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Metastable Liquid Crystal as Time-Responsive Reaction Medium: Aging-Induced Dual Enantioselective Control

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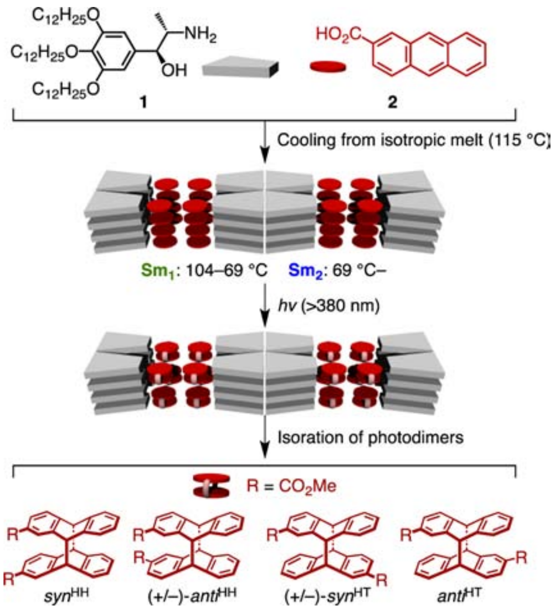
Supporting Information

ABSTRACT: A metastable liquid crystal (LC) was found to serve as a time-responsive reaction medium, in which the enantioselectivity of a photoreaction was perfectly switched through isothermal annealing of the reaction system. When the LC salt of an enantiopure amine with a photoreactive acid was irradiated with UV/vis light, *in situ* photodimerization of the acid moiety proceeded smoothly to afford the (+)-isomer of the photodimer with high enantioselectivity (+86% ee). In contrast, photoirradiation of an aged sample, isothermally annealed for 20 h, gave predominantly the (−)-isomer (−94% ee). Systematic studies revealed that the reversal in selectivity originated from metastability of the LC system, which gradually transformed into a crystalline phase during annealing. This finding demonstrates the potential use of metastable aggregates as dynamic time-responsive media, reminiscent of biological systems.

In asymmetric chemical transformations, a well-designed chiral source usually gives one enantiomer as the major product. However, there have been reported several notable exceptions,[1] in which a single chiral source can provide both enantiomers through the switching of selectivity depending on reaction conditions, such as reaction time,[2a,d] temperature,[2b,e] solvent,[2f] presence of an additive,[2c] or catalyst preparation method.[2g] These phenomena, termed "reversal of enantioselectivity" or "dual enantioselective control", have attracted a considerable degree of attention recently, owing to their scientific curiosity and their practical utility.[1] Here we report an unprecedented type of enantioselectivity reversal. Unlike earlier examples,[1,2] our report describes a kinetically controlled system in which two samples treated under identical conditions, except for the aging time before the reaction, showed stereochemical outcomes that were almost perfect opposites of one another. A thorough investigation of this phenomenon revealed unique aspects of nonequilibrated supramolecular aggregates as time-dependent dynamic systems reminiscent of biological systems.

The phenomenon reported here was unexpectedly found through our ongoing studies on liquid crystalline (LC) salts, consisting of an enantiopure amphiphilic amine (e.g., **1**, Scheme 1) and a photoreactive acid (e.g., **2**), as chiral reaction media.[3]

Scheme 1. *In Situ* Photodimerization of Acid 2 in a Chiral Liquid-Crystalline Reaction Environment Based on Amine 1



Such LC salts are expected to serve as a new type of reaction environment that provides structural order while permitting molecular mobility.[4,5] As a model reaction to demonstrate the utility of chiral LC reaction media, we have studied the [4+4] photocyclodimerization of 2-anthracenecarboxylic acid (**2**). Although the photodimerization of anthracene derivatives is

