



Scientific Background on the Nobel Prize in Chemistry 2016

## MOLECULAR MACHINES

compiled by the Class for Chemistry of the Royal Swedish Academy of Sciences



## Molecular Machines

**The Royal Swedish Academy of Sciences has decided to award *Jean-Pierre Sauvage*, *Sir James Fraser Stoddart* and *Bernard (Ben) L. Feringa* the Nobel Prize in Chemistry 2016 “for the design and synthesis of molecular machines”**

### Introduction

Machines of different types are an integral part of human development, helping us for example to perform tasks that fall beyond our capacities. Continuously developed in response to our needs over many millennia, our society has enjoyed an ever increasing plethora of useful machines, with an enhanced quality of life as a consequence. This progress has accelerated, in particular, since the industrial revolution, with its key discoveries resulting in a giant leap forward and dramatically changing the world.

Today, we are at the dawn of a new revolution that will bring us yet another giant leap forward. Humankind has always striven to push the limits of machine construction and of what machines can do, and as a consequence attempted to build miniaturised machines of ever smaller size. The ultimate limit of this endeavour is to make molecular-sized machines, a research frontier that has intrigued scientists for many years, and that has required the creation of a range of new tools. Although development towards highly complex and useful molecular machines is still in its infancy, the laureates have successfully demonstrated that the rational design and synthesis of molecular machines are indeed possible.

### Background

A molecular-level machine can be defined as “*an assembly of a distinct number of molecular components that are designed to perform machinelike movements (output) as a result of an appropriate external stimulation (input)*”.<sup>1</sup> Furthermore, a machine requires a supply of energy for its operation, and can be driven by suitable energy sources.

In parallel with his influence in many other areas, *Richard Feynman* (Nobel Prize for Physics 1965) has also been a source of inspiration in this field. In a visionary talk at the Annual Meeting of the American Physical Society in 1959, he drew attention to the possibility of building small machines from atoms, and to the challenge of, for example, making an infinitesimal machine like an automobile.<sup>2</sup> He also briefly highlighted some of the possibilities and problems associated with the atomic scale, and later discussed the analysis of a miniature ratchet and pawl device,<sup>3</sup> which to some extent became an inspiration for further progress towards molecular machinery.

In order to construct a complex machine, a number of building blocks are generally required, and the function of the device is intended to be a consequence of their assembly. The *design of the components*, and the control of their integral connectivity, is thus at the heart of machine development. Furthermore, a high degree of *controlled relative motion* between its parts is essential for the machine to produce the desired operation. By controlling the translational and

rotational movements of the components in the machine, coupled to an inflow of external energy, it is possible to obtain the predetermined function. A machine also needs to interface with its environment and, when its operations occur at the molecular scale, to be able to overcome thermal fluctuation (Brownian motion) that influences its mechanical action. This challenge has been addressed by (theoretical) chemists and physicists with the objective of escaping random noise or harnessing it for controlled motion.<sup>4,5</sup> Ultimately, controlling and driving the machine through external fuelling by light or other energy sources will lead to it operating out of equilibrium in dissipative systems. This action is essentially maintained by the machine's motor components, which drive the relative movement and functioning of other incorporated parts.

Two major technology advances have proven particularly useful in addressing the complex challenge of constructing machines at the molecular scale. The first of these involves *topological entanglement* and so-called *mechanical bonds*, while the second is based on *isomerisable (unsaturated) bonds*, and both advances have resulted in large ranges of complex structures with machine-like functions.

