



Growing community of artificial molecular machinists

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Over the past decades, chemists have been pursuing the creation of man-made molecular machines with either designed engineering-like operations or with higher performances compared with biological machines. The promise of creating an artificial molecular world traces its origins in the well-known lecture of Richard Feynman, *There's plenty of room at the bottom* (1). Feynman's insights into the immense possibilities of such small artificial machines, assembled in a straightforward manner, were deeply inspiring for the scientific community. The design of machines on the molecular scale is not an easy task to accomplish. Instead of gravity and inertia, which are omnipresent in the macroscopic world, random thermal fluctuations are prevalent and dominate movements on the molecular scale. Two main approaches are being considered for the construction of artificial molecular machines (AMMs): namely, bio-inspiration and miniaturization. The former consists of integrating concepts from naturally occurring machines and unnatural building blocks into AMMs, while the latter involves engineering nano-devices based on the mechanical actions of macroscopic machines. Perhaps a better way to design AMMs with unprecedented functions would be to follow neither of these routes, but rather to construct molecularly precise architectures based on recent advances in supramolecular chemistry: explore what has not been built by Nature. This unnatural route would only share with the biological world its fundamental laws at small scales, but differentiates it from its working processes.

It is clear that the design of AMMs is a critical step in the process. It requires novel chemical building blocks to assemble and produce functioning systems. In this regard, mechanically interlocked molecules (MIMs) have paved the way for the synthesis of AMMs. MIMs, introduced by Jean-Pierre Sauvage (2) more than 30 years ago, signaled a breakthrough in introducing a new type of bond—the mechanical bond (3)—into chemistry. Examples of rotaxanes, catenanes, and other MIMs have been developed and are now commonplace. An important aspect of molecular machines is

their dynamic behavior in conjunction with their response to various inputs, such as redox control, metal complexation, pH, and temperature changes, in addition to light. Controlling the molecular-level motion of molecules is of crucial importance in relation to their use in AMMs. The molecular shuttle, introduced in 1991 (4), was the first example of the controlled movement in an AMM, followed by a molecular switch in 1994 (5). Another variety of AMMs has been developed by Ben Feringa, focusing on unidirectional rotary movements in chiral overcrowded alkenes (6). Based on these molecules, Feringa's group has synthesized light-responsive rotors and used their rotary motions in mesoscopic and nanoscale applications, such as their familiar nanocar. A wide variety of molecular architectures, often dominated by noncovalent bonding interactions that lead to chemical functions and mechanical processes, are proposed every single day. The molecular machine community continues to grow by gathering experts from other disciplines.

In 2016, the Royal Swedish Academy of Sciences emphasized the importance of AMMs by awarding the Nobel Prize in Chemistry jointly to Jean-Pierre Sauvage, Ben Feringa, and J. Fraser Stoddart for the "design and synthesis of molecular machines" (2, 6, 7). This prize recognizes the importance of AMMs and highlights their potential for applications in years to come. Two years later, this Special Feature on Artificial Molecular Machines gathers together a selection of original research papers and perspective articles, presenting significant advances in this field. Recent progress is discussed in this issue by scientists from many different fields in the AMM community.

The issue begins with an original investigation of the mechanochemical properties of oligorotaxane foldamers at the single-molecule level. Sluysmans et al. (8) use atomic force microscopy (AFM) to stretch individual donor–acceptor oligorotaxanes mechanically and to break sequentially the intramolecular interactions responsible for their folding in solution. AFM-based single-molecule force spectroscopy and dynamic force spectroscopy, which have been used

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to determine thermodynamic and kinetic parameters related to biological processes, are now able to probe the operation of AMMs. Here, Sluysmans et al. show that the near-equilibrium regime of these molecules is extended at high loading rates, surpassing the performance of natural folding proteins. The authors also suggest that the molecular design is of crucial importance in the force performance of wholly synthetic molecules. This single-molecule technique is a valuable tool for obtaining fundamental information, such as the force performance of AMMs.

