SYNTHETIC MOLECULAR MOTORS

Reported by Jordan R. Quinn May 1, 2003

INTRODUCTION

Biological molecular motors such as ATP synthase[1] and muscle tissue[2] (Figure 1) produce motions that are reminiscent of macroscopic machines. Though difficult to reproduce synthetically, the construction of such microscopic devices from atoms[4] (the "bottom-up" approach) is being pursued because of the intrinsic limitations of manipulating smaller and smaller pieces of matter (the "top-down" approach).[5] Artificial molecular devices such as wires and switches have been studied extensively, but molecular motors are becoming popular synthetic targets. A long range goal of this technology is to assemble molecular devices into molecular-scale machines capable of processing and storing data.[6]

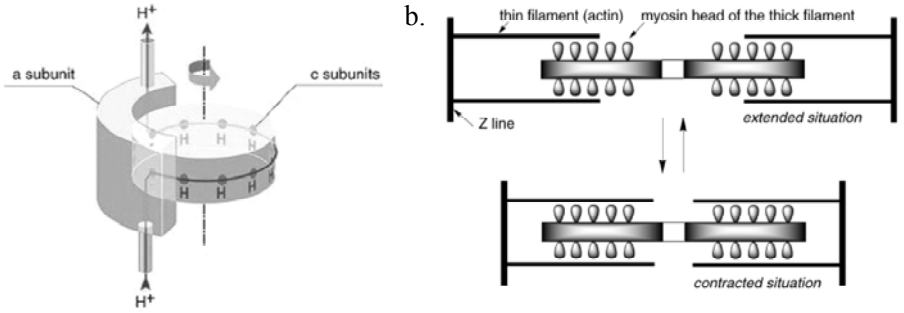


Figure 1. (a) The rotation of the F_o domain of ATP synthase is driven by a proton gradient.[1b] (b) The linear motion of muscle is driven by chemical energy as ATP is hydrolyzed.[3] (reproduced with permission)

Defining Molecular Motors

A molecular motor is composed of a discrete number of atoms and produces molecular or supramolecular motions of its component parts.[7] The motor responds to an input (energy) with an output (work) and must produce a unidirectional, cyclic process (Figure 2). Energy is often in the form of light, heat, chemical energy, or an electrochemical potential difference. Contemporary motors are usually powered by light or a potential difference because thermal gradients are difficult to maintain over small distances and chemically powered motors produce waste products. Motors are dependent on Brownian motion, but according to the 2nd law of thermodynamics, work cannot be derived from random movement.[8,9] Movement on the molecular scale is not as intuitive as it is on the macroscopic scale so molecular motor activity is simplified with a classical mechanical description of motion.[10]

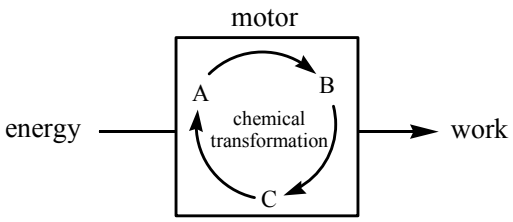


Figure 2. Schematic of a molecular motor.

Motors can be either rotary or linear, depending on the types of motion they produce. The most prominent examples of biological rotary and linear motors are ATP synthase (Figure 1a) and muscle tissue (Figure 1b). The types of motions in synthetic motors include rotation about a bond, conformational changes, or movement induced by non-covalent interactions. Rotary motors have the

