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Journal:	<i>ChemComm</i>
Manuscript ID	CC-COM-05-2020-003413.R1
Article Type:	Communication

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Holding of Planar Chirality of Pillar[5]arene by Kinetic Trapping Using Host-Guest Interactions with Achiral Guest Solvents

Received 00th January 20xx,
Accepted 00th January 20xx

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DOI: 10.1039/x0xx00000x

We report a solvent-dependent switching and holding of planar chirality of pillar[5]arene with stereogenic carbons at both rims by host-guest complexation with achiral guest solvents. The planar chirality could be held for a given length of time at 25 °C in long linear guest solvents by kinetic trapping through host-guest complexation. The kinetic trapping worked at 25 °C, but not at 60 °C, thus a planar-chiral inversion using kinetic trapping based on host-guest complexation in the long linear solvents was demonstrated.

Solvent effects play an important role in a variety of thermodynamic and kinetic chemical events, as a solute is surrounded by an excess number of solvent molecules and forms non-covalent interactions with them. For example, solvent has a big impact on host-guest complexation events using macrocyclic hosts as these occur in the presence of a large amount of solvent molecules.¹ Therefore, when guest molecules in the liquid state are used as a solvent (in bulk), inclusion of the guest molecule into the cavity of the macrocyclic host efficiently takes place, even with only weak binding ability between the macrocyclic host and guest.² The host-guest interaction with solvents contributes to stabilization of chemical species.³ In this study, we investigated new solvent effects to induce and hold planar chirality of pillar[5]arenes by host-guest complexation with achiral guest solvents. Pillar[n]arenes, first reported by one of the author's in 2008, are a new type of

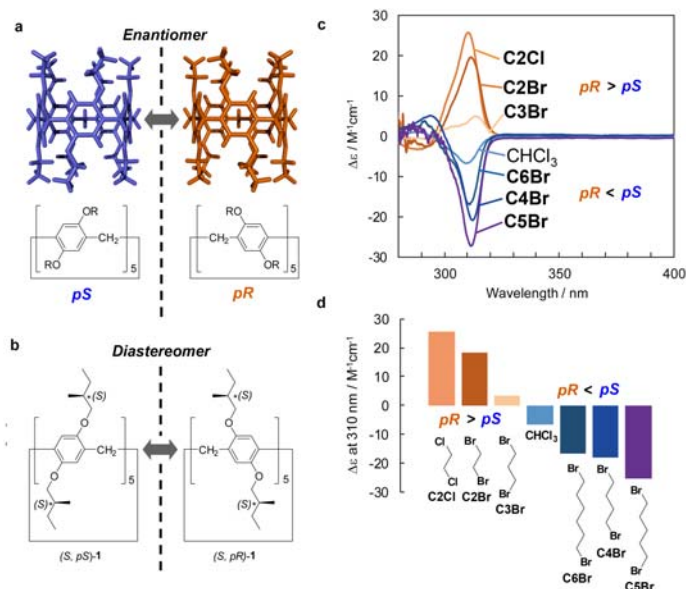


Fig. 1 (a) Planar chirality of pillar[5]arene. (b) Diastereomer of pillar[5]arene carrying 10 stereogenic carbons **1**. (c) CD spectra (0.1 mM, 25 °C) of **1** in various solvents after 168 h at 25 °C. (d) CD intensities at 310 nm in **Fig. 1c** in various dihalogenated solvents.

cylindrical-shaped macrocyclic hosts in supramolecular chemistry.⁴ One of the characteristic features of pillar[n]arenes is planar chirality.⁵ Due to the position of the alkoxy groups, pillar[n]arenes show planar chirality; *pS* and *pR* forms (**Fig. 1a**).^{5b} In solution, in most cases, interconversion between the *pS* and *pR* forms takes place by rotation of the units, resulting in a racemic mixture. In this study, we investigated planar chirality of pillar[5]arene with 2-(*S*)-methylbutoxy groups at both rims **1** (**Fig. 1b**) using various achiral solvents. Interestingly, we discovered that **1** formed mainly the *pR* form in short linear dihaloalkane guest solvents, including 1,2-dichloroethane (**C2Cl**), while **1** adopted mainly the *pS* form in long linear dihaloalkane guest solvents, including 1,4-dibromobutane (**C4Br**) in the equilibrium state. Therefore, both *pS* and *pR* states of **1** were successfully induced using linear achiral dihaloalkane guest solvents with different alkyl chains. We also observed

