Chapter 1: Introduction

Herein is reported: What can be defined as a molecular motor? Using examples, the boundaries of the definition are determined and the various fuels and sources of directionality required to drive motors are discussed. The control motors have over their own fuel use and directionality provide a degree of autonomy and determine to which degree an operator is required. The underlying mechanisms which govern unidirectional motion in molecular motors are presented and highlighted by examples from literature.
An introduction into molecular motors first demands a clear definition of what constitutes a molecular motor. Going by its dictionary definition it is anything, “consisting of molecules” “that imparts motion.”[1] Several biological machines have been labelled molecular motors, long before their detailed functioning was elucidated.[2–4] After much effort – well rewarded – the rotary motion of ATP synthase was revealed and due to its behaviour, it much deserves the characterization of molecular motor, all the more since its fuelled rotary motion is reminiscent of both a combustion engine as well as an electric motor (Figure 1.1).[5] The largest group of motor proteins arguably constitutes the class of cytoskeletal motors such as myosin and kinesin.[6] These biological motors exhibit a walking motion along filaments upon the consumption of chemical fuel and thereby act as the main cargo-transporters of the cell. More recently, prestin was discovered as an exceptional motor protein, being mechanically responsive to voltage changes, assumed to be aiding in auditory perception.[7] By the aforementioned definition, rhodopsin can also be regarded as a biological motor, as it undergoes a conformational change upon the absorption of a photon initiating the phototransduction cascade.[8] Furthermore, the cofactor retinal by itself can even be regarded as a molecular motor, since the $Z$–$E$ isomerization upon irradiation imparts motion to its structure.[9,10] If one follows such reasoning to its end, any enzyme that undergoes conformational change upon substrate binding, or any molecule changing its structure by chemical transformation can be included, which suggests a need for a narrower definition of molecular motor.

A more specific definition of motor, is that of prime mover – i.e. an initial source of motive power designed to drive machinery. This amendment to the definition allows for a facile distinction between the first and last examples. The rotary motion of ATP synthase fuelled by an electrochemical gradient is what drives the ATP producing machine and the translational motion of kinesin fuelled by ATP is what drives the cargo-transporting machine. However, an enzyme’s conformational change fuelled by substrate binding and a molecule’s structural change fuelled by a chemical reaction by themselves do not drive a machine. The case of rhodopsin is at the boundary of the definition and requires scrutiny before rhodopsin is labelled a molecular motor. The photoreceptor cell is a vital biological piece of machinery responsible for vision through the phototransduction cascade. However, rhodopsin and rhodopsin bound retinal are not so much driving this cascade as they are triggering it. One might argue that it lacks the repetitive progressive nature such as found in motors of the macroworld (e.g. combustion engines and clockwork motors). Therefore, it might be more fitting to label rhodopsin as a molecular motor.
trigger or switch, which sets the phototransduction cascade in proverbial motion instead of driving it.

Scientists and inventors have long strived to construct smaller and smaller motors of their own.[11] For the engineering of ever more complex machinery the approach has long been one of miniaturization. This has been successful to such an extent, that when Feynman during his famous lecture offered a prize for anyone who was able to make a motor fit into a 1/64th inch cube (~1/4 mL), it was claimed and awarded within a year by means of miniaturization of a regular electric motor.[12] His desire, however, was for the motor to have been made bottom up instead of top down, which would eventually become possible through the rise of nanotechnology.[13]

A wide array of nanomotors has since been developed; some operate very similar to conventional electric motors,[16,17] whereas even more operate in ways conventional macroworld motors never did.[18–20] These nanomotors exhibit rotary, translational or other motion and while many of them do not actually drive any machinery yet, they are designed to do so, stocking the toolkits of future nanoengineers. Molecular motors – spanning dimensions of about twenty-six nanometres[21] down to one nanometre (Figure 1.1f)[15] – can be considered a subclass of nanomotors. Until relatively recently this class has entirely been made
up of biological molecular motors, but the scientific advances made in the last three decades, inspired by Nature’s example, have provided a multitude of synthetic molecular motors.

Besides the dimensions of a motor as discussed above, several features can be identified which characterize the properties of any motor – (i) the type of motion produced by the motor; (ii) fuel is to be consumed by the motor and converted into motion; (iii) directionality is to be achieved to avoid random motion; (iv) turnover is required for a functional motor; and (v) autonomy of the motor over fuel consumption, directionality, and itself as a whole determines to which degree an operator is required.

