The Art of Building Small: from Molecular Switches to Motors

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At the start of my journey into the uncharted territory of synthetic molecular motors I consider it apt to emphasize the joy of discovery that I have experienced through synthetic chemistry. The molecular beauty, structural diversity and ingenious functions of the machinery of life [1, 2], which evolved from a remarkably limited repertoire of building blocks, offers a tremendous source of inspiration to the synthetic chemist entering the field of dynamic molecular systems. However, far beyond Nature's designs, the creative power of synthetic chemistry provides unlimited opportunities to realize our own molecular world as we experience every day with products ranging from the drugs to the displays that sustain modern society. In their practice of the art of building small, synthetic chemists have shown amazing successes in the total synthesis of natural products [3], the design of enantioselective catalysts [4] and the assembly of functional materials [5], to mention but a few of the developments seen over the past decades. Beyond chemistry's contemporary frontiers, moving from molecules to dynamic molecular systems, the molecular explorer faces the fundamental challenge of how to control and use motion at the nanoscale [6]. In considering our first successful, albeit primitive, steps in this endeavor, my thoughts often turn to the Wright brothers and their demonstration of a flying airplane at Kitty Hawk on the 17th of December 1903 [7]. Why does mankind need to fly? Why do we need molecular motors or machines? Nobody would have predicted that in the future one would build passenger planes each carrying several

hundred people at close to the speed of sound between continents. While admiring the elegance of a flying bird, the materials and flying principle of the entirely artificial airplane are quintessentially distinct from Nature's designs. Despite the fabulous advances in science and engineering over the past century, manifested most clearly by modern aircraft, we are nevertheless humbled by the realization that we still cannot synthesize a bird, a single cell of the bird or even one of its complex biological machines.

It is fascinating to realize that molecular motors are omnipresent in living systems and key to almost every essential process ranging from transport to cell division, muscle motion and the generation of the ATP that fuels life processes [8]. In the macroscopic world, it is hard to imagine daily life without our engines and machines, although drawing analogies between these mechanical machines and biological motors is largely inappropriate. In particular the effect of length scales should be emphasized when comparing, for instance, a robot in a car manufacturing plant and the biological robot ATPase. While in the first case size, momentum, inertia and force are important parameters, in the world of molecular machines non-covalent interactions, conformational flexibility, viscosity and chemical reactivity dominate dynamic function [9]. In addition, when operating at low Reynolds numbers, we go beyond the question "How to achieve motion?" and face the question "How to control motion"? In the molecular world where Brownian motion rules, and noting that biological motors commonly operate as Brownian ratchets [10], the design of molecular systems with precisely defined translational and rotary motion is the main challenge [11].

Making the leap from molecules to dynamic molecular systems while drawing lessons from life itself, an important challenge ultimately is to achieve out-of-equilibrium phenomena. Molecular switches and motors are perfectly suited to introduce dynamic behavior, reach metastable states and drive molecular systems away from thermal equilibrium. We focused on three key aspects—triggering and switching, dynamic self-assembly and organization, and molecular motion—with a future perspective directed towards responsive materials, smart drugs and molecular machines among others.

MOLECULAR SWITCHES

Chiroptical molecular switches and information storage

In our initial attempts to design molecules with the intrinsic dynamic functions that ultimately evolved into molecular rotary motors, we took inspiration from the process of vision [12]. This amazing natural responsive process is based on

an elementary chemical step, the photochemical cis-trans isomerization around a carbon–carbon double bond in the retinal chromophore (Figure 1a). We envisioned the exploration of this simple switching process in the design of molecular information storage units and responsive elements in dynamic molecular systems and materials. Although molecular bi-stability can be induced by various input signals including light, redox reactions, pH changes, metal ion binding, temperature, and chemical stimuli, the use of photochemical switching has distinct advantages as it is a non-invasive process with high spatial-temporal precision [13]. Building on seminal work by Hirshberg on azobenzenes [14], Heller on fulgides [15], Irie on diarylethylenes [16] and others [17], numerous photochromic molecules have been explored in recent years in our group to achieve responsive function, including control of optical and electronic properties of materials [18], supramolecular assembly processes [19, 25] and biological function [20].

In our journey towards bistable molecules with excellent photoreversibility and high fatigue resistance, we focused on the synthesis of chiral overcrowded alkenes (Figure 1b) [21]. Non-destructive read-out of state is a central aspect of any potential molecular information storage system, and was addressed by taking advantage of the distinct right (P)- and left (M)-handed helicities in this system, enabling read-out by chiroptical techniques far outside the switching

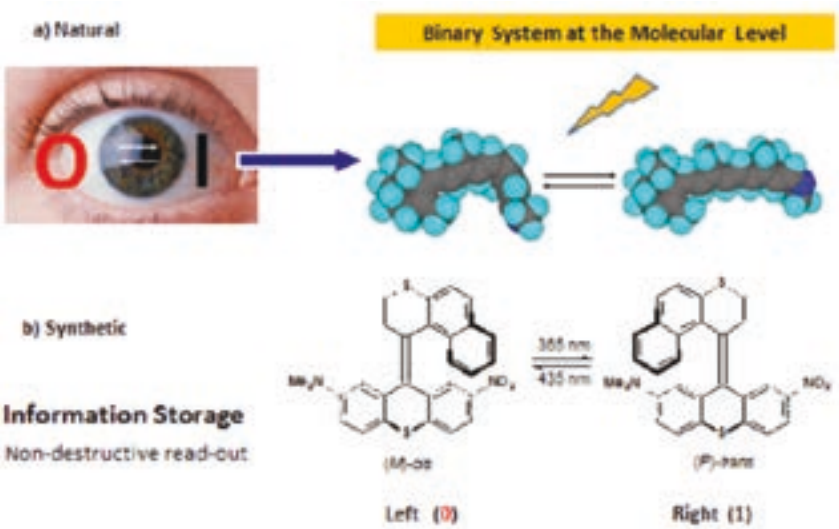


FIGURE 1. Optical switching systems based on bistable molecules. a) Retinal photoisomerization in the process of vision. b) Chiroptical molecular switch based on overcrowded alkenes as a molecular information storage system.

regime. The interconversion between two isomers with distinct chirality, i.e. a chiroptical molecular switch, defines a zero-one digital optical information storage system at the molecular level. Although high-density optical information storage materials based on this approach are promising, the fundamental challenge of addressing individual molecules at the nanoscale in a closely packed assembly in an all-optical device remains to be solved, despite the spectacular advances in single molecule detection techniques seen over the last decades [22].

At this point it is appropriate to emphasize two aspects of these studies. Firstly, the chiral overcrowded alkenes that formed the basis for the chiroptical molecular switches have their genesis in my PhD studies under the guidance of Hans Wijnberg on biaryl atropisomers. The idea that twisted olefins might show atropisomerism was explored, using the then recently invented McMurry coupling reaction, in the synthesis of cis- and trans-isomers of inherently dissymmetric overcrowded alkenes (see Figure 2 for a time line) [23]. The realization that these novel structures had an intrinsic chiral stilbene type chromophore that was immune from the notorious photocyclization seen in stilbenes, provided a stepping stone more than a decade later to chiroptical switches and two decades