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Electronic Supplementary Information (ESI) available: Experimental section, ¹H NMR, UV, CD, Eyring plots, computational details and X-ray crystalline data. See DOI: 10.1039/x0xx00000x

planar-chiral inversion by desolvation of **C2Cl** guest solvent from the cavity of **1** in the solid state upon heating; The **C2Cl**-solvated solid **1** was mainly the *pR* form, but this changed to the *pS* form after the desolvation. Furthermore, the planar chirality of **1** induced in the solid state could be held in a given level of time in long linear dihaloalkane guest solvents, including **C4Br**, by kinetic trapping at 25 °C by complexation with the **C4Br** guest solvent. The kinetic trapping worked at 25 °C, but not at 60 °C. Based on the kinetic trapping, we demonstrated temperature-induced planar-chiral inversion.

In our previous report, we investigated the planar chirality of pillar[5]arene **1**.^{5d} In CHCl₃, toluene, *n*-hexane and acetone, **1** showed negative CD signals at 310 nm in the range of the π - π^* transition of the benzene groups in **1** (Fig. S2).^{5d} From previous reports, the negative and positive CD signals are assigned as *pS* and *pR* forms, respectively.^{5b} Therefore, formation of *pS* occurred in these solvents. Herein, we used various linear dihaloalkane guest solvents for CD measurements, as linear dihaloalkanes are good guests for pillar[5]arenes.^{6,7} To measure the CD spectra after reaching the equilibrium state, the solutions of **1** were measured after 168 h at 25 °C (Figs. 1c and d). Negative CD signals at 310 nm were found in long linear dihaloalkane guest solvents such as **C4Br**, 1,5-dibromopentane (**C5Br**) and 1,6-dibromohexane (**C6Br**). These results are the same as described in our previous report,^{5d} and indicated formation of the *pS* form. In contrast, in the cases of short linear dihaloalkane guest solvents such as **C2Cl**, 1,2-dibromoethane (**C2Br**) and 1,3-dibromopropane (**C3Br**), unexpectedly, **1** showed positive CD signals at 310 nm, indicating formation of the *pR* form. We discovered that the planar chirality of **1** depends on the length of linear dihaloalkane guest solvent. To understand the solvent-dependent planar-chiral inversion, we obtained single crystals of **1** from **C2Cl** and **C4Br**. In both cases, pillar[5]arene **1** formed a 1:1 host-guest complex with these

solvents. Only the *pR* forms were observed in the **C2Cl**@**1** complex (Fig. 2a). In contrast, the **C4Br**@**1** complex only formed the *pS* form (Fig. 2b). The planar chirality of the crystal structures is consistent with the results of the planar chirality of **1** in these solvents (Figs. 1c and d). The planar chirality difference comes from the arrangement of the chiral centre of the substituents. In the **C2Cl**@**1** complex, the relatively bulky ethyl groups of the chiral substituents are located inside the cavity due to the short length of the **C2Cl** guest (Fig. 2a). The height of the pillar[n]arenes is ca. 8 Å, which is longer than the length of **C2Cl** guest (ca. 4 Å). In contrast, in the **C4Br**@**1** complex, the ethyl groups are found outside the cavity due to the long length of the **C4Br** guest (ca. 7 Å, Fig. 2b). This difference would result in a solvent-dependent planar-chiral inversion.⁸