The second paper, by Reddy et al. (9), also concerns the fundamental analyses of rotaxane-type molecules using statistical mechanics. MIMs present additional degrees of freedom compared with covalently linked compounds because the ring of a rotaxane, for example, is able to slide freely along a dumbbell. The position and orientation of these subcomponents can lead to a variety of molecular shapes and sizes. Focusing exclusively on mechanical bonding, the authors compare the shape and size fluctuations of two kinds of cyclic [3]rotaxanes, with and without attractive recognition sites. The unbiased molecules form planar triangles, characterized by the distributions of side lengths, perimeters, and interior cycle areas obtained using Monte Carlo simulations. When placing one attractive recognition site along each of the three threads, the triangle lengths tend to decrease as a result of the movements of the rings sliding along the axles of the dumbbells. Bimodal distributions of side lengths, perimeters, and inscribed radii provide evidence for the entropy–enthalpy balance between the free movement of the ring and attractive noncovalent forces associated with the recognition sites. In addition to possible guest-inclusion properties related to size fluctuations, this investigation highlights the promise of mesoscopic-scale rotaxanes.

Following these fundamental studies, the third and fourth papers in this Special Issue feature different surface phenomena leading possibly to ferroelectric properties and information storage based, respectively, on molecular rotors and switches. Using experimental and theoretical tools, these papers discuss separately the structure of azimuthal molecular rotors on aqueous subphases and the efficiencies of photoswitches in confined environments. Kaleta et al. (10) characterize 2D assemblies of artificial dipolar molecular rotors on the surfaces of aqueous subphases in a Langmuir trough. The authors compare data from grazing-incidence X-ray diffraction and molecular modeling. Fitting the strongest peaks from the grazing-incidence X-ray diffraction major lattice reveals the arrangement of the rotors on the surfaces. The reproduction of these parameters computationally reveals the presence of seven water molecules near each dipole in the rotor monolayer. It is expected that this monolayer presents perfect lattice conditions to sustain ferroelectricity. It remains for this property to be demonstrated on a solid surface. Indeed, the confinement of AMMs is a necessary step for their successful realization in applications. In this regard, Samanta et al. (11) describe how they have tackled the encapsulation issue by studying the behavior of azobenzene derivatives under confinement. Using UV/Vis absorption spectroscopy, X-ray crystallography, and NMR spectroscopic techniques, the authors show that azobenzene derivatives, encapsulated in an octahedral cage in aqueous solution as either monomer or dimer guests, can exhibit *cis-trans* photoisomerization. Different mechanisms are presented to describe the switching of these guests inside the cavity and their reorganization in solution. The flexibility of the cage is considered to be important for accommodating the photoswitching. In addition, fluorinated azobenzenes are used elegantly in rewritable information storage devices.

The next two articles deal with the use of MIMs as model systems to (i) explain the allosteric control involved in many biological processes and (ii) understand and simplify a “three-body problem.” First, Ragazzon et al. (12) describe the transfer of information between two sites on the dumbbell of a [2]rotaxane resulting from the shuttling of the ring. The authors use cyclic voltammetry and electron paramagnetic resonance spectroscopy to prove that the transfer of an electron on one recognition site—on reduction of a bipyridinium unit—is followed by a proton transfer from a mild base to the second recognition site—a dibenzylammonium one—and requires the movement of the ring from the first to the second site. This movement is achieved by Brownian fluctuations and leads to an apparent pK_a modulation of the secondary ammonium site. The electrochemical-chemical mechanism is reversible and is also rationalized by means of thermodynamic analysis. This coconformational allostery could be extended to other effectors acting on one another from distal sites without direct communication and used in the design of more complicated AMMs. The three-body problem, presented by Benson et al. (13), describes the formation of a [3]pseudorotaxane composed of two cyanostar macrocycles threaded along a reduced tetrazine axle. The authors show that the rings can thread in an inchworm-like movement when coupled by either π – π interactions or with a small covalent tether. This mechanism is evidenced in the cyclic voltammetry by the absence of intermediates. The authors go on to determine the kinetics of threading and develop a mechanical model to reduce dimensionally the three-body problem. This approach, based on experimental results, could be applied to other complex systems involved in molecular-scale motions.

