complex systems are inherently difficult to understand, beauty must be sought in tension and challenge rather than simplicity and harmony. Emergence, however, is immediately pleasing when we encounter it: the ‘Eureka’ moment, the recognition that the whole is greater than the sum of its parts, that the output could not be predicted by inspection of the input. Emergence arises out of complexity—it is the diamond at the bottom of a dark mine.

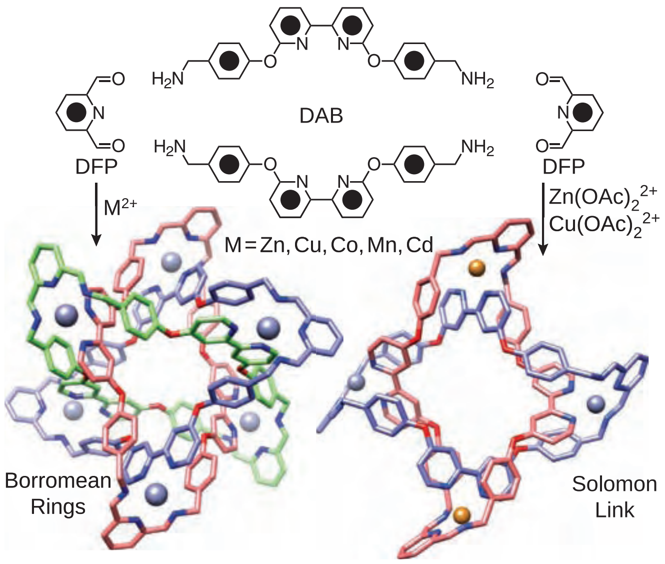
We are in danger of conflating ‘complex’ with ‘complicated’. While there is undoubtedly beauty to be found in both, in science they have different meanings. Complexity is related to chaos—dynamic, non-equilibrium, and practically unpredictable phenomena. Chaos theory was borne out of meteorology and mathematics and is conceptually (and hypothetically) demonstrated by the famous “butterfly effect,” a metaphor coined by Lorenz[349] which questioned if the flap of a butterfly’s wings could trigger catastrophic weather weeks later and many miles away. Complexity and chaos is a growing and highly multidisciplinary field of research, characterized by systems that are highly sensitive to variations in initial conditions. By contrast, ‘complicated’ only refers to things that are, well…complicated—something with many parts or intricacies, perhaps. Again we find ourselves in muddy waters, where we must admit that there is a prominent subjective air to this business of complexity and emergence. What is complex to one person might seem only complicated to another, wiser person. What is emergent now will not be emergent in 100 years when it is more deeply understood. For example, the literature is sprinkled with tales of serendipity—unexpected discoveries of mechanical bonds in reactions that were intended for other purposes. Among the most famous of these allegories are the fortuitous discoveries of hydrogen-bonded catenanes of the neutral variety—see **Figure 1.22** and **Section 2.3.4.1**. Hunter’s seminal synthesis[211] of a tetralactam [2]catenane was an unexpected result of an attempt to make a simple macrocycle. Likewise, Leigh’s first benzylic amide catenane was isolated[131] serendipitously as the unexpected product of a reaction intended to prepare a macrocyclic host for CO_2. These stories reflect the subjective and temporal dependence of discovery and knowledge—although they were unexpected at the time of their discovery, these hydrogen-bonded molecular recognition systems are now well understood and employed with high frequency and success in mechanostereochemistry. Today, few would argue that they are extraordinary in terms of emergence and complexity. On the other hand, Whitesides[343] has noted that even the simplest organic reactions are complex when considered rigorously—substrates can adopt an unlimited number of conformations and reactants have an enormous variety of interactions with solvent molecules, ions, other reactants, and so on. Hence, chemistry is an empirical science. We understand these truly complex reactions by correlating structure and reactivity in the light of lots of data. In this sense, emergence might be an area of chemistry where our data is too incomplete to give us a reliable understanding of structure-response relationships. With this disclaimer, we share a few examples that we find of emergence in mechanostereochemistry.

A promising arena for observing emergent phenomena is dynamic combinatorial chemistry[350] (DCC), which involves a pool of molecules interacting through reversible covalent bonds. Often, preferred species in the dynamic combinatorial library (DCL) of these reactants can be selected and/or amplified under certain experimental conditions, such as the addition of a template or a change in solvent polarity or temperature. It can take days or weeks for a DCL to reach equilibrium and pass through an array of complex and emergent structures. Even at equilibrium, DCLs can easily be complicated, even complex or chaotic when they are highly sensitive to initial conditions. Sanders[351] demonstrated (**Scheme 1.2**) this idea beautifully in 2005, when he reported a DCL composed of a peptide (*p*PFm) that equilibrates over three days into a variety of macrocyclic oligomers ranging in size from a dimer (**M2**) up to a hexamer (**M6**), yet a more elaborate [2]catenane comprising two 42-membered **M3** rings is formed as the dominant species in the presence an acetylcholine additive, if given enough time to equilibrate—see **Section 3.3.2**.

Another possible case[325] of emergence (**Scheme 1.3**) is the fortuitous isolation of a Solomon Knot from the same pool of precursors employed in the self-assembly of the molecular Borromean Rings. Whereas a dynamic combinatorial library (DCL) of 2,6-diformylpyridine (DFP) and 2,2´-bipyridine derived diamine (DAB) ligands leads to the self-assembly[237,328] of molecular Borromean Rings in the presence of several metal templates, including Zn^{II} or Cu^{II}, the unexpected emergence[325] of a doubly-interlocked [2]catenane (Solomon Knot) is observed[325] upon crystallization of a DCL containing an equimolar mixture of Zn^{II} and Cu^{II} templates. The outcome's high sensitivity to subtle changes in initial conditions, with solvent, counterions, and templates all playing an important role in the (not yet well understood) crystallization process indicates a complex interplay of interactions. The crystallization of the Solomon Knot is most likely a kinetically controlled process, since the Borromean rings are the dominant species in solution, and indeed crystals of a Solomon knot possessing only Zn^{II} templates can be hand-separated from the crystals of Borromean rings under different crystallization conditions.[328] More recently, a subtle structural modification to the DAB ligand involving the addition of methylene spacers in between the amino and bipyridine moieties was found to lead to the simultaneous self-assembly[352] of a [2]catenane, trefoil knot, and Solomon knot in one pot, providing further evidence for the complexity of the equilibrium governing the formation of these molecular topologies.

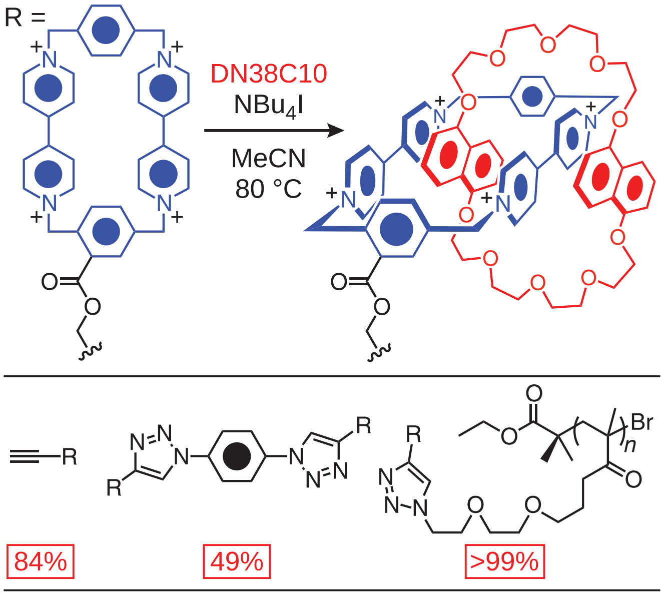


Scheme 1.2 Sanders' dynamic combinatorial library based on the reversible imine bonds of the dipeptide building block *p*PFm, which yields mainly oligomeric macrocycles (**M2–M6**) until an acetylcholine template is added, which selects and amplifies an exquisite hexameric [2]catenane.[351]



Scheme 1.3 The self-assembly of molecular Borromean Rings[237,328] from a dynamic combinatorial library (DCL) containing DFP and DAB ligands with divalent metal combinatorial library (DCL) of 2,6-diformylpyridine (DFP) and 2,2´-bipyridine derived diamine (DAB) ligands leads to the self-assembly[237,328] of templates, as well as the unexpected emergence of a Solomon Knot[325] upon crystallization of a DCL containing a 1:1 mixture of Zn^{II} and Cu^{II} templates. Tubular representations of solid-state structures are illustrated with protons, counterions, and solvent molecules omitted for the sake of clarity.

