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Switching Process Consisting of Three Isomeric States of an Azobenzene Unit

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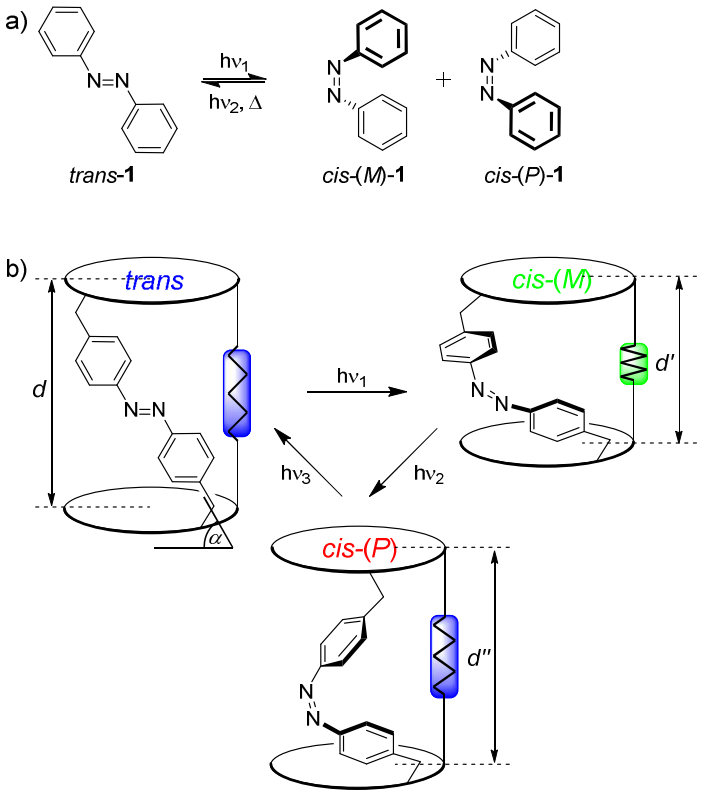
ABSTRACT: Azobenzene and its derivatives are one of the most commonly used switching units in organic chemistry. The switching process consists of two states, in which the *trans* isomer has a stretched and the *cis* isomer a compact form. Here, we have designed a system in which all isomeric states of an azobenzene moiety (*trans* → *cis*-(*M*) → *cis*-(*P*)) are passed step by step. The first step involves the change in the distance between the benzene units, which is common for azobenzene derivatives; in the second step an inversion of the helicity (*M* → *P*) of the *cis* azobenzene unit takes place; the third step leads back to the stretched *trans* isomer. This switching cycle is achieved by coupling the azobenzene unit with two chiral clamps and with a further azobenzene switching unit.

Introduction

Photochromic molecules that can be reversibly switched between two isomers of different structures are of great interest for the development of molecular host-guest systems and molecular machines.[1-4] One of the most commonly used switching unit is azobenzene and its derivatives:[5-16,]The *trans* isomer has a stretched and the *cis* isomer a compact form. Usually, the *trans* → *cis* isomerization takes place by UV light and the *cis* → *trans* back relaxation by visible light or heat.[5,17] The reasons for the popularity of azobenzene derivatives as a switching units are the high reversibility, the simple synthesis and the high photostability, which allows a large number of switching cycles. The high range of variation in excitation wavelength, stability and movement pattern are other crucial features of these compounds.



Scheme 1. a) Light-induced switching process of azobenzene (**1**) consisting of the two states: *trans*-**1** and *cis*-**1** (racemate). b) Light-induced switching processes of a chiral azobenzene cage consisting of the three states *trans*-**2**, *cis*-(*M*)-**2** and *cis*-(*P*)-**2**. Compound **2** shows – additionally to the azobenzene unit – a further switching element (blue or green rectangle); the black ellipses in compound **2** represents the chiral clamp **3** (for the detailed chemical structure of compounds **2** and **3** see Scheme 2).