#### **Topological entanglement – mechanical bonds**

A substantial part of the progress made towards molecular machinery has its roots in the emergence of interlocked molecular assemblies based on mechanical bonds. In such assemblies, the individual parts are not directly connected and held together by covalent bonds, but inseparably entangled through, for example, loops and stoppers. The individual parts can in principle move freely relative to each other, though they are confined in space owing to their mutual mechanical interconnections, resulting in discrete overall molecular structures. The notion of molecular entities held together by mechanical bonds was proposed as early as the 1950s, in the description of interlocked oligosiloxane- and cyclodextrin-based rings,<sup>6,7</sup> but not until the 1960s could such structures be synthesised and isolated. The syntheses proved exceedingly challenging, resulting in very low yields and statistical or complex routes of limited practical consequence. Nonetheless, both *catenanes*, based on two interlocked rings, and *rotaxanes*, based on a ring threaded over an axle with stoppers at each end, were proposed and synthesised at the time (Figure 1).<sup>8-14</sup>

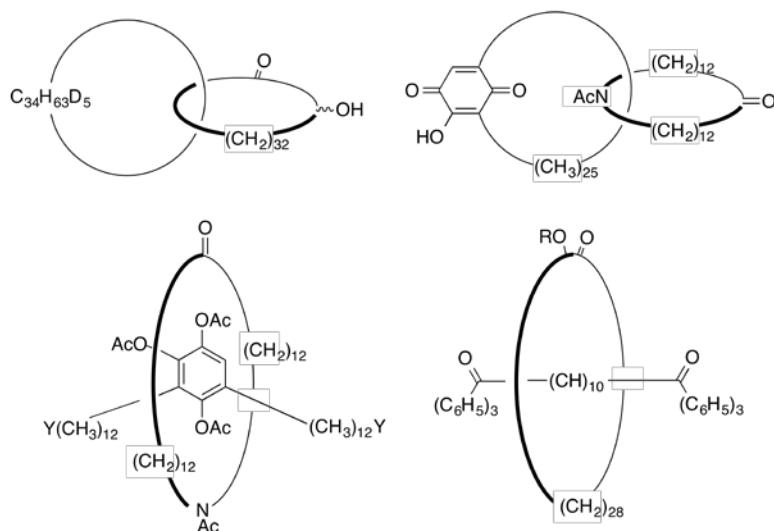


Figure 1: Early structures based on mechanical bonds: catenanes (top),<sup>8,9</sup> and rotaxanes (bottom).<sup>10,12</sup>

Development in this area continued to some extent throughout the 1970s and early 1980s, resulting in a better understanding of the principles for the formation of such structures. However, in 1983 the field took a giant leap forward when **Jean-Pierre Sauvage** and his co-workers at CNRS, Louis Pasteur University, Strasbourg, France, introduced template synthesis as a straightforward route to catenanes and rotaxanes (Figure 2).<sup>15</sup> Using metal coordination, the threading of the chains could easily be accomplished, with much higher overall yields as a consequence. The synthetic strategy was based on previous development using coordination of phenanthroline units to Cu(I) centres,<sup>16</sup> thereby essentially enforcing a sizeable dihedral angle between the interacting components. One phenanthroline moiety was introduced in a macrocyclic unit and another in a crescent-shaped fragment. Assembly of the two components in the presence of Cu(I) resulted in a complex in which threading was favoured. Finally, ring-closing followed by removal of the metal ion produced the [2]catenane.