Planar-chiral inversion was also observed by desolvation of **C2Cl** guest solvent from the cavity of **1** in the solid state upon heating. Compound **1** was dissolved in **C2Cl**, then the solvent was evaporated to obtain the solids. After drying the solids **1** in vacuum at 25 °C for 24 h, the sample was analyzed by ¹H NMR (Fig. S1). A signal corresponding to **C2Cl** was observed, indicating formation of **C2Cl**-solvated solid **1**. The **C2Cl**-solvated solid **1** was dissolved in **C2Cl**, then the CD spectrum was quickly measured in **C2Cl** as solvent (detail experiment procedure in ESI). The solution showed a positive CD signal at 310 nm (Fig. 2c), indicating formation of *pR* form. The **C2Cl**-solvated solid **1** after drying was heated at 150 °C for 20 min. The resulting solid was analyzed by ¹H NMR (Fig. S1). In this case, the signal from **C2Cl** was not observed, indicating desolvation of all **C2Cl** molecules from the solid by heating (Fig. 2d). The desolvated solid **1** was dissolved in **C2Cl**, and the CD spectrum was quickly measured. The sample showed a negative CD signal at 310 nm (Fig. 2c), indicating formation of *pS* form, and planar-chiral inversion by the desolvation. The planar chirality of **C2Cl**-solvated solid was the *pR* form, which was consistent with the X-ray crystal structure of the **C2Cl**@**1** complex (Fig. 2a). Compound **1** after the desolvation would be stable as the *pS* form, thus, the planar-chiral inversion would take place by the desolvation. To better understand the planar-chiral inversion, we calculated the energy level of **1** in both *pS* and *pR* forms without a guest (Fig. S7). To measure the energy level of **1** without a guest, calculation was performed in gas phase. The *pS* form without a guest was 14.8 kJ/mol more stable than the *pR* form without a guest. Therefore, the planar chirality change from *pR* to *pS* form occurred by the desolvation.

The desolvated solid **1** showed a negative CD signal at 310 nm (Fig. 3b, -60 mdeg) on immediate measurement after dissolution in **C2Cl** (detail experiment procedure in ESI), but this gradually changed to a positive CD signal by keeping the solution at 25 °C. Finally, the CD signal changed to positive (+100 mdeg) by reaching an equilibrium state after 1.5 h. The **C2Cl**-solvated solid **1** showed a positive value (+105 mdeg) when the CD signal was measured immediately after dissolution in **C2Cl**, then the positive CD signal gradually decreased on keeping the sample at 25 °C. After 1.5 h, the CD signal also reached an equilibrium state. Overall, we could monitor the CD signal changes on a real time scale using **C2Cl**-solvated and desolvated

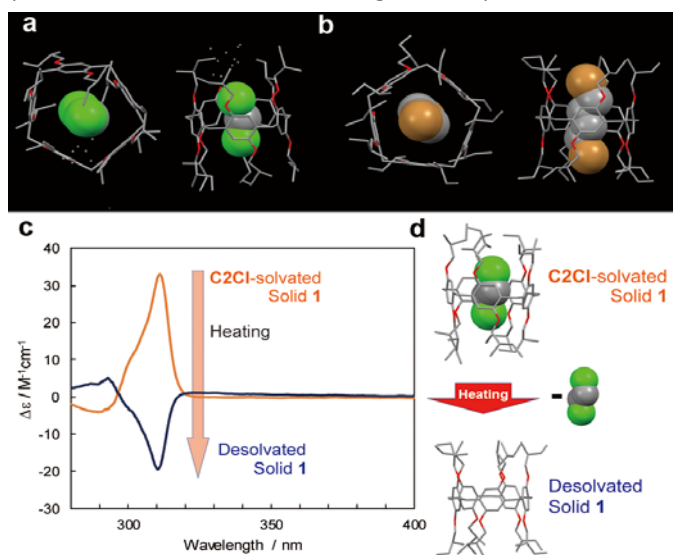


Fig. 2 Single-crystal X-ray structures of (a) **C2Cl**@**1** and (b) **C4Br**@**1** host-guest complexes. In the X-ray structures, O=red; C=gray; Cl=green; Br=brown; H atoms are omitted for clarity. (c) CD spectra (0.1 mM, 25 °C) of solutions **1**, which was quickly measured after dissolving **C2Cl**-solvated solid **1** and desolvated solid **1** in **C2Cl**. (d) Schematic illustration of planar-chiral inversion by the desolvation on heating.

