Research Article

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.

References and Notes

21. Materials and methods are available as supporting material on Science Online.

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
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 stages.

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 is determined 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 enantiomeric 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)-6H-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 benzyl alcohol on the stator. Subsequent orthogonal protection of the phenol with an allyl group, then oxidation of the benzyl 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 reactions 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. 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 x 15 cm); eluant 75:25 heptane-isoproplanol; flow rate 0.6 ml/min; detection at 225 nm, temperature 40°C. The use of achiral NaBH4 instead of (S)-2-methyl-CBS-oxazaborolindione 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 asymmetric 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.

References and Notes

35. Materials and methods are available as supporting material on Science Online.
36. The configurational stability of the open forms was confirmed by chiral HPLC analysis, which showed no change in the enantiomeric ratio of the open forms throughout the chemical transformations.
37. The configurational stability of 1b and 1d was also verified by following its circular dichroism with respect to time. No change was observed after monitoring for 2 hours at 100°C.
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