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In Control of Motion: From Molecular Switches to Molecular Motors†

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ABSTRACT
The design of molecular systems in which controlled linear and rotary motion can be achieved under the influence of an external signal is a major endeavor toward future nanoscale machinery. In this Account we describe the development of molecular switches and the discoveries that culminated in the first light-driven molecular motor. Various chiral optical molecular switches and their use as trigger elements to control organization and functions will be discussed. The construction of the first and second generation molecular motors is presented.

Introduction

The bottom-up construction of motors and machines of nanosize dimensions offers a formidable challenge to science, and its realization might have far-reaching consequences in view of the impact of their macroscopic analogues in daily life.[1,2] It is fascinating to see how Nature has found elegant solutions to control movement at the molecular level by the conversion of chemical energy into mechanical energy.[3] Among the most prominent examples of such biomolecular motors are the muscle linear and ATP-ase rotary motors.[4] In approaches toward artificial machinery, a variety of molecular and supramolecular systems have been designed in recent years in which changes in shape, switching processes, or movements occur in response to external chemical, electrochemical, or photochemical stimuli.[5,6]

The efforts in our group that led ultimately to the first light-driven molecular motor, which can undergo repetitive 360° rotations in a unidirectional manner, started in 1989 with the challenge to construct chiral photobistable molecules (chiroptical molecular switches) that could be applied as molecular memory elements in optical data storage systems.[6] But the molecular basis was already established more than 10 years earlier, when the author as a student synthesized the first sterically overcrowded inherent dissymmetric alkenes of which both cis and trans forms exist as stable enantiomers.[7]

In this Account will be described how we came from chiral molecular switches via triggering of the organization and controlled motion of many molecules to the construction of our present second generation light-driven molecular motors.

Chiroptical Molecular Switches

Stimulated by the dazzling success of miniaturization in information technology and the prophecy that molecular memory elements for data storage and processing by light are the ultimate goal, we embarked on the construction of molecular switches. From the numerous early studies on photochromic compounds, we soon learned that, although the basic condition of photochemical bistability is often fulfilled, several other requirements including fatigue resistance, thermal stability, and nondestructive read-out are essential for applications as trigger elements.[6,8] In our approach, we exploited the unique properties associated with chiral photoresponsive molecules (Figure 1). The design is based on the interconversion by light of the right- (*R* or *P*) and left-handed (*S* or *M*) forms of a chiral molecule which represent two distinct states in a molecular binary logic element. Switching between diastereomeric (or pseudoenantiomeric) photobistable molecules (*P* and *M′*) can be accomplished at two different wavelengths λ_1 and λ_2 (Figure 1A). On the other hand, two enantiomers (*P* and *M*) can, in principle, be interconverted at a single wavelength using left or right circular polarized light (*l*- or *r*-CPL) (Figure 1B).

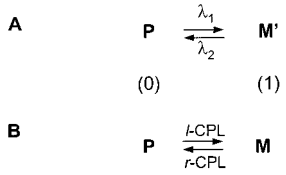

FIGURE 1. Chiroptical molecular switches. The right-handed helical structure (*P*-isomer) and left-handed helical structure (*M*-isomer) represent the 0 and 1 states in a binary logic system. The two states can be interconverted by light irradiation. (A) Switching between pseudoenantiomers *P* and *M′* at two wavelengths λ_1 and λ_2. (B) Switching between enantiomers at a single wavelength with *l*- and *r*-CPL.

We reasoned that a major advantage of such *chiral optical switches,* compared to other photochromic systems, is nondestructive read-out of an optical recording system containing these materials by monitoring the change in optical rotation at wavelengths remote from the wavelengths used for switching. In contrast, detection is, at present, often based on UV/visible spectroscopy in or near the absorption bands, leading to partial reversal of the photochromic process used to store information.[9] The principle of an information storage system based on chiroptical molecular switches is shown in Scheme 1.

The design of the chiroptical switch, depicted in Scheme 2a, involves a lower half, considered the static

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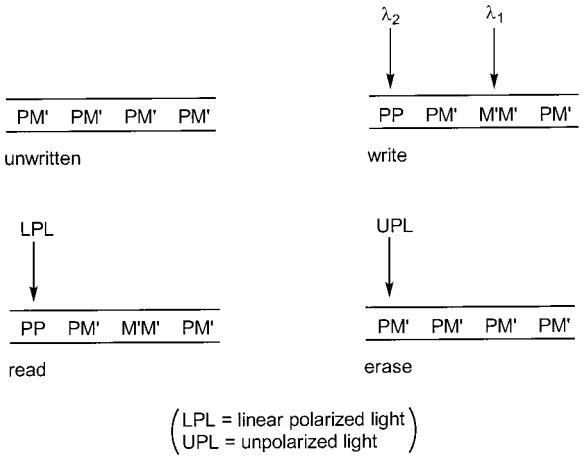
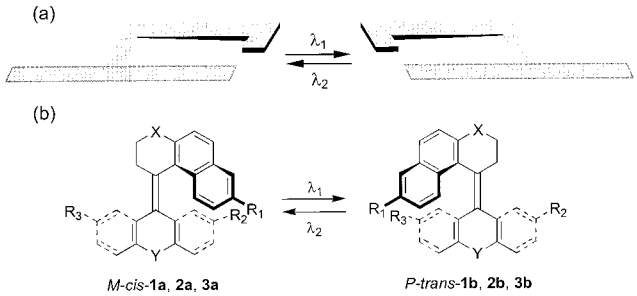
Scheme 1

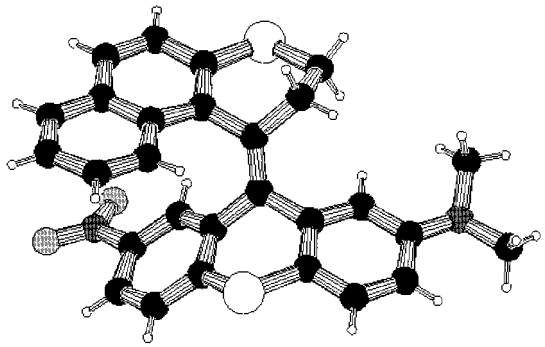


Scheme 2



part, and an upper half, which turns from right to left upon irradiation. The molecular structures (Scheme 2b) comprise unsymmetric sterically overcrowded thioxanthenes **1**−**3**.