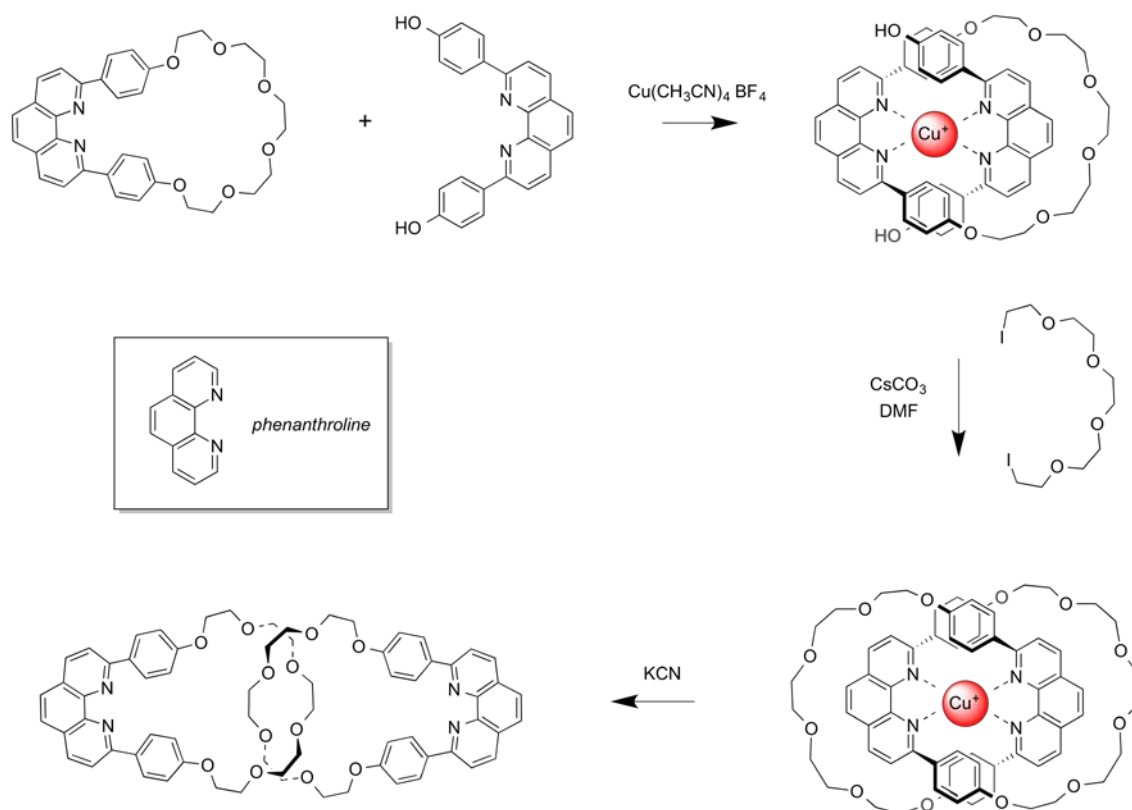


Figure 2: Synthesis of [2]catenane using metal coordination.<sup>15</sup>

This discovery marked a true breakthrough that dramatically invigorated the field of topological chemistry and subsequently led to molecular machinery. As a consequence, the scientific community gained access to substantial amounts of these complex entities, and the methodology has resulted in a vast range of structures of differing topology. The approach has, for example, enabled Sauvage and co-workers to produce topologically very challenging species, such as [3]catenanes, trefoil knots and Solomon links (Figure 3).<sup>17–19</sup>

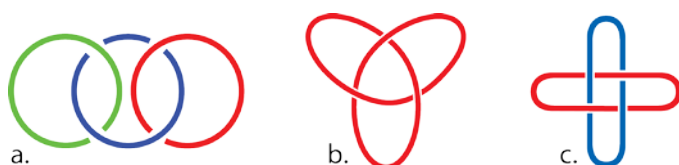


Figure 3. Topologically challenging structures: (a) [3]catenane; (b) trefoil knot; (c) Solomon link.

Based on the catenanes developed, Sauvage and co-workers were subsequently able to demonstrate the potential of the structures for *translational isomerism*.<sup>20</sup> Dramatic, reversible changes in the catenanes' molecular shape were thus observed upon decomplexation and

recomplexation of the metal coordination entities with Cu(I). The process resulted in a phenanthroline distance of 11 Å between the states, interchangeably accessible through external action.

The field took another big leap forward in 1991, when a clear demonstration of translational isomerism was reported by the group of Sir **James Fraser Stoddart** at the University of Sheffield, UK.<sup>21</sup> Stoddart and co-workers had been working in the 1980s with an alternative template-based method to synthesise mechanically interlocked molecules, in which interactions between electron-rich and electron-poor aromatic entities were used. These studies resulted in the development of a paraquat cyclophane structure,<sup>22</sup> which could be “clipped” around an axle containing two hydroquinol units separated by a linker. Since the axle ends were blocked by bulky groups, a [2]rotaxane was produced in a good yield (Figure 4). The resulting rotaxane cyclophane ring could be shown to act as a molecular shuttle, able to move between the two hydroquinol stations on the axle. Together with Sauvage’s demonstration of reversible catenane shape-shifting, this work marked the start of applying topological entanglement in the development of molecular machinery.

