On conformational and configurational aspects of molecular motors

van Leeuwen, Thomas

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Chapter 1:

Introduction to artificial rotary molecular motors

Herein an overview is given of the recent developments of artificial rotary molecular motors.

This chapter has been published:
Chapter 1

1.1 Introduction

Biological molecular machines are ubiquitous in life and perform important tasks at the cellular level. When it comes to essential functions ranging from motility to metabolism, biological machines such as motors, ion pumps and ribosomes are at the basis of it. Inspired by the ingenuity of these machines and the envisioned potential of artificial analogs, chemists embarked on a bottom-up journey to create non-biological molecular machines.

The term (artificial) molecular machine is difficult to define precisely. Credi, Balzani, Venturi and others defined the term molecular machine as an assembly of a discrete number of molecular components designed to perform mechanical-like movements (output) as a consequence of appropriate external stimuli (input). Later, Leigh et al gave a slightly different definition: molecular machines are a defined subset of molecular devices (functional molecular systems) in which some stimulus triggers the controlled, large amplitude or directional mechanical motion of one component relative to another (or of a substrate relative to the machine) which results in a net task being performed.

Under these definitions, the groups of Shinkai and Rebek were one of the firsts to develop non-biological molecular machines, although at that time those designs were not classified as such. Shinkai’s system consisted of an azobenzene switch bearing two crown ethers. Under the influence of light, the azobenzene undergoes a photochemical $E$-$Z$ isomerization. As a result of this motion, the two crown ether moieties are brought together which significantly alters the affinity for alkali cations. In the $trans$ configuration the crown ethers display a high affinity for Na$^+$, while for the $cis$ isomer larger metal ions like Cs$^+$ and Rb$^+$ are preferred. The photoinduced change in affinity was used in extraction experiments and for light-driven ion transport. This molecule can be viewed as a molecular tweezer, able to pick up and release alkali cations upon demand. Rebek and co-workers showed how the efficiency of Na$^+$ transport can be controlled by allostERIC regulation upon binding of transition metals.

A great number of molecular machines are based on mechanically interlocked molecules, such as rotaxanes and catenanes (Figure 1). Initially, the research on mechanically interlocked molecules was spurred by the interest how to make these compounds. The first synthesis of the first catenane dates back to 1960, while the first synthesis of a rotaxane was reported in 1967. The transition from interesting molecules to synthesize to important building blocks for molecular machines can be traced back to 1991, when Stoddart et al reported on the first rotaxane shuttle. The design featured a rod with two equivalent stations between which a ring could shuttle back and forth. Stoddart predicted then with great foresight that the possibility of controlled movement of one molecular component with respect to another will enable the design of molecular
machines. After this report a whole variety of rotaxanes shuttles were reported which could be operated with different stimuli, such pH or redox processes.\(^\text{10}\)

A similar history can be described for the development of catenanes.\(^\text{11}\) After the first reported synthesis of a catenane and pioneering studies by Lüttringhaus and Schill,\(^\text{12}\) Sauvage and co-workers revolutionized the field by the development of the metal-templated synthesis of these compounds.\(^\text{13}\) In the context of molecular machines, the controlled rotation of one catenane ring within another via either electrochemical or photochemical means, was an crucial accomplishment.\(^\text{14,15}\) Note however that the achieved rotary motion, was not directional. Later, Leigh et al demonstrated by elegant designs of catenanes how unidirectional motion can be realized in these systems.\(^\text{16,17,18}\)

![Figure 1](image)

**Figure 1**: (a) Rotaxane: molecules in which a ring encloses another, rod-like molecule having end groups too large to pass through the ring opening, and thus holds the rod-like molecule in position without covalent bonding.\(^\text{19}\) (b) Catenane: hydrocarbons having two or more rings connected in the manner of links of a chain, without a covalent bond.\(^\text{19}\) Figure adapted from ref 28j.

Since these initial discoveries, increasingly complex and functional machines have been developed. Major achievements include the design of molecular valves,\(^\text{20}\) elevators,\(^\text{21}\) muscles,\(^\text{22}\) processive catalysts\(^\text{23,24}\) and pedals,\(^\text{25}\) as well as the discovery that these molecules which are called machines are actually able to perform work.\(^\text{26}\) Also the design of artificial molecular walkers is an important milestone in this line of research.\(^\text{27}\)

The field of molecular machines have expanded rapidly in the last decades and is too large to review in this introduction. Here an overview is given of the development of a subclass of molecular machines, the synthetic rotary molecular motors. For reviews on other molecular machines the reader is referred to other reports in the literature.\(^\text{28}\)

1.2 Rotation around a single bond

A rotary molecular motor exhibits rotational motion around a covalent bond which fulfills the following requirements: (i) the rotation is powered by a fuel, (ii) the direction of rotation is controlled and (iii) the process should be repetitive to enable continuous motion. Early investigations on unidirectional rotors focused at the development of molecular ratchets, but failed to meet the criteria above. These molecules contain a gear which is able to rotate freely in one direction while a pawl attempts to prevent rotation in the other direction. The group of Kelly developed several ratchet-type molecules,\(^\text{29–31}\) leading up to their report of a chemically driven rotor, capable of performing 120°
unidirectional rotation around a single bond in two chemical steps (Scheme 1).\textsuperscript{32,33} This device, much like their previous designs, consists of a triptycene ‘wheel’ and a helicene ‘brake’, connected by a single bond. The brake raises the barrier of rotation around the aryl–aryl bond to \(~105\,\text{kJ mol}\textsuperscript{-1}\), thereby severely hindering rotation of the wheel. Although the helicity of the system induces a desymmetrization of the energy profile of the rotation around the single bond, the rate of rotation is equal in both directions as predicted by the Second Law of Thermodynamics.\textsuperscript{34} The authors manage to force unidirectionality on the rotation by the modification of the structure with a primary alcohol tethered to the helicene, and an amine group on one of the wheels of the triptycene. At room temperature, the compound exists as a mixture of three atropisomers. Addition of phosgene to atropisomer 1a generates an isocyanate on the triptycene moiety (Scheme 1).