![Figure 1.2. Rotational molecular motor using translational movement of a macrocycle along three different binding sites in a [2]catenane. Reprinted with permission from [27].](image)

**Types of motion**

Rotational and translational are common types of motion, however, the distinction between these two types is not always clear-cut. The system devised by Leigh et al. shown in Figure 1.2 is based on a catenane in which a small macrocycle binds sequentially to stations A, B, and C situated on a larger macrocycle. A rotaxane is a macrocycle on an axle, and when that macrocycle is able to move – translationally – between stations on the axle it becomes a machine well known as a molecular shuttle. Connecting the ends of the axle of a three station molecular shuttle yields a catenane such as the one shown in Figure 1.2. The authors report the resulting motion as rotary, which begs the question whether translation in a circle constitutes rotation. A possible analogy is that of an ice speed skater racing on a straight track or around a rink – does the speed skater’s motion over the ice change from translational to rotational going from a straight track to an oval rink? It all depends on the reference frame, nevertheless, once the translational motion can be described using an angle it can be considered as rotation, even when the axis of rotation is outside of the body in motion. For situations where the axis of rotation...
is inside the body in motion, this axis is usually characterized as the motors axle, as is the case for all examples in Figure 1.1.

**Turnover**

With motors being designed to be the initial source of motive power to drive machinery, turnover or repetitive motion is essential. Were ATP synthase and kinesin to stop working after a single 120 degrees turn or a single step, one could hardly claim that they were able to drive machinery using their motive power. Hence, a certain amount of repetitive rotations or steps is required of a motor, and for many motors their turnover can be determined. For the motors in Figure 1.1 the operational turnovers depend strongly on the specific design, despite that, the turnovers of some high-speed examples have been summarized in Table 1.1.

<table>
<thead>
<tr>
<th>Turnover (rpm)</th>
<th>Fuel</th>
<th>A</th>
<th>Directional source</th>
<th>A</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>2.0·10¹</td>
<td>Water current</td>
<td>✓</td>
<td>Water flow</td>
</tr>
<tr>
<td>b</td>
<td>7.0·10³</td>
<td>Combustion</td>
<td>X</td>
<td>2D asymmetry</td>
</tr>
<tr>
<td>c</td>
<td>1.0·10⁵</td>
<td>Electric current</td>
<td>✓</td>
<td>Electric flow</td>
</tr>
<tr>
<td>d</td>
<td>8.0·10³</td>
<td>Proton gradient / ATP</td>
<td>✓</td>
<td>Chirality</td>
</tr>
<tr>
<td>e</td>
<td>1.8·10⁸</td>
<td>Light</td>
<td>✓</td>
<td>Chirality</td>
</tr>
<tr>
<td>f</td>
<td>1.8·10²</td>
<td>Electric current</td>
<td>✓</td>
<td>Chirality</td>
</tr>
</tbody>
</table>

**Fuel and autonomy**

Any source of energy might qualify as a fuel, to be used by a motor, limited only by the ingenuity of the engineer (Table 1.1). Rotary molecular motors using chemical sources as fuel will be the subject of Chapter 8 whereas in the other chapters, light will serve as the main fuel for rotary motion. An interesting group of motors constitutes those classified as Brownian motors, particularly those which operate using tilting or information ratchet mechanisms. It should be noted that while for these motors their motion is facilitated by Brownian motion, it is not fuelled by it – preserving the second law of thermodynamics. The fuel of these motors is whatever drives their ratchet mechanisms, such as temperature pulses, force fluctuation or chemicals (vide infra and Chapter 8). Most of the examples presented in Figure 1.1 are autonomous with respect to their fuel use, meaning that when a motor is offered the appropriate fuel it is able to operate by itself. However, numerous motors do not possess such autonomy of which the internal combustion engine is an example. Whether the fuel of an internal combustion engine is the combustible gas mixture or the combustion itself is irrelevant, what matters is that
simply providing the motor with either does not allow the motor to function. It needs a timed combustion during operation and to initiate operation the motor has to be brought in motion by other means (**vide infra**). Other examples of non-autonomous motors are several systems derived from the catenane shown in Figure 1.2, which require a specific sequence in which several different chemical fuels have to be supplied. Providing these fuels all at once or out of the specific sequence would prevent the correct operation of the motor, illustrating the motor’s lack of autonomy with respect to its fuel use and the need for an operator. In a recent example this limitation has been addressed,[31] and even though the rotation is slow and fuel use rather substantial,[32] it theoretically functions as an autonomous chemically fuelled rotary motor.