The four perspective articles in this Special Feature are devoted to discussion of recent developments in AMMs, from (i) bio-inspired systems and (ii) nonequilibrium assembled structures to (iii) molecular switches and (iv) molecular rotors. The authors of these articles envision design improvements and the next challenges that face the molecular machine community. Zhang et al. (14) begin their discussion by comparing two design approaches, namely (i) technomimetics and (ii) biomimetics. With reference to recent examples in the literature, they present their hypothesis of building “compound machines” (i.e., connection of simpler ones) that are able to achieve more complex tasks. Working at low Reynolds numbers, these machines must operate in an environment dominated by Brownian fluctuations. The authors describe the use of these fluctuations to move components of MIMs directionally using ratchet mechanisms. The first (i) energy ratchets, (ii) information ratchets, (iii) linear molecular motors, and (iv) rotary molecular motors are presented, as well as (v) programmable molecular robotics. Their selection of recent advances in the design of AMMs illustrates how the integration of multiple simple machines can work together like the subcomponents of biological motors. In his perspective article, Astumian (15) discusses the theoretical requirements for AMMs to harness energy from environmental fluctuations to carry out a task. He investigates the formation of nonequilibrium steady states and the use of external energy to drive directional movements. Based on stochastic thermodynamics at the molecular scale and on the principle of microscopic reversibility, Astumian stresses the importance of kinetic asymmetry to achieve directional motion. As discussed by Zhang et al. (14), Astumian also analyzes ratchet mechanisms and extends the discussion to stochastic pumping with examples of wholly synthetic molecular pumps. Understanding and creating AMMs that can call on the surrounding energy to activate directional motions is one of the greatest challenges to the AMMs community.

In addition to MIMs, other switches and rotors are reviewed in the final two perspective articles. Harris et al. (16) focus on the development of molecular switch architectures during the past 10 years. In the first part of their article, the authors illustrate recent advances in chemically activated switches. They survey new architectures and properties that are important in designing the next generation of molecular switches with complex functions. From both redox and acid/base hydrazone switches to biphenyl motors, Harris et al. draw attention to the drawbacks that need to be overcome to design more efficient chemically controlled AMMs. In the second part of their article, they feature photo-switches, which they claim have many advantages over the chemically activated switches. The authors review different types of chemical compounds that undergo isomerization at specific wavelengths and comment on their synthesis and switching properties, as well as their thermal and photostabilities. The future designs and applications of AMMs lead the authors to propose a toolbox potentially working in synergy with other molecular machines. The perspective article by Roke et al. (17) focuses on rotary motors with a double-bond axle. The evolution of rotary motors based on overcrowded alkenes is presented from the first example that was able to perform a 360° rotation up as far as third-generation rotary motors. To demonstrate useful applications based on these motors, many improvements in design will be necessary. Roke et al. review the progress on: (i) adjusting the rotational speed, (ii) red-shifting the excitation wavelength for biomedical applications, and (iii) increasing the efficiency of the photochemical isomerization steps. Remarkable advances have been made in understanding the thermal helix inversion process, which is of crucial importance in defining rotational movements and limiting rotational speeds. Although increasing the photochemical efficiency is proving to be more complicated, theoretical calculations are being performed in parallel with advanced spectroscopic techniques to understand the intimate mechanisms involved in the photochemical isomerization steps. Other types of rotary motors, such as redox-driven ones, are presented in the context of future challenges and overcoming hurdles. There is a lot of room for seminal advances to be made in the field of artificial molecular rotors, with many opportunities for their application in chemical catalysis, responsive materials chemistry, and biomedical science.

The final research paper, by Veetil et al. (18), describes the use of a nanocage to investigate a complex biological process. It involves the use of a DNA nanocapsule for the chemically controlled release of a signaling steroid. In the context of two steroid signaling processes investigated in the past, the membrane-initiated steroid signaling one is rapid and less well understood because of the lack of ways of manipulating signaling steroids. By encapsulating estradiol molecules in DNA icosahedra, Veetil et al. are able to control their release chemically in human umbilical vein endothelial cells and monitor postrelease modifications. The steroid is released through the pores of the nanocapsule following thiol-disulfide exchange. In addition to usual drug delivery promises of nanocages, this work illustrates the possibilities of controlled delivery in the context of biological fundamental studies. The potential of this DNA technology could be extended to a larger group of molecules, such as AMMs.