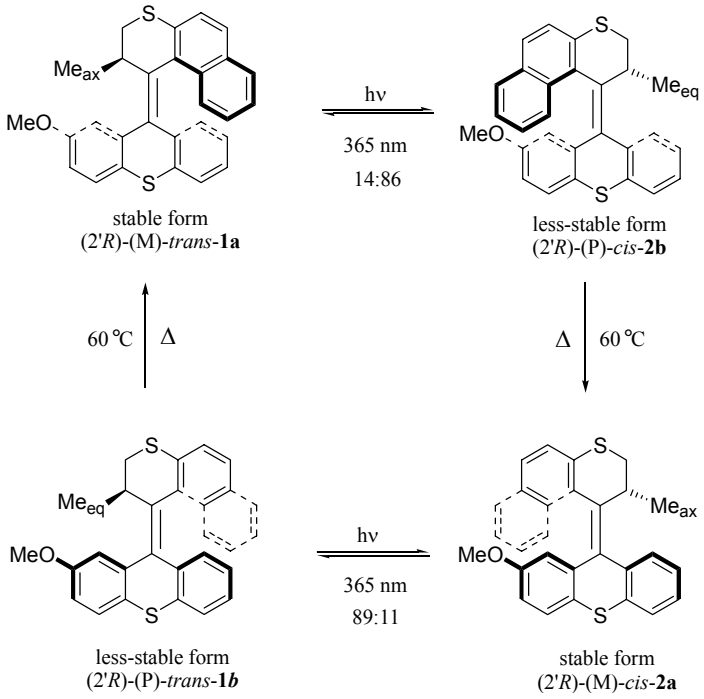
additional proviso of continuous 360° rotation, and must be chiral to produce unidirectional motion. Although most synthetic molecular motors do not fulfill all of these specifications, they must have the potential to perform work. Several of the existing motors are based on the cis-trans isomerization of a double bond[11,12] or the intermolecular interactions of rotaxanes.[3,13,14] Others employ bulky triptycene[15] or porphyrin[16] substituents as rotors. There has even been an attempt to produce a motor from DNA.[17] This review will cover these recent efforts to replicate macroscopic instruments with molecular analogs.

ROTARY MOLECULAR MOTORS

Crowded Alkene-Based Molecular Motors

Feringa and coworkers[11] have synthesized a rotary motor that operates by isomerization about a sterically crowded C=C double bond. The motor shown in Scheme 1 was obtained in five steps as a mixture of racemic **1a** and **2a**. A crystal structure of (2′*R*)-(M)-*trans*-**1a** confirmed that the methyl substituent adopts a pseudoaxial orientation to minimize steric interaction with the thioxanthene heterocycle. The thioxanthene moiety adopts a folded structure and the thiopyran takes on a pseudo-boat conformation. Together these structural features give the molecule its helical shape. When enantiopure **1a** was irradiated at 10 ºC, a cis-trans isomerization occurred with concomitant inversion of helicity (M to P helicity). Changes in helicity were confirmed by CD absorption spectroscopy.

Scheme 1



Semiempirical calculations (AM1) estimate that conformer **2b** is 4.65 kcal/mol higher in energy than **2a**; hence thermal isomerization is essentially quantitative at 60 °C. When the methyl group adopts the pseudoaxial orientation, the reverse rotation pathway is effectively blocked. Subsequent irradiation of (2′*R*)-(M)-*cis*-**2a** at low temperature produced **1b** with inversion of helicity (P to M) and double bond isomerization (cis to trans) with a modest 89:11 photoequilibrium. When the motor was irradiated at 60 °C, a continuous, unidirectional rotation resulted. The imperfect photoequilibrum does not affect the repetitive unidirectional nature of this motor because each photochemical and thermal step still produces a helix inversion.

The prominent feature of the crowded-alkene motors is the ability to control both rotational rate and direction. The direction of rotation is determined by a single stereogenic center, but the thermal isomerization barrier must be adjusted to control rotational rate. Scheme 2 shows modifications to the motor that result in attenuated rates of rotation (Table 1). As the bonds to X and Y become longer, the upper and lower halves of the molecule overlap more, and the energies of activation are increased for the thermal steps. The crowded-alkene motors display continuous, unidirectional 360° rotation with rates that can be adjusted by varying X and Y.