The use of suitable substituents on the benzene units allows the variation of the thermal *cis* → *trans* back isomerization,[18] the orthogonal switching of azobenzene double switches[19] and

the switching with visible light.[20-26] The latter feature is of particular importance for *in vivo* switching processes[27] or those of biomolecules[28-29]. Recently, it has also been shown that the *cis* → *trans* back isomerization can be accelerated by electrochemical catalysis.[30] The form of the motion (rotation around the N=N-bond or inversion on a nitrogen atom) can be controlled by incorporation into polycyclic structures.[31-33] A closer look at the switching process of azobenzene (**1**) shows that the *trans* → *cis* isomerization implies not only a structural change but also a generation of helical chirality: the *cis* isomer is an enantiomeric pair of *cis*-(*M*)-**1** and *cis*-(*P*)-**1** (Scheme 1a). In the literature there are some examples in which the conformation of the *cis* or the *trans* isomers is controlled by chiral bridges.[34-37,33,38] But a system in which all *three* isomers are incorporated into a switching cycle consisting of three states has to the best of our knowledge not yet been described in the literature. The design of such a system would be a very worthwhile goal and would add invaluable insight into the rich photophysical processes and properties of azobenzene based molecular switches and machines. The process would consist on the one hand of a switching between the stretched and the compact form (*trans* and *cis*) and on the other hand of a switching between the helicities of the *cis* isomers (*M* and *P* arrangement). Here we describe the synthesis and the investigation of a system which can adopt all three different states of an azobenzene unit. In the following we will call this system as triple switch.

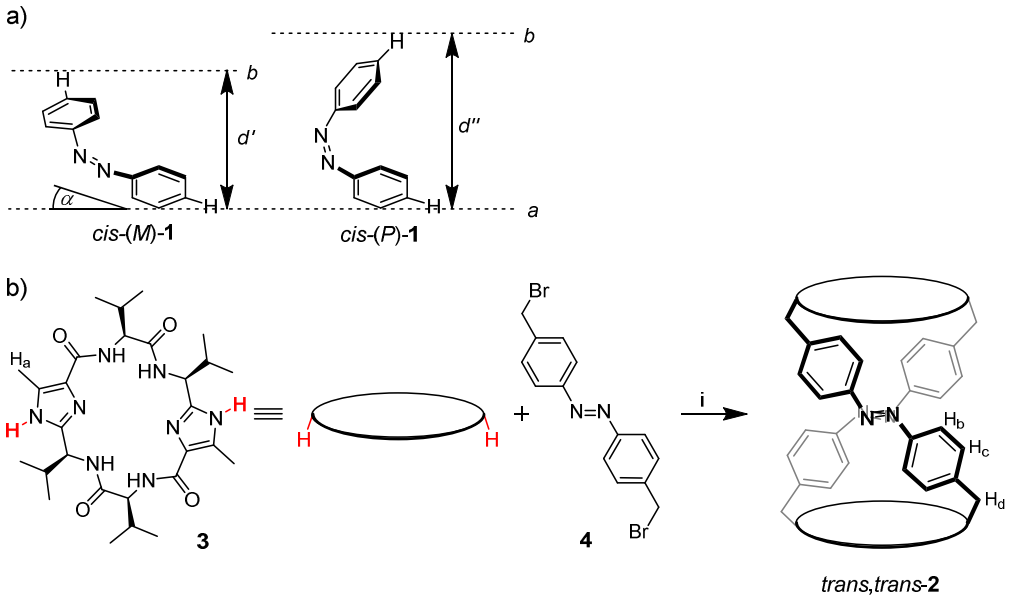
Results and Discussion

a) Concept and synthesis of the triple switch

For the design of a switching system, which can adopt all three different states of an azobenzene unit, a dilemma arises: In order to switch from the *trans* isomer to only one of the *cis* isomers (for example: into the *cis*-(*M*) isomer of the azo switch **2** in Scheme 1b), it is necessary to implement a chiral unit, which energetically excludes the formation of the *cis*-(*P*) isomer. However, this chiral induction – which is necessary for the first step – prevents the second switching process to the *cis*-(*P*) isomer. In order to solve this problem, the introduction of a second switching unit into the system **2** is absolutely necessary. This should also be present in a stretched (blue rectangle in Scheme 1b) or in a compact form (green rectangle in Scheme 1b). The switching cycle should proceed as following: 1) In the *trans* isomer of **2**, the *trans* azobenzene unit is connected to two chiral clamps (black ellipses in Scheme 1b). These are subsequently necessary for the chirality induction in the formation of the *cis*-(*M*) isomer. However, due to their chirality they also cause, that the *trans* azobenzene unit is fixed at a certain angle α ($\alpha < 90°$; Scheme 1b) relative to the lower chiral clamp. The second switching element (blue rectangle in Scheme 1b) is present in a stretched form. Therefore, the distance *d* between the clamps is large. 2) In the *cis*-(*M*) isomer, the azobenzene unit and the second switching element are present in the compact form; the

