

Cyclic Kinetics during Thermal Equilibration of an Axially Chiral Bis-Spiropyran

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Supporting Information

ABSTRACT: A compound combining the features of a molecular rotor and a photoswitch was synthesized and was shown to exist as three diastereomers, which interconvert via a reversible cyclic reaction scheme. Each of the three diastereomers was isolated, and by following the equilibration kinetics, activation barriers for all reactions were calculated. The results indicate that the properties of molecular switches depend heavily on their immediate chemical environment. The conclusions are important in the context of designing new switchable molecules and materials.

In an era when the behavior of many switchable molecules is fairly well understood, increasing attention is devoted to integrating these moieties within mechanically interlocked architectures,^{1,2} polymeric systems,³ nanoparticles,^{4,5} and ultimately solid-state materials.^{6–8} These efforts are largely motivated by emerging applications of the switchable materials, most of which require that the molecular switches are covalently attached to a solid/macromolecular support.⁹ Some important points to consider when moving from monomeric switches in solution to more complex architectures are electronic interactions with inorganic supports,¹⁰ intermolecular coupling between the switchable molecules,¹¹ and the conformational freedom that the molecules need in order to efficiently isomerize.^{12–14} This last issue is well exemplified by spiropyran (SP), one of the most widely investigated switchable molecules.¹⁵ As Figure 1a shows, the two states of the switch have significantly different molecular geometries, which can suppress isomerization within sterically hindered environments.

An attractive approach for studying the behavior of molecular switches in such crowded environments could be based on molecules featuring two (or more) switchable moieties placed in close proximity. Such model compounds would be particularly interesting in the case of the inherently chiral SP, since they would also allow us to investigate the fundamentally important issue of chirality inversion (Figure 1a). While in monomeric SPs, chirality inversion results in overall enantiomerization, which is difficult to follow,^{16,17} enantiomerization of one SP unit that takes place in proximity to another (that is, overall epimerization) leads to the formation of easily resolvable diastereomers.¹⁸ With these considerations in mind,¹⁹ we synthesized compound **1** (Figure 1b)^{20,21} in which two SP moieties are linked directly via indolines' phenyl

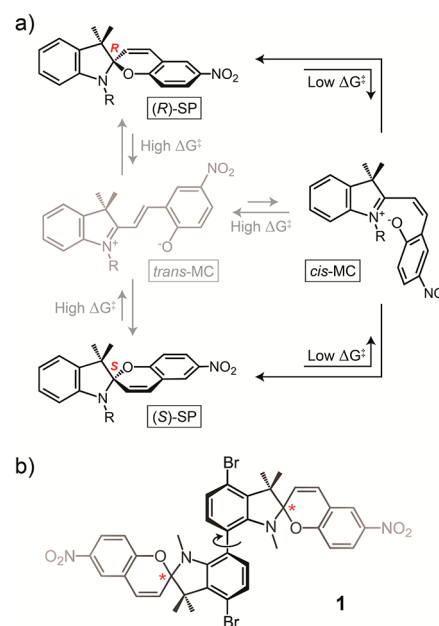


Figure 1. (a) Spiropyran (SP) enantiomerization can occur both via the UV-induced formation of *trans*-merocyanine (MC), or thermally, via the *cis*-MC intermediate. (b) Structural formula of bis-SP **1**.

rings, giving rise to the biphenyl moiety.^{22,23} **1** can exist as three diastereomers: looking down the chiral axis, the two benzopyran moieties can face each other (diastereomer **1**_{in-in}, which is a mixture of enantiomers *S*₁*R*₂*S* and *R*₁*S*₂*R*; see Figure 2a, left), away from each other (**1**_{out-out}; *R*₁*R*₂*R* + *S*₁*S*₂*S*; Figure 2a, center), or “follow” each other (see Figure 2a, right; **1**_{in-out}; *S*₁*R*₂*R* + *R*₁*S*₂*S*).

