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### Molecular motors in new media

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*Document Version*

Publisher's PDF, also known as Version of record

*Publication date:*

2017

[Link to publication in University of Groningen/UMCG research database](#)

*Citation for published version (APA):*

Lubbe, A. S. (2017). *Molecular motors in new media*. Rijksuniversiteit Groningen.

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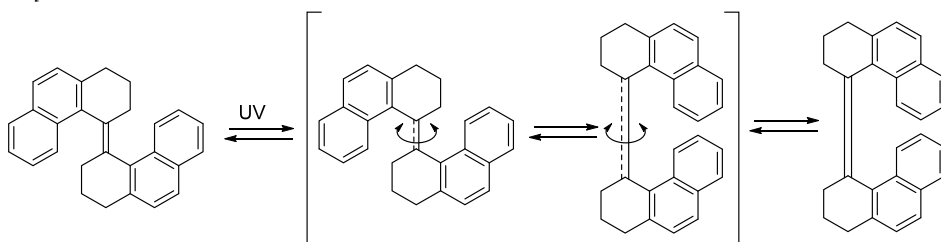
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## Summary

Everything around us, everything that we can touch or see or smell, consists of atoms. Scientists have thus far observed more than 100 different varieties, which together constitute the building blocks of our universe. By forming chemical bonds, atoms may combine to molecules. Most of the matter that we encounter in daily life is in a molecular form. These particles are so small, that they experience the laws of nature differently than we do. One of the most dominant process at the molecular scale is a random movement of all molecules, called Brownian motion. It may not be obvious from looking at a glass of water, but the individual water molecules are continuously tumbling around each other.

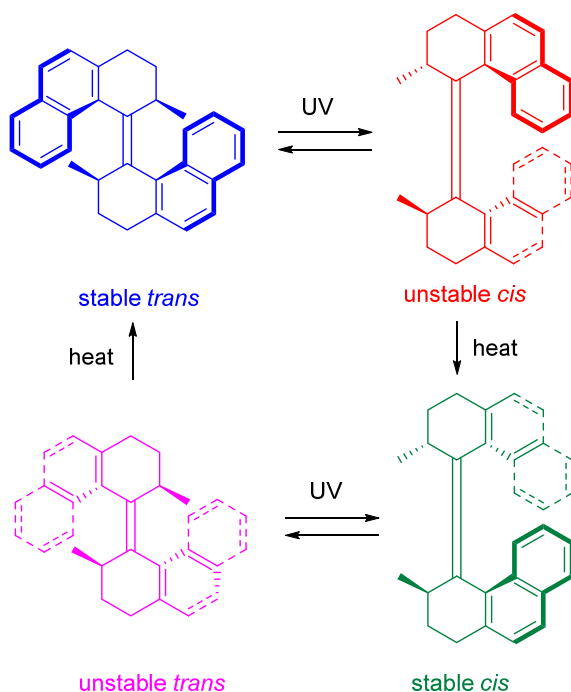
Directional movement on the molecular scale is required by the human body, for example to transfer fuel or for muscle contraction. However, to purposely move something in what can be called a non-stop molecular hurricane of Brownian motion is not easy. Nature has solved this issue by employing so-called molecular motors, i.e. enzymes which purposely move from A to B. Taking inspiration from nature, chemists sought to create directional motion using molecules in order to drive synthetic machinery at the nanoscale. Enzymes, though much smaller than the machines of the macroscopic world, are conglomerates of macromolecules and consist of thousands of atoms. Since in organic chemistry much smaller molecules are employed a redesign was required.



**Figure 1:** Switching an overcrowded alkene based switch.

Early attempts towards controlled rotational motion focused on molecular switches, molecules that can interconvert between two states under the influence of a trigger (e.g. light, pH, a chemical etc.). Overcrowded alkene switches (Figure 1) contain a central double bond, around which free rotation is not possible. Irradiation with UV light temporarily breaks one of the bonds, after which rotation around the remaining bond is possible. After a very short time period, the second bond is reformed. The molecule is then locked in either its original configuration, or with the top half rotated  $180^\circ$  with respect to the lower half. This rotation is non-directional and reversible. However, through the introduction of only a very small design modification, such molecules can undergo unidirectional rotation. In light-driven overcrowded alkene-based molecular motors (Figure 2, from here on referred to as ‘molecular motors’), the direction of the UV induced rotation could be fixed.

Upon irradiation with UV light, an equilibrium is established in which part of the molecules are in their starting configuration (*stable trans*), and part have their top half rotated almost 180° with respect to the lower half (*unstable cis*). Furthermore, the *unstable cis* isomer can undergo two different processes: UV induced backward rotation or thermally induced forward rotation. Therefore, if after the equilibrium is established, the irradiation is halted, all the formed *unstable cis* isomer will undergo a slight irreversible forward rotation towards the so-called *stable cis* isomer, a process which can be accelerated by heating. Because the *stable trans* isomer remains unaffected under these conditions, a combination of a photochemical and thermal cycle leads to a unidirectional, irreversible 180° rotation of part of the molecules, while part returns to its original configuration. By repeating this process, the *stable cis* isomer can be converted, through the intermediate *unstable trans* isomer, to the *stable trans* isomer, thereby completing one full rotation around the central axis.



