



Mechanically Interlocked Molecules (MIMs)—Molecular Shuttles, Switches, and Machines

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PREAMBLE

One of the most influential books ever to have been written in the field of chemistry is *The Nature of the Chemical Bond* by Linus Pauling [1], the first edition of which was published in 1939. In this classic work, Pauling distinguishes between electrostatic, covalent and metallic bonds, while recognizing that chemical bonds between two atoms or groups of atoms exist when the forces acting between them lead to the formation of aggregates we call molecules. Three decades later came the realization that there is another field of chemistry that exists beyond the molecule, which Donald Cram [2, 3] referred to as host-guest chemistry, and Jean-Marie Lehn [4, 5] as supramolecular chemistry. Chemistry beyond the molecule relates to organized entities that can be neutral molecules, or even cations, anions or radicals, which come together to form higher-order aggregates—call them adducts or complexes—under the influence of stabilizing intermolecular forces that are considerably weaker than are the covalent bonds which define the entities themselves.

The process involving the coming together by organized entities is often referred to [6] as self-assembly and the noncovalent bonding that accompanies it as molecular recognition. The noncovalent bonds include hydrogen and

halogen bonds amidst a gamut of weak interactions which have been exploited to considerable effect during the past half century. On this time scale, another type of bonding in chemistry had been lurking in the background. That bond is the *mechanical bond* [7], which was the subject of an extensive treatise [8] entitled, *The Nature of the Mechanical Bond: From Molecules to Machines*, published as recently as 2016. Just as the chemical bond is associated in our minds with *attractive* forces, such as those associated with the sharing of electrons between atoms or the electrostatic forces that exist between ions of opposite charges, the mechanical bond is first and foremost a physical bond which is governed in the final analysis by *repulsive* forces that prevent chemical bonds from intersecting. Whereas chemical bonds are shared between atoms or groups of atoms, mechanical bonds are shared between molecular entities called *component parts*. It follows that a mechanical bond can be defined as an entanglement in space between two or more component parts such that they cannot be separated without breaking or distorting the chemical bonds between atoms.

MECHANICALLY INTERLOCKED MOLECULES

We have referred to molecules that possess mechanical bonds as mechanically interlocked molecules or *MIMs* for short. The two archetypal examples (Figure 1) of MIMs are the *catenanes* and the *rotaxanes*, which were the subject of a monograph [9] published in 1971 entitled *Catenanes, Rotaxanes, and Knots* by Gottfried Schill. A catenane, whose name is derived from the Latin word *catena*, meaning chain, is a molecule with two or more topologically linked macrocyclic component parts, while a rotaxane, whose name is derived from the Latin words *rota* for wheel and *axis* for axle, is a molecule comprising at least one macrocyclic component part, i.e., ring(s) with at least one linear component part, i.e., axle(s), threaded through the ring(s) and terminated by bulky end-groups (stoppers) large enough to prevent dethreading of the dumbbell(s) resulting from the existence/formation of chemical (covalent and/or coordinative) bonds between the stoppers and the axle(s). Two points are worthy of mention at this juncture. Catenanes and rotaxanes are molecules: they are *not* supramolecular entities or supermolecules despite the fact that they most likely will harbor intramolecular noncovalent bonds. While catenanes assume the trivial topologies of links, rotaxanes are topologically non-trivial for the simple reason that their component parts may be separated by continuous deformation, e.g., expanding the diameter of a ring or shrinking the cross-section of a stopper, both of which have been demonstrated [8] chemically. Related is the physical process of making rotaxanes known as slippage [10, 11].

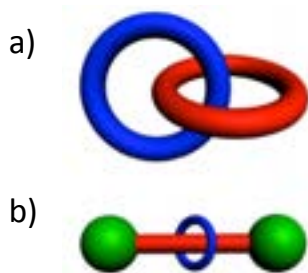


FIGURE 1. Graphical representations of a) a catenane and b) a rotaxane. A catenane is a mechanically interlocked molecule consisting of two or more interlocked rings. The word catenane is derived from the Latin *catena* meaning chain. A rotaxane is a mechanically interlocked molecule consisting of a dumbbell component threaded by one or more rings. The word rotaxane is derived from the Latin *rota* for wheel and *axis* for axle.

OLYMPIADANE

In the early 1990s the community was somewhat skeptical about the existence and worth of MIMs. Did they really exist and, if they did, how easy were they to make? If they were easy to make, in what context would they become useful? These were not unreasonable questions and they had to be addressed. In the event, it might well take, as of today, a decade or more to start providing answers to the second question. As far as the first question was concerned, it could be addressed rather easily, given the ability of X-ray crystallographer and structural chemist David Williams at Imperial College London to provide a fast turnaround on the solid-state structures of catenanes, and occasionally rotaxanes as well. In the case of donor-acceptor catenanes [12], we were intent on demonstrating that higher-order analogues could be produced using a template-directed protocol [13]. In this manner, both [3]- and [4]catenanes were synthesized in good yields overall and fully characterized. The envelope was pushed by two postdoctoral researchers, Anatoly Reder and David Amabilino, who, one after the other, took up the formidable challenge of making a [5]catenane (Olympiadane) whose constitution was confirmed [14] in 1996 by a solid-state structure (Figure 2), courtesy of David Williams. Ju-Young Lee gilded the lily by synthesizing a branched [7]catenane [15] in one step from Olympiadane. Both the collection of the crystallographic data, which took a couple of weeks, and the solving of the solid-state structure of the branched [7]catenane after a period of five months constituted a tour de force at the time by David Williams. The presence of 20 disordered PF_6^- counterions plus disordered solvent molecules on top of a crystallographic symmetry highlights the complexity of the task from both an experimental point of view and a computational one. The solid-state structures of these two

higher-order catenanes revealed a veritable array of noncovalent bonding interactions in the form of face-to-face [$\pi \cdots \pi$] stacking interactions (cf. DNA) and [C–H $\cdots \pi$] edge-to-face alignments of aromatic rings which are commonplace in proteins rich in aromatic amino acids, along with multiple [C–H \cdots O] hydrogen bonds. It is the installing of these (ultimately) intramolecular interactions that aids and abets the templation that makes it possible to synthesize these higher-order donor-acceptor catenanes. The point one learns from all this information is that it is the same weak interactions that are present in naturally occurring compounds that show up time and time again in exotic unnatural products. At the level of noncovalent bonding interactions, their presence is ubiquitous throughout biology, chemistry and materials science.

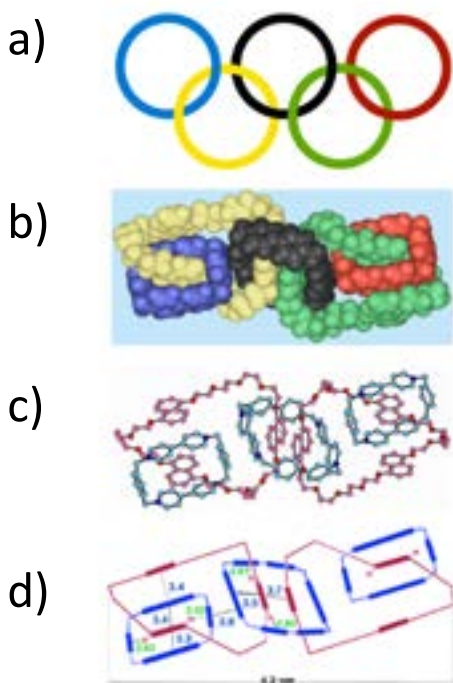


FIGURE 2. a) The Olympics logo consisting of five interlocked rings picked out from left to right in blue, yellow, black, green and red. b) A space-filling representation of the solid-state structure of a [5]catenane called olympiadane in which the five mechanically interlocked rings are colored according to the Olympics logo. c) A ball-and-stick structure of olympiadane which reveals that two outer blue rings are the same while the blue ring in the middle is a larger homologue of the two terminal rings. The other two red rings enjoy the same constitution in which three 1,5-disubstituted naphthalene rings are linked in a circular fashion, by tetraethylene glycol links. d) A graphical representation of Olympiadane where the (red) π -electron rich rings are mechanically interlocked with three (blue) π -electron poor rings.

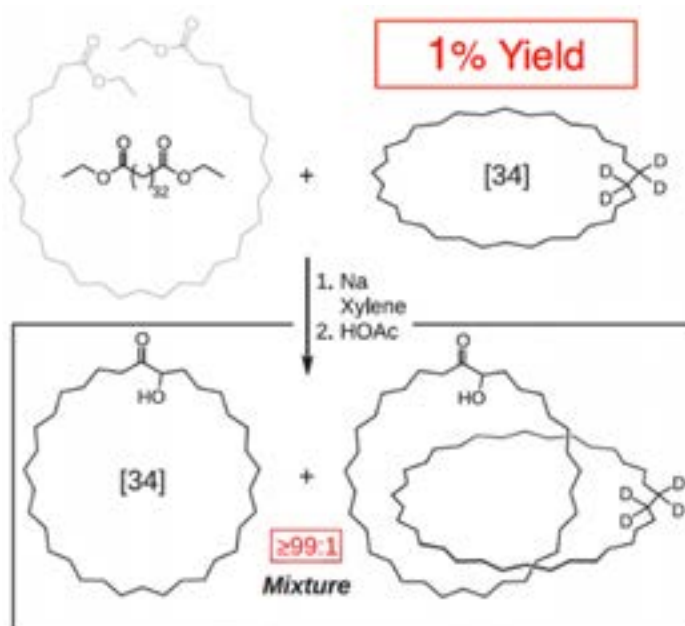


FIGURE 3. Wasserman's statistical synthesis reported in 1960 of arguably the first wholly synthetic [2]catenane employing an acyloin condensation in order to clip an acyclic diester around a deuterated cyclohexane derivative. The ring sizes, expressed as the number of carbon atoms in the rings, are denoted in square brackets. Deuterium labeling was employed as evidence in support of catenation following cleavage of the α -hydroxyketone functions with alkaline hydrogen peroxide.



FIGURE 4. Photograph of Ed Wasserman.

