Molecular rotary motors: Unidirectional motion around double bonds

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The field of synthetic molecular machines has quickly evolved in recent years, growing from a fundamental curiosity to a highly active field of chemistry. Many different applications are being explored in areas such as catalysis, self-assembled and nanostructured materials, and molecular electronics. Rotary molecular motors hold great promise for achieving dynamic control of molecular functions as well as for powering nanoscale devices. However, for these motors to reach their full potential, many challenges still need to be addressed. In this paper we focus on the design principles of rotary motors featuring a double-bond axle and discuss the major challenges that are ahead of us. Although great progress has been made, further design improvements, for example in terms of efficiency, energy input, and environmental adaptability, will be crucial to fully exploit the opportunities that these rotary motors offer.

Control of motion at the molecular scale has intrigued chemists for a very long time. The quest for overcoming random thermal (Brownian) motion has culminated in the emergence of synthetic molecular machines (1–7), including motors (8–12), muscles (13), shuttles (14), elevators (15), walkers (16), pumps (17–19), and assemblers (20). By taking inspiration from the fascinating dynamic and motor functions observed in biological systems (e.g., ATPase and bacterial flagella) (21), the field of synthetic molecular machines has evolved rapidly in recent years. This is due to major advances in supramolecular chemistry and nanoscience, the emergence of the mechanical bond (7), and the development of dynamic molecular systems (22). A variety of potential applications is now being considered in areas ranging from catalysis (23) and self-assembly (24) to molecular electronics (25, 26) and responsive materials (27, 28). Furthermore, translation of motion from the molecular scale to the macroscopic scale allows for dynamically changing material properties and the movement of larger objects. Cooperativity and amplification across several length scales can be achieved, for example, by incorporating molecular machines in gels (29, 30), liquid crystals (27, 31), and polymers (32) or by anchoring them to surfaces (33, 34), allowing the control of a variety of properties including surface wettability (33, 34), contraction or expansion of gels (29), and actuation of nanofibers in response to their environment (35). This leap from static to dynamic materials clearly demonstrates the potential of molecular machines. Although much effort has already been devoted to the development of molecular motors and machines as well as the elucidation of their operational mode, a great deal of design improvements are needed to fully exploit the potential in practical applications. Ideally, molecular motors can operate with high efficiency and durable energy input (fuel), can be easily adapted to a specific environment or application, are compatible with specific functions, and can be synchronized and act in a cooperative manner.

Where the pioneering work of Sauvage, Stoddart, and others successfully led to stimuli-controlled translational and rotary motion in mechanically interlocked systems (1, 36–39), the induction of unidirectional rotary motion posed a major challenge. Distinct approaches, including those based on catenanes (39), surface confined systems (40), and aryl–aryl single-bond rotation (8, 41, 42), have been taken over the last two decades to develop molecular motors capable of such unidirectional rotation when supplied by energy in the form of light, chemical stimuli, or electrons (11). In this paper, we focus on rotary motors that contain a double-bond axle (Fig. 1). Although it may
Rotational motion

Fig. 1. Schematic representation of unidirectional rotary motion around a double-bond axle.

seem unusual to use a double bond as rotary axle since the rotation is restricted, stimuli such as light can induce rotation (cf. isomerization), as is most elegantly seen in the process of vision (43). As such, autonomous and repetitive unidirectional rotation has been successfully achieved in multiple systems, all of them driven by light. Here, we discuss the key design principles of these systems and furthermore a perspective on key challenges and possible future developments is provided.

