Control of Rotor Function in Light-Driven Molecular Motors

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Supporting Information

ABSTRACT: A study is presented on the control of rotary motion of an appending rotor unit in a light-driven molecular motor. Two new light driven molecular motors were synthesized that contain aryl groups connected to the stereogenic centers. The aryl groups behave as bidirectional free rotors in three of the four isomers of the 360° rotation cycle, but rotation of the rotors is hindered in the fourth isomer. Kinetic studies of both motor and rotor functions of the two new compounds are given, using 1H NMR, 2D-EXSY NMR, and UV—vis spectroscopy. In addition, we present the development of a new method for introducing a range of aryl substituents at the α-carbon of precursors for molecular motors. The present study shows how the molecular system can be photochemically switched between a state of free rotor rotation and a state of hindered rotation and reveals the dynamics of coupled rotary systems.

INTRODUCTION

Molecular motors are ubiquitous throughout nature and perform essential tasks in biological systems.1 Well-known examples are bacterial flagella,2 kinesine and myosin,3 and ATPase motors.4 These intricate natural molecular motors have been a source of inspiration for the development of a variety of artificial molecular mechanical devices,5 including switches,6 shuttles, muscles, and rotary and translational motors.5 Because potential applications are highly diverse, artificial molecular motors are considered extremely useful in powering future nanodevices.8 Dynamic control of a myriad of functions, transmission of motion in multicomponent systems, and out-of-equilibrium assembly are important perspectives offered by rotary molecular motors. Various approaches toward synthetic rotary molecular motors have been reported, especially systems powered by light9 and chemical energy.10 A particularly versatile design is based on chiral overcrowded alkenes. The “first-generation” light-driven molecular motor 1 (Figure 1) consists of two identical chromophores linked through a central alkene,11 which serves as the axle of rotation. This motor contains two stereogenic centers with methyl substituents in pseudoequatorial orientation and the directionality of the rotary motion of 1 is governed by the chirality at these stereogenic centers in the helical molecule.

With this system, the unidirectional 360° rotation of the upper half relative to the lower half in the molecular motor is performed through a four-step switching cycle. There are two irradiation steps (energetically uphill), during which photochemical cis→trans isomerization occurs, forcing the methyl substituents in an unfavorable pseudoequatorial position. Each photoisomerization step is followed by an irreversible thermal isomerization step (energetically downhill) that re-establishes the favorable pseudoequatorial orientation of the methyl substituents. The four-step cycle provides full 360° unidirectional rotation of one-half of the molecule with respect to the other. Since the introduction of motor 1, several advanced light-driven molecular motors have been designed and their dynamic properties studied.12 To investigate the unidirectional rotation of the overcrowded alkene in more detail, the size of the substituent next to the double bond was varied in “second-generation” molecular motors.13 Exchanging the methyl group in the second-generation motor for a more sterically demanding phenyl group at the stereogenic center in motor 2 (Figure 1) only slightly increased the barrier for the thermal helix inversion step (t1/2 = 9.8 min at rt) compared to that in the corresponding methyl substituted analogue (t1/2 = 3.2 min at rt). Light-driven molecular motor 2 was found particularly suitable to demonstrate transmission of motion to control the organization of a supramolecular system and to perform work. Specifically, the photochemical and thermal isomerizations involved with motor 2, embedded as chiral dopant in a liquid crystal (LC) film, were used to induce the rotational reorganization of LC surface textures and rotate a microscale object on top of the LC film.14 Moreover, it was found that motor 2 with a phenyl substituent has a higher helical twisting power and enhanced ability to control the direction of rotational reorganization of the LC’s surface texture compared to the corresponding motor with a methyl substituent.14b

Another notable example of a functional molecular motor is the so-called “molecular gearbox” motor 3 (Figure 1).15 In this system, two rotary units are present, representing two coupled dynamic functions. Molecule 3 contains a freely rotating...
1,5-dimethylphenyl group attached to the stator unit, which behaves as a bidirectional rotor unit. It was found that the rate of rotation of the rotor moiety (1,5-dimethylphenyl) in this molecular system was different for each of the four isomers formed during a full 360° rotary cycle of the motor. This rotor control is considered an important step in the development of future coupled rotary systems. In these two examples, the aromatic group in the motor structure has played an important role to perform distinct functions. A major question arises regarding the first-generation motors: if the methyl groups in 1 are replaced by aromatic groups (as in 4 and 5) at the stereogenic centers of a first-generation molecular motor (Figure 1), will it still be possible to control coupled dynamic functions as described above?

We present here new molecular motors 4 and 5 to address this pertinent question and to further study the dynamic properties of coupled rotary systems. Both of these molecules were designed based on the structures 1–3, but for motor 4 the methyl groups are exchanged for phenyl groups, and for 5 m-methoxyphenyl groups are present at the stereogenic centers (structures 4 and 5 illustrate the modifications introduced to first-generation motor 1, Figure 1). These aryl substituents are expected to behave as bidirectional rotors, as observed for motor 3. Using UV–vis and temperature-dependent NMR spectroscopy, we are able to show that 4 and 5 function as first-generation motors and that in these molecules the rotation of the rotor part is coupled to the unidirectional rotation of the motor part. The design of motors 4 and 5 is anticipated to provide a convenient handle for analyzing the rotation of the rotor moiety (at the stereogenic center) using dynamic (EXSY) NMR experiments. In this paper, we focus on studies toward the rate of rotation (k) of the rotor moiety including the behavior of light-driven rotary molecular motors. Likewise, we present a study toward the development of a new method for introducing a range of new substituents at the α-carbon of ketones (precursors for molecular motors). This new design is the key to achieving conclusive evidence of the coupled rotation while still preserving the proper light-driven motor function.