Scheme 2

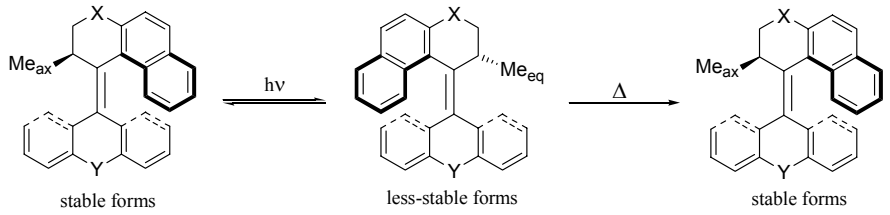


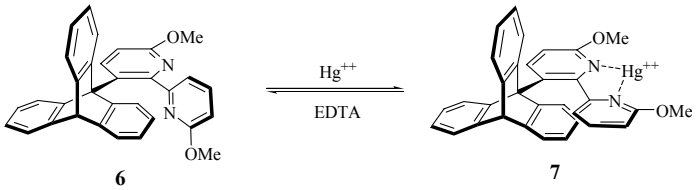
Table 1. Rotational Rates of Crowded-Alkene Motors

motor	X	Y	$t_{1/2}^{\theta}$ (h)
3	CH_2	S	0.67
4	S	O	26.3
5	S	S	215

Triptycyl-Based Molecular Motor

Kelly's triptycyl-based molecular motor[15] evolved from a molecular brake[18] and a failed molecular ratchet.[19] The arrest of motion in a molecular machine is often just as difficult to control as its creation. The molecular brake shown in Scheme 3 functions by inhibiting the rotation of a triptycyl unit around an sp^3 C-C bond. The triptycene wheel spins rapidly at 30 °C, as the twelve aromatic triptycene protons of **6** gave rise to 4 NMR resonances. Addition of $Hg(O_2CCF_3)_2$ produced significant broadening of these peaks, and cooling to –30 °C resolved the triptycene protons into two sets. In the presence of EDTA, the Hg^{2+} was sequestered and the brake was disengaged. The molecular brake was extended to a molecular ratchet, but rotation of the triptycene in the ratchet was found to be bidirectional.

Scheme 3



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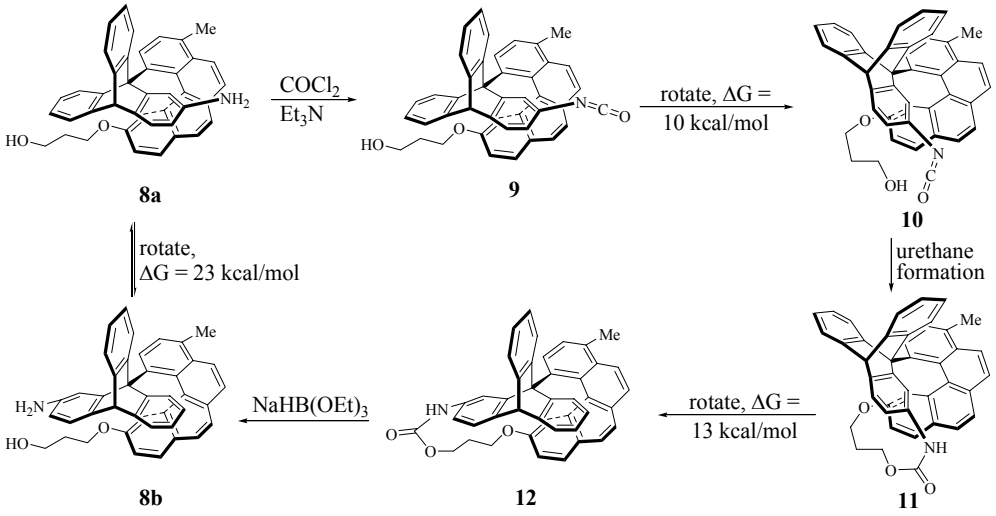
A prototype of a molecular motor (Scheme 4) was created using concepts developed in the brake and ratchet studies. Compound **8** was synthesized as a mixture of three atropisomers with a rotational barrier of 25 kcal/mol for the triptycene rotor. The atropisomers were separated by semipreparative thin layer chromatography and characterized by 1-D and 2-D variable temperature NMR spectroscopy. Reaction of isomer **8a** with phosgene "fuel" gave the corresponding isocyanate (**7**). Clockwise rotation of the triptycene brings the isocyanate and the hydroxyl groups sufficiently close to react (**10**). When the hydroxypropyl tether and the isocyanate groups are in proximity, irreversible formation of urethane **11** occurs. Ambient thermal energy then drives the exergonic, unidirectional rotation of **11** to **12**.

