Molecular Switches

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An Azobenzene Unit Embedded in a Cyclopeptide as a Type-Specific and Spatially Directed Switch**

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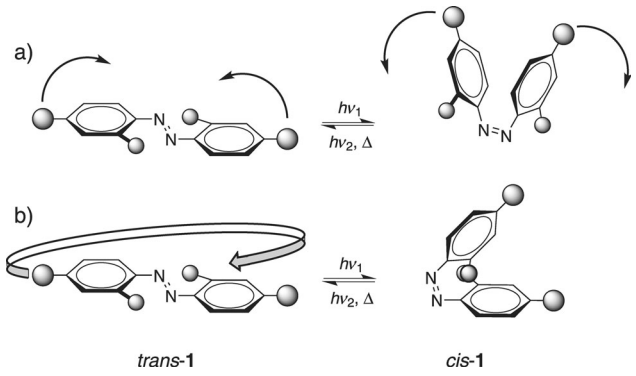
Azobenzene is one of the most frequently used switching elements.[1,2] During light-induced *trans*→*cis* isomerization of azobenzene and its derivatives, the elongated *trans* isomer changes over to the compact *cis* form.[3–9] A reason for the popularity in using it as a switching element is its high reversibility and high photostability, which offer a multitude of switching cycles. However, in systems described to date, only states and not the way from one isomer to the other were made utilizable. A reason for that is the diversity of possible movements during transition from *trans*- to *cis*-azobenzene. As an example, the *trans*→*cis* isomerization of azobenzene **1**, which is substituted in the *ortho* and *para* position, is considered (Scheme 1). If the isomerization proceeds by



Scheme 1. Switching processes of azobenzene **1**. a) During the flipping process, the phenyl rings move towards each other (motion around the N=N bond). b) During the rotation (inversion at one nitrogen atom), one phenyl ring slides sideways past the other.

rotation around the N=N bond, both phenyl rings directly move towards each other (Scheme 1 a). During this flipping process the phenyl rings can move up (illustrated by black arrows) or down and the *cis* isomer is formed. Thermal reisomerization can be effected in the same way (black arrows) or vice versa. If the isomerization takes place by inversion at one nitrogen atom, the phenyl rings do not move towards each other but one of them slides sideways past the other (Scheme 1 b). The difference in movement mechanisms is easily recognizable by the positions of the *ortho* substituents. If these are positioned *anti* in the *trans* isomer they are also *anti* in the *cis* isomer in case of an isomerization by N=N rotation. In contrast, after an inversion, a *syn* conformation is obtained.

For using the isomerization of azobenzene as a central unit in a molecular motor it is necessary to determine the type of movement (flipping process versus rotation) as well as the direction of the movement (unidirectionality); this means the switching process has to be type-controlled and spatially directed. Examples are known that show a controlled type of movement by incorporation into polycyclic structures,[10] but here the processes are not unidirectional. There are also systems in which the configurations of the *cis* and *trans* isomers are controlled by chiral bridges.[11] This is mostly important for directional control, but in these cases the type of movement cannot be determined.

In Scheme 2, a system is shown in which the switching of the azobenzene unit is both controlled and directed. The concept is based on three principles: 1) The azobenzene is embedded into a chiral scaffold and is therefore surrounded from below and sideways. This composition guarantees a flipping process during isomerization, because only during this process the residues in *ortho* position are *anti* in the *trans* and *cis* isomer. In contrast to a simple bridging by a chiral scaffold,[11a,b] a sidewise rotation of one phenyl ring, which would lead to a *syn* orientation of both *ortho* substituents, is not possible.[12] 2) The direction of the *trans*→*cis* flipping is predetermined by embedding because the phenyl rings can only move into one direction (black arrows at *trans*-(*P*)-**2** in Scheme 2). 3) The direction of the *cis*→*trans* flipping should be effected by chirality induction of the scaffold. If the energy differences between the diastereomeric *trans* isomers are small,[11a,b] the *trans*-(*P*) isomer as well as the *trans*-(*M*) isomer can be formed after flipping. However, temperature-induced flipping of the embedded azobenzene **2** leads to the formation of the *trans*-(*P*) isomer (black arrows at *cis*-(*P*)-**2** in Scheme 2), because there is no thermodynamic driving force leading to the *trans*-(*M*) isomer. The pictured switching process from *trans*-(*P*)-**2** to *cis*-(*P*)-**2** is therefore unidirectional, but the initial state is not reobtained by a cyclic process as it is in case of the rotors by Feringa et al.[1]