Motors Based on Overcrowded Alkenes

At the very basis of overcrowded alkene-based molecular motors is a photochemical cis–trans isomerization around their central carbon–carbon double bond. For stilbene, this process has been studied already for more than half a decade (44). Due to the symmetry of stilbene, there is no directional preference in the isomerization process. It was shown in 1977 that the introduction of steric bulk around the double bond distorts the otherwise planar geometry, giving rise to helical chirality (45). This feature was further exploited to develop a chiroptical switch, in which two pseudoenantiomeric forms with opposing helical chirality could be selectively addressed (46). This work formed the basis for the design and synthesis of the first molecule capable of undergoing unidirectional 360° rotation around a double bond, which our group reported in 1999 (9). It is based on an overcrowded alkene, with two identical halves on each side of the double bond (the rotary axle) ([P,P]-trans-1 in Fig. 2A). Due to steric interactions between the two halves, in what is referred to as the fjord region, the molecule is twisted out of plane, resulting in a helical shape. The first molecular motor featured two stereogenic methyl substituents which are preferentially in a pseudoaxial orientation due to steric crowding. These stereocenters dictate the helical chirality in both halves of the molecule and hence the direction of rotation. A full rotary cycle consists of four distinct steps: two photochemical and energetically uphill steps and two thermally activated and energetically downhill steps.

Starting from ([P,P]-trans-1 (Fig. 2A), irradiation with UV light (>280 nm) induces a trans-to-cis isomerization around the double bond leading to isomer (M,M)-cis-1 with opposite helical chirality. This photoisomerization is reversible and under continuous irradiation a photostationary state (PSS) is observed in which for this particular case the ratio of cis to trans is 95:5. In (M,M)-cis-1 the methyl substituents end up in an energetically less favorable pseudoequatorial position. To release the built-up strain, a thermally activated process occurs, in which both halves slide along each other, inverting the helicity from left- (M,M) to right-handed (P,P) and allowing the methyl substituents to readopt the energetically favored pseudoaxial orientation. The photogenerated states, which are prone to such a thermal helix inversion (THI) process, have often been referred to as “unstable” or “meta-stable” states. The THI is energetically downhill and effectively withdraws the higher-energy isomer such as (M,M)-cis-1 from the photoequilibrium mixture and hence completes the unidirectional 180° rotary motion. The second part of the cycle proceeds in a similar fashion as a second photoisomerization step affords (M,M)-trans-1 (PSS trans to cis ratio of 90:10) with the methyl substituents again in the pseudoequatorial position. A second THI then reforms ([P,P]-trans-1 and a full 360° rotation cycle is completed.

The so-called second-generation light-driven molecular rotary motors, consisting of distinct upper (rotor) and lower (stator) halves and bearing only a single stereogenic center (Fig. 2C), were presented shortly after (47). Analogous to the first-generation motors, 360° rotary motion can be achieved by a sequence of photochemical and thermal steps. The design, with nonidentical halves, allowed for a much broader scope of functionalization, in particular for surface anchoring through the stator, and paved the way for many different applications (12), as shown in Fig. 3.

Fig. 2. (A) Rotary cycle of a first-generation motor based on overcrowded alkene. (B) Top view of the rotary cycle. (C) Structures of second- and third-generation molecular motors.
Rotational Speed Adjustment. For every different application of molecular motors, for example in soft materials or biological systems, often a distinct frequency of rotation is desired. The photochemical steps proceed on a timescale of picoseconds, making the usually much slower THI the rate-limiting step (50). Considerable research effort in our group has been devoted to fully understanding of their functioning, especially the key parameters that govern the isomerization processes, and the use of new insights to adapt the structural design (11). This has resulted in a large collection of overcrowded alkene-based motors with different properties, which have been applied successfully to induce motion at the molecular scale as well as the nano scale and macro scale (27, 34, 49). The main aspects that have been investigated and that will be discussed in the next sections are the speed of rotation, the excitation wavelength, and the efficiency of the motors.

For first-generation motors, the THI processes for unstable cis and trans isomers are different and therefore have different rates (9). Modifications to the design of the molecular motor can have complex and sometimes opposite effects on these rates. For example, the introduction of more steric bulk at the stereogenic center, by replacing the methyl substituent in motor 4 with an isopropyl group, accelerates the rate of thermal isomerization from the unstable to the stable cis form but decreases the rate going from the unstable to the stable trans isomer (Fig. 5) (54). The latter process was found to be so slow that an intermediate state could be observed with mixed helicity, that is (P,M)-trans-5, suggesting that the THI is a stepwise process. This kind of behavior was already predicted for related overcrowded alkenes that do not have stereogenic methyl substituents, which according to calculations racemize between (M,M) and (P,P) helical structures via an intermediate structure with (P,M) helicity (55). This example, however, remains so far the only case in which such a stepwise mechanism for the THI in first-generation motors is observed. To decrease the amount of steric hindrance in the fjord region, and hence lower the energy barrier for THI, the central six-membered ring was changed to a five-membered ring (Motor 6 in Fig. 5) (56). It has to be noted that upon reducing the ring size from six- to five-membered, conformational flexibility is lost. As a consequence, the unstable states are most likely further destabilized as the steric
hindrance cannot be relieved by folding, which additionally contributes to increased rates for the THI.

