

*Nobel Prize winners in the areas of physiology or medicine, physics, chemistry, literature, peace and economics for the year 2016 have been announced. Nobel Prize in Physiology or Medicine was awarded to Yoshinori Ohsumi, Tokyo Institute of Technology, Japan for his 'discoveries of mechanisms for autophagy'. Nobel Prize in Physics was shared by David J. Thouless, F. Duncan M. Haldane and J. Michael Kosterlitz affiliated to University of Washington, USA; Princeton University, USA and Brown University, USA respectively. They were recognized for their 'theoretical discoveries of topological phase transitions and topological phases of matter'. Nobel Prize in Chemistry was awarded to three scientists for 'design and synthesis of molecular machines'. The three scientists are Jean-Pierre Sauvage, University of Strasbourg, France; J. Fraser Stoddart, Northwestern University, USA and Bernard L. Feringa, University of Groningen, The Netherlands. Current Science is publishing more detailed accounts of some of these prizes in this issue.* —Editor

## 2016 Nobel Prize in Chemistry: conferring molecular machines as engines of creativity

The 2016 Nobel Prize in Chemistry is conferred on three organic chemists, Jean-Pierre Sauvage, J. F. Stoddart and Ben Feringa, who share the Prize for spearheading a new area of chemistry that converges the ideas of molecular synthesis with the principles operating in materials and biology. The trio has contributed immensely in the past 2–3 decades to establish a new direction that relies on exploiting the forces, in the form of chemical energy, in order to conduct a work at the expense of the energy, and the work being conducted at the molecular level, the tiniest possible machine measuring few nanometers in a length scale. The idea of conducting a work at the expense of chemical energy at the molecular level has led nicely to the emergence of the new area of query, namely, 'the molecular machines'. Within this new area, the sub-sets are terms, such as, molecular switches, valves, rotors, actuators, elevators and more. Work done at the expense of chemical energy is abundant in nature, an example *par excellence* is the photosynthesis. However, ways by which a work can be done on completely isolated molecular systems have not been fully obvious, although the anticipated practical benefits of the same are just enormous, from replacing a diesel-driven motor to targeting an impaired cell with a drug, as guided by a carefully orchestrated molecular machine. Overcoming the emptiness of this space, these three chemists envisaged an ingenious method, wherein the basic tenet is controlling the energy-input and work-output precisely at the molecular level, without encountering a reversible equilibrium driven state(s). The masterful art and practice of chemical syntheses of small,

large, complex molecules, super- and supramolecules are developed over several decades now. However, the emergence of nanoscience and technology in the previous decades has given a definite fillip to contemporary advancements, wherein extracting a function out of synthetic molecules has become as exciting as their synthesis itself. Unlike the miniaturization protocols that typify a top-down approach, extracting the function at the molecular level requires a precision control over the manner in which the molecule is constituted, which warrants construction of the molecule in a precise manner through a 'bottom-up' approach. Tapping enormous potential which the bottom-up approach awaited to offer, the Nobel Prize-winning organic chemists of this year have contributed to break-open a new area of chemical sciences. Advancements spearheaded by the trio are appropriately remarked by the Nobel Foundation as: 'for the design and synthesis of molecular machines' and continued to state that 'the molecular motor is at the same stage as the electric motor was in the 1830s'. Developments made individually by the trio are elaborated below.

Early developments to the emergence of 'molecular machine' can be traced back to the desire to control non-covalent bonding interactions in order to bring together many complementary molecular sets together, so as to result in designed molecules, supra- and super-molecules, with a precisely defined composition and shape, and without a statistical combination of the sets or truncations in the molecular shapes. A very fruitful approach to implement pre-organization of molecular sets is through template-driven strategies. In effect, such template-driven strategies to synthesize molecules that are otherwise difficult to make, were recognized by an early Nobel Prize in Chemistry to C. J. Pedersen, D. J. Cram and J.-M. Lehn in 1987.