HISTORY

It was an absence of appreciation by chemists, in the era before there was a realization of the importance of noncovalent bonds and a recognition regime beyond the molecule, i.e., supramolecular chemistry, that led to a lack of success in the making of catenanes and rotaxanes. Wasserman's synthesis (Figure 3) of a [2]catenane [16] in no more than a 1% yield in 1960 bears witness to the fact that, without any appreciable noncovalent bonding interactions between the precursors to the component parts, the possibility of achieving mechanical interlocking to afford a [2]catenane was largely down to chance, hence the use of the term statistical synthesis to describe much of the research carried out in the 1960s. The achievement of Ed Wasserman (Figure 4) was to serve notice on the chemical community that, although catenation which relies on a chance event is, most likely not going to be efficient, it can be demonstrated. While Wasserman was carrying out his research at Bell Laboratories in Murray Hill, New Jersey, Gottfried Schill and Arthur Lüttringhaus at the University of Freiburg in Germany were devising ways [17] by which the component parts of a [2]catenane could be brought together using a covalent bond that could be cleaved in the final steps of the synthesis. The key compound shown at the top in Figure 5 was obtained crystalline after 14 initially linear steps towards the directed synthesis of the [2]catenane shown at the bottom in Figure 5. The authors described the key compound as *“one which is linked intra-annularly and in which the chains of the double ansa-system are situated on opposite sides of the benzene ring.”* They also drew attention to the fact that the chain in the precursor to the key compound, which is attached by means of a cyclic acetal to the benzene ring, is held at right angles to the plane of the ring on account of the tetrahedral configuration about the aliphatic (acetal) carbon atom, thus ruling out the formation of the isomer with the extra-annular attachment of the ring. The final four steps of the 18-step synthesis all went in nearly quantitative yields to afford the [2]catenane. Aside from it being a long and difficult synthesis, the fact that once all the covalent bonds holding the component parts together have been cleaved, the two mechanically interlocked rings are essentially devoid of any ‘cross-talk’ between them. Nonetheless, Schill continued to be active in the field of directed synthesis of MIMs, including rotaxanes, until the early '90s. I have commented elsewhere [18] that Gottfried Schill (Figure 6) can be looked up as the father of the mechanical bond: he is a chemist who was decades ahead of his time!

A seminal publication [19] by Jean-Pierre Sauvage (Figure 7) in 1983 describing (Figure 8) the use of a copper(I) ion to template the formation of

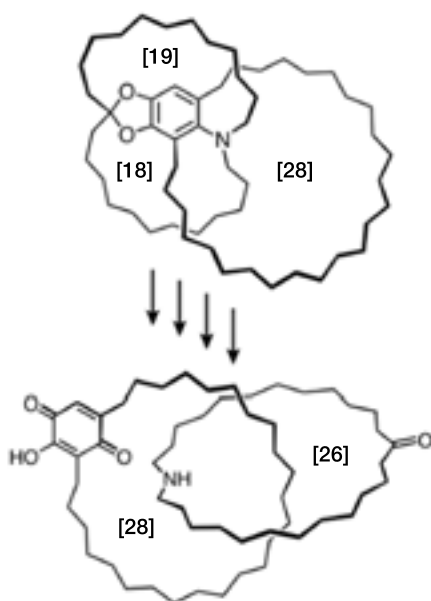


FIGURE 5. The telescoped final four steps in a 22-step covalent-directed synthesis of a [2] catenane reported by Schill and Lüttringhaus in 1964. The ring sizes, given in terms of the number of carbon atoms present in the rings, are denoted in square brackets.



FIGURE 6. Photograph of Gottfried Schill.



FIGURE 7. Photograph of Jean-Pierre Sauvage.

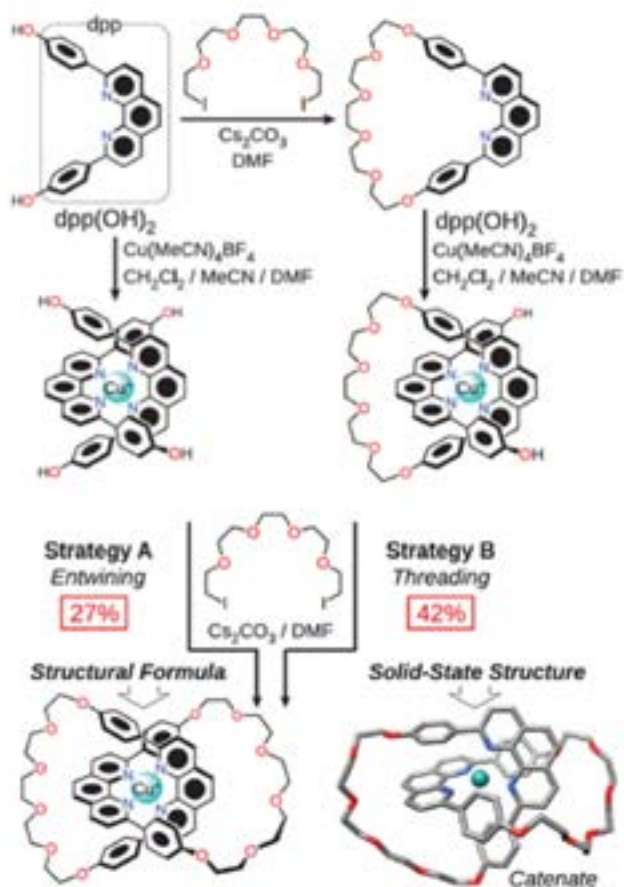


FIGURE 8. Sauvage's entwining (Strategy A) and threading (Strategy B) for the copper(I)-templated synthesis of the first catenane in 1983. In the bottom right-hand corner is a tubular representation of the solid-state structure of the catenane.

catenates—from whence, on demetallation, catenanes can be obtained—was a game-changer. His introduction of transition metal templation into the field of MIMs was transformative: it demonstrated that catenanes and rotaxanes were readily accessible and set the stage for the subsequent emergence and rapid growth of the field.

COMMERCIAL BUILDING BLOCKS

During a three-year secondment to the ICI Corporate Laboratory between 1978 and 1981, I joined forces with Howard Colquhoun in the investigation of the

second-sphere coordination of transition metal amines by crown ethers [20]. This program of research was sustained in its speed and efficiency by our striking up a highly fruitful collaboration with David Williams. One of the solid-state superstructures he obtained in 1981 was to set us on a road to discovery and invention. The superstructure (Figure 9a,b) in question was that of a 1:1 crystalline adduct that is formed [21] when a dicationic platinum ligand in addition to two *cis*-diammine ligands is crystallized ($\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}$) in the presence of a molar equivalent of dibenzo[30]crown-10 (**DB30C10**). While the two ammine ligands from $[\text{N}-\text{H} \cdots \text{O}]$ hydrogen bonds with the two polyether loops of **DB30C10**, the bipyridyl ligand finds itself slotted (Figure 9c) in between the two catechol rings of the crown ether. The structural similarity between the platinum

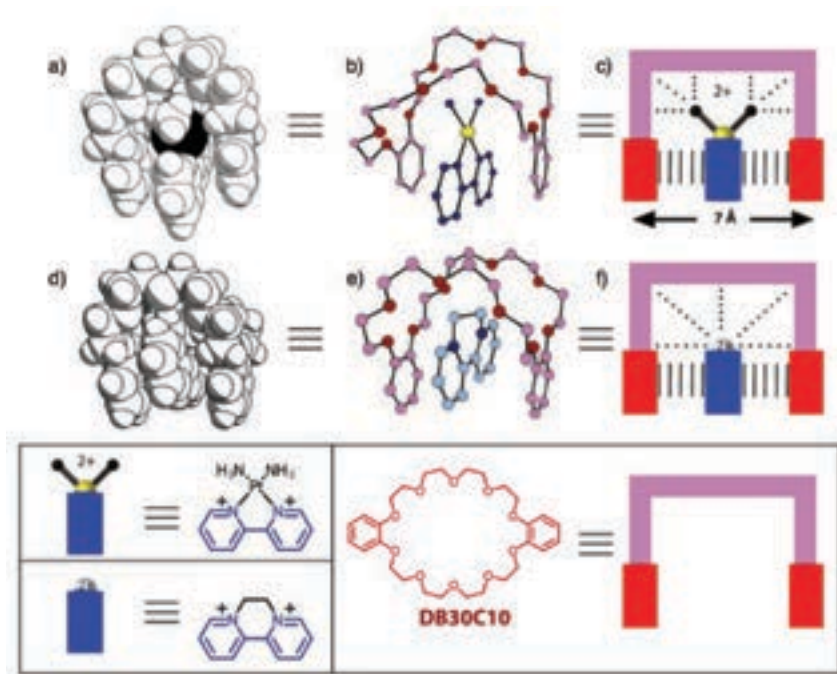


FIGURE 9. a) Space-filling and b) ball-and-stick representations of the 1:1 adduct formed between $[\text{Pt}(\text{bipy})(\text{NH}_3)_2]^{2+}$ and **DB30C10** in the solid state. c) A graphical representation of the 1:1 adduct showing the $[\pi \cdots \pi]$ stacking interactions (sets of vertical lines) and the $[\text{N}-\text{H} \cdots \text{O}]$ hydrogen bonds and pole-dipole interactions between the dicationic transition metal diammine and some of the oxygen atoms in the polyether loops of **DB30C10**. d) Space-filling and e) ball-and-stick representations of the 1:1 complex formed between the diquat dication and **DB30C10**. f) A graphical representation showing the $[\pi \cdots \pi]$ stacking interactions (sets of vertical lines) and the $[\text{C}-\text{H} \cdots \text{O}]$ hydrogen bonds between the bismethylene bridge in the diquat cation and some of the oxygen atoms in the polyether loops of **DB30C10**.

complex and diquat—a compound marketed by ICI at the time in admixture with paraquat as a ‘wipe-out’ weedkiller—led us to show that it forms [22] a 1:1 crystalline complex with **DB30C10** as well. Its solid-state superstructure (Figure 9d,e) mirrors that of the 1:1 adduct **DB30C10** forms with the platinum complex. The diquat dication finds itself enjoying (Figure 9f) charge transfer and π - π stacking interactions with the two catechol rings in the crown ether, aided and abetted by [C-H...O] hydrogen bonds.