Because we were already able to carry out unidirectional switching[13] and chirality induction[14,15] by chiral cyclic imidazole peptides,[16] we also used the chiral clamp **7** for generating the embedded azobenzene **2**. We used phenyl units as side branches which are bound to the chiral clamp by

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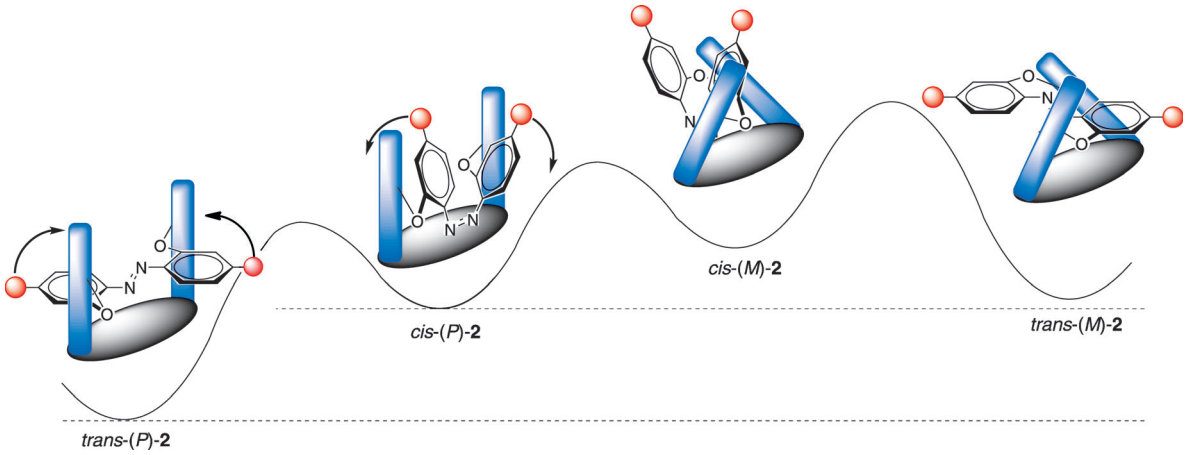
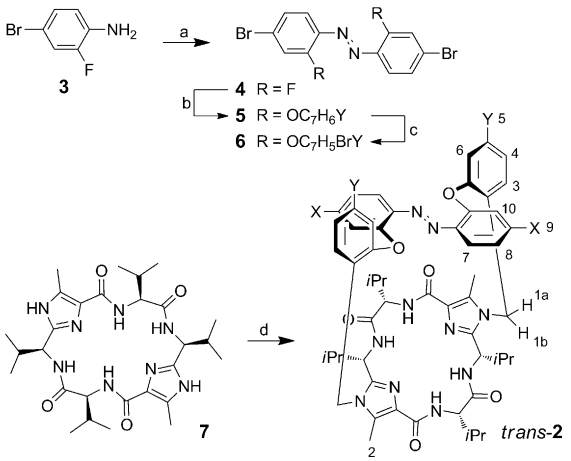


Scheme 2. Switching process of the embedded azobenzene **2**. Because of the embedding of the azobenzene unit into a chiral scaffold, the switching proceeds from the *trans*-(*P*) isomer to the *cis*-(*P*) isomer and back (black arrows). The embedding also causes that the phenyl rings can only move directly towards each other.

methylene groups and connected with the azobenzene unit by ether bridges (Scheme 3).