**Figure 2:** Switching an overcrowded alkene based molecular motor.

In 1999, the first molecular motor of this kind was reported by our group. Early investigations focused mainly on gaining a theoretical understanding of the photochemical and thermal processes. However, in the last few years, successful applications have been found in catalysis, materials design and nanotechnology. For example, the unidirectional rotation of a molecular motor was used to drive a molecular nanocar in a straight line over a surface. Additionally, the motors could be made to

work cooperatively by fixing them on a surface. By the combined effort of millions of molecular motors, a water droplet visible to the naked eye could be moved.

Notably, applications of molecular motors under biological conditions are scarce, even though light is such an ideal trigger. Light does not interfere with most processes in the cell, its wavelength and intensity can be regulated precisely and it can be applied with high precision. As many other molecular photoswitches have been successfully used in biochemical applications for decades now, there is a real opportunity to implement molecular motors in a new environment, where their multistage switching cycle and other rotational properties may open up new possibilities. However, the aromatic core structure renders molecular motors strongly hydrophobic: they simply do not dissolve in water. In this thesis, the first steps are made towards successful application of molecular motors under physiological conditions. The core issue of solubility is addressed, and various strategies towards interference with and control over processes in the cell are employed.

Chapter 1 provides an overview of recent developments in reversible photoregulation of oligonucleotide structure and function. Poly- and oligonucleotides, such as DNA and RNA, carry our genetic information in every cell. A variety of diseases is thought to have an underlying genetic cause, DNA mutations are closely related to cancer and even ageing is thought to be associated with naturally occurring DNA damage. Therefore, the ability to exert control over the function of oligonucleotides would enable scientists to influence and regulate such processes. Since most processes involving DNA require the single stranded form, as opposed to the naturally occurring double helix, there is a focus on controlling the unwinding process. Molecular photoswitches are inserted into the oligonucleotide in a variety of manners. By switching the molecule, a destabilization of the double helix is induced, which can lead to unwinding into the single stranded form. First attempts towards switch inclusion were made over two decades ago, but in the past few years the technique has seen real refinement and even extended to first applications, by interfering with key processes of the cell such as DNA ligation or transcription.

Chapter 2 describes the design, synthesis and investigation of a DNA/molecular motor hybrid. Aided by computational studies, a molecular-motor-based linker was designed, which was incorporated in the backbone of a small DNA hairpin. After it was confirmed that the self-complimentary structure indeed forms a hairpin, the motor was demonstrated to undergo unidirectional rotation under physiological conditions, although the thermal process may be impaired at body temperature. Moreover, the 180° rotation of the motor could significantly influence the stability of the hairpin, as a 6 °C decrease in double strand melting temperature was recorded upon switching.

In chapter 3, a molecular motor was functionalized with thymine, one of the five naturally occurring nucleobases. The motor showed strong aggregation behaviour and formed micrometre-sized, regular hexagonal sheets, which were examined using transmission electron microscopy. After electron diffraction experiments confirmed that the sheets were crystalline, rotation of the molecular motors was attempted. Upon

irradiation with UV light and subsequent heating, the hexagonal sheets were broken up into smaller pieces. UV-vis analysis confirmed that rotation of the motors had occurred. This chapter thus constitutes the first example of molecular motor rotation in the solid state.

In chapter 4, the core issue of the application of molecular motors under physiological conditions is addressed: solubility. Quaternary ammonium groups were expected to be the most suitable solubilizing groups for molecular motors, and two designs were synthesized and analysed. The first of these design degraded fast in aqueous solution, most likely due to elimination of the ammonium groups on a benzylic position. The other design, however, could undergo both thermal and photochemical processes in buffered solutions at a pH range from 2 to 10, as confirmed by a range of analytical techniques. A minor degradation was observed upon prolonged irradiation, which was identified as water addition to the double bond of a photogenerated intermediate of the motor. To compliment these findings, a previously reported molecular motor was studied in micelles, as a model for the lipid bilayer that constitutes the cell membrane. It was demonstrated the rotation of a motor under these conditions proceeds as desired. Chapter 5 ventures into the field of photopharmacology. This new research area uses light to activate and deactivate drugs. A photoswitch is incorporated into the core structure of a known drug. By switching, the structure of the drug changes and it is no longer active. As a result, a drug can be activated only in a desired position. This approach is particularly attractive for chemotherapy agents, which can cause devastating side effects in cancer patients. Here, two different anticancer drugs were targeted. A molecular motor analogue of cisplatin was synthesized and analysed, but cytotoxicity assays could not be performed due to insufficient solubility. Additionally, a photoswitchable colchicine analogue was designed and studied. The compound proved to be rather unstable, however, this problem is expected to be resolved by the addition of a solubilizing group. This water soluble derivative is proposed at the end of the chapter.

Finally, chapter 6 provides a deeper insight into the relation between molecular motors and the medium in which they operate. For many photoswitches, it has long been established that both photochemical and thermal processes can be highly dependent on the properties of the solvent. The thermal isomerisation process of a molecular motor was therefore investigated in 50 solvents and solvent mixtures. As expected, a strong correlation was found between the rate of rotation and the solvent viscosity. However, other solvent properties also clearly influenced the rotation rate. Statistical analysis was employed to identify the diffusion coefficient and the cohesive energy density as the most influential solvent properties. Overall, these findings indicate that solvent influence on the thermal isomerization properties of a molecular motor arise from a complex interplay of solvent-solvent and solvent-solute interactions.