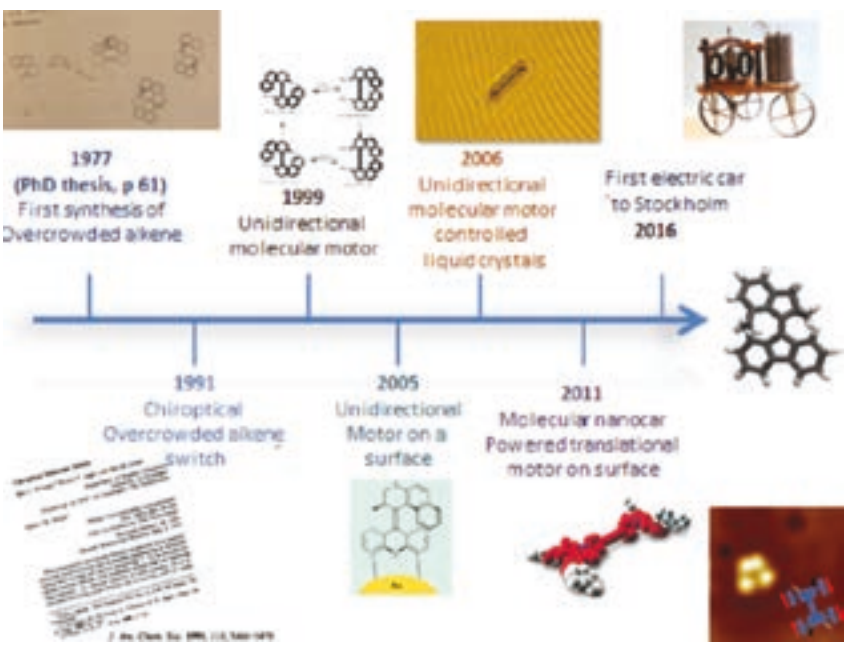


FIGURE 2. Journey of discovery from the chiral overcrowded alkene in 1977 that led to the light-driven molecular rotary motor in 1999 and the presentation of the first electric car (designed at the University of Groningen in 1835) and the molecular nanocar (developed in 2011) to the Nobel Museum in Stockholm.

later to light-driven rotary molecular motors. Secondly, with the photoisomerization of these chiral overcrowded alkenes, reported in 1991 [24], we demonstrated that controlled clockwise or counterclockwise motion in either direction of one half of the molecule with respect to the other half was achieved simply by changing the wavelength of irradiation. Control of directionality of rotary motion was key to the latter development of molecular rotary motors. The photoresponsive overcrowded alkenes were used as chiral dopants in mesoscopic materials to achieve chiroptical switching between cholesteric liquid crystal phases [25], as well as control elements for molecular rotors [26]and for photoswitching the handedness in circular polarized luminescence [27].

The wavelengths of switching and the stereoselectivity of the isomerization process were tuned, for instance, via donor-acceptor substituents. In a series of studies together with the Harada group at Tohoku University, we established the chiroptical properties, absolute configuration and racemization pathways of biphenanthrylidenes [28]. An important milestone was our discovery of dynamic control and amplification of molecular chirality by circular polarized light (CPL) [25]. Here CPL irradiation shifted the equilibrium between P or M helices of chiroptical switches to achieve a tiny chiral imbalance that was amplified through formation of a twisted nematic liquid crystalline phase. This discovery strengthened the idea that unidirectional rotary motion was in principle possible using CPL irradiation although, on the basis of the Kuhn anisotropy factor for such systems, the efficiency and directionality parameter will be very low [29].

Responsive materials and self-assembly

Molecular switches offer tremendous opportunities to introduce dynamic behavior into materials and as part of our program on responsive functions, over the past 30 years, we have explored a wide variety of both photochemical and redox switches far beyond the initial chiral overcrowded alkenes. The few examples discussed here illustrate the potential in areas ranging from soft materials to biomedical applications. Modulation of electronic properties through photoswitching has potential in integrating optics and electronics in molecular based devices provided that the molecular components operate properly when incorporated in semiconductor based systems. For instance, self-assembly of diarylethene photoswitches in mechanically controlled break junctions enabled single molecule optoelectronic switching, although bistability was initially compromised [19]. In later designs, large array devices were fabricated using an inorganic semiconductor and conducting polymer hybrid system in combination with monolayers of photoswitches [30]. In the bottom-up approach to molecular electronics [31]

numerous other approaches have been explored [32]. The pioneering work by the Heath and Stoddard team on rotaxane based devices [33] and the use of alternative switches such as azobenzenes and spiropyrans spring immediately to mind [34]. It is now apparent that photo- and redox-switchable molecules are a fertile test ground for potential information storage, sensing, molecular electronics, imaging and responsive optical systems and smart materials.

The introduction of optical switches in components that are designed to undergo self-assembly allows the construction of supramolecular systems that can adapt and reconfigure in response to an external light signal. For instance, a photo- and redox active bisthioxanthylidene unit formed the core of amphiphiles specifically designed to form highly stable nanotubes (Figure 3a). Following this approach self-assembled multicomponent nano-objects, i.e. vesicle capped nanotubes and vesicles embedded in nanotubes, were obtained and the disassembly of these responsive supramolecular systems can be controlled by with

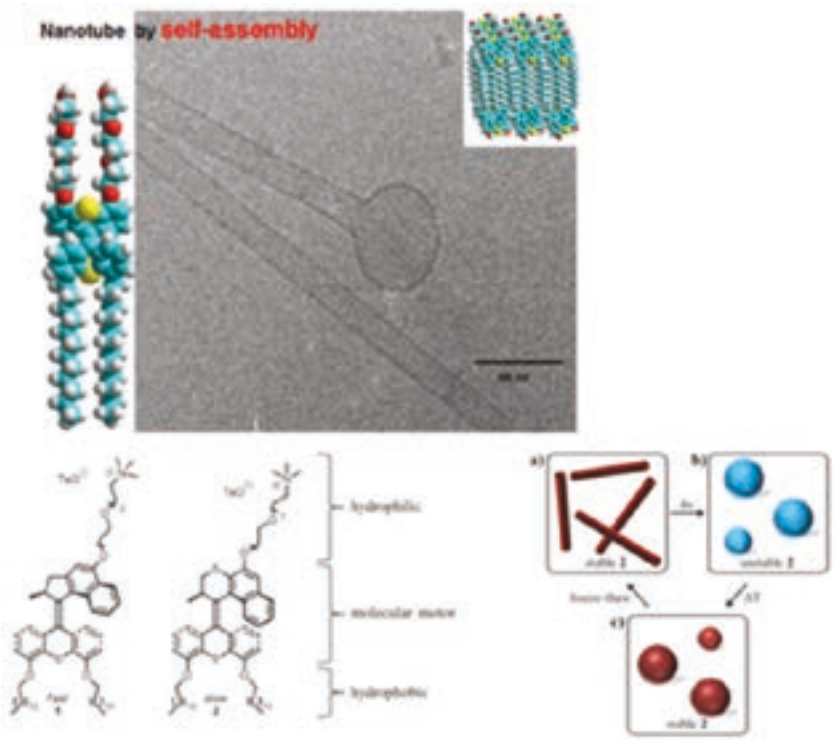


FIGURE 3. Light-responsive self-assembled nanoobjects. a) Bisthioxanthylidene-based amphiphiles that self-assemble into nanotubes and vesicle capped nanotubes. b) Overcrowded alkene based amphiphiles that can undergo nanotube to vesicle to vesicle to nanotube transitions.

light [35]. Slight structural modification of these photo-responsive amphiphiles resulted in bidirectional optical control of surface tension in Langmuir layers. [36] Taking this design a step further we have recently used overcrowded alkenes to achieve nanotube to vesicle to vesicle to nanotube transitions illustrating a more complex adaptive behavior as the system is responding to light and heath in a fully reversible behavior (Figure 3b) [37]. Small molecule gelators are another class of fascinating structures which we studied in the context of responsive self-assembly. For instance, bisamide based gelators with diarylethene photoswitchable core units allowed modulation between several distinct gel-states [19, 38]. An intriguing aspect of these light-responsive gels is the observation of metastable aggregates that are formed in a non-invasive manner (in response to irradiation with light) setting a stage for out-of-equilibrium assembly of soft materials. Embedding intrinsic switching functions in supramolecular systems and macromolecules will likely provide fascinating opportunities for responsive materials and smart surfaces for future applications such as drug delivery, cell growth or responsive coatings.