1 was prepared in six steps from commercially available reagents.²¹ Interestingly, the NMR spectrum of the final product (Figures S1, S2) indicated the presence of only one diastereomer, which we identified by X-ray crystallography as **1**_{in-in} (Figure 2a, left). When the crystals of the **1**_{in-in} diastereomer were left in cold (*T* = 276 K) dichloromethane for several weeks, they changed the morphology (from prisms to needles); X-ray crystallography revealed that the differently shaped crystals comprised the **1**_{out-out} diastereomer (Figure 2a,

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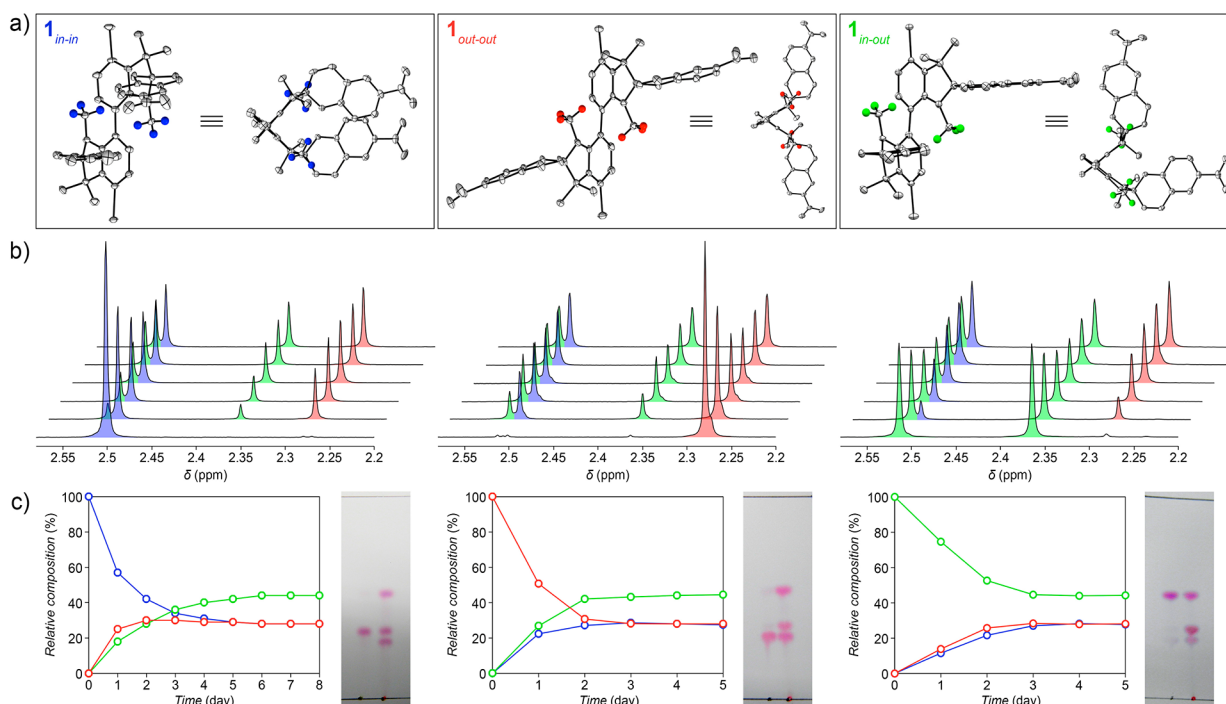


Figure 2. (a) Crystal structures of the $\mathbf{1}_{in-in}$, $\mathbf{1}_{out-out}$ and $\mathbf{1}_{in-out}$ diastereomers. Hydrogen atoms are omitted for the purpose of clarity except for the *N*-methyl protons (indicated in colors). (b) Time-resolved, partial NMR spectra following thermal equilibration of $\mathbf{1}_{in-in}$ (left), $\mathbf{1}_{out-out}$ (center), and $\mathbf{1}_{in-out}$ (right) in CD_2Cl_2 at $T = 295$ K. The spectra for $\mathbf{1}_{in-in}$ are shown at $t = 0, 1, 2, 4, 6, 9$ days. The spectra for the other two isomers are shown at $t = 0-5$ days. (c) Equilibration profiles and TLC plates (3:2 hexane-diethyl ether) before (left) and after (right) equilibration.

center). In both cases, the mother liquors showed the presence of all three compounds (see the TLC plates in Figure 2c).