It has been discovered[353] that a polymer can demonstrate emergent phenomena when catenated under thermodynamic control. The previously-developed[312] iodide-catalyzed self-assembly of donor-acceptor [2]catenanes has been applied to a polymerizable monomer containing a derivative of cyclobis(paraquat-*p*-phenylene) (CBPQT^{4+}) in 84% yield. When dimerized, the catenation proceeds in an unsurprising 49% yield. However, when the catenation is performed on the poly-CBPQT^{4+} compound, the reaction unexpectedly proceeds (**Scheme 1.4**) to >99% completion. This result[353] has been rationalized by postulating a cooperative,



Scheme 1.4 A polymerized derivative of the tetracationic cyclophane CBPQT^{4+} displays the emergent property of quantitative thermodynamic catenation by iodide-catalyzed self-assembly with the DN38C10 crown ether macrocycle. The analogous monomeric and dimeric species do not react quantitatively.[353]

synergistic templating effect by nearby tetracationic cyclophanes on the backbone of the polymer that are not present in the monomeric and dimeric compounds.

Owing to the ambiguous meanings of complexity and emergence, spectacular examples of emergent phenomena in mechanostereochemisty may abound, or they may be exceedingly rare, depending heavily on one's opinion. Nevertheless, the chemistry of complexity is sure to become a busier and ever more pleasing avenue that chemists will continue to traverse.

1.3.6 Beautiful Machines with Mechanical Bonds

Humanity has beautified machines since at least the time of the European Renaissance—as exemplified by the fusion of art and natural philosophy (the forerunner to modern science) in the manuscripts of the one and only Leonardo da Vinci—and probably for almost as long as machines have existed. Countless modern marketing campaigns are aimed at portraying the beauty of machines—automobiles, timepieces, electronic devices, and so on—in order to gain business. Molecular machines, such as the protein-based enzymes and assemblies that carry out life-sustaining nanoscopic work inside of cells, are perhaps the most beautiful machines of all because they were crafted by Nature over billions of years of evolution to express astonishing feats of mechanical work and motion against the enormous chaotic thermal fluctuations that dominate objects on the nanoscale, embodied by the "wiggles and jiggles" known as Brownian motion.[354,355] One of the most compelling aspects of MIMs is that their architectures are well suited for designing artificial molecular switches and machines. See **Chapter 6**. The motion of one component part relative to another can often be controlled by an external stimulus in bistable and multistable MIMs. The fact that MIMs can express these mechanical motions in response to an influx of energy is the reason why they are often referred to as "molecular machines" or "motor molecules", though it would be more accurate to call most of them switches unless the motions are harnessed to do work.

The ring of a catenane or rotaxane can be shuttled (**Figure 1.33**) from one site to another under the influence of a wide variety of stimuli, including redox, light, pH, cations, anions, solvents, covalent reactions, temperature, molecular recognition, pressure, and mechanical force. Seminal examples[175,356–365] of molecular switches employing these stimuli are illustrated in **Figure 1.33**, representing another case of beauty in diversity. In more recent years, a number of important examples[188,366–369] of mechanically interlocked systems expressing biased, mechanostereoselective, or "unidirectional" motion have been described, as well as a number of molecular ratchets that exhibit[369–376] energetically demanding and entropically unfavorable transport—see **Section 6.15.2**. These molecules are setting the foundation for artificial molecular machines that can perform complex tasks more akin to biological molecular machines. Reviews and monographs on the subject of mechanically interlocked molecular machines, such as switches and motors, are abundant in the literature.[377–396]

A car that doesn't start or a computer that doesn't boot up are machines that many people would more likely describe as 'useless' rather than 'beautiful'. Likewise, molecular switches that simply bump around and tumble randomly in solution aren't very useful—they must carry out a functional task to be considered machines in the true sense of the word. Thus, the most beautiful molecular machines are those that we put to work for us. One of most promising strategies for garnering function from artificial molecular machines is to organize them at interfaces or in bulk.[397–400] See **Sections 6.14** and **Section 6.15.1**. Here we highlight several noteworthy examples of molecular machines that go beyond being simple switches.

Wouldn't it be amazing if the tiny nanomotions of artificial molecular machines could be cooperatively scaled up to do work on macroscopic objects? Nature has implemented this strategy in muscle tissue, where the chemically driven mechanical motions of molecular machines known as myosin are scaled over many orders of magnitude, courtesy of their integration within a hierarchically organized material comprising bundles of aligned filaments. Rotaxanes have been recognized[180,288–291] for their ability to express muscle-like extensile and contractile motions. Furthermore, some single-molecule investigations[401,402] of switchable rotaxanes by force spectroscopy have shown unequivocally that they are capable of generating force, even against an external load, an observation which bodes well for the future of artificial molecular machines.

An enticing demonstration[403–405] of the possibility of doing macroscopic work with mechanically interlocked artificial