**Directionality and autonomy**

Directionality is an essential requirement without which a motor would not be a motor. For example, molecular rotors[33] differ from rotary molecular motors, in that the motion in the first group is random, while in the latter it has a preference for a specific direction. Unidirectionality in any motor requires the breaking of symmetry in order to achieve a motion in a non-random direction. In some systems this is achieved by an asymmetric unit installed a priori, as in ratchets, diodes, or the stereogenic centre in rotary molecular motors based on overcrowded alkenes. In other systems directionality is introduced by an asymmetric induction of fuel by the operator, for example, the direction of water flow for a waterwheel or the direction in which current is fed to an electromotor. For several systems the directionality is only set at the initial motion and maintained by forces such as momentum. An interesting example of such a system is the well known combustion engine (**vide supra**), for which in the early days a dangerous hand-crank was required to set the engine in motion, which was soon replaced by an electric starter engine. Common internal combustion engines arguably are not clear examples of rotary motors, but of reciprocating motion, and it is the piston and crankshaft which convert it into rotary motion. This setup is the underlying reason for the engine’s lack of autonomy over its rotational direction, since a so called kick back can readily reverse the rotation. A true rotary internal combustion engine has been invented by Felix Wankel and bears his name (Figure 1.1b).[34] Wankel engines are built in an asymmetric fashion, and therefore possess a predetermined directionality, however, they still need a starter engine to provide the motor with its initial momentum due to a lack of autonomy of the motor over its fuel use. When it comes to molecular motors, the symmetry breaking process to achieve directionality is often explained by means of ratchet mechanisms.[26]
Ratchet mechanisms

The term ratchet is used in analogy to the process capturing property of real ratchets, which is achieved in molecular motors with the use of asymmetric energy barriers for its motion. This does not necessarily require a potential energy surface (PES) to resemble the saw-tooth pattern of ratchets, since the shape of the PES of a barrier does not alter microscopic reversibility.\cite{30,35} Two mechanisms used by synthetic molecular motors are the information ratchet and the pulsating ratchet.\cite{36}

The essential property of an information ratchet is the need for a feedback mechanism of the position of the motor on its PES in order to lower energy barriers leading towards the desired direction. Motors for which this feedback mechanism is executed by an operator lack autonomy in both fuel use as well as directionality. Such an example is the chemically driven rotary molecular motor developed by Fletcher et al. depicted in Figure 1.3.\cite{37}

![Figure 1.3](image)

Figure 1.3. Reversible rotary molecular motor chemically driven by an information ratchet mechanism. Left: identified structures in the motor’s rotational cycle; right: reaction coordinate diagram with corresponding labels. Adapted from [37], for further details see Chapter 8.

Using a chiral source in the form of asymmetric catalysis allows for the selective formation of 1b over 1d from 1a (Figure 1.3). Random rotation around the single biaryl bond – the axis of the motor – of 1b to 1d is restricted due to steric effects. Selective deprotection of 1b facilitates reformation of a lactone in 1c, in which the upper half has undergone a 180 degrees rotation with respect to the lower half. Repeating these steps using the appropriate chemical fuels gives state 1a’, completing the rotational cycle. The information ratchet mechanism is evident in motor 1, where a random provision of fuel would yield random rotation and where each step can be reversed using a different chemical fuel if so desired.

An example of a translational molecular motor using an information ratchet mechanism has been developed by Leigh and co-workers (Figure 1.4).\cite{38} Even though the four-step sequence constitutes a single full displacement, they report that in theory it could be extended to a polymeric backbone along which the
translating unit can move in either direction. The steps ii and iv (in which the translating unit moves a single leg) represent the selective steps which require information regarding the molecules position on the PES. Applying the conditions of steps ii and iv to 2a or 2e leaves the translating unit mostly in place, even if the backbone were extended to a polymer. This is due to the presence of the stilbene moiety in a trans configuration, which was introduced to lock the translating unit in place and prevent a leg from taking a big step (for example preventing the hydrazone leg of 2a to step to its terminal aldehyde).[39] Random application of steps ii and iv to 2d should accordingly lead to random translations to 2a and 2e, and on a polymeric backbone similarly for positions 2b and 2f, signifying the crucial presence of an information ratchet mechanism. The switching between different potential energy surfaces for governing directional movement is known as a pulsating ratchet mechanism, and is used by motor 2 when it photoisomerizes its stilbene moiety (steps i and iii). Even though it is not essential for system 2,[39] it greatly improves its directional yield. There is a large group of molecular motors for which a pulsating ratchet mechanism is the only and essential mechanism for control over directionality (Figure 1.5).