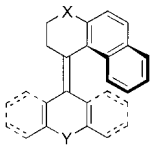
To avoid unfavorable steric interactions at the fjord region, these molecules adopt a helical shape. The molecular structure of *cis*-2-nitro-7-(dimethylamino)-9-(2,3′-dihydro-1′*H*-naphtho[2,1-*b*]thiopyran-1′-ylidene)-9*H*-thioxanthene (*P-cis*-**2a**) is illustrative for the antifolded helical shape of these chiral switches (Figure 2). The central double bond has a normal bond length (1.353 Å), and only slight deviation from planarity (dihedral angle 5.4°) is observed. The extent of twisting and folding shows, however, considerable variation among the approximately 50 different chiral overcrowded alkenes we have synthesized so far. It was particularly rewarding that the racemization barriers of symmetric overcrowded alkenes could be tuned over a range from 12 to >30 kcal mol^{-1} by modification of the bridging units X and Y in the upper and lower halves. Typical data for nonsymmetric overcrowded alkenes **1** are given in Table 1.[10] There appears to be a delicate balance between ground-state distortion due to twisting and folding of the molecules and helix inversion. The ability to tune the barriers for the various thermal and photochemical isomerization processes turned out to be essential in our approaches toward the construction of molecular switches and motors. It might not come as a surprise that the photochemical properties can



P-cis-**2a**

FIGURE 2. Pluto diagram of the crystal structure of *P-cis*-**2a**.

Table 1



1

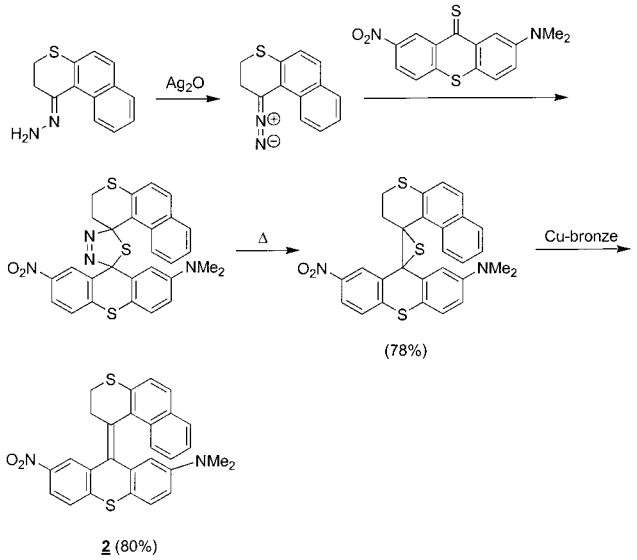
X	Y	racemization barrier (kcal mol^{-1})
O	O	24.9 ± 0.3
CH_2	O	27.4 ± 0.2
S	O	28.0 ± 0.2
S	S	28.9 ± 0.1
S	CHCH	29.0 ± 0.3

also be readily tuned through the substituents R_1−R_3 in the upper and lower halves of **1**−**3**.

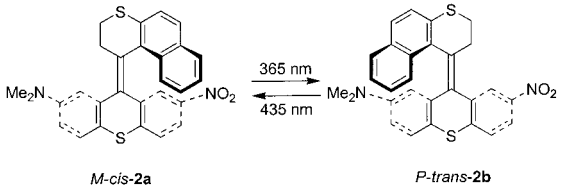
A photochemically induced stilbene-type cis−trans isomerization of **1** simultaneously results in reversal of the helicity (from *M* to *P* and vice versa) (Scheme 2). The first successful chiroptical switch was realized with **1** (X = CH_2, Y = S, R_1 = Me, R_2 = OMe, R_3 = H).[11] A stereospecific interconversion of *M-cis*-**1a** and *P-trans*-**1b** was found. Alternated irradiation with 250 and 300 nm light resulted in a 4% shift of the photostationary state and modulation of the ORD and CD signals. Taking advantage of the helicene-like chirality, large changes in chiroptical properties occur in these systems, which allow easy detection. We observed, however, about 10% racemization after 20 switching cycles.

Once we had realized our first goal of repetitive chiroptical switching, we focused on the following key issues: (i) improving the stability toward racemization; (ii) tuning the wavelengths for photoisomerization; and (iii) enhancing the stereoselectivity. Introduction of the naphtho[2,1-*b*]thiopyran moiety in the upper half and donor and acceptor substituents in the thioxanthene lower half was particularly rewarding.[12] The synthesis of the target switch **2** is outlined in Scheme 3. The coupling of the lower and upper halves by formation of the central, sterically demanding double bond is the crucial step in the synthetic routes to the switches and motors described here. After many failures with a plethora of olefination procedures at our disposal, the diazothioketone coupling method proved to be successful.[13] It should be emphasized

Scheme 3



Scheme 4



that steric constraints are introduced gradually via a sequence involving 1,3-dipolar cycloaddition to give a five-membered thiadiazoline. A three-membered episulfide results from nitrogen elimination, and finally sulfur extrusion affords the alkene.

A remarkable enhanced stability (ΔG_{rac} = 29.2 kcal mol^{-1}) and a large bathochromic shift in the absorption spectra, which allows switching to take place near the visible wavelength region, were observed. *M-cis*-**2a** and *P-trans*-**2b** (Scheme 4) have nearly mirror image CD spectra (Figure 3), illustrating the pseudoenantiomeric nature of these compounds and the fact that the overall helicity is a dominant chirality factor. Note that the naphthalene chromophore in the upper part is facing either a donor or an acceptor moiety in the two isomers.

Large differences in isomeric composition, with ratios of *M*-**2a** and *P*-**2b** of 30:70 (at 365 nm) and 90:10 (at 435 nm), in the photostationary states were readily achieved upon irradiation (Scheme 4). The photomodulation of chirality, as detected by CD, is illustrated in Figure 4. Besides the reversal of helicity, it was possible to perform 80 switching cycles without deterioration or racemization.