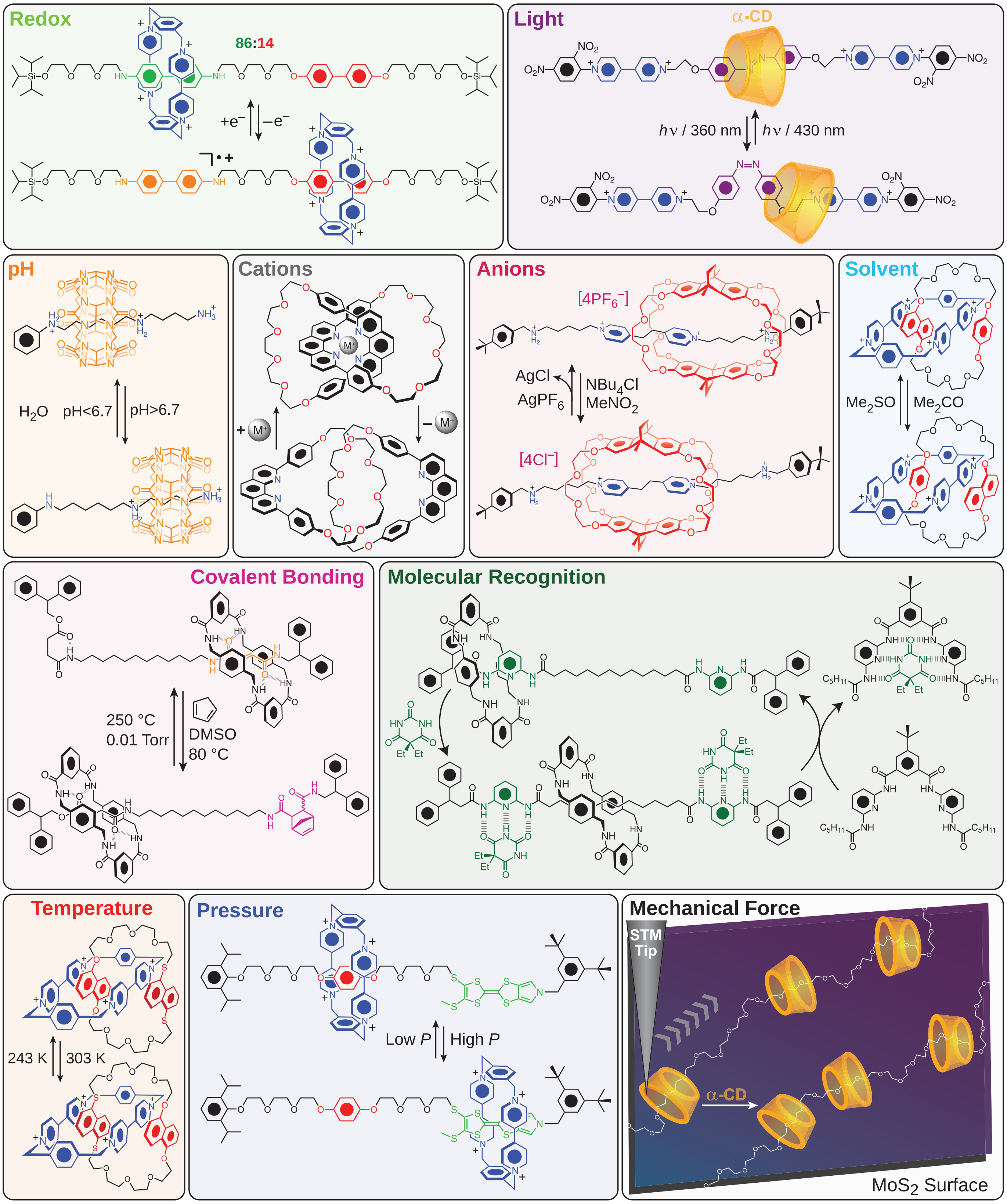


Figure 1.33 Beauty in diversity. Different types of stimuli that drive mechanically interlocked molecular switches include redox,[175] light,[356] pH,[357] cations,[358] anions,[359] solvent,[360] covalent bonding,[361] molecular recognition,[362] temperature,[363] pressure,[364] and mechanical force.[365]

molecular machines been devised by immobilizing zillions of redox-switchable, palindromic bistable [3]rotaxane 'molecular muscles' on the surface of a thin gold-coated microcantilever. Remarkably, the chemical or electrochemical redox actuation (**Figure 1.34**) of these anchored molecules bends the cantilever up and down, a movement that can be detected with a laser beam focused on its surface. Although it remains below the macroscopic scale, this experiment demonstrates that energy can be transduced and work can be done by molecular switches organized at an interface. More recently, Giuseppone[406,407] has demonstrated that the concerted acid/base actuation of bistable [*c*2]daisy chain monomers embedded in a long metallosupramolecular polymer can change its countour length by several microns—orders of magnitude greater in scale than the individual switches embedded in the backbone, and that aggregates of hydrogen-bonded [*c*2]daisy chain supramolecular polymers exhibit very different morphologies when the monomers are in the contracted and extended states. These experiments provide a strong proof-of-concept that rotaxanes are capable of serving as artificial muscles—see **Section 6.15.1.2**.

Leigh[408] described an experiment in 2005 that also utilizes molecular switches to transport (**Figure 1.35**) a macroscopic droplet across a surface. Bistable rotaxanes were physisorbed onto a surface and irradiated with UV light, which led to the photoisomerization of an olefin in a

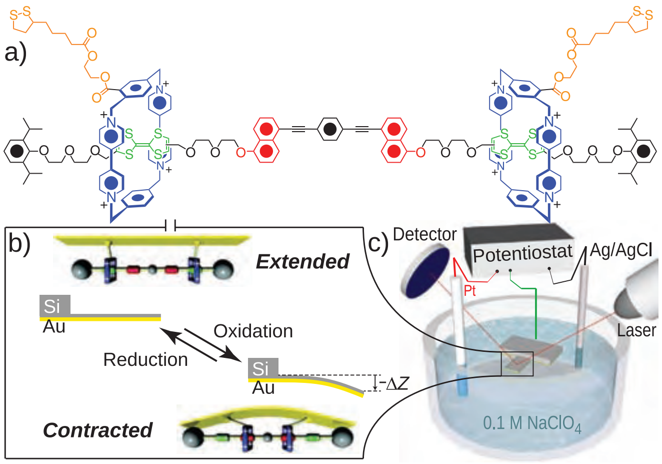


Figure 1.34 Electrochemically driven mechanical actuation of a gold-coated microcantilever by bistable [3]rotaxane 'molecular muscles.'[405] (a) Structural formula of a palindromic bistable [3]rotaxane with gold-binding dithiolanes attached to the rings. (b) Graphical representation of the reversible bending of a cantilever by actuation of a self-assembled monolayer (~8 billion molecules) of the rotaxanes on its surface. The rotaxanes 'contract' when stereoelectronic changes induced by redox stimuli cause them to glide in opposite directions. (c) Diagram of the electrochemical cell (Ag/AgCl, Pt, and the cantilever are the reference, counter, and working electrodes, respectively) and combined AFM device used to measure the bending by detecting a laser beam reflected off of the cantilever's surface. Adapted with permission from ref. 33 (copyright 2012 Springer)

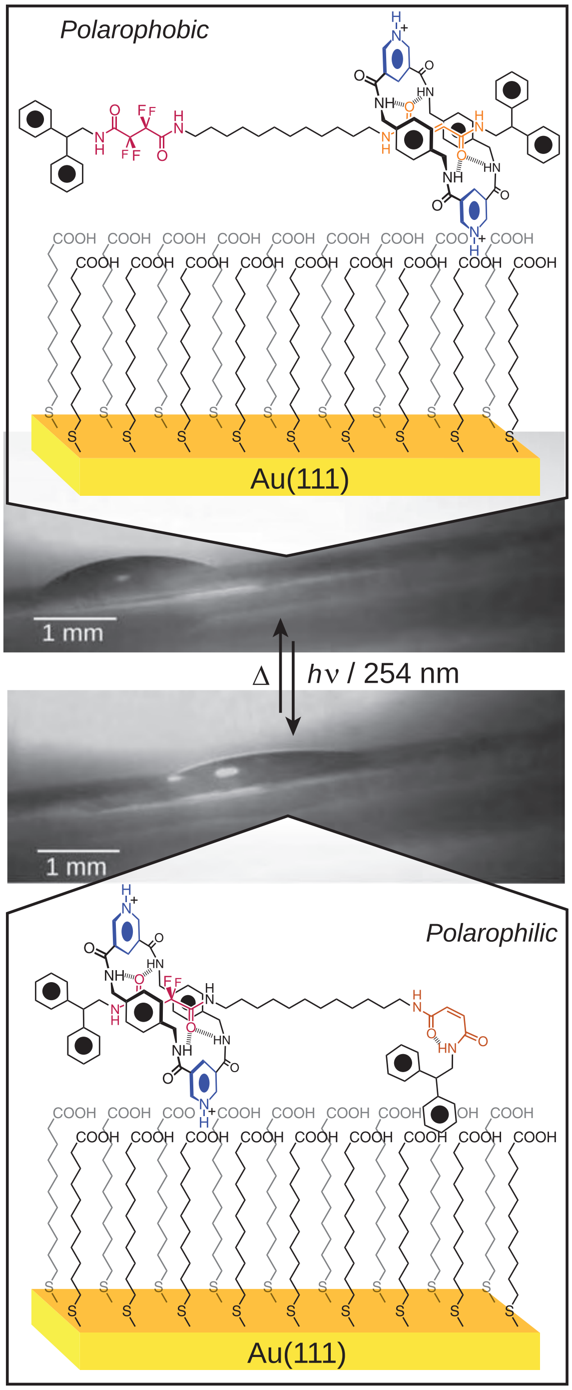


Figure 1.35 Light-driven transport of a diiodomethane droplet up a 12° incline on a Au(111) surface coated with a SAM of 11-mercaptoundecanoic acid and physisorbed, photoswitchable bistable [2]rotaxanes.[408] In the ground state (top), the ring preferentially encircles an unfluorinated fumaramide recognition site and the exposed tetrafluorosuccinamide recognition site contributes to the polarophobicity of the surface. When a light beam focused on one side of the droplet causes some of the fumaramide (*trans*-olefin) units to isomerize to maleamide (*cis*-olefin), the ring within this population of the photostationary state shuttles to encircle the fluorinated recognition unit (bottom), which decreases the surface polarophobicity and causes the droplet to move several millimeters uphill. Photographs reprinted with permission from ref. 408 (copyright 2005 Nature Publishing Group)

population of the rotaxanes and caused the ring to shuttle over to a fluorinated recognition site, which in turn changed the polarophobicity of the surface. Photoswitching the surface in this manner underneath one side of a diiodomethane droplet causes it to move several millimeters up a 12° incline.