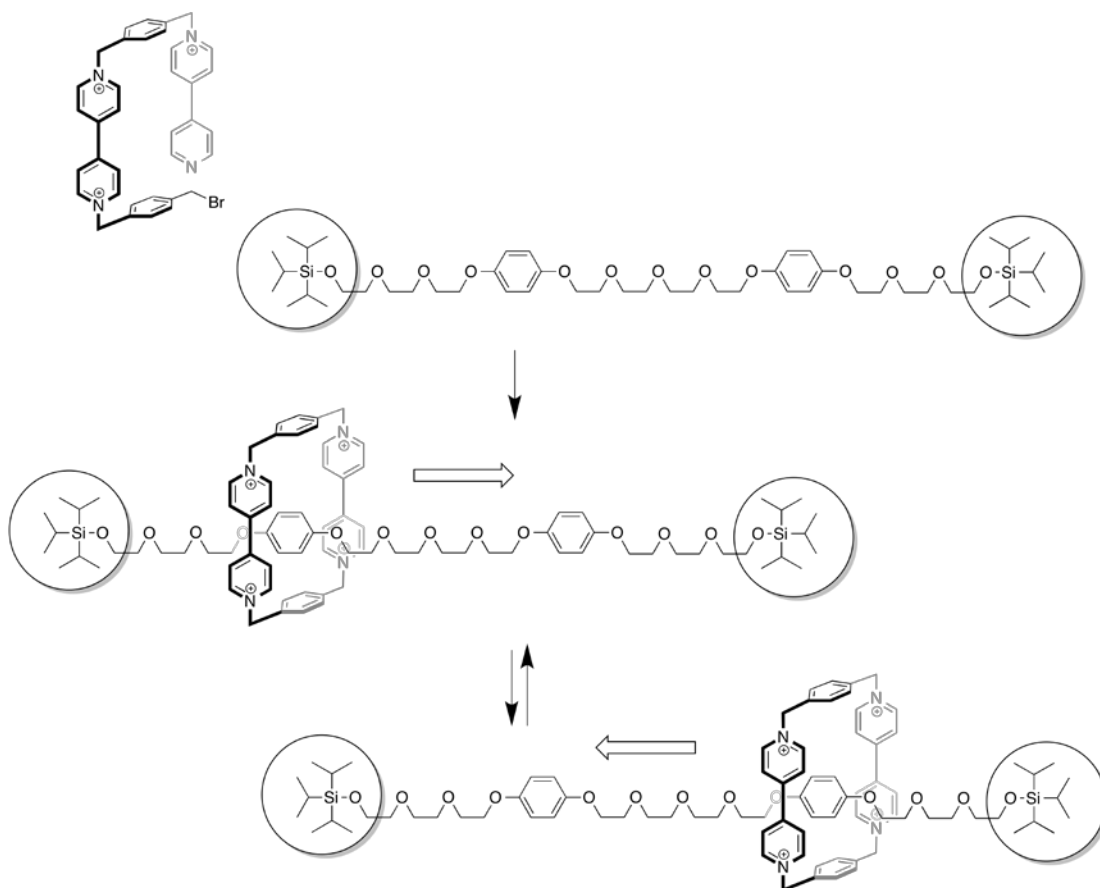


Figure 4: Synthesis and translational motion in [2]rotaxane.<sup>21</sup>

In 1994, both research groups were able to demonstrate externally controlled translational and rotational motion in mechanically interlocked molecules by introducing asymmetries in the structures (Figure 5).<sup>23,24</sup> The Stoddart group introduced two different  $\pi$ -electron-donating units in the rotaxane axle, benzidine and diphenol groups, and could show that a bis-paraquat cyclophane ring could be persuaded to move between the two stations upon cycles of electrochemical oxidation and reduction or through pH-changes, providing energy input. The Sauvage group engineered a catenane structure to comprise two different coordination sites in one of the rings, phenanthroline and terpyridine entities, leaving a single phenanthroline unit in the other ring. Rotation could subsequently be obtained upon cycles of electrochemical oxidation and reduction of the central copper ion.

