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Rotary Molecular Motors: A Large Increase in Speed through a Small Change in Design

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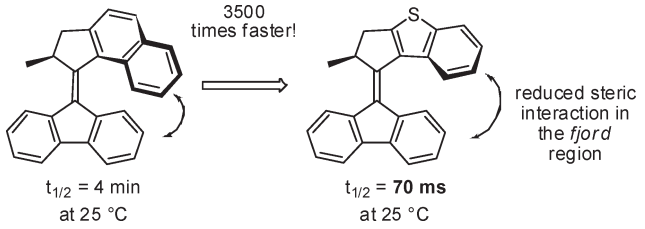

Reducing the steric interaction between the upper-half and the lower-half of a light-driven rotary molecular motor by decreasing the size of the aromatic moiety in the upper-half from a naphthalene to a benzothiophene results in an almost 3500 times faster rotation.

Biological nanoscale rotary motors are used to perform crucial cellular tasks including ion pumping and cellular translocation.[1a] The design and construction of synthetic motors with comparable or superior speed and efficiency is one of the key challenges in contemporary chemistry.[1] Several ways that synthetic molecular motors can be harnessed to perform macroscopic work have been demonstrated recently.[2]

The so-called second-generation light-driven rotary motors based on overcrowded alkenes are able to undergo repetitive unidirectional rotation around the central olefin (the rotary axle) involving two photochemical geometric isomerizations of the alkene, each followed by a thermal helix inversion.[3] The speed of the rotary motion is limited by the thermal helix inversion step since the photochemical isomerization of the alkene is extremely fast.[4] One of the key steps toward using the motion generated by synthetic light-driven rotary molecular motors to perform a useful task is to make their rotary action fast enough to compete with the surrounding Brownian motion and convert energy into controlled motion.

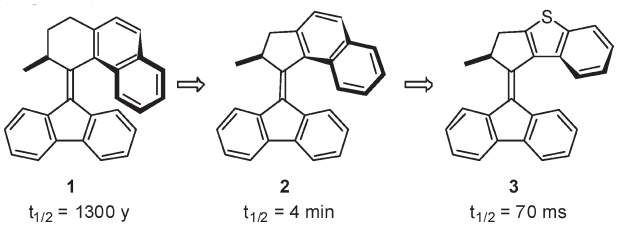

FIGURE 1. Effect of the steric interactions in the fjord region on the speed of the rotation at 25 °C.

To achieve precise control over the rotary motion, the interplay between stereochemical, electronic, conformational, and steric factors in the design of these light-driven rotary motors has been the subject of extensive research.[5] It has been shown that the steric hindrance in the fjord region and the nature of the substituent at the stereogenic center are key factors that control the speed of the thermal isomerization step.[6] For example, it was previously shown that contracting the ring-system fused to the central alkene from a 6-membered to a 5-membered ring (i.e., **1** → **2**, Figure 1) reduced the steric interaction between the upper-half and the lower-half in the fjord region, which in turn reduced the Gibbs energy of activation of the thermal step, which leads to an increase of the speed.[6d] Additionally, introducing bulkier substituents to the stereogenic center leads to the acceleration of the rate-limiting thermal isomerization step by increasing the strain energy of the unstable isomer more than that of the stable isomer.[6c] Surprisingly, however, it was also shown that the removal of one of the upper-half arene moieties leads to a *deceleration* in the rate of thermal isomerization. This change was attributed to a change in the energy of the ground-state conformation, wherein the

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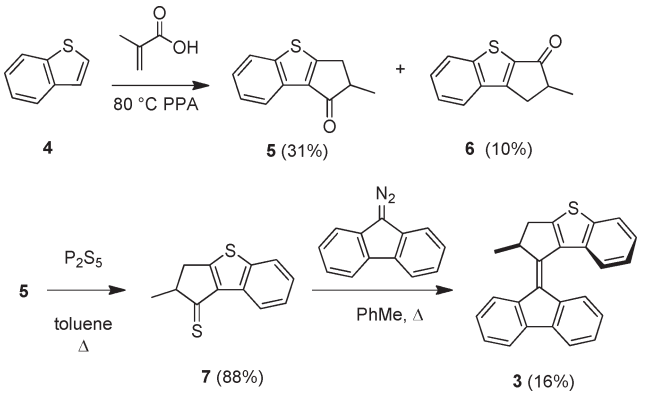
SCHEME 1. Synthesis of Molecular Motor 3



truncation allowed the molecule to adopt a conformation with less strain.[6f]