Now for a bit of science fiction: what if single molecules could be utilized to perform logic operations or store information, like transistors? A joint effort toward this end between ourselves and Heath,[409–416] which addressed the organization and electrochemical actuation of bistable donor-acceptor MIMs as molecular monolayers within crossbar interfaces known as molecular switch tunnel junctions (MSTJs), culminated[416] after a decade in a high density memory device (**Figure 1.36**) in 2007. The monolayer of bistable rotaxanes was incorporated into a crossbar logic architecture (**Figure 1.36c**) in a size regime corresponding to little more than 100 molecules per junction. Actuation of the bistable switches in these MSTJs validated them as storage elements; about 25% of the bits had sufficient on/off ratios to be configured into a device. The resulting 160-kilobit memory circuit had a density of 10^{11} bits·cm^{-2}, for a total memory cell size of 0.0011 mm^2, which is approximately the cross-sectional area of a white blood cell (**Figure 1.36d**). A memory circuit of these dimensions is roughly on par with that of a storage density projected[417] to be available in 2020 if Moore's Law continues to be obeyed.

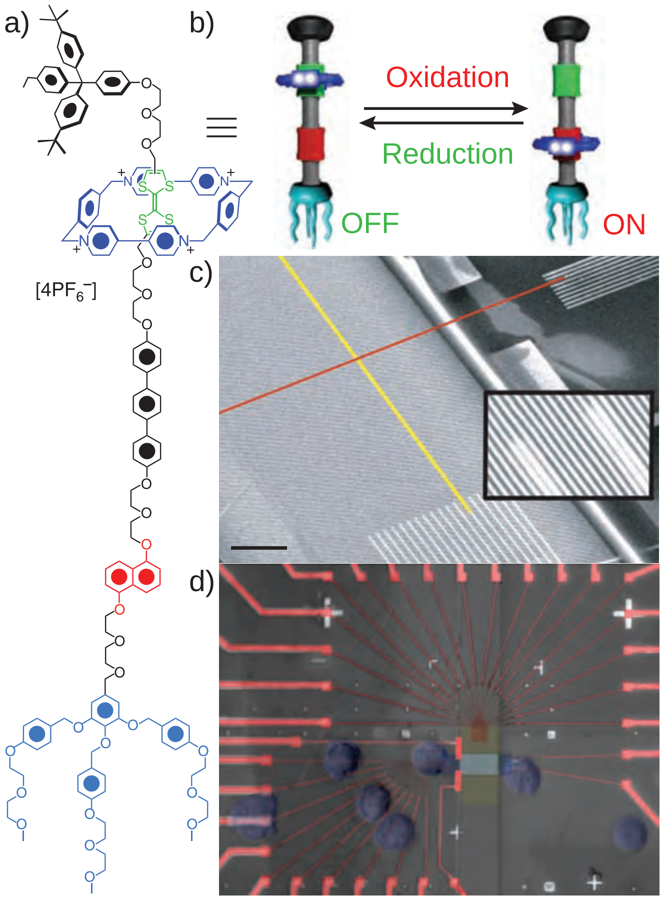


Figure 1.36 A 160-kbit molecular electronic memory device.[416] (a) Structural formula of the molecular switches used in the device. (b) Technomorph representations depicting how the molecular switches can be electrochemically toggled "on" and "off" in the device into co-conformational states with different conductivities. (c) SEM image of the intersection between top (red) and bottom (yellow) electrodes for the MSTJs. (d) Microscopic image of the memory device (blue area) and its electrical contacts (red) with white blood cells (green) as a reference of scale. Reprinted with permission from ref. 33 (copyright 2012 Springer)

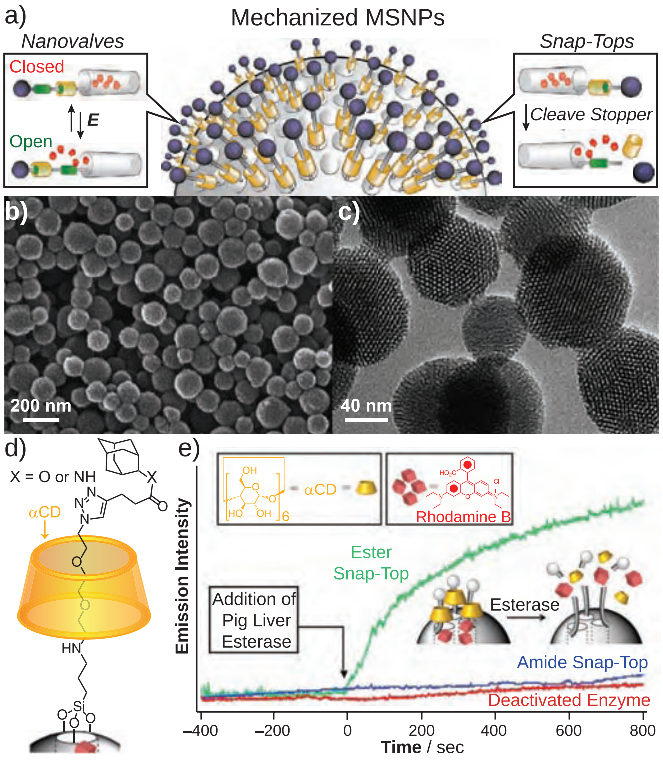
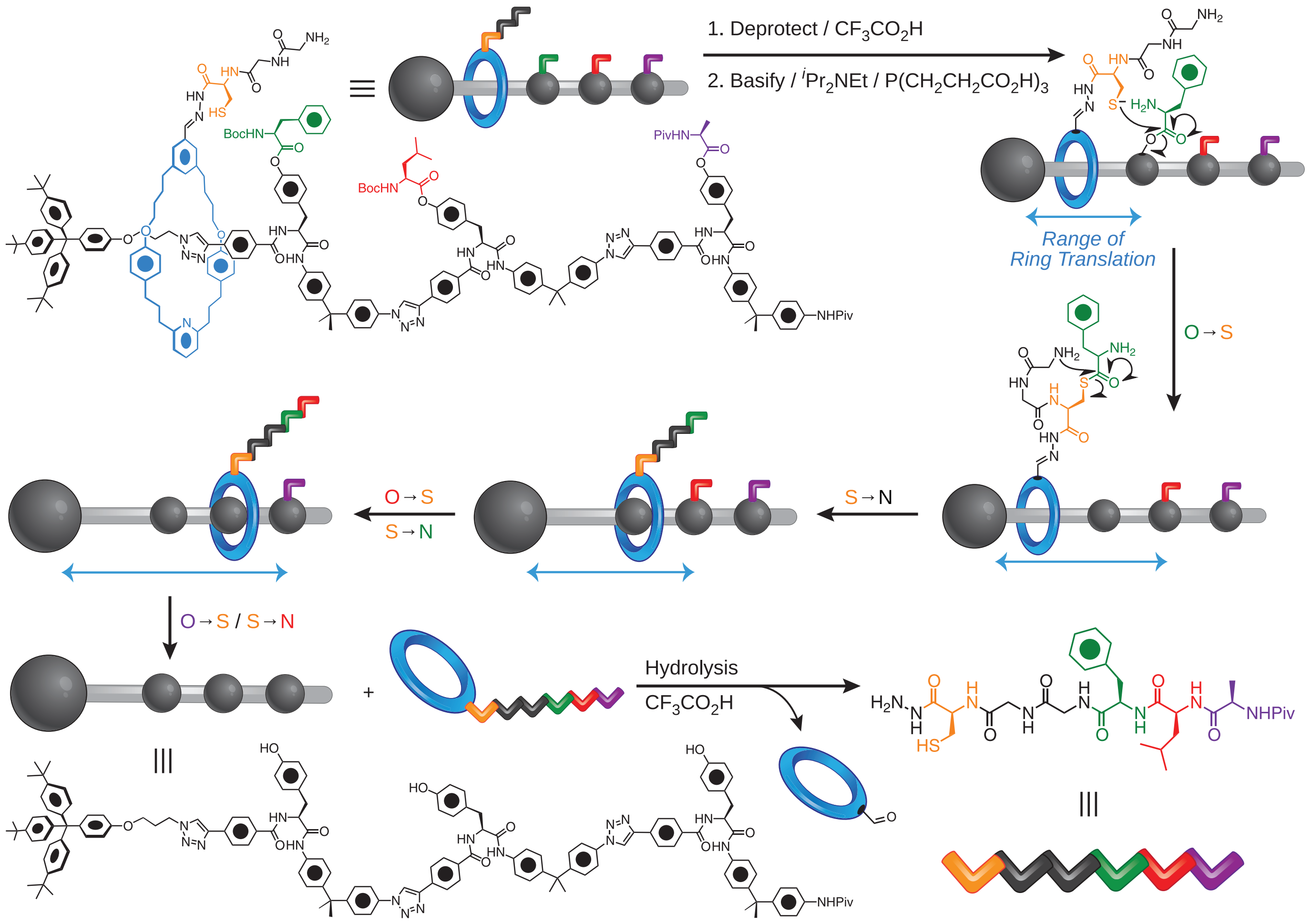