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one of the most well-explored photoreactions,[6] its stereocontrol still remains an attractive challenge.[7] Because of the dissymmetric shape of **2**, its dimerization can provide six isomers through regioisomerism [*head-to-head* (HH) or *head-to-tail* (HT), diastereoisomerism (*syn* or *anti*), and stereoisomerism (+ or −)]. The resulting dimers are denoted syn^{HH}, (+)-$anti^{HH}$, (−)-$anti^{HH}$, (+)-syn^{HT}, (−)-syn^{HT}, and $anti^{HT}$ (Scheme 1, bottom). As a chiral source to control the stereochemistry of this reaction, we developed an enantiopure amphiphilic amino alcohol (**1**), which has a high propensity to form LC salts with various carboxylic acids, for example, **2**.[3c,d] In fact, the salt of **1** with **2** (**1·2**) exhibits two types of smectic phases with bilayer-like structures (Sm_1 and Sm_2), as confirmed by differential scanning calorimetry (DSC; Figure S8) and by X-ray diffraction analysis (XRD; Figure S9). Considering the XRD patterns at a wide-angle region, the Sm_1 phase is considered to be smectic A phase, while the Sm_2 phase is likely to be a higher order smectic phase, such as smectic B, smectic F, or smectic I phases.[8]

Owing to the benefits of LCs as reaction media, as described above, irradiation of the LC salt **1·2** with UV/vis light gave photodimers of acid **2** in satisfactory yields and excellent selectivities. In a typical procedure, **1·2** was melted at 115 °C, slowly cooled to 45 °C at 0.33 °C min^{-1} to form the Sm_2 phase, and then irradiated with UV/vis light (>380 nm) at 45 °C for 1 h to afford the $anti^{HH}$ dimer selectively in +86% ee (Figure 1, procedure I).[3c,d] To improve the selectivity further, we hypothesized that long-time isothermal annealing before photoirradiation might have a favorable effect as a result of the error-correction ability that is characteristic of supramolecular aggregates. We therefore used a well-annealed sample for the same *in situ* photodimerization. Salt **1·2**, in its Sm_2 phase, was kept at 45 °C for 20 h before being photoirradiated for 1 h. From the well-annealed salt, the $anti^{HH}$ dimer was again obtained as the major product. To our great surprise, however, the stereochemical outcome was almost the exact opposite to that of our original experiment, and the $anti^{HH}$ dimer was obtained in −94% ee (Figure 1, procedure II).

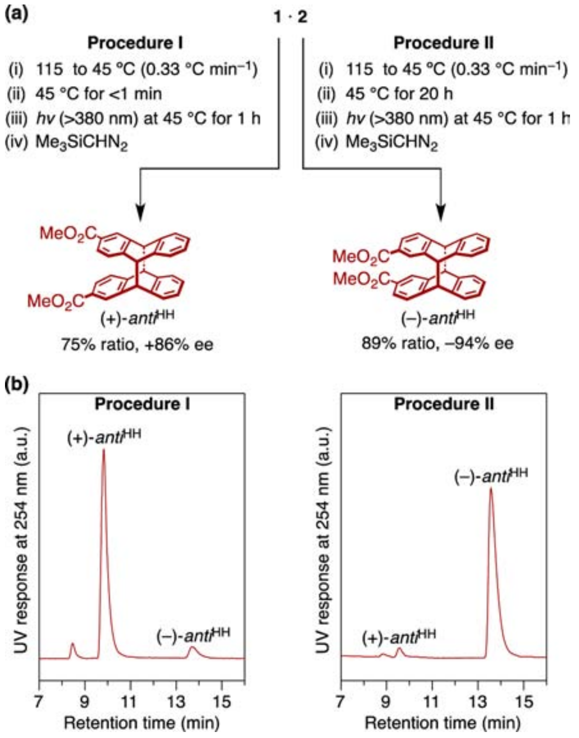

Figure 1. (a) Reversal of enantioselectivity in the asymmetric photodimerization of **2**. Salt **1·2** was melted at 115 °C, cooled to 45 °C at a rate of 0.33 °C min^{-1}, annealed at 45 °C for <1 min (procedure I) or for 20 h (procedure II), irradiated with UV/vis light (λ > 380 nm), and methylated with Me_3SiCHN_2. (b) Chiral HPLC (Daicel Chiralpak IB) traces for the enantiomers of the $anti^{HH}$ dimer obtained by the *in situ* photoreaction of salt **1·2**. The enantiomers that showed positive and negative CD signals at 300 nm are denoted by + and −, respectively.

