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A chemically driven rotary molecular motor based on reversible lactone formation with perfect unidirectionality

Yu Zhang, Zhe Chang, Heng Zhao, Stefano Crespi, Ben L. Feringa* and Depeng Zhao*

¹School of Pharmaceutical Sciences, Sun Yat-sen University, Guangzhou 510006, China

²Stratingh Institute for Chemistry, University of Groningen, Nijenborgh 4, 9747 AG, Groningen, The Netherlands

³Lead Contact

* Correspondence: zhaodp5@mail.sysu.edu.cn

** Correspondence: b.l.feringa@rug.nl

SUMMARY

Among the amazing variety of ingenious molecular machines present in living organisms, enabling motility, responsiveness and out-of-equilibrium behavior among others, rotary motors, like the ATPase and bacterial flagellar motors, hold a special position. While these biological machines are mainly powered by chemical conversion and artificial light-driven rotary molecular motors have been well established, genuine chemically-driven rotary motor systems are very limited. Designing a sequence of highly selective chemical transformations inducing a perfect unidirectional rotary motion around a carbon-carbon single bond axle has shown to be particular challenging. Here, we report a chemically powered rotary molecular motor based on biaryl structures which allows complete unidirectional rotation i.e. > 99% based on simple esterification chemistry. A chiral lactone has been designed which shows stepwise movements fueled by chemical energy completing a full 360° unidirectional rotation. All the stereoisomers involved in the 4-stage rotary process have been characterized using X-ray crystallography confirming the relative stereochemistry of each isomer in accordance with the sequential and complete stereoselective operation of the rotary system. The present molecular motor features a very basic design, powered using fundamental reactions, operates with relative high efficiency in its steps, and shows exceptional control of directionality. Having established the basic principles of this novel molecular rotary motor, it will facilitate the design of more sophisticated future artificial machine systems driven solely by chemical energy.

Keyword : molecular motor, out-of-equilibrium, chemical energy, biaryl, lactone, dynamic covalent bond, unidirectional rotation, isomerization, chirality, system chemistry

The Bigger Picture

As the primary molecular machines in nature, biological molecular motors are capable of performing many complicated mechanical and chemical functions. ATPase, the molecular rotary motor *par excellence* of life itself, produces the fuel in our body while on the other hand biological molecular motors frequently convert chemical energy into mechanical energy, thus enabling controlled movements. Bringing motion to otherwise mechanical inert materials represent a major contemporary challenge and the design of artificial molecular motor and machines is a key step on the route leading from molecules to future dynamic systems. Compared to biological molecular motors, artificial molecular motors have several advantages including flexible design, wide range of building blocks and energy sources, high stability and compatibility, providing great potential to realize novel and sophisticated functions ultimately well beyond those of natural molecular motors. Despite major success with light driven molecular motors, the design of artificial molecular motors driven by chemical energy is still in its infancy. Pertinent challenges include straightforward synthesis, unidirectionality and simple operating conditions learning from the operational principle of biological molecular motors. Here, we report the design of a chemically driven rotary molecular motor, based on biphenyls using dynamic covalent bonds, with perfect unidirectionality. This study shows proof of concept of chirality induced directionality in a chemical fueled molecular motor and paves the way for further discoveries towards new molecular motors with chemically simple operational principles. The ability to control motion

INTRODUCTION

RESULTS AND DISCUSSION

A

Point chirality

Induced helicity

Dynamic covalent bond

B

Energy

Reaction Progress

C

Rotor

MeOCOC

MOMO

OBn

Stator

(S,S') -M1

- Energy barrier without fuel: ~136 KJ/mol
- Clockwise rotation
- 100% unidirectionality

D

Station I

Station II

Station III

Station IV

Step 1

Step 2

Step 3

Step 4

cyclization step **A**, helix inversion step **B**, and ring-opening step **C**. (C) Structure and key features of molecular motor (*S*, *S'*)-**M1**. (D) Schematic representation of the 360° rotation of molecular motor (*S*, *S'*)-**M1** (top view).