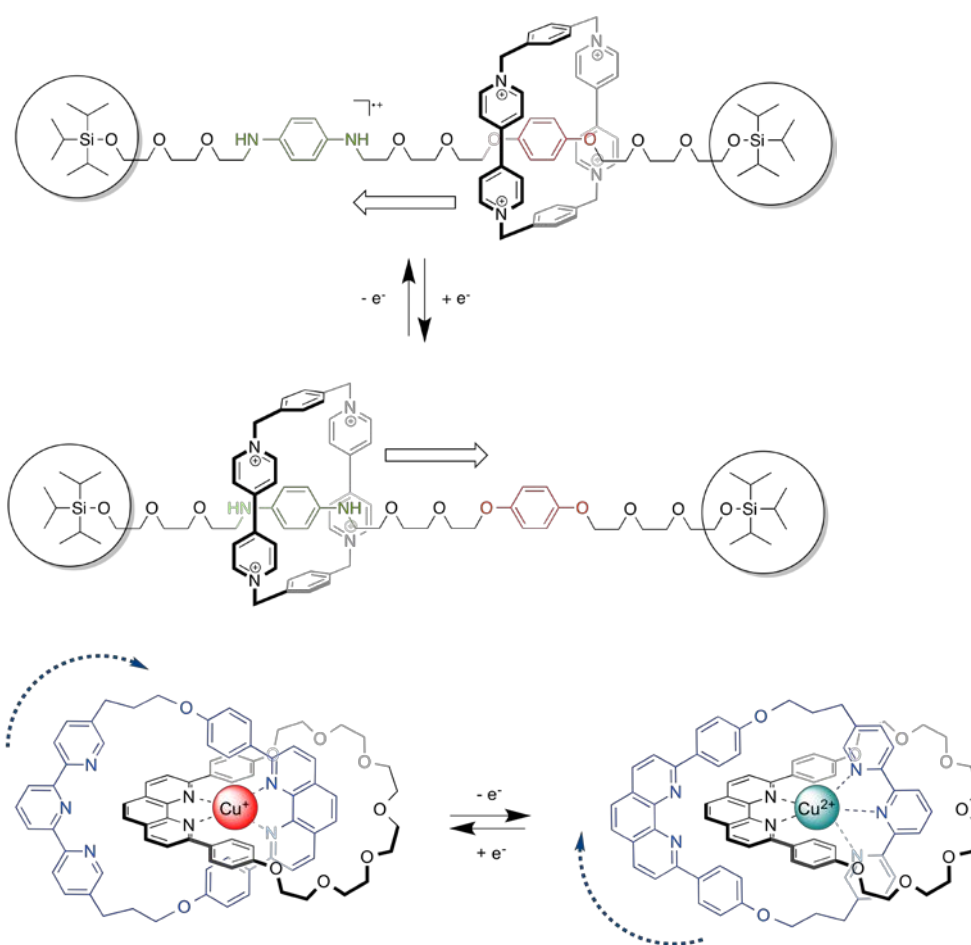


Figure 5: Electrochemically controllable motion in [2]rotaxanes (top) and [2]catenanes (bottom).<sup>23,24</sup>

Following these breakthrough discoveries, several other systems were designed, synthesised and evaluated by the groups in the ensuing years. In 1996, for example, electrochemically controlled



translation in a pseudorotaxane structure was reported by the Sauvage group;<sup>25</sup> and controlled rotation in catenanes was shown in collaboration between the Sauvage and Stoddart groups.<sup>26</sup> The same year, the Stoddart group, together with colleagues, also demonstrated chemically controlled threading/unthreading in pseudorotaxane devices.<sup>27</sup> Rotation controlled by either electrochemical or photochemical induction was demonstrated by Sauvage and colleagues in 1997,<sup>28</sup> and electrochemically induced rotation in a rotaxane was described by Sauvage's group in 1999.<sup>29</sup> Photochemical and thermal control of rotation in a catenane system was also presented by the Sauvage group in 2004.<sup>30</sup>