In an attempt to further destabilize the unstable states, overcrowded alkene 7 was synthesized, which has two tert-butyl instead of methyl substituents at the stereogenic center (57). However, these substituents cause too much steric hindrance impeding the unidirectional motion. Another approach is to replace the naphthalene moieties with xylene moieties (motor 8) (58). In this design, the xylyl methyl substituents cause the necessary steric hindrance in the fjord region. X-ray analysis shows that these methyl substituents are more sterically demanding in the trans isomer, forcing the molecule in a more strained conformation, also leading to destabilization of the unstable trans isomer. The barrier of the THI from unstable trans to stable trans was found to be lower in motor 8 with respect to motor 6. However, the increased steric hindrance in the fjord region causes a higher barrier for the unstable cis to stable cis isomerization, reflecting the complex and opposite effect that (often subtle) changes in the molecular design may have on the rates of these two THI processes.

Similar systematic structural modifications have been made to second-generation motors to alter their speed of rotation. Initial studies mainly involved motors of the general structure 9 (Fig. 6) in which the bridging atoms (X and Y) were varied (47, 51, 52). Half-lives of the unstable states ranging from 233 h [X = S, Y = C(CH3)] to 0.67 h (X = CH2, Y = S) were measured. The conformationally flexible six-membered rings allow for the molecule to release some of the strain around the double bond that is built up in the photoisomerization step. DFT calculations have shown that, in case of a six-membered ring, the THI is a stepwise process and multiple transition states have been identified (51, 52).

Also here the change to a five-membered ring in the stator makes the molecule more rigid. Again, this results in an increased barrier for the THI in compound 10, up to the point where a thermal E–Z isomerization becomes favored over the THI and a bistable switch is obtained (59). When only in the upper-half rotor a five-membered ring is introduced (motor 11), the rotational speed dramatically increases up to the megahertz regime (60). Motor 12, bearing two five-membered rings, however, has a lower barrier, in analogy to the first-generation motors, due to a decrease in the steric hindrance in the fjord region (61). The steric hindrance, and as a consequence the THI barrier, was further reduced by replacing the naphthalene moiety in the upper half with xylene or benzothiophene (motor 13) (58, 62). Furthermore, larger substituents have been placed at the stereogenic center to increase the rate of the THI (63, 64) and DFT calculations showed that this decrease is due to destabilization of the unstable state, effectively lowering the barrier for THI.

The speed of the rotary motors is also dependent on the solvent (65, 66). In a systematic study of motors with pending arms of varying flexibility and length it was established that solvent polarity plays a minor role, but that in particular enhanced solvent viscosity for motor systems with rigid arms decreases THI drastically (67). The results were analyzed in terms of a free volume model and it is evident that matrix effects (solution, surface, polymer, and liquid crystal) comprise a challenging multiparameter aspect in applying molecular motors. In all these examples, changing the speed of rotation of a molecular motor requires a redesign of the molecule and multistep synthesis. Dynamic control of the rotational speed would be the next logical step in the development of molecular motors. Locking the rotation by employing an acid–base-responsive self-complexing pseudorotaxane was the first example that allowed for such dynamic control over the rotary motion (68). More recently, an allosteric approach was reported in which metal complexation was used to alter the speed of rotation (69). Complexation of different metals to the stator part of a second-generation molecular motor caused different degrees of contraction of the lower half. As a consequence the steric hindrance in the fjord region decreased, which resulted in a lower barrier for the THI.