distance between the clamps *d′* is accordingly reduced considerably compared to *d* in the *trans* isomer. The chiral induction of the two clamps leads to the fact, that the *cis*-(*M*) conformation of the azobenzene is energetically much more preferred than the *cis*-(*P*) conformation. 3) In order to obtain the *cis*-(*P*) conformation of **2**, the following trick is applied: The second switching element is switched from the compact (green) to the stretched state (blue), whereby the distance *d″* between the clamps becomes larger (*d″* > *d′*). The greater distance favors the *cis*-(*P*) conformation of the azobenzene unit. This assumption seems to be irritating at first glance, because *cis*-(*M*) and *cis*-(*P*) azobenzene have the same sizes. However, the spatial fixation of the azobenzene unit and the relative position to further units (e.g. the linking sites) must also be taken into account. This can be easily illustrated by holding one of the two benzene units of *cis*-(*M*) and *cis*-(*P*) azobenzene (**1**) at a fixed angle α (α < 90°) relative to the plane *a* (see Scheme 2a and Figure S1). The distance of plane *a* to the second plane *b*, which also touches the azobenzene, is significantly larger for the *cis*-(*P*) isomer than for the *cis*-(*M*) isomer (*d″* > *d′*).

Hence, if the distance of the chiral clamps in **2** is increased by the second switching element (Scheme 1b), the actual preference of the chiral clamps for the *cis*-(*M*) conformation is reversed. In this step, an inversion of the helicity of the *cis* azobenzene unit occurs.



Scheme 2. a) The spatial fixation of an azobenzene unit relative (α <90 °) to plane *a* leads to different distances (*d″* > *d′*) to the second plane *b* for the two enantiomers *cis*-(*M*) and *cis*-(*P*) azobenzene (**1**). Both planes (*a* and *b*) should touch the azobenzene unit. b) Synthesis of the chiral azobenzene cage *trans*,*trans*-**2**. Reaction conditions: i) Cs_2CO_3, CH_3CN, Δ, 27%.

Looking for suitable chiral clamps and a second switching element, we have carried out a series of preliminary calculations. Among the different chiral systems we have used for chirality induction,[39-41] the imidazole-containing clamp **3**[42] was the one with the greatest prospect of success (Scheme 2b). This clamp has already been used in many other unidirectional switching processes.[43-46] As a second switching element, we have decided for a further azobenzene unit. The advantage of azobenzene is the already mentioned reversibility, easy switchability and the great structural difference between the isomers. The disadvantage of the use of azobenzene as a second switch is the indistinguishability of the two switching units. Thus, the six possible states in which the chiral azobenzene cage **2** can be present are: *trans*,*trans*, *cis*,*trans*-(*M*), *cis*,*trans*-(*P*), *cis*,*cis*-(*M*,*M*), *cis*,*cis*-(*M*,*P*) and *cis*,*cis*-(*P*,*P*). The states of the desired three-step switching process are: *trans*,*trans*, *cis*,*trans*-(*P*) and *cis*,*cis*-(*M*,*M*).

The synthesis of the switching system **2** takes places from the chiral clamp **3**[42] and the dibromide **4**[47] (Scheme 2b). Both can be synthesized in only few steps from commercially available compounds. After the synthesis of **2**, three isomers are obtained which are according to the HPLC chromatogram present in the ratio of 71:27:2 (see Figure S19). According to the symmetry of the signals in the ^{1}H NMR spectra, these are the isomers: *trans*,*trans* (71%), *cis*,*trans* (27%) and *cis*,*cis* (2%). Using NMR spectroscopy (^{1}H NMR and NOESY spectra), a determination of the conformation (*M* or *P*) of the *cis* azobenzene units could not be achieved (see Figures S10-15).