BLUE INSIDE RED AND RED INSIDE BLUE

The next step, on my return to Sheffield in 1981, was to uncover a good crown ether receptor for paraquat. We had observed that **DB30C10** was able to form a weak 1:1 complex with diquat and so we argued that a small change to the constitution of the crown ether might be all that is required in order to pinpoint a good crown ether receptor for paraquat. This strategy proved to be successful. We found that a constitutional isomer of **DB30C10**, namely bisparaphenylene[34] crown-10 (**BPP34C10**), forms [23] a strong 1:1 complex with paraquat. Moreover, the solid-state superstructure (Figure 10a) of the crystalline 1:1 complex, when compared with the solid-state structure of **BPP34C10**, carried two very

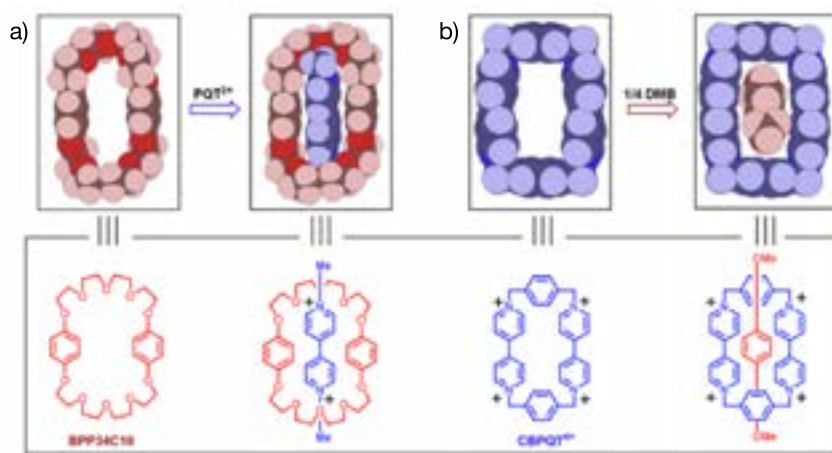


FIGURE 10. Comparison of the space-filling representations of the solid-state (super) structures of the two receptors a) BPP34C10 and b) CBPQT⁴⁺ and their 1:1 complexes obtained, respectively, with paraquat (PQT²⁺) and 1,4-dimethoxybenzene (1/4DMB). The box at the bottom relates the solid-state (super)structures to the structural formulas for the two receptors, BPP34C10 and CBPQT⁴⁺ and their 1:1 complexes with PQT²⁺ and 1/4DMB, respectively.

strong messages. One was the fact that the crown ether, at least as portrayed in the solid state, is preorganized to complex with the paraquat (PQT^{2+}) dication. The other was that the manner in which the PQT^{2+} dication threads through the **BPP34C10** ring is highly suggestive of it being a MIM precursor. In the context of molecular recognition, we had established how to bind a π -electron rich host—or using our color scheme, we could put blue inside red. The next question was—could we reverse the recognition motif and put red inside blue? Or expressed another way, could we bind a π -electron rich guest, e.g., 1,4-dimethoxybenzene (**1/4DMB**), inside a π -electron deficient host? With his synthesis [24] of cyclobis(paraquat-*p*-phenylene) (CBPQT^{4+}), Mark Reddington was able to show that **1/4DMB** does indeed bind, albeit somewhat weakly, with CBPQT^{4+} . Once again the solid-state superstructure (Figure 10b) of the crystalline 1:1 complex, when compared [25] with the solid-state structure of CBPQT^{4+} , reveals a highly preorganized match between the guest and the rigid host.

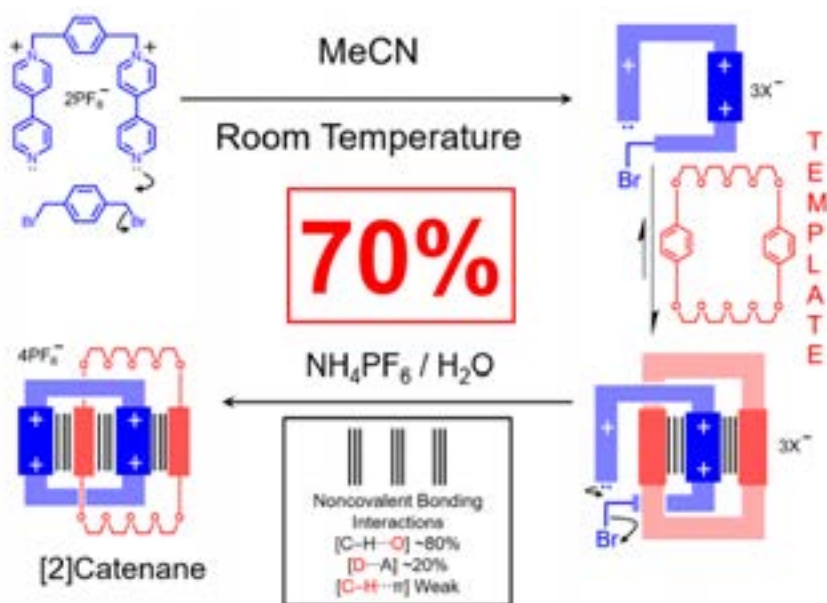


FIGURE 11. The template-directed synthesis of the first donor-acceptor [2]catenane under kinetic control at room temperature in acetonitrile. BPP34C10, which was present in 3 molar equiv, acts as a template in the stepwise formation of the CBPQT^{4+} ring in a process where covalent bond formation leads to the production of a bipyridinium unit which is recognized noncovalently by the BPP34C10 when threading occurs: thereafter a second covalent bond is formed resulting in the formation of the [2]catenane where the noncovalent bonding interactions ‘live on’ inside the MIM. They are indicated by the parallel vertical lines.

FIRST DONOR–ACCEPTOR CATENANE

We were now poised to perform the all-important experiment which would answer the question—what would happen if we carried out the synthesis of **CBPQT**⁴⁺ in the presence of **BPP34C10**? Cristina Vicent and Neil Spencer provided the answer by carrying out the reaction (Figure 11) in acetonitrile at room temperature in the presence of **BPP34C10** as a template. The outcome from the first reaction exceeded our wildest dreams: we were able to isolate our first donor-acceptor [2]catenane in a remarkable 70% yield. Our excitement did not stop there: a space-filling representation of the solid-state structure (Figure 12), which graced the front cover of the October 1989 issue of *Angewandte Chemie* [26], was a sight to behold. Moreover, both ¹H NMR spectroscopy and electrochemical experiments, performed in Miami by Angel Kaifer, conveyed a very strong message. The weak noncovalent bonding interactions (Figure 13a) that are accrued during the template-directed synthesis ‘live on’ in the [2]catenane afterwards. The implications of this observation were to be profound when it

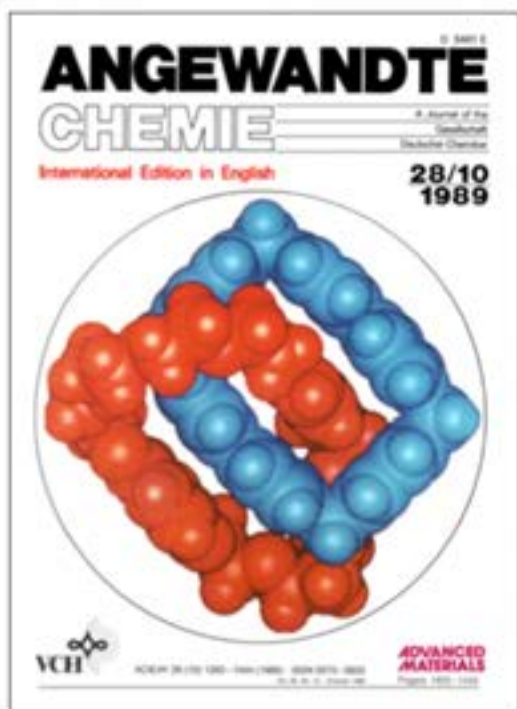


FIGURE 12. A space-filling representation of the solid-state structure of the first donor-acceptor [2]catenane adorning of the front cover of the October issue of *Angewandte Chemie* in 1989.

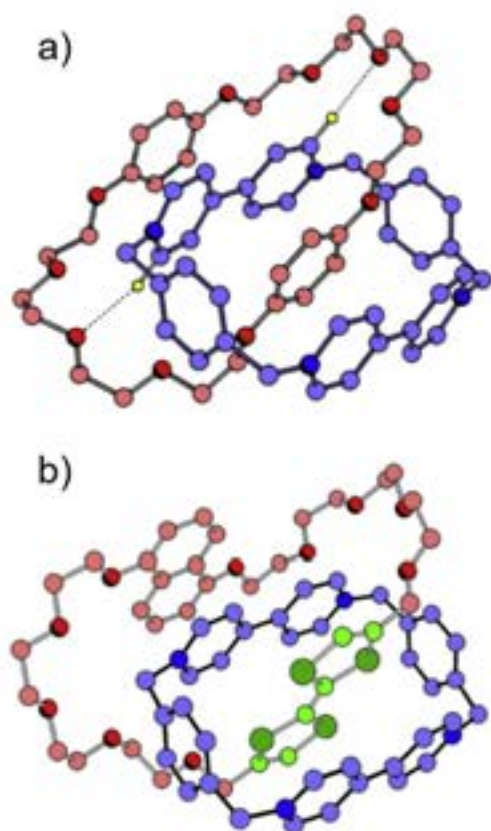


FIGURE 13. The solid-state structures, depicted in ball-and-stick representations, of a) the first donor-acceptor [2]catenane and b) a switchable donor-acceptor [2]catenane based on a stronger tetrathiafulvalene (green) and a weaker 1,5-dioxynaphthalene donor (pink). Note the presence in both [2]catenanes of π - π stacking interactions (3.5 Å) between the aromatic donors and acceptors. In the degenerate [2]catenane, note the presence of strong [C-H...O] interactions.

came to designing and synthesizing, first of all molecular switches, and then ultimately molecular machines.