Jean-Pierre Sauvage (University of Strasbourg, Strasbourg, France): The template-driven strategies were developed further initially by Sauvage, CNRS, France, in early 1980s. In this instance, development of synthetic route to make interlocked molecules received the focus. Earlier to his approach, preparation of inter-locked molecules was thought through statistical methods, wherein the



Jean-Pierre Sauvage



J. F. Stoddart



Ben Feringa

reactive molecules would come together and form inter-locked molecules, in addition to the predominant formation of kinetically driven linear chains. Inter-locked molecules by this route form much less than even 1% yield, the rest being linear chain products. Sauvage and group implemented template-driven strategies, such that, inter-locked molecules form predominantly on reactions between suitably functionalized complementary monomer building blocks. The example which constituted the cornerstone of template-driven strategy to make inter-locked molecules is the suitably functionalized phenanthroline-linked ethylene glycol derivatives that undergo facile reactions, in the presence of metal-ion chelation with the phenanthroline segment (Figure 1)<sup>1</sup>. Metal-ion chelation enabled two interacting monomer segments to pre-organize and provide the reactive ends to come together in a manner that facilitate interlocking of the monomers and afford the new supramolecular entity, namely, the catenane. Subsequent removal of the metal-ion, i.e. the template, leads to metal-free supramolecule, wherein two cyclic molecules are mechanically interlocked. The

yield of catenation reaction is impressive, catenane being the major product of the reaction, thus breaking the mold of catenation being synthetically difficult and a thermodynamically unfavourable process. The mechanically interlocked supramolecule does not have the ability to fall apart on its own unless a covalent bond is cleaved, thus was the birth of a new bond called 'mechanical bond'. However, the individual rings in the catenane are constantly in the regime of thermal fluctuations and attendant molecular motions infinitesimal at least at room temperature, in which the rings constantly revolve around themselves. Realizing the importance of such inter-locked molecules can be considered as the conception stage towards many more sophistications and advancements in subsequent period.

J. F. Stoddart (Northwestern University, Evanston, IL, USA): In 1988, Stoddart and co-workers discovered synthesis of a catenane, under a metal-free environment, the reaction being guided precisely by non-covalent interactions between two reactive monomer building blocks. An electron-deficient 4,4'-bipyridinium derivative and an electron-rich

crown ether with aromatic substituents readily form donor-acceptor type complexes, through C-H- $\pi$  and C-H...O non-covalent interactions, in order to not only bring the monomer proximally closer together, but also to facilitate catenation to occur seamless, and provide a higher-order stability to the resulting catenane. The catenation reaction is very high-yielding, when conducted under a high-pressure condition. A [2]-catenane is constituted with one crown ether macrocycle interlocked with one bis-bipyridinium containing macrocycle. The macrocycles are under constant thermal motion around each other and are no longer separable unless a bond is broken. An appealing aspect of this type of catenation is that the newly formed catenane is pretty purple in colour, such a chromism is absent to both macrocycles in isolation as well as the individual components of the macrocycles. The visible coloration provides an alertness to the practitioner that the complex is indeed forming, the coloration aids further during the course of the purification of the catenane, wherein the coloured band can be seen separating visibly, as opposed to other remnants of the reaction. The complexes further form single crystals, studies of which provide immense information about the catenane for further developments. Monumental heights of this preparation are the formations of a [5]-catenane and a [7]-catenane. Five distinct macrocycles interlock in series, closely akin to the shape of Olympic Games logo, and thus coined appropriately as 'Olympiadane' (Figure 2 a)<sup>2</sup>.