As an attempt to tune further the speed of the rotary motion by reducing the steric hindrance in the fjord region, a novel second-generation molecular motor **3** with a benzothiophene upper-half was designed, and its dynamic behavior upon illumination was investigated and compared to analogues **1** and **2** (Figure 1).[6b,c]

Alkene **3** was prepared in a short synthetic sequence starting from benzothiophene (Scheme 1).[7] A one-pot tandem Friedel–Crafts/Nazarov reaction of methacryclic acid with benzothiophene **4** in polyphosphoric acid at 80 °C gave the isomeric ketones **5** and **6** in 31% and 10% yield, respectively. Ketone **5** was then treated with P_2S_5 in toluene at 45 °C for 2.5 h to give thioketone **7** in 88% yield. Treatment of this thioketone with an excess of diazofluorenone in toluene at 80 °C for 2 h initiated the expected [2+3]-cycloaddition with rapid subsequent extrusion of N_2,[8] and finally spontaneous extrusion of the sulfur atom afforded the product alkene **3** in 16% yield. The spontaneous extrusion of sulfur from similar thiiranes has been observed previously.[9]

On the basis of its structural similarity to known second-generation light-driven rotary molecular motors,[6b] we anticipated that **3** would also perform unidirectional rotation of the upper-half relative to the lower-half when illuminated with UV light (Figure 2).

When irradiated at a suitable temperature, these chiral overcrowded alkenes isomerize through a 4-step cycle involving two pairs of degenerate photochemical and thermal isomerizations. Initially, the stable isomer (i.e., stable-**3**, Figure 2) undergoes a photoisomerization of the central overcrowded olefin, which leads to the formation of the unstable isomer. After the photoisomerization, the methyl group at the stereogenic center gets trapped in a high-energy conformation where it is positioned on the opposite side of the fluorene as is the benzothiophene moiety. In the rate-limiting second (thermal) step, the conformational strain is released as the benzothiophene ring slips past the lower-half

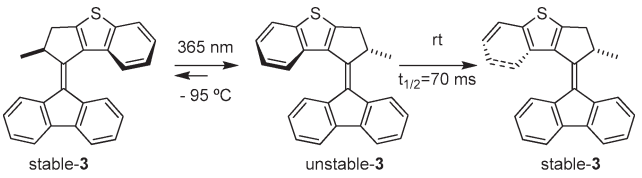


FIGURE 2. Photochemical and thermal steps in the rotary cycle of **3**.

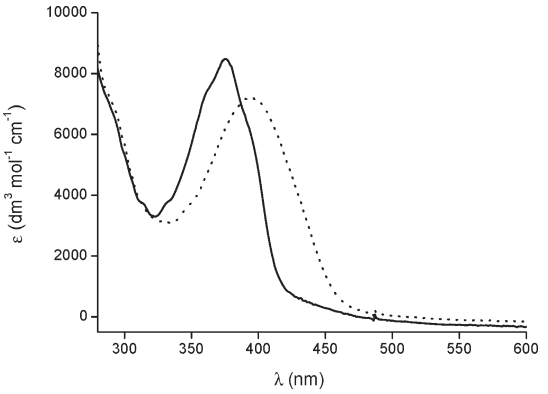


FIGURE 3. UV–vis spectrum of **3** in methylcyclohexane/methylcyclopentane at −153 °C (black) and after irradiation at 365 nm for 30 min (dotted).

arene to regenerate stable-**3**. A repetition of these steps leads to a complete, 360° rotation of the upper-half relative to the lower-half.

The photochemical and thermal behavior of alkene **3** was determined by UV–vis and ^{1}H NMR spectroscopies.[7] A sample of **3** (0.06 mmol/L) in a 1:1 mixture of methylcyclohexane and methylcyclopentane was irradiated (λ_{max} = 365 nm) at −153 °C until no further changes were observed in its UV–vis spectrum (Figure 3). Upon irradiation the longer wavelength absorption of stable-**3** centered at 355 nm red-shifted to a broader absorption band centered at 410 nm. On the basis of data gathered on related overcrowded alkenes, this change is consistent with the formation of unstable-**3**.[6b,c] After allowing the solution to warm to rt, the UV–vis spectrum of the sample was identical with the spectrum of stable-**3**, which is consistent with the regeneration of the stable isomer through a thermal isomerization step.

