

and that the constellation of all eight genes together make an exceptionally virulent virus in the model systems examined. In fact, no other human influenza viruses that have been tested show a similar pathogenicity for mice 3 to 4 days after infection. This information provides a partial explanation for what made this virus so lethal. In this regard, it should be noted that the U.S. Food and Drug Administration (FDA)-approved antiviral drugs, oseltamivir and amantadine, have been shown to be effective against viruses carrying the 1918 NA and the 1918 M gene, respectively (22). Furthermore, vaccines containing the 1918 HA and NA were protective in mice (26).

Note added in proof: This research was done by staff taking antiviral prophylaxis and using stringent biosafety precautions (15) to protect the researchers, the environment, and the public. The fundamental purpose of this work was to provide information critical to protect public health and to develop measures effective against future influenza pandemics.

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Materials and Methods

Fig. S1

Table S1

References and Notes

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REPORTS

A Reversible, Unidirectional Molecular Rotary Motor Driven by Chemical Energy

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With the long-term goal of producing nanometer-scale machines, we describe here the unidirectional rotary motion of a synthetic molecular structure fueled by chemical conversions. The basis of the rotation is the movement of a phenyl rotor relative to a naphthyl stator about a single bond axle. The sense of rotation is governed by the choice of chemical reagents that power the motor through four chemically distinct stations. Within the stations, the rotor is held in place by structural features that limit the extent of the rotor's Brownian motion relative to the stator.

One of the most challenging components required for the fabrication of molecular machines (1–5) is the rotary motor (6, 7): the element that converts energy into controlled rotational motion (8). Natural systems often use adenosine triphosphate (ATP) as an energy source. Rotation in these systems is powered by the energy released upon the hydrolytic conversion of ATP to the diphosphate ADP (6, 9, 10). The system introduced here analogously uses exothermic chemical reactions to power unidirectional rotary motion.

Previous synthetic molecular motor designs have often relied on external light or voltage as an energy source. Recent reports include repetitive, light-driven unidirectional motion about double bonds (11–13), as well as multistep reaction sequences that induce unidirectional (14) and reversible (15) mechanical motion in interlocked molecular rings, partly through photochemistry. A nanometer-scale rotational actuator based on multiwalled carbon nanotubes has also been demonstrated (16). Theory further predicts the feasibility of inducing unidirectional rotation about a single bond in a chiral system by applying linearly polarized laser pulses within optimized electric fields (17, 18), and inducing mechanical motion in a double-walled carbon nanotube by applying axially varying electrical voltage (19).

Purely chemical strategies have been scarcer (7, 20, 21). Limited unidirectional (120°) rotation about a single bond in a helically shaped molecule (22, 23) has been achieved with a modified molecular ratchet (24–26). Here, we report a system that uses chemical energy to achieve unidirectional 360° rotation of one half of the molecule relative to the other half (Fig. 1). The rotation is driven by a combination of chemical reactions and random thermal (Brownian) motion. Understanding these processes may be relevant to natural molecular motors, which work on similar principles.

Our system consists of a rotor half and a stator half, connected by a single carbon-carbon bond which acts as the axis of rotation (Fig. 1). Chemical reactions control movement of the rotor through four structurally distinct stations, with the net effect of turning the rotor 360° relative to the stator. Bonding and steric constraints limit the extent of the rotor's uncontrolled Brownian motion. In two of the stations (Fig. 1, stations A and C) the rotor's position is restricted by the action of additional chemical bonds, although helix inversion can occur. In stations B and D (Fig. 1), the rotor and stator cannot pass each other due to nonbonding interactions. Movement between the stations is guided by four power strokes, or chemically induced rotational events. The complete cycle involves two bond-breaking steps (step 1 and step 3) and two bond-making steps (step 2 and step 4), each of which provides the driving force for approximately 90° unidirectional rotation to the next station.

Two general mechanisms (27) for the conversion of energy into mechanical motion have

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been identified: the power stroke (28, 29) and the Brownian motor (30, 31). The present motor relies on a power stroke mechanism to achieve unidirectional motion, the sense of which is solely dependent on chemical reactivity and not on inherent asymmetry within the motor itself. In a power stroke mechanism, the chemical reaction is mechanically coupled to movement and force is directly generated to move the motor forward (28, 29).

The locking of the upper rotor and lower stator was achieved by the presence of a lactone unit (structures **1a** and **1c** in Fig. 2). The *ortho* substituents on the aryl rings in structures **1b** and **1d** (Fig. 2) block free axial rotation for steric reasons and thereby prevent thermal helix inversion in the unlocked states.