Similarly, seven distinct macrocycles interlock in series, leading to a [7]-catenane. Even more impressive of this type of donor-acceptor based complexation and subsequent reactions among the constituent reactive ends is the construction of the so-called rotaxane, the name qualitatively refers to a wheel threaded around an axle, and the axle is capped large enough at the ends such that the wheel has no ability to dislodge. Clearly, the absence of capping at the dumb-bell shaped axle is a disadvantage and, at best, only a pseudorotaxane would form. Similar to the possibility to add more and more macrocycles to interlock each other in a serial fashion, or in a sophisticated branched fashion, rotaxanes can be synthesized with a dumb-bell having multiple interactive sites or stations, on which

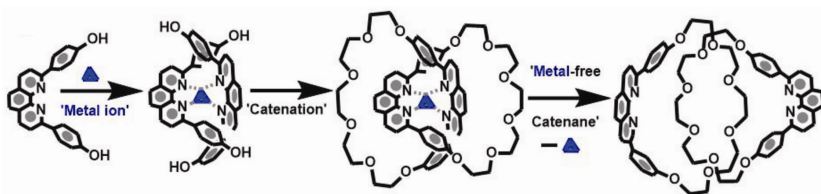


Figure 1. An early example of the catenane formation by the template assisted route<sup>2</sup>.

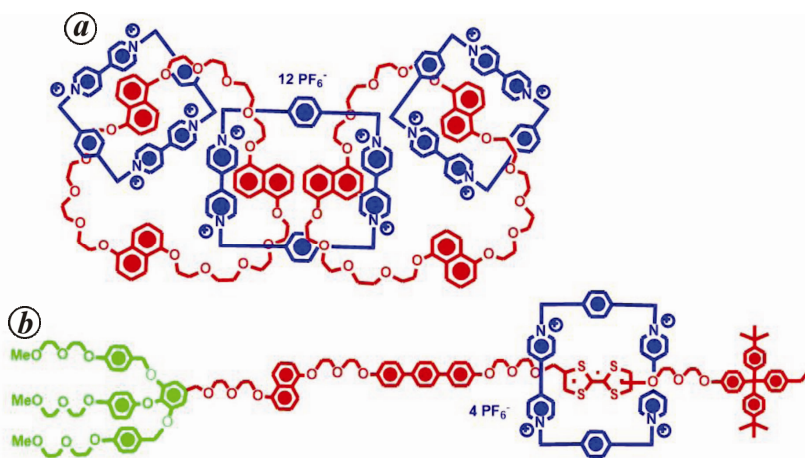


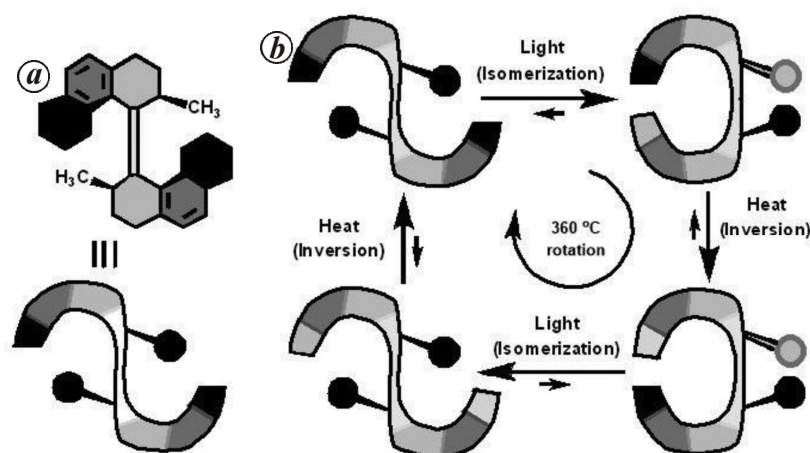
Figure 2. **a**, A five macrocycles interlocked catenane called 'olympiadane'<sup>2</sup>. **b**, A rotaxane molecular switch with two stations, one the tetrafulvalene (TTF) site and the second the naphthyl site, possibilities for the entrapped macrocycle to switch between the stations<sup>6</sup>.

