Chapter 3: Second Generation Molecular Motors

Herein is reported: An introduction into second generation molecular motors and the use of molecular modelling in the study thereof. The potential energy surface of the smallest second generation molecular motor known to date is investigated. The relation between structure and speed is studied, leading to an even smaller overcrowded alkene which is predicted to be the fastest molecular motor known to date. Computational studies are presented describing the effects of quaternization of the stereogenic centre, as well as exploring chirality transfer in a molecular motor from its stereogenic centre to an internal biphenyl moiety providing viable switchable chiral ligands.

Parts have been published as:


Introduction

While advances were being made on the functionality, properties and applications of first generation molecular motors (see Chapter 2), curiosity arose to whether the \(C_2\)-symmetry and the inherent double stereogenic centres were a necessity for the proper functioning of the molecular motor. This question had been discussed decades earlier for the overcrowded alkenes analogue to first generation molecular motors in which the stereogenic centres were still absent ([1], Figure 3.1).\(^{[1]}\)

Replacing one side of the \(C_2\)-symmetric overcrowded alkene \(1\) with a symmetric moiety which is large enough for the molecule to retain its helical shape \([(P)-2,\) Figure 3.1] changes the molecule to a \(C_1\)-symmetric overcrowded alkene with its descriptors for chirality reduced from two to one.\(^{[2]}\) It is most noteworthy that there is a loss of identifiable isomeric forms; whereas the \(E\) and \(Z\) isomers of \(1\) with a specific helicity (e.g. \((P,P,E)-1\) and \((P,P,Z)-1\)) are easily distinguished from each other by most analytic techniques, the \(E\) and \(Z\) isomers of \(2\) with one specific helicity are identical \([(P)-2 \equiv (P)-2']\).

\[\text{Figure 3.1. Adaptation of the } C_2\text{-symmetrical nature of overcrowded alkene } 1 \text{ to } C_1 \text{ in } 2.\]

Due to the symmetry of the lower half of the overcrowded alkene \(2\), its two isomers \([(P)-2 \text{ and } (M)-2]\) are enantiomers and therefore not selectively addressable by a photochemical \(E\text{–}Z\) isomerization (PEZ) using unpolarized UV-light. Polarized light on the other hand, has been shown to selectively drive the PEZ to either isomer.\(^{[3]}\) To allow for selective photochemical switching using unpolarized light, asymmetry was reintroduced and several structural modifications provided a novel range of molecular switches based on overcrowded alkenes.\(^{[4–8]}\) Koumura et al. modified the core structure of these molecular switches by the amendment of the alpha carbon (with respect to the overcrowded alkene) into a stereogenic centre by the addition of a methyl group (3 and 4, Figure 3.2).\(^{[9,10]}\) This overcrowded alkene was proven to function as a molecular motor while featuring a single stereocentre, thereby answering the aforementioned question (\textit{vide supra}). These motors were recognized as a novel class, dubbed \textit{second generation molecular motors}. A Barton-Kellogg coupling afforded the overcrowded alkenes in molecules 3 and 4.
in the final step of their synthesis after which their enantiomers were resolved by chiral HPLC.\cite{11,12}

The stable diastereoisomers were found with their methyl group at the stereogenic centre in a pseudo-axial orientation and the six membered rings in boat conformations \textit{anti}-folded with respect to each other to minimize steric hindrance (Figure 3.3). Due to additional strong steric hindrance in the fjord region (Figure 3.2) the aromatic moieties are forced from planarity (Figure 3.3), and the boat conformation of the six membered ring of the upper half puts the naphthalene moiety in a \textit{syn}-folded orientation with respect to the stereogenic methyl group. This geometrical feature of \textit{syn}-folding of the aromatic moiety with respect to the larger group at the stereogenic centre is found for the stable diastereoisomer of all second generation molecular motors studied to date, regardless of ring size or substitution pattern.\cite{9,10,13–18} Additionally, this entails that the helicity of the aromatic moieties of second generation molecular motors is governed by their absolute stereochemistry, therefore, the absolute stereochemistry is inferred from the molecule’s helicity.

Irradiation with UV-light of a solution of stable-(\textit{R},\textit{M})-3 allows it to undergo a unidirectional photochemical \textit{E}–\textit{Z} isomerization to form a metastable (MS) species in which the helicity of the aromatic moieties has inverted: MS-(\textit{R},\textit{P})-3. In the
metastable species, the six membered rings again adopt boat conformations anti-folded with respect to each other, however, the stereogenic methyl group has adopted a pseudo-equatorial orientation introducing steric strain due its proximity to the lower half. A thermal helix inversion (THI) of MS-(R,P)-3 releases the steric strain through two subsequent flips of the six membered rings which has been studied extensively, most recently by Cnossen et al.\[19\] The THI produces stable-(R,M)-3’ which is identical to the initial stable-(R,M)-3, thus completing a 180 degrees rotation of the upper half with respect to the lower in a PEZ-THI sequence, and two of such sequences make up a full 360 degrees unidirectional rotation.

Figure 3.3. Geometry of stable-(R,M)-3 [DFT B3LYP/6-31G(d,p)]. Left: side-view with alkene on the y-axis. Middle: front-view with alkene on the y-axis. Right: top-view with alkene on the z-axis. In all projections in this chapter the y-axis is oriented vertically and the x-axis horizontally in the plane of the paper and the z-axis is oriented perpendicular to said plane.

The reduction of two to one stereocentres greatly benefits the simplicity of the system and its operation. Instead of two separate PEZ-THI sequences with each its own quantum yield and thermal barrier, the second generation molecular motors are characterized by a single PEZ-THI sequence. However, due to the symmetric nature of the lower half in second generation molecular motors, the steps in a PEZ-THI sequence have not unequivocally been proven to occur in the manner proposed. Theoretically, in the first step the motor could retain its E/Z configuration while undergoing a photochemical helix inversion producing its metastable state. Furthermore, in the second step the motor could theoretically undergo a thermal E–Z isomerization instead of a THI while still producing the stable state. To positively identify the proposed behaviour, the lower half was desymmetrized by the introduction of a functional group which could easily be followed using spectroscopic techniques (4, Figure 3.2). The behaviour of the desymmetrized motor 4 was near identical to that of 3 and confirmed the proposed sequence of a photochemically driven E–Z isomerization followed by a thermally activated helix inversion and proves the fully autonomous unidirectional rotation of this generation of molecular motors based on overcrowded alkenes. The verification of the
rotational behaviour of second generation molecular motors by the desymmetrization of the lower half has been performed each time a significant change was made to their structural design which in most cases re-established the characteristic behaviour,[13–16,18,20–26] however, in a few cases an interesting deviation was observed (see Chapter 5).

The elucidation of the exact behaviour of the molecular motors during either step in their rotary cycle and the influence of its environment on it, is fascinating as well as crucial research, not only from a fundamental point of view – which should provide ample motive of its own accord – but also from a technological point of view.[27] Two key functions in the toolkit of a nano-engineer can be performed by these overcrowded alkenes: (i) unidirectional rotary motors, as their name implies, and (ii) molecular switch, employing only their photoisomerizable property.[28] The requirements of these two key functions are so dissimilar, that they are in some ways opposite to one another. Where the molecular switch benefits from a high yielding photostationary state (PSS) and – depending on purpose – stable states, the molecular motor benefits mostly from a high speed and a high unidirectional yield.[29] The two steps of the molecular motor have therefore been studied in detail.

![Figure 3.4](image)

**Figure 3.4.** The characterizing steps of a second generation molecular motor $x$.

The photochemical $E$–$Z$ isomerization (PEZ) of a second generation molecular motor, or for that matter any chiral overcrowded alkene, can be characterized by several properties: (i) the excitation energy of the overcrowded alkene (expressed as the wavelength of the corresponding absorption band), (ii) the reaction rate of the PEZ, and (iii) the PSS ratio. Modification of the absorption band serves two purposes: addressability and functionality. For the purpose of a switch, one would like the individual isomers of the overcrowded alkene to possess significantly distinct absorption bands, since too much overlap prevents each state to be addressed individually. In molecular motors the absorption spectrum of the metastable state is distinct from the stable state by definition, being diastereomeric. One might expect the strain over the double bond to increase going from the stable to the metastable state, since overall steric strain increases, causing a corresponding bathochromic shift of the absorption band. This holds true for a group of molecular motors (e.g. all with a fluorene lower half: $Y = -$ in Figure 3.4),[16,30] however, a
A high PSS ratio in both directions is a desirable function in a molecular switch. A high PSS ratio is not essential for the function of a molecular motor, as explained before, however, high PSS ratios are desirable since they facilitate easier
characterization of the metastable diastereoisomer. Generally, moderate to nearly maximum PSS ratios are obtained for second generation molecular motors (Table 3.1) which can often be improved by a thorough screening of solvents and irradiation wavelength and modification of peripheral functional groups.\cite{19,20,36,37,41}

After the PEZ of a second generation molecular motor, a metastable species is generated, ready to take the second step in its rotary cycle: a thermal helix inversion. The THI returns the metastable diastereoisomer of the molecular motor to its global minimum. Finally, even though it has undergone a 180 degrees rotation, the molecule is indistinguishable from its initial diastereoisomer due to the symmetry of the lower half. The stability of the metastable state determines the usefulness of a certain design depending on its purpose. Maximum speeds of a molecular motor benefit from minimal barriers for THI, maximum bistability of a molecular switch benefits from maximal barriers for THI, and when specific lifetimes are required, the design should be tailored accordingly. For these reasons, the barrier for THI of a large range of structural motives has been studied. As an example, the barriers for THI of the most basic design of second generation molecular motors (those with a methyl group at the stereogenic centre and a naphthyl moiety appending the upper half, Figure 3.4) have been summarized in Table 3.2.