### RESULTS AND DISCUSSION

In our synthetic approach toward target molecules 4 and 5, we anticipated developing a short procedure to prepare a number of different α-aryl substituted ketones 6 as precursors being part of a more general route to “first-generation” aryl-substituted molecular motors. As we reported previously, the upper-half α-phenyl ketone 6.3 (Scheme 1) can be synthesized in six steps (in an overall yield of 30%) from methyl 2-bromo-2-phenylacetate. This procedure does not allow for facile synthesis of motors with different aryl substituents introduced at the α-position. Here, we present a new synthetic route toward various α-aryl substituted ketones 6. This new route consists of two steps and therefore allows us to easily vary the aryl substituents at the α-position. Consequently, several α-aryl-substituted ketones 6 have been synthesized and the reaction conditions have been optimized.
Although the development of an efficient method for the formation of a bond between an aryl moiety and the α-carbon of a carbonyl compound has long been a challenging problem in organic synthesis, Buchwald and co-workers have reported the α-arylation of ketones via palladium catalyzed reaction. This methodology forms the basis for the shorter synthetic route toward α-aryl substituted ketones described here.

The two-step synthetic approach toward the desired α-aryl-substituted ketones is shown in Scheme 1. The first step involves a Friedel–Crafts acylation of the naphthalene with β-chloropropionyl chloride, leading to ketone 7. The results of the subsequent Pd-catalyzed α-arylation reaction using XPhos as ligand for a variety of conditions and aryl compounds are shown in Table 1.

In order to establish the optimal arylation conditions (Table 1), the amount of Pd/XPhos was varied (Table S1, Supporting Information). The use of 50/100 mol % of Pd/XPhos resulted in arylation of 1-iodo-3,5-dimethylbenzene, 1-iodo-2,6-dimethylbenzene, and iodobenzene to provide α-aryl ketones 6.1–6.3 in yields up to 70% (entries 1–3). We have also observed the arylation reaction with an electron donating group (EDG) present at the phenyl moiety, as shown for m- and p-iodoanisole (entries 4 and 5). It is evident that the arylation reaction is dependent on the position of the methoxy group on the aryl halide reagent. The use of p-iodobenzyl bromide, which has acidic benzylic protons, resulted in side products (possibly from the SN2 reaction) rather than the desired product (entry 6).

In order to further functionalize the aryl moiety, we have also performed the arylation reaction with tert-butyl(3-iodobenzyloxy)diphenylsilane, providing aryl ketone 6.7 in 64% (entry 7). These results illustrate that it is possible to synthesize the α-arylated ketone upper-half in two steps from naphthalene. Future optimization of this new procedure, especially for large-scale synthesis, is required in view of the rather large amount of palladium catalyst and ligand that is used in the α-arylation reaction. Although these arylation reactions so far need a higher

### Table 1. α-Arylation Reaction Using Pd(OAc)2 and XPhos with Different Aryl Halides

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aryl Halide</th>
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<th>%Yield</th>
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<tr>
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<td><img src="image6.png" alt="Image" /></td>
<td>70</td>
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<tr>
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</tr>
<tr>
<td>5</td>
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<tr>
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</table>

* Smaller amounts of Pd(OAc)2/XPhos (1/2 mol%, 5/10 mol%, and 20/40 mol%) did not result in product formation or produced poor yields. 
* The aryl halide was prepared in one step from iodobenzyl alcohol with tert-butyldiphenylsilyl chloride (t-BDPS).
loading of palladium catalyst and ligand than anticipated,\textsuperscript{16} it is a significantly more efficient route than the original six-step procedure in terms of yield and time.\textsuperscript{13} Moreover, we found it to be a valuable alternative for small scale synthesis to access a range of different \( \alpha \)-aryl substituted ketones suitable as molecular motor precursors to be tested in several applications.

**Synthesis of the Molecular Motors.** Because of severe steric hindrance in the structures of 4 and 5, most olefination reactions are not suitable for the formation of the central olefinic bond in these molecules. We were pleased to find that sterically overcrowded alkenes 4 and 5 were prepared in one step by a McMurry coupling reaction of the corresponding ketone as shown in Scheme 2. Ketones 6.3 and 6.4 were coupled in the presence of TiCl\(_4\) and zinc powder by refluxing in THF overnight, providing alkenes 4 in 16\% yield and alkenes 5 in 35\% yield, both as a mixture of \textit{cis} and \textit{trans} isomers.

Separation of the isomers of motors 4 and 5 was achieved with flash column chromatography and provided pure stable \textit{cis}-4 (5\%) and stable \textit{trans}-4 (11\%) and pure stable \textit{cis}-5 (14\%) and stable \textit{trans}-5 (21\%), respectively. The assignment of the structures of \textit{cis} and \textit{trans} 4 and 5 is based on related “first-generation” motors and is supported by calculations (Figures S1 and S2, Supporting Information). To analyze the light-driven motor function, the photochemical and thermal behavior of compounds 4 and 5 as determined by UV–vis spectroscopy, kinetic analysis and \(^1\)H NMR spectroscopy is first described. This is followed by a study of the rotation of the aryl moieties (the rotor function) of these compounds by 2D-EXSY NMR spectroscopy.

**Photochemical and Thermal Behavior of Molecular Motor 4.** The overcrowded alkenes 4 can undergo a full 360° unidirectional rotation of one-half of the molecule relative to another half upon irradiation followed by a thermal helix inversion process (Scheme 3).

The thermal and photochemical steps in the rotation process of 4 were studied by \(^1\)H NMR spectroscopy. Figure 2a shows the spectrum of a solution of stable \textit{cis}-4 in dichloromethane-\(d\_2\) at \(-50^\circ\)C. Distinctive features are absorptions of the aliphatic protons \( H_a \), \( H_b \), and \( H_c \). The absorptions of \( H_b \) and \( H_c \) can be found at 3.3 and 3.5 ppm, and all absorptions shifted downfield and upfield, respectively, and appear together as two multiplets at 3.3 and 3.5 ppm. Extended irradiation results in a photoequilibrium which strongly favors the formation of unstable \textit{trans}-4 (92:8, unstable \textit{trans}/stable \textit{cis}) as is evident from the \(^1\)H NMR spectra shown in Figure 2a,b. An interesting observation is that in Figure 2b all five protons of the phenyl moiety absorb at different chemical shift (four in the region 6.4–6.7, one at 7.25 ppm). This indicates that the phenyl group is not rotating freely.

