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Sequential Chiral Induction and Regulator-assisted Chiral Memory of Pillar[5]arenes

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Abstract: Chirality transfer is widely observed in life processes, and many artificial chiral transfer systems have been developed. In these systems, chiral information is transferred from chiral inducers to chiral acceptors by a direct chiral induction process and a direct chiral memorization process. Herein we developed ternary nondirect chiral transfer systems based on pillar[5]arenes, in which a third factor was introduced as a regulator. The planar chirality of an acceptor was induced and memorized by a chiral inducer with precise control by a =regulator. In the chiral induction period, the feed sequence of the chiral inducer and regulator affected the chiral induction behavior of the chiral acceptor. The chiral memory ability of the acceptor was substantially improved by the combined action of the chiral inducer and regulator.

Chirality transfer is widely observed in life processes,^[1] and has been successfully used to develop chiroptical sensors^[2] and asymmetric syntheses.^[3] Chirality transfer involves the induction and memorization of chirality in acceptors through noncovalent interactions with chiral inducers.^[4] Systems capable of chiral memory have been developed, including discrete small molecules,^[4a,5] mechanically interlocked molecular architectures,[6] polymers,^[4b,7] self-assembled helical onedimensional stacks,^[8] nanotubes,^[9] cages,^[10] molecular imprinting materials,^[11] and gels.^[12] Most of the reported systems are binary, with the chirality of acceptors being directly induced by chiral inducers and the induced chiral information being directly memorized upon removal of the chiral inducers (i.e., direct chiral transfer). Kinetic stabilization of acceptors by steric hindrance or through interactions such as metal coordination^[1d,8a,b,13] is needed to achieve chiral memory in these systems.

Nature frequently regulates life processes and expresses variable functions in one simple system through the synergistic interactions of multiple components. For instance, only the regions of a DNA molecule influenced by gene-regulatory proteins are transcribed and expressed in cells. As a result, specific proteins are synthesized under the guidance of gene-regulatory proteins. Inspired by this natural behavior, subtly regulating the chiral induction and memory processes within a single system via the synergistic interactions of multiple components (i.e., nondirect chiral transfer) is an interesting target for chiral transfer systems.^[5a,8d,9] For example, memory of axial chirality of a porphyrin dimer^[5a] and helicity of polymers^[8d]

and one-dimensional aggregates^[9] via multi-component strategies have been investigated. However, the planar chiral transfer of macrocyclic molecules using a multi-component strategy has not been reported.

Pillar[n]arenes are cylindrical macrocyclic host molecules with rims that are easy to functionalize.^[14] Pillar[n]arenes possess two planar chiral isomers (i.e., pR and pS), which interconvert between each other via oxygen-through-the-annulus-rotation (Figure 1a).^[14,15] This rotation of pillar[n]arenes can be suppressed by guest complexation^[16] or modification of the rim substituent groups.[17] In the current study, we used rimdifferentiated pillar[5]arene 1^[18] as a chiral acceptor, and its chirality is induced by chiral amine 2 as a chiral inducer (Figure 1b) in direct chiral transfer. However, this system possesses poor chiral memory ability (Figure 1c). Therefore, we introduce linear guest molecule 3 as a regulator (Figure 1b) to provide a ternary system that displays nondirect chiral transfer (Figure 1d). In the chiral induction period of the ternary system, the feed sequence of 2 and 3 to the solution of 1 strongly affects the chiral induction efficiency. This sequential effect has not been observed in binary chiral transfer systems. Moreover, the chiral memory ability of 1 is markedly improved by the combined action of 2 and 3.