Focusing on the development of new rotary motor with rotation around a biaryl C-C bond we build on the principle that biaryl rotation i.e. atropisomer interconversion³⁵⁻³⁸ is facilitated by bridging (in ortho-positions) both aryl moieties. Previously, we demonstrated atropisomer selectivity using enantioselective reduction of a lactone with an additional chiral catalyst or Pd-based redox cycle using a chiral sulfone as bridging (ligand) group.^{24,25} Although showing a proof of principle, in the first system 8 steps were required with an overall yield of 28% for one full rotation whereas in the second one, unidirectional rotation of one cycle was realized in an overall yield of 19% over 5 steps. In contrast, in the novel approach presented here to direct the biaryl interconversion, the system undergoes a full 360° rotation with complete (>99%) unidirectionality in an overall yield of 57% in 6 steps based on simple esterification, ester hydrolysis as the key steps.

The design, structure and key components of a chemically driven molecular motor are shown in Fig 1A. The following principles are essential to achieve the unidirectional rotary motion: i) the biaryl unit should have three or four substituents in ortho positions to ensure restricted rotation about the sp²-sp² aryl bond.³⁹ With a sufficient high barrier of biaryl rotation, thermal isomerization between distinct atropisomers would be extremely slow and thus random Brownian motion around the single bond is prohibited. ii) the presence of a chiral element on one ortho substituent. Point chirality is preferred since it is readily introduced into the side chain of the compound, which is expected to induce a preferred helicity once two aryl rings are bridged to give two helical conformers (diastereoisomers eg. *S*, *M* and *S*, *P*). iii) finally, the upper ring with functional group **B** and the lower ring with two functional group **A** (Fig 1A) should form a dynamic covalent bond in a ring structure which can readily cyclize and open on demand. Two orthogonal protecting groups for group **A** should be employed to realize selective protection/deprotection which are crucial to achieve directional motion of the biaryl rotor.

The energy diagram of fueled 180° unidirectional rotation is depicted in figure 1B. The activation barrier of the atropisomerization process of the biaryl molecular motor without fuel is high (Fig 1B, left panel). Once fueled with chemical energy as shown in figure 1B (right panel), the upper half and the lower half are cyclized to form a bridge. This provides a thermodynamically less favored isomer (step **A**) and meanwhile the energy barrier of thermal helix inversion is dramatically reduced due to smaller biaryl twist angle approaching a planar transition state.^{35,36,38} Subsequent helix inversion step **B** gives the thermodynamically favored isomer. The 180° unidirectional rotation is accomplished by the subsequent ring-opening step **C**. Following the same mechanism, the next half cycle can be achieved following the same sequence of steps enabling a full 360° rotary cycle.

This mechanism is reminiscent of the operation of myosins in biological system, which are responsible for a variety of movements of muscle and non-muscle cells, where myosin binds to actin and forms a bridge and generate a power stroke by hydrolysis of ATP.⁴⁰

The clockwise 360° rotation of the molecular motor is illustrated in Figure 1D. Viewed along the biaryl C-C bond (the axle of rotation), the rotary process consists of four steps including two cyclization steps (step 1 and step 3) and two ring-opening steps (step 2 and step 4). In the present system, the upper ring is assigned as the rotor and the lower ring is assigned as the stator. The chemical fueled cycle starts from station I (top-view). In step 1, the functional group (orange) on the rotor with a chiral element (green) forms a bridge with the functional group on the left side (blue) of the stator selectively using a chemical conversion. The cyclization gives a high-energy intermediate which undergoes further helix inversion to the more stable station II with the rotor part flipping from front to back. In step 2, the ring is opened with another transformation reaching open-chain station III without back flipping and a net 180° rotation is achieved in a unidirectional manner. Similarly, the remaining half cycle can be achieved with the same sequence of steps. The only difference is that the rotor forms a bridge with stator on the right side (red) in step 3 with the rotor flipping to the front side. After step 4, the rotor returns to its initial conformation and the whole 360° rotary motion is completed. In all four steps, chemical energy is directly coupled with movement and force is generated to achieve directional motion.