Detailed studies of these and related chiroptical switches revealed that the composition of the photostationary states, and as a consequence the ratio of *P* and *M* helices, depends on substituents, wavelength, and medium.

For instance, the difference in donor−acceptor interactions in the bistable forms could be further enhanced by the introduction of a dimethylamino donor moiety in the upper part as shown in **3** (Scheme 2). A highly stereoselective switching process in one direction was

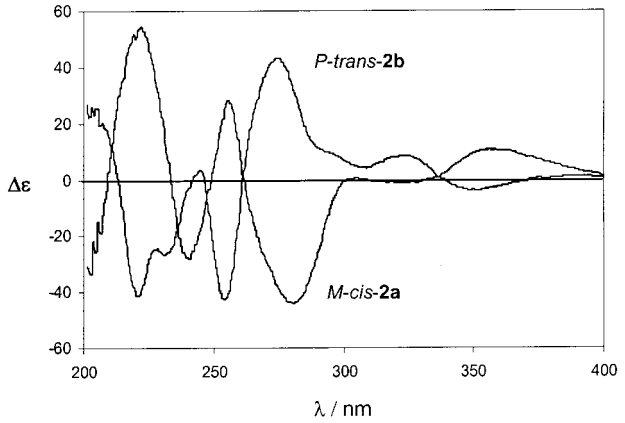


FIGURE 3. Circular dichroism spectra of *P-trans*-**2b** and *M-cis*-**2a**.

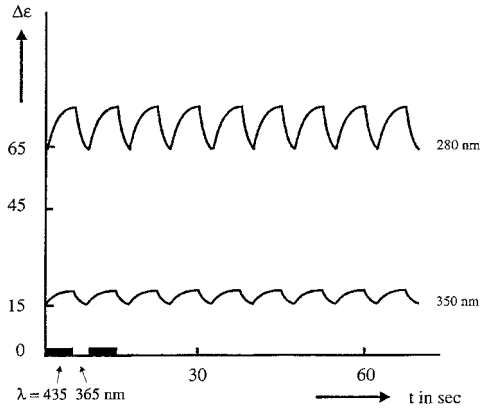


FIGURE 4. Plot of $\Delta\epsilon$ at 280 and 350 nm versus the irradiation time for the *M-cis*-**2a**−*P-trans*-**2b** isomerization. Irradiation alternately at λ = 435 and 365 nm.

observed using 435 nm light (*M-cis*-**3a**:*P-trans*-**3b** = 99:1), but irradiation at various wavelengths showed only modest reversibility.[14]

Photomodulation of chirality in thin polymer films, using either covalently attached chiroptical switches or doped systems, was also successful. However, matrix effects play a prominent role, as these strongly influence the diastereoselectivity and irradiation times required to reach the photostationary states.[14,15] This aspect will be particularly important in future applications as photoactive materials or data storage systems.

The response time is another important issue in the pursuit of molecular switches. Realizing the extremely fast retinal cis−trans photoisomerization in the process of vision,[16] we recently embarked on a femtosecond spectroscopy study.[17] For a number of symmetrically overcrowded alkenes, we indeed found fast isomerization (<300 ps) via a so-called phantom state.[18]

The chiroptical switches described here represent the first examples of synthetic systems in which unidirectional rotary motion was accomplished (Scheme 2a). The relative direction of the movement can be controlled by the wavelength of the light and depends on the chirality of the molecule.

But how do we switch between enantiomers, e.g., *P* and *M* (Figure 1B)?

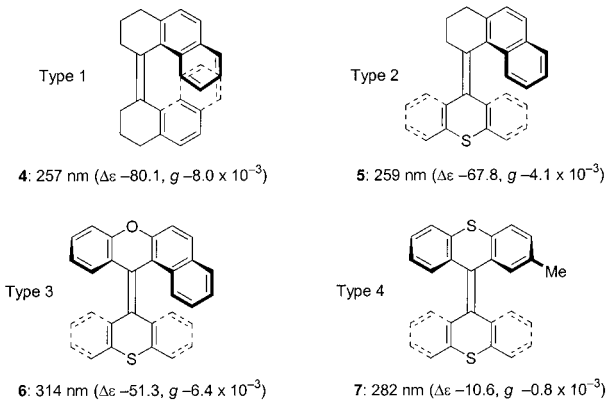
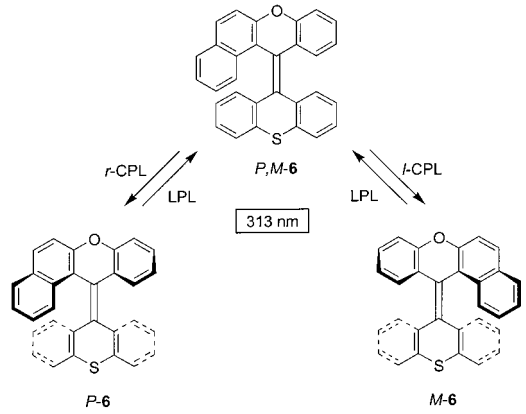


FIGURE 5. Different classes of chiral overcrowded alkenes. Characteristic absorptions (λ, nm) and the corresponding $\Delta\epsilon$ and g factors are indicated (see text).

Scheme 5



Single Wavelength Switching

When the photochemical process involves the interconversion between two enantiomers, irradiation will always lead to racemization, irrespective of the wavelength of the light. Using chiral light (right- or left-circular polarized light), enantioselective switching in either direction should, in principle, be possible.[19] Facing the challenge to design a suitable chiral molecule to demonstrate switching at a single wavelength, we realized that the following factors are decisive for success: (i) irradiation with CPL should lead exclusively to interconversion of the enantiomers without competing photochemical processes; (ii) the enantiomers have to be thermally stable ($\Delta G_{rac} > 21$ kcal mol^{-1}); (iii) the chiral photoactive compound should exhibit a sufficiently high anisotropy factor g[20] (it should be noted that the enantiomeric excess that can be expected in the photostationary state is given by $ee_{pss} = g/2 = \Delta\epsilon/2\epsilon$, and for inherently dissymmetric alkenes $g <$ 1% is usually found); and (iv) the quantum efficiency for photoracemization should be high since the rate of photoresolution is exponentially related to this quantity. A large number of sterically overcrowded chiral alkenes, comprising four distinct subclasses (type 1 through type 4, Figure 5), were synthesized, and the chiroptical properties and thermal and photochemical isomerization processes were examined. Compound **6** satisfied the requirements given above (Scheme 5).

