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Molecular Motor

A Molecular Four-Stroke Motor**

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Dedicated to Professor Rolf Gleiter on the occasion of his 75th birthday

One of the most challenging aspect in the construction of molecular analogues of mechanical devices[1–4] is the creation of synthetic molecular motors which utilize the unidirectional movements of smaller parts and which thus should be able to perform a physical task.[5,6] Almost all synthetic molecular motors described to date are rotary motors. The axis of the rotation in these motors is a single or a double chemical bond or a mechanical bond, and is coincident with the center where energy is transformed into mechanical work.[7,8] As their flexible parts remain the same size during a cycle, they perform a simple rotation like that found in the F1-ATPase in nature.[9] Thus they are designed to transport an attached molecule in a rotation movement of 360°, but they are not able to transport surrounding molecules in one definite direction—they just distribute them in a circular movement.

Herein we present a synthetic molecular motor that has a motion sequence which resembles the movement of motile cilia.[10] Motile cilia are widely found in nature and, through their beating movement, are used either for the transport of particles and surrounding medium or for the locomotion of cells. As our motor works in a similar way, it should automatically push surrounding molecules in a definite direction during a four-stroke cycle. The essential principle is the spatial separation of the area where chemical energy is transformed into mechanical work, from the rotation axis.

The design and the concept of our molecular four-stroke motor is illustrated in Figure 1. The central part of the motor is a chiral clamp,[11] which we have already successfully used for the control of unidirectional movements and for the design of a molecular chirality pendulum.[12,13] Through the chiral clamp, the clamp-bound pyridine rings of the bipyridine units are fixed in a cycle, and thus adopt a *P* configuration with respect to each other. One of the bipyridine units carries a light-switchable azobenzene unit and is the chemically driven pushing blade of the motor. The other bipyridine unit acts as a stopper and controls the direction of the movement. An alternating stimulation of the whole blade and the azobenzene unit of the blade leads in sum to a 360° rotation of the phenyl group of the azobenzene unit around a virtual axis.

Let's consider the states of the rotation process in detail. The molecule *trans*-(*P*)-**1** corresponds to state **I** of the rotation cycle. As non-complexed 2,2′-biypridine units have an N-C-C-N dihedral angle of about 180°,[14] the arm of the blade (azobenzene unit) and the arm of the stopper (bromine) in *trans*-(*P*)-**1** have a definite relative spatial configuration (the *P* configuration).[13] The addition of salts containing metal ions, such as Zn^{2+}, leads to a complexation of the 2,2′-bipyridines and thus the complex *trans*-(*M*)-**1***Zn_2^{4+} is formed which represents state **IV** of the rotation cycle. As metal-complexed 2,2′-bipyridines have a N-C-C-N dihedral angle of around 0°, the transition from state **I** to state **IV** is accompanied by a movement of the blade. The reversibility of this movement—the backward movement of the blade—is achieved chemically by the addition of cyclam which complexes the Zn^{2+} ions better than the bipyridine units of **1**. The second important process for the cycle is the light-induced switching of the azo group.[15] In the *trans* configuration of the azo group (state **I**) the *para*-bonded hydrogen atom points away from the bipyridine unit whereas in the *cis* configuration (state **II**) it is orientated toward the bipyridine unit. Thus, the *trans*→*cis* isomerization of the azobenzene group triggered by UV irradiation ($\lambda = 355$ nm) is accompanied by a folding of the blade. This transition (**I**→**II**) is also reversible. The reverse state change from **II**→**I** takes place on a brief irradiation of the *cis* isomer with visible light. The whole rotation cycle consists of an alternating combination of the rotation movement of the blade and its light-induced folding and opening: Exposure of *trans*-(*P*)-**1** to UV light at 20 °C induces *trans*→*cis* isomerization and results in a transition from state **I** to state **II** (first stroke). The addition of Zn^{2+} leads to a movement of the blade (second stroke) and the complex *cis*-(*M*)-**1***Zn_2^{4+} representing state **III** in the cycle is formed. This stroke resembles the recovery stroke of motile cilia. The third stroke (**III**→**IV**; opening of the blade) is the *cis*→*trans* back isomerization to *trans*-(*M*)-**1***Zn_2^{4+} induced by visible light. The backward movement of the opened blade triggered by the addition of cyclam (fourth stroke) resembles the effective stroke of motile cilia. As the opened blade can push more molecules in one direction (fourth stroke) than the closed blade in the other (second stroke) there should be a net transport of the surrounding molecules in one direction.