Precise control of the speed of rotation in a dynamic fashion remains challenging but the first examples have shown that lengthy syntheses can be avoided and motor speed can be altered in situ. Controlling speed by external effectuators (metal/ion binding, pH, and redox) or tuning in response to chemical conversions (catalysis) or environmental (matrix and surface) constraints offer exciting opportunities for more advanced motor functioning.

**Shifting the Excitation Wavelength.** A major challenge in the field of photochemical switches and motors is to move away from the use of damaging UV light because it limits the practicality in soft materials and biomedical applications (70, 71). For this reason, it is important to shift the irradiation wavelengths toward the visible spectrum (72). The most straightforward method is to make changes to the electronic properties of the motors in such a way that the molecule is able to absorb visible light. However, such changes may be detrimental to the photoisomerization process. The first successful example of a visible light-driven molecular motor made use of a push–pull system to red-shift the excitation wavelength (73). This second-generation motor comprised a nitroacceptor and a dimethylamine-donor substituent in its lower half, which allowed for photoexcitation with 425-nm light. An alternative strategy that is often used to red-shift the absorption of molecular photoswitches relies on the extension of the π system. Indeed, upon extension of the aromatic system of the stator half of second-generation motors unidirectional rotation could be induced by irradiation at wavelengths up to 490 nm (74).

Apart from these methods that focus on altering the highest occupied molecular orbital–lowest unoccupied molecular orbital gap, alternative strategies based on metal complexes are highly promising. For example, palladium tetraphenylporphyrin was used as a triplet sensitizer to drive the excitation of a molecular motor (75). Isomerization of the motor was shown to occur by triplet-triplet energy transfer, upon irradiation of the porphyrin with 530- to 550 nm light. In a related example, a molecular motor was incorporated as a ligand in a ruthenium(II)–bipyridine complex (76). Irradiation with 450 nm into the metal-to-ligand charge transfer band resulted in unidirectional rotation.
These examples illustrate that there are multiple viable strategies to red-shift the excitation wavelength of molecular motors. However, the change of the wavelength region at which these motors can be operated is still modest. Moving further away from UV light toward red light or even near-IR remains a major challenge. There are several strategies that have shown promising results for photoswitches, such as diarylethenes and azobenzenes, that have not been applied to molecular motors yet (72). For example, multiphoton absorption processes using upconverting nanoparticles (77) or two-photon fluorophores (78) should be considered in future studies.

**Improvement of the Photochemical Efficiency.** Improving the efficiency of the photochemical isomerization process has proven to be difficult as it is not as well understood as the thermal isomerization process. Typically, quantum yields below 2% are observed for E/Z photoisomerization of second-generation motors (52, 79). To improve the yield, a detailed understanding of the excited state dynamics is required. Over the last decade, a combination of advanced spectroscopic studies and quantum chemical calculations has been used to gain insight in the mechanism of the photochemical isomerization. Using time-resolved fluorescence and picosecond transient absorption spectroscopy, a two-step relaxation pathway was observed after the initial excitation to the Franck-Condon excited state (50, 79, 80). Within 100 fs, a bright (i.e., fluorescent) state relaxes to an equilibrium with a lower-lying dark (i.e., nonfluorescent) state. Based on femtosecond stimulated Raman spectroscopy, supported by quantum chemical calculations, it has been postulated that this process is accompanied by elongation and weakening of the central double bond (81–84). Solvent viscosity studies showed that this process is independent of solvent friction, which is consistent with a volume-conserving structural change (79, 85). The dark excited state, formed after this first relaxation, has a lifetime of ~1.6 ps and relaxes back to the ground state to either the stable or unstable form via conical intersections (CIs). Relaxation to the ground state leaves excess vibrational energy which is dissipated to the solvent at the tens of picoseconds timescale (81). The relatively long lifetime of the dark state is attributed to the fact that a high degree of twisting and pyramidalization of one of the carbons of the central double bond is required to reach the CI (84). Recent studies showed that this relaxation to the ground state, which is associated with twisting and pyramidalization, is not dependent on the size of the substituents (85), while it is dependent on viscosity. This observation suggests that the motion that accompanies the relaxation to the ground state is not necessarily a complete rotation of the halves but rather occurs only at the core of the molecule.