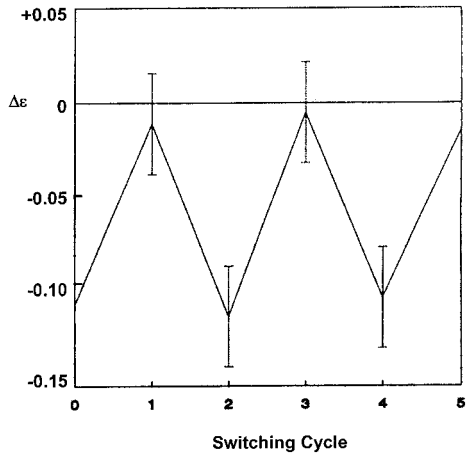


FIGURE 6. Difference in CD absorption at 313 and 400 nm ($\Delta\epsilon_{311} - \Delta\epsilon_{400}$) for a solution of **6** (9×10^{-5} mol L^{-1}) in *n*-hexane upon alternating irradiation with *l*- and *r*-CPL at 340 nm ($\Delta\epsilon_{400}$ is used as an internal reference value to enhance accuracy).

The enantiomers of **6** show fatigue resistance, a stereospecific photoisomerization process that reverses the helicity and sufficient stability at ambient temperature ($\Delta G_{rac} = 25.9$ kcal mol^{-1}). A rapid photoracemization of *P*-**6** was found upon irradiation at 300 nm with unpolarized light ($\Phi_{rac} = 0.40$, *n*-hexane), and the experimental g value ($g = -6.4 \times 10^{-3}$ at 314 nm) indicates that, under ideal conditions, an ee of 0.3% might be observed. We could, indeed, accomplish deracemization and switching of *P,M*-**6** by irradiation with *l*- and *r*-CPL at 313 nm (Figure 6).[21] At this wavelength, switching occurred between photostationary states with ee values of 0.07% and −0.07% for *P* and *M* helices, respectively. Upon irradiation of either *P*-**6** or *M*-**6** at 313 nm with LPL, racemic *P,M*-**6** was obtained. Ways to reach more efficient CPL irradiation and higher g factors are currently under scrutiny.

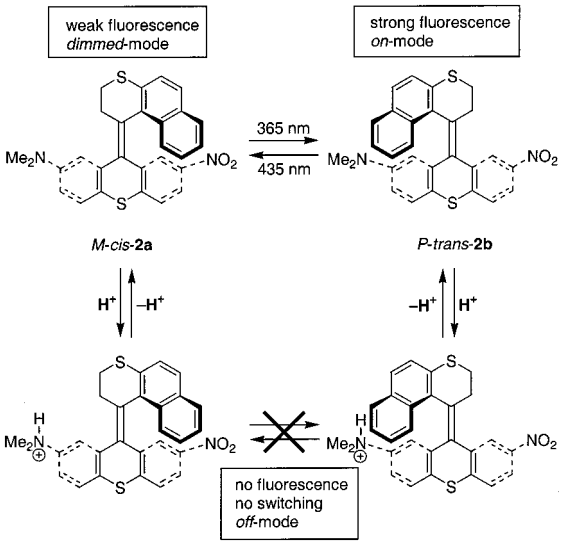
The system shown in Scheme 5 comprises a three-position optical switch of racemic (*P,M*), *P*-enriched, and *M*-enriched **6** with the distinct feature that all the switching processes can be performed at a single wavelength simply by changing the chirality of the light employed.

Dual-Mode Photoswitching

It was anticipated that the incorporation of a kind of brake in the photoswitch might enable us to use an additional control element for the movement induced by irradiation. We found that the photochemical process in the case of donor−acceptor-substituted overcrowded alkenes **2** could be regulated by reversible protonation of the *N,N*-dimethylamine donor moiety.[22] Dual-mode photoswitching with *M*-**2a** and *P*-**2b** is illustrated in Scheme 6.

The switching process was effectively blocked by addition of trifluoroacetic acid, for example. The presence of a donor- and acceptor-substituted lower half in *M*-*cis*-**2a** and *P*-*trans*-**2b** is essential for stereoselective photoisomerization, and protonation of the amine results in an ineffective acceptor−acceptor (ammonium and nitro)-substituted lower half. Therefore, by simple (de)protonation, the on mode (switching) and off mode (no switching)

Scheme 6



are addressed. Simultaneously, photomodulation of fluorescence was observed. *M*-*cis*-**2a** and *P*-*trans*-**2b** show distinct differences in fluorescence, whereas the protonated forms are nonfluorescent. As a consequence of these properties, the multifunctional photochromic system shown in Scheme 6 exhibits gated response behavior[6,9] involving proton-dependent photomodulation of chirality and fluorescence and switching between three distinct states: on, dimmed, and off.

A major advantage of the reversible protonation, beside the "brake effect", is the possibility to lock stored information in this chiroptical switch.