An important requirement for the motor is that the movement of the blade must proceed unidirectionally. To check if this is true for the motor **1**, the reference compound **2** was investigated. The only difference between **1** and **2** is the absence of the azobenzene unit in molecule **2**. In principle there are two possible ways for the movement of the blade. In

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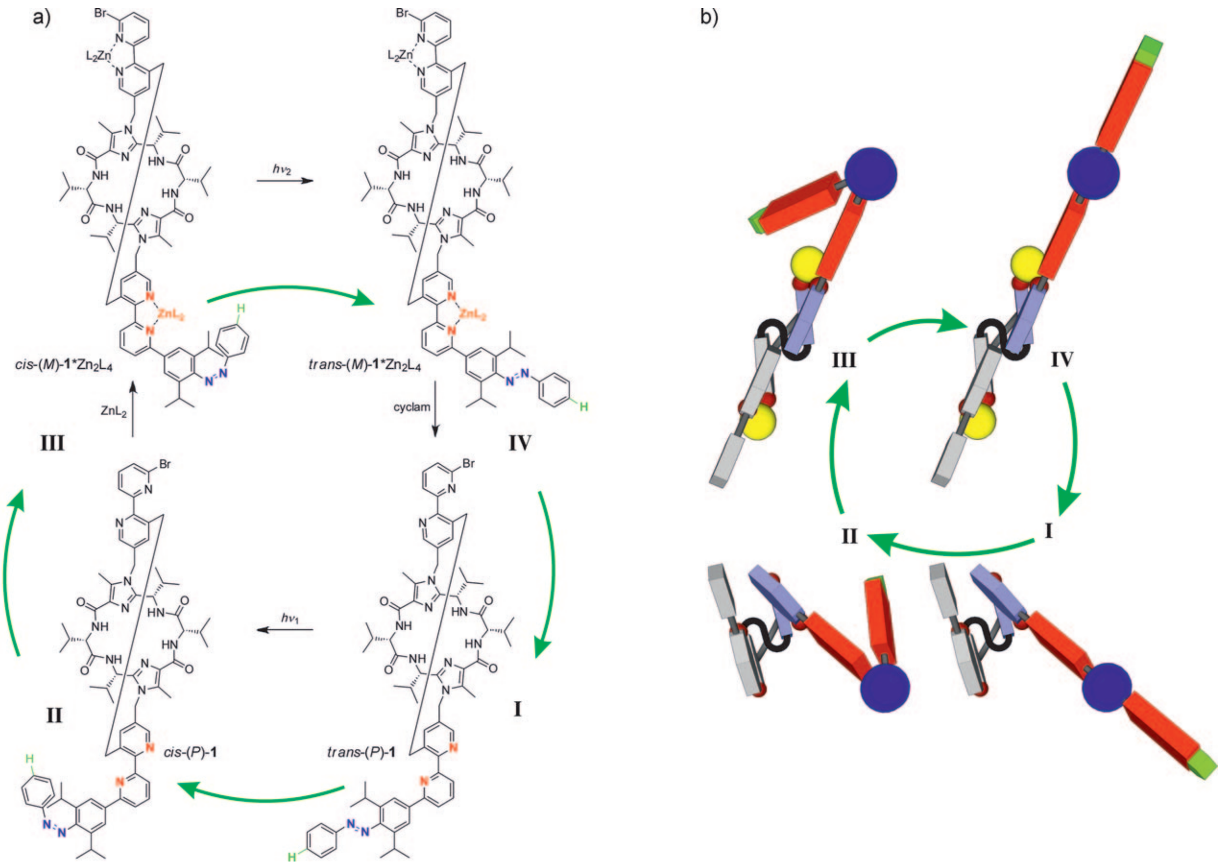

Figure 1. Design and concept of the molecular four-stroke motor. a) Structure formulas of the four states. b) Schematic representation of the four states. The bipyridine unit which acts as a stopper is gray. The bipyridine unit to which the (red) pushing blade is bound, is light blue. The azo group is the dark blue pivot and the hydrogen atom which performs a 360° rotation during one cycle is green.