The structure and key features of molecular motor (*S*, *S'*)-**M1** are given in Fig 1C. As for the dynamic covalent bond, a lactone was chosen and therefore the upper ring of the biaryl incorporates a chiral carboxylic ester group in the ortho position while the lower one has two phenolic groups orthogonal protected with benzyl (Bn) and methoxymethyl (MOM), respectively. Due to the presence of three bulky ortho functional groups, the molecule exists as atropisomers, (*S*, *S'*)-**M1** and (*S*, *R'*)-**M3**. Here, *S* and *R* denote the configuration at the

stereogenic center, *S'* and *R'* are used to define the axial chirality of atropisomers, and *P* and *M* denote the helicities of the lactone (vide infra). It should be noted that the rotation direction in the present system is dictated by the stereogenic center of the molecular motor, i.e. the (*S*)-enantiomer undergoes clockwise rotation around the single bond and the (*R*)-enantiomer undergoes anti-clockwise rotation. Hence enantiomerically pure compounds are required in the present study because if the compound is partially racemized during any of the rotation steps it would undergo rotation in the opposite direction.

Synthesis of the molecular motor.

Key procedures for synthesis of enantiomeric and diastereomeric pure (*S*, *S'*)-**M1** are given in Scheme 1. Methyl (*S*)-2-(2-bromophenyl) propanoate (**S**)-**1** was obtained by asymmetric synthesis with >99% ee as shown in the Supplemental Information (Figure S1). (**S**)-**1** was coupled with boronic acid **2** using a Pd catalyzed Suzuki coupling to give (**S**)-**3** in 90% yield without affecting the stereochemical purity as determined by chiral HPLC analysis. Subsequently, demethylation was carried out with BBr₃ and mono-hydroxyl lactone (*S*, *M*)-**4** was obtained as the exclusive product with >99% ee. Key to our design is the seven-membered ring lactone formation, since the unidirectionality of the motor is determined in this step by the preferred helicity that is induced (e.g. *S*, *M* over *S*, *P*). To our delight, lactone formation showed only one set of absorptions at ambient temperature in the ¹H NMR spectrum of the product attributed to (*S*, *M*)-**4**. Overlapping of signals from (*S*, *M*)-**4** and (*S*, *P*)-**4** due to fast interconversion was excluded by low temperature NMR studies. The sample showed cleanly one set of peaks in CDCl₃ at -50 °C as well as in CD₃OD at -90 °C without any phase domain separation, whereas related seven-membered ring lactams have been reported to form another diastereomer at room temperature.³⁶ Subsequently, (*S*, *M*)-**M4** was obtained by protection of the hydroxyl moiety with a methoxymethyl group using NaH and MOMCl in DMF. Again, ¹H NMR study of (*S*, *M*)-**M4** in CDCl₃, both at ambient temperature and -50 °C, revealed that only one helical configuration existed in the compound. The relative configuration and helicity of (*S*, *M*)-**M4** was determined using single crystal X-Ray diffraction of a racemic sample (Figure 3B). Ring opening of (*S*, *M*)-**M4** with MeONa in MeOH and THF gave (*S*, *S'*)-**5** in 94 % yield as the exclusive product. Finally, protection of the hydroxyl in (*S*, *S'*)-**5** with benzylbromide afforded (*S*, *S'*)-**M1** with 92% yield (99% ee). The relative configuration of (*S*, *S'*)-**M1** was unambiguously established by single crystal X-Ray diffraction of a racemic crystal. The energy barrier for atropisomerization was studied using **S6**, an analogue of (*S*, *S'*)-**M1** obtained after methyl ester hydrolysis, at elevated temperature (Figure S2). Analysis of the kinetic data provided $\Delta G^\ddagger = 136$ kJ/mol at 160 °C and identical ground-state energies (final ratio of atropisomers of **S6** ~1:1). The high energy barrier guarantees its conformational stability during transformations (Figure S4).

Scheme 1. Synthesis of molecular motor (*S*, *S'*)-M1**.** (i) K₂CO₃, PdCl₂ (dtbpf), (THF: H₂O = 1:1), 65 °C, 16 h, 90 %. (ii) BBr₃, DCM, -78 °C overnight and 30 min at rt, 97 %. (iii) NaH, MOMCl, DMF, 5 h, 90 %. (iv) MeONa, MeOH/THF, 0 °C, 10 h, 94 %. (v) benzyl bromide, K₂CO₃, DMF, rt, 12 h, 92 %.