\begin{center}
\textbf{Scheme 1:} Phosgene induced 120° unidirectional rotation around the triptycene–helicene single bond. (i) Fuel addition, (ii) thermally driven single bond rotation, (iii) linking, (iv) unidirectional rotation leading to strain release, (v) release. Figure adapted from ref 32.
\end{center}

Thermal rotation of the wheel brings the isocyanate sufficiently close to the primary alcohol for urethane formation, generating a sterically constrained conformer. Thermal energy drives the unidirectional rotation, overcoming the barrier of rotation around the single bond. Subsequent cleavage of the urethane leads to formation of atropisomer 1b. Although the unidirectional motion is limited to a single, nonrepeatable 120° rotation this work does however constitute a milestone in the search for continuous directed molecular motion. Follow-up publications explored the possibility of continuous rotation, although these efforts have not yet been successful.\textsuperscript{35,36}

In 2003, Mock and Ochwat presented what is perhaps the most basic approach towards a molecular motor design reported thus far (Scheme 2).\textsuperscript{37}
Scheme 2: Acylketenimine fueled oscillation of anhydride motor.\(^{37}\)

The tricarboxylate system oscillates between two anhydride forms and is fueled by an acylketenimine. The process is continuous as long as fuel is present. Although one cycle causes a 180° unidirectional rotation, the following cycle causes the reverse rotation and no net directional rotation is generated. A very different approach towards directional motion is the system developed by Haberhauer, which utilizes metal complexation and decomplexation as vital steps in the rotary cycle.\(^{38}\) The system consists of two bipyridine moieties, linked by a cyclic peptide and an ethane bridge. One of these bipyridines has an azobenzene substituent. A full 360° rotation proceeds in four steps of alternating azobenzene photoisomerisation and bipyridine complexation decomplexation steps. Unidirectionality was not proven experimentally but predicted by DFT calculations.

Certain biaryls exhibit hindered rotation around the central single bond and are therefore a practical starting point for the design of directional rotors. Several attempts towards directional rotors have been undertaken based on diastereoselective nucleophilic ring-opening of biaryl lactones.\(^{39}\) The initial design 2 (Scheme 3), based on studies by Bringmann,\(^{40}\) featured a biaryl functionalized with an alcohol and a carboxylic acid functionality in the ortho positions on each side of the aryl-aryl bond.\(^{41}\) Lactonization and subsequent ring-opening were successful, but due to the fast equilibrium of the atropisomers the directionality of this system could not be determined. Subsequently, Branchaud and co-workers developed a tri-ortho substituted biaryl 3 (Scheme 3), functionalized with two carboxylic acid moieties on one aryl group and an alcohol substituent on the other aryl group.\(^{42}\) This modification raised the barrier of rotation around the single bond sufficiently compared to their previous design, and the efficiency of unidirectional rotation was determined to be 20% or 50%, depending on the choice of chiral auxiliary. The unidirectionality could be improved by introducing a slight change in the design and using a bulkier nucleophile (compound 4, Scheme 3).\(^{39}\) Using this combination of biaryl and nucleophile, diastereoselective ring-opening followed by chemoselective relactonization causes a 180° rotation with a very high
diastereoselectivity (>99% by $^1$H NMR analysis) and 72% yield. The authors note that if the resulting amide could be cleaved selectively, the system should be capable of a six step $360^\circ$ rotation. No such conditions have been reported thus far.

Scheme 3: Structure of biaryl rotors reported by Branchaud and co-workers. All operate through a sequence of lactonization followed by asymmetric ring opening. The sequence is illustrated for biaryl 4. (i) Lactonization, (ii) diastereoselective ring opening under Weinreb conditions, (iii) chemoselective lactonization.40-42

Feringa and co-workers demonstrated a sequentially operated chemically-driven rotary motor, when they reported on a tri-ortho substituted biaryl, 5, capable of unidirectional rotation (Scheme 4).43 They achieved a higher unidirectionality and $360^\circ$ rotation by making a few modifications. Starting from atropisomer 5a the allyl protecting group can be selectively removed, after which the newly deprotected phenol can be lactonized with the carboxylic acid functionality on the lower half. An asymmetric reductive ring-opening using a chiral reducing agent generates a phenol and a primary alcohol. After selective reprotection of the phenol with an allyl protecting group, the alcohol can be oxidized to the carboxylic acid and the atropisomer 5b is formed. In analogous fashion, the para-methoxy benzyl (PMB) protecting group can be removed selectively, after which the sequence of lactonization, asymmetric ring opening, reinstallation of the protecting group and oxidation can be repeated and atropisomer 5a is regenerated. Because the ring openings both proceed with excellent enantioselectivities, both halves of the cycle are >90% directional. Crucially, racemization of the atropisomers does not occur at room temperature since the barrier of rotation around the aryl–aryl bond is too high. Additionally, due to the choice of protecting groups, the two deprotection steps are completely orthogonal. Furthermore, this system has the capacity to reverse its rotary direction by changing the sequence of chemical steps. Although ten steps are required and the overall yield for a cycle is 21%, this reversible rotary motor is the first
system reported to undergo a chemically driven 360° rotation around a carbon–carbon single bond.