Since the late 1990s, the application part of the field has increasingly been addressed by the groups, and also pursued by many other researchers. Chemical control of molecular contraction/extension, resembling the action of muscles in living systems, was for example demonstrated in a topologically challenging daisy-chain structure by the Sauvage group in 2000 (Figure 6).<sup>31</sup> By integrating two mutually entangled rotaxane functionalities, they were able to achieve high control of translational contraction and extension of ca. 2 nm under chemical stimulus.

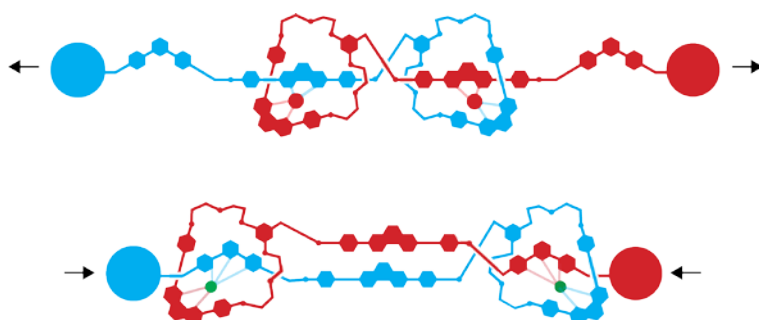


Figure 6. Extension and contraction in a daisy-chain rotaxane structure.<sup>31</sup>

Similarly, the Stoddart group developed a complex rotaxane device called a “molecular elevator” in 2004,<sup>32</sup> where high control of the motion of a moving plane between two “floors” separated by a distance of 0.7 nm could be achieved (Figure 7). The force exerted could also be estimated in this case, at up to 200 pN. In addition, in 2004–5 the Stoddart group developed molecular actuators resembling muscles, in which [3]rotaxane structures could be controlled to bend a thin gold cantilever structure.<sup>33,34</sup> By attaching the macrocyclic components to the gold surface, while leaving the axle part free to move, it was possible to control contraction and extension of up to 2.8 nm, which in the case of contraction resulted in bending of the gold cantilever by ca. 35 nm. A force of ca. 10 pN per molecule could also be estimated.

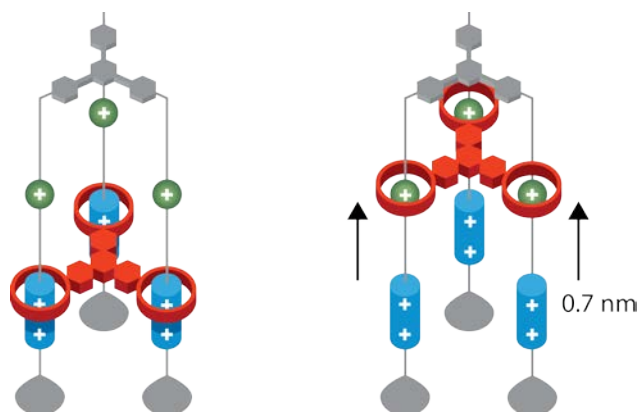


Figure 7. Rotaxane-based molecular “elevator”.<sup>32</sup>

Together with colleagues, the Stoddart group has in addition pursued the development of molecular-scale electronic devices based on rotaxanes and catenanes, with the intention of fabricating molecular logic gates and memories.<sup>35–37</sup> Having demonstrated the potential of the systems and addressed several challenges, these studies resulted in a rotaxane-based device with memory function in 2007.<sup>38</sup> The rotaxanes were mounted between electrodes in a microelectronic device and could be shown to respond to writing potentials, resulting in closed and opened states that could be read at a non-perturbing potential. 160 kbit memories, composed of a few hundred rotaxanes/bit and a density of ca. 100 Gbit/cm<sup>2</sup>, could be fabricated using this methodology.