To ascertain whether the azo compounds **2** exhibit the desired properties, namely embedding into a chiral scaffold and massive energetic discrimination of one planar-chiral



Scheme 3. Illustration of the embedded azobenzenes *trans*-**2b**,**c**. Reaction conditions: a) MnO_2, toluene, Δ, 87%; b) **5a** (Y = H): 2-methylphenol, Cs_2CO_3, acetonitrile, Δ, 72%; **5b** (Y = Cl): 5-chloro-2-methylphenol, Cs_2CO_3, acetonitrile, Δ, 87%; c) **6a** (Y = H): NBS, CCl_4, Δ, 57%; **6b** (Y = Cl): NBS, CCl_4, Δ, 45%; d) *trans*-**2b** (X = Br, Y = H): **6a**, Cs_2CO_3, acetonitrile, Δ, 36%; *trans*-**2c** (X = Br, Y = Cl): **6b**, Cs_2CO_3, acetonitrile, Δ, 66%. NBS = *N*-bromosuccinimide.

isomer, the structures of *trans*-(*P*)-**2a**, *trans*-(*M*)-**2a**, *cis*-(*P*)-**2a**, and *cis*-(*M*)-**2a** (X = H, Y = H) were geometrically optimized by means of B3LYP/6-31G*.[17] A comparison of the energies shows that the *trans*-(*P*) isomer is about 56.3 kJ mol^{-1} lower in energy than the *trans*-(*M*) isomer, so that only the *trans*-(*P*) isomer is present under standard conditions in solution. The energy difference between the *trans*-(*M*) isomer and the *cis*-(*P*) isomer amounts to 0.3 kJ mol^{-1} in favor of the *cis* isomer. The *cis*-(*M*) isomer is about 21.6 kJ mol^{-1} higher in energy than the *cis*-(*P*) isomer.

A look at the calculated molecular structure of *trans*-(*P*)-**2a** (X = H, Y = H) shows that the azobenzene is embedded into the chiral scaffold as desired (Figure 1). The chiral clamp

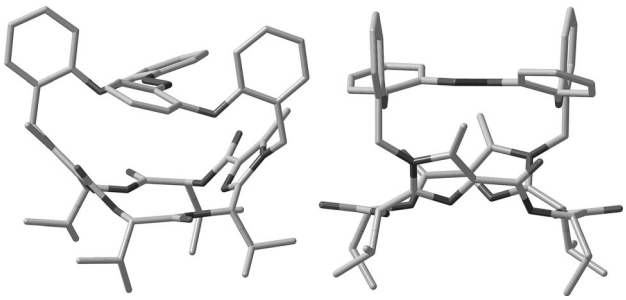


Figure 1. Molecular structure of *trans*-(*P*)-**2a** (X = H, Y = H) calculated by B3LYP/6-31G* viewed from different sides. All of the hydrogen atoms were omitted for clarity.

makes sure that the two phenyl units are positioned exactly to point upwards. Because the azobenzene is only connected to one oxygen atom at each side, the azobenzene unit is "pushed" downwards. Corresponding to the calculations, all conditions for a controlled and directed switching of system **2** should therefore be fulfilled.

That the isolated *trans*-**2** compounds are the desired *trans*-(*P*)-**2** isomers is shown by 2D NMR measurements. In these experiments, cross-peaks between the protons H7 and H8 of the azobenzene unit with the protons H2 of the methyl groups of the imidazole were found (see Supporting Information; for numbering, see Scheme 3). This can only be explained by the embedding of the azobenzene, which exhibits a *P* configuration. Furthermore we managed to grow crystals of *trans*-**2b** which were investigated by X-ray analysis. Unfortunately, a discussion of the exact bond lengths and angles is not possible because of the disorder that is due to enclosed solvent. The connectivity of the switch is, however, absolutely certain and the *trans*-(*P*) isomer showing the embedded azobenzene unit is found (see Supporting Information).