Subsequently, the sample was heated to \( 0^\circ\)C for 15 min to induce thermal helix inversion, whereby the conformational strain due to the pseudoaxial orientation of the phenyl moiety in unstable \textit{trans}-4 is released. A \(^1\)H NMR spectrum was recorded at \(-50^\circ\)C \((\lambda = 365\text{ nm})\) (Figure 2c). Again, all absorptions shifted and the absorptions of \( H_a \) and \( H_c \) can be found at 1.7 ppm (d, \( H_a \)) and 3.5 ppm (m, \( H_c \)) and the new isomer is assigned stable \textit{trans}-4. In this isomer, the phenyl groups at the stereogenic center adopt a favored pseudoaxial orientation.

The sample was irradiated for a second time \((\lambda \geq 365\text{ nm}, 4\text{ h,} -75^\circ\)C\)) and a \(^1\)H NMR spectrum was recorded at \(-50^\circ\)C (Figure 2d). All absorptions shifted again, and no residual stable \textit{trans}-4 was visible, implying full conversion. The absorptions of \( H_a \) and \( H_c \) can be found as two multiplets at 3.3 and 3.5 ppm, and the new isomer is assigned unstable \textit{cis}-4 (unstable \textit{cis} > 95\%/stable \textit{trans} < 5). It is noted that for this isomer, as well as in stable \textit{cis}-4 and stable \textit{trans}-4, the absorptions of the phenyl moiety appear as a single peak at \( \sim 7.2 \text{ ppm} \), implying free rotation around the

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**Scheme 2. Synthesis of “First-Generation” Light-Driven Molecular Motors 4 and 5**

**Scheme 3. Rotary Cycle of “First-Generation” Molecular Motor 4**
Kinetic analysis was performed on both thermal helix inversions. For unstable trans-4 → stable trans-4, ΔG° was calculated to be 78 kJ·mol⁻¹ (t₁/₂ = 9.4 s at rt), and for unstable cis-4 → stable cis-4, ΔG° = 98 kJ·mol⁻¹ (t₁/₂ = 8.2 h at rt) was obtained. These data reveal that the half-life (t₁/₂ = 9.4 s) of unstable to stable trans-4 is not very different compared to the analogue with the methyl substituent (unstable trans-1 → stable trans-1) at the stereogenic center (t₁/₂ = 18 s at rt). In contrast, the thermal isomerization step of unstable cis-4 to stable cis-4 (t₁/₂ = 8.2 h at rt) is much slower than the corresponding isomerization of the analogous unstable cis-1 → stable cis-1 (t₁/₂ = 74 min at rt).

An interesting feature of this motor 4 is that free rotation of the phenyl “rotor” moiety (at the stereogenic center) is observed in three of the four isomers (stable cis-, stable trans-, and unstable cis-) during a 360° cycle, but the rotation is hindered in the fourth isomer (unstable trans-4). 1H NMR data of motor 4 show that the free rotation of the phenyl group is hindered in the unstable trans isomer because of the significant steric hindrance of the naphthalene moiety in the opposite half of the motor. This is the reason why five protons of the phenyl rotor moiety in unstable trans-4 show five distinct absorptions as shown in Figure 2b; the rotation is slow at the NMR time scale as compared with the other isomers. In stable cis-, stable trans- and unstable cis-4 all the five protons of the phenyl “rotor” moiety are observed as a single absorption (Figure 2a,c,d). Consequently, the phenyl substituent of motor 4 might be used as a switching system (between free and slow rotation) accompanying the motor switching between the stable cis and unstable trans isomers.

Unfortunately, because of overlap in the aromatic region of the 1H NMR spectrum between the absorptions of the rotor (phenyl) and the absorptions of the naphthalene moieties, the rotor properties could not be studied in more detail. Further research into the rotation of the bidirectional rotor was therefore conducted on molecular motor 5, which has a methoxy-substituted rotor unit.

Photochemical and Thermal Behavior of Molecular Motor 5. Before studying the dynamic properties of the rotor part (m-methoxyphenyl) of motor 5, the motor function itself was examined. Initial studies on the behavior of the motor unit were performed with the stable isomers of cis-5 and trans-5 and the photochemical isomerization and thermal helix inversion processes were analyzed by UV–vis and 1H NMR spectroscopy. Likewise, it was anticipated that motor 5 should function as a light-driven molecular rotary motor which proceeds through a four-step switching cycle, similar to the cycle of motor 4 (Scheme 3).

A solution of stable cis-5 (3.7 × 10⁻⁵ M) in dichloromethane and a solution of stable trans-5 (3.0 × 10⁻⁵ M) in 1,2-dichloroethane were used for the UV–vis spectroscopic studies. Starting with stable cis-5 at −20 °C, a photochemical isomerization (with UV light ≥ 365 nm) generates unstable trans-5 and the UV–vis absorption spectrum was measured at regular intervals until the photostationary state (PSS) was reached. An
The isosbestic point was formed at 380 nm and a red-shift of the maximum at 375 nm (ε = 15.8 × 10^5 dm^3⋅mol^−1⋅cm^−1) to 387 nm (ε = 15.8 × 10^5 dm^3⋅mol^−1⋅cm^−1) was observed. The bathochromic shift can be attributed to the generation of an unstable trans isomer, where the ground state is destabilized compared to the stable trans isomer due to increased strain. This decreases the energy gap, as seen with other first-generation molecular motors (dotted line, Figure 3a). The sample was then left for 100 min at −20 °C to allow the thermal helix inversion process to occur. The UV−vis spectrum indicates that the unstable trans-5 has converted to stable trans-5 (λ_max = 375 nm, ε = 16.8 × 10^3 dm^3⋅mol^−1⋅cm^−1) (dashed line, Figure 3a). On the basis of these data, it can be concluded that one-half of the rotary cycle (180°) has been completed (stable cis → stable trans). Figure 3b shows the UV−vis spectra of the isomers observed during the other half of the 360° rotary cycle from stable trans-5 via unstable cis-5 to stable cis-5. A UV−vis spectrum of stable trans-5 was acquired at rt. As expected, this spectrum (Figure 3b, solid line) is similar to the spectrum obtained after the thermal isomerization step as shown in Figure 3a (dashed line).