The construction of a nanovalve by which we might be able to control transport through artificial membranes or deliver on demand molecules from vesicles or other capsules was another appealing target in our program on molecular switches. Towards this goal we focused the mechanosensitive channel MsCl protein complex of large conductance from the cell membrane of E-Coli (Figure 4) [39]. This pentamer peptide system is sensitive to osmotic pressure opening a 3–4 nm pore allowing material to flow out of the cell, preventing cell damage. Using genetic modification five cysteine moieties were introduced at specific sites in the constriction zone of the protein complex and the thiol moieties enabled the attachment of photoswitches. After initial failures to achieve a proper response in the biohybrid system we focused on spiropyran photoswitches. The reasoning was that light-induced switching resulted in opening of the rigid spiropyran units to the zwitterionic and more flexible merocyanine form, simultaneously enhancing hydrophilicity. Electrostatic repulsion of the five zwitterionic units and the enhanced propensity to recruit water molecules near the constriction zone of the protein complex was anticipated to result in sufficient conformational change to open the pore of the MsCl protein complex. The successful incorporation of the spiropyran photochromic units and the proper functioning of the photoswitches in the modified MsCl protein were readily demonstrated, but it required extensive electrophysiology studies using patch-clamp techniques to establish photochemically induced opening and closing (using distinct wavelengths of light) of the MsCl nanopore. The critical test came with a system in which the photoresponsive MsCl hybrid was embedded in the membrane of a giant vesicle.

Calcein efflux measurements showed transport out of vesicles upon triggering with light and proper functioning of the modified MsCl as a photoresponsive nanovalve was demonstrated. Follow up studies focused on pH sensitive MsCl channels [40] and the incorporation of photoswitches in Sec-Y channels to control protein transport through membranes with light [41]. The ability to control molecular transport from capsules, such as the vesicles discussed here, through photoresponsive nanopores provides ample opportunities to design responsive systems for control drug delivery or self-healing materials.

Photopharmacology

Light offers superb opportunities as a noninvasive regulatory element in biological and biomedical applications. With a variety of molecular photoswitches available, a novel approach to control drug activity dynamically is within reach with the potential to bypass key issues associated with drug selectivity [20, 42, 43]. Light can be delivered with high spatial temporal precision, a key feature for tuning the action of bioactive molecules. It shows a high degree of orthogonality and usually low toxicity, which are attractive aspects in order to regulate

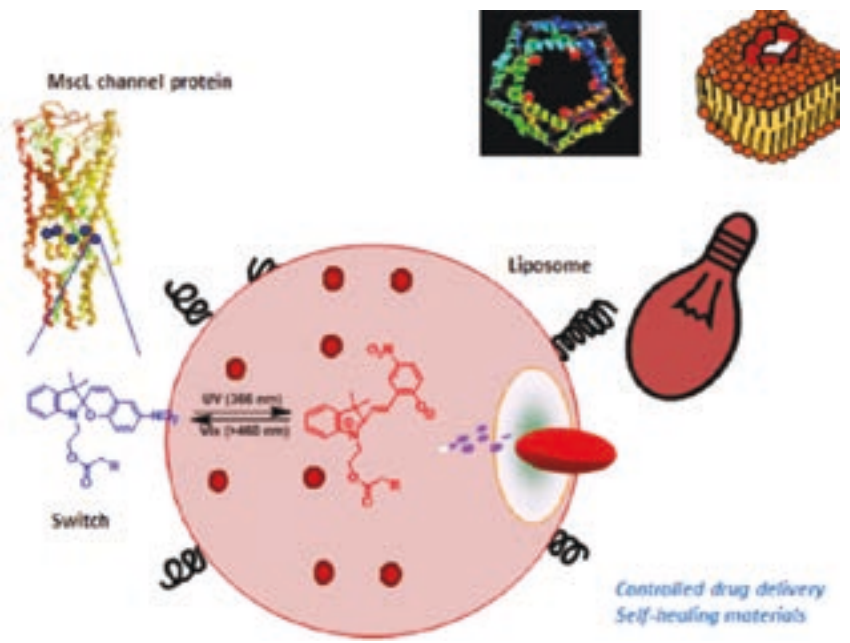
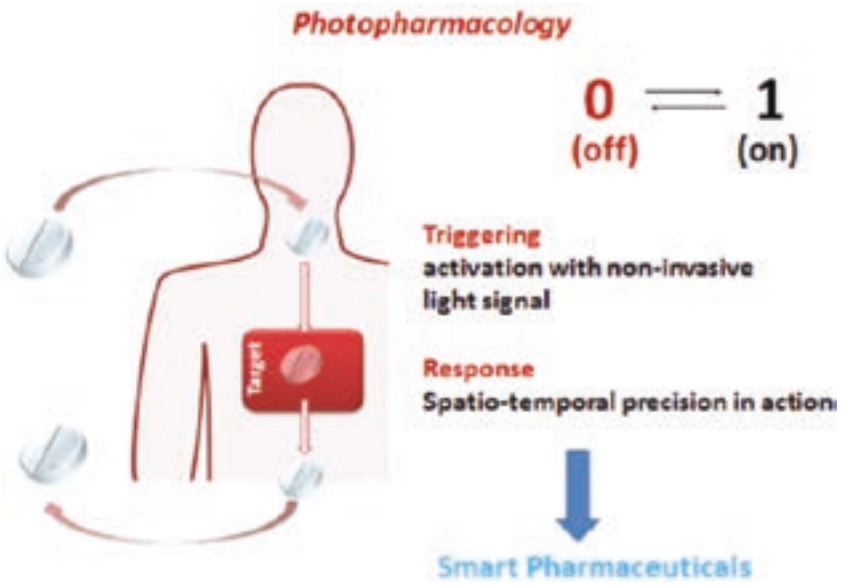


FIGURE 4. Giant vesicle with photoresponsive nanopore based on engineered MsCl protein complex with intrinsic spiropyran photochromic units as delivery system.

biological processes. By adjusting wavelength and intensity, switching processes can be readily controlled in a quantitative manner. The term photopharmacology was coined for this approach [42], as it is based on small molecule bioactive compounds with intrinsic photoswitchable functions; indeed, a drug that can be activated/deactivated with light (Figure 5). Of course a clear perspective on photopharmacology necessitates the realization that light-responsive molecules have seen extensive application in biomedicine Photodynamic therapy and the use of sophisticated fluorescence imaging techniques are now routine in the clinic while optogenetics, in particular for the control of neural functions, and photocleavable groups to activate prodrugs for precision therapy offer exciting opportunities.

Antibiotic resistance is an increasingly urgent global societal problem, with many strategies now being pursued to overcome and avoid it. The conceptual approach we took was to switch antibiotic activity on (cis-isomer) and off (trans-isomer) using light by incorporated azobenzene switching motifs in quinolone based broad spectrum antibiotics [44]. This design enabled the photoactivation of the responsive antibiotic and demonstrated in patterning of bacterial growth on plates using photomask techniques. The wealth of experience the organic photochromism community has built up over the last century is essential in such efforts, with rational tuning of the thermal stability of the cis-isomer through structural modifications to allow time taken to switch back to the off state to be controlled precisely. The proof of principle of light-activated antibiotics offers the prospect of enhanced efficacy by high-precision treatment at the point of infection and avoiding the harmful effects of antibiotics to beneficial bacteria in the organism. Arguably a more important possibility is that antibiotic activity is automatically switched off within a given time after treatment, providing an unconventional way to fight build-up of bacterial resistance towards antibiotics.