![Scheme 4](attachment:image.png)

**Scheme 4:** Rotational cycle of unidirectional biaryl system (i) Allyl deprotection and lactonization, (ii) asymmetric lactone reduction, reinstallation of the allyl protecting group and oxidation to reform the carboxylic acid, (iii) para-methoxy benzyl deprotection and lactonisation, (iv) asymmetric lactone reduction, reinstallation of the PMB protecting group and oxidation to reform the carboxylic acid.\(^{43}\)

A major disadvantage of all the systems discussed in this section is the need for sequential addition of fuels. For the generation of motion, a synthetic molecular motor should be able to operate continuously under a specific set of reaction conditions. Recently, Feringa and co-workers made significant steps towards such a system with a unidirectional biaryl, fueled by a palladium redox cycle.\(^{44}\) Scheme 5 shows the 360° rotation cycle. The rotor contains two elements of chirality: a fixed chirality at the sulfur atom which governs the direction of rotation, and an axial chirality around the biaryl single bond. Practically no atropisomerization of \((S,M)\)-6 to \((S,P)\)-6 occurs since the barrier for single bond rotation is too high. Starting from atropisomer \((S,M)\)-6, palladacycle Pd\([(R,P)-7]XL\) can be formed via a C–H activation. As the sulfoxide acts as a directing group, this process is selective for the ortho C–H bond on the upper aryl ring. In this palladacycle the barrier of rotation around the biaryl axis is greatly reduced. DFT calculations show that \(M\) helicity around the biaryl axis is favored, leading to a net clockwise rotation. Therefore, when the C–H bond is subsequently reintroduced, the reductive elimination proceeds mainly from Pd\([(R,M)-7]XL\) and \((S,P)\)-6 is obtained in excellent (>98%) stereoselectivity and a 45% overall yield. The unidirectional transformation of \((S,P)\)-6 in \((S,M)\)-6 could be achieved in analogous fashion. By addition of a Pd(0) source, C–Br activation could be achieved and palladacycle Pd\([(R,P)-8]BrL\) was formed. \(M\) helicity is favored in this palladacycle too, and the subsequent bromination occurred mainly on Pd\([(R,M)-8]BrL\). \((S,P)\)-6 was obtained with
92% selectivity and 42% overall yield. The two 180° unidirectional rotations that are thus achieved, are completely orthogonal to each other and connected through a redox cycle: one rotation leads to a conversion of a palladium(II) source into a palladium(0) source and the other converts a palladium(0) source into a palladium(II) source. In fact, after unidirectional transformation of \((S,M)-6\) to \((S,P)-6\), the in situ formed palladium(0) could be used to catalyze the transformation \((S,P)-6\) to \((S,M)-6\), thereby completing a 360° unidirectional rotation. By careful selection of reaction conditions, and provided chemical fuel is present, this system may be used to generate continuous rotational motion without the need of sequential fuel addition or purification.

![Scheme 5](image)

Scheme 5: Unidirectional rotation around the biaryl single bond, driven by a palladium redox cycle.44

### 1.3 Rotation around a double bond

In 1999 Feringa et al. reported on the first light-driven molecular motor \((9)\) capable of performing repetitive unidirectional 360° rotation.45 The motor was based on an overcrowded alkene featuring a double bond connecting two identical halves or rotor parts, both containing a stereocenter. Due to the severe steric interaction present in the system, the double bond is forced out of planarity, introducing an additional helical chirality to the molecule. Thus for e.g. \((R,R)\) enantiomer of \(9\), various conformational isomers exist, which can be interconverted in four discrete steps with light and heat in such a way that unidirectional rotation around the carbon-carbon double bond (the rotation axle) is achieved (Scheme 6). Starting from \((P,P)\)-trans-\(9\), irradiation with UV light induces a photochemical trans-cis isomerization of the double bond leading to the formation of \((M,M)\)-cis-\(9\). During this event, the helicity of each half inverts, while the methyl groups change from a pseudoaxial to a pseudoequatorial orientation.
Scheme 6: Mechanism for unidirectional 360° rotation for the first generation light-driven molecular motor.45

Figure 2: General energy profile for the 360° unidirectional rotation. The terms unstable or in some cases metastable refer to the isomer’s propensity to undergo a thermal isomerization reaction and do not concern its chemical instability. Figure adapted from ref 28j.

The newly formed (M,M)-cis-9 is higher in energy, due to increased strain caused by the equatorial orientation of the methyl groups. These methyl groups can again adopt their energetically favored position by a thermal relaxation process of the molecule, in which one half flips over the other half, affording (P,P)-cis-9. In addition to the reorientation of the methyl groups, the helicity of the molecule is inverted once again. This relaxation is called a thermal helix inversion (THI) and is, in principle, an equilibrium reaction but
since the energy difference between the two isomers is large, this step can be considered irreversible, thereby biasing the direction of rotation. A second photochemical isomerization gives rise to the isomerization of \((P,P)\)-cis-9 to give the unstable \((M,M)\)-trans-9. \((M,M)\)-trans-9 undergoes a THI to return to \((P,P)\)-trans-9, the starting point of this 360° cycle. During these four isomerization steps, one half has completed a 360° rotation relative to the other half around the double bond. The energy profile of the ground state and excited state of this light-driven process are schematically depicted in an energy diagram (Figure 2). This mechanism is from a stereochemical point of view a beautiful interplay between the dynamic helical chirality present in the molecule and the fixed point chirality of the stereogenic centers. The helicity inverts in every isomerization step, while the configuration of the stereogenic center dictates the direction of rotation. The energetically uphill \(E\)-Z isomerization drives the system out of equilibrium, while the subsequent energetically downhill THI ensures that the motor return to its stable form, from which it can be excited again, leading to a repetitive process as long as light is supplied as fuel for this rotary motion.