Scheme 4



Cleavage of the urethane gave atropisomer **8b** that was spectroscopically identical to a previously synthesized sample. Urethanes are usually hydrolyzed at high temperature, but low temperature was needed to avoid equilibration of atropisomers. Sodium borohydride in ethanol cleaved the urethane at 0 ºC, but only in 11% yield. The barrier to rotation for **8a** to **8b** was estimated by semiempirical calculations (AM1) to be 23 kcal/mol, which corresponds to a $t_{1/2}$ of 3 h at 25 ºC. These calculations also indicated that the rate of rotation could be changed by adjusting the urethane rotational barrier (**11** to **12**). A hydroxyethyl tether would decrease the rate of rotation by increasing the E_a; however, geometric constraints prevented cyclization to the urethane. Although rotation is not continuous and the rate could not be regulated, the triptycene-based motor displays unidirectional 120º rotation. Kelly proposed that for repeated rotation, the triptycyl substituent needs to be armed with three amine groups, and the delivery of phosgene and hydride must be directed to the proper face of the molecule.

Rotaxane-Based Molecular Motors

A supramolecular approach to rotary motors has been investigated by Vögtle and coworkers using rotaxanes.[13] The motor consists of two wheels around an axle with a bulky stopper on each end (Figure 3). Although the components of the rotaxane are achiral, together they become a cycloenantiomeric [3]rotaxane.[20] The enantiomers were synthesized by allowing the dibromide "axle" (**13**) to react with the alcohol "stopper" (**14**) in the presence of the wheel (**15**). Cycloenantiomers are formed when the directionality of the wheels is opposite, but when the wheels are oriented with the same directionality, meso rotaxanes are formed. The cyclostereoisomers

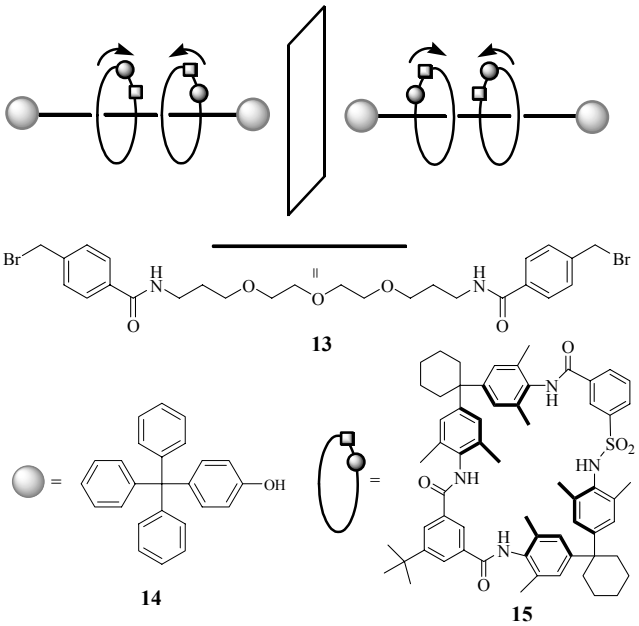


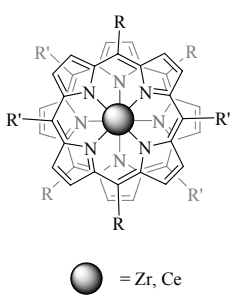
Figure 3. Cycloenantiomeric rotaxane motor and its molecular components.