The fact that the $\mathbf{1}_{in-in}$ ($R_f = 0.36$ in 3:2 hexane-diethyl ether) and the $\mathbf{1}_{out-out}$ ($R_f = 0.31$) isomers can be crystallized out from the mixture of all three diastereomers indicates their relatively low solubilities in a given solvent mixture. The third isomer ($R_f = 0.52$ in Figure 2c) had the highest solubility in all solvents that we tested, and attempts to selectively crystallize it from the diastereomeric mixture proved unsuccessful. Fortunately, its high R_f value enabled us to isolate it by column chromatography; subsequent crystallization at a low temperature yielded single crystals before other diastereomers were generated in significant amounts. These crystals were indeed of the “missing” $\mathbf{1}_{in-out}$ isomer, as shown in Figure 2a, right.

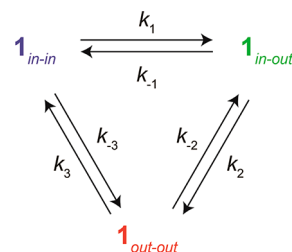
With the pure diastereomers in hand, we could investigate their thermal equilibration in solution (in the crystalline state in the dark, all isomers were stable for at least 1 year²⁴). For example, $\mathbf{1}_{in-in}$ isomerizes to $\mathbf{1}_{in-out}$ by enantiomerization on either of its *spiro* carbon atoms (epimerization) and to $\mathbf{1}_{out-out}$ by rotation about the C–C chiral axis (atropisomerization). Once $\mathbf{1}_{in-out}$ and $\mathbf{1}_{out-out}$ are generated, each of them equilibrates as well until a steady state is reached. Pure $\mathbf{1}_{in-out}$ and $\mathbf{1}_{out-out}$ equilibrate analogously,²⁵ giving rise to the identical final mixture of the three diastereomers. Overall, thermal equilibration of the system can be represented by a reversible cyclic reaction scheme²⁶ involving six first-order reactions with rate constants k_1 , k_{-1} , k_2 , k_{-2} , k_3 , and k_{-3} (Scheme 1).

Equations for the rate constants are as follows:

$$\frac{\partial c_{in-in}}{\partial t} = -k_1 c_{in-in} - k_{-3} c_{in-in} + k_{-1} c_{in-out} + k_3 c_{out-out}$$

$$\frac{\partial c_{in-out}}{\partial t} = -k_{-1} c_{in-out} - k_2 c_{in-out} + k_1 c_{in-in} + k_{-2} c_{out-out}$$

Scheme 1. Cyclic Reversible Reaction Scheme Involving Three Components



$$\frac{\partial c_{out-out}}{\partial t} = -k_3 c_{out-out} - k_{-2} c_{out-out} + k_{-3} c_{in-in} + k_2 c_{in-out}$$

The number of unknown variables is reduced to three, given that at the steady state,

$$k_{-1} = k_1 \frac{c_{in-in,eq}}{c_{in-out,eq}}, k_{-2} = k_2 \frac{c_{in-out,eq}}{c_{out-out,eq}}, \text{ and } k_{-3} = k_3 \frac{c_{out-out,eq}}{c_{in-in,eq}}$$

To calculate the rate constants k_1 through k_{-3} , we followed the changes in the NMR spectra of $\mathbf{1}_{in-in}$, $\mathbf{1}_{out-out}$ and $\mathbf{1}_{in-out}$ dissolved in CD_2Cl_2 at room temperature ($T = 295$ K) under ambient light (Figure 2b). We focused on the chemical shifts of the *N*-bound CH_3 protons because they differed most significantly among the three diastereomers, providing unique signatures for each of them (see Figure 2b). As Figure 2c shows, it took several days for each of the pure diastereomers to reach equilibrium with the other isomers. We also noted that $\mathbf{1}_{in-in}$ isomerizes to $\mathbf{1}_{out-out}$ faster than to $\mathbf{1}_{in-out}$ (even though the $\mathbf{1}_{in-out}$ isomer prevails once the steady state was reached), i.e., the rotation about the chiral axis was faster than the

spontaneous racemization of the SP group under these conditions. At the same time, racemization could be rapidly accelerated by alternating cycles of UV–vis irradiation, each generating the achiral merocyanine groups (*trans*-MC in Figure 1a) and then regenerating (*R*)- or (*S*)-SP with similar probabilities. Under these irradiation conditions, the equilibrium was reached after only 30 min (or three cycles of UV–vis; Figure 3a); a time frame in which the rotation about the

