University of Groningen

Braking of a Light-Driven Molecular Rotary Motor by Chemical Stimuli

van Leeuwen, Thomas; Danowski, Wojciech; Pizzolato, Stefano F.; Stacko, Peter; Wezenberg, Sander J.; Feringa, Ben L.

Published in:
Chemistry

DOI:
[10.1002/chem.201704747](https://doi.org/10.1002/chem.201704747)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2018

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

Citation for published version (APA):

van Leeuwen, T., Danowski, W., Pizzolato, S. F., Stacko, P., Wezenberg, S. J., & Feringa, B. L. (2018). Braking of a Light-Driven Molecular Rotary Motor by Chemical Stimuli. *Chemistry*, 24(1), 81-84. <https://doi.org/10.1002/chem.201704747>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

Molecular Motors

Braking of a Light-Driven Molecular Rotary Motor by Chemical Stimuli

Thomas van Leeuwen, Wojciech Danowski, Stefano F. Pizzolato, Peter Štacko, Sander J. Wezenberg,* and Ben L. Feringa*[a]

Abstract: Artificial molecular motors hold great promise for application in responsive functional materials as well as to control the properties of biohybrid systems. Herein a strategy is reported to modulate the rotation of light-driven molecular motors. That is, the rotary speed of a molecular motor, functionalized with a biphenol moiety, could be decreased in situ by non-covalent substrate binding, as was established by ^1H NMR and UV/Vis spectroscopy. These findings constitute an important step in the development of multi-responsive molecular machinery.

Molecular motors and switches are receiving major interest, as the precise tuning of motion at the molecular level enables dynamic control of various functions.^[1] The development of artificial molecular machines has taken inspiration from the variety of biological motors found in nature,^[2] as well as the designs of macroscopic machines.^[3] Although synthetic molecular motors have recently been applied in various fields,^[4] they are still surpassed by their biological counterparts in terms of regulation and adaptability. One of the main characteristics of biological motors, which stands out compared to artificial motors, is their ability to regulate activity in response to multiple stimuli.^[5] While in principle synthetic molecular switches and motors are stimuli-responsive, examples in which an additional orthogonal stimulus can be used to exert an increased level of control are limited.^[6–8] In order to approach the level of complexity found in biological machines, it is crucial to control the behavior of synthetic motors with multiple stimuli.

In our efforts to make light-driven rotary molecular motors multi-responsive, several approaches have been followed. For a motor functionalized with a pseudo-rotaxane, it has been shown that the rotation can be blocked and unblocked by the addition of acid and base.^[6] Also, the direction of rotation of a specific molecular motor could be inverted by using a base as

stimulus.^[7] Most recently, we showed that the rotational speed of light-driven molecular motors can be increased by transition-metal complexation.^[8]

A typical example of a light-driven molecular motor based on an overcrowded alkene and its mode of action are shown in Scheme 1. Irradiation of *(P)*-(*R*)-1, gives rise to a photochemi-

Scheme 1. Four step cycle of the 360° rotation of light-driven rotary motors.

cal isomerization of the double bond (the axle of the rotation). During this process, the stereogenic methyl group, initially in the pseudo-axial orientation, adopts a less favorable pseudo-equatorial position. The obtained *meta*-stable isomer *(M)*-(*R*)-1 can undergo a thermal helix inversion (THI), in which the upper half moves over the lower half, with a concomitant re-orientation of the stereogenic methyl group. The result of the two isomerization steps is a 180° rotation of the upper half relative to the lower half. Another photochemical and subsequent thermal isomerization completes the 360° rotation. It should be noted that for the proper functioning as a rotary motor, the steric interactions between the upper and lower half in the fjord region are crucial. The steric hindrance in the fjord region (Scheme 1) determines the speed of rotation^[9] and furthermore, gives the essential helical chirality to the molecule.