MOLECULAR SHUTTLE

As we took our leave of Sheffield in 1990 to move to Birmingham, Pier Lucio Anelli had completed the template-directed synthesis (Figure 14) of a degenerate [2]rotaxane [27] modeled on that of the degenerate [2]catenane. The lower yield of 32% reflects the fact that the dumbbell template is much less preorganized

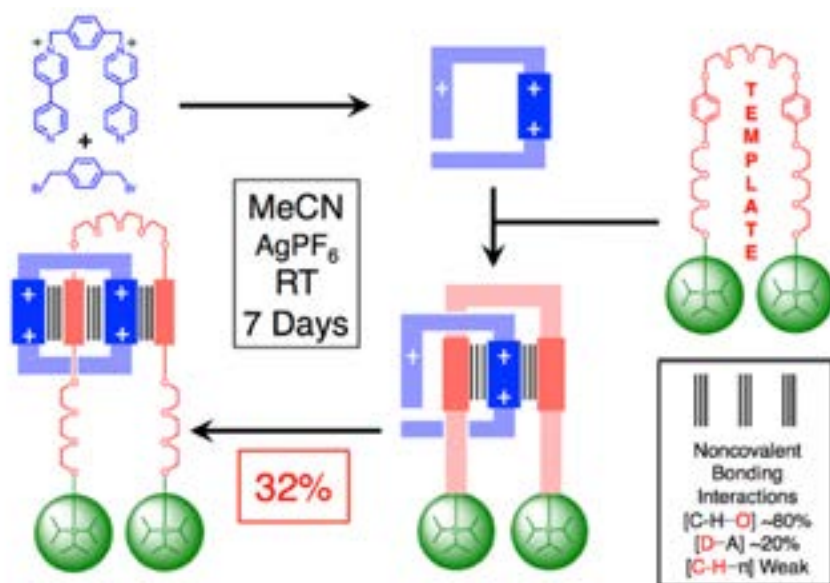


FIGURE 14. The template-directed synthesis of a degenerate donor-acceptor [2]rotaxane, also known as a ‘molecular shuttle’ under kinetic control at room temperature in acetonitrile. The dumbbell acts as the template for the formation of the CBPQT⁴⁺ ring in a stepwise manner. The noncovalent bonding interactions which ‘live on’ inside the [2]rotaxane are indicated by parallel vertical lines.

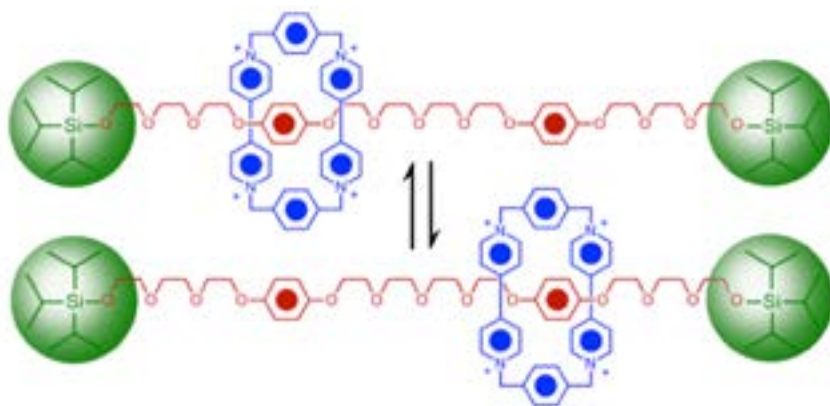


FIGURE 15. A degenerate donor-acceptor [2]rotaxane for which the phrase ‘molecular shuttle’ was introduced in 1991. The CBPQT⁴⁺ ring darts back and forth between the two hydroquinone recognition sites about 1000 times a second in acetone at room temperature. The molecular shuttle was seen as a prototype for the construction of molecular switches and machines based on molecules containing mechanical bonds.

than **BPP34C10**. Dynamic ^1H NMR spectroscopy, performed on the rotaxane in hexadeutero acetone, revealed that the CBPQT $^{4+}$ ring shuttles (Figure 15) back and forth between the two hydroquinone units ('stations') around 1000 times a second. For obvious reasons, I found myself referring to the compound as a molecular shuttle and was prompted to draw the following conclusion in the communication [27] published with this title in the *Journal of the American Chemical Society* in 1991—

The opportunity now exists to desymmetrize the molecular shuttle by inserting nonidentical 'stations' along the polyether 'thread' in such a manner that these different 'stations' can be addressed selectively by chemical, electrochemical, or photochemical means and so provide a mechanism to drive the 'bead' to and fro between 'stations' along the 'thread'. Insofar as it becomes possible to control the movement of one molecular component with respect to the other in a [2]rotaxane, the technology for building 'molecular machines' will emerge.

The molecular shuttle described in this communication is the prototype for the construction of more intricate molecular assemblies where the components will be designed to receive, store, transfer and transmit information in a highly controllable manner, following their spontaneous self-assembly at the supramolecular level. Increasingly, we can look forward to a 'bottom up' approach to nanotechnology, which is targeted toward the development of molecular-scale information processing systems.

MOLECULAR SWITCHES

The next challenge we faced was to desymmetrize the degenerate [2]rotaxane in an attempt to obtain a rotaxane with two recognition units on the dumbbell component, one of which is more attractive to being encircled by the CBPQT $^{4+}$ ring than the other. After much initial experimentation we settled on a design where one of the hydroquinone units in the molecular shuttle is replaced by a benzidine unit and the other by a biphenol residue. Since we were prevented from using benzidine in the United Kingdom, postdoctoral scholar Richard Bissell made the journey across the Pond in order to complete the template-directed synthesis of the non-degenerate [2]rotaxane in collaboration with Angel Kaifer. On this occasion, dynamic ^1H NMR spectroscopy revealed [28] that the CBPQT $^{4+}$ ring spends 84% of its time on the benzidine unit and 16% on the biphenol unit at

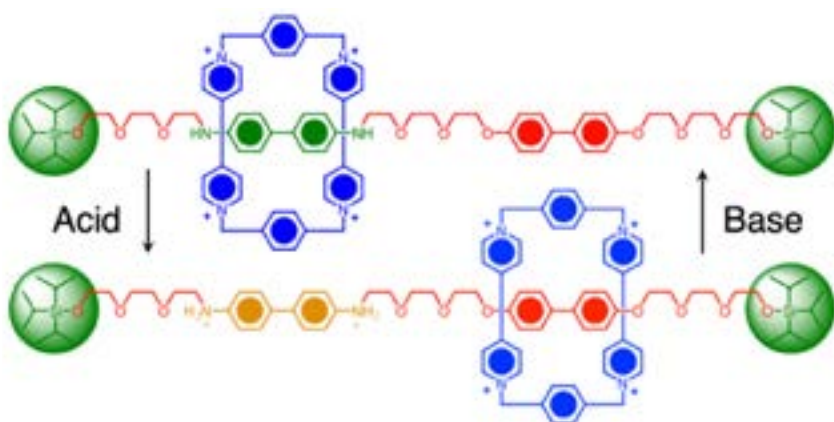


FIGURE 16. The first switchable donor-acceptor [2]rotaxane, where switching can be implemented by adding a drop of acid to protonate the benzidine recognition unit (the more preferred site for the location of the ring) whereupon the CBPQT⁴⁺ ring migrates to the biphenol unit, the less preferred site for the location of the ring on the neutral dumb-bell component. The switch can be reset by adding base.

equilibrium at room temperature in CD₃CN solution. The unequal distribution of the ring between the two recognition units was sufficient to allow us to intervene in the equilibrium between the two translational isomers. It was possible, by adding acid to protonate the nitrogen atoms on the benzidine unit, to induce (Figure 16), as a result of Coulombic forces, the CBPQT⁴⁺ ring to move to the neutral biphenol unit rather than reside on the deprotonated benzidine unit carrying its two positive charges. While this bistable [2]rotaxane was to rank as



FIGURE 17. Photograph of Jim Heath.

our first switchable donor–acceptor MIM, a bistable [2]catenane, [29] in which one of the two hydroquinone rings in the BPP34C10 component of the original [2]catenane (Figure 13a) was replaced by a tetrathiafulvalene (TTF) unit and the other with a 1,5-dioxynaphthalene (DNP) unit was designed and synthesized by Gunter Mattersteig. The solid-state structure (Figure 13b) of this bistable [2]catenane reveals that the TTF unit resides inside the cavity of the CBPQT⁴⁺ ring, while the DNP unit is located outside and alongside one of the two bipyridinium (BIPY²⁺) units in the CBPQT⁴⁺ ring.

MOLECULAR ELECTRONICS

This bistable [2]catenane was used [30] to construct a solid-state electronically reconfigurable switch in a simple crossbar device by Jim Heath (Figure 17) when we entered into a highly fruitful collaboration, following my move from Birmingham to the University of California, Los Angeles (UCLA). Prior to introducing

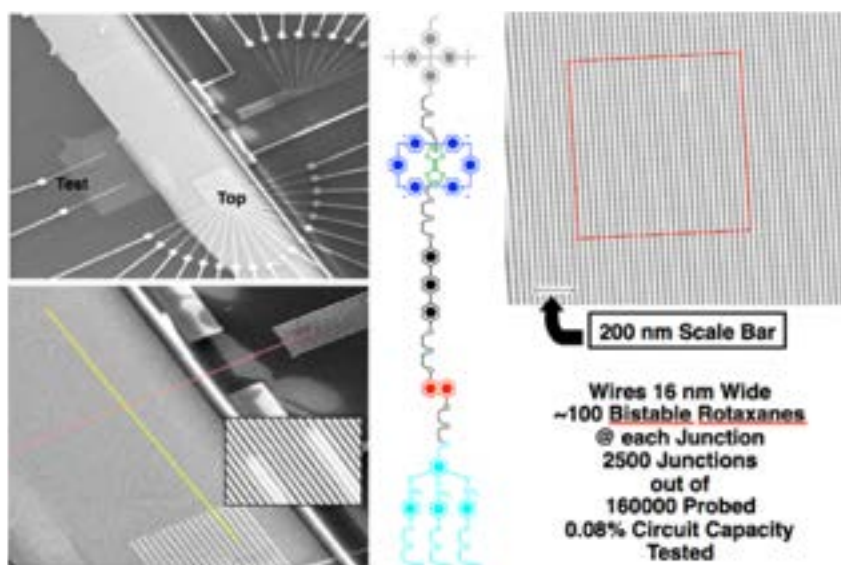


FIGURE 18. Scanning electron microscope image (top left) of the nanowire crossbar memory. The array of 400 Si bottom nanowires is portrayed as the light grey rectangular patch extending diagonally up from the left. Scanning electron microscope image (middle) showing the cross-point of the top (red) and bottom (yellow) nanowire electrodes. Each cross-point corresponds to an ebit in memory testing. High resolution scanning electron microscope image (top right) of approximately 2500 junctions out of a 160,000-junction nanowire crossbar circuit. The red square highlights an area of the memory that is equivalent to the number of bits tested. Positioned in the center of the illustration is the structural formula of the bistable [2]rotaxane used in the memory.