**Table 3.2.** Summary of Gibbs free energy, enthalpy and entropy of activation for a series of second generation molecular motors (X & Y as in Figure 3.4, standard condition is atmospheric pressure and 20 °C)

<table>
<thead>
<tr>
<th>Y: \ X:</th>
<th>O</th>
<th>CH₂</th>
<th>S</th>
<th>–</th>
<th>O</th>
<th>CH₂</th>
<th>S</th>
<th>–</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₂-CH₂</td>
<td>57.7 [21,42]</td>
<td>44.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N-Boc</td>
<td>110 [23]</td>
<td>41.8 [23]</td>
<td>103</td>
<td>–23.3</td>
<td>35.2</td>
<td>–22.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>O</td>
<td>83.2 [38]</td>
<td>101 [10]</td>
<td>40.3 [21,42]</td>
<td>58.6</td>
<td>89.5</td>
<td>–16.3</td>
<td>101</td>
<td>–17.8</td>
</tr>
<tr>
<td>C(CH₃)₂</td>
<td>94.3 [10]</td>
<td>106 [10]</td>
<td>26.0 [42]</td>
<td>83.4 [42]</td>
<td>91.6</td>
<td>–37.3</td>
<td>85.4</td>
<td>–57.4</td>
</tr>
<tr>
<td>CH=CH</td>
<td>103 [10]</td>
<td>102 [30]</td>
<td>83.4 [42]</td>
<td>46.2</td>
<td>91.9</td>
<td>–91.9</td>
<td>86.0</td>
<td>–19.2</td>
</tr>
<tr>
<td>S</td>
<td>73.2 [38]</td>
<td>91.6 [10]</td>
<td>34.5 [21,42]</td>
<td>46.2</td>
<td>91.9</td>
<td>–91.9</td>
<td>86.0</td>
<td>–19.2</td>
</tr>
</tbody>
</table>

[a] Diagonal lines separate enthalpy (top left) and entropy (bottom right) for each entry.

Enthalpy and entropy are determined experimentally and the related Gibbs energy is extrapolated to room temperature, which allows for an easy comparison between
the barriers of different designs. Additionally, the half-life at rt is often reported, since it allows for a more intuitive comparison between different designs (Table 3.3). While helpful, there is degree of uncertainty in the Gibbs energy and half-life at rt, since for very fast (such as X/Y = −/S) and very slow (such as X/Y = S/−) molecular motors the temperatures at which their barriers are determined lie far from rt and must be extrapolated. It would therefore be useful to compare the THI barriers without extrapolation, which is achieved by comparing temperatures at which the half-life equals one hour (one-hour-half-life temperature). For the techniques usually employed in the determination of the activation parameters (such as CD, UV and NMR-spectroscopy) the one-hour-half-life temperature falls within the measured temperature range. Furthermore, the one-hour-half-life temperature might be intuitively superior to half-life at room temperature – comparing half-lives of one nanosecond versus thousands of years is far more abstract than comparing one-hour-half-life temperatures of, for example, −196 °C (boiling nitrogen) versus 100 °C (boiling water). The Eyring equation (eq. 1) can be rewritten to provide the one-hour-half-life temperature (eq. 2) in which \( W \) is the solution to the Lambert W function. Equation 2 has been applied to the available data of the series of second generation molecular motors and summarized in Table 3.3.

\[
k = \frac{k_B}{h} \cdot T \cdot \exp \left( -\frac{\Delta H^\circ}{RT} + \frac{\Delta S^\circ}{R} \right)
\]

\[
T_{t_{1/2}=1\text{h}} = \Delta H^\circ \cdot \left( R \cdot W \left( \frac{3600 \cdot k_B \cdot \Delta H^\circ \cdot \exp \left( \frac{\Delta S^\circ}{R} - 1 \right)}{h \cdot R \cdot \ln(2)} \right) \right)^{-1}
\]

**Table 3.3. Summary of half-life at rt and one-hour-half-life temperature calculated from Table 3.3.**

<table>
<thead>
<tr>
<th>( Y: )</th>
<th>( X: )</th>
<th>( \text{half-life, } t_{1/2} \text{ at rt} )</th>
<th>T at ( t_{1/2}=1 \text{ h (°C)} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{CH}_2-\text{CH}_2 )</td>
<td>O</td>
<td>2.2 ms</td>
<td>−105.5</td>
</tr>
<tr>
<td></td>
<td>CH(_2)</td>
<td>S</td>
<td>−</td>
</tr>
<tr>
<td></td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>( \text{N-Boc} )</td>
<td>57 d</td>
<td>3.1 μs</td>
<td>78.4</td>
</tr>
<tr>
<td>O</td>
<td>1.3 min</td>
<td>1.1 d</td>
<td>1.7 μs</td>
</tr>
<tr>
<td></td>
<td>46.7</td>
<td>−148.6</td>
<td></td>
</tr>
<tr>
<td>( \text{C(CH}_3)_2 )</td>
<td>2.0 h</td>
<td>9.7 d</td>
<td>4.8 ns</td>
</tr>
<tr>
<td></td>
<td>63.3</td>
<td>−200.1</td>
<td></td>
</tr>
<tr>
<td>( \text{CH=CH} )</td>
<td>2.5 d</td>
<td>2.2 d</td>
<td>1.4 min</td>
</tr>
<tr>
<td></td>
<td>56.0</td>
<td>−15.9</td>
<td></td>
</tr>
<tr>
<td>S</td>
<td>1.2 s</td>
<td>40 min</td>
<td>8.9 d</td>
</tr>
<tr>
<td></td>
<td>16.7</td>
<td>62.1</td>
<td>−191.3</td>
</tr>
<tr>
<td></td>
<td>2.6 y</td>
<td>1.4 y</td>
<td>46 ky</td>
</tr>
<tr>
<td></td>
<td>120.7</td>
<td>122.2</td>
<td>−3.8</td>
</tr>
</tbody>
</table>

A noteworthy observation regarding the extrapolation to rt of half-life versus the one-hour-half-life temperature is the situation in which the motors with substitution patterns X/Y equal O/O and –/CH=CH. Even though their half-lives differ marginally, there is a marked difference in their one-hour-half-life temperatures, and while the former is not wrong *per se*, its associated relative errors are
significantly larger than those of the one-hour-half-life temperatures. As such, the one-hour-half-life temperatures allow for a more accurate comparison of thermal barriers.

It should be noted that the design of second generation molecular motors is not limited to those shown in Figure 3.4, but is generally characterized by an isomerizable alkene connecting two rings of any size to which three aromatic moieties are fused and a single stereogenic centre usually at the alpha carbon with respect to the double bond (though not exclusively\cite{13,43}). As such, many variations have been investigated, both experimentally as well as theoretically.\cite{10,13,16,19,26,30,35}

In this chapter, second generation molecular motors will be studied computationally and, where possible, compared to experimental data or serve as the foundation for further experimental research.

**Calculated Behaviour of 2nd Generation Molecular Motors**

The pathways of the thermal helix inversions of second generation molecular motors have been studied computationally and marked differences are observed for the various designs. The large group of motors with six membered rings on both sides of the alkene have been studied in increasing detail, and are shown to share similar complex pathways which only differ in relative energies.\cite{10,19,30,44} The THI of this family goes through ring flips of each six membered ring, and two pathways are possible which differ in the order in which the upper and lower half rings flip.

![Calculated Behaviour of 2nd Generation Molecular Motors](image_url)

*Figure 3.5. Photo-chemical and thermal isomerizations of 5.*
A strong increase in speed was achieved by contracting both rings from six to five membered,[14] which reduced the flexibility in the rings and thus brought about an increase in overall rigidity. A beneficial side effect of such rigidity is a reduction in computation time due to a smaller amount of degrees of freedom, and the THI of such systems have been studied computationally.[16,26,45-47] The second generation molecular motor 5 is the smallest of its kind known to date, and serves well as an example. The experimental behaviour of 5 was studied by Pollard et al. and is summarized in Figure 3.5.[48] Irradiation of stable-5 brought about a PEZ indicated by a bathochromic shift in its UV-vis absorption spectrum, yielding a PSS consisting of approximately 75% MS-5 at low temperature. Increasing the temperature to room temperature allowed MS-5 to undergo a THI to stable-5', which was identical to stable-5 due to the symmetric lower half. An Eyring analysis revealed a Gibbs energy of activation of 79.1 kJ·mol⁻¹ for the THI.

The Gaussian software package was used to study the THI of motor 5 computationally.[49] Using the semi-empirical PM6 method the potential energy surface (PES) of 5 was scanned by restraining a single dihedral angle. One dihedral was found which describes the THI either without or with a small drop in energy along the scan (φ, Figure 3.6). The two reaction coordinates follow the same restricted dihedral though differ in the initial geometry of the scan, starting either from stable-5 (Figure 3.6 Left) or starting from metastable-5 (Figure 3.6 Right).