The solution of stable trans-5 (λ_max = 360 nm, ε = 17.6 × 10^3 dm^3⋅mol^−1⋅cm^−1) was then irradiated with UV light (≥365 nm) at 40 °C until the PSS was reached. In the UV−vis spectrum of unstable cis-5 (λ_max = 401 nm, ε = 8.3 × 10^3 dm^3⋅mol^−1⋅cm^−1) (dotted line, Figure 3b), the expected red-shift was observed once again and a clear isosbestic point was displayed at 385 nm. Subsequently, the sample was left at 40 °C for 5 h. The final spectrum (λ_max = 377 nm, ε = 12.8 × 10^3 dm^3⋅mol^−1⋅cm^−1) (dashed line, Figure 3b) is similar to the spectrum of stable cis-5 in Figure 3a (solid line) and it can be concluded that the other half of the 180° rotary cycle has been completed. However, the spectra of stable cis shown in Figure 3b (dashed line) and Figure 3a (solid line) are not completely identical, as was also observed for stable trans (Figure 3a, dashed line and Figure 3b, solid line). This indicates that, although the isomerization step proceeds as expected, the conversion in both halves of the cycle is less than 100%. Further 1H NMR studies will provide more information about the actual conversion during the photochemical and thermal isomerization processes (vide infra).

In addition, UV−vis spectroscopy was used to study the kinetics of the two thermal isomerization steps. The changes in UV−vis absorption at 410 nm were monitored as a function of time at different temperatures (−5, −10, −12, −15, and −20 °C for unstable trans-5 → stable trans-5; 30, 40, 50, and 60 °C for unstable cis-5 → stable cis-5). Using these data, an Eyring plot was made for both thermal steps, from which the half-life and Gibbs free energy of activation were calculated. It was found that t_1/2 = 9.45 s at rt (Δ^‡G° = 78.14 kJ⋅mol^−1; see Figure S3a, Supporting Information) for the isomerization of unstable trans-5 to stable trans-5, a value similar to that of the analogous helix inversion of the related motor 4 which was determined to be 9.4 s at rt. The t_1/2 of unstable cis-5 to stable cis-5 is 6.2 h (Δ^‡G° = 97 kJ⋅mol^−1, at rt) (see Figure S3b, Supporting Information). This thermal isomerization step is slightly faster than the isomerization of the analogous unstable cis-4 to stable trans-4 (t_1/2 = 8.2 h, at rt).

1H NMR Measurements of Molecular Motor 5. The isomerization steps during the rotation process of motor 5 were studied in more detail by 1H NMR spectroscopy. Solutions of pure stable trans-5 and stable cis-5 isomers in dichloromethane-d_2 were both irradiated with UV light (λ ≥ 365 nm) at −40 °C.

Distinctive features in the 1H NMR spectrum of stable trans-5 (Figure 4a) are absorptions of the aliphatic protons at 2.75 ppm (d, H_b), 3.48 ppm (dd, H_c), and 4.21 ppm (d, H_a). Upon irradiation of the solution of stable trans-5, the doublet absorption at 2.75 ppm is shifted downfield and the doublet doublet at 3.50 is shifted upfield so these absorptions appear together at 3.23−3.45 ppm (m, H_b + H_c) (Figure 4b). Comparison with data obtained for motor 4 confirms that the unstable cis isomer is formed. In addition, no residual trans isomer is left in the solution, so the photochemical isomerization step gives a conversion >95% toward unstable cis-5. A subsequent thermal helix inversion (at rt, overnight) produced stable cis-5, but also a considerable amount of stable trans-5 (cis/trans ratio 43:57) was observed (Figure 4c). In contrast, performing the thermal step at 40 °C for 2 h gave a different ratio of stable cis and stable trans isomers (cis/trans ratio 77:23) (Figure 4d). To confirm these results, the soluble trans to stable cis isomerization was examined in a different solvent by 1H NMR measurements. After the

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**Figure 3.** UV−vis spectra of molecular motor 5: (a) photoisomerization and thermal helix inversion steps from stable cis- to stable trans-5; (b) photoisomerization and thermal helix inversion steps from stable trans- to stable cis-5.
photochemical isomerization step of stable trans-5 in toluene-$d_8$ (unstable cis > 95%), $^1$H NMR spectra were recorded first at rt, and it was found that under these conditions the unstable cis-5 undergoes a forward isomerization to stable cis-5 as well as a competing backward isomerization to the stable trans isomer (stable cis/stable trans ratio, 63:37). When unstable cis-5 (>95%) in toluene-$d_8$ was used at higher temperatures, it was observed that the thermal isomerization process of unstable cis-5 at 70 °C gave a considerable amount of stable cis-5 (cis/trans ratio, 76:24) (see Figure S2, Supporting Information). Formation of the stable trans isomer means that isomerization from unstable cis-5 to stable cis-5 is not a completely unidirectional rotation process (reversible). Even in a different solvent and at different temperatures, the unstable cis isomer still shows competition between forward rotation to stable cis-5 and backward rotation to stable trans-5. This behavior of molecular motors showing a competing backward thermal helix inversion was also observed for some other systems, and the consequences for the unidirectional nature of the overall motor function were expressed in a mathematical model. The present system shows similar behavior and the competing backward thermal helix inversion is the consequence of the replacement of the substituent at the stereogenic center and the relatively high barrier for thermal isomerization. From these results, it is evident that the ratio of stable cis and trans isomers depends on the temperature at which the thermal helix inversion process takes place. Nevertheless, there is a large preference for the forward direction, which allows a major unidirectional rotary motion.