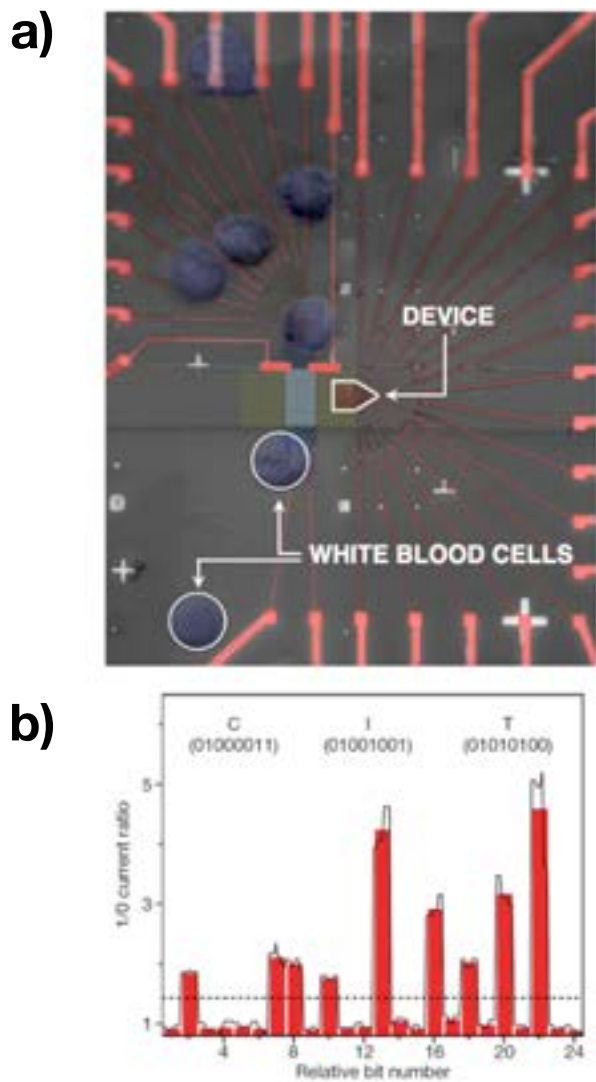


FIGURE 19. a) A 160-kilobit crossbar molecular memory device (orange in the middle of the illustration) is smaller than the cross-sectional area of a white blood cell (purple). b) A demonstration of point-addressability within the crossbar. Good ebits were selected from the defect mapping of the tested portion of the crossbar. A string of 0s and 1s corresponding to the ASCII characters for ‘CIT’ (California Institute of Technology) were stored and read out sequentially. The dotted line indicates the separation between the 0 and 1 states of the individual ebits. The black trace is raw data showing 10 sequential readings of each bit while the red bars represent the average of these 10 readings.

this bistable [2]catenane into the crossbar device we had ascertained [31] how to effect its transfer onto the device using the Langmuir-Blodgett (LB) technique from a Langmuir monolayer where the counterions are dimyristoylphosphatidyl anions. The ON/OFF ratios for the molecular switch tunnel junctions (MSTJs) in crossbar devices, incorporating the bistable [2]catenane, were only around 2. The desire to increase this ratio took us inexorably in the direction of bistable [2]rotaxanes (Figure 18) which, it transpired, can be switched with an order of magnitude higher ON/OFF ratios. Reversible, electronically driven switching was not only observed in MSTJs incorporating a molecular monolayer of this bistable [2]rotaxane sandwiched between a bottom polysilicon electrode and a top titanium/aluminum electrode, but a 160,000-bit molecular electronic memory circuit has also been fabricated (Figure 19a) at a density of 100,000,000,000 bits per square centimeter [31, 32]. The entire 160-kbit crossbar assembly was smaller than the cross-section of a white blood cell and could be switched (Figure 19b) up to around 100 times. The search for a more robust setting [34] in metal-organic frameworks for these bistable MIMs continues [35].

DRUG DELIVERY SYSTEMS

In a collaboration with Jeff Zink (Figure 20) at UCLA, we have functionalized the surfaces of mesoporous silica nanoparticles (MSNPs) with both rotaxane-based nanovalves and snap-tops (Figure 21) for the controlled release of drugs. The nanovalves which adorn the surfaces of the MSNPs can be bistable donor-acceptor [2]rotaxanes [36] where redox chemistry can be used to open and close the



FIGURE 20. Photograph of Jeff Zink.

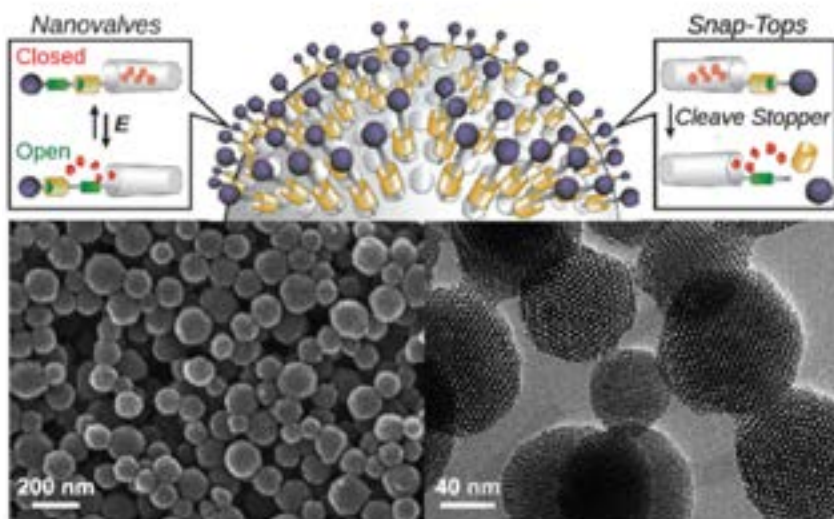


FIGURE 21. Examples of mechanized mesoporous silica nanoparticles (MSNPs). Illustrations of the mode of operation of rotaxane-based nanovalves and snap-tops for the controlled release of drugs. Scanning electron microscopic (bottom left) image of MSNPs. Transmission electron microscopic (bottom right) image of MSNPs.

nanovalves. This type of integrated device holds considerable promise for drug delivery systems.

MOLECULAR MACHINES

A fundamental property of biological molecular machines, e.g., the motor proteins [37–44], is that they consume energy and drive systems away from equilibrium by controlling kinetic barriers. The emergence of the science of artificial molecular machines (AMMs) in the hands of chemists, for the most part, presents us with a steep learning curve to negotiate. Nonetheless, it is a challenge that the chemistry community has embraced increasingly during the past two decades with much of the teaching of the fundamental theory coming from the physics community, and, in particular, one very prominent physicist from the University of Maine, namely Dean Astumian [45–48] with whom we have collaborated as well as published several reviews [49–51] that stand alongside a crop [52–69] that can be traced back for at least two decades from the present day. In my Nobel Lecture, I chose to highlight the progress [50, 51] we have made in recent times on the design and synthesis of artificial molecular pumps, based on the building blocks that found their origins almost 40 years ago in the ICI

Corporate Laboratory and were used by us [21–27] to put the mechanical bond on a firm footing before introducing [28] them into molecular switches in the first instance.

UNIDIRECTIONAL TRANSPORT

At the outset, we designed and synthesized a constitutionally unsymmetrical dumbbell [34] and demonstrated (Figure 22) that it transports the **CBPQT**⁴⁺ ring in a unidirectional manner. In its midriff, the dumbbell houses an electron rich 1,5-dioxynaphthalene (DNP) unit which is capable of recognizing the electron poor **CBPQT**⁴⁺ ring. Kinetic control of the threading and dethreading of the dumbbell by the ring is managed by arranging to have a neutral isopropylphenyl (IPP) unit at one end of the dumbbell and a positively charged 3,5-dimethylpyridinium (PY⁺) unit at the other end. The **CBPQT**⁴⁺ ring finds its most thermodynamically stable location on the DNP unit by passing over the IPP unit for the simple reason that the positively charged ring is repelled by the PY⁺ unit. When the **CBPQT**⁴⁺ ring is reduced to **CBPQT**^{2(•+)}, the relative heights of the two barriers change on account of the significantly decreased Coulombic barrier confronted by the ring which also, most likely, undergoes a reduction in size, resulting in increasing steric interactions with the PY⁺ unit. At the same time, the donor–acceptor interactions between the **CBPQT**^{2(•+)} ring and the DNP recognition unit are nullified, resulting in a preference for the rings to dethread into solution over the charged end of the dumbbell. In what is essentially a supramolecular system, no work is done: rings are extracted out of solution onto the dumbbell momentarily before being released back into solution.