The ability to control CIs could lead to major improvements, as they play an important role in the efficiency of the photochemical step. To improve the efficiency of molecular motors, Filatov and coworkers investigated the factors influencing the CIs in a theoretical study (86, 87). The calculations predict that by placing electron withdrawing groups close to the central axle, such as an iminium, the character of the CI changes from a twist-pyramidalization to a twist-bond length alteration. This effectively changes the mode of rotation from a precessional motion for current motors to an axial motion with higher efficiency. These computational designs have already inspired the development of new photoswitches with increased efficiency (88) but have not yet been applied to molecular motors.
motors and should be taken into account in attempts to increase the efficiency.

Redox-Driven Motors. As an alternative to the use of (UV-visible) light to power molecular motors we considered designing an electromotor taking advantage of redox processes. Preliminary studies toward using overcrowded alkenes as redox-driven molecular motors are promising (89). A rotary cycle is envisioned, in which consecutive oxidation/reduction cycles would electrochemically form the unstable state, which then undergoes a THI to afford the stable state, completing 180° rotation (Fig. 7). Unfortunately, the stereogenic center was found to be susceptible to deprotonation, leading to an irreversible double-bond shift in which the central axis is converted to a single bond. As this type of degradation pathway impedes any successful directional motion, a different design has to be made. Quaternionization of the stereogenic center by replacing the hydrogen for a fluorine atom would prevent deprotonation. It was recently shown that such fluorine-substituted molecular motors with quaternary stereocenters are still capable of unidirectional rotation when irradiated by light, making them excellent candidates to be studied as redox-driven molecular motors (90).

Alternative Motor Designs
In 2006, Lehn (91) proposed a new type of light-driven molecular motor derived from imines. The design is based on the two types of E/Z-isomerization processes that imines can undergo, namely a photochemical isomerization and a thermal nitrogen inversion. A two-step rotational cycle was proposed, starting with a light-induced E/Z isomerization, which has an out-of-plane rotational mechanism (Fig. 8). A thermally activated in-plane nitrogen inversion involves a planar transition state which would convert the system back to the original state. These two combined processes would lead to a net rotational motion as both follow a different pathway. Placing a stereogenic center next to the imine leads to preferential rotation by favoring the direction of the photochemical isomerization. This is different from the other examples of double-bond motors, as directionality is induced here in the photochemical step, rather than the thermal isomerization step.

Based on these design principles, Greb and Lehn (92) reported in 2014 on the synthesis of the first rotary motor based on imines (i.e., N-alkyl imine 14) bearing a stereocenter next to the central imine (Fig. 9). Because of the twisted shape of the lower half and E–Z isomerism of the imine four stereoisomers are formed. A helicity inversion does not occur under the experimental conditions due to the relatively high barrier for this process compared with the nitrogen inversion. Under thermodynamic equilibrium, there is a preference for (S,M)-cis over (S,P)-trans, whereas there is not a major preference for either (S,P)-cis or (S,M)-trans. Photochemical isomerization occurs upon irradiation with 254-nm light and at PSS the ratio is shifted toward (S,P)-trans relative to (S,M)-cis, while the ratio of the other two isomers remains unaffected by irradiation. Heating up the mixture of isomers to 60 °C for 15 h allows for the nitrogen inversion to occur, restoring the original distribution of diastereomers. Both processes are equilibrium reactions and therefore both forward and backward reactions can occur. However, due to preferred formation of one of the isomers in each step, overall a net rotation occurs.

During their investigations, it was found that annealing a benzene ring to the lower half is essential for this two-step motor as it effectively increases the thermodynamic barrier for the helicity inversion. Interestingly, when this inversion can occur, a molecular motor with a four-step rotary cycle is obtained, reminiscent of the cycle for motors based on overcrowded alkenes. That is, two photochemical isomerization steps and two thermally activated ring inversions give rise to 360° rotation. To show that imines can be used as two-step molecular motors in a more general sense and to provide more experimental and theoretical proof for the rotational behavior, camphorquinone imines were synthesized in a follow-up study (93).