The next step in the rotary cycle was performed with stable cis-5; two of the three aliphatic protons of stable cis-5 (CD$_2$Cl$_2$, 40 °C) are found at 2.95 ppm (d, H$_b$) and at 3.85 ppm (dd, H$_c$) as shown in Figure 5a. Irradiation of stable cis-5 resulted in a downfield shift of the absorption of H$_b$ from 2.95 to 3.25 ppm and upfield shift of the absorption of H$_c$ from 3.85 to 3.50 ppm (Figure 5b). Formation of the unstable trans isomer was also confirmed by comparison with data obtained for motor 4. Moreover, in this spectrum of unstable trans-5, the decrease in the rate of rotation of the rotor part (m-methoxyphenyl) is clearly visible.
For all three other isomers (stable trans, stable cis, and unstable cis), the singlet of the methoxy group appears at 3.6 ppm (s, 3H). However, in the spectrum of unstable trans-5, this absorption appears as two singlets at around 3.40–3.45 ppm. This implies that the rotation of the rotor moiety is slow on the NMR time scale, which in turn implies that 1H NMR spectroscopy can be used to distinguish between two different relative positions (A and B) of the methoxy substituent in this isomer and to establish the barrier of rotation by temperature dependent 1H NMR measurements (Scheme 4).

In the 1H NMR spectrum of unstable trans-5 at $-40 \, ^\circ\mathrm{C}$, some residual stable cis-5 is still visible after irradiation, and the PSS was calculated to consist of 75% of unstable trans-5 and 25% of stable cis-5 (see Figure S5b, Supporting Information). The 1H NMR spectrum of the sample after heating (20 °C for 20 min) revealed that all of the absorptions of unstable trans-5 were replaced by the absorptions expected from stable trans-5, exemplified by the shift of one of the protons in the aliphatic region from 3.25 to 2.75 ppm (see Figure S5c, Supporting Information). These 1H NMR data indicated that the thermal isomerization of unstable trans-5 quantitatively gave stable cis-5, and as a consequence, a ratio of stable trans-5 to stable cis-5 of 75:25 was found. This means that this thermal isomerization from stable cis-5 to stable trans-5 is a unidirectional process. These photochemical and thermal isomerization steps (from stable cis to stable trans isomers) result in a 180° rotation of the upper half of the molecule with respect to the other half (as for 4 in Scheme 3).

2D-EXSY Measurements for the Rotor Functions of the Molecular Motor. Initial studies of the rate of rotation of the rotor moiety were carried out with the unstable trans isomer, generated by photoisomerization of stable cis-5. However, because of the high activation barrier of the rotor, coalescence studies using 1H NMR are not suitable to determine the rate of exchange (rate of rotation, $k$) of the anisole group. 23 Because the half-life of unstable trans-5 to stable trans-5 is very short at rt, thermal isomerization occurs before the rotation of the rotor unit can be examined. Therefore, the exchange of the methoxy group of the m-methoxyphenyl substituent is only visible on the NMR time scale at low temperature. 2D-EXSY spectra of unstable trans-5 were obtained at different temperatures of $-50, -45, -40$, and $-35 \, ^\circ\mathrm{C}$, with different mixing times of 0.1, 0.2, 0.3, 0.5, 0.7, 0.9, and 1.1 s in dichloromethane-$d_2$. Figure 6a shows a 2D-EXSY spectrum (see general remarks). The presence of exchange cross peaks immediately showed that, as expected, the rotation of the rotor around the biaryl bond connecting the rotor moiety to the motor in the unstable trans isomer is hindered. 24,25

Unstable trans-5 can be approached as an asymmetrical two-site exchange system between a proton and a methoxy at the m-anisole...
moiety (Scheme 4). By rotating around a single bond that connects the rotor (m-anisole) to the motor, the methoxy group exchanges its position with that of the proton on the other side of the phenyl moiety. One of these conformations is higher in energy than the other because of steric interaction between the methoxy group and the naphthalene moiety. This means the conformations will not be equally populated and, therefore, the ratio of cross peaks and diagonal peaks will not converge to 1.

This can be resolved by adding an extra parameter \( p \) to the equation (eq 1; see the Experimental Section, general remarks) when fitting a line to the data points in Figure 6b. Parameter \( p \) represents the population of one of the exchange sites, the population of the other site being \( 1 - p \). In case of symmetrical exchange, \( p \) is 0.5. Because the ratio of cross peaks and diagonal peaks is directly proportional to the population of the exchange sites, the peak ratio will approach to \( p/(1 - p) \). In this case this is 0.23, as can be observed in Figure 6b, where peak ratios are plotted versus mixing times. From the peak ratio, the extra parameter \( p \) can be calculated for the rotor part of molecular motor \( S \) to be 0.19.26

From this graph, the Gibbs free energy of activation \( \Delta^\ddagger G^0 \) for the rotation of the rotor was calculated to be 11.6 \( \text{kJ mol}^{-1} \). Using the Eyring equation, the rate of exchange (rate of rotation; \( k \)) has been calculated to be \( 8.1 \times 10^9 \text{s}^{-1} \) at 20 °C. The \( ^1H \) NMR spectra of the other three isomers (stable \( \text{trans} \), unstable \( \text{cis} \), and stable \( \text{cis} \)) show that the rotation of the rotor part is unhindered (free rotation around the single bond). This means that motor \( S \) behaves as a coupled rotary system. By simple isomerization from stable \( \text{cis} \)- to unstable \( \text{trans} \)-, the rotation rate of the bidirectional rotor can be altered significantly. Thermal helix inversion to stable \( \text{trans} \)- or photoisomerization to stable \( \text{cis} \)-returns the rotor to its original, unhindered state. Although this molecular motor \( S \) is not as sophisticated as the “second-generation” molecular gearbox 3, this motor can be used as a rotation-on-rotation—off switching system by photoisomerization from stable \( \text{cis} \)- to unstable \( \text{trans} \)- and back again (Scheme 4). Due to its simple design, this will be a very useful function in more advanced coupled rotary systems.