the first case (**A** in Figure 2) the sterically crowded diisopropylphenyl group (red box) moves outside of the molecule. In the second case (**B**) it must move through the other bipyridine group (the stopper) which should lead to high steric repulsions. This assumption can be confirmed by calculating the energy profile as a function of the dihedral angle $\theta_{(\text{N-C-C-N})}$ using the B3LYP/6-31G* level of theory.[16] During the movement **A** only a small energy barrier of about 15 kJ mol^{-1} must be overcome. The energy barrier for path **B** is much higher (37 kJ mol^{-1}) as this movement causes strong

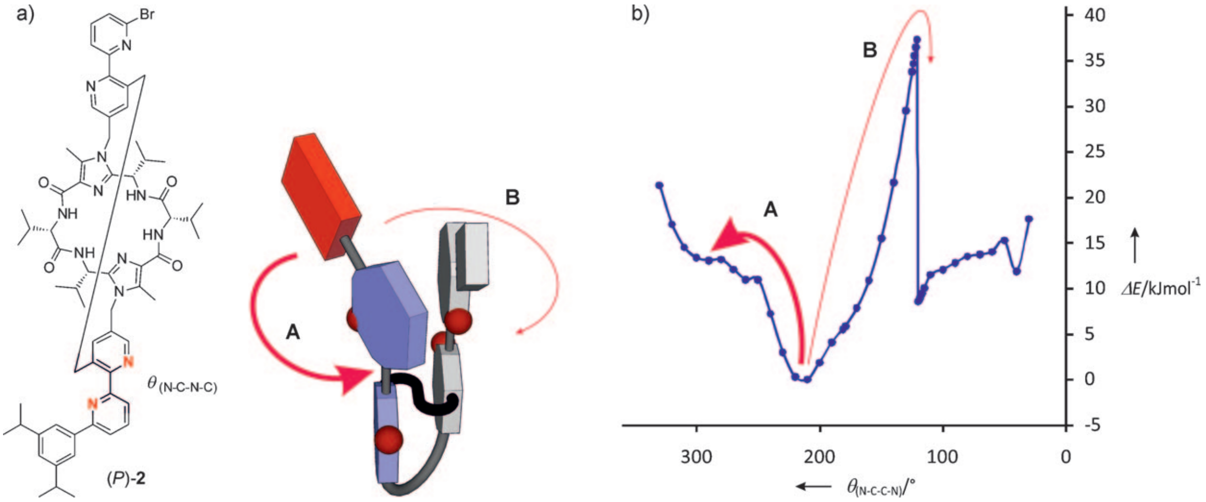

Figure 2. Unidirectional movement of the blade. a) Structure formula of reference compound **2** and the two possible ways **A** and **B** for the movement of the diisopropylphenyl group (red box) around the N-C-C-N axis. b) Energy profile as a function of the dihedral angle $\theta_{(\text{N-C-C-N})}$ calculated at the B3LYP/6-31G* level.

steric interactions. In the presence of Zn^{2+} ions in solution this energetic discrimination would be enhanced, as the metal ions wouldn't affect the early transition state (path **B**) but would stabilize the late transition state of path **A**. According to the Boltzmann distribution between the two transition states, the movement of the blade of reference compound **2** should be almost completely ($> 99.99\,\%$) unidirectional at 20 °C. As the motor **1** contains a blade which is even more sterically crowded than that of **2**, the movement of the blade in **1** should be definitively unidirectional.

The experimental demonstration of the whole four-stroke cycle can be provided by UV and circular dichroism (CD) spectroscopy. The *trans*→*cis* isomerization of the azobenzene unit (**I**→**II**) caused by UV irradiation ($\lambda = 355$ nm) can be observed in the UV spectrum by the decrease of the absorption band at 335 nm (Figure 3). This change in the $\pi\rightarrow\pi^*$ band is typical for isomerization of azobenzene derivatives. The shape of the CD spectrum is mainly caused by the relative configuration of the bipyridine arms which is not changed during the *trans*→*cis* isomerization. Thus, the isomerization does not lead to any significant change of the CD spectrum. The ^{1}H NMR spectra show that after synthesis, the azo compound (*P*)-**1** is present in a *trans*/*cis* ratio of 80:20. At the photostationary state at $\lambda = 355$ nm a *trans*/*cis* ratio of 42:58 is achieved. The reverse isomerization (**II**→**I**) triggered by visible light leads back to the basic ratio which can be seen in the change of the UV and the NMR spectra. This result means that 38 % of all the molecules of the motor are involved in the light-induced switching.