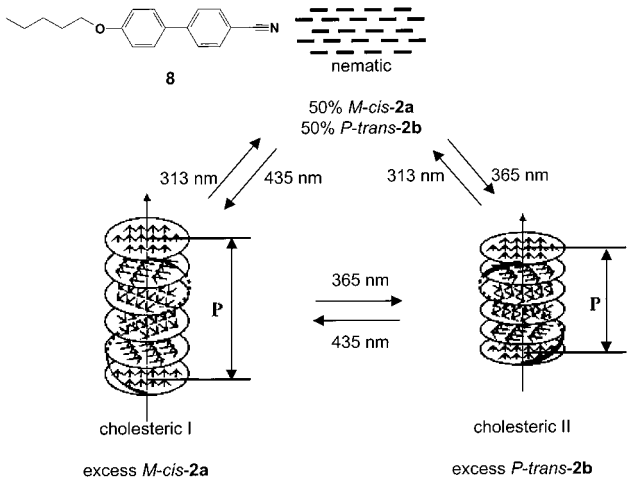
Control of Organization

With several chiroptical molecular switches in hand, we addressed the following questions. Are these suitable molecular triggers to control the organization of a large ensemble of molecules? Will the light-induced motion and change in helicity in the chiroptical switch be able to induce changes in orientation of other molecules?

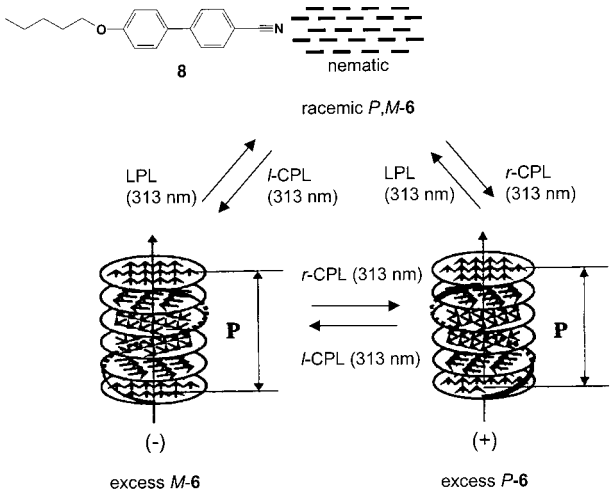
We considered liquid crystalline (LC) materials as particularly attractive candidates for this purpose. Doping with photochromic guest molecules might allow control of the strongly anisotropic properties associated with LC materials via change in mesophases and molecular orientation.[23] In addition, the modulation of mesophases by light, i.e., photoswitching of LC phases, offers an intriguing alternative to current methods of addressing display materials.[24]

The photoswitching between different LC states was, indeed, successful when *P*-*trans*-**2b** or *M*-*cis*-**2a** was employed as chiral dopant (1 wt %) in nematic 4′-(pentyloxy)-4-biphenylcarbonitrile **8** (Scheme 7). Addition of one of these chiral guests to **8** provides cholesteric phases of opposite handedness. Furthermore, when an excess of *P*-*trans*-**2b** is present in the photostationary state, a distinct decrease in pitch of the cholesteric phase is seen (cholesteric II), whereas an excess of *M*-*cis*-**2a** results in an increase in pitch (cholesteric I). Alternated

Scheme 7



Scheme 8

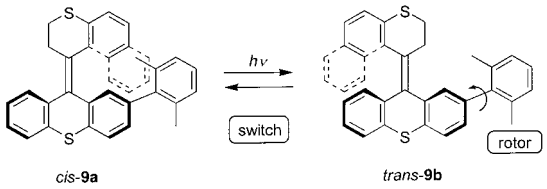


irradiation at 435 and 365 nm results in photomodulation of the pitch between values of 12.29 and 5.31 μm and reversal of the cholesteric helical screw sense. The observation that the cholesteric phase turned into a nematic phase again when the host−guest system was irradiated at 313 nm was unexpected. Apparently, a nearly 50:50 ratio of opposite helices of the photoactive guest molecule (a pseudoracemate) is formed, which results in a compensated nematic phase. It was delightful to observe that the chirality of the mesophase could be switched on again at 435 or 365 nm.

Scheme 8 shows an alternative system in which switching between LC states is achieved using **6** as a photoresponsive chiral guest.[21] In this case, the nematic phase obtained by doping **8** with racemic *P*,*M*-**6** is turned into a cholesteric phase by deracemization of the guest by CPL irradiation.

Although larger amounts of dopant (up to 20 wt %) are required as a consequence of the very low ee reached in the photostationary state, we were able to demonstrate for the first time the photomodulation of nematic and cholesteric phases at a single wavelength simply by changing the chirality of the light. Switching between *l*-CPL and *r*-CPL inverts the screw sense of the cholesteric

Scheme 9



phase, whereas switching between CPL and LPL results in a change from cholesteric to nematic and vice versa. Both types of LC switches comprise a three-state system (Schemes 7 and 8). Furthermore, it should be emphasized that the change in chirality induced in the guest is, indeed, amplified in the change in orientation of a large ensemble of molecules and expressed in the chirality of the LC phase.

Switchable Molecular Rotor

The successful photochemical switching of molecular helicity led us to the concept of the switchable molecular rotor illustrated in Scheme 9.[25] The questions pertain to the control of speed of rotation or even blocking rotation around a single bond. In this system, reminiscent of the molecular brake described by Kelly et al.,[26] a biaryl-type rotor and a thioxanthene-based switch are present in the same molecule. It was envisioned that photoisomerization of *cis*-**9a** to *trans*-**9b** would result in a distinct decrease in steric hindrance for biaryl rotation. The xylyl rotor moiety faces the naphthalene unit in the case of the cis isomer **9a**, whereas in trans isomer **9b** the naphthalene unit cannot obstruct the biaryl rotation.

Much to our surprise, barriers for biaryl rotation of $\Delta G^{\ddagger} = 19.0$ and 19.7 kcal mol^{-1} were found for *cis*-**9a** and *trans*-**9b**, respectively. The unexpected higher barrier for the trans isomer was supported by semiempirical calculations and model studies. It appears that the methyl substituents of the rotor moiety interfere with the methylene groups in the upper part in *trans*-**9b**, while in the cis isomer **9a** the naphthalene unit easily bends away to allow passage for the rotor. These and related findings have drastically changed our initially rather primitive view on steric and conformational effects and dynamic behavior in these and related chiral overcrowded alkenes.[27,28]

A Light-Driven Molecular Motor

Three basic requirements need to be fulfilled in order to be able to construct a molecular motor: (i) repetitive rotary motion; (ii) consumption of energy; and (iii) unidirectional rotation. Although we could induce unidirectional rotary motion by light with a number of the switches discussed so far, a full 360° rotary motion remained a dream.