the mechanically entrapped one or more macrocycles can reside upon, so as to result in [2]-, [3]-, [4]-, [5]-, etc., rotaxanes. The concept of stations in a dumb-bell is truly remarkable, as multiple stations with one macrocycle shuttle (donor or acceptor site) has now the opportunity to occupy any one of the stations (acceptor or donor site), only to be determined by the relative binding affinities between the station (e.g. TTF versus naphthyl moiety in Figure 2 *b*) and the shuttle. Thus, in a molecular train, the shuttle moves from one station to another and the process could be manipulated with the aid of an external stimulus, such as, light, pH and electrochemical input. Combination of first generation catenanes and rotaxanes leads to more sophisticated systems, such as a daisy chain. The most impressive and intuitive aspects can be categorized two-fold: (i) the ability to add many donor or acceptor sites (stations) in the dumb-bell, and entrapping one or more complementary macrocycle (shuttle), and (ii) the ability to activate or deactivate a station with the aid of an external stimulus, such that the shuttle's preference to reside in a particular station is altered. In this manner, an 'on-off' state of the shuttle in a particular station is augmented. This on-off state dynamics of the inter-locked molecules brings with it the opportunity to open-up an environment for energy storage and release or information storage and retrieval or work input and output, as a function of the applied external stimulus on the shuttle movement of the macrocycle around the dumb-bell. Thus, a molecular shuttle is the immediate possibility,

which was demonstrated very elegantly in mid-90s by Stoddart, co-workers and collaborators, through implementing redox processes on suitably chosen components to construct the dumb-bell and the corresponding rotaxane<sup>3</sup>. The demonstration led to a very important development to install the ideas of logic gate and read-write capability, which is an operational guideline in electronic circuits. Circuits adhering to typical gating system, such as, AND, OR, NOT, YES, XNOR, etc., were established on these tiniest molecular machinery rotaxanes for the first time. Although such developments were harbingers for further advancements, rotaxanes or catenanes as single supramolecular entity would not withstand the energy input and work output equations, as the work output is nowhere closer to a practically applicable regime. This impracticality runs against even at the highest possible energy input and work output efficiencies and circumventing the principle of microscopic reversibility. Important to these developments is the fact that the forward and reverse shuttling of the shuttle along the dumb-bell axle do not follow the same energy landscape in the forward and reverse direction movements, thus a hysteresis exists. In order to overcome the impediments and attempt to reach a usable working regime, organization of the individual supramolecular system into arrays, through monolayer formation or organization at a nanoparticle surface or as nodes in metal-organic frameworks, were developed as a logical progression. An early achievement in this direction is the organization of

rotaxanes as a monolayer. Assembling the rotaxane system on the layer and subsequent application of electrochemical stimulus led to impressive on-off capability. Further, the system allowed fabrication in the densest possible manner – an impressive ~100 billion bits per square centimeter, and with that the memory chip with the read-write capability. Clearly, the top-down approach does not have an equivalent tool to draw such a dense and nanosize memory chip, as the chip is formulated atom-by-atom or molecule-by-molecule through bottom-up approach. Future developments in these molecular machines to deliver a practically usable work output at the expense of chemical energy input are awaited, the foundation is laid strong and is robust at this point in time.

Ben Feringa (University of Groningen, The Netherlands): Whereas molecular machines developed by Sauvage and Stoddart relied on movement of one of the two components over the other in supramolecular entities and overcome microscopic reversibility issues to do a useful work on the environment, Ben Feringa considered stereochemical and conformational possibilities on molecular entities as a distinct source to extract a usable work output out of the molecular motions. For this approach to be meaningful, thermodynamic irreversibility remained the most important factor. In this approach involving only the rotation of one-half of a molecule over the other half of the same molecule, important requirements are the unidirectionality of the motion and emergence of intermediate local minima conformational states. These intermediate conformational states act as boosters in the course of completing the rotation, by strictly keeping in register unidirectionality of the rotation. Within this preamble, systems that adhere to the requirements are those that are sterically hindered alkenes (Figure 3 *a*)<sup>4</sup>. A molecular rotation on such a system is initiated from the ground state conformation with an energy input, which results in a half-rotation of one-half of the molecule about the axis of central alkene: a *trans*-conformation translating to a *cis*-conformation. The newly formed conformer is yet unstable and flips or inverts to reside in a more stable *cis*-conformation. A second energy input initiates another half-rotation process on the *cis*-conformer, leading to an unstable *trans*-conformer, inversion of