Having established the principle of photoswitchable antibiotics and applying this to patterning of bacterial growth using photomask techniques, we were excited by the prospect of non-invasive interference with bacterial communication [45]. Bacteria rely on communication through quorum sensing (QS) to synchronize the gene expression processes that are essential for, e.g., biofilm formation. We incorporated azobenzene photochromic units in N-acyl homoserine lactones, which are an important class of small molecule QS auto-inducers that play a role in the communication system of gram-negative bacteria. Two switchable QS molecules were identified that show opposite effects under UV irradiation in bioluminescence assays with E-coli; either gaining or losing QS activity upon trans-cis isomerization of the azobenzene unit. These compounds were also used to control the expression of virulence genes in Pseudomonas



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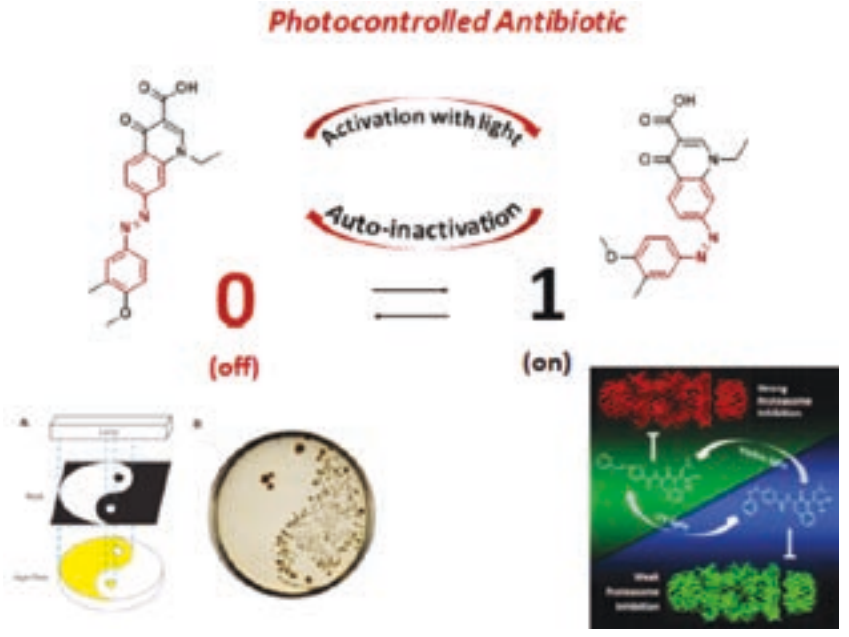

b)

FIGURE 5. a) Photopharmacology, on-off switching of the biological activity of a small molecule drug. b) A ciprofloxacin-based photoresponsive antibiotic. c) patterning of bacterial growth and photoresponsive analogue of Bortezomib® proteasome inhibitor.

aeruginosa by light. These findings offer a new approach to control bacterial growth and biofilm formation.

Photodynamic therapy has a long history in oncology, primarily through singlet oxygen generation strategies. We imagined that photoresponsive antitumor agents where the use of light is combined with molecular switching of drug activity could offer tremendous opportunities for precision therapy through control of drug function. As a proof of principle study, we focused on Bortezomib, a chemotherapeutic agent in clinical use, which was modified with an azobenzene motif [46]. The biological activity could be switched between strong (trans-isomer) and weak (cis-isomer) proteasome inhibition using UV and visible light, respectively. Instead of switching antitumor activity off with light, a much more desired function is on-switching of biological activity. This was realized with an azobenzene modified version of SAHA, a histone deacetylase (HDAC) inhibitor used in anti-cancer chemotherapy [47]. Here the photochemically accessible less-stable cis isomer is nearly as active (in vitro) as the clinically applied drug and it reverts to the inactive form, either by visible light irradiation or a thermal isomerization process, the rate of which can be controlled by molecular design. These approaches could provide unconventional solutions to mitigate the often severe side effects of commonly used chemotherapeutic agents. A particular attractive scenario is to directly use the information acquired by modern imaging techniques to guide the light activation of the switchable chemotherapeutic agent for high precision treatment of, e.g., inaccessible and small tumors. Of course, it should be emphasized that, prior to clinical use of such drug switching strategies, many hurdles need to be overcome.

We identified several of the challenges including high drug efficacy of photoresponsive analogs, drug delivery and most importantly the wavelengths of light that need to be applied i.e. irradiation with visible/near-infrared light is needed to avoid side effects and enable deep tissue penetration Recently several groups focused on the design of photoswitches that operate in the therapeutic window of interest in biomedical applications [48]. Using such principles we have designed potent photoswitchable mast cell inhibitors [49] while other groups have reported photoswitchable nociception, human carbonic anhydrase inhibition, cell division and control of neural processes among others, demonstrating the broad scope and potential of photopharmacology [42, 43, 50]. A next step in addressing future challenges and arriving at more effective medical therapies might be the design of more complex responsive systems in which sensing, transport and delivery and therapeutic action are combined and with multiple functions that can be addressed orthogonally with external stimuli. Recently, we have taken the first steps towards highly selective orthogonal control in multifunctional systems

using photocleavable or photoswitchable groups [51]. It should be emphasized that there are ample opportunities to combine photochemical switches with various other switching functions. The noninvasive up- and down-regulation of competitive chemical and biological pathways in complex (bio-) molecular networks will open fascinating opportunities in chemical biology and the study of dynamic molecular systems [50].

MOLECULAR MOTORS

Our work on chiral overcrowded alkenes [23] and chiroptical molecular switches [24] paved the way for the discovery of the first light-driven unidirectional rotary motor [52]. See the time line in Figure 2. Chirality is central to function, and it is pertinent that a few lines are devoted to the magnificent phenomenon that is stereochemistry, which has fascinated me over my entire scientific career. Standing on the shoulders of the first Nobel Laureate in Chemistry, Jacobus van 't Hoff, who together with LeBel was a founding father of stereochemistry, and taking inspiration from scholars such as Cram, Mislow, Prelog, Wijnberg and Eliel, I was driven to explore chirality as a handle to control structure and function ranging from asymmetric catalysis to molecular machines. Here again Mother Nature sets the stage, with homochirality playing a central role in its essential molecules as emphasized by Albert Eschenmoser: "Chirality is a signature of life". To build a molecular rotary motor, the fundamental questions we were facing was how to induce rotary motion and how to control right- (clockwise) or left- (counterclockwise) handed rotation at the nanoscale. The unique stereochemistry of the motor molecules allowed us to continue our exploration in the right direction.

First Generation Light-driven Rotary Motors

The first light-driven unidirectional rotary motor reported in 1999, shown in Figure 6 [6], has two distinct stereochemical elements: a helical structure (P or M helicity as in the chiroptical switches) and stereocenters (R or S) both in upper and lower halves [52]. The methyl substituents, originally introduced for the purpose of absolute stereochemical determination, can adopt a pseudo-axial or pseudo-equatorial orientation. Photochemical switching experiments revealed a surprising result; helix inversion as detected by CD spectroscopy was commonly associated with trans-cis isomerization in our chiroptical switches but in this case CD measurements indicated the same helicity for starting material and product. NMR, chiroptical and kinetic studies, supported by calculations, revealed "the missing isomer" and a sequential process of photoisomerization

from stable trans to unstable cis followed by a thermal helix inversion to stable cis. We could show that the photochemically generated unstable cis isomer has the methyl groups in a sterically crowded pseudo-equatorial orientation and by helix inversion restoring the pseudo-axial orientation, strain is relieved. With this serendipitous discovery of a 180-degree unidirectional rotary process, based on energetically uphill photochemical alkene isomerization followed by an energetically downhill thermal helix inversion, we quickly realized that a full unidirectional rotary cycle was within reach by simply repeating the two-step process. The combination of four steps, two ultrafast photochemical steps [6, 53] each followed by a rate determining thermal step, add up to a 360-degree unidirectional rotary cycle that can be repeated many times. This system has all characteristics of a power-stroke rotary motor [6, 52]; rotary motion is achieved, fueled by light energy, shows control over directionality, and is a repetitive rotary process.

