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

Pintu K. Kundu,† Avishai Lerner,‡ Kristina Kučanda,§ Gregory Leitus,∥ and Rafal Klajn*†

†Department of Organic Chemistry and ‡Chemical Research Support, Weizmann Institute of Science, Rehovot 76100, Israel
§Department of Chemical Engineering, Ben-Gurion University of the Negev, Beer Sheva 84105, Israel
∥Department of Chemistry, Faculty of Science, University of Zagreb, 10002 Zagreb, Croatia

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,1−3 polymeric systems,4 nanoparticles,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 can 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, we synthesized compound 1 (Figure 1b) in which two SP moieties are linked directly via indolines’ phenyl 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 1in−in), which is a mixture of enantiomers S,R,S and R,S,R (see Figure 2a, left), away from each other (1out−out: R,R,R+ S,S,S; Figure 2a, center), or “follow” each other (see Figure 2a, right; 1in−out: S,R,R+ R+S,S).

1 was prepared in six steps from commercially available reagents.24 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 1in−in (Figure 2a, left). When the crystals of the 1in−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 1out−out diastereomer (Figure 2a, right).

Received: June 17, 2014
Published: July 29, 2014

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.
cyclic reaction scheme involving six equilibration of the system can be represented by a reversible example, either of its rate constants low solubilities in a given solvent mixture. The third isomer (the mixture of all three diastereomers indicates their relatively N and the equilibrates as well until a steady state is reached. Pure and 1 by rotation about the C carbon atoms (epimerization) and to spiro 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 1 (Rf = 0.36 in 3:2 hexane-diethyl ether) and the 1out (Rf = 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 (Rf = 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 Rf 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” 1in-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, 1in-in isomerizes to 1in-out by enantiomerization on either of its spiro carbon atoms (epimerization) and to 1out-out by rotation about the C–C chiral axis (atropisomerization). Once 1in-out and 1out-out are generated, each of them equilibrates as well until a steady state is reached. Pure 1in-out and 1out-out equilibrate analogously, 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 k1, k2, k3, k4, k5, and k6 (Scheme 1). Equations for the rate constants are as follows:

$$\frac{dc_{1\text{-in}}}{dt} = -k_1c_{1\text{-in}} - k_2c_{1\text{-out}} + k_3c_{3\text{-in}} + k_4c_{3\text{-out}}$$

$$\frac{dc_{1\text{-out}}}{dt} = -k_5c_{1\text{-out}} - k_6c_{1\text{-in}} + k_3c_{3\text{-in}} + k_4c_{3\text{-out}}$$

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

$$k_{-1} = k_1 \frac{c_{1\text{-in,eq}}}{c_{3\text{-in,eq}}}$$

$$k_{-2} = k_5 \frac{c_{1\text{-out,eq}}}{c_{3\text{-out,eq}}}$$

$$k_{-6} = k_6 \frac{c_{1\text{-out,eq}}}{c_{3\text{-in,eq}}}$$

To calculate the rate constants k1 through k6, we followed the changes in the NMR spectra of 1in-in, 1out-out, and 1out-in dissolved in CD2Cl2 at room temperature (T = 295 K) under ambient light (Figure 2b). We focused on the chemical shifts of the N-bound CH3 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 1in-in isomerizes to 1out-out faster than to 1in-out (even though the 1in-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 1_{in-in} isomer in CD2Cl2. Note that steady state is reached within 30 min; a point at which no noticeable transformation of pure 1_{in-in} has taken place under ambient light conditions (Figure 2c, left). (b) Free energy diagram of 1 in CD2Cl2 at T = 295 K. (c) Equilibration profile (left) and free energy diagram (right) of 1 in CDCl3 at T = 295 K. (d) Equilibration profile (left) and free energy diagram (right) of 1 in DMSO-d6 at T = 295 K. For equilibration experiments in additional solvents, see SI, Section 4. All values in the free energy diagrams are in kJmol⁻¹.

chiral axis proceeded to a negligibly extent. In other words, the vast majority of the 1_{out-out} isomer formed via 1_{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 1_{in-in} in CD2Cl2 (rt; Figure 2c, left), we obtain k₁ = 0.194 day⁻¹, k₂ = 0.122 day⁻¹, k₃ = 0.259 day⁻¹, k₄ = 0.410 day⁻¹, k₅ = 0.493 day⁻¹, and k₆ = 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 free energy of activation, ΔG², for each of the six reactions, using the Eyring equation, $k = k_b T / h e^{(-ΔG^2 / RT)}$, 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 atropoisomerization (1_{in-in} ↔ 1_{out-out}) in CD2Cl2 at T = 295 K is ~101.84 ± 101.84 kJ•mol⁻¹, which is consistent with the previously reported values for other di-ortho-substituted biphenyls (e.g., 101.4 ± 101.4 kJ•mol⁻¹ for 1,1’-binaphthyl²⁷).

ΔG² for enantiomerization of a single SP unit was calculated by taking into consideration that the rate of epimerization (e.g., 1_{in-in} → 1_{in-out}) is twice the rate of SP enantiomerization (since only one of two of the 1 SP groups needs to isomerize to achieve overall epimerization).⁸ For example, the obtained values, 105.2 ± 105.2 kJ•mol⁻¹, is much higher than the barrier determined previously (97.5 ± 97.5 kJ•mol⁻¹) (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•mol⁻¹), corroborated by a recent computational study,³³ which yielded 88 kJ•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 ↔ 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 CDCl₃ and DMSO-d₆ show that, similar to CD₂Cl₂, 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 1_{in-out} ultimately prevailed. The calculated rate constants $k_1$ through $k_{-3}$ and the corresponding ΔG² values are shown in Figure 3c,d; it is worth pointing out that while the ΔG² value for SP enantiomerization was similar to CD₂Cl₂ and CDCl₃ (105.2 and 104.5 kJ•mol⁻¹, respectively), it was clearly lower for DMSO (ΔG² = 102.8 ± 102.8 kJ•mol⁻¹). This finding can be rationalized by the significantly more polar nature of DMSO, facilitating the formation of charge-separated open-ring forms, such as cis-MC in Figure 1.⁶,⁵ It is also interesting to compare the ΔG² values for SP enantiomerization in 1_{in-in} ↔ 1_{in-out} to those in 1_{in-out} ↔ 1_{out-out} (see Figure 3 and the low-temperature data in SI, Section 4). In both CD₂Cl₂ and CDCl₃, the former values were noticeably higher, which can be explained by the close proximity and unfavorable interactions between the ethereal oxygen atom in one-half of the molecule and the phenolato oxygen atom in the other. No such differences were observed in DMSO-d₆, 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 $I_{\text{in-out}}$ and $I_{\text{out-air}}$ 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.

**AUTHOR INFORMATION**  
Corresponding Author  
rafael.klajn@weizmann.ac.il

Notes  
The authors declare no competing financial interest.

**ACKNOWLEDGMENTS**  
This work was supported by the Israel Science Foundation (grant no. 1463/11) and by the G. M. J. Schmidt-Minerva Center for Supramolecular Architectures.

**REFERENCES**  
(19) A more straightforward way to calculate the free energy barrier for SP enantiomerization would be based on a model compound comprising a fixed chirality in the proximity of the SP moiety. However, our intention was also to examine the behavior of one molecular switch in the proximity of another and within a molecule having the features of a molecular rotor.  
(20) Having the title compound appended with two bromide groups makes it amenable for straightforward incorporation within higher-order architectures, such as nanoporous frameworks (e.g., ref 21).