b) Structural investigation of the states of the triple switch 2

To clarify whether the system has the desired switching properties, a series of isomers were optimized by means of the B3LYP[48-50] functional and the 6-31G*[51-52] basis set (Figures 1 and S2). Subsequently, the energies of the isomers were computed by using B3LYP-D3[53-54] and the basis set def2-TZVP[55-56]. The calculations show that the distance between the two chiral clamps strongly depends on the configuration (*trans* or *cis*) and also on the conformation (*M* or *P*). The size of *trans*,*trans*-**2** (14.7 Å) is significantly larger than that of *cis*,*cis*-(*P*,*P*)-**2** (12.1 Å) and *cis*,*cis*-(*M*,*M*)-**2** (10.7 Å). The difference between the two *cis*,*cis* isomers matches well with the above mentioned hypothesis for the different space requirements of the *cis* isomers (Scheme 2a and Figure S1). The size of *cis*,*trans*-(*P*)-**2** and *cis*,*trans*-(*M*)-**2** is about 12.3 Å and is approximately as large as that of *cis*,*cis*-(*P*,*P*)-**2** (12.1 Å). This means that the *cis*-(*M*) moiety differs strongly, whereas the *cis*-(*P*) moiety differs only slightly from its "ideal" geometry. The calculated energy differences verify the success of this strategy: *cis*,*cis*-(*M*,*M*)-**2** is much more stable than *cis*,*cis*-(*P*,*P*)-**2** (42.7 kJ/mol), whereas the *cis*,*trans* isomers show a reversed preference. However, the difference between *cis*,*trans*-(*P*)-**2** and

cis,*trans*-(*M*)-**2** is with 2.0 kJ/mol relatively small. A "mixed" *cis*,*cis*-(*M*,*P*) isomer could not be found.

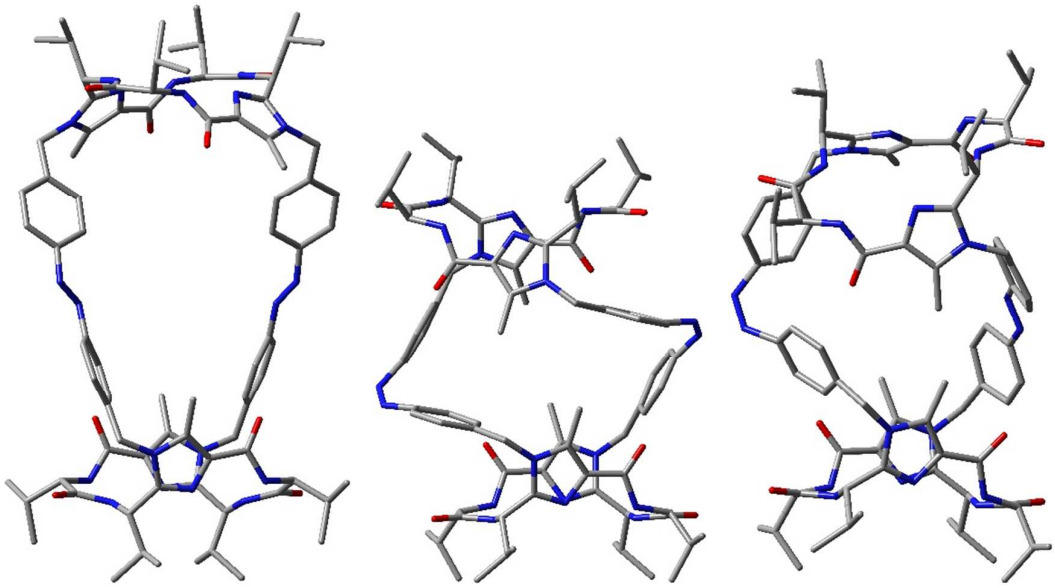


Figure 1. Molecular structures of *trans*,*trans*-**2** (left), *cis*,*cis*-(*M,M*)-**2** (middle) and *cis*,*trans*-(*P*)-**2** (right) calculated with B3LYP/6-31G*. All hydrogen atoms are omitted for the sake of clarity.

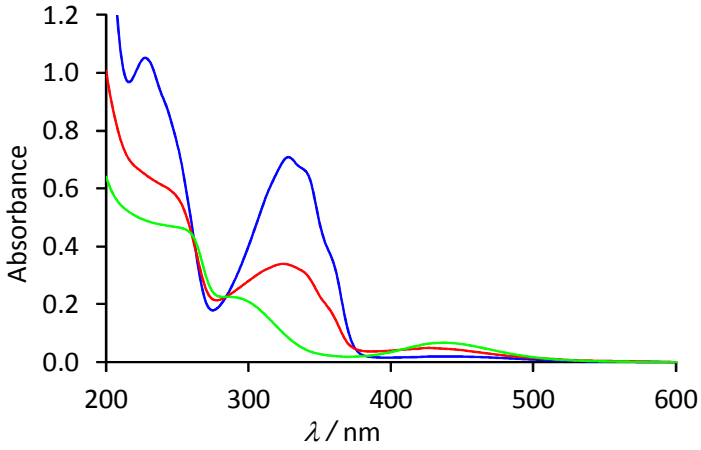


Figure 2. UV spectra of *trans*,*trans*-**2** (blue), *cis*,*trans*-**2** (red) and *cis*,*cis*-**2** (green) in methanol/water (95/5) (c = 1.0 × 10^{-5} M).