It is interesting to note here that the mechanism of the Anabaena sensory rhodopsin photoresponsive systems is closely related to that of our synthetic motor, as revealed recently by the team led by Olivucci [54]. Again, two olefin photoisomerizations and two thermal interconversions of helical conformations are involved in a four-step rotary cycle in this biological realization of a rotary molecular motor, emphasizing Nature's seemingly limitless number of elegant designs towards achieving complex functions. After our initial discovery, a large number of first generation rotary motors were synthesized in our group [55] in order to enhance rotary speed, shift absorption wavelengths into the visible

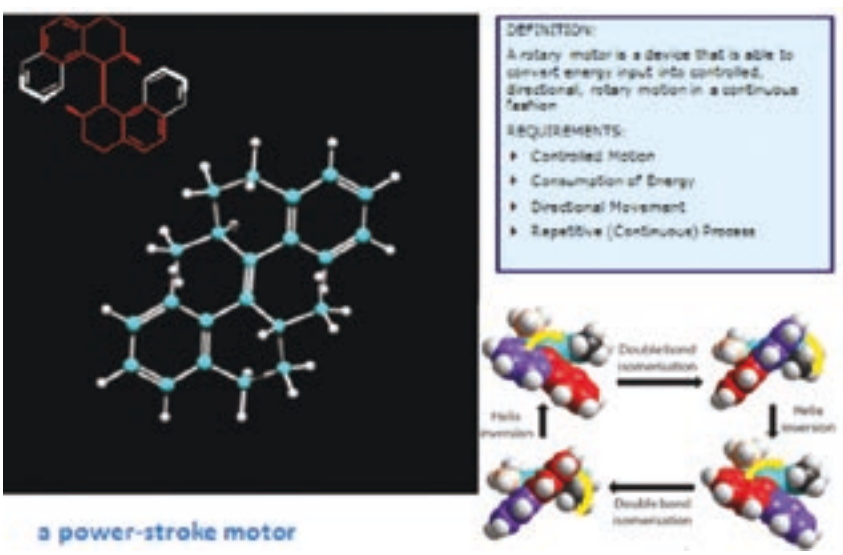

FIGURE 6. First generation light-driven rotary molecular motor and four stage rotary cycle.

region and attach functional groups [6, 56]. Through systematic change in steric parameters, especially by widening the "fjord region" to facilitate the rate determining thermal helix inversion and by changing the size of the substituents at the stereogenic centers, the rotary speed was enhanced from one cycle per hour to seconds. However, it should be noted at this stage that overall rotary speeds and efficiency of light-driven molecular motors are strongly dependent on parameters such as energy input, quantum yield, medium effects and surface confinement.

An important issue we were facing in view of potential application of these rotary motors controlling function is to what extent the medium and size will affect rotary behavior. A series of first generation motors with pendant rods of different lengths and flexibility were prepared and kinetic and thermodynamic parameters of the thermal isomerization processes determined [57]. These studies revealed that solvent viscosity is the dominant factor showing strong retardation for longer rigid arms. Analysis of the fraction of the molecule involved in the rotary process in terms of free volume model and solvent displacement shows a rather exceptionally high alpha factor for these motors. Extending these studies to excited state dynamics of the photochemical isomerization process, in cooperation with the teams led by Meech and Browne, confirmed that isomerization and relaxation to the ground state is largely polarity independent but governed by solvent viscosity [53].

Molecular motors are perfectly suited to drive far-from-equilibrium systems. Recently, we developed motor-driven responsive self-assembled helicates that can reconfigure between distinct supramolecular states. Taking inspiration from the self-assembled double-stranded copper helicates pioneered by Lehn, we have introduced functional rod like (oligo-)bipyridine ligands to the first-generation motors [58]. Upon copper(I) binding both monomer and oligomer copper helicates are obtained, and photochemical and thermal isomerization processes enable interconversion between different aggregation states and helicities in these complex dynamic assemblies.

Second Generation Light-driven Rotary Motors

As the two thermal isomerization steps in the first-generation motors typically have very distinct barriers, we designed a large series of second generation motors to achieve more uniform rotary behavior and to facilitate chemical modification [59]. A single stereocenter is present in the upper rotor half of these systems and, as in the first-generation motors, photochemical isomerization around the double bond axle generates an unstable isomer with the methyl-substituent in

a higher energy-pseudo-equatorial conformation. Strain is released in the subsequent thermal isomerization, with the methyl group again adopting a favorable pseudo-axial orientation. It was highly rewarding and an essential point in our motor program, to establish that a single stereogenic center bearing a small methyl substituent is sufficient to govern a unidirectional rotary cycle feature, four helix inversion steps and four pseudo-enantiomeric states as revealed by NMR and CD spectroscopy. In the second-generation motor design, the lower stator half is derived from a symmetric (except for substituents) tricyclic unit, which offers distinct advantages. First, the barrier for helix inversion is nearly the same in both thermal steps of the rotary cycle, drastically reducing complexity in our efforts to accelerate overall rotation rates. Second, the inherent difference between stator and rotor facilitates selective functionalization, for instance, for surface assembly (see below). A third important aspect is that both rotor and stator parts can be synthesized independently, which proved especially important for the synthesis of complex (functional) motors. This also allowed the use of the Barton-Kellogg modification of a Staudinger diazo-thioketone olefination as the method of choice for the late stage introduction of the sterically demanding central double bond (rotary axle) in the total synthesis. Using various classes of second generation motors, a systematic structural variation was performed to elucidate parameters that govern rotary speed [60]. The example of fluorene-based second-generation motors is illustrative for the accelerations that can be achieved by modification of ring size and substituents resulting in, for instance, motor 9 with a half-life of 5.7 ms at room temperature (Figure 7).

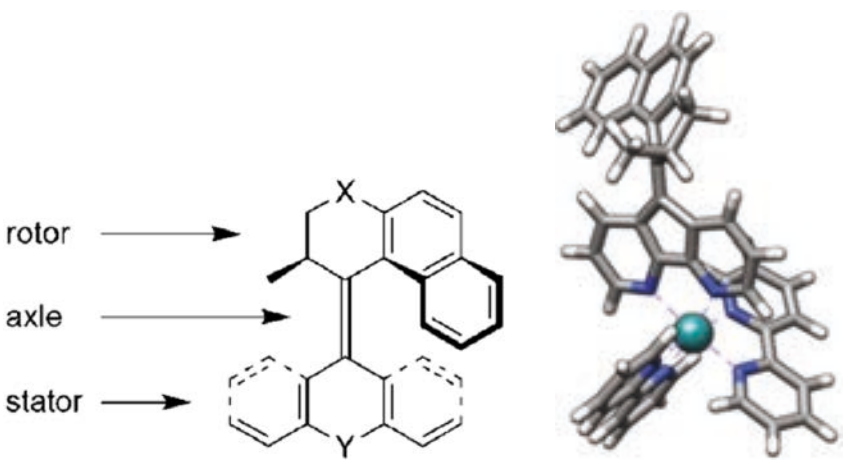

FIGURE 7. a) Second generation rotary molecular motor. b) Visible light driven Ru(II)-bipyridine based second generation motor.