**Figure 1.4.** Molecular ‘walker’ driven by light and chemical fuel. Left/top: identified structures in the motor’s translational path; bottom right: reaction coordinate diagram with corresponding labels. i) UV light; ii) base; iii) blue light; iv) acid. Adapted from [38].

**Light driven rotary motors**

All molecular motors depicted in Figure 1.5 use similar stimuli and pathways to achieve full autonomous unidirectional rotation. Each motor possesses a central double bond which serves as the axle of rotation. Due to the size of the substituents at the double bond, the appending moieties are forced from planarity giving rise to
helical chirality. Combined with a form of point chirality at the stereogenic centres provides diastereoselectivity where the helical chirality is dynamic while the point chirality remains fixed. Excitation of state a to b* using light allows for a photochemical E–Z isomerization to take place forming state c (Figure 1.5). During this process the molecules are brought onto a PES with a different shape allowing for a thermal relaxation to take place. After this relaxation the molecules return to a different position on the original PES where another thermal relaxation is possible. These switches between different potential energy surfaces, with subsequent relaxations to new positions, are what characterizes a pulsating ratchet mechanism. The process from state a to c provides the opposite configuration over the double bond (E/Z), as well as an inversion of the helicity (M/P) while retaining point chirality (R/S). This yields an unfavourable diastereoisomer, making it a metastable state. Metastable state c is able to undergo a thermally activated helix inversion to produce stable state d, in which the upper half has rotated 180 degrees with respect to the lower half. A repetition of the conditions of steps i, ii and iii brings the molecular motors through states e* and f to a full 360 degrees rotation in state a*. The clockwise unidirectional rotation of the motors depicted in Figure 1.5 is explained using a pulsating ratchet mechanism which relies on a positional asymmetry between the potential energy surfaces. This asymmetry in the PESes is inextricably linked to the asymmetry of the molecules. The shape of the PES of the excited state favours clockwise rotation in the examples since for counter clockwise rotation an additional barrier would have to be crossed where the upper half clashes with the lower half such as in the helix inversion step iii. The shape of the ground state for step iii again favours clockwise rotation due to the asymmetry of the molecules’ structure where in an equilibrium the other diastereoisomer is favoured over the one initially formed. It is the chirality of these molecular motors that allows for autonomous government over their rotational direction. Note that for all these molecular motors their enantiomers rotate in the opposite direction. C2 symmetric molecular motors based on overcrowded alkenes with stereogenic centres in the two alpha positions (3 in Figure 1.5 and e in Figure 1.1) were the first synthetic motor systems for which repetitive rotary motion was reported by Feringa and co-workers.[40] Being the first fully functional synthetic molecular motors, the group of motors represented by 3 was dubbed the first generation when a modified class was introduced by the Feringa group.[41] The second generation of C1 symmetric molecular motors represented by 4 (Figure 1.5) feature only a single stereogenic centre and a symmetric lower half. A plethora of structural modifications have allowed for finely tuned and functional molecular motors based on 3 and 4 (Chapter 2 and Chapter 3). Greb and Lehn constructed functional molecular motor 5, based on an ‘overcrowded’ imine.[42] Similarly, Guentner et al. developed a molecular
motor based on hemithioindigo with point chirality at a sulphur atom instead of a carbon atom and fuelled by visible instead of UV light.\[^{43}\]

Figure 1.5. Light driven unidirectional rotary molecular motors (all depicted examples rotate clockwise). Top to bottom: 3, 1\(^{st}\) generation molecular motors\[^{40}\] (Chapter 2); 4, 2\(^{nd}\) generation molecular motors\[^{41}\] (Chapter 3); 5, imine based motor\[^{42}\]; 6, hemithioindigo based motor\[^{43}\]; 7, chiral dibenzosuberane based motors\[^{44–46}\]; 8, chiral hydrogen bond based motor\[^{47}\]; general reaction coordinate diagram with corresponding labels. \(i\) UV/vis light; \(ii\) thermal relaxation; \(iii\) thermally activated helix inversion.
Interestingly, Chen and co-workers have reported several overcrowded alkenes based on dibenzosuberane (7) which have all the ingredients for a molecular motor.\textsuperscript{[44–46]} They have shown steps $i$ and $ii$ to function as required as well as the presence of diastereoselectivity required for step $iii$, although they do not report on any occurrence of a thermal helix inversion (step $iii$). It is possible that the barrier of activation for step $iii$ is of such a magnitude for the reported examples of 7 that it prevents their motor function. However, these barriers have been shown to be fully adjustable,\textsuperscript{[48]} which would open up the possibility for overcrowded alkenes 7 to join the ranks of unidirectional molecular motors.