**CONCLUSIONS**

In summary, a new synthetic route toward functionalized first-generation molecular motors has been developed, reducing the number of synthetic steps from seven to three. A number of different aryl-substituted ketone precursors for first-generation motors are readily accessible.

First-generation molecular motors with phenyl and m-anisole groups at the stereogenic centers have been synthesized, and the dynamic behavior of these new first-generation molecular motors has been studied in detail. Even though the UV–vis studies confirm the four-step rotary cycle and \(^1H\) NMR studies show that conversion for both photochemical steps is near 100%, the thermal step from unstable \( \text{cis} \) to stable \( \text{cis} \) in the rotary cycle is not completely unidirectional for motor 5. A major goal of this study was to examine how the rotary motion of an appending rotor unit can be controlled by the light-driven motor function. It has been demonstrated that the rate of rotation of the m-anisole rotor embedded in these molecular motors can be controlled using light and heat as external triggers. The rotation properties of the m-anisole moiety have been studied in detail using \(^1H\) NMR and 2D-EXSY spectroscopy. The results show that the rotation of the m-anisole moiety in 5 is unhindered in the stable \( \text{trans} \), unstable \( \text{cis} \), and stable \( \text{cis} \) isomers but hindered in the unstable \( \text{trans} \) isomer. Therefore, the system can be used as a light-switch between a state of free rotor rotation and a state of hindered (slow) rotor rotation. Our findings on the control of the speed of rotation of the rotors will be useful in the design of more advanced molecular motors, in particular to control coupled motion.

**EXPERIMENTAL SECTION**

**General Remarks.** All reactions were carried out in oven-dried glassware under a nitrogen atmosphere. Solvents were reagent grade, distilled and dried before use according to standard procedures. Other commercially available reagents were used without purification. Irradiation experiments were performed using an ENB-280C/FE lamp (\( \lambda \geq 365 \text{ nm} \)). Samples irradiated for \(^1H\) NMR spectroscopic analysis were placed 2–3 cm from the lamp. Photostationary states were determined by monitoring composition changes into time by taking UV–vis spectra or \(^1H\) NMR spectra at distinct intervals until no additional changes were observed. Kinetic analysis of the thermal isomerization steps was performed by UV–vis spectroscopy. A high-pass filter was mounted in front of the UV light source to cut off all light with a wavelength below 380 nm to minimize photochemical isomerization occurring upon data recording. Changes in UV–vis absorptions were measured at different temperatures: for unstable \( \text{trans} \)- to stable \( \text{trans} \)-isomers in DCM at \(-20, -15, -12, -10, \) and \(-5 \text{ °C} \) and for unstable \( \text{cis} \)- to stable \( \text{cis} \)-isomers in DCE at 30, 40, 50, and 60 °C. From the obtained data the rate constants (\( k \)) were obtained and an Eyring plot was made for both thermal steps.
and \(\Delta^s H^\ddagger, \Delta^s S^\ddagger, \Delta^s G^\ddagger, \text{and} \ t_{1/2} \) (at 20 °C) of both cis- and trans-isomerizations were calculated from these data.

For the 2D-EXSY measurements, signals on the diagonal line are referred to as “diagonal peaks”; these are the two-dimensional depiction of the \(^1H\) NMR spectrum of the compound. Signals deviating from this line are called “cross peaks”. Every cross peak can be connected to two corresponding diagonal peaks and one other cross peak, and this set of information is indicative of an exchange process. By assigning and integrating the cross peaks and corresponding diagonal peaks, information about exchange processes in the compound 5 can be obtained (for details, see ref 25).

A cross peak and one of its corresponding diagonal peaks were then selected from the 2D spectrum, in this case, protons 1A and 1B (Figure 6a); for accuracy, it is important that there is the least possible amount of overlap with any other absorption. For these peaks (protons 1A and 1B), the integrals are calculated and divided by each other to give the peak ratio \((p/(1-p))\).

First, the ratio of diagonal peaks and their corresponding cross peaks in the 2D-EXSY spectrum were plotted against the different mixing times \((\tau_{mix})\) for the different temperatures (Figure 6b). Subsequently, a curve was fitted for each different temperature using the following function:

\[
f(T, \tau_{mix}) = p(1 - \exp(-\Delta^s G^\ddagger/(1-T) - (1/T)\tau_{mix}))/1 - p(1 - \exp(-\Delta^s G^\ddagger/(1-T) - (1/T)\tau_{mix}))
\]

In this function, \(T\) and \(\tau_{mix}\) represent the different temperatures and mixing times, respectively. \(R\) is the gas constant (8.3 J·K\(^{-1}\)·mol\(^{-1}\)·K) and \(p\) (population), \(\Delta^s G^\ddagger\) (Gibbs free energy of activation at temperature \(T_0\)), and \(k_0\) were used as fitting parameters. Subsequently, the rate of exchange \((k)\) was calculated using the Eyring equation. The notebook in which the 2D-EXSY calculations were performed was developed by Dr. E. Otten and Dr. R. Scheck, based on the literature.\(^{27}\)