were obtained in 29% yield and in a statistical ratio of stereoisomers (*meso*:(+):(–) = 2:1:1). The enantiomers were separated by chiral HPLC, and CD confirmed their opposite chirality. Cycloenantiomeric [2]rotaxanes have also been synthesized from achiral components by using two different stoppers to encage a single wheel around an axle.[21] Both of these approaches to unidirectional, large-amplitude motion gave rise to potential motors, but controlled movement of these rotaxanes has yet to be developed.

Porphyrin-Based Molecular Motors

The rotation motion of porphyrin ligands of metal bisporphyrinate double-decker complexes can be controlled by redox reactions.[16] This phenomenon originates from the π-electron interaction between the facing porphyrins of the complex. In D_2-chiral complexes such as those shown in Table 2, the rate of rotation corresponds to the rate of racemization. Therefore, the optical activity of enantiomers **16-18** could be used to investigate the rotation dynamics of the porphyrin ligands. One-electron reduction of $Ce^{(IV)}$ complexes produced a 300-fold rotational rate increase. This was attributed to weakened π-interactions resulting from an increased ionic radius (from 0.97 Å to 1.14 Å). Acid-catalyzed oxidation of Zr^{4+} complexes gave rise to varying rate decreases, corresponding to an ionic radius decrease and stronger π-interactions. The directionality of porphyrin-based motors cannot be controlled, but chiral substituents may induce a preferred direction of rotation.

Table 2. Structures of Bisporphyrinate Double-Decker Complexes

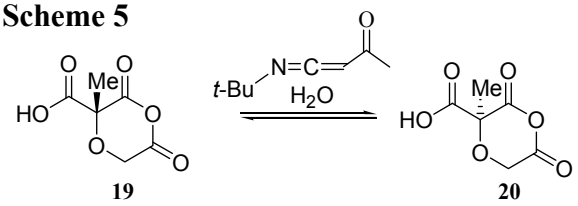


compound	R	R'
16	—H	—Me
17	—OMe (2)	—Me
18	—OMe (2)	—F (5)

Tricarboxylate Molecular Motor

The tricarboxylate motor devised by Mock and Ochwat[22] (Scheme 5) functions by continuous epimerization of a stereocenter as it consumes acylketenimine fuel. Cyclic anhydride **19** catalyzes the exothermic hydration of the acylketenimine to the corresponding amide, and in the process, the R-enantiomer is epimerized to the S-enantiomer (**20**). Reaction of **19** with the acylketenimine, followed by hydrolytic opening of the cyclic anhydride gives a diacid intermediate. One acid group then displaces an amide waste product to give **20**. This motor produces a forced repetitive motion, but the authors do not show that chirality is inverted with each catalytic cycle. The oscillatory motion of stereocenter epimerization may be capable of producing motion suitable for a rotary or linear motor, but the tricarboxylate catalytic cycle should not yet be called a motor.