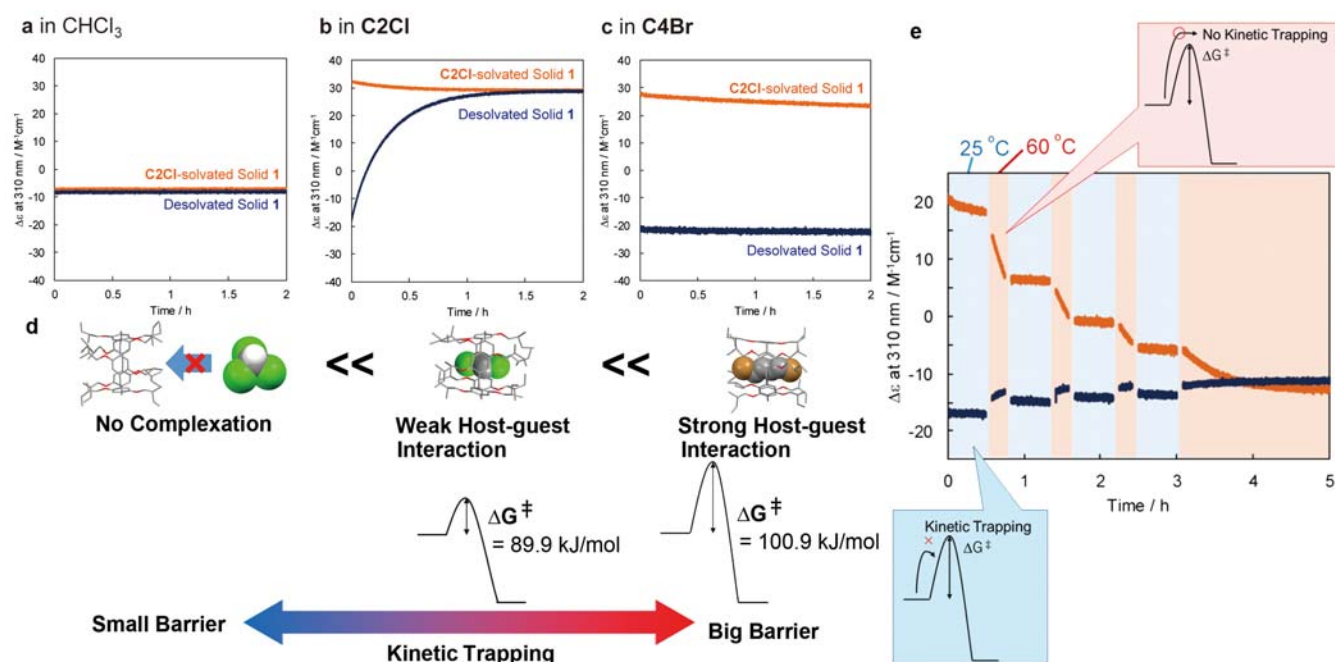


Fig. 3 CD changes at 310 nm of the solutions **1** (0.1 mM, 25 °C) after solubilizing **C2Cl**-solvated solid **1** and desolvated solid **1** in (a) CHCl₃, (b) C2Cl and (c) C4Br. (d) Schematic illustration of holding of planar chirality of **1** by host-guest complexation. (e) CD changes at 310 nm of the solution **1** (0.1 mM) after solubilizing **C2Cl**-solvated solid **1** and desolvated solid **1** in **C4Br** by alternative heating at 60 °C and cooling at 25 °C.

solids **1** and **C2Cl** as a solvent for CD measurements. The CD change comes from the diastereomeric ratio change over time, confirmed by ¹H NMR (Fig. S3). We also monitored the CD signal change with **C3Br** as a solvent (Fig. S4). The CD signal change in **C3Br** was slower than in **C2Cl**. When we used the longer **C4Br** as a solvent (Fig. 3c), the CD signal was negative after dissolving the desolvated solids **1**, and did not change quickly even after keeping the solution at 25 °C. It took ca. 1 h to change 10% CD intensity. A positive CD signal was observed in the **C2Cl**-solvated solid **1**, and also did not change quickly by keeping the solution at 25 °C. Therefore, using **C4Br** as a solvent, the planar-chiral information of the solids **1** in **C2Cl**-solvated and desolvated states was successfully held for a given length of time. The same holding effects were observed in longer dihaloalkane solvents such as **C5Br** and **C6Br** (Fig. S4). In CHCl₃ (Fig. 3a), the CD signals of the **C2Cl**-solvated and desolvated solids **1** were completely the same after dissolving in CHCl₃, indicating that they quickly reached an equilibrium state. No holding effect was observed in CHCl₃.

To understand the solvent-dependent planar chirality holding, we monitored the CD signal change by altering the measurement temperatures. The CD signal change was faster when the measurement temperatures were increased (Fig. S5). The barrier (ΔG^\ddagger) at 25 °C in **C2Cl** was 89.9 kJ/mol using an Eyring plots. ΔG^\ddagger at 25 °C in **C4Br** was 100.9 kJ/mol (Fig. S6), which was 11 kJ/mol more than in **C2Cl**. Due to the larger barrier in **C4Br**, the planar chirality could be held at 25 °C for a given length of time by kinetic trapping (Fig. 3d). Long, linear dihaloalkanes including **C4Br** are better guests for pillar[5]arenes than short linear dihaloalkanes including **C2Cl**.