Rotation cycle of the molecular motor.

The 360° rotatory cycle of the molecular motor (*S*,*S'*)-**M1** is shown in Figure 2 and the individual steps as well as the various isomers studied by NMR, UV/Vis, chiral HPLC, CD spectroscopy and X-ray analysis. The first half cycle involves unidirectional rotation from (*S*, *S'*)-**M1** to (*S*, *R'*)-**M3**. It should be noted the sequence of deprotection of the protected phenolic hydroxyl groups is critical. Release of the proper hydroxyl group ensures the formation of thermodynamically less favored (*S*, *P*)-isomer of the lactone primarily, which subsequently isomerizes to the favored isomer (*S*, *M*)-isomer and as a consequence generates unidirectional movement (>99% stereoselective for **M2** after lactonization/isomerization). Selective deprotection of MOM under acidic conditions and hydrolysis of the methyl ester with NaOH afforded (*S*, *R*)-**6** in a one-pot procedure in 95 % yield. This deprotection is highly selective without affecting the benzyl group and no biaryl rotation is taken place. (*S*, *R*)-**6** was then lactonized with EDCI, which is the fuel of rotation. (*S*, *P*)-**M2** was supposed to form during cyclization as a transient species which rapidly

isomerized to (*S, M*)-**M2** with the upper ring rotating about 90° clockwise. Similar as seen for (*S, M*)-**M4**, only one diastereomer is observed in the ¹H NMR spectrum indicating >99% unidirectionality. DFT calculations of the transient and stable lactones confirm the helix inversion step and unidirectional rotation of (*S, P*)-**M2** to (*S, M*)-**M2**. The movement of the methyl from a pseudo-axial position in (*S, P*)-**M2** to a pseudo-equatorial one in (*S, M*)-**M2** drives the atropisomerization of the biphenyl core (predicted unidirectionality > 97%, see Figure 2, right insert). The absolute configuration of (*S, M*)-**M2** was unambiguously established by single crystal X-Ray diffraction as well.

Figure 2. The 360° rotation of molecular motor (*S, S'*)-M1**.** Six steps for 360° rotation of the molecular motor: (A) HCl, MeOH, rt, overnight, then NaOH aq., 15 h, 95 %. (B) EDCI, Et₃N, DCM, 26 °C, 16 h, 97%. (C) MeONa, MeOH/THF, 0 °C, 10 h then NaH, MOMCl, DMF, 0 °C, 5 h, 82%. (D) Pd/C, H₂, and then added aq. NaOH, 15 h, 92%. (E) EDCI, Et₃N, DCM, 26 °C, 16 h, 94%. (F) MeONa, 10 h, with following benzyl bromide, DMF, rt, 12 h, 87%. In the inserts, the calculated energy differences between less stable and stable atropisomers of **M2** and **M4** and the barriers for the unidirectional rotation in step B (right side) and E (left side) are shown.

Subsequent ring opening by nucleophilic substitution with MeONa and reprotection of the phenol moiety with a MOM protecting group gave (*S, R'*)-**M3** exclusively without observation of (*S, S'*)-**M1** as confirmed by both ¹H NMR and HPLC (Figure 3A and 5B). The absolute configuration of (*S, R'*)-**M3** was also unambiguously confirmed by single crystal X-Ray diffraction of an optical pure sample. The remaining half cycle was accomplished following the same principle. The rotary motion from (*S, R'*)-**M3** to (*S, S'*)-**M1** started from selective debenzilation with Pd/C and H₂ and hydrolysis of methyl ester of (*S, R'*)-**M3**. The corresponding product (*S, R'*)-**7** was cyclized with EDCI to give (*S, M*)-**M4** after a thermal helix inversion of (*S, P*)-**M4**. Also in this case DFT analysis confirmed the atropisomerization of (*S, P*)-**M4** to (*S, M*)-**M4** and as a consequence the unidirectionality of the motion (predicted unidirectionality > 97%, see Figure 2, left inset). The obtained product showed exactly the same characteristics as the isomer obtained from the preparation of (*S, S'*)-**M1** as confirmed by ¹H NMR and CD spectroscopy. Similar as shown in Scheme 1, ring opening and benzylation of (*S, M*)-**M4** afforded (*S, S'*)-**M1** exclusively again indicating nearly perfect (>99%) unidirectionality. It should be mentioned there is no inversion at stereocentre during the whole cycle of unidirectional rotation as confirmed by NMR, CD and HPLC (Figure 4C and Figure 5) although it is well known that the α position of the carbonyl group might enolize under strong acidic or basic conditions.