For a more detailed structural investigation, the single HPLC peaks were collected and measured within few minutes by means of UV and CD spectroscopy. The fact that the collected fractions are indeed the pure isomers could be confirmed as following: After collection and a waiting time of about 20 minutes, HPLC chromatograms of the single fractions were recorded. These chromatograms show that the isomers are present in purities

of 91-98% (see Figures S16-18). The UV and CD spectra of the three isomers are depicted in Figures 2 and 3. As anticipated, the *trans*,*trans* isomer exhibits the highest absorption band at 330 nm and the *cis*,*cis* isomer the lowest one (Figure 2). This absorption band corresponds to the $\pi \rightarrow \pi^*$ transition and its change is typical for isomerization of azobenzene derivatives. On the other side, the $n \rightarrow \pi^*$ transition at ca. 450 nm is more pronounced for the *cis*,*cis* isomer than for the other isomers. This is consistent with the UV spectra of other simple alkyl-substituted *cis* azobenzenes. The isosbestic point for the three isomers can be found at 284 nm.

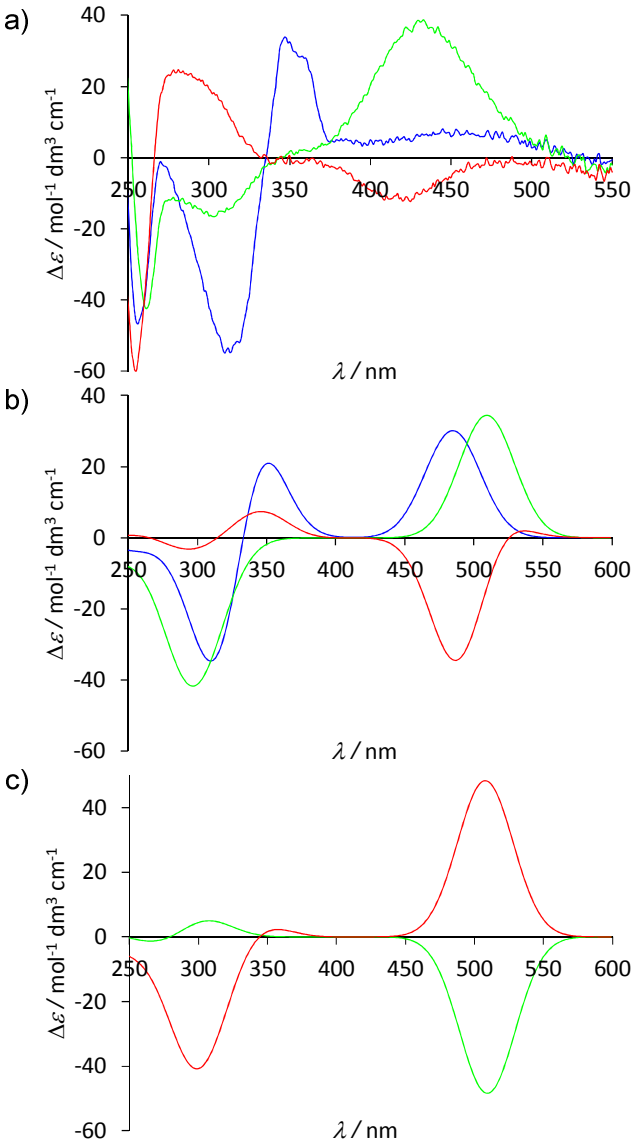


Figure 3. a) CD spectra of *trans*,*trans*-**2** (blue), *cis*,*trans*-**2** (red) and *cis*,*cis*-**2** (green) in methanol/water (95/5) (c = 1.0×10^{-5} M). b) By means of TD-B3LYP/6-31G* calculated CD spectra of *trans*,*trans*-**2** (blue), *cis*,*cis*-(*M,M*)-**2** (green) and *cis*,*trans*-(*P*)-**2** (red). c) By means

of TD-B3LYP/6-31G* calculated CD spectra of *cis*,*cis*-(*P,P*)-**2** (green) and *cis*,*trans*-(*M*)-**2** (red).