Scheme 5



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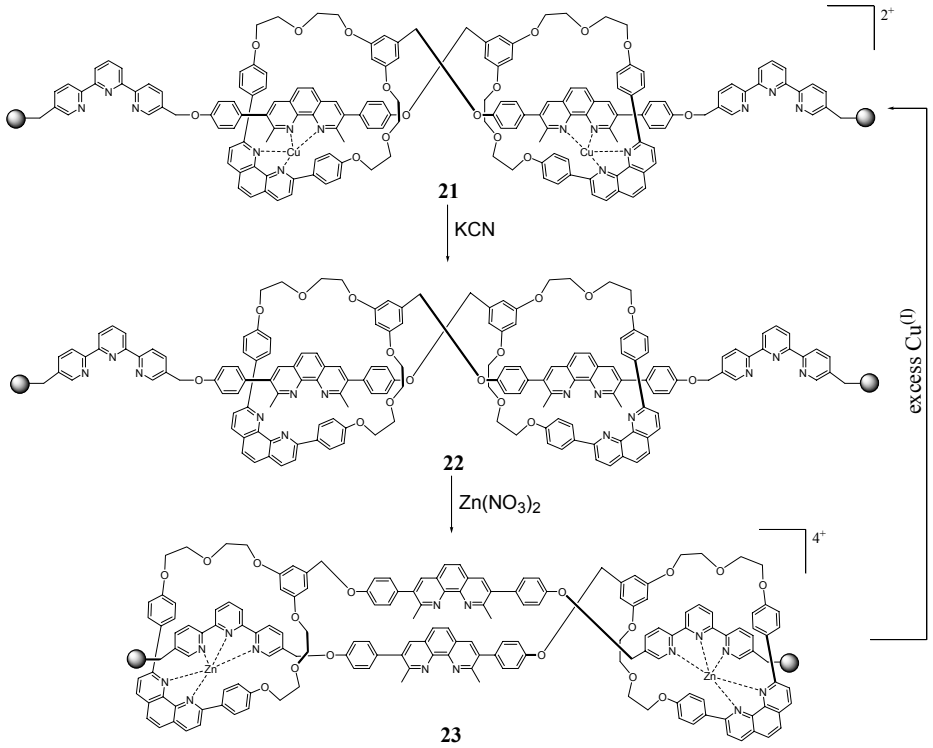
LINEAR MOLECULAR MOTORS

Rotaxane-Based Molecular Motor

Sauvage et al.[3,14] synthesized a rotaxane dimer (Scheme 6) that mimics the action of natural muscle tissue. This artificial molecular muscle is capable of stretching and contracting when exposed to different reagents. Similar rotaxane-based devices have been termed shuttles,[23] but molecular muscle is referred to as a motor because of the resemblance to its biological counterpart (Figure 1b). The motor was designed so the components would glide along each other like the filaments of natural muscle. CPK modeling suggested that a 31-member macrocycle would be large enough to allow the "threading" of a phenanthroline belonging to an opposite rod, but small enough to avoid intramolecular $Cu^{(I)}$ complexation between the two phenanthrolines of the same unit. After dimerization, bulky substituents were introduced at the ends of the motor to prevent "dethreading." The motor was synthesized in 23 steps from commercially available phenanthroline starting material.

Scheme 6



Movement of the motor was induced by a chemical reaction as metals exchange. When bound to $Cu^{(I)}$ the motor is contracted (**21**$^{2+}$), and it becomes extended when bound to $Zn^{(II)}$ (**23**$^{4+}$). The extended state results from the coordination of a $Cu^{(I)}$ ion with the phenanthroline units of each monomer. Addition of excess KCN frees the ligands, and **22** is subsequently remetalated with $Zn(NO_3)_2$. The motor is contracted when one phenanthroline and one terpyridine bind to pentacoordinate $Zn^{(II)}$. Reaction with $Cu(CH_3CN)_4 \bullet PF_6$ returns the motor to its extended conformation. Extensive 1D and 2D ^{1}H NMR analysis of isolated intermediates **21**$^{2+}$ and **23**$^{4+}$ supported the proposed motion of the motor. From CPK model estimations, the length of the dimer changes from ~83 Å to ~65 Å (22% change), comparable to the 27% change in natural muscle length.