Recently we introduced an alternative way to control the rotary speed of molecular motors by replacing the fluorene stator part by introducing a 4,5-diazafluorenyl-ligand moiety [61]. This allowed binding of metal ions of different sizes and as a consequence of metal-coordination the bond angles change as well as the barrier for thermal helix inversion. Fine tuning of rotary speed upon binding of metals of different sizes had the additional benefit that we can induce photoisomerisation with visible light.

A different approach to achieve visible light driven molecular motors was to use metallo-porphyrin sensitizers, including a Pd-porphyrin covalently attached as an antenna to the motor, taking advantage of inter- or intra-molecular energy transfer to drive rotary motion [62].

Dynamic Control of Function

We considered that a key next challenge in our motor program, on the way to molecular machine-like behavior, was how to dynamically control function and allow specific tasks to be performed. The structure of first- and second-generation motors is particular suited to the introduction of functional groups that allow, e.g., physical properties, distance, cooperativity and stereochemistry to be modulated in a directional and sequence controlled manner. An illustrative example of a responsive chiral catalyst based on a rotary motor is shown in Figure 8 [63], which was inspired by Jacobsen's chiral organocatalysts with

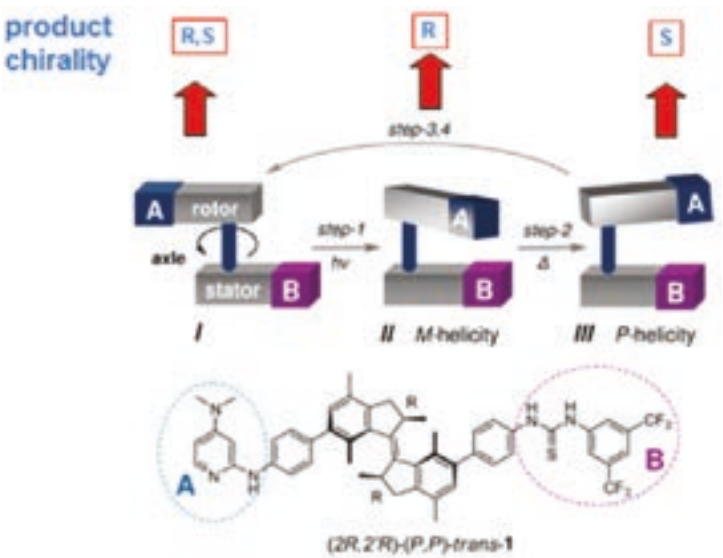

FIGURE 8. Dynamic control of chiral space in a molecular motor-based organocatalyst.

DMAP and thiourea moieties introduced in the trans isomer of a specific first-generation motor.

Here, the hydrogen donor and acceptor moieties do not cooperate effectively, resulting in low catalyst activity and a racemic product of a thiol 1,4 addition. Irradiation results in the formation of the cis-isomer with M-helicity and the catalytic moieties can cooperate. As a consequence, catalytic activity is dramatically enhanced as well as preferential formation of the R-product enantiomer. The next thermal step in the rotary cycle leads to cis-isomer with P-helicity and the S-enantiomer of product of the catalytic reaction. In this case the motor-based chiral organocatalyst functions as a multi-state switch, allowing not only the modulation of catalytic activity but also formation of racemic (R,S) or either enantiomer (R and S) in a sequence dependent manner. The sequence of events is strictly controlled by the clockwise or counterclockwise rotation of the motor unit. These concepts were subsequently extended in the design of responsive organocatalysts for asymmetric Michael and Henry reactions [64]. An important next step was the proof of concept of switchable chiral phosphines based on rotary motors as shown in highly enantioselective Pd-catalyzed desymmetrization reactions [65]. Again, depending on an external input signal (light or heat), distinct product stereoisomers are accessible with a single (responsive) catalyst. Bringing the principle of switchable chiral catalysts into the realm of transition metal catalysis opens many new avenues including multitasking and cascade transformations, adaptive and responsive behavior and ultimately up-down regulation of catalytic activity in complex catalytic networks. It should be noted that dynamic control of function is not limited to catalysis as we demonstrated for instance in modulation spin-spin interactions [66], and fluorescence [67], gel [68] and amyloid fiber formation [69], and chiral recognition and phosphate binding [70]. The recent demonstration of intramolecular cargo transport [70] and a variety of other mechanical tasks—elegantly shown by the Sauvage, Stoddart, Leigh, Guiseppone, Harada and Aida groups and others—illustrate the potential of molecular machine-like functions.

Motion at Different Length Scales

A major part of our research program on molecular motors has been devoted to the control, use and visualization of motion at different length scales (Figure 9). As is evident from the ATPase rotary motor embedded in the cell membrane and myosins moving along actin filaments, most biological motors operate at interfaces. We considered as a crucial step in the design of molecular devices based on rotary motors their assembly on surfaces and interfacing to macroscopic systems.

Second generation motors are particularly suited, as the stator part allows the introduction of various "legs" for surface anchoring, leaving the rotor part free to undergo light-driven rotary motion (Figure 9) [71]. Our initial attempts with short legs and thiol groups for self-assembly on Au failed due to quenching of the excited state isomerization pathways of the motor by the surface, but extending the legs with hydrocarbon moieties (lifting the motor from the surface) solved the problem. The presence of two legs prevented uncontrolled motion of the entire motor molecule, while sufficient conformational flexibility allowed uncompromised rotor movement. This design enabled self-assembly of rotary motors on Au nanoparticles and flat Au surfaces, resulting in our first "nanoscale windmill park" powered by light [72]. It was also the basis for several years of synthesis and surface science studies in order to design a variety of responsive interfaces. This included the assembly of motors in azimuthal and altitudinal orientations on quartz, Au, etc. and the anchoring with bis-, tris-, or tetrapodal-units to the surface to control rigidity, orientation with respect to the surface and spacing between individual motors on the surface. The surface bound motor shown in Figure 9 illustrates the concept elegantly; the tripodal anchoring, its size and the altitudinal orientation enables not only proper functioning of individual motors but also dynamic orientation of the hydrophobic perfluoroalkyl moiety towards or away from the surface. In this way photoresponsive behavior of the surface is readily achieved and precisely controlled, allowing both thickness and surface wettability to be modulated by light [73]. Currently we are investigating the rotary function of individual motors assembled on surfaces, using single molecule fluorescent techniques, to mimic the elegant experiments on visualization of rotation motion of the single ATPase protein motors [74].

Our next goal was the amplification of motion from the molecular to the mesoscopic and microscopic level. Overcrowded alkene-based rotary motors, due to their inherent dissymmetric structure and helical chirality, turned out to be excellent chiral dopants for nematic liquid crystal (LC) materials. Twisted nematic (cholesteric) LC films were obtained using small amounts (1 wt. %) of rotary motors and upon irradiation the change in helical chirality of the motors was amplified to induce dynamic changes in the supramolecular organization in the mesoscopic film as well as the surface structure at the LC-air interface. These responsive LC films allowed color change through the entire visible spectrum (color pixel formation) and rotation of micro-objects floating on its soft surface in a unidirectional sense when illuminated, resulting in an amplification over four orders of magnitude [75]. These discoveries marked a milestone in our motor research; for the first time, we observed the manifestation of autonomous

rotary motion with the naked eye, induced by the dynamic function of a molecular rotary motor. It also laid the foundation for dynamic reorganization inside and at the surface of LC microdroplets triggered by light [76].