A major advantage in the interpretation of CD spectra of simple alkyl-substituted *cis* azobenzenes is the fact, that the conformation (*M* or *P*) can be directly identified from the sign of the Cotton effect at 450 nm. This is due to the fact, that this area is dominated by only one transition (n→π*). Previous investigations have shown that the *cis*-(*M*) isomer has a positive and the *cis*-(*P*) isomer exhibits a negative Cotton effect in this region (see also Figure S3).[34]

For a better assignment and interpretation, the CD spectra of *trans*,*trans*-**2**, *cis*,*trans*-(*M*)-**2**, *cis*,*trans*-(*P*)-**2**, *cis*,*cis*-(*M*,*M*)-**2** and *cis*,*cis*-(*P*,*P*)-**2** were calculated by means of time-dependent density function theory[57] (TD-B3LYP) and the 6-31G* basis set (Figure 3). A comparison of the simulated and the experimentally determined CD spectrum of *trans*,*trans*-**2** shows a good agreement between theory and experiment (Figure 3). The spatial fixation of the two *trans* azobenzene units can be recognized by the positive Cotton effect for the n→π* transition and especially by the intense CD pair at about 340 nm. For the interpretation, the exciton chirality method can be applied:[58] Because of the positive band at a higher wavelength (350 nm) and the negative band at a lower wavelength (315 nm), the two *trans* azobenzene units are fixed at an angle $\alpha < 90°$ relative to the chiral clamps (Figure S1).

The experimentally determined spectrum of the *cis*,*trans* isomer matches only with the simulated spectrum of *cis*,*trans*-(*P*)-**2**, but not with that of *cis*,*trans*-(*M*)-**2**. For the experimentally determined and the simulated spectra of *cis*,*trans*-(*P*)-**2** the Cotton effect for the n→π* transition is negative and for the π→π* transitions positive. The latter one can be find in the area at about 320 nm. In comparison, *cis*,*trans*-(*M*)-**2** has a strongly positive Cotton effect at 500 nm and a negative Cotton effect at 300 nm. The CD spectrum of *cis*,*cis*-**2** can be interpreted analogously: The Cotton effects for the n→π* and the π→π* transitions clearly indicate the presence of the *cis*,*cis*-(*M,M*) isomer, while the *cis*,*cis*-(*P,P*) can be excluded.

c) Investigation of the Switching Process

The switching processes were investigated by means of UV and NMR spectroscopy as well as with HPLC in methanol as solvent (Figures 4, S4-S7 and S19-S23).

The UV spectra obtained during the switching processes are as anticipated: The UV spectrum of the triple switch **2** after UV irradiation with λ = 365 nm resemble that of the *cis*,*cis* isomer (Figures 2 and S23). After irradiation with visible light (λ = 530 nm) the above mentioned increase of the π→π* transition at 330 nm is observed and the spectrum is similar to the UV spectrum of the isolated *cis*,*trans* isomer. A subsequent irradiation with UV light of

the wavelength λ = 405 nm results in an even more pronounced increase of the $\pi \rightarrow \pi^*$ band at 330 nm. This spectrum matches with the UV spectrum of the *trans*,*trans* isomer (Figures 2 and S23). Using UV spectroscopy, a quantitative determination of the ratio of the three isomers is not reasonable. For this purpose, NMR spectroscopy and HPLC are more appropriate. However, the determination of the isomer ratios by NMR studies was difficult, as the relevant peaks of the single isomers partly overlap with other peaks. Due to the multitude of signals in the ^{1}H NMR spectrum of **2**, we wanted to check if all signals belong to the triple switch **2**. Therefore, compound **2** was dissolved in $C_2D_2Cl_4$ (c = 10^{-2} M) and heated stepwise to a temperature of 120 °C (Figure 4). Beside a slight upfield shift, all signals except those belonging to the *trans*,*trans* isomer disappeared. After cooling down to 20 °C, only the signals of the thermodynamic most stable the *trans*,*trans* isomer are present (Figure 4). Hence, the multitude of signals in the ^{1}H NMR spectrum indeed can be assigned to the triple switch **2**.