A disadvantage of these first generation molecular motors is that the activation barrier for the thermal isomerization steps are not similar. One half of the 360° rotation is therefore considerably faster than the other, which results in an irregular rotation. This issue was addressed by a second design of the overcrowded alkene molecular motor.\(^46\) One of the halves connected to the double bond was replaced by a symmetrical (apart from the methoxy substituent) lower half to afford motor 10 (Scheme 7).

**Scheme 7**: Mechanism for unidirectional 360° rotation for second-generation light-driven molecular motor.\(^46\)

For second generation overcrowded alkene molecular motors, the upper half is usually referred to as the rotor, while the lower half is called stator, although in reality it
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cconcerns a relative rotation of one half to the other, rather than one part moving and one part standing still. The structural modification resulted in very similar barriers for both THIs and therefore a more uniform rotation. In addition, a major advantage of second generation motors is the ready functionalization of upper (rotor) and lower (stator) parts, for instance for surface anchoring. Although the second generation overcrowded alkene molecular motors are structurally different from first generation overcrowded alkene rotors, the same mechanistic steps account for its functioning as a unidirectional molecular motor.

A key finding in the development of the second generation overcrowded alkene molecular motor was that one stereogenic center proved to be sufficient in achieving unidirectionality. The reduction in chiral information led to the question how much chirality is actually needed to achieve unidirectionality in these systems. To this end the so called third generation overcrowded alkene molecular motor was developed. The design of this motor was conceived by merging two second generation overcrowded alkene motors together in such a way that the stereocenter becomes a pseudo asymmetric center, thereby making the whole molecule achiral. The design of the third generation overcrowded alkene motor and its mode of rotation are depicted in Scheme 8.

![Scheme 8](image)

Scheme 8: Rotational behavior of molecular motor with a pseudo-asymmetric center.

As is the case for the first and second generation overcrowded alkene molecular motors, the (pseudo) asymmetric center has groups of two distinct different size (CH$_3$ and H/F) attached to it. The thermodynamically favored isomer is the isomer where the bigger methyl group adopts a (pseudo) axial position, while the smaller H or F atom is forced in the more sterically hindered (pseudo) equatorial position. In the study published in
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2015, the isomer 11 (R=H) was synthetically inaccessible and thus the variant with the fluorine substituent was synthesized (12). It was found that for the more stable isomer, the fluorine adopts the pseudoequatorial position where it is sandwiched between the two fluorene lower halves. Starting from meso-(r)-12, irradiation with UV light (365 nm) leads to the isomerization of either one of the double bonds, giving a PSS mixture of 7.5:92.5 = (r)-12 : (M)-12 + (P)-12. The isomerization of both double bonds to give meso-(s)-12 was not observed, which was attributed to the asymmetric excited state surface of (P)-12 and (M)-12. The photogenerated enantiomeric pair thermally relaxes via a THI (\(\Delta G^\circ = 75.3 \pm 0.3 \text{ kJ mol}^{-1}\)) to return to the starting meso-(r)-12. The possibility of a thermal relaxation via a backward thermal E–Z isomerization (TEZI), could not be ruled out in this system, since the product of the two reactions are the same. For this reason a second design was conceived in which the rotor parts were desymmetrized by the introduction of the methoxy group. It was found that 12 functions as a unidirectional rotor and no thermal back TEZI occurs. From studies on the thermal behavior of many other molecular motors, it is evident that in general the TEZI becomes a competing pathway, only when the \(\Delta G^\circ\) for THI is sufficiently high (>110 kJ mol\(^{-1}\)). In this sequence of light and heat induced isomerization steps for 12, one rotor part performed a 180° clockwise rotation, while the other rotor performed a 180° anticlockwise rotation, relative to the middle stator part (Scheme 8). For an external observer, both rotor parts thus move in the same forward direction, similarly to wheels on an axle. From the point of a single molecule, the absorption of a photon can lead to either 180° anticlockwise rotation of the upper rotor or a 180° clockwise rotation of the lower rotor in equal probability. For a system where R=CH\(_3\) (13), no directionality would be expected in the rotational behavior of the rotor parts. A pseudoasymmetric center is therefore, to date, the minimal chiral requirement for dictating the directionality of rotation in overcrowded alkenes. As well as addressing the issue of required stereochemistry for directionality, this study brought forth overcrowded alkene based motors with interesting rotational behavior. The observed motion for these systems could potentially be harnessed for directional movement on e.g. a surface, similarly as has been reported for the nanocar (vide infra).