In a recent study it was shown that the THI in biaryl functionalized motors is accompanied by a synchronized rotation around the single bond of the biaryl moiety.^[10] This coupled motion is the consequence of the system's tendency to reduce steric hindrance during the THI. We reasoned that restraining of the biaryl moiety, thereby limiting the rotation around the

[a] T. van Leeuwen, W. Danowski, S. F. Pizzolato, P. Štacko, Dr. S. J. Wezenberg, Prof. Dr. B. L. Feringa
Stratingh Institute for Chemistry, University of Groningen
Nijenborgh 4, 9747 AG Groningen (The Netherlands)
E-mail: s.j.wezenberg@rug.nl
b.l.feringa@rug.nl

Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under:
<https://doi.org/10.1002/chem.201704747>.

single bond, would result in an increase in steric hindrance. In this way, the rotational speed of the light-driven molecular motor may be influenced by chemical stimuli. In this respect biphenol is an especially interesting motif as the straightforward covalent functionalization or the supramolecular binding of a guest is known to influence the conformational mobility substantially.^[11] The biphenol moiety could thus form a “handle” to alter the rotary behavior of the motor (Scheme 2). Herein we describe the synthesis and study of the biphenol functionalized molecular motor **2** in which the chemically-induced restriction of the conformational freedom in the biaryl moiety results in a decrease in rotational speed.

Scheme 2. Molecular motor **2** in which chemically-induced changes in the biphenol moiety translate into a different speed of rotation.

Motor **2** was synthesized in seven steps starting from the commercially available ketone **3**, which was brominated using *N*-bromosuccinimide (NBS) to obtain bromoketone **4**. Suzuki coupling with (2-methoxyphenyl)boronic acid, using the conditions developed by Buchwald et al.,^[12] gave ketone **5**. Deprotonation with lithium diisopropylamide (LDA), followed by the addition of CH_3I , afforded ketone **6**. Conversion of the ketone into the hydrazone was accomplished using hydrazine monohydrate in boiling ethanol. The corresponding diazo com-

pound of hydrazone **7** was obtained by oxidation with phenyliodine bis(trifluoroacetate) (PIFA). Subsequent coupling to freshly prepared thiofluorenone gave the episulfide **8**. Desulfurization with hexamethylphosphanetriamine (HMPT) provided the overcrowded alkene **9**. Finally, motor **2** was obtained by deprotection of the phenol groups using CH_3MgI (Scheme 3).

With the target compound in hand, a series of UV/Vis and ^1H NMR experiments were conducted to study the behavior of compound **2** upon irradiation. ^1H NMR spectroscopy showed that irradiation of **2** with 365 nm light at -50°C , led to the formation of the metastable isomer in a photostationary state (PSS) ratio of 43:57 (metastable:stable) (Figure S16 in the Supporting Information). Heating the sample to room temperature resulted in the conversion of the metastable isomer to the stable isomer, in line with the expected behavior of these overcrowded alkenes. In the UV/Vis spectrum a bathochromic shift with isosbestic points was observed upon the formation of the metastable isomer by irradiation of a solution **2** with 365 nm light at -53°C , (Figure S19 in the Supporting Information). The thermal isomerization of the metastable isomer was followed in time at seven different temperatures (-53°C to -38°C with 2.5°C intervals) using UV/Vis spectroscopy. Eyring analysis was used to determine $\Delta^\ddagger G$ (20°C) for the THI, which was found to be 69.9 kJ mol^{-1} (Figure S33 in the Supporting Information). As the THI of light-driven molecular motors is the rate-determining step of the rotary cycle,^[13] the barrier of the THI is a direct measure of the rotational speed. The found $\Delta^\ddagger G$ for the THI of 69.9 kJ mol^{-1} for **2** corresponds to a rotational frequency of 1.1 Hz at room temperature (Table 1).

Table 1. Characteristics of motors **2**, **10** and complex **2·11**.