A second approach to amplify motion is via dynamic macromolecules with the perspective to design responsive and mechanical polymer materials i.e. fibers, networks, gels and films. For instance, amide-functionalized second-generation motors were applied as initiators in the polymerization of hexylisocyanate to provide a photoreponsive helical polymer [77]. Upon irradiation, the unidirectional rotary cycle of the single motor unit at the terminus of the polymer induces helix reversals in the polymer chain. This amplification of motion mimics a kind of flagellar function, while continuous irradiation drives the system to a steady state out-of-equilibrium. Large array surface patterning by self-assembly and responsive polymer LC films were obtained depending on the anchoring position of rotor and stator to the helical polymer chain. This design allows the transmission of motion and helical chirality over different length scales e.g. from the molecular, to macroscopic and finally mesoscopic hierarchical level. The use of rotary motors in polymer gel networks by Giuseppone is another elegant example showing the potential of molecular motors controlling mechanical functions in soft materials [78].

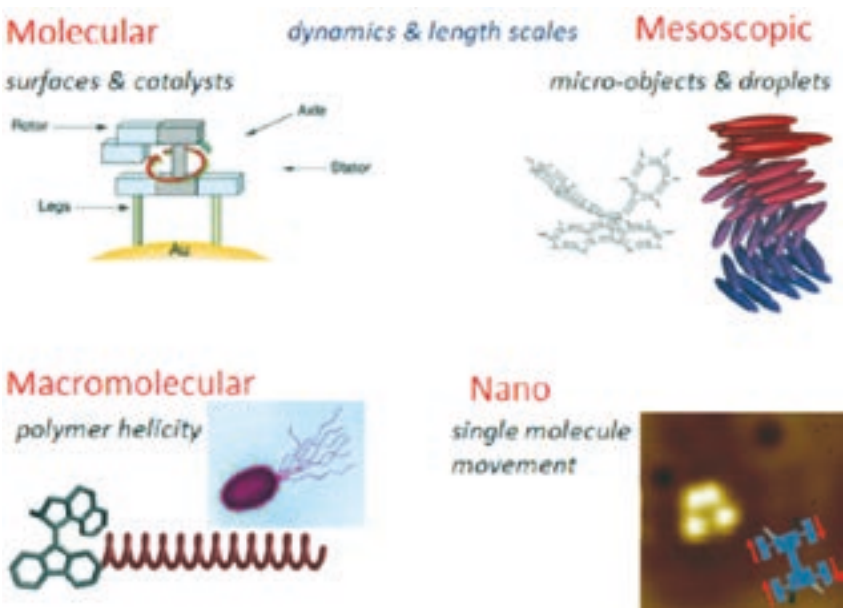

FIGURE 9. Control of motion across different length scales.

From rotary motion to translational motion

The idea of building a "four-wheel-drive molecular nanocar" started at the point where we were confronted with two fundamental questions; i) how to demonstrate single molecule motion? ii) How to convert rotary motion into translational motion? At the start of our lengthy journey, which ultimately resulted in the realization of a nanocar moving autonomous over a Cu surface, critical design features that we explored were a rather rigid frame with four second generation rotary motor units functioning as "wheels" [79]. We envisioned cooperativity of the motors which, due to their helical structure, also could

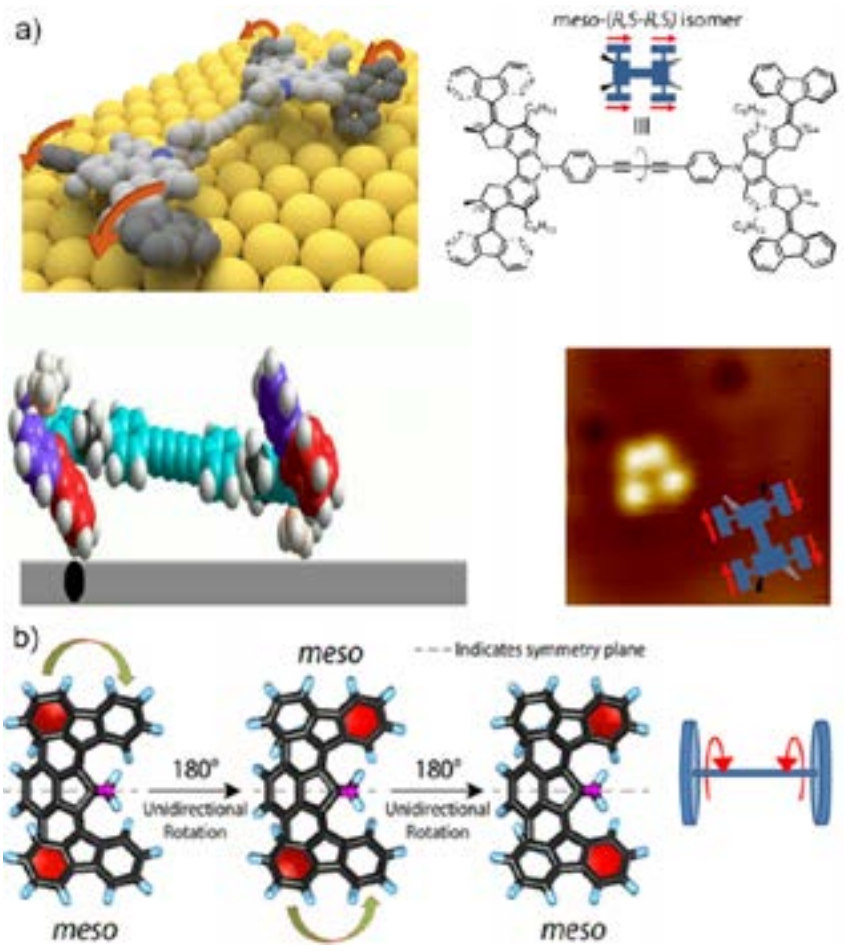

FIGURE 10. a) Four-wheel drive molecular car based on rotary motors; models, molecular structure and STM image. b) Third generation symmetric molecular motor.

lift the entire molecule a little from the surface, but sufficiently to overcome the strong adhesive interactions. In a combined effort with the Ernst group at EMPA Zurich, it was found that electrical excitation with an STM tip (at low temperature) of the meso-(R,S-R,S) isomer of the nanocar deposited on a Cu(1,1,1) surface induced propulsion over the surface along a more or less linear trajectory. Changing the stereochemistry of the "wheels", a single enantiomer of the nanocar was prepared with all the motor units having the same (R,R-R,R) chirality. Now the motion on the surface changed from more linear to random or rotary motion without significant translation in accordance with expectation on the basis of symmetry considerations (*see below*). It should be noted that molecular modeling indicates a "walking type" of motion for the nanocar reminiscent of the movement of kinesin proteins motors on actin filaments. Exploring these molecular propulsion systems, we demonstrated intrinsic motor function, cooperative action, autonomous movement on electrical excitation and control to some extent of directionality of movement at the single molecule level. With these findings, the stage is set for autonomous directional movement along tracks and cargo transport.

These results brought us also to another fundamental question: Is intrinsic molecular chirality needed to achieve unidirectional motion in a molecular rotary motor? To avoid an equal probability of clockwise and counterclockwise rotation around a single rotary axle connecting stator and rotor, our rotary motors rely on the chirality of the system [52, 59, 60]. It should be remembered that in a mechanically interlocked system, directionality in rotary motion has been achieved due to a specific sequence of chemical steps [80] while a non-symmetric environment can govern directionality in surface assembled rotors [81]. In the overcrowded alkene motors the directionality of rotary motion is controlled by point chirality as it dictates the thermodynamically preferred helical chirality. To guide our design of third generation motors we started with symmetry considerations of rotary motion at macroscopic length scales, e.g., the disrotary motion of two (car) wheels on an axle. [82]. The directionality of rotary motion from an observer at the symmetry plane is opposite (Figure 1A) while, despite the entire system being symmetric (C_s, with a mirror plane of symmetry), the rotary motion of the two wheels on an axle with respect to the surrounding is identical (e.g., both forward rotation for an external observer) enabling concerted rotary motion to induce directional linear motion. Translating these symmetry considerations to a stereochemical design featuring two integrated rotor moieties in a meso compound, we demonstrated that a symmetric (achiral) light-driven molecular motor is indeed feasible. The presence of a pseudo-asymmetric carbon atom bearing a methyl and fluor substituent, which proved to be

of sufficiently different size to govern directionality, exclusive disrotary motion of two appending rotor moieties was achieved. Besides providing important insight in how to control nanoscale movement, these third-generation motors are particularly suited to build molecular dragsters and responsive materials.