^{1}H NMR spectroscopy was used to verify that low-temperature irradiation of **3** led to the isomerization of stable-**3** to unstable-**3**.[7] A solution of **3** in THF-d_8 was irradiated at 365 ± 10 nm at $T < -95$ °C until no further changes in the spectrum were observed. Over the course of 2 h, a new set of absorptions appeared in the ^{1}H NMR spectrum (taken at −98 °C) of the sample. By comparison with chemical shifts observed in the photolysis of **2**, these changes were consistent with the clean formation of unstable-**3**. The most diagnostic changes include the downfield shift of the absorption from the methine proton at the stereogenic center from 4.57 to 4.81 ppm, as well as the downfield shift of the absorption from the methyl group at the stereogenic center from 1.40 to 1.62 ppm. Comparison of the integrations of the stable and unstable isomers showed that the photostationary state (PSS) at −95 °C comprised both unstable-**3** and stable-**3** in 2/1 ratio. After allowing the sample to warm to rt, only absorptions from the stable isomer were observed in the ^{1}H NMR spectrum, indicating that the molecule had thermally isomerized to give exclusively stable-**3**.

(7) See the Supporting Information.

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To quantitatively determine how much faster this new motor was compared with **2**, we followed the thermal isomerization process using UV−vis spectroscopy in the temperature range −93 to −53 °C. Applying the Eyring equation,[7] we used the first-order rate constants to determine a Gibbs energy of activation ($\Delta^{\ddagger}G°$) of 66 kJ mol^{-1}. From these data, we extrapolated that the half-life of this unstable isomer at rt is ∼70 ms, thus the isomerization is 3.5×10^3 times faster than that of its predecessor **2**.

We found that truncating the size of the aromatic upper-half from a naphthalene moiety (as in **2**) to a benzothiophene moiety (as in **3**) leads to a dramatic acceleration in the thermal helix inversion. We suggest that the origin of this acceleration could be the reduction of the steric interactions between the upper- and lower-halves of the molecule in the fjord region. We note that this motor-molecule is much faster than its predecessor, making it attractive for future development. One challenge that has to be addressed is that the synthesis of functionalized derivatives of **3** must allow attachment to surfaces and integration in complex molecular machines.

Experimental Section

2-Methyl-2,3-dihydro-1*H*-benzo[*d*]cyclopenta[*b*]thiophen-1-one (5) and 2-Methyl-1*H*-benzo[*d*]cyclopenta[*b*]thiophen-3(2*H*)-one (6). Benzothiophene (1.23 g, 10.0 mmol) was added to stirred polyphosphoric acid (∼20 mL) at 80 °C. After 5 min, methacrylic acid (1.00 g, 11.6 mmol) was added. The mixture was stirred for 1.3 h, allowed to cool to 50 °C, and poured onto ice (∼20 g). The resulting mixture was stirred for 4 h and extracted with EtOAc. The crude product was purified by careful flash chromatography (hexane → hexane:EtOAc, 20:1) to give mixed fractions that could be recrystallized from EtOH to give **5** (630 mg, 31%) and **6** (209 mg, 10%) as white crystals. **5** (first eluting isomer): mp 102.5−103.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (d, J = 7.2 Hz, 3H), 2.88 (dd, J = 17.8, 3.0 Hz, 1H), 3.11 (dquin, J = 2.4, 5.6 Hz, 1H), 3.54 (dd, J = 18.0, 6.8 Hz, 1H), 7.36 (t, J = 7.6 Hz, 1H), 7.45 (t, J = 7.4 Hz, 1H), 7.81 (d, J = 8.0 Hz, 1H), 8.25 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.7, 33.9, 47.3, 122.9 (2C overlapping), 125.4, 125.7, 131.4, 138.8, 144.3, 172.5, 200.7; HRMS (EI) calcd for $C_{12}H_{10}OS$ 202.0452, found 202.0449. Anal. Calcd : C, 71.25; H, 4.98. Found: C, 71.16; H, 4.94. **6** (second eluting isomer): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.41 (d, J = 7.5 Hz, 3H), 2.80 (dd, J = 2.4, 17.4 Hz, 1H), 3.12 (dquin, J = 2.4 7.3 Hz, 1H), 3.48 (dd, J = 17.4, 6.6 Hz, 1H), 7.46 (t, J = 7.5 Hz, 1H), 7.51 (t, J = 7.5 Hz, 1H), 7.88 (d, J = 7.8 Hz, 1H), 7.90 (d, J = 7.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.0, 31.9, 46.2, 123.5, 124.5, 125.0, 128.1, 134.3, 140.0, 148.4, 163.3, 201.5; HRMS (EI) calcd for $C_{12}H_{10}OS$ 202.0452, found 202.0448.