Key to the overall unidirectional motion of the rotor are asymmetric reductive ring opening reactions of lactones **1a** and **1c** (32–34). The use of (*S*)-2-methyl-oxazaborolidine [(*S*)-CBS reagent] (32) resulted in an excellent enantioselectivity (ratio of 96.8:3.2 and 90.3:9.7 starting from **1a** and **1c**, respectively) and high preference for the rotor to move in the clockwise direction (Fig. 2). The sense of rotation induced in breaking the lactone bond (Fig. 2, step 1, **1a** → **1b** and step 3, **1c** → **1d**) is determined solely by the chirality of the fuel—i.e., the chiral reducing agent. Thus (*R*)-CBS could be used to drive counterclockwise rotation instead. Similarly, the sense in steps 2 and 4 is also controlled by the choice of chemical reagents, in this case the order of deprotection of the rotor's enantiotopic hydroxyl groups. After deprotection, the selectively released phenol group undergoes lactonization to return the rotor to **1c** or **1a**.

The order of the chemical transformations is essential (Fig. 2). The phenolic alcohols, which are the initial reduction products of **1a** and **1c**, must first be protected at the phenol position. After protection of the phenol moieties, the alcohols must be oxidized to the acids **1b** and **1d** before the opposite (orthogonally protected) phenol group is deprotected (in subsequent steps 2 and 4). Oxidation of an unprotected hydroxy phenol would form a lactol in situ. The rotational barriers of such biphenolic lactols are expected to be low (34), so the rotor would cross the plane of the stator and wide-angle oscillation would occur. When the rotor moves from **1b** → **1c** and **1d** → **1a**, complete unidirectionality is achieved by selectively unmasking only one of the phenolic hydroxyl groups.

Sterically congested 1-(4-methoxybenzyloxy)-6*H*-naphth[2,1-*c*]chromen-6-one (**1a**) was prepared from 1-bromo-2-naphthoic acid (35). Step 1 entailed first the asymmetric reduction of the lactone moiety in **1a** to a configurationally stable diol intermediate (34, 36) with a phenol on the rotor and a benzylic alcohol on the stator. Subsequent orthogonal protection of the phenol with an allyl group, then oxidation of the benzylic alcohol provided carboxylic acid **1b** (35). In step 2, removal of the *para*-methoxybenzyl (PMB)

protecting group induced spontaneous cyclization to lactone **1c**. Step 3, like step 1, involved asymmetric reduction of lactone **1c**, protection of the phenol with a PMB group, and alcohol oxidation to provide carboxylic acid **1d**. Finally, in step 4, removal of the allyl protecting group is followed by lactonization to regenerate **1a**. The whole reaction sequence produces a net unidirectional rotation of the rotor about the stator. Not all of the chemical manipulations in this cycle actually produce motion; however, each chemical conversion is currently a necessary component of the motor's design. These reac-

tions are used either to interconvert functionality so that motion is energetically favorable, or to ensure that the entire 360° rotational process occurs exclusively in one direction.

Although the lactone bond locks the rotor in place in **1a** and **1c**, these species are configurationally unstable and have a low barrier to racemization of the atropisomers (Fig. 3) (33, 34). Because the rotor and stator can pass through coplanarity by means of limited partial rotation (shown for **1a** in Fig. 3), the lactones exist as a racemic mixture of rapidly inverting helices. From this dynamic equilibrium, a stereoselective

Fig. 1. Schematic illustration for the operation of unidirectional power stroke motor **1**. A rotor (yellow and blue) is driven, about an axis, in the clockwise direction relative to the position of a stator (red). Four stations A to D are involved. Directionally selective bond breaking processes (step 1 and step 3) drive movement between stations.

These steps alternate with directionally selective bond-making chemical reactions (step 2 and step 4). The bond-breaking processes rely on chiral nonracemic chemical fuel that discriminates between the two dynamically equilibrating helical forms of A or C. The bond-making processes between the rotor and the stator use the principle of orthogonal chemical reactivity to achieve unidirectionality: Either the yellow or the blue end of the rotor can be selectively bound to the stator to form A or C.