![Figure 3.6. Relaxed PES scan of 5. Scans using semi-empirical PM6 with a single dihedral angle constrained. φ = dihedral 10-7-9a'-1'. Left: starting from stable-5; Right: starting from MS-5 (IRC indicated by dotted line, vide infra).](image)

The minima and transition states (TSes) were optimized and the side views of their geometries are depicted in Figure 3.7 to clearly show the fjord region (Figure 3.5). The two pathways for the THI resemble gymnastic vaults (jumps) in which the upper half vaults over the lower half. As such the two TS’s are labelled kong (a kong vault is a leap over an object in which the upper body goes before the feet) and dash (a vault where the feet go before the upper body) and they differ significantly in energy (ΔΔ‡G° 19.3 kJ·mol⁻¹ in favour of TSdash-5`). The minima
and relevant TS were optimized using density functional theory (DFT), the B3LYP functional and 6-31G(d,p) basis set and remain geometrically close to those obtained by the semi-empirical method (Figure 3.8).

**Figure 3.7.** Side views of geometries of 5 optimized by PM6.

**Figure 3.8.** Front views of geometries of 5 optimized by DFT B3LYP/6-31G(d,p), HOMO-LUMO gaps of minima, IRC of THI, reaction coordinate of the thermal E–Z isomerization to guide the eye, arrows indicate the 360° rotational pathway.

The transition state (TS\textsubscript{dash-5有关部门}) was confirmed by the presence of a single imaginary frequency in its vibrational analysis and the transition state’s connectivity to the
two minima was verified by an intrinsic reaction coordinate (IRC) calculation (Figure 3.8), performed using the Firefly QC package,[50] which is partially based on the GAMESS (US)[51] source code, using the Gonzalez-Schlegel second order method. The other pathway going through the geometry of TSkong-5‡ was higher in energy and two imaginary frequencies were found for its TS. Optimization [DFT B3LYP/6-31G(d,p)] of this geometry eventually led to a structure identical to TSdash-5‡, exposing the existence of only a single pathway for THI for 5 at this level of theory. The IRC has been projected on the scan in Figure 3.6 to reveal the similarity between the two and highlight the functionality of the disconnected dihedral scan (Chapter 2).

Table 3.4. Calculated thermochemistry of 5 (DFT B3LYP/6-31G(d,p), rt).

<table>
<thead>
<tr>
<th></th>
<th>MS-5</th>
<th>TSdash-5‡</th>
<th>S-5</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔG° (kJ·mol⁻¹)</td>
<td>13.6</td>
<td>97.3</td>
<td>0</td>
</tr>
<tr>
<td>ΔH° (kJ·mol⁻¹)</td>
<td>13.5</td>
<td>90.7</td>
<td>0</td>
</tr>
<tr>
<td>ΔS° (J·mol⁻¹·K⁻¹)</td>
<td>−0.1</td>
<td>−22.6</td>
<td>0</td>
</tr>
</tbody>
</table>

The calculated behaviour agrees well with the experimental observations. Going from S-5 to MS-5 the HOMO-LUMO gap drops corresponding to the experimentally observed bathochromic shift (schematic excited state depicted in Figure 3.8) and the helicity of the overcrowded alkene is inverted.[48] MS-5 is calculated to have increased by 13.6 kJ·mol⁻¹ in energy with respect to the initial S-5. The THI (TSdash-5‡) returns the motor to the global minimum and the calculated barrier of this THI (83.6 kJ·mol⁻¹) agrees well with the experimentally determined barrier (79.1 kJ·mol⁻¹).[48]

Structure and Speed Relationship (1)

The relation between structure and speed has been the subject of extensive studies as shown in the introduction for the different ring sizes connected to the central overcrowded alkene and summarized in Figure 3.9, of which each group can be considered a family of motors within the second generation. The family with the largest upper half and rigidity in the lower half provide the highest barriers. Introduction of flexibility in the lower half facilitate easier passing during the THI and strongly increases the speed, however, removal of flexibility in both upper and lower half increases steric hindrance in the ground states which effectivly lowers the barrier for THI. Finally, the family with a rigid upper half to provide strain (and therefore high energy minima) and a flexible lower half to facilitate easy passing during the THI, allow for the largest increase in speed.
Figure 3.9. Increase in speed as a function of ring size. Numbers shown for X = CH₂: above arrow the reduction in one-hour-half-life temperature, below arrow increase in extrapolated rate at rt.

Structure–Speed Relationship 2

Another structure–speed relationship is found by Vicario et al. for the size of the substituent at the stereogenic centre (Figure 3.10). Increasing the size from a methyl (6), to an isopropyl to a tert-butyl group increases the steric strain more in the metastable state than in the TS of the THI, thus effectively lowering the thermal barrier. The substituent size series of Me<i-Pr<i-t-Bu is well known, and visually apparent, however, the phenyl substituent is commonly found to be significantly larger than the methyl substituent whereas for the molecular motor the phenyl substituent is found to bring about the smallest amount of steric strain. The former is based on the 1,3-diaxial interaction in cyclohexane (where the clash occurs with two groups, hydrogens, spaced equally by ~60°), and the latter is based on the clash between the pseudo-equatorially oriented substituent at the stereogenic centre with the lower half of the molecular motor (a single moiety). The calculated geometry of the metastable state (Figure 3.10) reveals that the phenyl is able to orient the short axis of its oblate spheroid shape towards the clashing lower half, thereby lowering the steric strain to below that of the methyl substituted motor. A methoxy group extends only in a single direction (not in two like phenyl) and is therefore expected to exhibit a consistent substituent effect. The 1,3-diaxial interaction of the methoxy group is smaller than that of methyl, which predicts a methoxy substituted motor to be slower than the methyl substituted benchmark motor 6.

Figure 3.10. Increase in speed as a function of stereocentre substituent size, above arrow the reduction in one-hour-half-life temperature, below arrow the increase in rate at rt. Calculated side-view of metastable state of Ph substituted motor [DFT B3LYP/6-31G(d,p)].

The THI of the second generation motor substituted with a methoxy group at the stereogenic centre (7) was investigated theoretically (DFT B3LYP/6-31G(d,p), Figure 3.11). TS\text{dash-}7^\ddagger was found to be the only relevant pathway for THI, with
The甲oxy-rotamers of each minimum as well as the TS were found to differ significantly in energy, warranting a comparison of their thermochemistry. As expected, three methoxy-rotamers were found for stable-(S,M)-7 (methoxy torsion angles (φ, Figure 3.11) 171.3°, −50.0°, 62.4°) and from their calculated relative Gibbs energies at room temperature (ΔG° 0.0, 0.9, 10.1 kJ·mol⁻¹, respectively) their Boltzmann distribution can be calculated (1.00 : 0.69 : 0.02, respectively). For MS-(S,M)-7 a slightly more offset Boltzmann distribution was found (φ: 170.3°, −59.7°, 83.0°; ΔG° with respect to stable-(S,M)-7: 7.3, 9.9, 33.5 kJ·mol⁻¹; ratio of MS rotamers: 1.00 : 0.34 : 0.00). Of the three methoxy-rotamers of TS_dash-7‡ (φ: 159.4°, −64.7°, 80.2°) one is strongly favoured over the others, indicated by their difference in energy with respect to MS-(S,M)-7 (Δ‡G° 101, 112, 93.8 kJ·mol⁻¹, respectively). This provides a calculated barrier for the THI of 7 of 93.8 kJ·mol⁻¹, corresponding to a one-hour-half-life temperature of 23.8 °C. This predicts motor 7 to be ten times slower than the methyl substituted benchmark 6 which agrees with the hypothesis that a methoxy group imposes less steric hindrance than a methyl group. Pijper et al. investigated an enantioselective route towards second generation molecular motors which allowed them to synthesize enantiopure (S,M)-7.[18] Their experimental kinetic study revealed that the calculated barrier agrees well with the experimental barrier (Δ‡G° 91.3 kJ·mol⁻¹, T½=1h 15.9 °C) and reaffirms the structure–speed relation shown in Figure 3.10.

Figure 3.11. THI of 7. Side-view of optimized geometries [DFT B3LYP/6-31G(d,p)] of 7 as seen from the stereocentre with the plane of the fluorenyl moiety perpendicular to the plane of the paper. Methoxy group torsion angle indicated by φ.

The availability of an enantiopure second generation molecular motor of known absolute chirality provides an opportunity to establish an unequivocal relationship between the motor’s experimental circular dichroism (CD) spectrum and its calculated CD spectrum. Such a relationship would strongly support an assignment of molecules of unknown absolute stereochemistry using the correlation between experimental and calculated CD spectra,[55,56] and has previously been achieved for motor 3 and three of its analogues all with six membered rings on both sides of the overcrowded alkene.[19] It would, however, be useful to ascertain the strong
correlation between experimental and calculated CD also for the family of second generation motors with five membered rings on both sides of the double bond. Hence, CD spectra for (S,P)-7 were calculated using the same methods as reported by Cnossen et al.\cite{19} and compared to the experimental CD spectrum provided by Pijper et al.\cite{18} However, in the current case we have found several rotamers contributing to the stable state of motor 7. Dissolution is expected to bring about a shift in the Boltzmann distribution, since a very small change in Gibbs energy can bring about a significant shift in the equilibrium. Therefore, a solvent correction in heptane was performed using IEFPCM, which indeed brought about small changes in the distribution (Table 3.5), although the barrier for THI was practically unchanged (less than 0.2 kJ·mol\(^{-1}\)). Additionally, the thermochemistry was corrected for the temperature at which the experimental CD-spectrum was recorded (−10 °C), however, the correction left the distribution nearly identical (Table 3.5).