The configuration of the stereocenter controls the direction of rotation around the double bond and this aspect was used in the development of a motor that can be switched between forward and reverse rotation by a chemical stimulus. A second generation overcrowded alkene molecular motor was designed with an acidic proton at its stereocenter, allowing for epimerization by the action of a base (Scheme 9). Notice that in this system the stereocenter was replaced from the \(\alpha\) to the \(\beta\) position, as deprotonation and subsequent reprotonation at the allylic position would lead to a double bond shift of the overcrowded alkene. It is known that a stereocenter at the \(\beta\) position can also bias the direction of rotation, but to a lesser degree, rendering the rotation of \(\beta\) substituted motors not fully unidirectional. Starting from the isomer
(S)-(M)-14, photoisomerization leads to the formation of the less stable isomer (S)-(P)-14, which after heating to 80 °C thermally relaxes to (S)-(M)-14. A second cycle of an irradiation and subsequent heating step would result in a 360° clockwise rotation. At room temperature the THI is slow; (S)-(P)-14 has a half-life of 22 d. The unstable isomer (S)-(P)-14 could be epimerized in this timeframe into the thermodynamically favored diastereoisomer (R)-(P)-14 in a ratio of 91:9 by the action of 1 equivalent of t-pentylONa in t-pentanol over the course of 15 h. The newly formed isomer (R)-(P)-14 will, under the influence of light and heat rotate in the opposite direction (i.e. anticlockwise) compared to the starting isomer. This work shows that precise control of stereochemical elements is crucial in achieving higher degrees of complexity of motion generated by molecular machines.

Scheme 9: Base catalysed epimerization leading to reversal of the direction of rotation.51

In addition to controlling the direction of rotation by a chemical stimulus, the photochemical step and therefore the whole rotation can also be inhibited by a chemical trigger.53 The system for which this behavior has been described consisted of a second generation overcrowded alkene molecular motor functionalized with a dialkyl ammonium group on the upper half and a dibenzo[24]crown-8-ether attached to the lower half (Scheme 10).

Scheme 10: Reversible locking/unlocking the rotation by chemical means.53
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It was found by $^1$H NMR spectroscopy that in CD$_2$Cl$_2$ the ammonium group is bound non-covalently to the crown ether. In this self-complexed state the photochemical cis-trans isomerisation is efficiently quenched, resulting in no rotation upon irradiation. Addition of the base DBU leads to deprotonation of the ammonium group, which resulted in the dethreading of the pseudorotaxane system. In this unlocked state, irradiation leads to photoisomerization of the double bond and the subsequent THI leads to unidirectional rotation. The rotation can again be stopped by threading the dialkylammonium group into the crown ether by the action of trifluoroacetic acid (TFA).

Numerous studies have been conducted on ways of increasing the rotational speed of first and second generation overcrowded alkene molecular motors by small structural modifications. Since the photochemical isomerization is substantially faster (picosecond timescale) than the thermal isomerization step,$^{54,55}$ these studies focused on reducing the barrier for the THI. It was found that increasing the steric bulk at the $\alpha$ position causes a large acceleration.$^{56}$ This finding can be rationalized by the fact that the bulkier substituents at the $\alpha$ position destabilize the metastable state to a greater extent than the TS.

Modifications that focus on reducing steric hindrance between the rotor part and stator part in the fjord region, also result in the acceleration of these molecular rotors. For second generation overcrowded alkene molecular motors with the general structure depicted in Figure 3, it was found that the nature of the bridging atoms X and Y have a considerable impact on the rotational speed of these structures.$^{57}$

![Figure 3: Various structural modifications in second generation molecular motors.](image)

The subtle conformational changes these modifications induce, amount to a difference in the speed of the motors up to a factor of almost 350. It was found that the contraction of the ring fused to the double bond had an even greater impact on the barrier for the THI (Scheme 11). Contracting the six membered ring upper half (see compound 15) to a five membered ring (see compound 16) resulted in a dramatic decrease in steric hindrance in the TS which accounts for a 2x10$^8$ fold acceleration of the rotational speed.$^{58}$ Further reduction of the steric hindrance in the TS by replacing the naphthalene with a p-xylyl (see compound 17) or benzothiophene (see compound 18) accelerates the motor with a factor of 12 and 2.7x10$^3$, respectively.$^{59,60}$
Although it is not always a priori clear whether a particular structural modification increases or decreases the activation energy of the THI, DFT calculations can accurately predict the Gibbs free energy of activation for this step and is therefore a valuable tool in the design of rotary motors. The continuous efforts in increasing the rotational frequency of the systems culminated in the development of motors which can operate in the MHz regime. One of the fastest motors up to date, combines a thioxanthene lower half and a cyclopentane naphthalene upper half. The extremely low barrier ($\Delta^\ddagger G^\circ = 33.5 \text{ kJ mol}^{-1}$) for the THI causes this motor to rotate at this exceptional speed. Computational research even suggests that by substituting the stereogenic methyl group with a methoxy moiety, these particular systems would in principle function way beyond the MHz regime into the GHz regime.

In 2016 a different strategy was followed for the tuning of the rotational speed. Rather than the synthesis of different variants, this approach relied on a post-synthetic modification to fine-tune the speed of the motor (Scheme 12).