A light-driven device, towards a prototypic linear molecular motor, was proposed by Stoddart and colleagues in 2006.<sup>39</sup> In a rotaxane structure incorporating a photosensitiser and two different paraquat groups in the axle, a cyclophane ring could be autonomously and repeatedly moved between the stations upon cycles of light excitation, electron transfer and charge recombination. The device operated at a frequency of ca. 1 kHz, developing an estimated power of ca.  $3 \times 10^{-17}$  W. More recently, the Stoddart group was also able to show an example of producing a chemical gradient using a rotaxane-type structure.<sup>40</sup> In response to repeated redox cycles, macrocyclic structures could be irreversibly threaded along the axle.

### Isomerisable unsaturated bonds

In parallel with the advances based on mechanically interlocked structures, isomerisable unsaturated bonds have also been at the core of progress on molecular machines. This pathway has witnessed a number of important contributions, in which different entities have been designed, synthesised and applied to rotation. The major challenge of achieving controlled unidirectional rotation, however, marks the most fundamental breakthrough in this development.

Motors are “central to any molecular machine”,<sup>41</sup> and these entities essentially drive the function of the overall mechanical construction. The motor component is also required to move the entire

system far from equilibrium,<sup>42</sup> and molecular motor development has therefore been key to promoting the field as a whole. In addition to the work on rotaxanes and catenanes, early steps towards rotational control involved, for example, restricted rotation around single bonds. In the 1970s, rotation in propeller-like molecules was thus studied, where in some cases large rotational barriers were found.<sup>43–46</sup>

Over the next decades, steps were taken towards controlled rotation, based for example on topological entanglement, but the goal remained elusive. It was not until 1999 that the first example of controlled unidirectional rotation, a feature typically expected of a rotary motor device, was reported by **Bernard (Ben) L. Feringa**.<sup>47</sup> This motor component was not based on single bonds, but on isomerisable double bonds. Using so-called overcrowded alkenes, and engineering asymmetries in the molecules, it was possible to obtain unidirectional rotation through cycles of light irradiation and thermal relaxation (Figure 8).

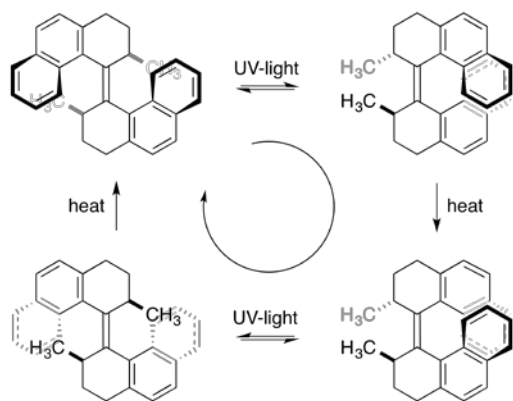


Figure 8: Unidirectional, light-driven molecular motor.<sup>47</sup>

This ingenious design represents a giant leap forward in the development of molecular machinery. Not only did Feringa and his co-workers address the fundamental task of light-driven structural change at the molecular scale, they also designed a solution to the central challenge of unidirectional motion. Over the ensuing years, several generations of motor designs emanated from the Feringa group, and the rotation frequency could be dramatically increased. In 2014, for example, an optimised motor structure was demonstrated to rotate with a frequency of over 12 MHz.<sup>48</sup>

Following the original breakthrough, several major advances were made. For example, the motor construct was mounted on a gold surface, anchoring the stator part of the device, leading to a surface-mounted, light-driven propeller-type function (Figure 9).<sup>49</sup> Feringa and co-workers could also show, in 2006, that a similar molecular motor design could be used to unidirectionally rotate micrometre-sized objects in a liquid-crystal film.<sup>50</sup> In 2005, another motor system was developed, in this case driven by selective protection/deprotection of phenolic groups coupled with

lactonisation, thus allowing for chemical fuelling of the rotational molecular motion.<sup>51</sup> It could also be shown that motor components can be made to controllably rotate in either direction upon addition of a base.<sup>52</sup>