Figure 1.37 Examples of mechanized mesoporous silica nanoparticles (MSNPs).[418–420] (a) Illustrations of the functions of rotaxane nanovalve and snap-top mechanisms for controlled release of cargo.[394] (b) SEM image of MSNPs. (c) TEM image of MSNPs.[418] (d) Structural formula of an α-cyclodextrin (αCD)-based snap-top rotaxane blocking the pores of a MSNP. The stopper is connected to the axle by an amide bond or an enzyme-cleavable ester bond. (e) Release profile of rhodamine B from the snap-top MSNPs.[449] The addition of pig liver esterase decomposes the mechanical bond by cleavage of the ester-linked stopper, which releases αCD and hence the cargo from the nanoparticles, an outcome which is monitored by the fluorescence intensity of rhodamine B. Controls employing an amide bonded snap-top or deactivated enzyme do not release significant amounts of cargo from the MSNPs. SEM and TEM images reprinted with permission from ref. 418 (copyright 2009 Royal Society of Chemistry), release profile adapted with permission from ref. 449 (copyright 2008 American Chemical Society)

The question inevitably arises: can we build artificial molecular machines that are "smart" enough to respond to signals within our bodies, releasing therapeutic drugs or diagnostic contrast agents, for example, only at a localized and desired site? Once again, reality is not so far from the dream. A number of research groups are developing a variety of "mechanized nanoparticles"[418–420] (**Figure 1.37**)



Scheme 1.5 Sequence-specific peptide synthesis by a rotaxane artificial molecular machine.[454] The ring adds monomers to the end of its peptide sidechain by a series of native chemical ligation reactions, the sequence of which is defined by the sequence of monomers confining the ring to the rotaxane's dumbbell.

with these applications in mind. Efforts thus far have been associated chiefly with the covalent functionalization of supramolecular and molecular switches on the surfaces of mesoporous silica nanoparticles[421] (MSNPs, **Figure 1.37b–c**) that can act as stimulus-responsive (**Figure 1.37a**) gates to the nanopores.[422,423] Since 2004, bistable rotaxanes and pseudorotaxanes at the surface of these nanoparticles have been demonstrated over and over again to release cargo selectively from MSNPs in response to changes in pH,[179,424–434] light,[435–442] redox stimuli,[183,443–446] and salt concentration,[447] as well as in oscillating magnetic fields[448] and as a result of the introduction of specific enzymes[449,450] or small molecules.[451–453] **Figure 1.37d–e** provides one example[449] of how these mechanized nanoparticles operate, depicting the release profile of 'snap-top' rotaxane-gated MSNPs that are activated with an enzyme to release their internal cargo. One of the pH-responsive systems has been shown to work autonomously to release cargo *in vitro*,[429] making these materials highly promising candidates as drug delivery vehicles. The large number of examples produced in a relatively short time span signifies these nanocarriers as useful, beautiful applications of artificial molecular machinery. See **Section 6.15.1.1**.

With the exception of muscles, most of Nature's machines do their work on the nanoscale. A particularly important apparatus is the ribosome—the large, complex protein assembly responsible for reading the information encoded in messenger RNA and synthesizing the corresponding polypeptide chains that fold into proteins. Leigh[454] has constructed an artificial molecular machine that relies intimately on the mechanical bond to perform the ribosome-like task (**Scheme 1.5**) of synthesizing an oligopeptide chain in a sequence-specific manner. The machine is constructed by a combination of active template synthesis and Cu^{I}-catalyzed azide-alkyne cycloaddition (CuAAC) click chemistry to display a short cystine–glycine–glycine peptide sequence appended by a hydrazone linkage to a ring, which encircles a dumbbell possessing a pre-defined sequence of protected, phenolic ester-linked monomers, each separated by a rigid spacer. Once assembled, the machine is set into action by acidic deprotection of these reactive monomers, as well as by the addition of a non-nucleophilic base, which facilitates a reaction known as native chemical ligation[455] (NCL), wherein (i) the dumbbell's peptide monomer in closest proximity to the ring is captured by trans-acylation to the thiolate site of the ring's reactive cystine residue, resulting in a thioester, which (ii) undergoes S→N shift, transferring the peptide monomer to the *N*-terminal residue, or "elongation site", at the end of the ring's peptide chain. Sequence specificity arises from the fact that each monomer displayed by the dumbbell acts as a stopper, forbidding the passage of the ring until it is cleaved, thus preventing any amino acids from being transferred to the elongation site out-of-turn. After the ring has picked up all three of the dumbbell's monomers by this sequential O→S / S→N acyl transfer process, it is no longer constrained by a mechanical bond and is therefore free to diffuse away from the dumbbell. The oligopeptide chain can then be isolated by hydrolysis of the hydrazone bond. Several limitations prevent this machine from competing with solid-phase peptide synthesis or the ribosome—long timescales (~12 h / peptide), short sequences limited to only a few amino acids, and loss of sequence information after it is "read" and "written". Despite these limitations, this ingenious piece of exquisite chemistry, which has been praised for its likeness to a Turing machine,[456] an automated peptide synthesizer,[456,457] and indeed the ribosome,[457,458] represents a major landmark for molecular machines and the mechanical bond.

The beauty of employing controlled molecular mechanical motions to do work and perform technologically important functions is similar to that of technomorphic representations (**Section 1.2.6**) in the sense that it draws a connection between the molecular and macroscopic worlds. Artificial molecular machines remind us of the classical machines we know and use every day, although they operate under completely different principles on account of the enormous thermal fluctuations that lead to Brownian motion on the molecular size scale. The tension between these two worlds presents a challenge that has led chemists to respond with creative, often bio-inspired solutions to operating machines at low Reynolds number. At the same time, the awesome molecular machinery of the cell has provided inspiration for the first artificial molecular machines that can perform complex tasks on the nanoscale, building a beautiful bridge between the synthetic and natural worlds.

1.3.7 The Art of the Mechanical Bond

We consider many of the figures and schemes of MIMs in the primary literature to be artwork in and of themselves, yet even more deliberate artwork inspired by MIMs has been created for journal covers and graphical abstracts over the years, along with the occasional work of art for arts' sake. We have curated a collection of over 100 cover art images in **Appendix A** paying tribute to publications that have been featured on journal covers on topics related to the mechanical bond. The large number and diversity of these titles reflects the interdisciplinary nature of the field and the highly creative and immensely productive attributes of its practitioners. Paintings (**Figure 1.38**) by Mike Thompson, which decorate the walls of the Evanston laboratory, are inspired directly by the topological beauty of mechanomolecules.