The studied system consisted of a 4,5-diazafluorenyl lower half and naphthalene upper half (see compound 19). The binding of different metals to the bidentate lower half led to conformational changes, most notably the contraction of the diazofluorenyl half. The decrease in steric hindrance in the fjord region resulted in an increase in rotational speed. The magnitude of this increase was dependent on the choice of the transition metal complex. While the parent motor has a $\Delta^\ddagger G^\circ$ of 83.5 kJ mol$^{-1}$ for the THI, binding of ZnCl$_2$ led to a $\Delta^\ddagger G^\circ$ of 81.5 kJ mol$^{-1}$. Complexation of PdCl$_2$ and PtCl$_2$ resulted in a
decrease in $\Delta^\circ G$ to 78.2 and 75.1 kJ mol$^{-1}$, respectively. The changes in $\Delta^\circ G$ reflect a more than factor 30 increase in rotational frequency and is thus a powerful method to fine-tune the speed with great accuracy in a reversible and dynamic way. This work shows that by emulating Nature, and the way it regulates processes at the molecular level, such as allosteric regulation, fascinating design principles can come to light which can be used in the design of molecular machines.

Tuning of the rotational speed by electronic effects was found to be more difficult. The placement of either electron donating or withdrawing groups did not affect the barrier for the THI significantly. The introduction of a donor-acceptor system along the double bond decreased the barrier for THI significantly, but also accelerated the thermal back reaction, rendering this type of molecular motor not fully directional. Tuning the rotational speed by electronic effects would be a nice complementary approach to tuning via steric effects, but has not yet been investigated thoroughly.

The application of light-driven motors and machines in e.g. biological systems or soft materials would require excitation with light that does not cause damage to the environment. To this end, various methods have been developed to red-shift the excitation wavelength from UV to less destructive visible light. In 2003 it was shown that the introduction of a donor and acceptor group in the lower half allowed for photoisomerization with 435 nm. Visible light fueled rotation was also accomplished by triplet sensitation (Figure 4a).

Figure 4: (a) Visible light-driven motor 20 using energy transfer. (b) Hemithioindigo based molecular motor 21.

Palladium tetraphenylporphyrin (Pd( TPP)) with a long triplet lifetime and strong absorption between 500–550 nm was a suitable sensitizer for intermolecular energy transfer to the molecular motor 16. Irradiation of the Q band of the porphyrin with 530 nm light led the successful photoisomerization of 16, while 16 only absorbs up to 450 nm. The covalent attachment of Pd( TPP), as in motor 20, increased the efficiency of this process considerably. Another example of visible light switching of molecular motors based on energy transfer has been reported in 2015. Dube and co-workers designed a novel hemithioindigo based molecular motor 21 to achieve visible light driven rotation of molecular motors (Figure 4b). The introduction of a hemithioindigo
moiety, originally used in photoswitches, resulted in a shift of the excitation wavelength up to 500 nm light, which offers important opportunities compared to the early second generation overcrowded alkene molecular motors, which are generally fueled with <450 nm light. Moreover this fragment has other interesting features. The relative small size of the hemithioindigo moiety allows for fast rotation and the directionality of the rotation is governed by the chirality at the sulfoxide of this hemithioindigo fragment. Hence, this fragment combines multiple functions in one and could therefore be a valuable building block for future motor designs.

Rotary molecular motors have the potential to achieve directed propulsion in aqueous solution via continuous rotational motion; an important challenge regarding the integration of molecular motors with biological function. The fundamental knowledge on how solvent properties such as viscosity affect the rotary motor is critical in achieving this goal. Several studies have been conducted on how solvent affects the THI of the rotary motors. It was found for a series of motors that the THI is retarded in media of higher viscosity. The effect is modest for non-functionalized motors, but become increasingly pronounced, when the motors are functionalized with larger substituents (Figure 5).

![Figure 5](image)

**Figure 5:** Molecular motors used in viscosity dependent kinetics. The $t_{1/2}$ refers to the half-life of the photogenerated metastable isomer at 20 °C. Figure adapted from ref 73.

A greater volume in rearranging solvent is needed with increasing substituent size, resulting in enhanced solvent displacement and consequently, retardation of the THI. Next to the size of the substituent also the rigidity plays an important role, with more rigid substituents slowing down the THI to a greater extent. The polarity of the solvent was shown to have minimal impact on the rotational speed. Next to the THI, the photochemical isomerization is also affected by increasing viscosity of the medium. Studies using ultrafast spectroscopy revealed some aspects of the mechanism for the photochemical isomerization. After absorption of a photon, a two step relaxation takes
place. First, one of the central carbon atoms of the alkene undergoes pyramidalization in a timeframe of about 100 femtoseconds. The second step is the torsional motion about the double bond, the power stroke of this motion, which occurs on a picosecond timescale. The pyramidalization was not affected by solvent viscosity, but the subsequent torsional motion was resisted by solvent friction and slows down by a factor of 2.5 when performed in the more viscous octanol/decalin mixture compared to acetonitrile. From these combined studies it was shown that surrounding solvent molecules influence the rotary motion of motors and that vice versa motors affect the solvent molecules.

Tour and co-workers studied if the continuous rotary motion could be used to achieve motion of the molecules in solution. To this end various motors with different rotational speeds were equipped with fluorophores (cy5) allowing these molecules to be tracked by single molecule fluorescence correlation spectroscopy. It was found that upon irradiation, these systems exhibit increased diffusion. The largest increase in diffusion was observed for the system functionalized with the fastest motor. Since in these experiments increased diffusion by local heating was excluded via careful control experiments and the correlation between increased diffusion and rotational speed, it can be concluded that the increased diffusion stems from the molecular motion of the employed motors. Although in these studies no directional motion was achieved yet, only increased diffusion, this study can be considered an important step in the development of nanomachines powered by molecular motors.