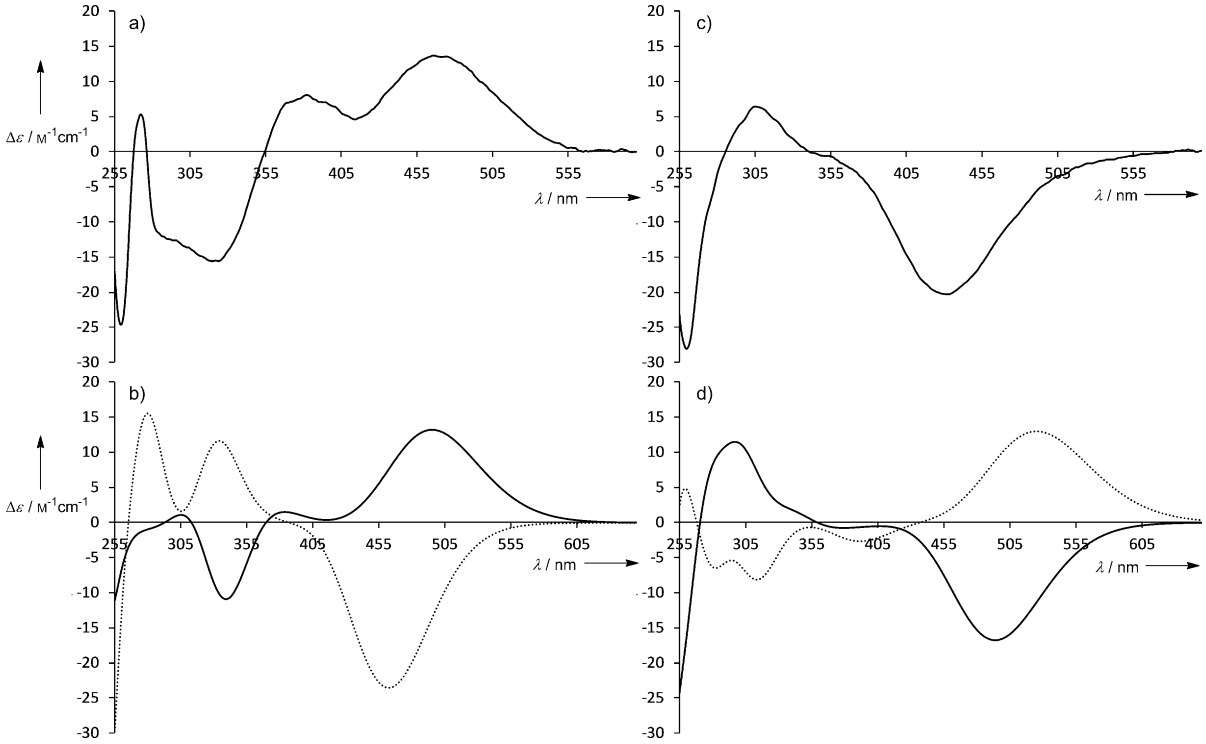


Figure 2. a) CD spectrum of the embedded azo switch *trans*-**2b** (X = Br, Y = H; peak in the HPLC spectrum at 5.7 min, MeOH/H_2O 98:2). b) CD spectra of *trans*-(*P*)-**2a** (——) and *trans*-(*M*)-**2a** (••••) calculated by means of TD-DFT-B3LYP/6-31G* (X = H, Y = H). c) CD spectrum of the embedded azo switch *cis*-**2b** (X = Br, Y = H) (peak in the HPLC spectrum at 4.2 min, MeOH/H_2O 98:2). d) CD spectra of *cis*-(*P*)-**2a** (——) and *cis*-(*M*)-**2a** (••••) calculated by means of TD-DFT-B3LYP/6-31G* (X = H, Y = H).