We do not need any convincing that the mechanical bond is indeed "a work of art". Although it is framed mostly outside the bounds of any formal aesthetic framework, molecular beauty is very much a part of chemists' experience. At the end of the day, MIMs are beautiful because they are researched by hard-working, passionate people who cannot help but to take pleasure in their work. We find beauty in many aspects of the mechanical bond, from its prevalence in nature (**Section 1.1.1**), art (**Section 1.1.2**), and daily life (**Section 1.1.3**), to the pleasure of building new supramolecular (**Section 1.3.1**) and molecular topologies (**Section 1.3.2**) and architectures (**Section 1.3.3**), to the appeal of elegant new protocols (**Section 1.3.4**), the prospect of uncovering complex and emergent phenomena (**Section 1.3.5**), not to mention the remarkable potential and functional utility of molecular switches and

Figure 1.38 MIM-inspired paintings by Mike Thompson.

machines (**Section 1.3.6**). At the same time, many chemists are surely artists at heart, sculpting molecules instead of clay, synthesizing masterpieces instead of painting them, even demonstrating a knack for visual presentation as evidenced by the development of new graphical modes (**Section 1.2**) of communication, such as the cartoons and technomorphs that simultaneously aid in communication and stimulate innovation. Roald Hoffman[197] has commented, "*It never ceases to amaze me how a community of people who are not talented at drawing, nor trained to do so, manages to communicate faultlessly so much three-dimensional information.*" We add to this comment our amazement at the beauty such images can bear, and their ability to draw connections between molecules and classical objects. Whether we speak of images, topologies and architectures, experimental elegance, or functional novelty, the research associated with mechanical bonds is indeed a pleasing, beautiful, and rewarding line of work.

1.4 Evolution of Mechanostereochemistry

We close this introductory Chapter with a perspective and brief assessment of the growth and development of the field of chemistry that deals with mechanical bonds—or, as we call it—mechanostereochemistry.[16,17] Without a doubt, the mechanical bond will continue to evolve. We believe that the publication of this book is timely because the evolution of MIMs appears to be approaching a turning point. The evolutionary tree is no longer a sapling as it enters a new stage of life. Soon it will not be possible to consolidate the diverse aspects of the mechanical bond in chemistry into a single volume. Consider the degree to which the field is growing (**Figure 1.39**)—the histograms tracking the approximate number of publications[F] (**Figure 1.39a**) and literature citations (**Figure 1.39b–c**) on the topic of catenanes and rotaxanes on a year-by-year basis reveals that the number of articles published in this field each year has undergone steady and linear growth for over two decades, beginning around 1990. At the close of 2015, there were well over 3000 publications and almost 100,000 citations related to catenanes and rotaxanes in chemistry. The journals with 10 or more publications indexed under the keywords 'catenane' or 'rotaxane' at the close of 2015 are ranked in **Figure 1.40**, with general chemistry journals such as the *Journal of the American Chemocal Society*, *Angewandte Chemie*, and *Chemical Communications* dominating the spread, in a testament to the interdisciplinarity of the field. Geographically, the publications on mechanical bonds originate (**Figure 1.41**) from all around the world: Japan and the United States are in close contention to be the most active countries in this particular field of research, with the UK and China not far behind. In spite of this evidence for a remarkable worldwide interest in mechanical bonds at the molecular level, we note that the whole of mechanostereochemistry is underrepresented in our statistics, since mechanical bonds are prevalent in many synthetic compounds (**Section 4.3**) and biomolecules that lie beyond the scope of catenanes and rotaxanes.

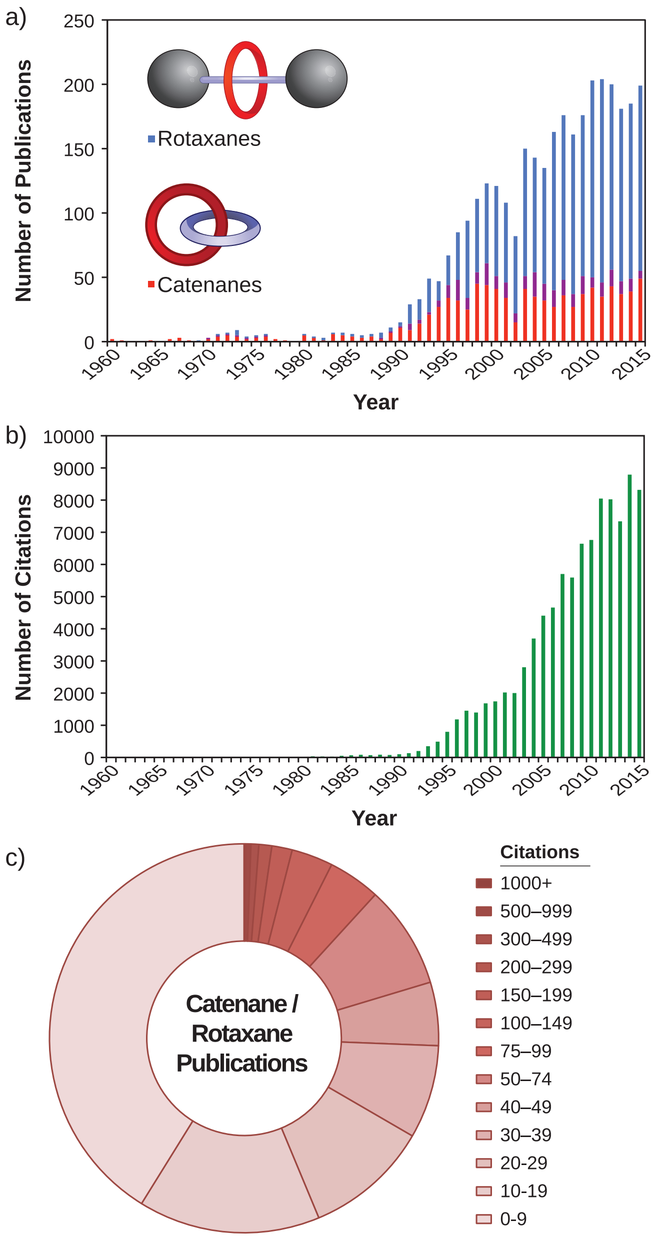


Figure 1.39 Statistics on journal publications indexed under the keywords, catenane or rotaxane. Histograms indicate the approximate number of (a) publications (total >3000) and (b) citations (total ~100,000) per year, from 1960 to 2015. Purple regions correspond to articles indexed under both keywords. The distribution of citations among these articles at the close of 2015 is represented by (c) a donut chart visualizing the proportionation of publications garnering different citation ranges. Citation counts are taken from Thomson Reuters Web of Science on 3 Jan 2016.

Another way to put perspective on the field is to look at the rhetoric of the literature in a time-resolved manner. The

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[F] Publications were tabulated in Scifinder (www.scifinder.com) using the keywords 'catenane' and 'rotaxane'