### Table 3.5. Heptane corrected distribution and barriers of 7 (DFT B3LYP/6-31G(d,p), IEFPCM).

<table>
<thead>
<tr>
<th>stable-(S,M)-7</th>
<th>MS-(S,M)-7</th>
<th>TS_dash-7‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\Phi (^\circ))</td>
<td>Boltzmann ratio at rt</td>
<td>Boltzmann ratio at -10 °C</td>
</tr>
<tr>
<td>171.3</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>-50.0</td>
<td>0.47</td>
<td>0.50</td>
</tr>
<tr>
<td>62.4</td>
<td>0.01</td>
<td>0.01</td>
</tr>
</tbody>
</table>

**Figure 3.12.** Left: Calculated CD-spectra of stable-(S,M)-7 and MS-(S,P)-7. Right: Boltzmann corrected CD-spectra (—) and the PSS corrected spectrum (········) overlaid on the experimental CD-spectrum of stable-(S,M)-7 (―) and the PSS of (S)-7 (········) adapted with permission from [18].

Using time-dependent (TD) DFT the CD-spectrum of the major rotamer of stable-(S,P)-7 was calculated using one, two and no diffuse functions and no large differences were found, furthermore, triplet states did not contribute to calculated spectra. Therefore, to conserve computational costs, the CD spectra were calculated without added diffuse functions and only the first thirty singlet states were
computed of each rotamer (Figure 3.12 left, Gaussian line broadening of 0.2 eV applied). For both stable as well as MS 7, the calculated CD-spectra of its relevant rotamers were found to be very similar, nonetheless, the Boltzmann corrected CD-spectrum of each was obtained (Figure 3.12). The calculated corrected CD-spectrum of stable-(S,M)-7 agrees with the experimentally obtained spectrum of that enantiomer by Pijper et al. (Figure 3.12 right). The experimental CD-spectrum of the PSS showed correlation to the calculated corrected spectrum of MS-(S,M)-7, and an additional correction of the calculated spectra to the experimental PSS ratio further improved the correlation (Figure 3.12 right).

**Structure–Speed Relationship 3**

A third structure–speed relationship can be found in the size of the rigid moiety in the fjord region (Figure 3.13). Modifications with respect to the benchmark motor 6 with a naphthyl moiety in the fjord regions have had various reasons: simplification of the synthesis of molecular motors, improved induction of chiral nematic phases, increase in speed, and improved self-assembly into monolayers. All changes in structure led to changes in speed, however, a relationship between size and speed is not directly apparent. For example, the size (by volume or mass) of the substituent on benzene (methyl, phenyl and methoxy in, respectively, 5, 8 and 10) does not correlate linearly with the speed of the motor.

**Figure 3.13.** Increase in speed as a function of fjord region hindrance, above arrow the reduction in one-hour-half-life temperature, below arrow the increase in rate at rt. On top: Corresponding side-view of optimized geometries of the calculated TS [DFT B3LYP/6-31G(d,p)] as seen from the fjord region with the plane of the fluorenyl moiety perpendicular to the plane of the paper.
To gain insight into this structure–speed relationship, their THI’s were studied computationally and the calculated TS’s are shown in Figure 3.13. The calculated barriers for THI are compared to the experimental barriers (Table 3.6) and reveal a similar trend, however, the calculated barrier of benzo-thiophenyl substituted motor 9 shows a significant deviation from the experimental value (>8 kJ·mol⁻¹). This might be due to additional hybridization or diffusion on sulfur yielding an error in the calculated barrier, although the deviation could also stem from the extrapolation of the experimental Gibbs energy from −90 °C to rt. Performing the thermochemical calculation at −90 °C lowers the deviation to 4.5 kJ·mol⁻¹ (Δ‡G at 183.3 K; exp: 56.4 vs. calc: 60.9 kJ·mol⁻¹).

To evaluate the effect of the steric hindrance in the fjord region, angles between the rigid aromatic moieties in the TS’s of 6, 5, 8, 9 & 10 were obtained from the calculated geometries (A–B and B–C, Figure 3.13 and Table 3.6). The folding of the fluorenyl moiety (A–B°) as well as the folding of the two clashing aromatic moieties in the fjord region (B–C°) correlates strongly with the experimental one-hour-half-life temperature and Gibbs energy of activation (Pearson’s r: A–B −0.856 and −0.623; B–C −0.749 and −0.792, respectively).[^59] The folding of both A–B and B–C are the result of steric hindrance in the fjord region; a larger upper half featuring a group such as naphthalene has to fold further away from the lower half to allow it to pass. At the same time, a larger upper half exerts more strain on the lower half forcing the fluorenyl further away from planarity. Hence, the closer to planarity groups A, B and C can remain during the TS, the lower the barrier for THI will be.

**Table 3.6.** Summary of the barriers for THI and two characteristic calculated properties of several motors with varying hindrance in the fjord region.

<table>
<thead>
<tr>
<th></th>
<th>6</th>
<th>5</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Texp at t½ =1 h (°C)</td>
<td>−3.8</td>
<td>−21.7</td>
<td>−44.0</td>
<td>−89.9</td>
<td>−113.5</td>
</tr>
<tr>
<td>Δ‡G°exp (kJ·mol⁻¹)</td>
<td>86.1</td>
<td>79.1</td>
<td>76.3</td>
<td>71.1</td>
<td>51.4</td>
</tr>
<tr>
<td>Δ‡G°calc (kJ·mol⁻¹)</td>
<td>88.3</td>
<td>83.6</td>
<td>76.0</td>
<td>62.7</td>
<td>55.7</td>
</tr>
<tr>
<td>A–B folding in TS (°)</td>
<td>151.5</td>
<td>152.8</td>
<td>155.5</td>
<td>158.0</td>
<td>156.0</td>
</tr>
<tr>
<td>B–C fjord angle in TS (°)</td>
<td>108.4</td>
<td>121.7</td>
<td>127.4</td>
<td>122.3</td>
<td>131.1</td>
</tr>
</tbody>
</table>

**Combining structure–speed relationships to improve speed**

With three different structure–speed relationships identified, it would be of significant interest whether the structural changes can be combined and thereby scale the speed of the molecular motor by a combination of the individual scalars. Three potential combinations of scalars are foreseen: (i) a threshold situation where
the largest individual scalar defines the combined result; (ii) addition of the scalars providing a combined summed scalar; (iii) multiplication of the individual scalars providing the largest change in the combined scalar. Looking for an increase in speed, multiple combinations of changes are optional. To test this approach the changes are evaluated in small steps starting with motor 11 (Figure 3.14).

**Figure 3.14.** Structures and corresponding calculated side-view geometries of 11.

**Figure 3.15.** Structural changes to benchmark 6. Red numbers above arrows indicate increases in rate at rt based solely on calculated barriers for THI. Below arrow experimental change in rate at rt and one-hour-half-life temperature.[16,26,48]

MS-11 was calculated to be 25.7 kJ·mol⁻¹ higher in energy than stable-11, and the THI was found to follow the dash pathway with TSdash-11‡ to be 57.8 kJ·mol⁻¹ high with respect to MS-11. Based on the calculated barriers of motors 6 and 11, an increase in rate at rt of nearly thirty thousand times is predicted. With respect to the scalars for the rates of the individual structural changes (Figure 3.15), the combination of these changes in structure achieves the maximum increase in speed – more than the multiplication of the separate scalars. The synthesis and kinetic analysis of 11 by Bauer et al. allowed for the experimental verification of the calculated scalars.[26] The experimental barrier for the THI of 11 (Δ‡G° 58.4 kJ·mol⁻¹, T½=1h −89.9 °C) agrees strongly with the calculated barrier. The experimental scalars for the rates of the structural modifications deviate variably from the calculated scalars (Figure 3.15); small variations in Gibbs energies of
activation result in much larger variations in rate, being on an exponential scale. Experimentally, the scalar for the combination of the two structural changes is still larger than the addition of the individual scalars; however, it is slightly smaller than a multiplication of the two.

Figure 3.16. THI pathways for 12. Top: side-views of calculated geometries corresponding to the structures of 12 directly underneath with the connecting TS’s (TS1, TS2 & TS3) in between (for the remainder of the chapter all side-views oriented with the overcrowded alkene on the y-axis and appending carbons in the lower half on the z-axis with the stereogenic centre in front, as well as all hydrogens omitted for clarity). Bottom left: reaction coordinate diagram for THI’s of 12 with abbreviated descriptors.