The investigations concerning the switching process between *trans*-**2b**,**c** and *cis*-**2b**,**c** were carried out in a dilute solution of methanol/water and in acetonitrile. The *trans*→*cis* isomerization was effected by irradiation with UV light at a wavelength of $\lambda = 366$ nm. Reisomerization was achieved by heating to 70 °C. The obtained HPLC spectra show that the azo compounds **2b**,**c** are present in a *trans*/*cis* ratio of 89:11 after synthesis (see the Supporting Information). In the photostationary state at 366 nm, a *trans*/*cis* ratio of 35:65 is gained. The CD spectra of *trans*-**2b** and *cis*-**2b** were obtained by measuring the different HPLC fractions. For a better assignment and interpretation, the CD spectra of *trans*-(*P*)-**2a**, *trans*-(*M*)-**2a**, *cis*-(*P*)-**2a**, and *cis*-(*M*)-**2a** were calculated by TD-DFT-B3LYP/6-31G*. A comparison of the CD spectrum of *trans*-**2b** with the simulated CD spectrum of *trans*-(*P*)-**2a** shows that both exhibit a strong positive Cotton effect (n→π* transition) at values around 470 nm (Figure 2a,b). However, for *trans*-(*M*)-**2a** a negative Cotton effect is found for the n→π* transition. The CD spectrum of *cis*-**2b** underlines the prediction of the calculations that the *cis* isomer is also *P*-configured: In the experimentally obtained CD spectrum of *cis*-**2b** as well as in the simulated CD spectrum of *cis*-(*P*)-**2a**, a strong negative Cotton effect is found for the n→π* transition (Figure 2c,d). In contrast, a positive Cotton effect is observed for *cis*-(*M*)-**2a**.

Reisomerization can either be achieved by irradiation with visible light or by heating (Supporting Information and Figure 3). If the solution is for example heated to 70 °C, the initial spectrum is reobtained within a few minutes. This switching process, which is controlled and directed from *trans*-(*P*)-**2b** to *cis*-(*P*)-**2b** and back, can be repeated virtually any number of times. The irradiation of the solution with UV light and simultaneous heating to 70 °C is especially fascinating (see green curve in Figure 3). Under these conditions a continuous controlled and spatially-directed transition from *trans*-(*P*)-**2b** to *cis*-(*P*)-**2b** and back is reached. In this stationary state a continuous flipping process of the phenyl rings of the azobenzene of **2b** takes place, which can be compared to the wingbeat of a bird.

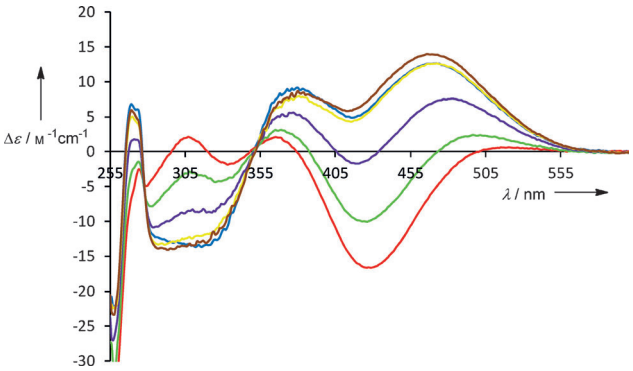


Figure 3. CD spectra of the embedded azo switch **2b** (X = Br, Y = H; $c = 1.0 \times 10^{-4}$ M in acetonitrile). Blue: before UV irradiation; red: after 5 min of UV irradiation ($\lambda = 366$ nm) at 20 °C; purple: 10 min at 70 °C; yellow: further 10 min at 70 °C; brown: further 10 min at 70 °C. Green: UV irradiation ($\lambda = 366$ nm) at 70 °C.

In summary, we were able to show for the first time that an azobenzene unit can be type-controlled and spatially directed by embedding it into a chiral scaffold. If the solution is irradiated and heated at the same time a stationary state is achieved in which a continuous flipping of the phenyl rings of the azobenzene unit takes place. As the described azobenzene derivatives can be synthesized in a few steps, **2** can in the future be introduced as a central switching element in molecular motors. It thus enlarges the range of applications for azobenzene derivatives enormously.

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