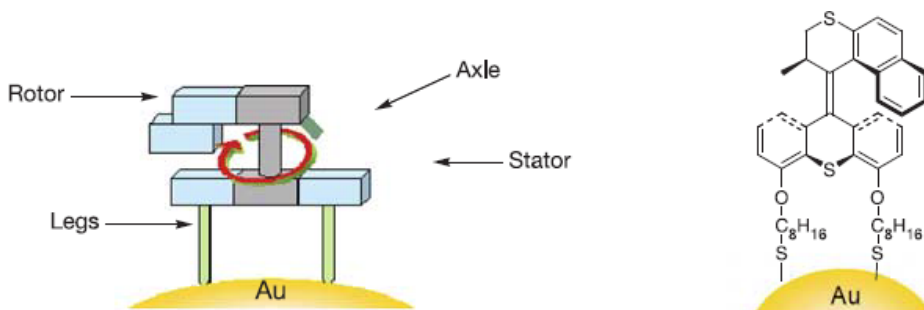


Figure 9: Molecular motor anchored to a gold surface.<sup>49</sup>

In response to Feynman's proposition of making an infinitesimally small automobile,<sup>2</sup> attempts have furthermore been made to use the motor components developed in structures that show car-like shape and behaviour.<sup>53–55</sup> The Feringa group, for example, was able to demonstrate the moving action of a chassis-like structure composed of four motor components, operating pairwise in different rotational directions, in the propulsion of a "nanocar" on a surface (Figure 10).

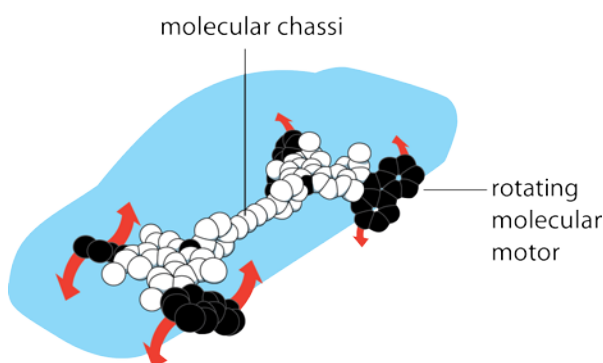


Figure 10: Feringa's proposed four-wheel-drive "nanocar".<sup>55</sup>

### Summary and outlook

All these important developments since the early 1980s, in which Sauvage, Stoddart and Feringa have incorporated the mechanical bond and unidirectional rotation into functional molecular machinery, constitute a true foundation for the entire field. Through the design and synthesis of topologically very challenging structures, combined with understanding and development of controlled motion and function, machine-like devices have been demonstrated. This work has formed the basis for rich progress towards molecular machines, for which the laureates have been major proponents and sources of inspiration.

Over the years, many other groups have also made very important contributions and discoveries, only very few of which are mentioned in this text, and a variety of ingenious devices and structures have been developed.<sup>42,56–58</sup> The molecular machine components have also increasingly been connected to the macroscopic world, leading to molecular-scale control of functional devices operating at visible dimensions.

Compared with the machines that changed our world following the industrial revolution of the nineteenth century, molecular machinery is still in a phase of growth. However, just as the world stood perplexed before the early machines, such as the first electric motors and steam engines, there is the potential for a similar explosive development of molecular machines. In a sense, we are at the dawn of a new industrial revolution of the twenty-first century, and the future will show how molecular machinery can become an integral part of our lives. The advances made have also led to the first steps towards creating truly programmable machines, and it can be envisaged that *molecular robotics* will be one of the next major scientific areas.

The progress achieved, however, would not have been possible without the vision and pioneering work of **Jean-Pierre Sauvage**, **J. Fraser Stoddart** and **Ben L. Feringa**. Sauvage and Stoddart have both brought the initially cumbersome chemistry of the mechanical bond into widespread use, and have exemplified this chemistry for a variety of devices. Feringa has been instrumental in applying restricted rotation in operational machines, and has successfully addressed the unidirectionality issue of molecular motors.

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