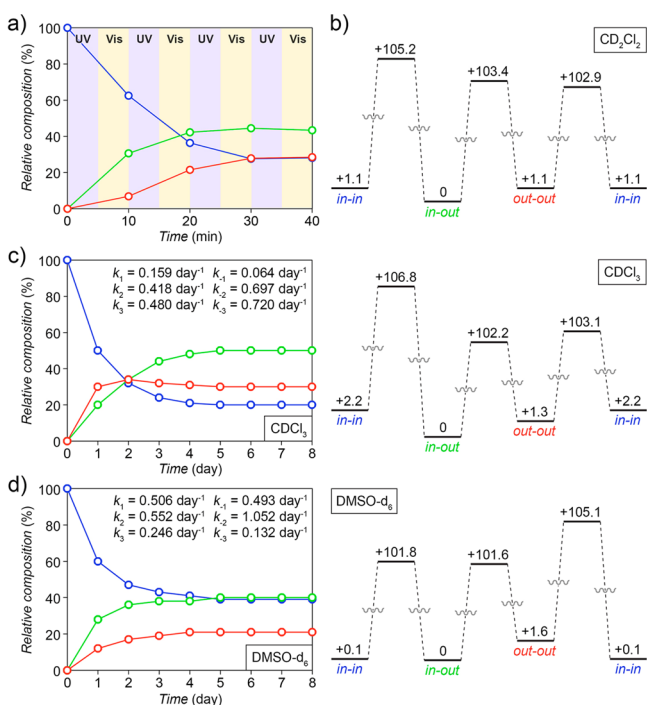


Figure 3. (a) Photochemically induced equilibration of the I_{in-in} isomer in CD_2Cl_2 . Note that steady state is reached within 30 min; a point at which no noticeable transformation of pure I_{in-in} has taken place under ambient light conditions (Figure 2c, left). (b) Free energy diagram of I in CD_2Cl_2 at $T = 295$ K. (c) Equilibration profile (left) and free energy diagram (right) of I in $CDCl_3$ at $T = 295$ K. (d) Equilibration profile (left) and free energy diagram (right) of I in $DMSO-d_6$ at $T = 295$ K. For equilibration experiments in additional solvents, see SI, Section 4. All values in the free energy diagrams are in $kJ\cdot mol^{-1}$.

chiral axis proceeded to a negligible extent. In other words, the vast majority of the $I_{out-out}$ isomer formed via I_{in-out} which explains the different concentration profiles for the spontaneous (Figure 2c, left) and the photochemically induced (Figure 3a) equilibration.

We solved the rate equations (see above) numerically, as described in the Supporting Information (SI), Section 4. For example, for a typical experiment involving thermal equilibration of I_{in-in} in CD_2Cl_2 (rt; Figure 2c, left), we obtain $k_1 = 0.194$ day^{-1} , $k_{-1} = 0.122$ day^{-1} , $k_2 = 0.259$ day^{-1} , $k_{-2} = 0.410$ day^{-1} , $k_3 = 0.493$ day^{-1} , and $k_{-3} = 0.493$ day^{-1} . To verify these results, we modeled concentration profiles based on the calculated rate constants. A good agreement between the experimental and calculated results for this and other experiments is shown in Figures S9, S10. We also calculated the Gibbs free energy of activation, ΔG^\ddagger , for each of the six reactions, using the Eyring equation, $k = k_B \cdot T / h \cdot \exp(-\Delta G^\ddagger / RT)$, where k is the reaction rate constant, k_B is the Boltzmann constant, T is the temperature, h is Planck's constant, and R is

the gas constant; the corresponding free energy diagram is shown in Figure 3b. We found that the energy barrier for atropisomerization ($I_{in-in} \leftrightarrow I_{out-out}$) in CD_2Cl_2 at $T = 295$ K is ~ 101.8 $kJ\cdot mol^{-1}$, which is consistent with the previously reported values for other di-*ortho*-substituted biphenyls (e.g., 101 $kJ\cdot mol^{-1}$ for 1,1'-binaphthyl²⁷).