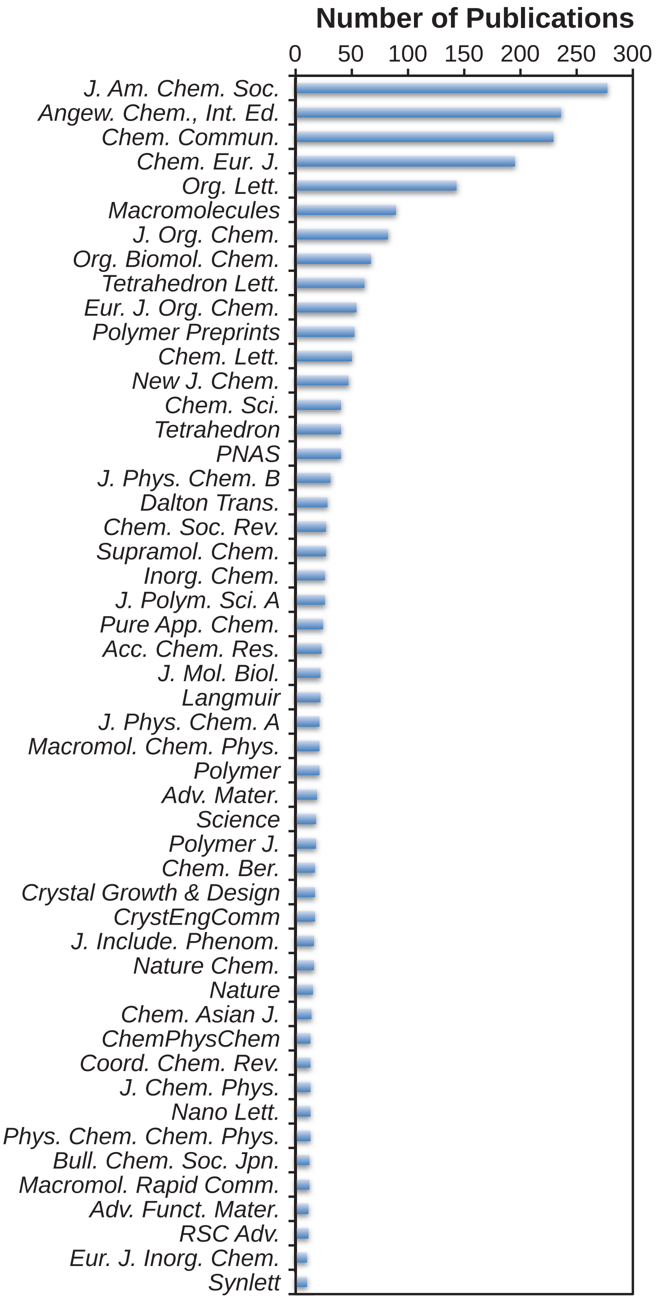

Figure 1.40 A comparison of international journals with 10 or more publications indexed under the keywords, catenane or rotaxane, at the end of 2015.

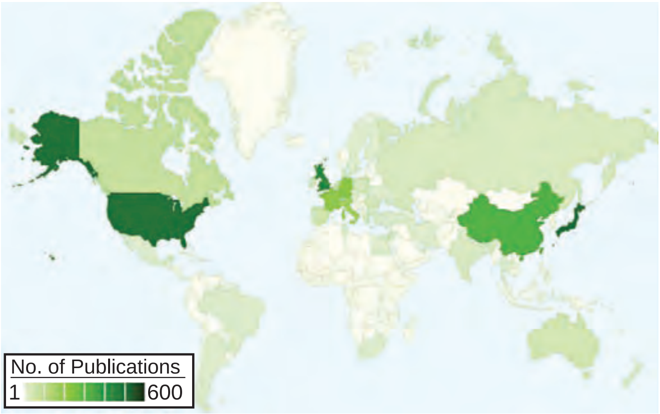

Figure 1.41 The distribution of publications indexed under the keywords, catenane or rotaxane, color-scaled on a world map according to country of origin.

artwork[G] in **Figure 1.42** portrays words that are scaled according to their frequency of appearance in the abstracts of the most highly cited papers from different eras of the mechanical bond. These eras are divided into four time periods: Pre-1990, 1990–1999, 2000–2010, and 2010–2015. Some trends can be identified by careful inspection of the most frequently used words during these eras. Prior to 1990, the prominence of words such as copper, catenate, catenand, and ligand reveal that the early literature prior to the boom of research beginning in 1990 was dominated by Sauvage's work on metallo-catenanes and rotaxanes. In the 1990s, words such as assemble, self-assembly, complex, and supramolecular become much more visible, reflecting the novel template-directed synthetic methods based on supramolecular chemistry which became a high priority. In the 2000s, we can see words such as systems, control, machine, device, movement, and switch come into the limelight, suggesting

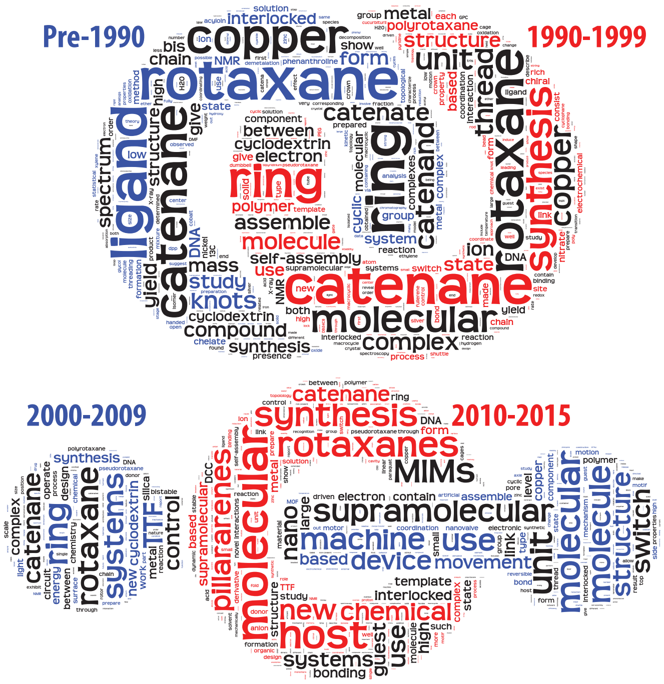

Figure 1.42 Word art based on abstracts from the most highly cited papers from various eras in the life of the mechanical bond. Each catenane or rotaxane component part is color-coded with respect to labels designating to which era the set of words belongs. Words are scaled according to the frequency with which they appear in the highly cited literature.

[G] These word art images are based on the first ~10,000 words to appear in abstracts, ranked in order of citation frequency for papers matching the keywords *rotaxane* or *catenane*.