Motor	PSS at 365 nm ^[a]	$\Delta^\ddagger G$ (20°C) [kJ mol ⁻¹]	$t_{1/2}$ [s] ^[b]	ω [Hz] ^[c]
2	43:57	69.9	0.32	1.1
10	91:9	93.4	5.0×10^3	7.0×10^{-5}
2·11	80:20	80.9	30	1.2×10^{-2}

[a] Metastable:stable. [b] $t_{1/2} = \ln(2)/k$. [c] $\omega = 1/2 k$.

Scheme 3. Synthesis of motor **2**.

After it was established that the dynamic behavior of motor **2** is as anticipated, it was investigated whether the rotary speed of the motor could be influenced by restraining the biaryl moiety. To this end, motor **10** and **2-11** were studied (see Scheme 2). Compound **10** was obtained from precursor **2** by alkylation with CH_2I_2 using K_2CO_3 as base. The behavior of this motor was also examined with ^1H NMR and UV/Vis spectroscopy. Characteristic shifts in the NMR spectra were observed upon irradiation of **10** with 365 nm light at -30°C , confirming the formation of the metastable isomer (PSS: 91:9 metastable:stable) (see Figure S17 in the Supporting Information). As was also found for compound **2**, a bathochromic shift was observed in the UV/Vis spectrum upon irradiation with 365 nm light at 20°C , indicating the formation of the metastable isomer (Figure 1).

Figure 1. UV/Vis absorption spectra of **10** in CH_2Cl_2 at 20°C upon irradiation with 365 nm light.

The subsequent thermal helix inversion was again followed in time at various temperatures (30°C to 42.5°C) using UV/Vis spectroscopy, and the $\Delta^\ddagger G$ (20°C) for this process was found to be 93.4 kJ mol^{-1} (Figure S34 in the Supporting Information). The increase of 23.5 kJ mol^{-1} in the Gibbs free energy for the THI as compared to the diol precursor signifies a large decrease in the rotational speed. While motor **2** rotates approximately once per second, tethering the biphenol with a methyl-

ene spacer, results in a decrease of the rotational speed by a factor of 1.6×10^4 , effectively braking the rotary motion. Importantly, the methylene spacer can be removed again using HCl (aq) in ethanol. Deceleration of the rotary motion can thus be achieved in a reversible manner. This approach, however, does not allow for in situ control of the behavior of the molecular motor, as it requires two reaction and purification steps. To address these issues, we explored non-covalent methods to restrict the conformational freedom in the biphenol moiety, and thereby alter the rotary motion of the motor. Importantly, it is known for 2,2'-biphenols that they can strongly interact with diamines and aminoalcohols by means of hydrogen bonding.^[11] ^1H NMR spectroscopy confirmed that *trans*-(±)-*N,N'*-dimethyl-1,2-cyclohexanediamine (**11**) can bind to motor **2** in CD_2Cl_2 (Figure S22 in the Supporting Information). In the UV/Vis spectrum a bathochromic shift with clear isosbestic points was observed upon successive addition of **11** to **2**. The binding constant was determined by a titration experiment with UV/Vis spectroscopy and was found to be $K_a = 6.3 \times 10^3\text{ M}^{-1}$ in CH_2Cl_2 (Figure S22 in the Supporting Information). Subsequently, the effect of the diamine binding on the behavior of motor **2** was investigated. To this end, the same experiments were conducted as for motors **2** and **10**. A sample of **2** (2.5 mM) with **11** (4 equiv) in CD_2Cl_2 was irradiated with 365 nm light at -30°C . The binding of **11** did not inhibit the photoisomerization of **2** from the stable to metastable isomer. (Figure 2a and Figure S18 in the Supporting Information). A PSS ratio of 80:20 (metastable:stable) was obtained. Upon heating to room temperature the metastable isomer reverted to the stable isomer. In the UV/Vis absorption spectrum of complex **2-11**, a bathochromic shift was observed with clear isosbestic points upon irradiation with 365 nm light (Figure 2b). The thermal relaxation of the metastable to the stable isomer of **2** complexed with **11** was followed in time at various temperatures (-10°C to 0°C). Eyring analysis of this process gave a $\Delta^\ddagger G$ (20°C) of 80.9 kJ mol^{-1} for the THI (Figure S35 in the Supporting Information). Binding of **11** to **2** thus leads to an increase in $\Delta^\ddagger G$ (20°C) of the THI of 11 kJ mol^{-1} , and hence a decrease of the rotary frequency of motor **2** from 1.1 Hz to 0.012 Hz (see Table 1).