The variety of original research papers and perspective articles presented in this Special Feature on Artificial Molecular Machines emphasizes the interdisciplinary spirit that unites this community. The aim of this issue is not only to present the recent advances in the AMMs field, but also to highlight the challenges that are ahead of the community. Biological molecular machines have been created by Nature during millions of years, while the creation of AMMs is still in its infancy. Nonetheless, research, which combines synthesis with computations and analytical tools, has already revealed the capabilities of wholly synthetic molecules with designed architectures to exhibit functions that cannot be delivered by biology. We hope that this Special Feature will lead to fruitful discussions between scientists from different backgrounds and will also serve as a jumping-off point for young researchers to join the community. Remarkable progress has already been made in realizing Feynman's dream of assembling artificial molecular machines, yet much remains to be done.

Scientific discovery is not yet predictable. If you have an exciting road to follow, do not be put off by those who say there is nothing at the end of it; they do not know. Persevere, and enjoy the excitement of exploring the unknown.

Joseph Chatt (19)

- 1 Feynman RP (1960) There's plenty of room at the bottom. *Eng Sci* 23:22–36.
- 2 Sauvage J-P (2017) From chemical topology to molecular machines (Nobel Lecture). *Angew Chem Int Ed Engl* 56:11080–11093.
- 3 Bruns CJ, Stoddart JF (2016) *The Nature of the Mechanical Bond* (John Wiley & Sons, Hoboken, NJ).
- 4 Anelli PL, Spencer N, Stoddart JF (1991) A molecular shuttle. *J Am Chem Soc* 113:5131–5133.
- 5 Bissell RA, Córdova E, Kaifer AE, Stoddart JF (1994) A chemically and electrochemically switchable molecular shuttle. *Nature* 369:133–137.
- 6 Feringa BL (2017) The art of building small: From molecular switches to motors (Nobel Lecture). *Angew Chem Int Ed Engl* 56:11060–11078.
- 7 Stoddart JF (2017) Mechanically interlocked molecules (MIMs)—Molecular shuttles, switches, and machines (Nobel Lecture). *Angew Chem Int Ed Engl* 56:11094–11125.
- 8 Sluysmans D, Devaux F, Bruns CJ, Stoddart JF, Duwez A-S (2018) Dynamic force spectroscopy of synthetic oligorotaxane foldamers. *Proc Natl Acad Sci USA* 115:9362–9366.
- 9 Reddy P, Sevick EM, Williams DRM (2018) Triangular cyclic rotaxanes: Size, fluctuations, and switching properties. *Proc Natl Acad Sci USA* 115:9367–9372.
- 10 Kaleta J, et al. (2018) Structure of a monolayer of molecular rotors on aqueous subphase from grazing-incidence X-ray diffraction. *Proc Natl Acad Sci USA* 115:9373–9378.
- 11 Samanta D, et al. (2018) Reversible photoswitching of encapsulated azobenzenes in water. *Proc Natl Acad Sci USA* 115:9379–9384.
- 12 Ragazzon G, et al. (2018) Remote electrochemical modulation of pK_a in a rotaxane by co-conformational allostery. *Proc Natl Acad Sci USA* 115:9385–9390.
- 13 Benson CR, et al. (2018) Inchworm movement of two rings switching onto a thread by biased Brownian diffusion represent a three-body problem. *Proc Natl Acad Sci USA* 115:9391–9396.
- 14 Zhang L, Marcos V, Leigh DA (2018) Molecular machines with bio-inspired mechanisms. *Proc Natl Acad Sci USA* 115:9397–9404.
- 15 Astumian RD (2018) Stochastically pumped adaptation and directional motion of molecular machines. *Proc Natl Acad Sci USA* 115:9405–9413.
- 16 Harris JD, Moran MJ, Aprahamian I (2018) New molecular switch architectures. *Proc Natl Acad Sci USA* 115:9414–9422.
- 17 Roke D, Wezenberg SJ, Feringa BL (2018) Molecular rotary motors: Unidirectional motion around double bonds. *Proc Natl Acad Sci USA* 115:9423–9431.
- 18 Veetil AT, Jani MS, Krishnan Y (2018) Chemical control over membrane-initiated steroid signaling with a DNA nanocapsule. *Proc Natl Acad Sci USA* 115:9432–9437.
- 19 Chatt J (1985) A half century of platinum metal chemistry. *Platin Met Rev* 29:126–130.