The majority of the molecular motors based on overcrowded alkenes, are fueled by light energy. Light is a very convenient way of supplying energy to motors in solution, due to the high spatiotemporal resolution one can achieve. For application of motors in e.g. surface confined or biological systems, the powering of these systems with other sources of energy such as electrical or chemical energy, would be highly beneficial. One of the challenges for the future is therefore the development of molecular motors which can be fueled by other energy sources than light. A major hurdle to overcome in the development of electrochemically-driven molecular rotors is the chemical stability of these compounds under oxidative conditions.

In 2006, Lehn proposed a new type of rotary molecular motor based on imine syn-anti isomerization. Like alkenes, imines may undergo both photochemical and thermal isomerization. Directionality can be forced on these processes by the introduction of a stereogenic center close to the carbon nitrogen double bond. In 2014, this idea resulted in the first imine-based unidirectional molecular motors. The design is based on diaryl-N-alkyl imines, which are stable towards thermal E-Z isomerization at ambient temperatures. Scheme 13 shows the structure of motor 27 and its rotational cycle. Irradiation of a diastereomeric mixture of (P)-27 and (M)-27 leads to photoisomerization of the carbon nitrogen double bond and a shift of the equilibrium towards (M)-27.
Scheme 13: Light-induced isomerization processes of imine-based molecular motor 27. The nitrogen inversion (NI) pathway is an effective back-and-forth switching, while the ring inversion (RI) pathway causes unidirectional 180° rotation.78

The original diastereomeric ratio was restored after a thermal relaxation. This thermal reaction might proceed through two different mechanisms. Inversion at the nitrogen moves the substituent back to its original position. Alternatively, ring inversion of the stator can release the steric strain in (M)-27, regenerating (P)-27 through an effective 180° rotation. Via the ring inversion mechanism, 27 is able to undergo a complete unidirectional 360° rotation in four steps. To distinguish between the two pathways, an asymmetric variation of 27 was synthesized. Irradiation of desymmetrized imines supports the ring inversion pathway, which means that upon irradiation and subsequent heating the compound undergoes a unidirectional 180° rotation reminiscent of the rotation of a second generation overcrowded alkene-based motor. As an alternative to this four-step 360° rotation mechanism, the barrier for ring inversion can be significantly increased by reducing the flexibility of the stator. Fusing a third benzene ring to the cycloheptene ring therefore efficiently blocks ring inversion. At higher temperatures, nitrogen inversion becomes feasible and these compounds are shown to function as directional two-step motors. The authors note that these new motors are not only a valuable addition to the field of molecular machines, but may also be used in dynamic combinatorial chemistry, merging motional dynamics with constitutional dynamics.

In a follow-up study, the authors give more details on the mechanism of the photochemical syn-anti isomerization of the carbon nitrogen bond.79 This process is expected to be directional due to the placement of a stereogenic center close to the imine. Though theoretical studies confirm this assumption, experimental proof is not included in the initial study.78 To address this prediction, several camphor-based imines
were synthesized. Camphorimine 28 (Scheme 14), bearing a cyclopropyl substituent at the nitrogen atom, undergoes both $E$-$Z$ isomerization and photorearrangement upon irradiation with 254 nm light.

![Scheme 14: Camphorimine-based motor 28 and its photoproducts endo-29, exo-30 and 31.](image)

Since both processes proceed through the photoinduced biradical state, the selectivity in the rearrangement is considered to be analogous to the selectivity of the isomerization. The diastereomeric ratio of endo-29 and exo-30 is 58:42, indicating a directional preference. The authors note that the selectivity for the biradical pathway (from the S2 state) may be different than from the S1 state. However, a preference of directionality was experimentally determined, completing the definite proof that chiral imines can be used as molecular motors. Since imine-based molecular motors were developed only recently, their properties remain largely unexplored. However, their potential to perform both a four-step and a two-step unidirectional 360° rotation is an intriguing addition to the existing nanomachinery toolbox. Although the principle is proven, a detailed computational and experimental study of the rotational properties is still needed to provide a thorough understanding of the mechanism. Furthermore, precise engineering of the structure will be required to increase directional selectivity.

### 1.4 Applications

For molecular motors based on overcrowded alkenes, numerous applications have been reported. Some of which are based on the motor functioning as a multi-state chiral switch. Here we focus on applications based on the actual continuous rotary motion of the motors. An obvious application is to convert the mechanical energy into motion and transport at the nanoscale. Nanovehicles are molecules resembling a regular car, containing wheels, axes and a chassis. In theory, these may be used to transport a cargo across a surface or track. The group of Tour has synthesized numerous nanovehicles including several cars, a dragster, a train, a worm and a truck using spherical wheels, connected to a flat aromatic chassis via single and triple carbon-carbon bonds. Although these compounds are not capable of independent motion, they can be deposited on a gold surface and pushed using an STM tip. In 2006, the group realized a motorized version of their nanocar (Figure 6).
This design incorporated an overcrowded alkene based rotary motor in the chassis. It was proposed that this motor might work as a type of propeller, moving the car over the surface with a skipping motion. The unidirectionality of the motor would enforce a directionality of the motion. The rotational properties of the motor embedded in the nanocar were studied in solution, and were found to be very similar to the parent motor.\(^5^7\) In a subsequent publication, STM studies were performed to study the behavior of motorized nanocars on a surface.\(^8^9\) Although deposition on a copper surface was successful and single molecules could be imaged, no lateral motion could be induced by light or STM tip pushing, indicating a strong interaction between the molecule and the surface. Movement of the motorized nanocar across the surface was induced by pulses from the STM tip. Recently, Tour and co-workers demonstrated light-induced movement of a motorized ‘nanoroadster’ on the surface (Figure 7).\(^9^0\)

The roadster consists of a fast unidirectional overcrowded alkene based molecular motor attached to an axle with two adamantane wheels. At temperatures above 150 K, the roadsters start to diffuse across the Cu(111) surface. Irradiation causes the molecular motor to skip across the surface and increase the speed of diffusion. Although the direction of movement in these roadsters is random, this work illustrates the possibility of light-induced movement at the surface.
Figure 7: (a) Structure of the nanoroadster, (b) difference image of the roadsters at their starting position (dark) and after thermally induced diffusion (white), (c) difference image of the roadsters at their starting position (dark) and after irradiation with a 266 nm laser (white). Figure adapted from ref 90.