DNA-Based Molecular Motor

The DNA nanomotor of Tan and Li[17] operates by cycling between open and closed forms of a 17mer DNA oligonucleotide (Figure 4). Guanosine forms tetramers in solution, and when strategically incorporated into DNA, a tetraplex (**17**) forms.[24] The ends of the tetraplex are forced away from each other when a complementary strand of DNA (α) is added. If the complementary strand is longer than the tetraplex, adding tetraplex with additional bases on one end (β) will displace the complementary strand α. The driving force is the production of a longer and more stable complex (αβ) with the overall effect being the back-and-forth movement of the ends of the tetraplex. This motion was detected by fluorescence when one end of the tetraplex was equipped with a fluorophore and the other with a quencher. A similar cycling of fluorescence was observed when one end of the motor was attached to biotin and immobilized on streptavidin-coated silica nanoparticles. The motion of the DNA motor resembles more closely the folding of a protein than the motion of other linear molecular motors.

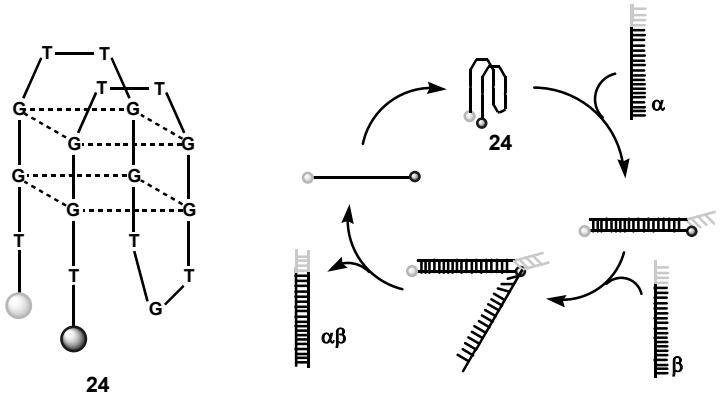


Figure 4. Schematic of a DNA molecular motor.

Azobenzene-Based Molecular Motor

The photoinduced cis-trans isomerization of azobenzene has been exploited in numerous molecular devices because of its simplicity and reversibility. Multiple azobenzenes were incorporated into a polymer (Figure 5) and induced to contract (cis conformation) or to extend (trans conformation), depending on the wavelength of irradiation.[12] Polymer **25** was synthesized by polycondensation of an azobenzene-containing peptide then coupling to Fmoc-Cys(Trt)-O(Succinimidyl). The cysteine end of the polymer was attached to a probe tip via a gold-sulfur covalent bond, and the carboxyl end was attached with an amide bond to an amino-functionalized glass surface. When irradiated with 365-nm light, the polymer length was shortened against an external load of 400 pN, as measured using single-molecule force spectroscopy. The polymer could then be extended by irradiating with 430-nm light to give a length change of ~3% for n = 46. The overall spring-like motion of the azobenzene motor could be useful for constructing complicated machines, but the small length change is a shortcoming of this motor.

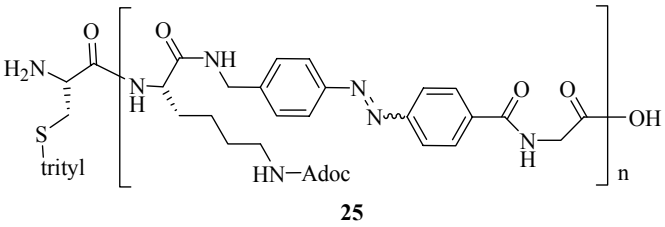


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Figure 5. Azobenzene polypeptide molecular motor.

CONCLUSION AND FUTURE DIRECTION

A variety of approaches to modulate the translational and rotational motion of molecules have been reported. Feringa's crowded-alkenes are the only synthetic molecular motors that display unidirectional, 360º rotation. Furthermore, the rotational rate and direction of these motors can be adjusted with simple synthetic substitutions. Immobilizing molecular motors onto surfaces is an area of active research that will allow the assembly of molecular devices into intricate molecular architecture. The crowded-alkene motors represent the standard in the field of molecular motors, but biological motors display near quantitative energy efficiency. Improvements will continue in the design of efficient synthetic motors that are easily synthesized and conveniently controlled.

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