Frutos and co-workers have used computational photochemistry to design molecular motor 8 which uses chiral hydrogen bonds as the source for unidirectionality.\textsuperscript{[47]} Their proposed molecular motor might suffer from several drawbacks such as a need for hard UV due to a lack of an extended aromatic system as well as stability issues stemming from the presence of an iminium group in conjugation with the overcrowded alkene. However, these practical limitations can potentially be resolved by small structural modifications, providing nanoengineers with another remarkable synthetic molecular motor.

**Temperature ratchets**

The information and pulsating ratchet mechanisms discussed above do not require their PES to exhibit a saw-tooth pattern for their functioning. Temperature ratchet mechanisms, also known as diffusion mechanisms, do require such a feature to allow for directional motion to take place (Figure 1.6 left).\textsuperscript{[26,49]} The mechanism utilizes a flat PES in an excited state at which free diffusion takes place in either direction (step $ii$ in Figure 1.6 left) followed by a return to an asymmetric ground state (step $iii$). With the initial minimum off centre between two barriers a net displacement occurs in the direction of the proximal barrier. Note that even though the ground state PES resembles the saw-tooth pattern of a ratchet, net displacement occurs in the opposite direction of a macroworld ratchet, highlighting the contrast between the underlying mechanisms governing the motion of macro- and nanomachines.

The molecular motors engineered by Tierney et al. (Figure 1.1f)\textsuperscript{[15]} and Perera et al. (Figure 1.6 right)\textsuperscript{[50]} are both driven by pulses with an STM tip while positioned on a metal surface and the underlying mechanism for the directional displacement which both motors exhibit is explained using a temperature ratchet mechanism (Figure 1.6 left). The mechanism for unidirectional rotation of these motors can also satisfactorily be explained using a pulsating ratchet mechanism (Figure 1.5 bottom). Both motors are chiral which could provide an asymmetrically placed
excited state instead of the relatively flat excited PES required for a temperature ratchet. Tierney et al. discuss at length the remarkable influence the asymmetry of the STM tip has on the rotation of the chiral butyl methyl sulphide. And while Perera et al. make no mention of chirality or the strong helical nature of the appending ferrocene moieties, they do present calculations substantiating the presence of the aforementioned asymmetric PES of the excited state. Ultimately it might even be possible for these motors to exploit both mechanisms in unison to achieve unidirectionality.

Figure 1.6. Temperature ratchet mechanism. Left: a population of a molecular motor a is excited to b using a stimulus (step i), diffusion to c takes place (step ii) after which return to the ground state gives population d with net displacement (size of circles indicate population sizes). Right: molecular system which functions as a rotational motor driven by STM on a gold surface, reprinted in part with permission from [50].

Outline of this thesis

Molecular motors driven by light based on overcrowded alkenes will be the focus of this thesis. Chapter 2 will provide a specific introduction into first generation molecular motors (3, Figure 1.5) and the use of computational chemistry in the study of their thermal behaviour. Chapters 3, 4 and 5 will deal with second generation motors where Chapter 3 will first provide a general introduction followed by studies of several structural modifications, Chapter 4 goes into the effect of viscosity on the motor and in Chapter 5 the limits of the bistability of the second generation molecular motors are explored. The seeming crucial role asymmetry plays in these molecular motors will be put to the test in symmetric third generation molecular motors in Chapter 6 and Chapter 7 examines how structural changes affect the behaviour of third generation molecular motors. Finally, Chapter 8 will switch to chemically driven molecular motors where autonomy over their behaviour is discussed and the design for a novel chemically driven motor is presented.
References


[10] It should be noted that free rotation about single bonds affecting unidirectional behaviour is not taken into account in the research cited above.


[32]  From the data presented it can be deduced that over the 48 h reaction time 0.54 steps of 180 degrees take place while consuming 124 equiv of fuel, averaging to 460 equiv of fuel and 8 days per full 360 degrees rotation.


[36]  Fluctuating potential ratchets and flashing ratchets are identified as synonymous as well as subclasses of pulsating ratchets.