<table>
<thead>
<tr>
<th></th>
<th>MS-A</th>
<th>TS1</th>
<th>MS-T</th>
<th>TS2</th>
<th>TS4</th>
<th>S-S</th>
<th>TS3</th>
<th>MS-S</th>
<th>TS5</th>
<th>S-A</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\Delta G^\circ$</td>
<td>36.7</td>
<td>67.0</td>
<td>33.6</td>
<td>46.6</td>
<td>47.1</td>
<td>22.5</td>
<td>47.2</td>
<td>34.5</td>
<td>85.3</td>
<td>0.0</td>
</tr>
<tr>
<td>$\Delta^2 G^\circ$</td>
<td>30.3</td>
<td>12.9</td>
<td>13.4</td>
<td>24.7</td>
<td>24.7</td>
<td>50.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The next logical step is to include all structure–speed relationships in the design of the molecular motor. Figure 3.9 and Table 3.3 show that motor 12 (Figure 3.16) provides the largest increase in speed with respect to benchmark 6, furthermore, motor 12 is the fastest second generation molecular motor reported at the moment of writing. Before combining all elements and studying the novel motor’s behaviour, it would be helpful to identify the pathway for THI of 12, which has an increased complexity – compared to the family with five-membered rings on both
sides of the alkene – due to the flexibility in the lower half. Two separate pathways were found for 12 (DFT B3LYP/6-31G(d,p), Figure 3.16) which reflects a behaviour similar to that observed for the family of second generation motors with six membered rings on both sides of the overcrowded alkene as described by Cnossen et al.\textsuperscript{[19]} Both pathways for the THI of 12 start by a reorientation of the stereogenic methyl group, and are followed by subsequent flips of the upper and lower half, although differ in the order in which the flips take place. The pathway in which the lower half flips first was calculated to possess a barrier for THI of 51.6 kJ·mol\textsuperscript{−1} (blue reaction coordinate going through MS-Syn-12, Figure 3.16) whereas the pathway in which the lower half flips second possesses TS’s significantly lower in energy. The barrier for THI through S-Syn-12 (green reaction coordinate, Figure 3.16) depends on which isomer is formed by the PEZ – 30.3 kJ·mol\textsuperscript{−1} for MS-Anti-12 and 24.7 kJ·mol\textsuperscript{−1} for MS-Twist-12, MS-Syn-12 or S-Syn-12 (thermochemistry summarized in Table 3.7). The experimental barrier for THI as determined by Klok\textsuperscript{[42]} (26.0 kJ·mol\textsuperscript{−1}) agrees sufficiently well with either calculated barrier for the optimal pathway, additionally, the low barrier barred spectroscopic characterization of the metastable state. The exact pathway was therefore not fully identified.

**Figure 3.17.** THI pathway for 13. Top: side-views of calculated geometries corresponding to the structures of 13 directly underneath with the connecting TS’s (TS1, TS2 & TS3) in between. Bottom: reaction coordinate diagram for THI of 13 with abbreviated descriptors and ΔG°.
In molecule 13 the three adaptations with respect to benchmark 6 are combined and its calculated thermal isomerizations are shown in Figure 3.17. The pathway for THI of 13 was found to be identical to 12, and therefore its barrier dependent upon knowledge of the isomer produced by a PEZ – 52.8 kJ·mol⁻¹ for MS-Anti-13 and 37.9 kJ·mol⁻¹ for MS-Twist-13 or S-Syn-13. Either barrier is clearly higher than those calculated and measured for 12, which suggests that the structure–speed relationships of one family (so far determined for that with five membered rings on both sides of the overcrowded alkene) cannot readily be transferred to another family. Insurmountable problems in the synthesis of compound 13 prevented the experimental determination of its barrier for THI.[60]

It is reasonable to attribute the synthetic problems with 13 to the tert-butyl group and not the xylene moiety, since the former is supposed to increase steric hindrance and the latter to reduce it. Synthetically feasible modifications to increase the speed should therefore focus on the rigid aromatic moiety in the fjord region. A reduction in steric hindrance beyond those shown in Figure 3.13 has been realized by Geertsema et al. in the form of an unsubstituted benzene moiety applied to the families of second generation motors with a six membered ring in the upper half.[61] For those with a six membered ring in the lower half, the adaption resulted in an undesired oxidation reaction, however, the orbital overlap for the oxidation reaction was unfavourable for those with a seven membered ring and were observed to exhibit typical motor behaviour. Unexpectedly, a retardation was observed with respect to its naphthyl substituted counterpart (107 vs 103 kJ·mol⁻¹). The thermal behaviour of molecule 14 was calculated to evaluate the effect of the size of the rigid moiety in the fjord region on the speed of the fastest family of second generation molecular motors (Figure 3.18).

![Figure 3.18. THI of 14: Structures and corresponding calculated side-view geometries.](image)

A scan of the PES of 14 revealed a significant difference with respect to its analogue 12; where for 12 intermediates with varying degrees of folding of the two halves were found, only two minima were found and calculated for 14, with an anti-folded geometry as its global minimum. Assuming the metastable state syn-(S,P)-14 can be produced photochemically from stable anti-(S,M)-14, two direct pathways are calculated for a THI to return the metastable state to the global
The THI through $\text{TS}_{\text{syn}}-(S)-14^\ddagger$ much resembles the rate determining TS of the lowest energy pathway of 12 (see TS3-$12^\ddagger$ in Figure 3.16), however, it was calculated to be the highest energy pathway for 14 measuring 62.8 kJ·mol$^{-1}$. The THI pathway through $\text{TS}_{\text{twist}}-(S)-14^\ddagger$ is calculated to be the lowest at 51.9 kJ·mol$^{-1}$. This is a drastically higher barrier than that calculated and measured for motor 12, which agrees with an increase in barrier as observed by Geertsema et al.$^{[61]}$, although in this case it is a much larger increase. Consequently, these findings indicate an opposite structure–speed relationship – of the steric size of the rigid aromatic moiety in the fjord region – for the second generation molecular motor families with a flexible six or seven membered lower half in contrast to the family with five membered rings on both sides as shown in Figure 3.13.

The series of motors for which the structure–speed relationship was exposed in Figure 3.13 did not include an unsubstituted benzene moiety in the fjord region. To ascertain that even such a comparably small moiety conforms to the overall trend, the THI of overcrowded alkene 15 (Figure 3.19) was calculated and its barrier was found to be remarkably lower than any of its analogues presented in Figure 3.13 ($\Delta G^0 21.7$ kJ·mol$^{-1}$). Based on the calculated barrier, this modification in 15 with respect to benchmark motor 6 is expected to increase the rate for THI by more than a quarter trillion times ($2.9 \cdot 10^{11}$), and lower the one-hour-half-life temperature to −216 °C, which would make it even faster than motor 12 (Table 3.3) and thereby the fastest motor to date. Based on the results of Geertsema et al.$^{[61]}$ one might be concerned for a potential degenerative oxidation pathway, however, experiments on overcrowded alkenes bearing a related structural motif did not reveal such a problem (see Chapter 7), making overcrowded alkene 15 a promising candidate for an experimental study.

Figure 3.19. THI of 15: Structures and corresponding calculated side-view geometries.

The calculated PES of overcrowded alkene 16 (Figure 3.20) exposes the limits of structural modifications, made to increase speed in this family of second generation molecular motors. Akin to the combination of structure–speed relationships in Figure 3.15, the combination of the tert-butyl group at the stereogenic centre and the benzene moiety in the fjord region of molecule 16 serves to increase the speed...
of the THI more than either modification individually. The barrier for THI of 16 has been calculated to be 19.6 \text{kJ}\cdot\text{mol}^{-1}, predicting an increase in rate of more than a half trillion times (6.9\cdot10^{11}), and lower the one-hour-half-life temperature to \(-228^\circ\text{C}\). This agrees with the experimental findings for the combinatorial motor 11 (vide supra): the increase in speed is larger than the addition of the scalars for individual modifications, though not as high as a multiplication of those scalars. The low barrier suggests molecule 16 to be an interesting target, however, the calculated PES reveals a problematic drawback with respect to unidirectional yield.

![Figure 3.20. THI of 16: Structures and corresponding calculated side-view geometries.](image)

All second generation molecular motors of the family with five membered rings on both sides of the alkene which have been discussed so far and have been studied experimentally strongly favour the stable state, and in the absence of a light source no metastable isomer is observed spectroscopically. Such an absence suggests the population of the metastable isomer to roughly be smaller than two per cent, and the difference in Gibbs energy between the stable and metastable isomer to be larger than 9.5 \text{kJ}\cdot\text{mol}^{-1}. For overcrowded alkene 15 this difference is calculated to be 7.7 \text{kJ}\cdot\text{mol}^{-1} predicting a small population of four per cent of the metastable isomer. However, for molecule 16 a difference of only 2.3 \text{kJ}\cdot\text{mol}^{-1} is calculated, resulting in 28\% of metastable isomer to be present under equilibrium conditions. Irradiation of such a mixture lowers the photochemical yield due to the presence of the metastable isomer (assuming comparable absorptivities for the stable and metastable state) and could even result in a partial reverse rotation of the metastable isomer (depending on the quantum yields of the two processes) lowering the unidirectional yield. Such properties are undesirable and point to a limit in how far structural modifications serve their purpose.

**Quaternization of the stereogenic centre**

The presence of a stereocentre is essential in second generation molecular motors for unidirectional rotation. The orientation of the substituent at the stereocentre affects, through steric hindrance, the energy of the two diastereoisomers, resulting in a stable state – with a pseudo-axial orientation of the substituent – and a metastable state in which the substituent is oriented pseudo-equatorially.
Overcrowded alkenes with two identical substituents at that position, such as two hydrogens or two methyl groups, can therefore not function as a unidirectional rotor (assuming achiral light is used for the PEZ).

Figure 3.21. Quaternized second generation molecular motors 17–22. Side-view of the calculated geometries [DFT B3LYP/6-31G(d,p)] of the metastable (MS) and stable (S) diastereoisomers as well as the transition state (TS).