Figure 3. ¹H NMR spectra and crystal structures of four stations of molecular motor. (A) ¹H NMR (400 MHz, CDCl₃, 298 K) spectra of four stations of the molecular motor: (S, S')-M1, (S, M)-M2, (S, R')-M3 and (S, M)-M4. (B) Crystal structures of (S, S')-M1, (S, M)-M2, (S, R')-M3 and (S, M)-M4.

Crystal structures of the isomers in the four stations of the molecular motor are given in Figure 3B. They unequivocally confirm the sequence of chemical driven isomerization steps. The twist angles θ in (S, S')-M1 and (S, R')-M3 are 75° and 66°, respectively, which are much larger than the angle of biphenyl (~45°) due to steric repulsions by these ortho groups. On the contrary, the twist angle θ in (S, M)-M2 and (S, M)-M4 are very similar with those of biphenyl, 44° and 45°, respectively.^{43,42} It is interesting to note that the seven-membered ring in (S, M)-M2 and (S, M)-M4 adopts a boat conformation with the methyl group in an equatorial position. The ultraviolet (UV) absorption and circular dichroism (CD) spectra of all isomers of the molecular motor were also measured as shown in Figure 4. It is known that biaryls and its derivatives without ortho substituents have intense absorption ($\epsilon_{\text{max}} > 10,000$) around 250 nm, due to extensive interaction of the electron π system between lower and upper arene rings. As shown in Figure 4A, the open-chain isomers (S, S')-M1 and (S, R')-M3 show very weak absorption around 250 nm. This can be explained by the fact that ortho substituents severely hinder a planar arrangement of the two aromatic rings resulting in the diminished π orbital overlap and a considerable lower molecular extinction coefficient of this characteristic band, especially for biaryls with two or more bulky ortho substituents.⁴³⁻⁴⁶ On the contrary, cyclized isomers (S, M)-M2 and (S, M)-M4 show considerably more intense absorption around 250 nm as non-substituted biphenyl which is in agreement with smaller dihedral angle revealed by the crystal structure. In the region of the $n \rightarrow \pi^*$ transition around 275 nm, (S, M)-M2 and (S, M)-M4 show further bathochromic shifts comparing with (S, S')-M1 and (S, R')-M3 due to increased conjugation. With respect to CD absorption spectra, (S, S')-M1 and (S, R')-M3 show distinct CD absorptions as shown in Figure 4C. However, weak CD bands at 280 nm with opposite sign were observed, coincident with $n \rightarrow \pi^*$ transition in the UV spectra. The CD spectra of (S, M)-M2 and (S, M)-M4 are very similar which is in consistent with the fact that their stereochemistry is the same. They both show strong positive Cotton effects at ~250 nm and a less intensive positive absorption band at ~285 nm (Figure 4D).

In summary, as shown in Figure 2, our novel molecular motor (S, S')-M1 can rotate 180° clockwise arriving at its diastereomer (S, R')-M3 upon deprotection, cyclization, helix inversion and reprotection. In a similar manner, (S, R')-M3 can rotate 180° clockwise realizing overall 360° rotary cycle with the same sequence of reactions. Each step and isomer are fully characterized by NMR (Figure 3A), CD (Figure 4), and uniquely X-ray structures of each isomer (Figure 3B), indicating high selectivity and unidirectionality over the entire 360° rotary cycle.