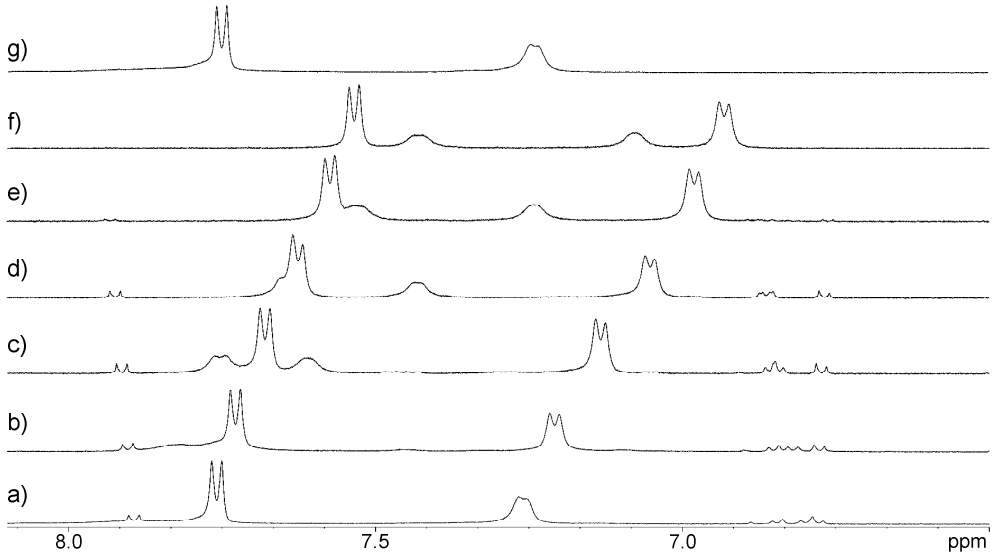


Figure 4. Section from the ^{1}H NMR spectra (protons H_b and H_c; for assignment see Scheme 1) of the chiral cage **2** at 500 MHz in $C_2D_2Cl_4$ (10^{-2} M) in the temperature range from 20 (a) to 120 °C (f) in steps of 20 °C and after cooling to 20 °C (g).

The switching process was investigated by NMR spectroscopy and HPLC in methanol. Please note that the ^{1}H NMR signals in methanol (especially the signals of the *trans*,*trans* isomer) are strongly shifted compared to those measured in $C_2D_2Cl_4$ (Figures 4-5). The ratio for the three isomers determined by NMR differs from that obtained by HPLC (Figures 5, S4-S7 and S19-S22). This discrepancy is due to the fact that the isomerization caused by the used LEDs is dependent on the concentration. The lower the concentration of the azobenzene, the higher is the switching rate (Figures S6 and S7). As the HPLC experiments

were carried out at significantly lower concentrations (10^{-4} M), higher degrees of isomerization were obtained. Hereinafter, only the values obtained by HPLC are discussed. In order to obtain the ratios for the three isomers by HPLC as accurate as possible, the wavelength of the detector was set to 284 nm. This is the isosbestic point for the three isomers (Figure 2).