A significant difference in size between two substituents suggests a significant difference in energy between the two isomers, and the larger the difference in size the larger the difference in energy (Figure 3.10), however, this trend does not follow for overcrowded alkenes 15 and 16 (vide supra). Nonetheless, if one follows the general trend – in order to retain a significant difference in energy between the diastereoisomers while at the same time one is interested in a quaternization of the stereogenic centre – the hydrogen atom has to be replaced by a small group. A fluorine atom exhibits one of the smallest A-values, for which it was selected, leading to a computational study of the series of second generation molecular
motors shown in Figure 3.21. The series is paralleled to the series shown in Figure 3.13 of which the speed spans several orders of magnitude, to reveal a suitable quaternized candidate for an experimental study. The calculated geometries of 17–22 are shown in Figure 3.21 exhibiting a large consistency in configuration between the different molecules. The global minimum, i.e. the stable isomer, for all quaternized motors is found to orient the fluorine at the stereogenic centre pseudo-equatorially towards the lower half analogous to the orientation of the stereogenic hydrogen in common second generation molecular motors. In the same way were all local minima, i.e. the metastable isomers, found to orient the stereogenic fluorine pseudo-axially. MS-17–22 were all connected to stable-17–22 by two THI’s of which the dash pathway was consistently found to be lower in energy. The calculated thermochemistry (Table 3.8) shows the barrier for THI to decrease going from 17 to 22, as expected from the behaviour of 5–10 and 15, however, the individual barriers of 17–22 are significantly higher than those of their hydrogen substituted analogues (Table 3.6). The barriers for 17–19 are of such magnitude that high temperatures would be required to bring about their THI which might lead to side-reactions (see Chapter 5 for such reactions). The increase in energy is caused by additional steric hindrance of the fluorine atom with the lower half. While the major part of the barrier stems from the hindrance of the moieties in the fjord region, the smallest substituent at the stereogenic centre comes into close proximity of the lower half as well (compare TS’s in Figure 3.21 with Figure 3.13). The result is that the lower halves of TSdash-17–22‡ require a larger degree of folding than their hydrogen substituted analogues.

Due to the fluorine replacing the stereogenic hydrogen the difference in Gibbs energy between the two configurations has dropped, leading to a measurable population of the metastable state under equilibrium conditions (Table 3.8), which might be problematic as discussed for overcrowded alkene 16 (vide supra). The drop in the difference in energy agrees well with the reduction in the difference in substituent size at the stereogenic centre, and suggests that a population of the metastable configuration can be reduced by, for example, a replacement of the methyl group by a tert-butyl group.

Table 3.8. Calculated thermochemistry of motors 17–22 (DFT B3LYP/6-31G(d,p), in kJ·mol⁻¹).

<table>
<thead>
<tr>
<th>Molecule</th>
<th>17</th>
<th>18</th>
<th>19</th>
<th>20</th>
<th>21</th>
<th>22</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔG° MS</td>
<td>8.7</td>
<td>9.5</td>
<td>9.3</td>
<td>4.3</td>
<td>6.5</td>
<td>6.2</td>
</tr>
<tr>
<td>Boltzmann population of MS at rt (%)</td>
<td>2.8</td>
<td>2.0</td>
<td>2.2</td>
<td>15</td>
<td>6.4</td>
<td>7.3</td>
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<tr>
<td>ΔG° TS</td>
<td>133</td>
<td>127</td>
<td>121</td>
<td>93.2</td>
<td>93.0</td>
<td>46.5</td>
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<tr>
<td>Δ²G° TS</td>
<td>124</td>
<td>118</td>
<td>111</td>
<td>88.9</td>
<td>86.5</td>
<td>40.3</td>
</tr>
</tbody>
</table>
The series of molecules shown in Figure 3.10 were compared for their apparent stereogenic centre substituent size effect and compared to the 1,3-diaxial interaction in cyclohexanes. A similar comparison can be made for molecules 18, 19, 21 and 22 which vary in their substituent size on benzene in the fjord region (methyl, chlorine, methoxy and hydrogen, respectively). A-values for the 1,3-diaxial interaction predict the sizes to be in the order of Me>MeO>Cl>H, whereas for the barrier for THI the chlorine is found to cause more steric hindrance than the methoxy group (Me >Cl>MeO >H, Table 3.8). This deviation stems from the C–X bond lengths which is about forty picometer longer for chlorine than for the oxygen in the methoxy group. While this actually brings about less 1,3-diaxial hindrance in chlorocyclohexane where the chlorine is extending away, it does the opposite in the TS\textasciitilde19, where the atom is pushed into the lower half (Figure 3.21).

From the quaternized second generation molecular motors under theoretical investigation here, compound 21 appears to possess the most useful characteristics for a subject of an experimental study. Its barrier for THI is neither too high nor too low with a predicted one-hour-half-life temperature of 21 °C, and of the faster candidates motor 21 has the lowest Boltzmann population of the metastable diastereoisomer at room temperature which not only ascertains a good unidirectional yield, but also facilitates a clean (or cleaner) NMR spectrum of the initial state. Several of these quaternized molecular motors have recently been synthesized by Peter Štacko and an experimental study has been undertaken to elucidate their dynamic behaviour.[62,63]

**Chirality Transfer to Biphenyl**

As shown throughout this chapter, overcrowded alkenes are forced from planarity and thereby made to adopt a helical structure which can be either $M$ or $P$. It is the steric hindrance caused by the largest substituent at the stereocentre which determines which of the two helicities is preferred, however, an absolute point chirality of the stereocentre cannot be inextricably coupled to a specific helicity (e.g. one cannot assign $R=\text{P}$ for molecular motors, due to the differing rules for either assignment). Nonetheless, there is a relation between the two chiral properties that is observed for all molecular motor based on overcrowded alkenes. The drive to minimize steric hindrance puts the larger substituent at the stereogenic centre in a pseudo-axial orientation, allowing the substituent to point away from the plane of the overcrowded alkene. The overall strain is minimized if the rigid moiety in the fjord region points in the same direction away from the plane of the overcrowded alkene, and the two groups (substituent at the stereocentre and the rigid moiety in the upper half) can be considered to be syn folded with respect to
the plane through the overcrowded alkene, whereas for the metastable state these groups can be considered to be anti folded. This relationship is evident upon examining any structure of the stable diastereoisomer of a molecular motor, which will always show the two groups in the upper half oriented in the same direction. From this relationship, it can be seen that the absolute chirality of the stereogenic centre dictates the preferred helicity of the overall molecule, thereby transferring point chirality to helical chirality. To add an additional level of transfer of chirality, molecule 23 (Figure 3.22) was designed with a biphenyl moiety in the fjord region of the upper half. To explain the induced chirality in the biphenyl moiety it would be helpful if the descriptors for biaryls are first specified clearly.

![Figure 3.22](image)

**Figure 3.22.** Stable and metastable structures of (S)-23 with corresponding front- and top-view geometries and schematic representations with the helicities specified [subscripts indicate axial helicity (a) and helicity of the major chromophore including the overcrowded alkene (=)].

The resolvability of biphenyl atropisomers depends on the size of their ortho substituents, where large substituents yield high barriers for atropisomerization (the racemization of the biphenyl conformations through biaryl rotation). The steric hindrance of large ortho substituents forces those biphenyls into a perpendicular conformation (for example in 24 in Figure 3.23) which are then found as enantiomeric pairs. Following CIP rules, the chirality of these atropisomers can be assigned by two different methods demonstrated in Figure 3.23: (i) axial chirality is assigned the designators $R_a$ and $S_a$ ($a$ for axial) and; (ii) conformational chirality involving two torsional energy hollows where a perpendicular conformation with a torsion angle of negative sign is indicated by $M$ and those of positive sign by $P$. For our purpose, we also need to consider the stereochemical assignment of unhindered biphenyls. The $\pi$-conjugation in a biphenyl molecule is maximized at a torsion angle of 0°, whereas the steric repulsion between the ortho substituents is minimized at a torsion angle of 90°, resulting in a torsion angle of ~44° for unsubstituted biphenyl. The planar and perpendicular conformations are transition states and their barriers are measured to be 6.0 and 6.5 kJ·mol$^{-1}$, respectively. Due to bearing only hydrogens CIP priority rules are not
applicable; hence, neither axial chirality nor conformational chirality can be assigned. However, the two discriminate conformations are each other’s mirror images and thus part of an enantiomeric pair. These conformations are clearly helical, and therefore they are assigned using the helicity rule which designates a left handed helix minus (M) and a right handed helix plus (P), in the same way we assign the overall helicity of our overcrowded alkenes.[65] Even though the enantiomers of biphenyl can only be resolved at temperatures below twenty Kelvin (half-life of at least one hour based on reported barriers, vide supra), they can be brought out of equilibrium – for example in chiral doping of nematic liquid crystals[69] – which makes their helicity a key characteristic. The use of the designators M and P for both helicity as well as conformational chirality becomes confusing in a molecule such as 26 (Figure 3.23) where the subscripts h and c are added to the descriptors, respectively, for clarity. The torsion angles of unhindered biphenyls deviate from perpendicular and can therefore be subjected to the Klyne-Prelog torsion angle definitions (syn (s) = 0°–±90°, anti (a) = ±90°–180°, clinal (c) = 30°–150°/−30°–−150°, periplanar (p) = −30°–30°/−150°–150°).[70] Four descriptors have hereby become available to describe a conformation of 26, where \( R_a / S_a \) and \( M_c / P_c \) are redundant, and a combination of either of those with the helicity descriptors (\( P_h / M_h \)) is able to uniquely characterize one of the four conformers, while a unique characterization is also achieved by a single Klyne-Prelog definition for substituted biphenyls. To avoid confusion between the helicity and conformational chirality designators, the latter will not be used here.

Figure 3.23. Biphenyls 24, 25 and 26 with the stereodescriptors for helicity, axial and conformational chirality shown on their schematic representations.