In 2011, the first motorized nanocar capable of directional motion across a surface was reported by Feringa et al.91 This design is based on a flat, aromatic chassis. However, instead of a single motor in the middle of the frame, four molecular motors are incorporated in the structure, functioning as the wheels of the car (Figure 8). In the proposed mechanism of the movement, the motors act as paddlewheels, propelling the structure forward. The nanocars could be sublimated on a copper surface and subsequently imaged using STM at 7 K. By placing the STM tip directly above the center of an individual nanocar, a voltage could be applied and movement was induced. After 10 steps, a linear, 6 nm long trajectory was completed by a single nanocar. Although an electric voltage was used to generate motion instead of the established photoexcitation followed by thermal relaxation, the authors theorize that the movement is still the result of the same rotational process. This hypothesis was supported by additional STM measurements. Since the central part of the chassis consists of single and triple bonds, rotation around these bonds is possible and there is a 50% chance that the nanocar will land the wrong way (Figure 8). In the ‘wrong landed’ nanocar, the front and back wheels are rotating in the opposite direction. Indeed, these ‘wrong landed’ nanocars show no displacement upon excitation. Moreover, the $R,R-R,R$ diastereomer of the nanocar was synthesized, in which the combination of stereocenters was expected to lead to circular movement. STM measurements of these diastereomers indeed showed a random trajectory.
Giuseppone and co-workers have developed a polymeric gel including second generation molecular motors, which contracts upon irradiation with UV light. The polymer motor conjugates were synthesized using conventional Huisgen click chemistry and consist of fast (MHz) second-generation motors crosslinked with PEG chains. The polymer forms a gel in 10 wt% toluene. A piece of this gel, suspended in toluene, was shown to contract visibly upon irradiation with UV light. It is hypothesized that this shrinking is the result of increasingly tighter coiling of the polymeric chains, induced by the continuous rotation of the motor units. At higher tensions the contraction slows down, until the gel ruptures and subsequently recovers its original size and shape. Complimentary fluorescence experiments indicate that the rupture is the result of the oxidation of the central double bonds of the motors, followed by unwinding of the coils. AFM analysis of smaller pieces of gel supports the coiling hypothesis, since pores in the compacted gel are stretched out to over twice their original size, and shrink again after rupture. The authors imagine these systems may be of use in energy storage, but other potential applications come to mind as well, such as artificial muscles. This research is an excellent example of translating molecular motion into macroscopic function and moreover, an impressive illustration of the power of molecular motors.
1.5 Thesis outline

This overview illustrates how the research on rotational molecular motors led to the development of large variety of molecular motors with different structure and with an increasing degree of control on their behavior.

This thesis focuses exclusively on molecular motors based on overcrowded alkenes, especially on the conformational and configurational aspects concerning their synthesis and their isomerization behavior. The interplay between the conformational and configurational elements lies at the basis of the functioning of overcrowded alkenes as unidirectional rotors. It is therefore vital to have control over the stereochemical elements of these compounds throughout their synthesis. In chapters 2, 3 and 4, new ways are investigated to obtain motors as single enantiomers. Other conformational and configurational aspects of motors are discussed in chapters 5, 6 and 7.

In chapter 2, a strategy is described which consists of an enantioselective protonation of a silyl enol ether derived from an racemic indanone precursor, followed by a McMurry coupling. This procedure gives access to functionalized first generation molecular motors in high enantiopurity.

The interaction between a hydroxyl-functionalized first generation molecular motor and a chiral resolving agent is investigated in chapter 3. The intermolecular non-covalent bonds were found to be dependent on the solvent, which allowed for a solvent-switchable chiral resolution.

The influence of an additional chiral center at the β position of second generation molecular motors on the synthesis and their isomerization behavior is examined in chapter 4. This structural modification enabled the synthesis of these compounds via the Barton Kellogg coupling without loss of optical purity of the starting material, while their isomerization behavior did not change significantly.

The synthesis and study of a molecular motor with an extended aromatic core is described in chapter 5. This modification resulted in a red-shifted absorption spectrum, although at the cost of a lower efficiency for photoswitching. Moreover, the motor showed unprecedented conformational behavior upon photochemical and thermal isomerization, as was concluded from DFT studies.

In chapter 6 the transfer of the switchable chirality from molecular motors to poly(phenyacetylene) polymers via non-covalent interactions is investigated. Binding of the motor to the polymer leads to a preferred helicity in the polymer backbone. Upon irradiation, the motor is able to photoisomerize which leads to the inversion of the overall helical chirality of the polymer.

In chapter 7, it is studied how the conformation of a 2,2′-biphenol moiety connected to a second generation motor core, influences the rotational speed of the motor. It was found that decreasing the flexibility of this fragment, decreases the speed of rotation.
1.6 References