Figure 4. UV/Vis and CD spectra of the isomers at the four stations of molecular motor. (A) and (C) UV-vis (CH_3CN , $2.5 \times 10^{-5} \text{ M}$, 298K) and CD spectra (CH_3CN , $2.5 \times 10^{-5} \text{ M}$, 298K) of (*S, S'*)-**M1**, (black line) and (*S, R'*)-**M3** (red line), respectively. (B) and (D) UV-vis (CH_3CN , $5.0 \times 10^{-5} \text{ M}$, 298K) and CD spectra (CH_3CN , $5.0 \times 10^{-5} \text{ M}$, 298K) of (*S, M*)-**M2**, (black line) and (*S, M*)-**M4** (red line).

Figure 5. Chiral HPLC chromatograms of (*S, S'*)-**M1** and (*S, R'*)-**M3** obtained during 360° rotation of molecular motor. Although (*S, S'*)-**M1** and (*S, R'*)-**M3** are diastereomers and the isomerization cycle can be monitored by NMR, the rotary cycle was also monitored by chiral HPLC to ensure there is no racemization during the reaction sequences. (A) Initial state: HPLC trace of enantiopure (*S, S'*)-**M1** (IA column, 25°C , 1.0 mL/min , n-hexane/i-propanol = 98/2, $\lambda = 254 \text{ nm}$). (B) HPLC trace of (*S, R'*)-**M3** after 180° rotation. (IA column, 25°C , 1.0 mL/min ,

n-hexane/i-propanol = 98/2, λ = 254 nm). (C) HPLC trace of (S, S')-**M1** after 360° rotation (IA column, 25 °C, 1.0 mL/min, n-hexane/i-propanol = 98/2, λ = 254 nm). (S, S')-**M1** was obtained with 99% ee after a whole cycle rotation. (D) Overlaid HPLC traces of racemic **M1** and **M3** as a reference. (IA column, 25 °C, 1.0 mL/min, n-hexane/i-propanol = 98/2, λ = 254 nm). The four diastereomers of **M1** and **M3** could not be separated with any available column.

CONCLUSION

Altogether, these experimental data clearly demonstrate that the molecular motor undergoes 360° unidirectional clockwise rotation driven by sequential addition of chemical fuels. In principle, the other enantiomer should rotate in the opposite direction under the same reaction sequences. Within the limits of the measurement using both NMR and chiral HPLC (and confirmed by DFT calculations) full (>99%) unidirectionality is achieved due to high preference for a preferred helicity induced by the stereogenic center in the key component seven-membered ring lactone and the ring opening with a small nucleophile NaOMe. Importantly, for the first time all the isomers of a molecular motor during the entire rotary process have been characterized using X-ray analysis providing an unequivocal proof of clockwise unidirectional rotation of the molecular motor. This molecular motor rotation proceeds through a series of stepwise movements which are crucial to design new dynamic multistate systems. The present system might help us to gain a better understanding of the mechanism of molecular machines and enabling to build more sophisticated artificial systems driven solely by chemical energy or a combination of light and chemical energy in future.

EXPERIMENTAL PROCEDURES

Full experimental procedures are provided in the Supplemental Information.

DATA AND SOFTWARE AVAILABILITY

Crystallographic data for the structures reported in this paper have been deposited at the Cambridge Crystallographic Data Center (CCDC), with accession numbers CCDC: 1914279 (**M1**), 1914275 (**M2**), 1914282 (**M3**) and 1914274 (**M4**).

SUPPLEMENTAL INFORMATION

Supplemental Information includes Supplemental Experimental Procedures, 61 figures, and 4 tables and can be found with this article online at

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AUTHOR CONTRIBUTIONS

Y.Z., D.Z. and B.L.F. conceived the project; Y.Z., Z.C., and H.Z. performed the experiments; S.C. performed the DFT analysis; D.Z. helped with the experiments and analysis; D.Z., B.L.F., Y.Z. and Z.C. wrote the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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A chemically driven molecular motor has been designed which proceeds through stepwise movements fueled by chemical energy and undergoes full 360° unidirectional rotation. A record, nearly 100% unidirectionality is realized during the whole rotary process.