With the necessary stereodescriptors specified, we can return to the assignment of overcrowded alkene (S)-23 (Figure 3.22). For both the stable and metastable isomer only a single geometry was found, where for each the helicity of the biphenyl corresponded to the helicity of the motor (specifically the major chromophore including the overcrowded alkene). A PES scan of the biphenyl rotation (BR) revealed the geometries with the biphenyl helicity opposite to the motor helicity to
be significantly higher in energy and close to the BR-TS, due to steric hindrance of the phenyl group with the lower half. In this way the steric environment of the motor chromophore governs the torsional energy hollows of the biphenyl, adding another layer of chirality transfer to the system.

Chirality transfer in a molecular motor was experimentally realized in motor 8 (Figure 3.24, the biphenyl helicity matches the motor helicity in all structures, consequently, a single helicity descriptor is sufficient) for which, with respect to motor 23, one methoxy group was added for a synthetic purpose and another methoxy group to provide a spectroscopic handle for the biphenyl rotation. The metastable state was found to be short-lived at rt ($t_{1/2} = 4.5$ s, vide supra) and for both diastereoisomers only a single set of NMR resonances was observed indicating either a strong preference for a single atropisomer ($R_a / S_a$) or fast exchange due to a low barrier for BR. Subsequent calculations pointed to the latter, providing a calculated barrier for BR of stable-$(S,M)$-8 of only 32.3 kJ·mol$^{-1}$ and a ratio of 1.0 : 1.4 for $R_a : S_a$ at rt.

![Figure 3.24. Behaviour of biphenyl motor 8. Adapted from [57].](image)

The possibility of transfer of chirality from the motor to the biphenyl as studied in motor 8 brings a whole range of potential applications into view (Figure 3.25). An observation made from the calculated THI of 8 was retention of the axial chirality from for example MS-$(S,P,S_a)$-8 to stable-$(S,M,S_a)$-8, which could not be observed experimentally due to the low barrier for BR. The PEZ was not calculated though it was hypothesized that retention of axial chirality might also take place during PEZ, which would facilitate a fixed axial chirality throughout the rotational cycle. A fixed axial chirality implies that only one face of the phenyl group consistently faces the lower half of the motor, analogous to the tidal locking of the moon to the earth where only one face of the moon consistently faces earth. To achieve tidal locking in this system the barrier for BR has to be raised significantly above that for THI, for example by the introduction of two sizeable ortho substituents such as the methoxy groups in 27 (Figure 3.25). Recently, Štacko et al. described a working
tidally locked system (28) based on a biaryl substituted molecular motor where one face of the naphthyl group continuously faces the lower half.\textsuperscript{[62,71]}

![Molecular structures](image)

**Figure 3.25.** Potential biphenyl chirality transfer applications. Tidal locking (27, 28), LC dopant (29) and catalyst/ligand (30) (R groups are intentionally not shown to be location specific).

Motor 8 was initially designed to possess improved doping abilities in a nematic liquid crystalline phase (LC) with respect to benchmark 6,\textsuperscript{[72]} however, the unanticipated lack of bistability at rt of 8 hindered its potential as a switchable chiral dopant.\textsuperscript{[57]} The first structure–speed relationship shown in Figure 3.9 offers a solution by increasing the size of the five membered ring in the upper half to a six membered ring (29, Figure 3.25). The transfer of chirality of the dopant to the liquid crystalline phase might be maximized by creating the strongest resemblance of dopant to LC mesogen, achieved by adding cyano and alkyl groups to the para positions of the biphenyl moiety.\textsuperscript{[72]} The investigation of systems such as 8 and 29 as switchable chiral dopants is currently ongoing.

A combination of chirality transfer capabilities and bistability in a molecular machine provides the ideal components for switchable asymmetric catalysis.\textsuperscript{[73]} Two heteroatoms in the ortho positions with respect to the biaryl bond in combination with the restricted rotation around that bond allow molecules 30–32 to mimic the chiral ligands based on binaphthyl.\textsuperscript{[74–77]} Molecules 31 and 32 can be derived from 30 and are expected to function as chiral ligands, their synthesis can, however, be quite challenging and it would therefore be useful to justify the effort a priori by supporting the design of their rotational behaviour using computational methods.

**Bianisole derived molecule 30**

Even though overcrowded alkene 30 is not expected to function as a ligand, an understanding of its behaviour would serve as a model or reference point for subsequent derivatives. A PES search revealed four diastereoisomers of 30 (Figure 3.26) analogous to those found for motor 8 (Figure 3.24), connected by thermal isomerization pathways. The metastable (MS) isomers are connected to stable (S)
isomers by a thermal helix inversion (THI) during which their axial chirality remains unchanged. In both the stable and metastable state two diastereoisomers are found differing in axial chirality which can interconvert through two distinct biaryl rotation (BR) pathways. The pathways for BR go through a periplanar conformation of the biaryl with the two methoxy groups either in a syn- or an anti-conformation as illustrated by the four calculated geometries in Figure 3.26 (TSBR-30‡, right, middle column).

\[ \text{Motor 28 exhibits retention of axial chirality during the photochemical } E-Z \text{ isomerization (PEZ) which is a feature also desired of motor 30, however, the computation of this process is cost-expensive and it would therefore be more practical to investigate the process solely experimentally. If axial chirality is maintained during the PEZ, the distribution for } S_a \text{ vs } R_a \text{ is expected to be identical} \]
in MS after PEZ as it was before in S. Two thermal isomerization pathways are available to MS-(S,P,Sa)-30; the motor can undergo a THI through TS_{THI}-(S,Sa)-30 to S-(S,M,Sa)-30 (103 kJ·mol⁻¹) or it follows a BR through TS_{BR}-(S,P,Syn)-30 to MS-(S,P,Ra)-30 (104 kJ·mol⁻¹). The similarity of these barriers allows for a significant degree of diastereomerization of axial chirality if one were to start with a non-Boltzmann distribution. Starting from pure MS-(S,P,Sa)-30, first an equilibrium of 57:41 of S-(S,M,Sa)-30 : MS-(S,P,Ra)-30 would be reached (after about two weeks) and eventually the equilibrium of the initial Boltzmann distribution would be reached (after about 25 years, vide supra). Starting from pure MS-(S,P,Ra)-30 the reaction is expected to proceed directly to the initial Boltzmann distribution taking about 25 years without the appearance of MS-(S,P,Sa)-30. While the half-life for the complete reversal to the stable atropisomers is five years, the initial decay of MS-(S,P,Sa)-30 is calculated to exhibit a half-life of only two days.

**Figure 3.27.** Reaction coordinate diagram for 30. Descriptors correspond to those assigned in Figure 3.26. Energies at room temperature by DFT/B3LYP/6-31G(d,p).

Thermal isomerization is not the only available pathway for the metastable species to return to stable species. Molecular motors of this design are very well suited for photochemical isomerization in both directions (see Chapter 5), and this theoretical study gives a clue regarding the limitations of the bistability of the system. An isolated sample of pure atropisomer (S*,Ra*)-30 is expected to be fully bistable with retention of axial chirality at room temperature (t½ = 1 year, on the condition that PEZ allows for retention), whereas a sample containing any amount of atropisomer (S*,Sa*)-30 is only expected to be bistable with respect to E/Z isomerism, although without retention of axial chirality (t½ = 2 days).

**Biphenol derived molecule 31**

Deprotection of the methoxy groups in 30 affords the biphenol derived overcrowded alkene 31. The PES search of 31 identified minima and transition
states very similar to those of 30, with the largest differences found in the dihedral angles that include the oxygen atoms (Figure 3.28). Of each minimum four rotamers were identified in which the orientations of the hydroxy groups varied as exemplified in Figure 3.29. The energies of the rotamers were consistently found to follow the same trend, where those with their hydroxy groups pointing to each other and thereby forming hydrogen bonds being lowest in energy (energies shown in Figure 3.30 and minimum energy conformations shown in Figure 3.28).

The calculated energies of 31 are shown in its reaction coordinate diagram in Figure 3.30 which exposes an interesting change with respect to its methoxy protected parent 30 (Figure 3.27). With most barriers remaining unchanged, the barriers for biaryl rotation through the synperiplanar conformation in both stable as well as metastable (TSBR-(S,P,Syn)-31‡ and TSBR-(S,M,Syn)-31‡) are significantly lowered. This might be explained by the seven membered ring in the TS facilitated by hydrogen bonding in which the hydrogen bond is shortest of all geometries under investigation. The formations of equilibria between the atropisomers in the stable and metastable states are relatively fast ($t_{1/2} = 11$ min and $16$ h, respectively) reaching their Boltzmann distributions of 76:2:20:1 ($S-(R,P,R_a)-31_a : S-(R,P,R_a)-31_b : S-(R,P,S_a)-31_a : S-(R,P,S_a)-31_b$) and 46:1:52:1 ($MS-(R,M,R_a)-31_a : MS-(R,M,R_a)-31_b : MS-(R,M,S_a)-31_a : MS-(R,M,S_a)-31_b$), respectively. The barrier for thermal helix inversion remains high ($t_{1/2} = 6.6$ years) allowing for bistability of the two helicities (i.e. stable and metastable).
Figure 3.29. Sideview of the biphenyl moiety in S-(R,P,S_a)-31 (the biaryl bond vertically in the plane of the paper and the hydroxy groups pointing towards the reader) and the calculated geometries of four rotamers labelled a–d in which the hydroxy O-H groups point towards each other, both up, both down and away from each other, respectively.