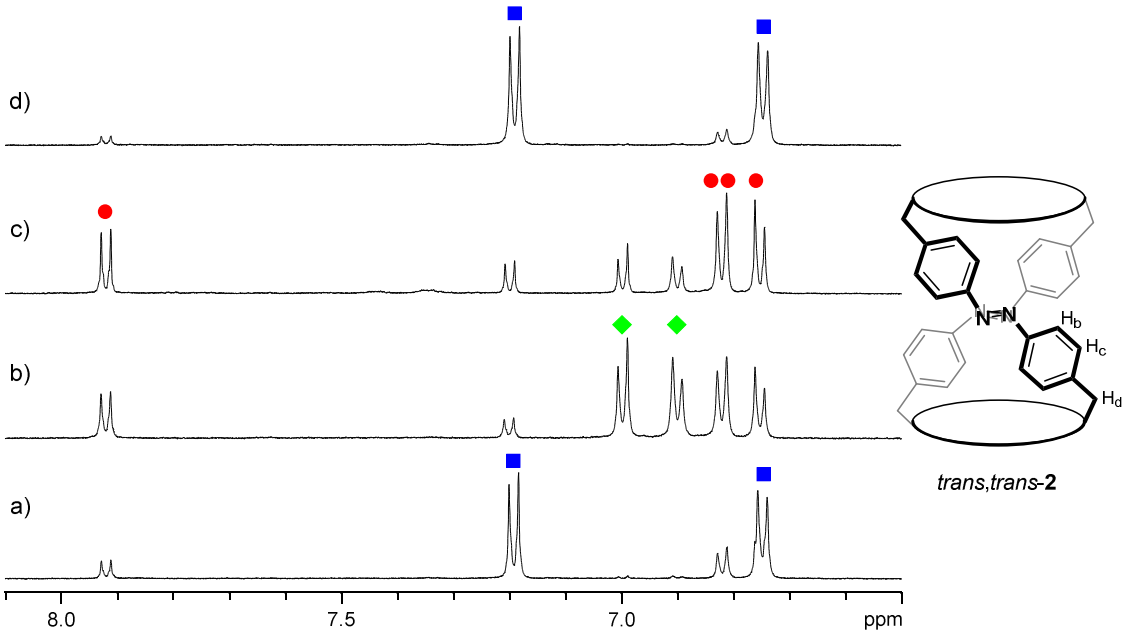


Figure 5. Section from the ^{1}H NMR spectra (protons H_b and H_c) of the chiral azobenzene cage **2**: (a) after synthesis, (b) after UV irradiation with λ = 365 nm, (c) after irradiation with visible light (λ = 530 nm) and (d) after subsequent UV irradiation with λ = 405 nm (MeOD, 500 MHz, 10^{-2} M). The protons H_b and H_c of the isomers *trans*,*trans*-**2** (blue), *cis*,*cis*-(*M,M*)-**2** (green) and *cis*,*trans*-(*P*)-**2** (red) are marked.

After the synthesis, the chiral azobenzene cage **2** is predominantly present as *trans*,*trans* isomer (ratio of *trans*,*trans* / *cis*,*trans*-(*P*) / *cis*,*cis*-(*M,M*) amounts to 71:27:2 see Figure S19). The first step in the switching cycle is the irradiation with UV light of the wavelength λ = 365 nm, which leads to an isomerization to the *cis*,*cis*-(*M,M*) isomer. A *trans*,*trans* / *cis*,*trans*-(*P*) / *cis*,*cis*-(*M,M*) ratio of 4:29:68 is achieved in the photostationary state at λ = 365 nm (Figure S20). The finding of the optimal trigger for the second step of the switching cycle, in which *one* azobenzene unit is switched from *cis* to *trans* and the *second* azobenzene unit undergoes an inversion of its helicity, was difficult. The best results are obtained when the solution is irradiated with visible light of the wavelength λ = 530 nm for only a few seconds. The ratio *trans*,*trans* / *cis*,*trans*-(*P*) / *cis*,*cis*-(*M,M*) is then changed to 20:66:14 (Figure S21). The third step of the switching cycle leads back to the initial state *trans*,*trans*-**2** and is

realized by irradiation with UV light of the wavelength λ = 405 nm. In the photostationary state at λ = 405 nm, a *trans*,*trans* / *cis*,*trans*-(*P*) / *cis*,*cis*-(*M,M*) ratio of 80:18:3 is achieved (Figure S22).

Experiments for the determination of the half-life of the energetically most unfavorable *cis*,*cis*-(*M,M*) isomer have shown that this has a value of 14 days (346 h) at 5 °C and 69 h at 25 °C (Figures S8, S9 and S24-S26). Accordingly, the single isomers are stable for a long time and rapid back relaxation does not occur. Here, the *cis*,*cis* isomer is slowly converted to the *cis*,*trans* isomer and the latter is obtained with a higher ratio than by the irradiation with visible light of the wavelength λ = 530 nm (Figure S8-S9 and S24). These results show that the *cis*,*trans* isomer can also be obtained from the *cis*,*cis* isomer by a certain temperature increase. The amount of the *trans*,*trans* isomer remains unchanged at about 8%, even after one month after irradiation.

Conclusion

In summary, we have shown that we have designed a system having a switching cycle that passes through all three isomeric azobenzene states (*trans* → *cis*-(*M*) → *cis*-(*P*)). This was achieved by means of two chiral clamps and the introduction of a further azobenzene switching unit. As the system can be synthesized in only few steps, a further substitution of the azobenzene unit should be possible. Therefore, it should be possible in the future to switch both the distance between two substituents and the relative position of the two units in space (inversion of the helicity). As compound **2** passes through a cycle of states showing reversed helicity, it is *per se* a chiroptical switch with inverted Cotton effects at 450 nm. Furthermore, modification of the substituents at the azobenzene unit should allow the design of molecular motors – which pass through the three isomeric states of the azobenzene – and of light-induced selective hosting of different chiral guests.

Acknowledgements

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Supporting Information

Synthesis of the new compounds, ^{1}H NMR and ^{13}C NMR spectra of the new compounds, calculated molecular structures, NMR, HPLC, and UV spectra, cartesian coordinates and absolute energies of all calculated compounds.

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