One of the major advantages of imine-based molecular motors is that many types of imines with different properties can be easily synthesized through simple condensation reactions starting from commercially available materials. Furthermore, fine-tuning of the speed of these motors can be achieved through controlling the barrier for N-inversion. The barrier for this process depends

Fig. 8. Proposed mechanism for an imine-based molecular motor.

![Mechanism](image)

Fig. 9. A two-step molecular rotary motor based on imines.
largely on the substituent at the N-atom, providing a good handle to alter the speed of rotation. The assumption that there is a preferred direction of rotation in the photochemical E/Z isomerization in chiral imines due to the unsymmetrical excited state surface is very plausible, but further experimental support to unequivocally prove their preferred direction of rotation is warranted. These photoinduced isomerization processes often occur at the picosecond timescale, making it very difficult to obtain direct evidence. Potentially, quantum mechanical calculations can aid in exploring the excited state surface.

In 2015, Dube and coworkers introduced a light-driven molecular motor based on a thioindigo unit fused with a stilbene fragment (Fig. 10) (94). The design and rotational cycle resemble that of the molecular motors based on overcrowded alkenes with the distinct difference that a sulfoxide stereogenic center is present. Due to the steric crowding around the central axle, the substituents of the central double bond are twisted out of plane, giving the molecule a helical shape. The helicity is dictated by the chirality of the sulfoxide. The behavior of this motor was examined by UV-visible and $^1$H-NMR spectroscopy, showing that, in analogy to the overcrowded alkenes motors, the rotational cycle consists of four steps: two alternating sets of photochemical and thermal isomerization steps. The photochemical isomerization could be induced by light of wavelengths up to 500 nm and a frequency of rotation of 1 kHz at room temperature was determined. During the $^1$H-NMR studies, only the (E,S,M)-15 unstable state was observed, whereas the (Z,S,M)-15 state could not be detected, presumably because the THI is too fast. This hypothesis was supported by detailed DFT calculations showing a four-step unidirectional rotary cycle. More recently, a more sterically crowded and, therefore, slower motor was synthesized, which allowed for the direct observation of the fourth state (95).

**Outlook**

Since the first development of light-driven molecular rotary motors two decades ago, great progress has been made in controlling unidirectional rotation around double bonds. In particular, the overcrowded alkene-based molecular rotary motors have been thoroughly investigated. Various designs are now increasingly applied to control dynamic functions (12); however, for a wider range of applications of these motors further improvements are essential (e.g., the use of longer irradiation wavelengths, as usually the photochemical isomerization steps are induced by UV light, which is harmful and thus impedes application in chemical biology and materials science). The first visible-light-driven motors that can be powered with light up to 500 nm have recently been introduced, but more powerful strategies such as multiphoton absorption or photon upconversion need to be explored since they will afford a major red shift in the irradiation wavelength, preferably even into the near-IR region. Although the influence of structural changes on the speed of rotation of these motors has been well established, supramolecular and metal-based approaches that allow for speed adjustments with multiple stimuli are highly promising.

Increasing the efficiency of molecular motors is a more complex problem that offers another nice challenge also in view of their potential use in nanoscale energy conversion and storage as well as performance of mechanical work by future rotary motor-based molecular machines. In this regard, theoretical studies could aid at improving the efficiency and motor design. Another major challenge for molecular motors that comprise a stereogenic center is to obtain sufficient quantities of enantiopure material, which is needed to explore new applications, in particular toward responsive materials. Enantioselective synthetic routes toward first- and second-generation motors have been recently developed (96, 97) and a chiral resolution method by crystallization of first-generation motors offers important perspectives (98).

All these fundamental challenges have to be considered in the perspective of molecular machines: control of functions and the design of responsive materials. Tuning molecular motors to operate in complex dynamic systems will require, among others, synchronization of rotary and translational motion, precise organization and cooperativity, and amplification of motion along length scales. A first approach toward coupled motion was recently reported by our group, in which the rotary motion of the molecular motor is transferred to the synchronized movement of a connected biaryl rotor (99). The prospects for controlling motion at the nano scale and beyond will continue to provide fascinating challenges for the molecular designer and many bright roads for the molecular motorist in the future.

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