**Figure 3.** *a*, Molecular structure of sterically hindered alkene molecular motor. *b*, Light and heat-driven unidirectional rotation of the one-half of the molecule over the other<sup>4</sup>.

which retrieves the original ground state stable *trans*-conformation (Figure 3 b). The cyclic process is made perfectly unidirectional, either clockwise or anticlockwise, fulfilling activation energy requirements and favourable free energy changes, permitting the lifetimes of the intermediate conformational states to be monitored by spectroscopic techniques. Key to the success of this molecular design is the role of side chain substituents on the bulky heads groups on the alkene. In practice, an isomerization of the sterically crowded alkene occurs when the ground state stable *trans*-conformation is activated upon photoexcitation, to an unstable *cis*-rotamer intermediate, which undergoes a thermal rearrangement to a stable *cis*-form. The stable *cis*-rotamer absorbs light energy, leading to a thermodynamically unstable *trans*-rotamer, a thermal inversion of which leads to retrieving the original *trans*-conformation of the molecule. With unidirectionality of this four-step process, two alternate photochemical activations and two alternate thermal activations, a machine-like motion is created at the molecular level. The speed of this unidirectional motion is now the determining factor for this molecular machine to provide work output on the environment. Feringa and co-workers fine-tuned each segment of the sterically hindered alkene, so as to achieve faster rotation. The unstable *cis*- and *trans*-intermediate conformers are akin to boosters and their efficient helicity inversions to the corresponding stable conformational states provide the key success to the unidirectional cyclic process. With the objective of achieving faster rotations, modifications and ring substitutions of the bulky groups about the alkene moiety help to improve upon the rotation characteristics. Faster rotation, in turn, correlates to more work output per unit time when

compared to slower rotation, the rotation here arising purely at the molecular level, thus nicely adhering to the description of being a molecular motor. A standard in these developments is to achieve work output analogous to that achieved by many essential biological functions. An example, often considered, is the rotary motion exhibited by ATPase enzyme, which transforms energy of hydrolysis of ~400 molecules of ATP into rotational motion at the rate of 130 rotations, both per second. The rotational motion of the enzyme is coupled intimately to pump cations across the membranes, from one intracellular membrane to another or from inside to outside the cell membrane against active concentration gradients, i.e. a thermodynamically unfavourable process becomes feasible upon coupling with the ATP hydrolysis and the rotor action of the enzyme. In the case of a molecular motor, the possibility to utilize the light- and thermally driven unidirectional rotation, occurring due to sequential conformational changes on the molecule, to rotate a microscopic-scale object was experimentally proven. In this instance, the molecular motor was a dopant on an aligned cholesteric liquid crystal film, the dopant facilitated inducing a helical organization of the film. The texture of the doped liquid crystalline film reorganizes either in a clockwise or anticlockwise fashion in response to either irradiation with light or thermal changes<sup>5</sup>. Such a textural reorganization of the bulk film is sufficient to enact rotation of an imbedded micrometer scale object, either clockwise or anticlockwise, in response to the applied either light or heat stimulus. These observations provide a sound basis for a mechanical work done by the molecular motor in prototype systems. Clearly future progress will be guided by these path-breaking experiments, when optimizations are

derived and executed to suit the macroscopic, real-time applications.

Chemists are armoured with imagination of molecules, their structures and functions, without necessarily demanding a high level of wherewithal sophistications to execute the same. This author had the privilege of having the experience in the laboratories of J. F. Stoddart, at University of Birmingham, UK, and at UCLA, USA, for over 5 years. In addition to molecular designs with in-built functions, higher order organizations of the molecules are becoming even more important in order to enable the characteristic molecular functions to be realized at the macroscopic level. This years' Nobel Prize theme has recognized the space that the molecular machines, built through bottom-up approaches, are offering, in the constant quest to generate very high energy efficient systems in a paradigm-shifting manner.

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