In an attempt to explain this phenomenon, we systematically examined the effects of various reaction conditions, such as the annealing time, the photoirradiation time, and the temperature (Figure 2 and Table S1). When the annealing time at 45 °C was changed from 0 to 20 h, the system retained an excellent regioselectivity (HH versus HT) and diastereoselectivity (*syn* versus *anti*), giving the $anti^{HH}$ dimer as the main product (Figure 2a). However, the enantiomeric excess (ee) of the main product (the $anti^{HH}$ dimer) changed dramatically on changing the annealing time (Figure 2b). In the initial stage of annealing (0−1 h), the change in enantioselectivity was sluggish (+86 and +81% ee). Annealing for 5 h caused an abrupt drop in the ee for the $anti^{HH}$ dimer to +12%, and further annealing for 10 h caused an inversion in the sense of the enantiomeric induction, giving the $anti^{HH}$ dimer in −44% ee. When the annealing time was prolonged to 20 h, an almost perfect reversal in enantioselectivity was achieved, and the $anti^{HH}$ dimer was obtained in −94% ee. Therefore, the selectivity reversal is a relatively slow event that takes about 20 h to reach its completion.

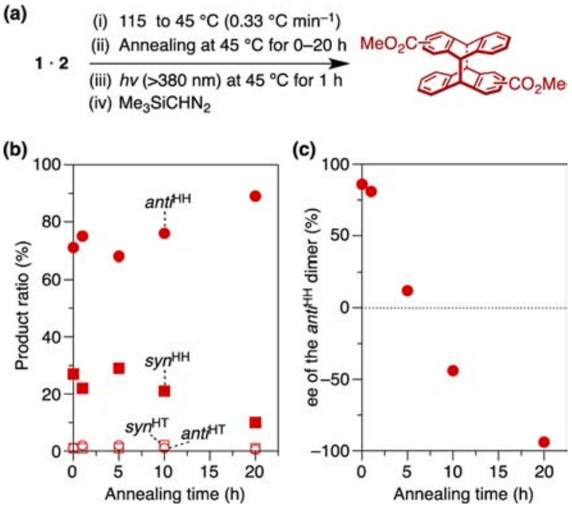

Figure 2. Effect of annealing time at 45 °C on the regio-, diastereo-, and enantioselectivity of the photodimerization of **2**. (a) Experimental procedure. (b,c) Plots of the product ratio (syn^{HH}, filled square; $anti^{HH}$, filled circle; syn^{HT}, open square; $anti^{HT}$, open circle) (b) and the ee of the $anti^{HH}$ dimer (c) versus the annealing time at 45 °C. The enantiomers that showed positive and negative CD signals at 300 nm are denoted by + and −, respectively.

In the above photoreaction, the irradiation was discontinued when the conversion of **2** reached 23−34% to permit fair comparison of the selectivities in the early stages of the process (Table S1, entries 3−7). In general, the conversion of a starting material can affect the enantioselectivity of a reaction, particularly when the products can participate in reaction pathways.[1b] However, even when the photoirradiation time was prolonged in our reaction system, the yield of the main product [the (+)- or