Figure 2. a) ^1H NMR spectrum of **2** (1 mg mL^{-1}) and **11** (4 equiv) in CD_2Cl_2 at -30°C . b) PSS mixture upon irradiation with 365 nm light, 80:20 (metastable:stable). c) The spectrum obtained after heating of the PSS mixture. d) UV/Vis absorption spectra of **2-11** in CH_2Cl_2 at -10°C and spectral changes upon irradiation with 365 nm light.

In order to show that the non-covalent binding of chemical additives to motor **2** enables dynamic control of the motor function, we looked for ways to accomplish decomplexation. The addition of either acetic acid or methanol, resulted in the dissociation of the complex **2**·**11**. (Figure S23–24 in the Supporting Information). Therefore, the use of hydrogen bonding enables dynamic control of the rotary speed of the molecular motor.

In conclusion, we have shown that the rotary behavior of a biphenol-functionalized molecular motor can be controlled via reversible covalent and non-covalent modifications. UV/Vis and ¹H NMR spectroscopy confirmed that **2** functions as a light-driven rotary motor. The tethering of the biphenol moiety with a methylene spacer resulted in a decrease of the rotational speed by a factor of 1.6×10^4 , thereby effectively braking the rotary motor. Furthermore, it was found that the biphenol moiety strongly binds diamine **11**, which also leads to a decrease in speed. As the diamine could be released by addition of either methanol or acetic acid, the behavior of the molecular motor could be reversibly modulated. This approach represents a new way of controlling the molecular motor's properties through chemical triggers and is a key step in the development of light-driven molecular motors that display responsiveness to changes in the environment.

Acknowledgements

Financial support from the Ministry of Education, Culture and Science (Gravitation program 024.001.035), the Netherlands Organization for Scientific Research (NWO-CW, Veni Grant No. 722.014.006 to S.J.W.); European Research Council (Advanced Investigator Grant, No. 694345 to B.L.F) and NRSC catalysis are gratefully acknowledged.

Conflict of interest

The authors declare no conflict of interest.

Keywords: alkenes · biaryl compounds · molecular motors · non-covalent interactions · photochromism

- [1] a) *Molecular Switches*, 2nd ed (Eds.: W. R. Browne, B. L. Feringa), Wiley-VCH, Weinheim, **2011**; b) *From Non-Covalent Assemblies to Molecular Machines* (Eds.: J. P. Sauvage, P. Gaspard), Wiley-VCH, Weinheim, **2010**; c) V. Balzani, A. Credi, M. Venturi, *Molecular Devices and Machines: Concepts and Perspectives for the Nanoworld*, Wiley-VCH, Weinheim, **2008**; d) S. Erbas-Cakmak, D. A. Leigh, C. T. McTernan, A. L. Nussbaumer, *Chem. Rev.* **2015**, *115*, 10081–10206; e) J. M. Abendroth, O. S. Bushuyev, P. S. Weiss, C. J. Barrett, *ACS Nano* **2015**, *9*, 7746–7768; f) A. Coskun, M. Banaszak, R. D. Astumian, J. F. Stoddart, B. A. Grzybowski, *Chem. Soc. Rev.* **2012**, *41*, 19–30; g) A. Credi, S. Silvi, M. Venturi, *Top. Curr. Chem.* **2014**, *354*, 1–34; h) K. Kinbara, T. Aida, *Chem. Rev.* **2005**, *105*, 1377–1400; i) P. K. Kundu, R. Klajn, *ACS Nano* **2014**, *8*, 11913–11916; j) J. M. Spruell, C. J. Hawker, *Chem. Sci.* **2011**, *2*, 18–26; k) D. H. Qu, Q. C. Wang, Q. W. Zhang, X. Ma, H. Tian, *Chem. Rev.* **2015**, *115*, 7543–7588; l) R. Klajn,