The exploitation of the following two fundamental principles led to the realization of the first light-powered molecular motor.[29] First, photochemical trans−cis isomerization around a carbon−carbon double bond is usually a very fast and energetically uphill process in nature.[30]

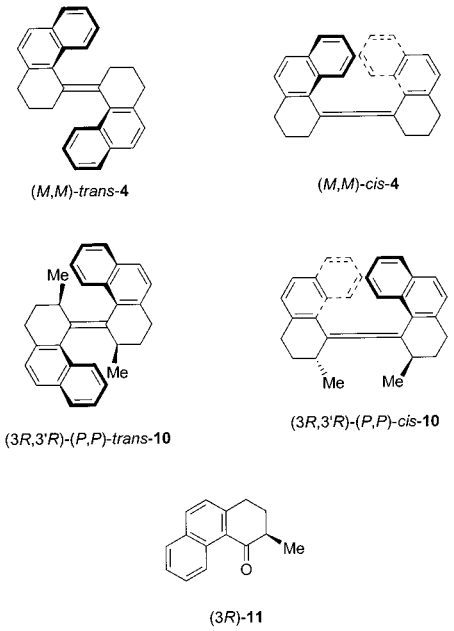


FIGURE 7. Structures **4**, **10**, and **11**.

Second, the concerted action of two chiral elements in a single chemical (or physical) event, by virtue of their diastereomeric nature, can lead to unique handedness.[31]

The solution of another key problem, the absolute configuration of overcrowded alkenes, played an important role in the route toward the molecular motor. As part of a long-standing cooperation with the group of Harada regarding absolute configuration determination of inherently dissymmetric alkenes, the methyl-substituted analogues **10** of phenanthrylidenes **4** were prepared (Figure 7).[32,33] In this case, McMurry coupling of ketone **11** was used to provide (3*R*,3′*R*)-(*P*,*P*)-*trans*-**10**.

The presence of stereogenic centers of known configuration in the upper and lower halves, and the analysis of the relative configurations of *cis*-**10** and *trans*-**10** through NMR and X-ray studies, allowed the unequivocal determination of the absolute stereochemistry. The calculated molecular structures (MOPAC93-AM1) of (3*R*,3′*R*)-(*P*,*P*)-*trans*-**10** and (3*R*,3′*R*)-(*M*,*M*)-*trans*-**10** are shown in Figure 8. A striking feature is that in the more stable configuration [(3*R*,3′*R*)-(*P*,*P*)-*trans*-**10**] the methyl substituents adopt an axial orientation.

Irradiation at $\lambda > 280$ nm of enantiomerically pure trans isomer (3*R*,3′*R*)-(*P*,*P*)-*trans*-**10** resulted in the formation of (3*R*,3′*R*)-(*P*,*P*)-*cis*-**10** (Figures 7 and 9). This was a very puzzling finding, as both the trans and cis isomers have *P*,*P*-helicity, whereas a key feature of all photoisomerizations studied so far is simultaneous helix inversion. These observations suggested that there might not be a direct pathway between (3*R*,3′*R*)-(*P*,*P*)-*trans*-**10** and (3*R*,3′*R*)-(*P*,*P*)-*cis*-**10** and indicated the possibility of the intermediacy of (3*R*,3′*R*)-(*M*,*M*)-*cis*-**10**.

A subsequent detailed study revealed the different stereoisomers and dynamic processes which are summarized in Scheme 10.

A photochemical isomerization of (3*R*,3′*R*)-(*P*,*P*)-*trans*-**10** at −55 °C indeed results in the formation of (3*R*,3′*R*)-

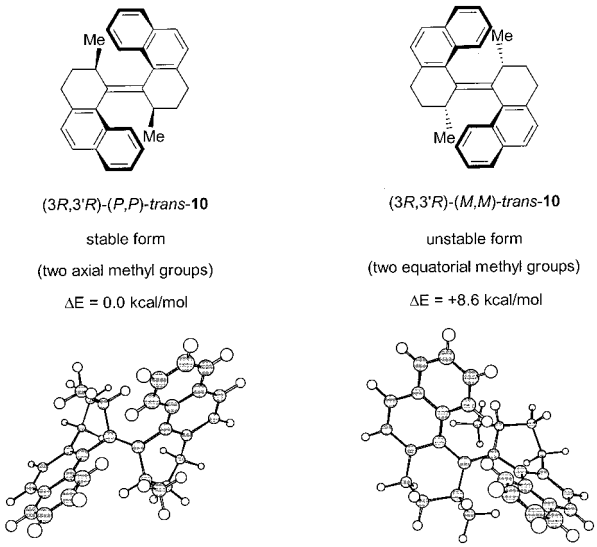
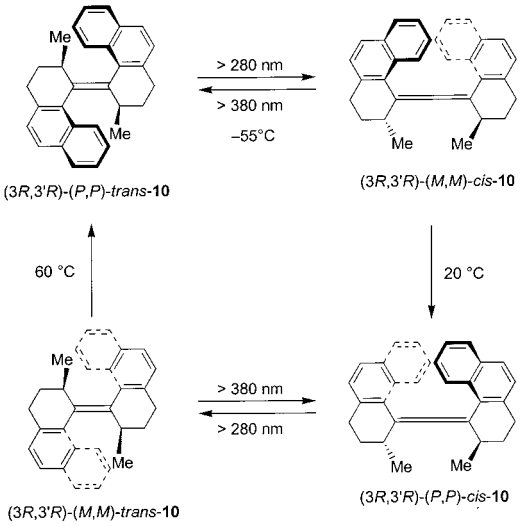


FIGURE 8. Molecular structures and conformations of stable (3*R*,3′*R*)-(*P*,*P*)-*trans*-**10** and unstable (3*R*,3′*R*)-(*M*,*M*)-*trans*-**10**.