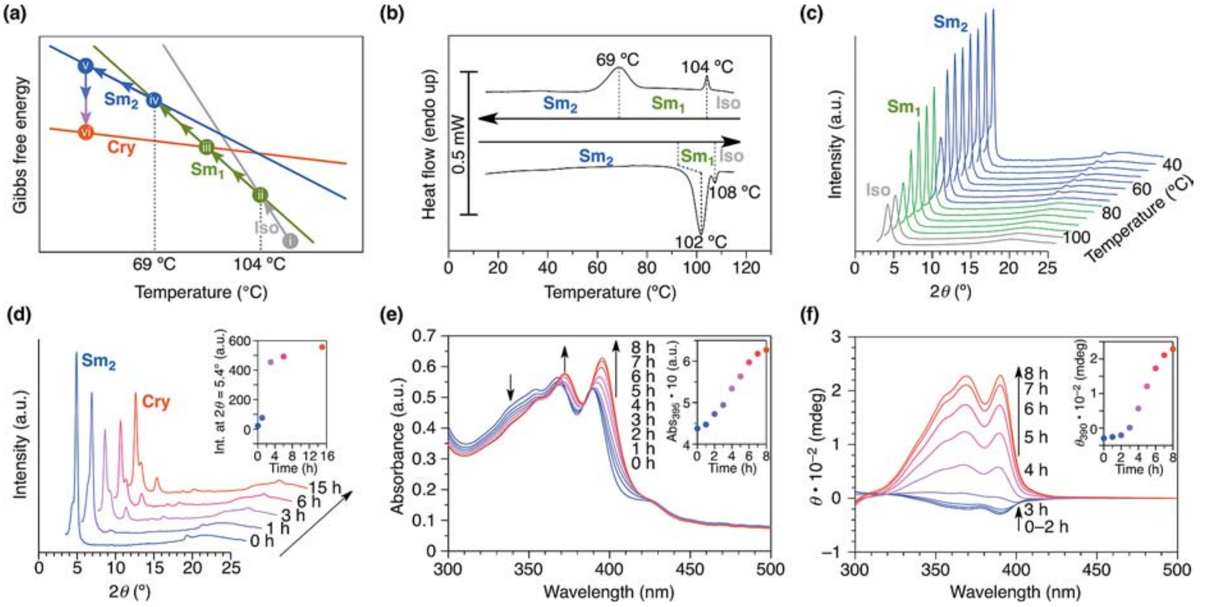

Figure 3. Phase transition of salt **1·2**. (a) Proposed phase transition diagram on cooling from an isotropic melt (i–v) and subsequent isothermal annealing (v–vi). (b) DSC traces for the first cooling (top) and the second heating (bottom) processes (scanning rate, 5.0 °C min^{-1}). (c) XRD patterns during cooling from 105 to 35 °C at a rate of 1.0 °C min^{-1}. (d–f) Time-dependent changes in the spectroscopic profiles. Salt **1·2** was melted at 115 °C, cooled to 45 °C at a rate of 0.33 °C min^{-1}, kept at 45 °C for the indicated period, and subjected to XRD (d), UV/vis absorption (e), or CD measurements (f). The insets show the time-dependent changes in XRD intensity ($2\theta = 5.4°$), UV absorption (395 nm), and the CD intensity (390 nm), respectively.

(−)-*anti*$^{\text{HH}}$ dimer] was simply improved up to 84 and 89% without losing selectivity to any serious extent (Table S1, entry 3 versus entries 8 and 9; entry 7 versus entries 10 and 11).

We also investigated the effects of the annealing temperature. When salt **1·2** in its Sm_2 phase was annealed at 35 °C for 20 h before photoirradiation, the same reversal in enantioselectivity occurred (Table S1, entries 1 and 2) as in the case of annealing at 45 °C. In sharp contrast, when the salt was annealed at 80 or 110 °C, at which temperatures the salt forms the Sm_1 and isotropic (Iso) phases, respectively, the reaction system did not show any sign of a reversal in enantioselectivity (Table S1, entries 12–15). From these results, we concluded that the reversal in enantioselectivity is a phenomenon that is specific to the Sm_2 phase.

On the basis of these observations, we hypothesized that the origin of the selectivity reversal is the metastability of the Sm_2 phase.[9] In the hypothesized phase diagram, a phase more stable than the Sm_2 phase exists (Figure 3a, red line) which was not detected in our DSC (Figure 3b) or variable-temperature XRD studies (Figure 3c) for salt **1·2**, probably because the Sm_2 phase has a longer lifetime than the time scale over which these measurements were performed. During cooling from the Sm_1 phase (Figure 3a; ii to v), the transition into the new phase would be bypassed because of the high kinetic energy barrier (iii). As a result, the Sm_2 phase can exist in a supercooled state (iv). However, because of its metastability, the Sm_2 phase can transform into a more-stable phase as time passes or by the action of an appropriate stimulus (v and vi).

To confirm our hypothesis, we evaluated the lifetime of the Sm_2 phase at 45 °C by means of XRD studies. Salt **1·2** was pretreated as described above (cooled from 115 to 45 °C at a rate of 0.33 °C min^{-1}) to form the Sm_2 phase, and then kept at 45 °C for 15 h. Throughout the annealing process, time-dependent changes in the nanostructure were monitored by XRD analyses (Figure 3d). In its original state, **1·2** showed a set of reflections characteristic of the Sm_2 phase with a lamellar structure. When **1·2** was annealed for 1 h, the XRD pattern was fairly similar to that of the original material, but a number of small reflections emerged in the wide-angle region, indicating partial crystallization of the salt. As the annealing time was extended, the reflections arising from the crystalline (Cry) phase increased in intensity, whereas those attributable to the Sm_2 phase weakened. After annealing for 20 h, no change in the XRD pattern was observed, indicating that the phase transition was complete. Therefore, the Sm_2 phase was confirmed to be a metastable state that is capable of persisting for several hours while gradually transforming into the Cry phase.