From previous reports, the association constants of the host-guest complexes of pillar[5]arenes with **C2Cl**, **C3Br**, **C4Br** and **C5Br** in CDCl₃ are 650, 300, 4900 and 1400 M⁻¹, respectively.⁷ Thus, formation of host-guest complexes with these long linear dibromoalkanes would provide a large barrier to keep the thermodynamically unstable intermediate. CHCl₃ is not a good guest due to its branched structure,^{3b,9} resulting in no holding effect.

Based on the kinetic trapping system, we demonstrated a temperature-dependent planar-chiral inversion (Fig. 3e). When we used the **C2Cl**-solvated solid **1**, the initial state gave a positive CD signal at 310 nm. The positive CD signal could be held at 25 °C due to the kinetic trapping at 25 °C. The solution was then heated to 60 °C. During the heating at 60 °C, the CD signal decreased due to no kinetic trapping. However, on re-cooling to 25 °C, the CD signal was held again; re-heating to 60 °C caused the CD signal to start to decrease, as the kinetic trapping worked at 25 °C, but not at 60 °C. Thus, the planar chirality was controlled by the kinetic trapping. When we used the desolvated solid **1**, we were able to induce a negative CD signal in the initial state. In this case, the negative CD signal could also be held at 25 °C, and this signal increased by heating to 60 °C. Over all, the planar chirality of **1** was successfully held using kinetic trapping by host-guest interaction of **1** with **C4Br** solvent.

In conclusion, we have demonstrated an achiral solvent-dependent planar-chiral inversion. Holding of planar chirality were also observed when these linear long dihaloalkane solvents were used. Based on the chiral holding behaviour, we demonstrated temperature-dependent planar-chiral inversion. Chiral induction has mainly been performed by relatively large molecules such as helical polymers¹⁰ and supramolecular assemblies,¹¹ using the dynamic changes of their helical structures. There are few examples of chiral induction and holding using a macrocyclic-based host-guest system.¹² To the best of our knowledge, this is first example of chiral induction

and holding using pillar[n]arene platform, while the planar chiral inversion behavior by complexation with achiral guests was reported using pillar[n]arene-based *pseudo*[1]catenane structures.^{5d-f} The kinetic trapping of the chirality is new concept to hold the chiral information. However, in this study, the kinetic trapping is not perfect to hold the chiral information at 25 °C for relatively long time, thus we now tune the bulkiness of the chiral substituents to achieve the perfect holding of the planar chirality.

This work was supported by Grant-in-Aid for Scientific Research on Innovative Areas; π -System Figuration (JP15H00990 and JP17H05148, TO), (JP15H00994, YN), Soft Crystal (JP18H04510, TO), and Kiban A (19H00909, TO) from MEXT Japan, JST CREST (JPMJCR18R3, TO), and World Premier International Research Center Initiative (WPI), MEXT, Japan. We thanks Prof. Katsuhiko Maeda and Ms. Mayu Fukuda (Kanazawa University) for optical rotation measurements.

Conflicts of interest

There are no conflicts to declare.

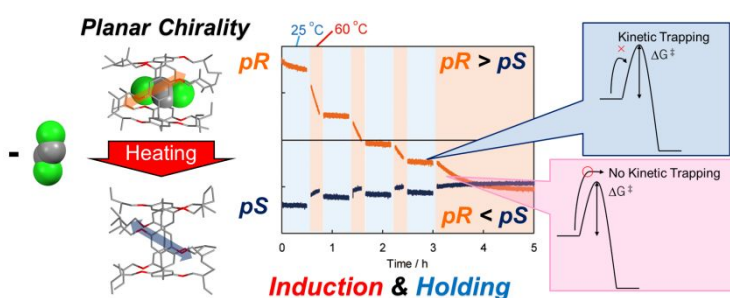
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Table of Contents (TOC) Graphic

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We report a solvent-dependent switching and holding of planar chirality of pillar[5]arene with stereogenic carbons at both rims by host-guest complexation with achiral guest solvents.