Scheme 10



(*M*,*M*)-*cis*-**10**, which interconverts in a selective and irreversible step into (3*R*,3′*R*)-(*P*,*P*)-*cis*-**10**. Subsequent irradiation of (3*R*,3′*R*)-(*P*,*P*)-*cis*-**10** at 20 °C provided (3*R*,3′*R*)-(*M*,*M*)-*trans*-**10**, which upon heating to >60 °C undergoes an irreversible thermal isomerization exclusively to the original isomer, (3*R*,3′*R*)-(*P*,*P*)-*trans*-**10**. The different isomers and their interconversions could be readily detected using NMR and UV spectroscopy. The cycle shown in Scheme 10 comprises four distinct states which can be populated, depending on the temperature and wavelength of the light. At higher temperature (>60 °C), irradiation results in a continuous 360° rotary motion. The directionality of the rotary motion was monitored by CD spectroscopy (Figure 9), and the modulation of the CD absorption at 217 nm (Figure 9, inset) during three full cycles is characteristic of repetitive unidirectional rotation.

When one half of the molecule is considered the static part, the other half (the rotor part) undergoes a 360° rotation exclusively in a clockwise sense (Figure 10).

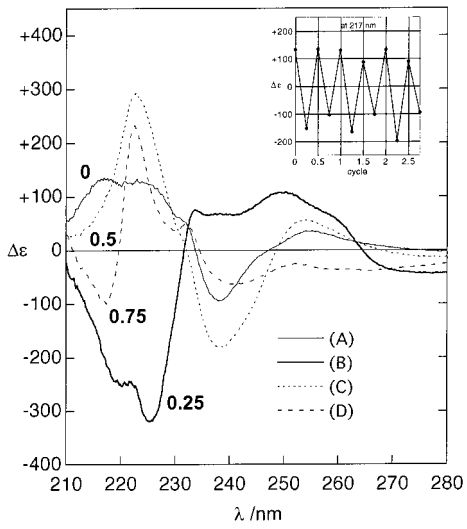


FIGURE 9. Circular dichroism spectra of each of the four stages of rotation. Trace A, (3*R*,3′*R*)-(*P*,*P*)-*trans*-**10**; trace B, (3*R*,3′*R*)-(*M*,*M*)-*cis*-**10**; trace C, (3*R*,3′*R*)-(*P*,*P*)-*cis*-**10**; trace D, (3*R*,3′*R*)-(*M*,*M*)-*trans*-**10**. Numbers indicate part of rotary cycle completed. Inset: Changes in the $\Delta\epsilon$ value during three full rotation cycles monitored at 217 nm.

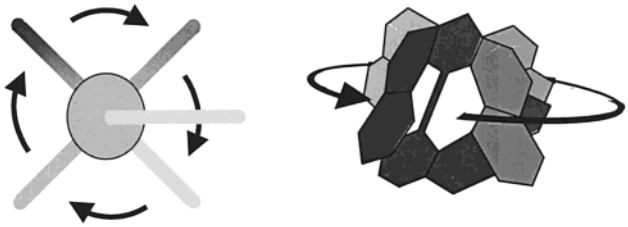
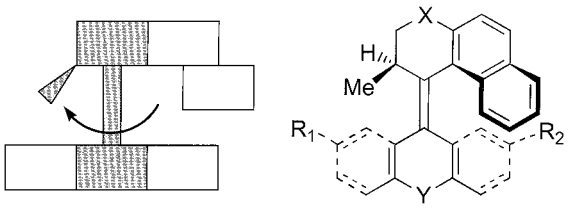


FIGURE 10. Schematic representation of unidirectional rotary motion of **10**.

Although a light-driven unidirectional rotary motor was realized,[29,34] the question remains why the thermal *M*,*M*- to-*P*,*P* helix interconversion is irreversible both for the trans and the cis isomers.

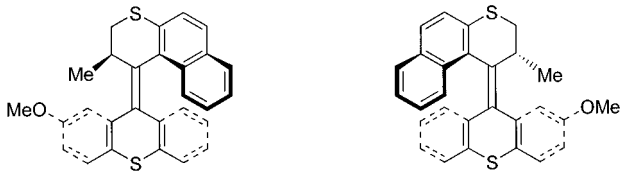
It turned out that the unidirectional rotation is dictated by the methyl substituents. In the more stable *P*,*P*-isomers, the methyl substituents adopt axial orientations to prevent steric hindrance. Calculations indicated that (3*R*,3′*R*)-(*M*,*M*)-*cis*-**10** and (3*R*,3′*R*)-(*M*,*M*)-*trans*-**10** (see Figure 8), with equatorial methyl groups, are less stable by 11.0 and 8.6 kcal mol^{-1}, respectively.[29] Photochemical trans−cis isomerization of (3*R*,3′*R*)-(*P*,*P*)-*trans*-**10** to (3*R*,3′*R*)-(*M*,*M*)-*cis*-**10** (Scheme 10) forces the methyl groups to adopt the unfavorable equatorial orientation. Thermal interconversion to (3*R*,3′*R*)-(*P*,*P*)-*cis*-**10** releases the strain as the methyl groups adopt again the more favorable axial orientation. A second photochemical cis−trans isomerization converts (3*R*,3′*R*)-(*P*,*P*)-*cis*-**10** into (3*R*,3′*R*)-(*M*,*M*)-*trans*-**10**, and once again the methyl groups are in the unfavorable equatorial orientation. The final thermal step gives the original isomer (3*R*,3′*R*)-(*P*,*P*)-*trans*-**10** with the more favorable axially oriented methyl groups.

Therefore, in one full cycle, which comprises four steps, each light-driven, energetically uphill process is followed by a thermal, energetically downhill process.



12: X = S, Y = S, R_1 = OMe, R_2 = H
13: X = S, Y = O, R_1 = H, R_2 = H

FIGURE 11. Schematic view and structures of second generation molecular motors.