ΔG^\ddagger for enantiomerization of a single SP unit was calculated by taking into consideration that the rate of epimerization (e.g., $I_{in-in} \rightarrow I_{in-out}$) is twice the rate of SP enantiomerization (since only one of two of the I SP groups needs to isomerize to achieve overall epimerization).¹⁸ Interestingly, the obtained value,²⁸ 105.2 $kJ\cdot mol^{-1}$, is much higher than the barrier determined previously^{29,30} (by time-dependent polarimetry)^{31,32} for a monomeric SP (1',3'-dihydro-1',3',3'-trimethyl-6-nitrospiro[2H-1-benzopyran-2,2'-(2H)-indole]); see **2** in Figure S12) (86 $kJ\cdot mol^{-1}$, corroborated by a recent computational study,³³ which yielded 88 $kJ\cdot mol^{-1}$). The high barrier for SP enantiomerization in **1** can be attributed to the steric crowding that stabilizes the orthogonal arrangement of the indoline and the benzopyran units and that prevents the configuration necessary to attain the transition state. These results are in agreement with our studies of the UV-induced ring opening of **1**: under the same conditions, the SP \rightarrow MC isomerization yield was significantly lower than for parent **2** (Figure S12), again emphasizing the high relative stability of closed-ring **1**.

Next, we investigated the effect of the solvent (because of the poor solubility of **1**, our analysis was limited to deuterated dichloromethane, chloroform, DMSO, acetone, and THF). Equilibration profiles in $CDCl_3$ and $DMSO-d_6$ show that, similar to CD_2Cl_2 , several days were required to reach steady state (Figure 3c,d). We found that the nature of the solvent determined the exact composition of the final mixture of diastereomers, although in all cases I_{in-out} ultimately prevailed. The calculated rate constants k_1 through k_{-3} and the corresponding ΔG^\ddagger values are shown in Figure 3c,d; it is worth pointing out that while the ΔG^\ddagger value for SP enantiomerization²⁸ was similar for CD_2Cl_2 and $CDCl_3$ (105.2 and 104.5 $kJ\cdot mol^{-1}$, respectively), it was clearly lower for $DMSO$ ($\Delta G^\ddagger = 102.8$ $kJ\cdot mol^{-1}$). This finding can be rationalized by the significantly more polar nature of $DMSO$, facilitating^{15,34,35} the formation of charge-separated open-ring forms, such as *cis*-MC in Figure 1.^{36,37} It is also interesting to compare the ΔG^\ddagger values for SP enantiomerization in $I_{in-in} \leftrightarrow I_{in-out}$ to those in $I_{in-out} \leftrightarrow I_{out-out}$ (see Figure 3 and the low-temperature data in SI, Section 4). In both CD_2Cl_2 and $CDCl_3$, the former values were noticeably higher, which can be explained by the close proximity and unfavorable interactions between the etheral oxygen atom in one-half of the molecule and the phenolate oxygen atom in the other. No such differences were observed in $DMSO-d_6$, again emphasizing the stabilizing effect of the more polar medium on the transition states.

In summary, we isolated, characterized, and followed the equilibration kinetics of all three diastereomers of the title compound, a biphenyl-based bis-SP combining the features of a photoswitch and a molecular rotor. The equilibration occurred via a reversible cyclic reaction scheme whereby epimerization and rotation about the chiral axis took place on similar time scales. The calculated rate constants of the diastereomerizations and the respective free energy barriers confirm the sterically hindered nature of **1**, and they agree with our studies of light-induced isomerization of the title compound. Overall, this work

demonstrates that the properties of SP depend heavily on its immediate chemical environment, with important implications for designing new switchable molecules and materials.

■ ASSOCIATED CONTENT

● Supporting Information

Synthesis, isolation, and structural characterization of $\mathbf{I}_{\text{in-in}}$, $\mathbf{I}_{\text{in-out}}$, and $\mathbf{I}_{\text{out-out}}$; details on the derivation of the rate constants; solid-state isomerization experiments. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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