- Chem. Soc. Rev.* **2014**, *43*, 148–184; m) J. Zhang, Q. Zou, H. Tian, *Adv. Mater.* **2013**, *25*, 378–399; n) M. M. Russew, S. Hecht, *Adv. Mater.* **2010**, *22*, 3348–3360; o) J. Broichhagen, J. A. Frank, D. Trauner, *Acc. Chem. Res.* **2015**, *48*, 1947–1960; p) M. Dong, A. Babalhavaeji, S. Samanta, A. A. Beharry, G. A. Woolley, *Acc. Chem. Res.* **2015**, *48*, 2662–2670; q) M. M. Lerch, M. J. Hansen, G. M. van Dam, W. Szymanski, B. L. Feringa, *Angew. Chem. Int. Ed.* **2016**, *55*, 10978–10999; *Angew. Chem.* **2016**, *128*, 11140–11163; r) S. Kassem, T. van Leeuwen, A. S. Lubbe, M. R. Wilson, B. L. Feringa, D. A. Leigh, *Chem. Soc. Rev.* **2017**, *46*, 2592–2621.
- [2] Selected examples: a) B. Lewandowski, G. De Bo, J. W. Ward, M. Papmeyer, S. Kuschel, M. J. Aldegunde, P. M. E. Gramlich, D. Heckmann, S. M. Goldup, D. M. D'Souza, A. E. Fernandes, D. A. Leigh, *Science* **2013**, *339*, 189–193; b) M. J. Barrell, A. G. Campaña, M. von Delius, E. M. Geertsema, D. A. Leigh, *Angew. Chem. Int. Ed.* **2011**, *50*, 285–290; *Angew. Chem.* **2011**, *123*, 299–304; c) S. Iamsaard, S. J. Abhoff, B. Matt, T. Kudernac, J. J. L. M. Cornelissen, S. P. Fletcher, N. Katsonis, *Nat. Chem.* **2014**, *6*, 229–235; d) N. Koumura, R. W. Zijlstra, R. A. van Delden, N. Harada, B. L. Feringa, *Nature* **1999**, *401*, 152–155.
- [3] Selected examples: a) T. R. Kelly, H. De Silva, R. A. Silva, *Nature* **1999**, *401*, 150–152; b) M. C. Jiménez, C. Dietrich-Buchecker, J.-P. Sauvage, *Angew. Chem. Int. Ed.* **2000**, *39*, 3284–3287; *Angew. Chem.* **2000**, *112*, 3422–3425; c) J. D. Badjić, V. Balzani, A. Credi, S. Silvi, J. F. Stoddart, *Science* **2004**, *303*, 1845–1849; d) T. Muraoka, K. Kinbara, T. Aida, *Nature* **2006**, *440*, 512–515; e) T. Kudernac, N. Ruangsapapichat, M. Parschau, B. Maciá, N. Katsonis, S. R. Harutyunyan, K.-H. Ernst, B. L. Feringa, *Nature* **2011**, *479*, 208–211; f) K. Zhu, C. A. O'Keefe, V. N. Vukotic, R. W. Schurko, S. J. Loeb, *Nat. Chem.* **2015**, *7*, 514–519; g) S. Liu, D. V. Kondratuk, S. A. L. Rousseaux, G. Gil-Ramírez, M. C. O'Sullivan, J. Cremers, T. D. W. Claridge, H. L. Anderson, *Angew. Chem. Int. Ed.* **2015**, *54*, 5355–5359; *Angew. Chem.* **2015**, *127*, 5445–5449; h) M. R. Wilson, J. Solà, A. Carlone, S. M. Goldup, N. Lebrasseur, D. A. Leigh, *Nature* **2016**, *534*, 235–240; i) H. Ube, Y. Yasuda, H. Sato, M. Shionoya, *Nat. Commun.* **2017**, *8*, 14296.