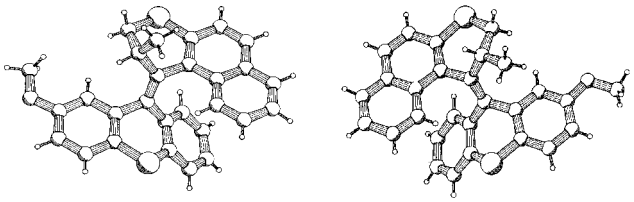


FIGURE 12. Molecular structures and conformations of stable (2′*R*)-(*M*)-*trans*-**12** and unstable (2′*R*)-(*P*)-*trans*-**12**.

The unique combination of axial chirality and two stereogenic centers and the absorption of light energy is essential for the observed unidirectional rotation in this molecular motor.

Second Generation Molecular Motor

The redesign of the molecular motor was focused on a system with distinct upper and lower parts, as shown in Figure 11.[35] The symmetric lower half can be used for connection to other molecules or surfaces, for example, whereas the upper half still acts as a rotor. Another challenge is to accelerate the rotary motion by lowering the thermal isomerization barriers for helix inversion.

The new motor contains a (2*R*)-methyl-2,3-dihydronaphthothiopyran upper part and a thioxanthene lower part. In this case, X-ray structures of both the stable [(2′*R*)-(*M*)-*trans*-**12**; axial-methyl] and unstable [(2′*R*)-(*P*)-*trans*-**12**; equatorial-methyl] isomers were obtained (Figure 12).

Scheme 11 shows the different stereoisomers and the thermal and photochemical isomerization steps that are observed starting with (2′*R*)-(*M*)-*trans*-**12**. Much to our delight, the four distinct stages of the rotation cycle could again be readily monitored by CD (Figure 13).

The experimental results show that the upper naphthothiopyran moiety undergoes a full 360° rotation in a counterclockwise direction relative to the lower thioxanthene unit. Compared to the first generation molecular motor (vide supra), the most remarkable and highly

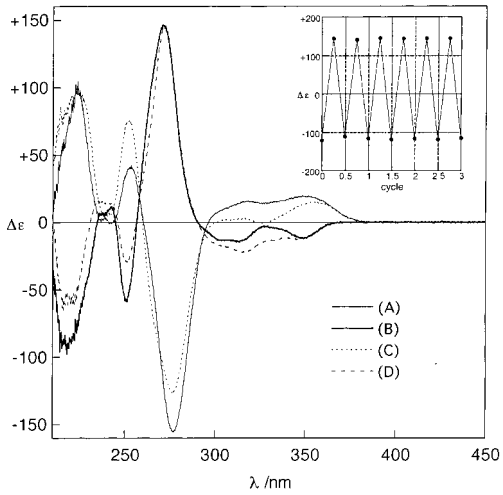
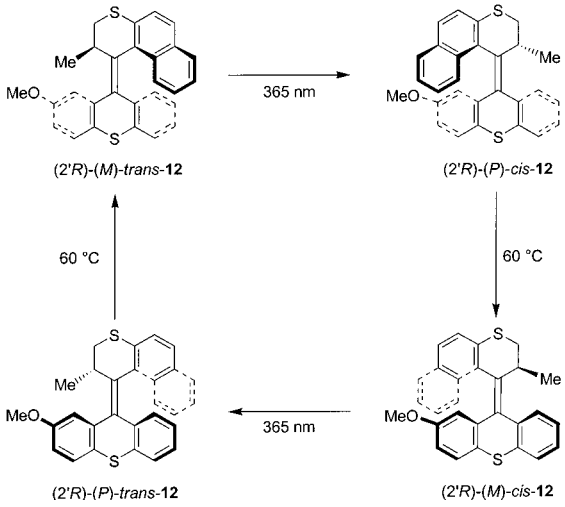


FIGURE 13. Circular dichroism spectra of each of the four stages of rotation. Trace A, (2′*R*)-(*M*)-*trans*-**12**; trace B, (2′*R*)-(*P*)-*cis*-**12**; trace C, (2′*R*)-(*M*)-*cis*-**12**; trace D, (2′*R*)-(*P*)-*trans*-**12**. Inset: Changes in the $\Delta\epsilon$ value during three full rotation cycles monitored at 272 nm.

Scheme 11



rewarding observation was that the presence of a single stereogenic center is a sufficient condition for unidirectional rotation.

But how can we get a faster rotation? Kinetic studies showed that the highest thermal isomerization barrier in **12** was already lowered by approximately 1.5 kcal mol^{-1} compared to that in the biphenanthrylidene molecular motor **10**. To tune the activation energies of the thermal steps further, as these govern the rotation rate, the bridging heteroatom Y in the lower part was changed from sulfur to oxygen (Figure 11). The presence of the smaller oxygen bridge in **13** further reduces the steric hindrance in the "fjord region" of the molecule, and as a result the thermal barrier for helix inversion decreased by 2 kcal mol^{-1} to 22.7 kcal mol^{-1}.

Conclusions

The control of chirality, being one of the intrinsic features of living nature, was the guiding principle in our synthetic

endeavor that ultimately culminated in the control of molecular motion. Starting with the basic idea that two enantiomers of a bistable molecule might function as the two distinct states in a molecular information storage system, we succeeded in designing chiroptical molecular switches and light-driven unidirectional rotary motors.

The next stage will be the connection of the motors to surfaces, nanoparticles, or other molecules. For this purpose, **12** and **13** (Figure 11) are excellently suited, as two "legs" are readily introduced at the bottom part without affecting the rotary motion of the upper part. The self-organization and concerted action of many such molecular motors is an issue that lies ahead of us.[36] Although the present systems are still very primitive, one can imagine that these studies may help to accomplish controlled movement of objects and ultimately guide us to molecular machines.

I am extremely grateful to the students and postdoc for all their accomplishments, and I consider it a privilege to work with such talented co-workers. Their names have been cited in the references. We thank Professor Nobuyuki Harada at Sendai for a very fruitful cooperation for many years and Ing. Marc van Gelder for his indispensable help with numerous chiral HPLC separations. Financial support from the Netherlands Foundation for Scientific Research (NWO-CW) and the Technology Foundation (NWO-STW) is gratefully acknowledged.

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