Catalytic Motors and Propulsion Systems

Although our research started with light-induced switching and motion, inspired by the process of vision, part of our program has been devoted to catalytic motors and propulsion systems. Typically, biological motors such as ATPase, kinesin or bacterial flagella motors rely on catalysis, converting the chemical fuel ATP into kinetic energy. Proof of principle of a chemical driven rotary motor was demonstrated with the biaryl rotor system. The underlying dynamic stereochemical features are: First, hindered rotation in a tetrasubstituted biaryl prevents interconversion of enantiomers, although there is sufficient conformational freedom in the molecule to position ortho substituents at the two aryl units in proximity or remote from each other. Second there is a sufficiently low barrier for helical interconversion via a planar transition state of the lactone bridged biaryl. Using asymmetric CBS oxaborolidine catalyzed ring opening of the lactone as the key step governing > 90 % unidirectionality and a sequence of orthogonal (de-) protection steps a four stage unidirectional rotary cycle was accomplished [83].

Although not yet fully catalytic, an additional benefit of this system is that the direction of rotary motion can be reversed by simply switching the chirality of the catalyst. Recently we have extended these basic principles of control of dynamic stereochemistry in combination with chemical driven directional motion in a biaryl motor to a metal-mediated system [84]. The presence of both axial chirality and a stereogenic centre in combination with Pd(0), Pd(II) redox cycles enabled for the first time unidirectional rotary motion induced by sequential transition metal catalyzed conversions of chemical fuels. Autonomous translational motion based on the catalytic conversion of chemical fuels was also achieved. In contrast to the use of metal-based micro/nano-rods for hydrogen peroxide decomposition, as shown by Whitesides and others [85] to achieve autonomous propulsion, we followed a molecular approach. For instance, bimetallic Mn-catalysts were designed as functional mimics of the active site of catalase enzymes followed by covalent attachment of these catalysts to various microparticles, including polymers [86]. These supported catalysts enabled autonomous swimming motion of particles by converting hydrogen peroxide as a fuel. In a more elaborate design carbon nanotubes were covalently modified with two enzymes, catalase and glucose oxidase [87]. The concerted action of

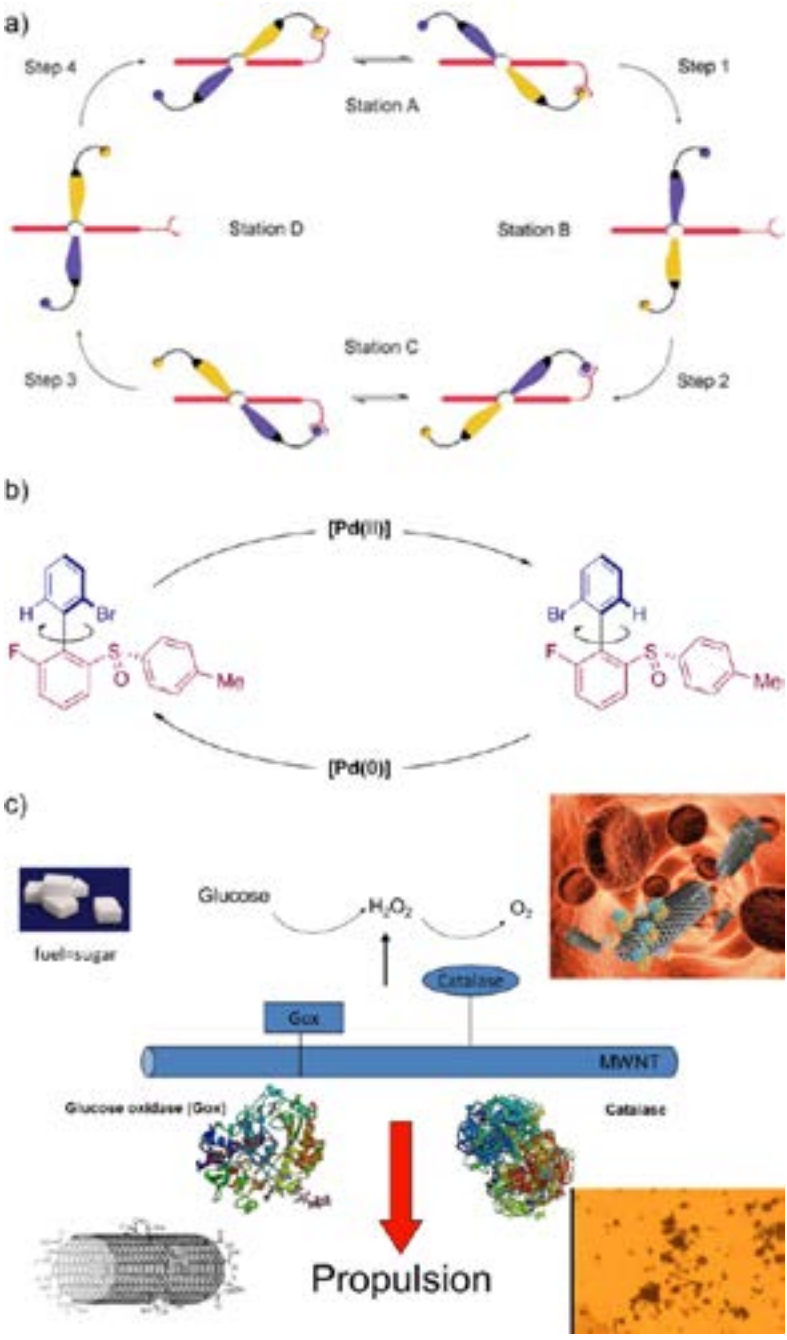

FIGURE 11. Chemical driven rotary and translational motion. a) Biaryl-based 4-step unidirectional rotary motor. b) Pd-mediated rotation in biaryl. c) Catalytic nanotube propulsion system powered by glucose.

these two enzymes, converting glucose and generating oxygen, induced autonomous movement of carbon nanotube aggregates in water, albeit with no control over directionality.

Although still rather remote from nanopropulsion systems carrying loads under physiological conditions in a highly controlled manner, our catalytic propulsion systems and related designs will likely guide the molecular motorist on a "fantastic voyage" in the world of autonomous operating molecular machines.

CONCLUDING REMARKS

The development of molecular motors arguably offers a fine starting point for the construction of soft robotics, smart materials and molecular machines. Our ability to design, use and control motor-like functions at the molecular level sets the stage for numerous dynamic molecular systems. Starting with the "synthesis of function", our focus was to program molecules by incorporating responsive and adaptive properties and being able to control motion. Molecular information systems, responsive materials, smart surfaces and coatings, self-healing materials, delivery systems, precision therapeutics, adaptive catalysts, roving sensors, soft robotics, nanoscale energy converters and molecular machines are just a small fraction of the systems where fascinating discoveries can be expected and where the ability to control dynamic functions will be essential. The practitioner of the art of building small will have to reach out to new levels of sophistication when dealing with complex dynamic molecular systems. In this endeavor, while trying to imagine the unimaginable, Nature's motors and machines can to some extent guide the molecular explorer. However, at the start of our next journey we should not forget the words of Leonardo da Vinci [89]: "*Where Nature finishes producing its own species man begins, with the help of Nature, to create an infinity of species.*"

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