Synthesis of the \(\alpha\)-Aryl Ketones 6 and Molecular Motors 4 and 5. 2,3-Dihydro-1H-cyclopenta[a]naphtalen-1-one (6). A solution of \(\beta\)-chloropropionyl chloride (7.5 mL, 78 mmol) and naphthalene (10 g, 78 mmol) in 25 mL of carbon disulfide (C\(_S^2\)) under a nitrogen atmosphere was added over 45 min to anhydrous AlCl\(_3\) (13 g, 94 mmol) in the presence of DMAP (1 mL). The mixture was stirred and heated at reflux overnight. Every cross peak in the \(\Delta^s G^\ddagger\) spectrum was added over 45 min to anhydrous AlCl\(_3\) (13 g, 94 mmol) and 1-iodo-3,5-dimethylbenzene (0.33 mL, 1.9 mmol) in toluene (5 mL) was added. The mixture was stirred and heated at reflux overnight. Every cross peak in the \(\Delta^s G^\ddagger\) spectrum was added over 45 min to anhydrous AlCl\(_3\) (13 g, 94 mmol) and 1-iodo-3,5-dimethylbenzene (0.33 mL, 1.9 mmol) in toluene (5 mL) was added. Every cross peak in the \(\Delta^s G^\ddagger\) spectrum was added over 45 min to anhydrous AlCl\(_3\) (13 g, 94 mmol) and 1-iodo-3,5-dimethylbenzene (0.33 mL, 1.9 mmol) in toluene (5 mL) was added. Every cross peak in the \(\Delta^s G^\ddagger\) spectrum was added over 45 min to anhydrous AlCl\(_3\) (13 g, 94 mmol) and 1-iodo-3,5-dimethylbenzene (0.33 mL, 1.9 mmol) in toluene (5 mL) was added.

The mixture was stirred and heated at reflux overnight. After the mixture was cooled to room temperature, water (25 mL) was added, and the mixture was extracted with diethyl ether (3 x 25 mL), washed with water (25 mL), dried (Na\(_2\)SO\(_4\)), and concentrated in vacuo. The crude product was purified by flash column chromatography (SiO\(_2\) powder: EtOAc/MeOH 1:10, 85:15). Every cross peak in the \(\Delta^s G^\ddagger\) spectrum was added over 45 min to anhydrous AlCl\(_3\) (13 g, 94 mmol) and 1-iodo-3,5-dimethylbenzene (0.33 mL, 1.9 mmol) in toluene (5 mL) was added. Every cross peak in the \(\Delta^s G^\ddagger\) spectrum was added over 45 min to anhydrous AlCl\(_3\) (13 g, 94 mmol) and 1-iodo-3,5-dimethylbenzene (0.33 mL, 1.9 mmol) in toluene (5 mL) was added. Every cross peak in the \(\Delta^s G^\ddagger\) spectrum was added over 45 min to anhydrous AlCl\(_3\) (13 g, 94 mmol) and 1-iodo-3,5-dimethylbenzene (0.33 mL, 1.9 mmol) in toluene (5 mL) was added. Every cross peak in the \(\Delta^s G^\ddagger\) spectrum was added over 45 min to anhydrous AlCl\(_3\) (13 g, 94 mmol) and 1-iodo-3,5-dimethylbenzene (0.33 mL, 1.9 mmol) in toluene (5 mL) was added.

The mixture was stirred and heated at reflux overnight. After the mixture was cooled to room temperature, water (25 mL) was added, and the mixture was extracted with diethyl ether (3 x 25 mL), washed with water (25 mL), dried (Na\(_2\)SO\(_4\)), and concentrated in vacuo. The crude product was purified by flash column chromatography (SiO\(_2\) powder: EtOAc/MeOH 1:10, 85:15). Every cross peak in the \(\Delta^s G^\ddagger\) spectrum was added over 45 min to anhydrous AlCl\(_3\) (13 g, 94 mmol) and 1-iodo-3,5-dimethylbenzene (0.33 mL, 1.9 mmol) in toluene (5 mL) was added. Every cross peak in the \(\Delta^s G^\ddagger\) spectrum was added over 45 min to anhydrous AlCl\(_3\) (13 g, 94 mmol) and 1-iodo-3,5-dimethylbenzene (0.33 mL, 1.9 mmol) in toluene (5 mL) was added. Every cross peak in the \(\Delta^s G^\ddagger\) spectrum was added over 45 min to anhydrous AlCl\(_3\) (13 g, 94 mmol) and 1-iodo-3,5-dimethylbenzene (0.33 mL, 1.9 mmol) in toluene (5 mL) was added. Every cross peak in the \(\Delta^s G^\ddagger\) spectrum was added over 45 min to anhydrous AlCl\(_3\) (13 g, 94 mmol) and 1-iodo-3,5-dimethylbenzene (0.33 mL, 1.9 mmol) in toluene (5 mL) was added.
2-(4-Methoxyphenyl)-2,3-dihydro-1H-cyclopenta[a]naphthalene-1-one (6,7). Ketone 6.5 was prepared via general procedure A from ketone 7 (93 mg, 0.51 mmol) and 1-iodo-3-methoxybenzene (100 mg, 0.43 mmol) using Pd(OAc)2 (47.9 mg, 0.21 mmol), r-BuONa (103 mg, 1.07 mmol), and 2-dicyclohexylphosphino-2′,4′,6′-trisopropylbiphenyl (204 mg, 0.43 mmol). The crude product was purified using flash column chromatography (SiO2, pentane/EtOAc; 4:1, Rf = 0.47). Ketone 6.5 was obtained as a pale yellow oil (161 mg, 0.065 mmol, 13%).1H NMR (400 MHz, CDCl3) δ 7.37 (d, J = 8.0 Hz, 1H), 7.17 (m, 2H), 7.16–7.21 (m, 3H), 7.27 (d, J = 8.8 Hz, 1H), 7.32–7.37 (m, 1H), 7.73 (d, J = 8.1 Hz, 2H), 7.84 (d, J = 8.0 Hz, 1H).13C NMR (101 MHz, CDCl3) δ 43.4 (CH2), 54.1 (CH), 123.7 (CH), 124.9 (CH), 125.4 (CH), 125.8 (CH), 127.8 (CH), 128.09 (CH), 128.13 (CH), 128.2 (CH), 128.7 (CH), 129.0 (C), 133.0 (C), 139.4 (C), 140.3 (C), 140.8 (C), 145.4 (C); HRMS (ESI) m/z calcd for C38H28Si 527.2401, found 527.2425.