RADICAL INTERACTIONS AND TEMPLATION

Our initial approach [70] to introducing unidirectionality into a supramolecular system employing donor–acceptor interactions demonstrated that we can control the relative motion between a dumbbell and a ring. The system, however, lacks the potential for it to be developed into a more sophisticated molecular machine where useful work can be done since the free energy change during the redox cycle is simply too small to be useful in a practical context. A discovery (Figure 23) made in my research laboratory in 2010 by Ali Trabolsi and Albert Fahrenbach was to come to the rescue. They showed [71] that a relatively strong tricationic triradical complex ($K_a = 10^4\text{--}10^5\text{ M}^{-1}$ in MeCN) is formed between **CBPQT**^{2(•+)} and bipyridinium (**BIPY**^{•+}) radical cations under reducing conditions. The strong binding affinity (attraction) can be switched back to being

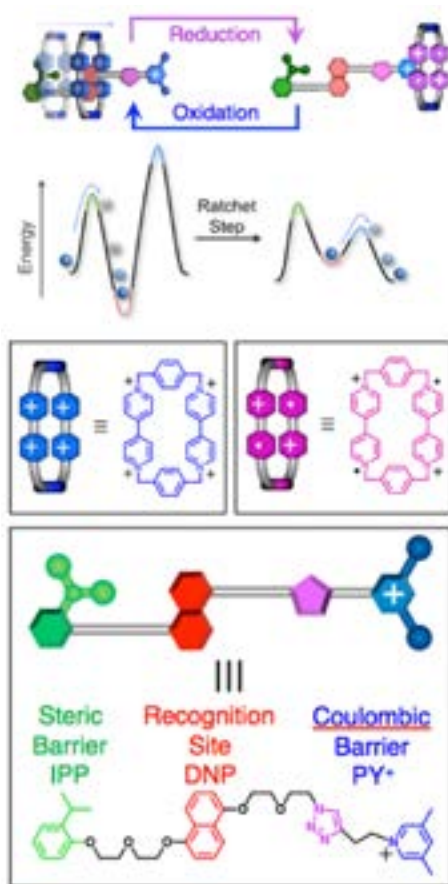


FIGURE 22. The redox-controlled unidirectional movement of a CBPQT^{4+} ring along a dumbbell with a neutral steric barrier (green) on the left, a recognition site (red) for the ring under oxidative conditions in the middle and a positively charged Coulombic barrier (blue) on the right. Underneath are energy profiles illustrating the operation of an energy ratchet. The cartoons are defined in the boxes below.

highly repulsive, following oxidation of the radical cations, in both instances, to give CBPQT^{4+} and BIPY^{2+} , resulting in a massive enthalpy change, something which struck us as being highly promising when it comes to designing and synthesizing AMMs to perform useful work.

We reasoned that we could achieve much better and more efficient unidirectional transport of CBPQT^{4+} rings if we were to replace (Figure 24) the DNP unit in the constitutionally unsymmetrical dumbbell with a BIPY^{2+} unit and employ radical chemistry to form a stable [2]rotaxane-like tricationic triradical on reduction of both the ring and the BIPY^{2+} unit. We had already employed

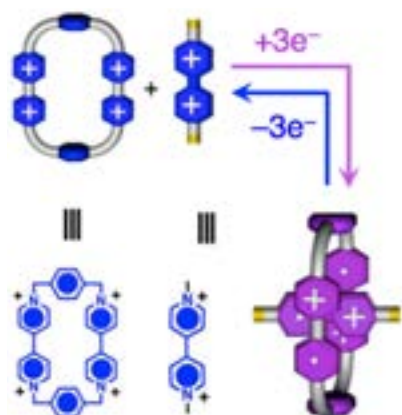


FIGURE 23. The formation of a CBPQT²⁽⁺⁺⁾ ring and PQT²⁺ on reduction. The dissociation of a CBPQT⁴⁺ ring and PQT²⁺ on oxidation of the 1:1 trisradical tricationic complex.

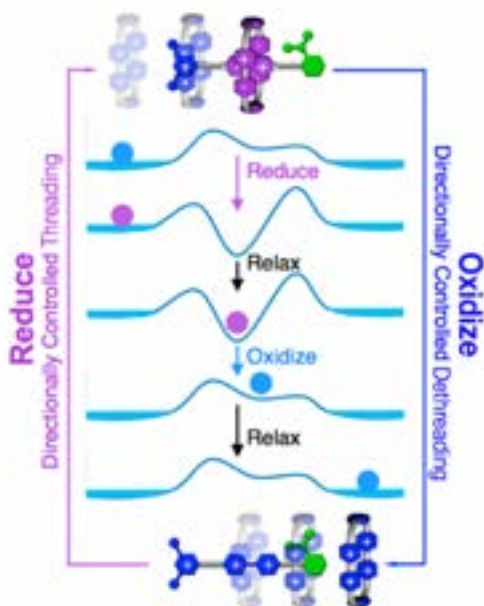


FIGURE 24. Graphical representations and energy profiles for an artificial molecular pump prototype based on radical-radical stabilizing interactions. In this prototype a bipyridinium radical cation (BIPY^{•+}) centered on a dumbbell with the charged end on the left and the neutral one on the right. The CBPQT²⁽⁺⁺⁾ bisradical dication threads onto the dumbbell over the charged end on the left. On oxidation, a push-button molecular switch comes into action as a result of the generation of six positive charges in place of three that were suppressed previously by radical-radical interactions. The net result is the generation of a lot of potential energy which obliges the CBPQT⁴⁺ ring to depart from the neutral right-hand end of the tricationic dumbbell. No work has been done.

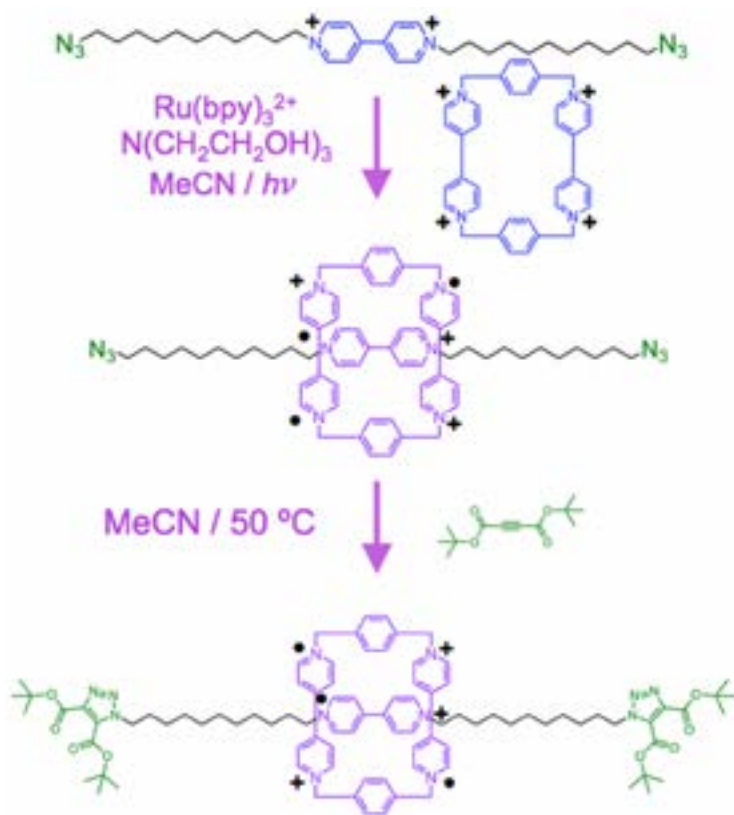


FIGURE 25. The use of radical templation, promoted by light in the presence of a photosensitizer and sacrificial electron donor, to obtain, following click chemistry, a trisradical tricationic [2]rotaxane.

radical templation [72] to synthesize (Figure 25) a [2]rotaxane—as well as a homo[2]catenane [73]—and demonstrated (Figure 26) the strong repulsion that comes into play when the ring and recognition unit are oxidized back to CBPQT^{4+} and BIPY^{2+} , respectively.

ARTIFICIAL MOLECULAR PUMP

Based on all these previous observations, and a large number of exploratory experiments conducted painstakingly by Chuyang Cheng, he settled on the design (Figure 27) of an artificial molecular pump [74, 75]—call it Mark I—where an oligomethylene chain terminated by a stopper is attached at its other end to an IPP speed bump so that this portion of the dumbbell can act as a

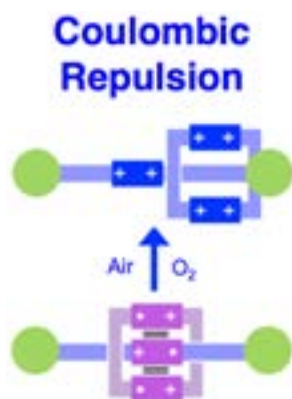


FIGURE 26. Exposing the trisradical tricationic [2]rotaxane to air produces a hexacationic [2]rotaxane which behaves like a molecular shuttle with an electrostatic barrier to shuttling.

collecting chain for the rings transported from solution. In the oxidized state, the $\text{CBPQT}^{2(\bullet+)}$ ring and the molecular pump portion of the dumbbell repel each other. Upon reduction, the $\text{CBPQT}^{2(\bullet+)}$ ring passes quickly over the PY^+ unit in search of the radical recognition site, namely a $\text{BIPY}^{\bullet+}$ unit, to form the thermodynamically favored trisradical tricationic complex. On oxidation, this complex becomes a highly unstable species carrying six positive charges. Under these circumstances, the CBPQT^{4+} ring would like to relax to a more favored location. Although its returning to the bulk solution is thermodynamically favored, this pathway is blocked kinetically by the PY^+ unit, which acts as a Coulombic barrier to deslipping of the ring. Hence, with the aid of thermal energy the ring passes over the IPP speed bump onto the collecting chain. When a second reduction is performed, the IPP unit prevents the association of the trapped ring with the $\text{BIPY}^{\bullet+}$ recognition site, enabling this site to attract a second $\text{CBPQT}^{2(\bullet+)}$ ring from solution. In this AMM two positively charged rings are collected by a positively charged dumbbell, reflecting a process that is neither entropically nor enthalpically favored. Work is done! The artificial molecular pump operates away from equilibrium by relying on the consumption of redox chemical energy. Our findings have shown that the kinetics associated with two cycles are the same to all intents and purposes (Figure 28), suggesting that the first ring to be trapped does not have a significant influence on the threading of the second ring. These results are promising since they indicate that it is possible to extend the two-cycle system into a multi-cycle one, opening up the possibility