We also examined time-dependent changes in the UV/vis spectra of salt **1·2** on annealing at 45 °C. We focused on absorptions in the range 300–450 nm that were attributable to the ^1L_a and ^1L_b bands of the anthracene moiety of **2**.[10] Because these bands do not overlap with the absorption of **1**, monitoring of these bands should provide reliable information regarding the microenvironment of the photoreactive unit **2**. As shown in Figure 3e, marked changes in the UV/vis spectra were observed throughout the annealing process, suggesting there were corresponding changes in the environment of the molecules of **2** during the phase transition. As additional evidence of such structural rearrangement, the induced circular dichroism (CD) spectra also showed marked changes in response to the progress of the phase transition (Figure 3f).[11] In its initial state, salt **1·2** displayed a weak Cotton effect with a negative sign at 300–450 nm. However, as the phase transition proceeded, the sign of the Cotton effect became positive, and its intensity continued to increase during 8 h.

It is worth noting that time-dependent changes in the enantioselectivity toward the *anti*$^{\text{HH}}$ dimer (Figure 2a) and those in XRD, UV/vis, and CD profiles (insets of Figures 3d–f) showed similar trends to one another. After an induction period of 1–2 h, the system underwent a marked change and reached its final static state after 8−20 h. This commonality reinforces our hypothesis that the changes observed in these measurements originate from a single event: the phase transition between the Sm$_2$ phase and the Cry phase. The Sm$_1$ phase, however, did not show any signs of time-dependent changes in these measurements (Figures S10−S12), which is also in good agreement with the results of the photodimerization at 80 °C (Table S1, entries 12 and 13).

In conclusion, we have identified a novel type of reversal in enantioselectivity in an asymmetric photoreaction that is induced by a phase transition of a metastable LC. Unlike related phenomena previously reported,[1,2] the novel reversal in enantioselectivity can be induced by means of a simple process: isothermal annealing. This finding raises an important note of caution with regard to general studies on asymmetric synthesis, in that the history of samples can have a significant effect on the enantioselectivity of an asymmetric reaction, particularly when a rapid equilibrium is not guaranteed. Furthermore, this phenomenon implies unexplored functions of nonequilibrium-state supramolecular assemblies. Although stimuli-responsive properties of LCs that are capable of adopting multiple equilibrated states have been well explored,[12] there have been remarkably few studies on the dynamics and kinetics of metastable LCs,[8] probably because the lability of these materials has rendered them unsuitable for use in fundamental studies or in practical applications. The present study is a rare successful example of the utilization of the metastability of an LC as a unique function. Further studies on metastable LCs and related supramolecular aggregates could lead to the creation of intriguing materials with dynamic and time-responsive properties.[13]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Preparation and characterization of salt **1**·**2** and details of the *in situ* photodimerization of acid **2**. 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.

■ ACKNOWLEDGMENTS

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(11) To ensure the accuracy of CD measurements on condensed matter, it is necessary to evaluate the linear birefringence (LB) and the linear dichroism (LD) that are produced by artifacts or by intrinsic macroscopic anisotropies in the samples. Therefore, the advanced high-accuracy universal polarimetry method was used to examine non-annealed and annealed samples of salt **1**·**2**, which clearly showed that LB and LD were negligible in both samples (Figure S13). For solid-state CD measurements, see: (a) Kobayashi, J.; Asahi, T.; Sakurai, M.; Takahashi, M.; Okubo, K.; Enomoto, Y. *Phys. Rev. B* **1996**, *53*, 11784. (b) Kuroda, R.; Harada, T.; Shindo, S. *Rev. Sci. Instrum.* **2001**, *72*, 3802. (c) Tanaka, M.; Nakamura, N.; Koshima, H.; Asahi, T. *J. Phys. D: Appl. Phys.* **2012**, *45*, 175303.

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