- [4] Selected examples: a) T. J. Huang, B. Brough, C.-M. Ho, Y. Liu, A. H. Flood, P. A. Bonvallet, H.-R. Tseng, J. F. Stoddart, M. Baller, S. Magonov, *Appl. Phys. Lett.* **2004**, *85*, 5391–5393; b) J. Berná, D. A. Leigh, M. Lubomska, S. M. Mendoza, E. M. Pérez, P. Rudolf, G. Teobaldi, F. Zerbetto, *Nat. Mater.* **2005**, *4*, 704; c) R. Eelkema, M. M. Pollard, J. Vicario, N. Katsonis, B. S. Ramon, C. W. M. Bastiaansen, D. J. Broer, B. L. Feringa, *Nature* **2006**, *440*, 163; d) Q. Li, G. Fuks, E. Moulin, M. Maaloum, M. Rawiso, I. Kulic, J. F. Foy, N. Giuseppone, *Nat. Nanotechnol.* **2015**, *10*, 161–165; e) J. T. Foy, Q. Li, A. Goujon, E. Moulin, O. Schiffman, D. P. Funeriu, *Nat. Nanotechnol.* **2017**, *12*, 540–545; f) J. Wang, B. L. Feringa, *Science* **2011**, *331*, 1429–1432; g) V. García-López, F. Chen, L. G. Nilewski, A. Aliyan, G. Wang, R. Pal, J. M. Tour, *Nature* **2017**, *548*, 567–572.
- [5] M. Schliwa, *Molecular motors*, Wiley-VCH, Weinheim, **2003**.
- [6] D. H. Qu, B. L. Feringa, *Angew. Chem. Int. Ed.* **2010**, *49*, 1107–1110; *Angew. Chem.* **2010**, *122*, 1125–1128.
- [7] N. Ruangsapapichat, M. M. Pollard, S. R. Harutyunyan, B. L. Feringa, *Nat. Chem.* **2011**, *3*, 53–60.
- [8] A. Faulkner, T. van Leeuwen, B. L. Feringa, S. J. Wezenberg, *J. Am. Chem. Soc.* **2016**, *138*, 13597–13603.
- [9] M. M. Pollard, M. Klok, D. Pijper, B. L. Feringa, *Adv. Funct. Mater.* **2007**, *17*, 718–729.
- [10] P. Štacko, J. C. M. Kistemaker, T. van Leeuwen, M.-C. Chang, E. Otten, B. L. Feringa, *Science* **2017**, *356*, 964–968.
- [11] a) T. Mizutani, H. Takagi, O. Hara, T. Horiguchi, H. Ogoshi, *Tetrahedron Lett.* **1997**, *38*, 1991–1994; b) H. Takagi, T. Mizutani, T. Horiguchi, S. Kitagawa, H. Ogoshi, *Org. Biomol. Chem.* **2005**, *3*, 2091–2094; c) Y. Ishii, Y. Onda, Y. Kubo, *Tetrahedron Lett.* **2006**, *47*, 8221–8225.
- [12] T. E. Barder, S. D. Walker, J. R. Martinelli, S. L. Buchwald, *J. Am. Chem. Soc.* **2005**, *127*, 4685–4696.
- [13] J. Conyard, K. Addison, I. A. Heisler, A. Clossen, W. R. Browne, B. L. Feringa, S. R. Meech, *Nat. Chem.* **2012**, *4*, 547–551.

Manuscript received: October 7, 2017

Version of record online: November 20, 2017