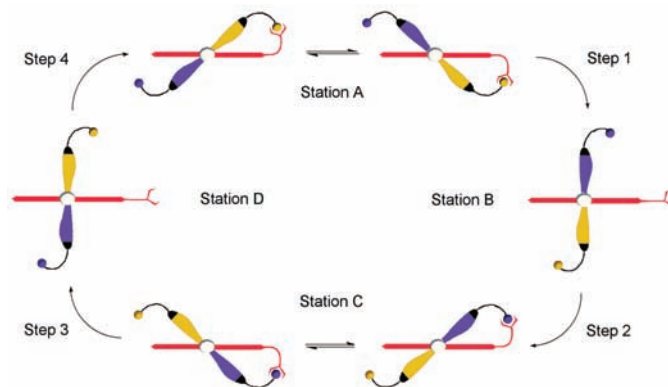
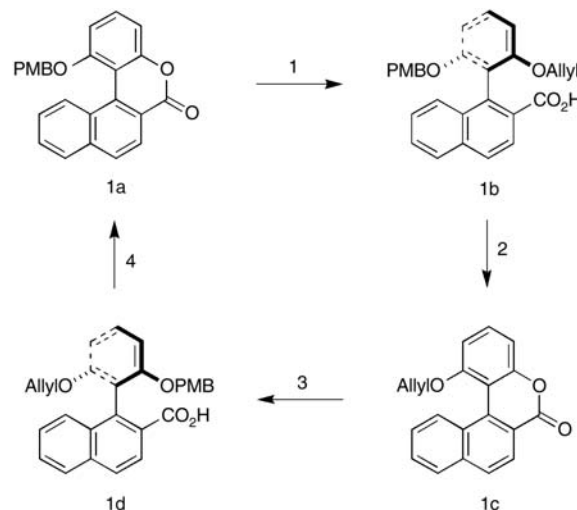


Fig. 2. Chemical structures and reaction scheme for unidirectional chemically driven rotary motor **1**. The rotary cycle had four steps employing the following reagents and conditions (unless otherwise stated, reactions were carried out at room temperature, and the percentage yields refer to preparatively isolated compounds). **Step 1** had two parts: (i) First, **1a** was reduced with (*S*)-2-methyl-CBS-oxazaborolidine and $\text{BH}_3\cdot\text{THF}$ in toluene and THF at 0°C for 25 min to give a 92% yield of a diol (bearing a phenol and an alcohol). The ratio of molecules that have undergone rotation in the indicated direction was 96.8 to 3.2. (ii) The phenol moiety was then alkylated by allyl bromide in a suspension of K_2CO_3 in DMF over 20 hours. Next, the alcohol moiety was oxidized to an aldehyde by $\text{CrO}_3\cdot\text{H}_2\text{SO}_4\cdot\text{H}_2\text{O}$ in acetone for 2 hours, and then to an acid by NaClO_2 in the presence of 2-methyl-2-butene in AcOH , H_2O , and THF over 1 hour to give **1b** in 76% overall yield. In **Step 2**, the PMB ether was cleaved by $\text{Ce}(\text{OTf})_3$ in MeNO_2 in the presence of 1,3-dimethoxybenzene at 60°C for 25 min to give **1c** in 76% yield. **Step 3** had three parts: (i) First, the lactone was reduced by (*S*)-2-methyl-CBS-oxazaborolidine and $\text{BH}_3\cdot\text{THF}$ in a solution of toluene and THF at 0°C for 7 min to give the diol (again bearing one phenol, one alcohol) in 56% yield. The ratio of molecules that underwent rotation in the indicated direction was 90.3 to 9.7. (ii) The phenol moiety was then alkylated by *p*-methoxybenzyl chloride in a suspension of K_2CO_3 and NaI in refluxing acetone over 30 hours to give the product in 87% yield. (iii) The alcohol moiety was oxidized first to the aldehyde by MnO_2 in CH_2Cl_2 for 48 hours, then to the acid by NaClO_2 in a solution of 2-methyl-2-butene, AcOH , H_2O , and THF for 1 hour to give **1d** in 82% overall yield. In **Step 4**, deprotection of the phenol by removing the allyl group was achieved with $\text{Pd}(\text{PPh}_3)_4$ and HCO_2H in refluxing THF over 24 hours and the product cyclized with *N,N'*-dicyclohexylcarbodiimide over 15 min to give the lactone **1a** in 99% overall yield. [The complete cycle including all intermediates is provided (35).]