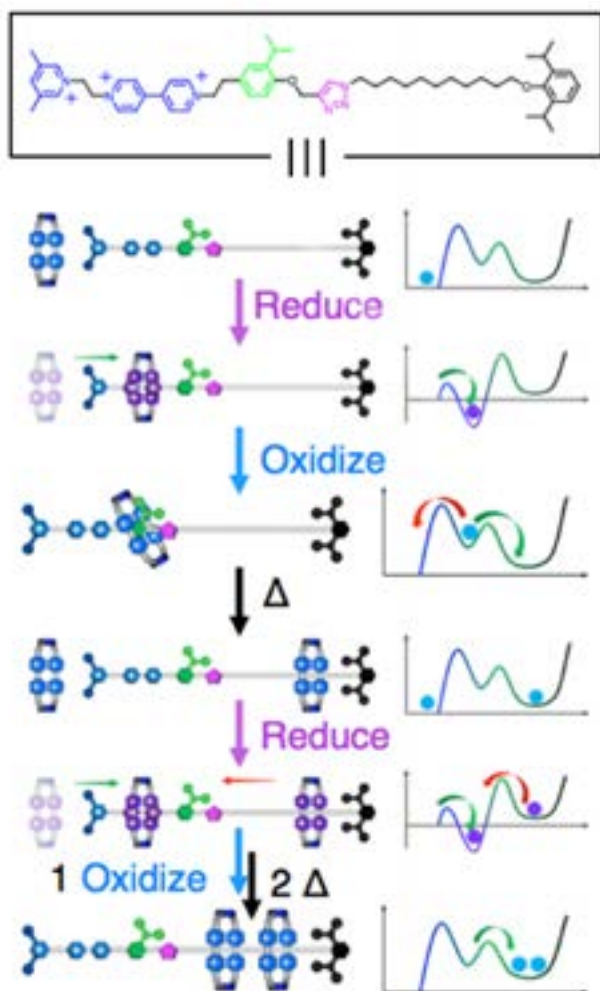


FIGURE 27. Graphical representations of the pumping mechanism which operates in the case of the artificial molecular pump, portrayed as its structural formula in the box atop the illustration. The energy profiles illustrate two strokes of the pump whereby the CBPQT^{4+} ring is plucked out of solution in its reduced $\text{CBPQT}^{2(++)}$ form and then forced over a steric barrier (green) onto a long collecting chain by thermal energy following oxidation. Work is done.

of synthesizing slide-ring materials [76]. A couple of design modifications to the artificial molecular pump are being explored currently: one is to speed up [77] the action of the pump in a Mark II version at least four-fold from two hours per redox cycle to 30 minutes, and the other is to double the addition of rings to polymer chains (Figure 29) by locating pumps at both ends of the chains.

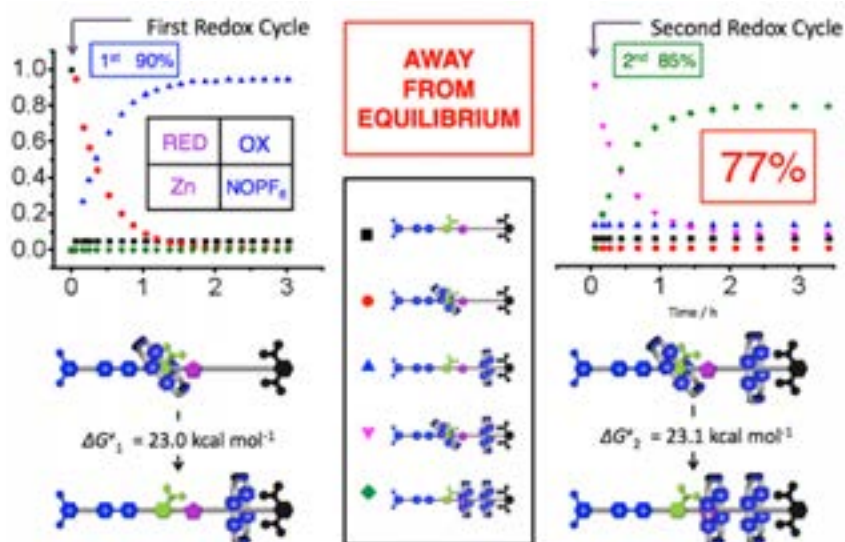


FIGURE 28. The artificial pump working away from equilibrium. Plots in the change of mole fractions of co-conformations over time in CD₃CN at 42 °C during the co-conformational rearrangements that occur after the first cycle to give the [2]rotaxane and after the second cycle to give the [3]rotaxane.

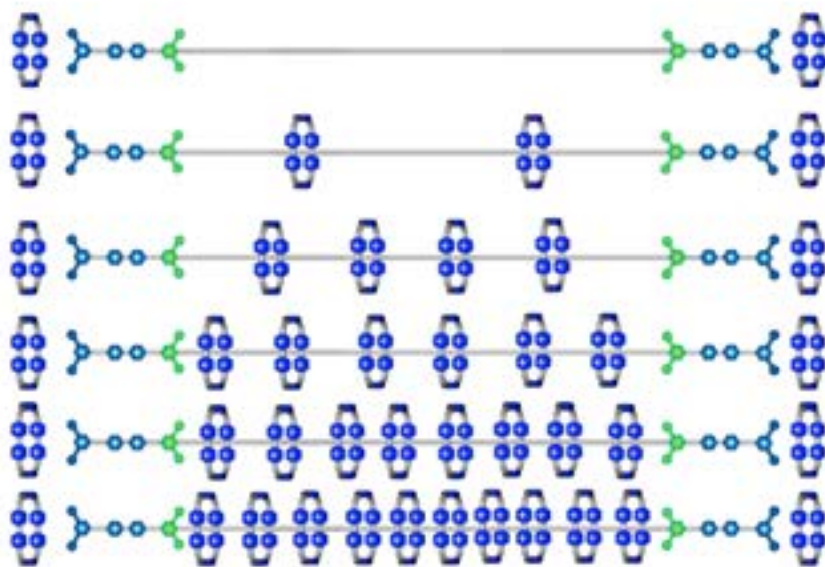


FIGURE 29. Pumping CBPQT⁴⁺ rings in pairs onto polymer chains terminated at both ends with artificial molecular pumps.

EPILOGUE

In summary, our interest in AMMs was given a considerable fillip in 1991 with the advent [27] of the molecular shuttle, and the demonstration [28] of the first donor–acceptor bistable switch in 1994. During the past couple of decades, there have been many investigations [52, 54, 57] carried out in collaboration with Vincenzo Balzani at the University of Bologna. Our entry into radical chemistry [71] and radical templation [72] in 2010 set the stage for going forward from entropically driven unidirectional translation with donor–acceptor systems under thermodynamic control in 2013 to enthalpically driven unidirectional transport in 2015 under kinetic control and continuing up to the present time.

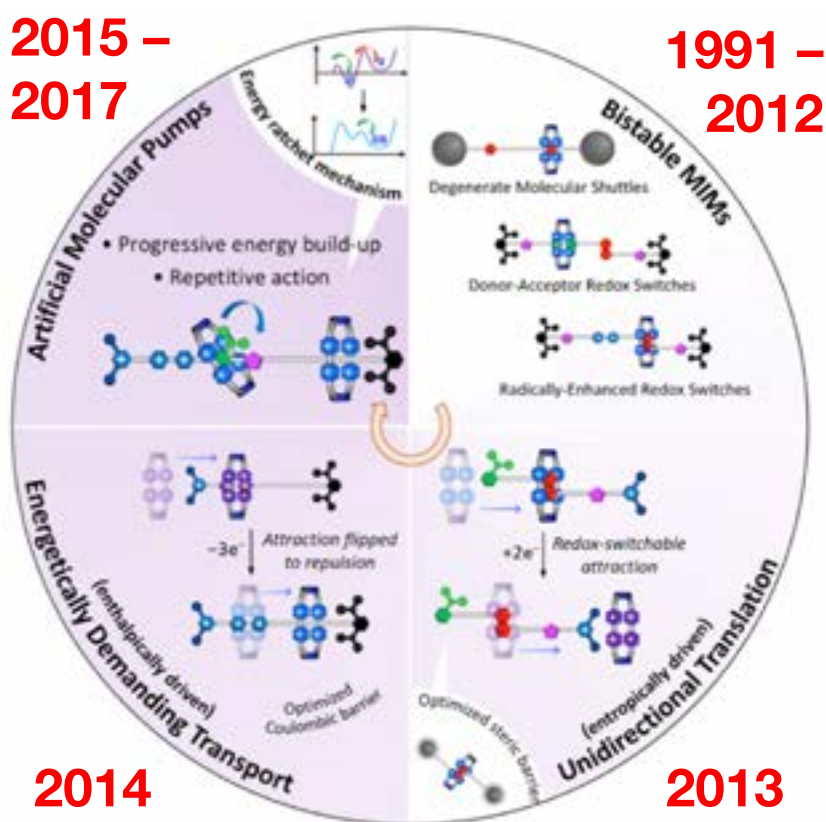


FIGURE 30. A timeline for the design and synthesis of bistable mechanically interlocked molecules (1991–2012), leading to unidirectional transport (2013) and energetically demanding transport (2014), and artificial molecular pumps (2015–2017).