The second moving process is caused by the complexation of the bipyridine units with Zn^{2+} ions (Figure 3). To prevent the formation of metal complexes with more than one bipyridine ligand per metal, the complexation experiments must be carried out in high dilution and with an excess of metal ions.[13] As a result of the metal complexation the UV absorption in the area of the bipyridine band at around 330 nm increases. The complexation and thus the movement of the blade can most clearly be detected in the change of the CD spectrum: Compound *trans*-(*P*)-**1** in which the bipyridine arms are *P* configured exhibits a positive Cotton effect at 281 nm ($\Delta\varepsilon = +25\,\text{mol}^{-1}\,\text{dm}^3\,\text{cm}^{-1}$) and a negative Cotton effect at 253 nm ($\Delta\varepsilon = -29\,\text{mol}^{-1}\,\text{dm}^3\,\text{cm}^{-1}$).[13] The complexation of the 2,2′-bipyridine units occurs not only very rapidly and almost completely, but also leads to a metal complex in which the bipyridine arms adopt the *M* configuration (**I**→**IV**). As a result a negative Cotton effect at 269 nm ($\Delta\varepsilon = -28\,\text{mol}^{-1}\,\text{dm}^3\,\text{cm}^{-1}$) and a strong positive one at 248 nm ($\Delta\varepsilon = +45\,\text{mol}^{-1}\,\text{dm}^3\,\text{cm}^{-1}$) is observed. The addition of cyclam leads back to the original spectrum (**IV**→**I**).

An alternating combination of these two switching processes leads to the desired four-stroke rotation. The first stroke (**I**→**II**; folding of the blade) is the light-induced *trans*→*cis* isomerization and leads only to a small decrease of the UV absorption at 330 nm (Figure 4). The second stroke (**II**→**III**; recovery stroke) is effected by the metal-triggered movement of the folded blade. The configuration change of the bipyridine arms during this stroke results in a dramatic change in the CD spectrum which becomes most pronounced at a wavelength of 250 nm ($\Delta\Delta\varepsilon = 68\,\text{mol}^{-1}\,\text{dm}^3\,\text{cm}^{-1}$). The third stroke, which is the light-induced *cis*→*trans* back isomerization (**III**→**IV**; opening of the blade), does not lead to a significant change in the CD spectrum. In the UV