First, direct chiral transfer without a regulator was conducted in solvents to induce chirality of 1a by addition of chiral amines (Figure S1). Chloroform and 1-cyclohexylethyl amine 2 were the best solvent and chiral amine, respectively, because of their suitable sizes. The planar chirality of 1a was induced by forming supramolecular diastereomers with R-2 and S-2 as was evidenced by the Cotton effect observed in the circular dichroism (CD) spectrum of the mixture of 1a and 2 (Figures 2a).^[17b,19] The diastereomeric excess (de) was ca. 11% (Figure S3). By adding mixtures of R-2 and S-2 with various ratios and keeping the total amount of amine constant, the induced CD intensity of 1a showed an approximately linear relationship with the enantiomeric excess (ee) of 2 (Figure S4). The real-time CD signal of 1a with R-2 decreased and then inverted upon addition of S-2 (Figures 2b and S5). By replacing the R-2 interacting with 1a with 100 equiv. of achiral isoamylamine, the positive CD signal of 1a decayed very fast. The half life period was only 40 min (Figure S6). These results suggest that 1a possesses high chiral induction ability and no chiral memory ability in the direct chiral transfer system, which was caused by the oxygen-

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through-the-annulus rotation enabled by the low steric bulk of the *n*-butyl rim substituents (Figure 1c).



Figure 1. (a) Planar chirality of pillar[5]arene 1. (b) Chiral inducer and regulator. Rational design of (c) direct and (d) nondirect chiral transfer systems.



Figure 2. (a) CD and UV-vis spectra of 1a (0.1 mM) upon addition of *R*-2 and S-2 at 20 °C. The inset of (a) shows $\Delta\epsilon$ at 308 nm recorded with different equivalents of chiral amine 2. (b) Real-time CD changes of a mixture of 1a (0.1 mM) and *R*-2 (5 equiv.) upon addition of S-2 (0–10 equiv.).

Guest complexation is an effective method to suppress the rotation of pillar[*n*]arenes.^[16] Guest complexation may slow the racemization between the two isomers of **1a**, which would improve its chiral memory ability. Thus, 1,4-dibromobutane **3**, an ideal guest for the cavity of pillar[5]arenes (with the association constant $K > 10^3 \text{ M}^{-1}$),^[14c,18b,20] was introduced as a third factor.

In this ternary system, the feed sequence of R-2 and 3 to the solution of **1a** was found to strongly influence the chiral induction efficiency (Figure 1d). We initially considered Path A, which involved induction first. The planar chirality of 1a was successfully induced with 5 equiv. of R-2. Further addition of 850 equiv. of 3 increased both the ultraviolet-visible (UV-vis) absorption and CD intensities of 1a (Figures 3a and S8). The de value increased to 13% (Figure S7) . In Path B, complexation was conducted first. In this case, after addition of 3 to form complex with 1a, further addition of R-2 failed to induce the planar chirality of 1a at 20 °C (red curve in Figure 3b). It is possible that the initial addition of 3 inhibited the free rotation of 1a because of guest inclusion. Consequently, the planar chiral induction by addition of R-2 was prevented at room temperature. Heating this second sample at 50 °C for 10 min resulted in an intense CD signal at 308 nm (blue line in Figure 3b). We believe that heating caused guest molecule 3 to dissociate from the cavity of 1a and then the 2 present induced the selective rotation of 1a (mechanistic details are shown in Figures S9-S10). The induction of the CD signal became slower as the temperature was decreased (Figure S11). Fitting the Eyring plots at various temperatures revealed that the Gibbs free energy of activation $(\Delta^{\ddagger}G \text{ at } 25 \text{ °C})$ of chiral induction of **1a** in the presence of 850 equiv. of 3 was 95.4 kJ mol⁻¹ (Figure S12).^[21] After heating, the

sequential effect of **2** and **3** was erased; both solutions showed almost the same CD intensity (Figures 3a and 3b).



Figure 3. CD and UV-vis spectra of 1a (0.1 mM) upon addition of R-2 and 3 by (a) path A and (b) path B at 20 °C.

The chiral memory ability of the ternary system of 1a + R-2 (5 equiv.) + 3 (850 equiv.) was investigated initially by chiral inversion experiments via the real-time CD changes upon addition of S-2. Negligible decrease was observed of the signal intensity after the addition of 10 equiv. of S-2 (Figure S20). This result suggested that the induced planar chirality of 1a was successfully memorized. Fitting the time-dependent CD decay in Figure 4a (light blue line) revealed that its half life period was 6.8 h.^[10d,22] In contrast, the half life period upon adding the same amount of S-2 to the binary system was too short to be determined (Figure 2b and dashed line in Figure 4a), illustrating that the chiral memory ability of 1a was improved in the ternary system compared with that in the binary system. One advantage of the ternary chiral transfer system is that the chiral memory ability could be easily regulated by varying the charge of the chiral regulator. By increasing the amount of 3 to 4250 equiv., the half life period increased to 20.4 h upon adding 10 equiv. of S-2 (dark blue line in Figure 4a and details in Figure S21).