In a recent Tutorial Review [51] in *Chemical Society Reviews* on *Mastering the Non-Equilibrium Assembly and Operation of Molecular Machines*, written in collaboration with Dean Astumian, we focus on the thermodynamics and kinetics associated with the operation of AMMs and discuss how theory can influence the design principles for constructing molecular machines going forward. A lot of

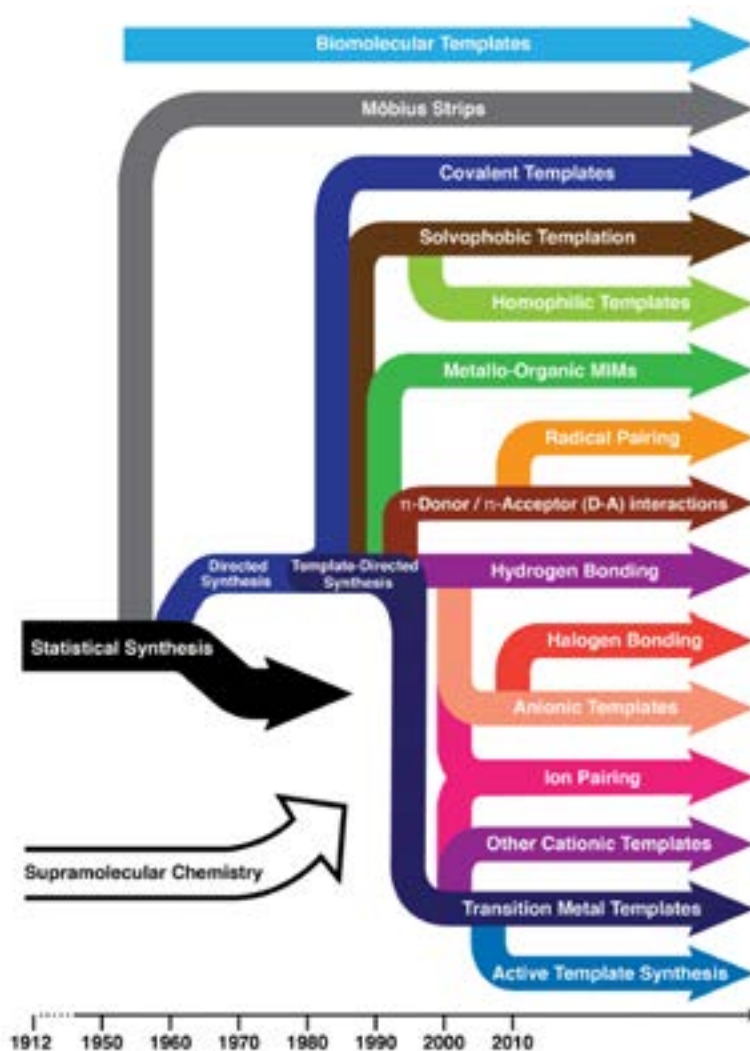


FIGURE 31. The evolution of the mechanical bond. A time-resolved evolutionary tree highlighting milestones and differentiation events in the template-directed synthesis of mechanical bonds. See ref [8].

fundamental work remains to be done. It is too early to speak in an authoritative and informed manner about what will be the killer applications of AMMs. We are at the very early stages of knowing how to build them, let alone use them. Let me use the analogy of manned flight, particularly in relation to where aviation had reached in 1927, the year in which Charles Lindbergh crossed the Atlantic Ocean in the Spirit of St Louis. An account of the practice of manned flight in 1927 is told [78] in all its amazing glory and gory detail in *One Summer* by Bill Bryson. Compare and contrast the situation for aviation in 1927 with where it stands today as a form of mass transport that has not only opened up country-wide travel, but has also brought Continents together on the grandest of scales. As far as MIMs and AMMs are concerned, they await the engagement of the next generation of chemists eager to exploit the nature of the mechanical bond in chemistry, while taking up the task of designing and synthesizing MIMs and putting them to good use. Figure 31 presents a time-resolved evolutionary tree which highlights the milestones and differentiation events in the synthesis of MIMs. Insofar as the template-directed protocols have established themselves as the most efficient ways to make ‘intelligent’ MIMs, a breakdown [8] of the recent literature, based on a random selection of 500 articles on catenanes and rotaxanes, has led to the visualization of the data in a pie chart (Figure 32). Presently, solvophobic, hydrogen bonding, donor–acceptor, and metal templation account for a good three-quarters of the chemical literature on the mechanical bond. The histogram illustrated in Figure 33a tracks the number of publications on catenanes (red) and rotaxanes (blue), and those containing both MIMs (purple), on a year-by-year basis. Publications relating to the mechanical bond originate (Figure 33b) from all over the world with the United States, Japan, and the United Kingdom at the top of the list and China not all that far behind. There is every reason to believe that the rapidly accelerating, widespread interest in the chemistry of the mechanical bond, which only started to grow in a linear fashion year-by-year in 1990, is all set now to experience an era of exponential growth.

ACKNOWLEDGEMENTS

I wish to put on record my most sincere thanks to the over 400 students, from close on 50 different countries during the past 45 years, who have contributed quite magnificently to the intellectual life as well as the research achievements and impressive productivity coming out of laboratories in four universities and one international company, situated in two different countries, namely the United States and the United Kingdom. I acknowledge the constant stimulation

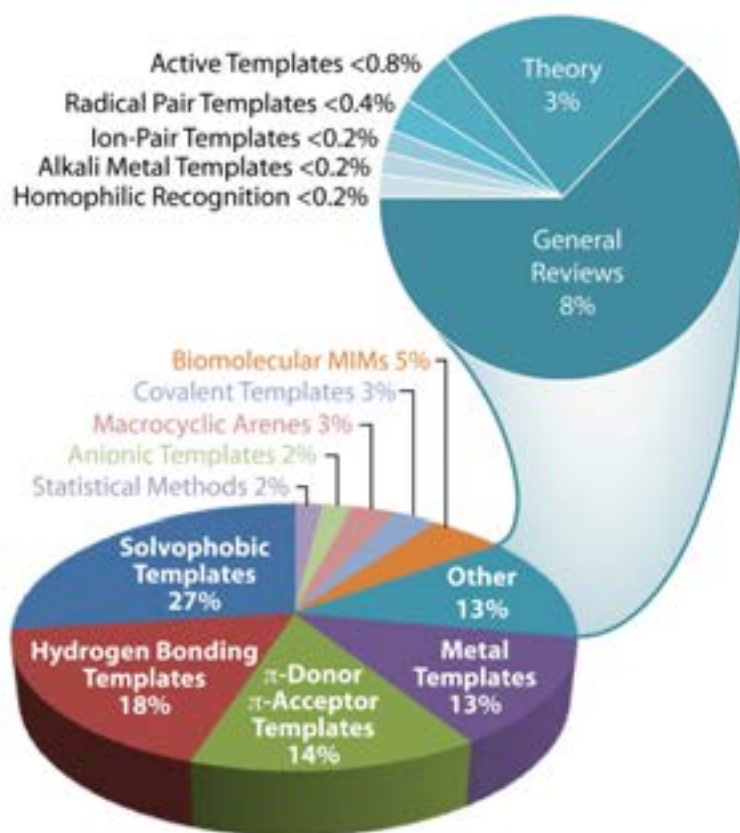


FIGURE 32. Breakdown of the literature on mechanical bonds according to the mechanisms of their formation / templation. See ref [8].

and invaluable support in research provided by more than 60 collaborators, some of them colleagues in the five institutions in which I have carried out research and others drawn from research centers of one sort or another, dotted all around the world. I thank all those universities, foundations, research councils, funding agencies and industries who have supported my research enthusiastically and generously—in particular, the Universities of Sheffield and Birmingham in the United Kingdom and at the University of California, Los Angeles (UCLA) and Northwestern University in the United States, Imperial Chemical Industries, the Engineering and Physical Sciences Research Council (and its predecessors), the Biotechnology and Biological Sciences Research Council (and its predecessors) in the United Kingdom, the California NanoSystems Institute, the International

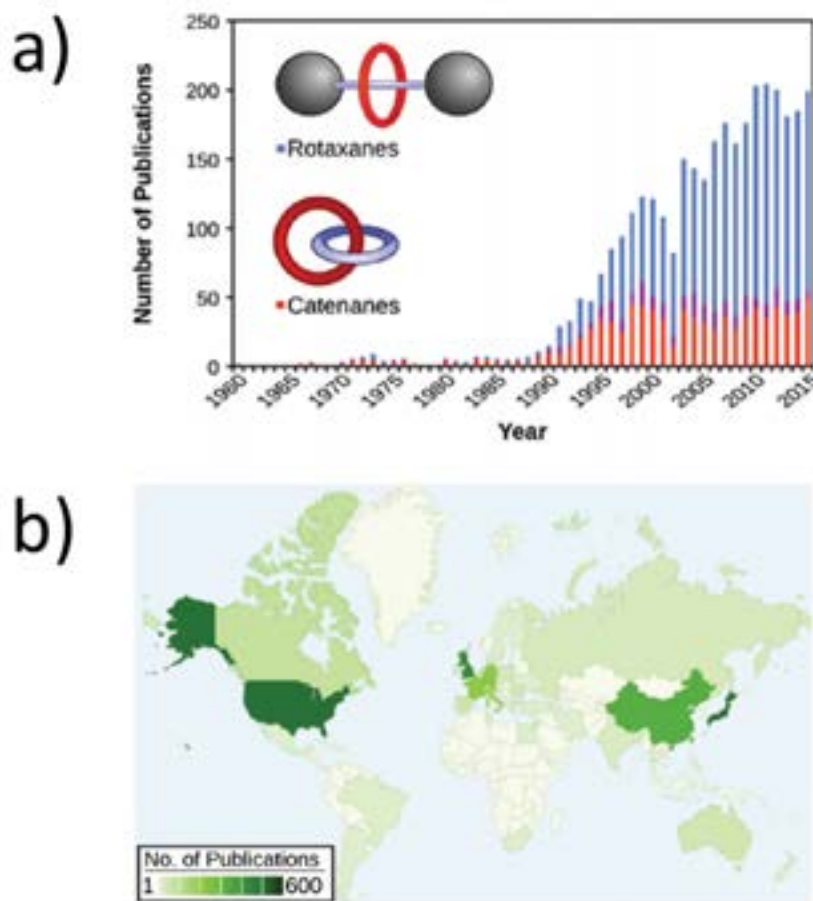


FIGURE 33. The statistics on journal publications indexed under the keywords, catenanes and rotaxanes. a) The histogram indicates the approximate number of publications (total >3000) from 1960 to 2015. Purple relates to articles indexed under both catenanes and rotaxanes. b) The distribution of publications, indexed under catenane or rotaxane as keywords, color-scaled in green on a map of the world according to their country of origin. See ref [8].

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