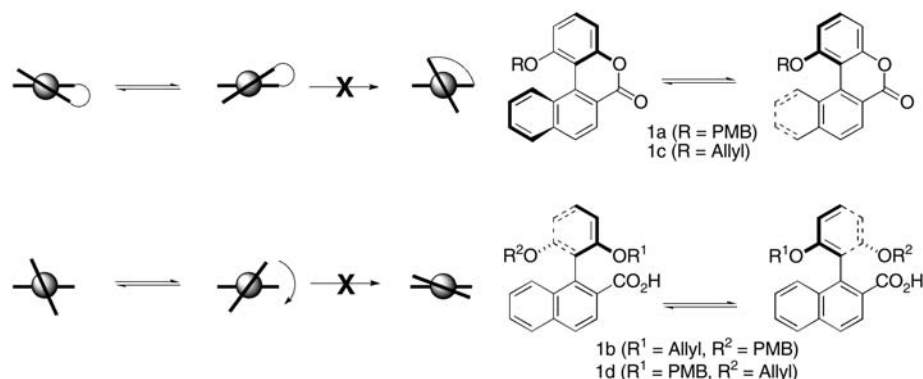


Fig. 3. Dynamic processes due to thermal rotary motion around the biaryl single bond in **1**. Projections are along biaryl single bond axis. In station A the lactone moiety locks the rotor in place relative to the stator. The lactone **1a** is configurationally unstable and limited movement in the form of dynamic helix inversion (biaryl rotation) occurs. In the open form of the motor **1b** partial rotation of the rotor relative to the stator can occur, but for steric reasons the rotor and the stator cannot pass each other. The same dynamic stereochemistry applies to **1c** and **1d**.

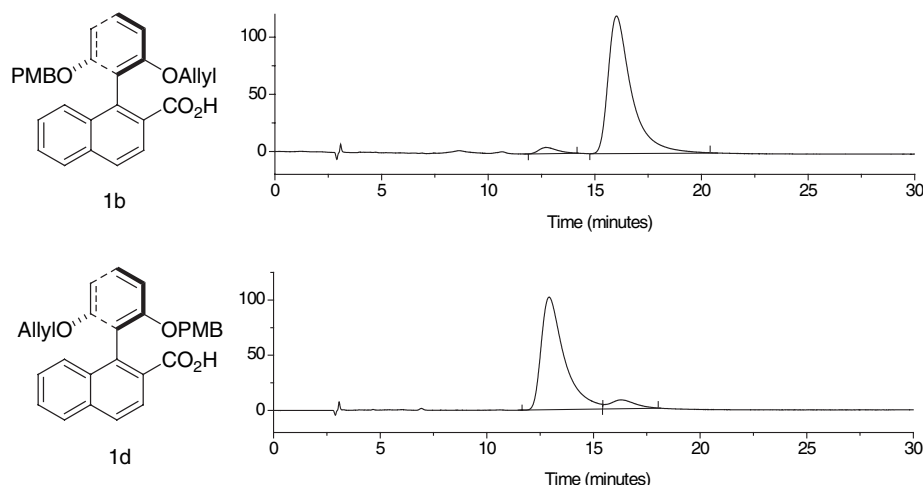


Fig. 4. Chiral HPLC chromatograms of **1b** and **1d** obtained from step 1 and step 3 (Fig. 2), respectively. Conditions: chiralpak AD column (0.46 × 15 cm); eluant 75:25 heptane-isopropanol; flow rate 0.6 ml/min; detection at 225 nm, temperature 40°C. The use of achiral NaBH₄ instead of (S)-2-methyl-CBS-oxazaborolidine produces two peaks of equal intensity (racemic **1b/1d**).

ring opening reaction with homochiral CBS reagents leads to unidirectional 90° rotation. In the open forms **1b** and **1d**, only partial rotation around the biaryl single bond can occur (shown for **1b** in Fig. 3); racemization is sterically precluded at room temperature (34, 36, 37).

The degree to which the rotation was unidirectional was determined by analyzing compounds **1b** and **1d** with the use of high-performance liquid chromatography (HPLC) with a chiral nonracemic stationary phase (Fig. 4 and supporting online material text). To confirm the location of the rotor relative to the stator, a mixture of **1b** and **1d** was prepared independently by performing the ring opening sequence of **1a** with racemic fuel (sodium borohydride). As expected, ring opening of **1a** occurred in both directions to generate an equal mixture of **1b** and **1d**. These species are enantiomers and have identical spectral data. Comparison of the HPLC traces of the racemic mixture with the HPLC traces of **1b** and **1d** generated by asym-

metric opening in our motor system revealed >90% directional selectivity for the motor sequence (Fig. 4). Thus, although motor **1** does require a number of synthetic steps, the absolute control in directionality for each of the four rotational events is between 90 and 100%.

The combination of reactions, purifications, and the time scale involved for the motor's function make it less practical than previously reported light-driven synthetic motors (11–13). However, this reversible rotary motor does establish that chemically driven 360° unidirectional rotation is feasible. The rotation is controlled, because the chemical events driving rotation are highly selective for a specific direction. Furthermore, each of the four stations provides a deep enough thermodynamic well to restrict thermal randomization of the rotational sense.

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SOM Text

Figs. S1 to S3

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