Figure 4. CD changes of 1a (0.1 mM) with *R*-2 (5 equiv.) and various concentrations of 3 recorded at 308 nm after addition of (a) *S*-2 (10 equiv.) and (b) isoamylamine (100 equiv.).

To evaluate the real chiral memory ability of 1a, 100 equiv. of achiral isoamylamine was used to completely replace *R*-2 interacting with 1a (Figure S23). The half life period of 1a with 4250 equiv. of 3 reached 5 days, whereas it was only 40 min for the binary system (Figure 4b).

Because of its longer alkyl chains on one rim than is the case for **1a**, the rotation barrier of **1b** (Figure 1a) was higher than that of **1a** and its free rotation was slower (see Figures S13–S19 for details of chiral induction of **1b**).^[17a] For instance, the *de* value of **1b** with 4250 equiv. of **3** increased to 31% (Figure S16). This resulted in **1b** possessing better chiral memory ability than that of **1a** (see Figures S22, S24 and S25 for details of chiral memory of **1b**). The half life period of **1b** with 4250 equiv. of **3** reached 23 days when *R*-**2** was completely replaced by isoamylamine. Overall, the chiral memory ability of both **1a** and **1b** was markedly improved by the combined action of the **2** and **3** (Table S1).

Different from binary chiral transfer systems, the input of the additional factor (i.e., **3**) was essential to help regulate the chiral memory ability of **1** in ternary chiral transfer systems. Other guest molecules of pillar[5]arenes also regulated the chiral induction and chiral memory abilities of **1**, providing a convenient method to increase the diversity of these systems (Figure S26).^[14c]



Figure 5. Temperature dependence of (a) planar chiral induction and (b) inversion of 1a (0.1 mM) with 3 (850 equiv.) caused by addition of 2 and alternating heating at 40 °C and cooling at 20 °C.

Based on the kinetic trapping properties of the nondirect ternary chiral transfer system of **1a**, the temperature-dependent planar chirality induction and inversion of **1a** were subtly demonstrated (Figure 5). At 20 °C, **1a** with 850 equiv. of **3** showed negligible CD signal after addition of 5 equiv. of *R*-2 or *S*-2 because of the kinetic trapping at this temperature. Upon heating the solution to 40 °C, the rotation barrier was crossed and the planar chirality induction occurred. Positive and negative CD signals at 308 nm were observed in the presence of *R*-2 and *S*-2, respectively (Figure 5a). However, cooling the solution to 20 °C fixed the CD

intensity again, indicating the memory of planar chirality of that level. In another demonstration, after inducing the planar chirality of **1a** by adding 1.5 equiv. of *R*-**2** in the presence of **3**, 8.5 equiv. of *S*-**2** was added to the system (Figure 5b). The initial positive CD signal was kept at 20 °C because of the kinetic trapping. By heating the sample to 40 °C, the positive CD signal intensity decreased because the rotation barrier was overcome. By alternately heating and cooling the sample, the CD signal change was incrementally controlled. Finally, the planar chirality of **1a** inverted to negative because of the excess amount of *S*-**2**. Overall, the planar chirality induction could be easily kept at any stage by alternately heating and cooling the sample.

In conclusion, based on rim-differentiated pillar[5]arene 1, chiral amine 2, and guest molecule 3, we developed well-controlled planar chiral induction and memory systems. In these systems, 2 induced planar chirality, while 3 worked as a regulator to control the memorization of planar chirality. The two-component input was needed to achieve chiral memory of 1, constituting a logic gate. The input order of 2 and 3 influenced the planar chiral memory ability of 1. These are the first examples of chiral memory systems based on macrocyclic molecules that show a sequential effect. Use of multiple components could simplify the molecular design of chiral transfer systems and make planar chirality memory systems to regulate. Thus, this work may expand the approaches to regulate chiral memory systems.

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The planar chirality of an acceptor was induced and memorized by a chiral inducer with precise control by a regulator.