Figure 3.30. Reaction coordinate diagram for 31. Descriptors correspond to those assigned in Figure 3.28 and Figure 3.29 (a–d only indicated once, the order is identical for each atropisomer). Energies at room temperature by DFT/B3LYP/6-31G(d,p).

The helicity-transfer of the motor’s chromophore to the biphenyl as shown for motor 8 in Figure 3.24 is not as strong in 31 due to the higher flexibility of the upper half’s six membered ring. This is expressed in the torsion angle of the biaryl moiety of the motor. The transfer is strong for the conformations in which the hydroxy group clashes with the lower half providing synclinal torsion angles in S-(R,P,S_a)-31 of +52.1°, and in MS-(R,M,R_a)-31 of −50.7° (representing clear P and M helicities, respectively). However, for the conformations in which the hydroxy group points away from the lower half, anticlinal torsion angles are adopted as in S-(R,P,R_a)-31 (−93.0°), and in MS-(R,M,S_a)-31 (±115.3°) which do not represent strong P and M helicities, respectively. Interestingly, the combination of these predicted properties make system 31 a highly desirable target. Since the purpose of 31 is to function as either as the chiral diol source for a phosphoramidite ligand (32) or as a bidentate ligand by itself, the only biaryl conformations of interest are those in which the diols are syn with respect to each other, otherwise no cyclization or coordination can be achieved. In the stable and metastable states, it is the syn biaryl conformation in which the chromophore helicity is transferred strongly to the biphenol moiety. Moreover, the barrier for biaryl rotation is sufficiently low to
allow the desired atropisomer to act as a thermodynamic sink (as it is only the syn
conformation that is used up). And finally, the predicted bistability allows for full
selectivity for \( P \) and \( M \) helicity in the biaryl by a two-step chirality transfer starting
from point chirality at the stereogenic centre through helical chirality in the major
chromophore moiety to the axial chirality of the biphenol. Extending such chirality
transfers to a next step in which a separate substrate in an asymmetric catalytic
reaction would be transformed enantioselectively, would be a marvellous
achievement which can potentially be achieved by the use of phosphoramidite 32.

**Phosphoramidite derived molecule 32**

The diol 31 can be converted into the corresponding phosphoramidite 32 (e.g. with
the use of hexamethylphosphorous triamide) which was expected to limit the
number of potential minima and transition states due to a decrease in freedom of
the biaryl moiety. This limitation was expressed in the removal of the transition
state for biaryl rotation through an anti conformation of the biaryl (Figure 3.31),
however, for both the stable and metastable state two atropisomers are found, as
usual, which differ in their axial chirality and are connected by a synperiplanar
transition state.

![Figure 3.31. Structures (left) and corresponding geometries [right, DFT/B3LYP/6-31G(d,p)] of
motor 32. Geometries corresponding to named minima and transition states structures depicted in
a top-view orientation with the alkene perpendicular to the plane of the paper.

The tetrahedral coordination of phosphorus allows the atom to be a stereogenic
centre, however, for ligands such as the BINOL derived phosphoramidite, being
chiral as a whole, the phosphorous atom itself is not asymmetric due to the two
identical substituents made up by BINOL. In the case of molecule 32 the
substitution pattern of the phosphoramidite is asymmetric making phosphorus a
stereogenic centre (\( S_P \) and \( R_P \)) which gives rise to a whole additional set of
structures (with \( R_P \)) besides those shown in Figure 3.31 (with \( S_P \)). The differences are highlighted in Figure 3.32 where the four stable stereoisomers are depicted, showing the amide pointing away from the lower half in the \( S_P \) configuration and towards the lower half in the \( R_P \) configuration. Conversely, the lone pair on phosphorous is oriented in the opposite directions, which is an important notion since its orientation will be paramount to the molecule’s function as a ligand. Due to the apparent significant differences in orientation, one might expect similar differences in energy of the isomers giving rise to diastereotopicity upon its initial formation. To assess the potential for diastereotopicity as well as the molecule’s overall thermal behaviour, the energies were calculated as depicted in Figure 3.33.

![Figure 3.32. Biaryl rotations (BR) and phosphorous inversion (PInv) of stable (S,M)-32 depicted in a top-view orientation with the biaryl bond perpendicular to the plane of the paper.](image)

The barriers for phosphorous inversion (PInv) were found to be much higher than those for thermal helix inversion (THI), which in turn have increased going from the diol 31 to the phosphoramidite 32. Two mechanisms were investigated for PInv – vertex inversion and edge inversion. The energies for the transition states of edge inversion were found to be much lower, by about 190 kJ·mol\(^{-1}\), than those for vertex inversion, which can be attributed to the restricted closed shell method. Nonetheless, the barrier is of such a magnitude that not just all other calculated isomerizations proceed at a high rate, the phosphorous inversion one-hour-half-life temperature is calculated to be over 300 degrees Celsius which is higher than the degradation temperature of most molecular motors. The high barrier for unimolecular phosphorous inversion – disregarding any potential bimolecular phosphorous inversion pathway – suggests the formation of the phosphoramidite to fix the stereochemistry at the phosphorous permanently. The global minimum energy configuration was found to be S-(S,M,R,a)-32 (Figure 3.31) with S-
$S(R_P,M,R_a)$-$32$ being only 2.3 kJ·mol$^{-1}$ higher in energy (Figure 3.33). Both isomers are connected to their atropisomers ($S(S,S,M,R_a)$-$32$ and $S(S,R_P,M,S_a)$-$32$, respectively) through a biaryl isomerization, however, they are higher in energy and are predicted to be present in negligible fractions of 0.01 and 0.05, respectively. If $S(S,S,M,R_a)$-$32$ and $S(S,R_P,M,S_a)$-$32$ were to be successfully photochemically converted to their corresponding metastable states they would quickly undergo full biaryl rotations ($R_a$ to $S_a$) to reduce steric hindrance with the lower half (calculated half-lives of 0.9 and 0.1 ms, respectively). The metastable states $MS(S,S,P,S_a)$-$32$ and $MS(S,R_P,P,S_a)$-$32$ are not expected to readily undergo thermal isomerization back to their stable states with the calculated one-hour-half-life temperatures measuring 147 and 157 °C, respectively. The further increase in the barrier for THI for $32$ with respect to $31$ and $30$ stems from the covalently bridged biaryl moiety, which reduces that moiety’s flexibility. This predicted bistability – combined with a preference for the opposite axial chirality in the metastable state with respect to the stable state – is ideal for the purpose of a switchable chiral ligand. One drawback might be found in the permanent nature of the point chirality at phosphorous. On the other hand, it provides a chemist performing an asymmetric catalysis study with not just two, but four chiral ligands, and eventually insight into the most useful orientation of the lone pair at phosphorous in the phosphoramidite ligand.

![Diagram](image)

**Figure 3.33.** Reaction coordinate diagram for $32$. Descriptors correspond to those assigned in Figure 3.31 and absolute stereochemistry at phosphorous indicated above ($S_P$ left, $R_P$ right). Energies at room temperature by DFT/B3LYP/6-31G(d,p).

Molecules $30$–$32$ have recently been synthesized and studied by Stefano Pizzolato aided by the findings presented above.$^{[79]}$
Conclusion

Like first generations molecular motors, second generation molecular motors are able to rotate unidirectionally with full autonomy, i.e. they function when presented with fuel and determine their own directionality. Contrary to the first, the second generation is able to do so with only a single stereogenic centre. Due to their symmetric lower half, the molecule’s behaviour has been greatly simplified, as it is characterized not by two separate and distinct photochemical $E-Z$ isomerization thermal helix inversion sequences, but only by a single sequence with the second sequence being identical to the first. The speed of the thermal helix inversions of second generation molecular motors is greatly influenced by their structure, with their one-hour-half-life temperatures spanning over three hundred degrees. The fastest motors feature flexible lower halves and rigid upper halves, exhibiting nanosecond half-lives, whereas the slowest feature a rigid lower half and flexible upper halves with half-lives up to several years.

The pathways for thermal isomerization of second generation molecular motors have been studied computationally. The results were used to analyse the relationship between the motors’ structure and speed, effects of quaternization of the stereogenic centre and chirality transfer of the motor’s chromophore to an integral biaryl moiety. Extrapolations of structure–speed relationships allowed for the design of faster motors, one of which coincidentally being the smallest molecular motor at the time of writing. The exchange of fluorine for hydrogen at the stereogenic centre brought about large changes in the energy levels of the motors under investigations – where the difference in energy between the stable and metastable states was lowered, the energy of the transition states was increased for the quaternized motors with respect to their hydrogen substituted analogues. The benefit of molecular modelling is best highlighted in the elucidation of the potential geometries and thermal isomerizations of biaryl substituted overcrowded alkenes. The delicate interplay between the steric moieties of molecules 30–32 is responsible for a sequence of chirality transfers from point chirality, to the helicity of the alkene chromophore, on to the helicity of the biaryl. The absolute axial chirality and the barriers for its inversion are influenced strongly by the substitution pattern on the biaryl.

Molecular modelling aids the experimental chemists both before and after an experimental study is undertaken. It reveals the viability of molecular systems to function in their intended manner, and new designs for overcrowded alkenes have been provided, many of which are or will be the subjects of current or future experimental studies. Furthermore, computational chemistry is able to support
expected and unexpected experimental observations and provide insights into the motor’s behaviour.

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[38] Edzard M. Geertsema, publication in progress.