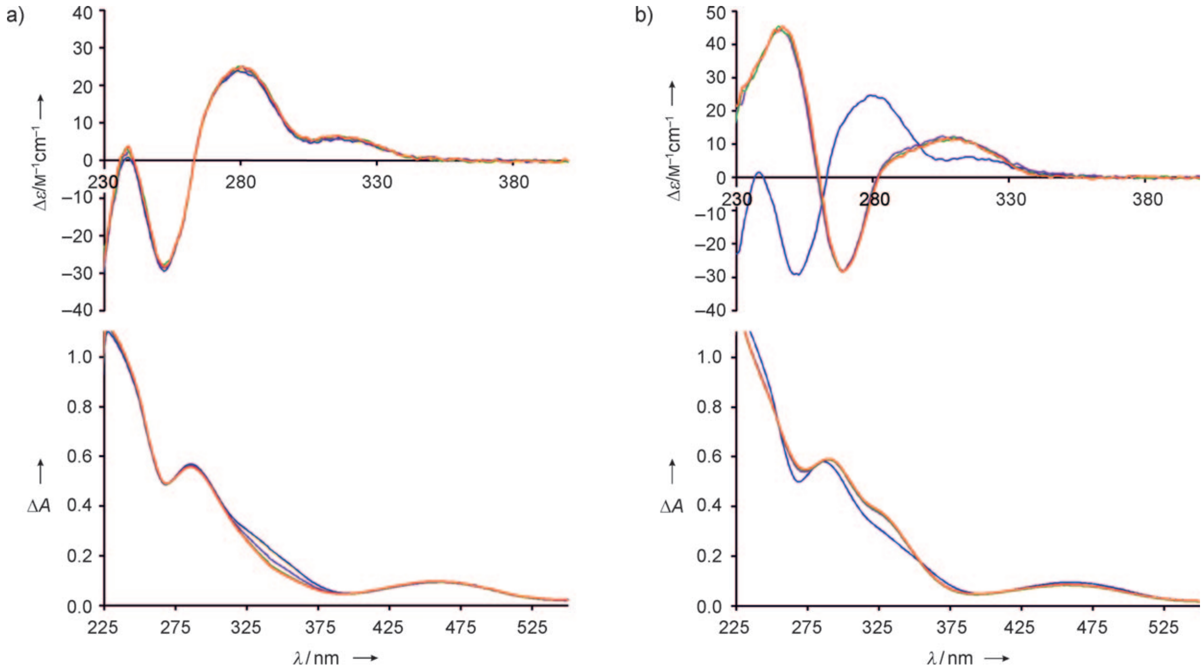

Figure 3. a) CD (top) and UV (bottom) spectral changes of *trans*-(*P*)-**1** (state **I**, blue) in dichloromethane/acetonitrile (95:5; $c = 2.0\times10^{-5}$ M) at 20 °C upon UV irradiation ($\lambda = 355$ nm) for 15 (violet), 30 (green), and 60 s (state **II**, *cis*-(*P*)-**1**, red). b) CD (top) and UV (bottom) spectral changes of *trans*-(*P*)-**1** (state **I**, blue) in dichloromethane/acetonitrile (95:5; $c = 2.0\times10^{-5}$ M) at 20 °C upon addition of 4.5 (violet), 5.0 (green), and 5.5 equivalents of $Zn(OTf)_2$ (state **IV**, *trans*-(*M*)-$1{*}Zn_2^{4+}$, red).

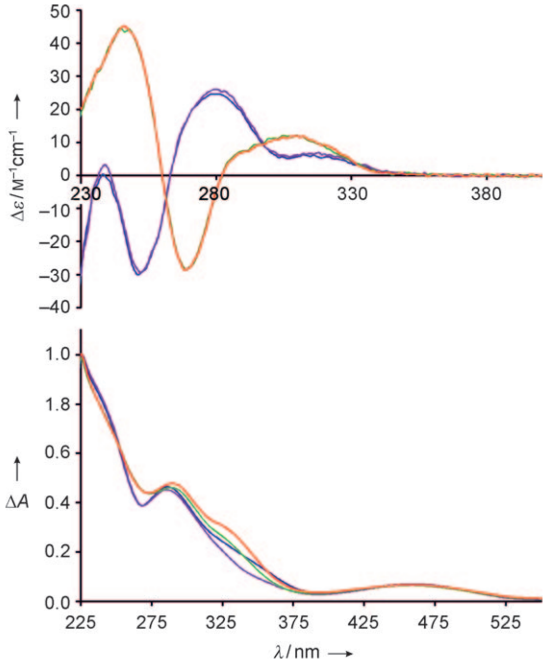

Figure 4. CD and UV spectra of the four-stroke cycle. CD (top) and UV spectra (bottom) of the states **I** to **IV** recorded during a four-stroke cycle in the following order: **I** (blue)→**II** (violet)→**III** (green)→**IV** (red) (dichloromethane/acetonitrile: 95:5; $c = 2.0\times10^{-5}$ M, 20 °C).

spectrum the absorption at 330 nm increases. The recorded spectra of state **IV** are completely identical with those obtained in the transition from state **I** to state **IV**. The fourth stroke is the backward movement of the opened blade (**IV**→**I**; effective stroke) and is caused by the addition of cyclam. The spectra after the fourth stroke are identical to the spectra of the starting state which provides confirmation of the assumed cyclic process. This forward and backward motion can be repeated several times.[17]

As the movement of the blade proceeds unidirectionally, the circular path for all motors in all four-stroke cycles is the same. Thus the physical task which is performed in the first four-stroke cycle is not annihilated in one of the subsequent four-stroke cycles. As the light-induced isomerization is not a complete process, only 38% of all the motors perform mechanical work during a cycle. In the other motor molecules during this cycle the pushing blade is only moved forward and backward. Note, these motor molecules are just resting during this cycle and do not annihilate the mechanical work performed in a previous cycle.

The simple design of this four-stroke motor resembling the movement of motile cilia should allow the construction of a variety of new motors designed for the directed transport of molecules or for their locomotion in a medium.

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