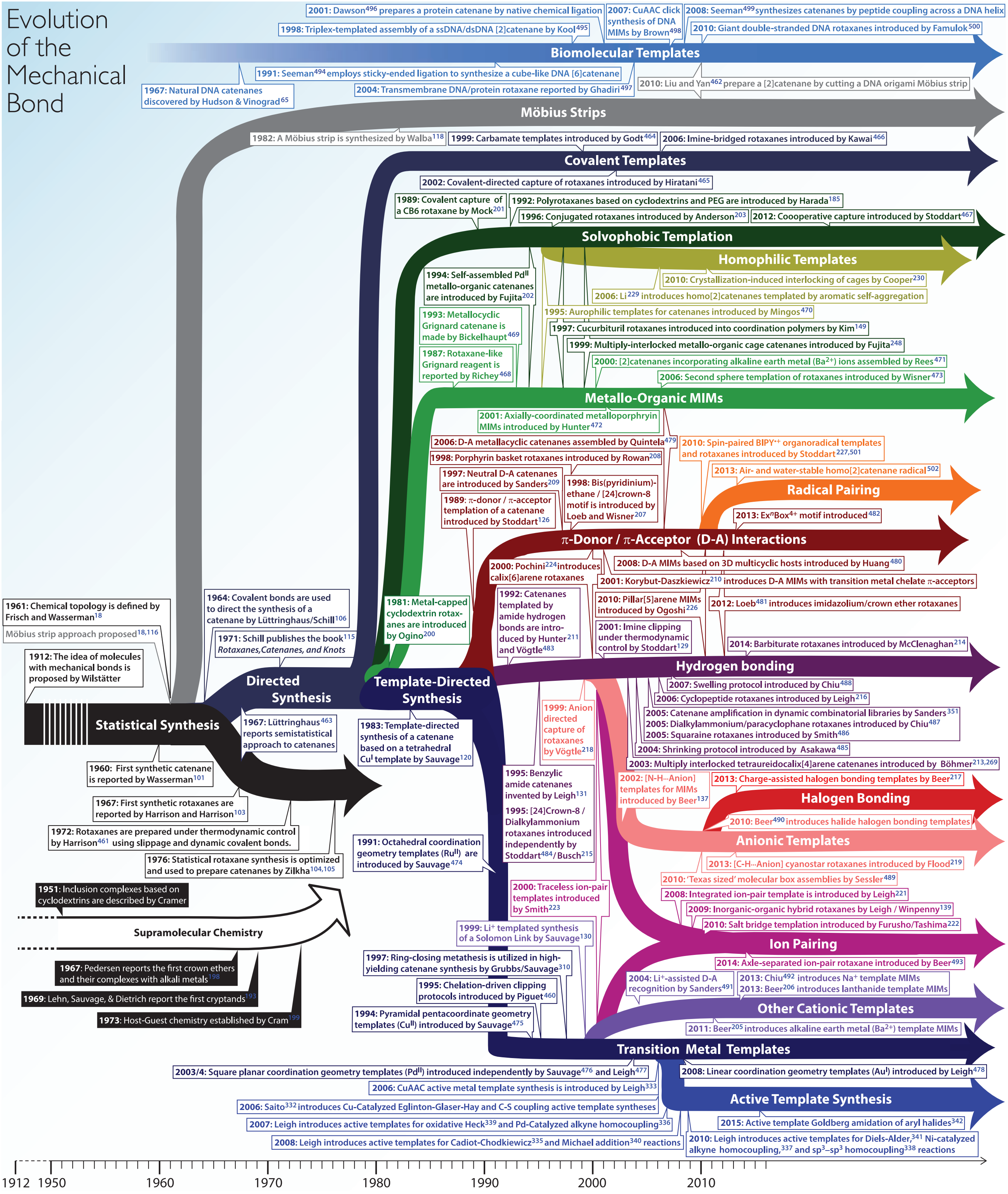

Figure 1.43 A time-resolved evolutionary tree, highlighting milestones and differentiation events in the synthesis of molecules with mechanical bonds and entanglements. See **Chapters 2–3**. A magnifying glass is prerequisite for readers who wish to explore the intricacies of the evolution of the mechanical bond in the molecular world.

that molecular switches were a heavy focus of this time period. Finally, a remarkable spike in research activity has placed pillararenes among the most frequent words in the highly cited abstracts of the current era, though we must wait at least another five years to find out which concepts will truly represent the hot topics of the present decade. An astute observer will notice from the information in the publication histogram (**Figure 1.39a**) and word art (**Figure 1.42**) that rotaxanes have been outcompeting catenanes in terms of research attention. Although much of the seminal work on mechanical bonds was done on catenanes, most of the growth of the field has been driven by rotaxane research. Catenane research, on the other hand, appears to have reached a plateau, at least for the time being. This inequality among the two main types of mechanically bonded molecules may be related to superior synthetic accessibility and potential applications of rotaxanes.

The evolution of the mechanical bond is not unlike Darwinian evolution by natural selection[459]—for example, events of differentiation can be identified in an evolutionary tree (**Figure 1.43**) describing milestones (see refs. 18,65, 101,103–106,115,116,118,120,126,129,131, 137,139,149,185,200–211,213–215,218,219,221–224, 226,227,229,230,248,269,307,310,324,332,333,335, 336,338–342,351,460–502) in the synthesis of mechanical bonds, where new strategies and template motifs have been introduced. An analogy to Darwin's 'survival of the fittest' mechanism for natural selection is also at play in mechanostereochemistry, since the majority of publications related to MIMs are attributable to only a handful of the 'fittest' types of recognition motifs: (i) hydrophobic forces (**Section 2.3.1**), especially those underpinning the supramolecular chemistry of the cyclodextrins and cucurbiturils, (ii) transition metal templates (**Section 2.3.2**), especially those based on copper, (iii) π-donor/π-acceptor templates (**Section 2.3.3**), especially those based on viologens, and (iv) hydrogen-bonded templates (**Section 2.3.4**), especially those based on macrocyclic lactams and crown ethers—which represent approximately 75% of the literature on mechanical bonds. See **Figure 2.87** in the conclusion of **Chapter 2** for a breakdown of the literature by template classification. Some of the newcomers to the field, such as anion binding (**Section 2.3.6**), active template synthesis (**Section 2.4**) and the host-guest chemistry of the pillararenes (**Section 2.3.9.2**), are proliferating rapidly.

The evolution of the mechanical bond is also captured in a timeline (**Figure 1.44**) showing how molecules with mechanical bonds have 'grown up' from a foundation of synthetic reactions and protocols, through to contemporary devices and applications. In the beginning, synthetic reactions and protocols for making mechanical bonds represented the only kind of research in mechanostereochemistry. As synthetic techniques (**Chapters 2–3**) became more highly developed—the most significant of which was the advent of template-directed synthesis—making mechanical bonds became more and more routine. As MIM synthesis was being mastered, more time and resources became available for the development of new mechanically interlocked architectures (**Chapter 4**), novel types of dynamics, isomerism, and chirality (**Chapter 5**), as well as molecular switches (**Chapter 6**). This stage of research is also reaching maturity, clearing a path for the next stage, which will be associated with artificial molecular machines (**Chapter 6**) and practical applications for mechanical bonds in science and technology. Although progress will continue on all of these fronts, the time is now upon us to cast aside our complacency, forsake our muddling along in solution, and press on to new frontiers—e.g., integrated systems, materials, solid-state chemistry, genuine molecular machinery, non-equilibrium self-organization and dynamics, applications in energy and medicine, complexity and emergence, and so on. We expect that, as the field pushes back these frontiers and others, a compilation of the important discoveries of the past will help to set the stage for this next act.

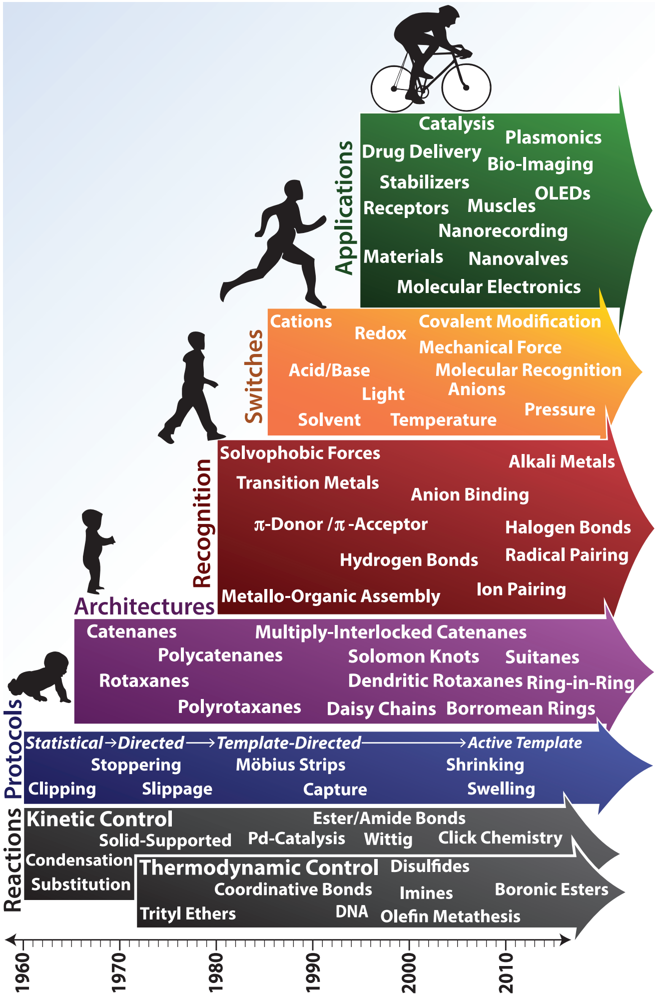

Figure 1.44 Timeline of research on the mechanical bond.

It is clear to us that the mechanical bond represents a flourishing field of chemistry, to the extent that a completely comprehensive review of the entire body of literature would be next to impossible. We have tried to strike a balance between being as comprehensive as possible in our coverage of topics related to MIMs, with the goal of summarizing synthetic protocols, molecular design motifs, techniques, dynamics, applications, significance, and future directions for the field, yet we have been forced in many cases to select only what we consider to be the most influential research. In this regard, we would be the first to admit that we might have been blind to or ignorant of some pieces of research that will give momentum to the mechanical bond's rise to prominence in chemistry.

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