 cis-4 (yellow solid): 1H NMR (400 MHz, CDCl3) δ 7.29 (d, J = 15.6 Hz, 1H), 3.86 (dd, J = 15.6, 7.3 Hz, 1H), 4.51 (d, J = 7.1 Hz, 1H), 6.48 (t, J = 7.6 Hz, 1H), 6.84 (d, J = 8.4 Hz, 1H), 7.04 (t, J = 7.5 Hz, 1H), 7.13–7.21 (m, 5H), 7.38 (d, J = 8.2 Hz, 1H), 7.68–7.75 (m, 2H).13C NMR (101 MHz, CDCl3) δ 42.4 (CH2), 52.9 (CH), 123.2 (CH), 124.4 (CH), 124.5 (CH), 126.1 (CH), 126.7 (CH), 127.2 (CH), 127.9 (CH), 128.5 (CH), 129.1 (C), 129.3 (C), 132.4 (C), 138.1 (C), 139.0 (C), 144.0 (C), 145.7 (C); HRMS (ESI) m/z calcd for C38H28Si 527.2425, found 527.2425.

 trans-5 (white solid, appearing as a yellow fluorescent spot on TLC): 1H NMR (400 MHz, CDCl3) δ 2.79 (d, J = 14.9 Hz, 1H), 3.30 (dd, J = 14.9, 6.7 Hz, 1H), 3.61 (s, 3H), 4.26 (d, J = 6.5 Hz, 1H), 6.70 (s, 1H), 6.72 (s, J = 7.9 Hz, 2H), 6.92 (t, J = 7.0 Hz, 1H), 7.10 (t, J = 7.8 Hz, 1H), 7.27 (d, J = 8.9 Hz, 1H), 7.35 (t, J = 7.5 Hz, 1H), 7.73 (d, J = 8.2 Hz, 1H), 7.78 (d, J = 8.5 Hz, 1H), 7.83 (d, J = 8.0 Hz, 1H).13C NMR (101 MHz, CDCl3) δ 43.3 (CH2), 54.0 (CH), 55.0 (CH2), 111.4 (CH), 113.8 (CH), 120.6 (CH), 123.7 (CH), 124.9 (CH), 125.5 (CH), 127.7 (CH), 128.2 (CH), 128.8 (CH), 129.0 (C), 129.1 (C), 133.0 (C), 139.4 (C), 140.2 (C), 140.8 (C), 147.1 (C), 159.3 (C); HRMS (ESI) m/z calcd for C38H28Si 527.2425, found 527.2425.

 cis-5 (yellow solid, appearing as a blue fluorescent spot on TLC): 1H NMR (400 MHz, CDCl3) δ 2.90 (d, J = 15.7 Hz, 1H), 3.63 (s, 3H), 3.86 (dd, J = 15.4, 7.2 Hz, 1H), 4.50 (d, J = 7.2 Hz, 1H), 6.47 (t, J = 7.0 Hz, 1H), 6.68 (dd, J = 8.2, 1.8 Hz, 1H), 6.77 (s, 1H), 6.80 (dd, J = 15.1, 8.5 Hz, 2H), 7.02 (t, J = 7.0 Hz, 1H), 7.09 (t, J = 7.8 Hz, 1H), 7.38 (d, J = 8.1 Hz, 1H), 7.68 (d, J = 8.2 Hz, 1H), 7.72 (d, J = 8.2 Hz, 1H).13C NMR (101 MHz, CDCl3) δ 42.4 (CH2), 53.0 (CH), 55.0 (CH2), 111.3 (CH), 113.2 (CH), 119.7 (CH), 123.1 (CH), 124.4 (CH), 124.6 (CH), 126.6 (CH), 127.8 (CH), 129.1 (C), 129.3 (C), 129.4 (CH), 132.4 (C), 138.1 (C), 140.4 (C), 147.3 (C), 159.6 (C); HRMS (ESI) m/z calcd for C38H28Si 527.2425, found 527.2425.

**ASSOCIATED CONTENT**

5 Supporting Information. 1H and 13C NMR spectra for all compounds, Eyring plots for the kinetic studies for cis- and trans-5, and 1H NMR spectra after photochemical and thermal isomerization experiments for molecular motor cis- and trans-5. This material is available free of charge via the Internet at http://pubs.acs.org.

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REFERENCES


(18) All of the UV–vis and NMR spectroscopic studies were performed on racemates.

(19) Because of the low rate of thermal inversion from unstable cis-5 to stable cis-5, the solvent was changed from DCM to DCE to allow temperatures above the boiling point of DCM (40 °C).


(22) See the Supporting Information for more details.


(24) This graph shows the region of the spectrum in which the absorptions are that were used to perform the calculations. These are not the methoxy protons (proton 4, see Figure 5) and its corresponding absorptions are that were used to perform the calculations. These are not the methoxy protons (proton 4, see Figure 5) and its corresponding proton (proton 2), but the other two protons (protons 1 and 5) on the m-methoxyphenyl. The latter were used for the calculations because their absorptions had less overlap with other absorptions, which is essential for the accuracy of the calculations.


(26) More details on the 2D-EXSY measurements and calculations can be found in the experimental general remarks section.