2-Methyl-2,3-dihydro-1*H*-benzo[*d*]cyclopenta[*b*]thiophene-1-thione (7). A solution of ketone **5** (50 mg, 0.25 mmol) in toluene (3 mL) was treated with P_2S_5 (0.500 mmol, 111 mg) and heated at 45 °C for 2.5 h, after which the TLC of the mixture showed near complete conversion of the starting material to a new, faster moving pink compound (R_f 0.6, heptane:EtOAc, 10:1). The mixture was cooled, filtered through a plug of Celite, reduced in vacuo, and purified by flash chromatography (SiO_2, heptane: EtOAc, 10:1) to give the thioketone (49 mg, 88%, 0.22 mmol) as a pink oil that solidified upon standing. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.55 (br s, 3H), 2.98 (d, J = 18.4 Hz, 1H), 3.46 (quin, J = 7.2 Hz, 1H), 3.54 (dd, J = 20.0, 6.0 Hz, 1H), 7.42 (t, J = 8.0 Hz, 1H), 7.50 (t, J = 8.0 Hz, 1H), 7.80 (d, 1H, J = 8.0 Hz), 8.83 (d, 1H, J = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.0, 38.1, 58.9, 122.9, 123.3, 126.0, 126.3, 132.2, 144.4, 149.0, 173.7, 236.2; HRMS calcd for $C_{12}H_{10}S_2$ 218.0224, found 218.0214.

1-(9*H*-Fluoren-9-ylidene)-2-methyl-2,3-dihydro-1*H*-benzo[*d*]-cyclopenta[*b*]thiophene (3). A solution of the thioketone **7** (150 mg, 0.680 mmol) and diazofluorenone (450 mg, 2.32 mmol) in toluene was heated at 80 °C for 3 h, then concentrated to dryness to give a dark red residue. Careful chromatographic purification (SiO_2, eluting with heptane to elute bisfluorenylidene, then heptane: EtOAc, 20:1, R_f(**3**) 0.35) followed by recrystallization from EtOH gave the product alkene **3** as a light orange solid (36 mg, 16%). Mp 139−140 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.46 (d, J = 6.4 Hz, 3H), 2.82 (d, J = 15.2 Hz, 1H), 3.63 (dd, J = 15.4, 6.5 Hz, 1H), 4.56 (quin, J = 6.0 Hz, 1H), 7.07 (t, J = 7.6 Hz, 1H), 7.24 (d, J = 8.0 Hz, 1H), 7.31 (t, J = 7.6 Hz, 1H), 7.30−7.42 (m, 4H), 7.82 (d, J = 7.6 Hz, 1H), 7.85−7.95 (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 19.9, 39.0, 49.1, 119.0, 119.8, 123.2, 123.7, 123.9, 124.1, 125.8, 126.3, 126.44, 126.5, 126.6, 126.8, 133.7, 137.4, 139.4, 139.5, 140.0, 140.3, 144.4, 145.5, 157.5; HRMS $C_{25}H_{18}S$ calcd 350.1129, found 350.1119. Anal. Calcd: C, 71.25; H, 4.98. Found: C, 71.24; H, 4.98.

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Supporting Information Available: Experimental details, characterization data, ^{1}H NMR and ^{13}C NMR spectra of alkene **3** and all the intermediates, low-temperature UV-irradiation. and ^{1}H NMR study of alkene **3**. This material is available free of charge via the Internet at http://pubs.acs.org.