Crystallization-Induced Diastereomeric Transformation of *N*-2'-*t*-Butyl-6'-iodobenzoyl-3-bromocarbazole

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We previously reported the atropisomeric properties of 2'-*t*-butyl-6'-iodo-substituted *N*-benzoyl-3-bromocarbazole, *i.e.*, the steric or electronic effects of the substituents restricted the rotation about the N–C7' and C7'–C1' bonds to separate four stereoisomers (*cis/trans* for the N–C7' axis, *aR/aS* for the C7'–C1' axis). Furthermore, the 2'-*t*-butyl-6'-iodo-substituted *N*-benzoyl 3-bromocarbazole was confirmed to be a gear molecule, in which the rotation about the C7'–C1' bond was in perfect concert with that about the N–C7' bond. Herein, we report a unique crystallization-induced diastereomeric transformation found in this molecule. In the isolation process, where the product is recrystallized from the diastereoisomeric mixture, *in situ* isomerization and selective crystallization could lead to a diastereomeric transformation, and a mixture of diastereomers (*trans/cis*=54:46) was converted to *trans*-isomer-enriched crystals (*trans/cis*>96:4) in 95% yield. Conformational analysis clarified the preference for the *trans* versus *cis* isomer.

Key words axial chirality; crystallization; diastereomer transformation; carbazole

Recently, we have reported on the atropisomeric properties of the 2'-*t*-butyl-6'-iodo-substituted *N*-benzoyl 3-bromocarbazole (**1**).¹⁾ Because the rotations about the N–C7' and C7'–C1' axes are fully restricted, four stereoisomers (*cis/trans* for the N–C7' axis, *aR/aS* for the C7'–C1' axis) of **1** were resolved on a chiral column (CHIRALPAK IB) (Fig. 1). Using the enantiomerically pure stereoisomer, the stereochemical stability was examined at 37°C. It was found that (*cis*, *aS*)-**1** was converted to (*trans*, *aR*)-**1** with a $\Delta G^\ddagger$ value of 102 kJ/mol, and no interconversion between any other pair [*i.e.*, (*cis*, *aS*)-**1**/(*cis*, *aR*)-**1**, (*cis*, *aS*)-**1**/(*trans*, *aS*)-**1**] was observed. Similarly, (*trans*, *aS*)-**1** was converted to (*cis*, *aR*)-**1** with a $\Delta G^\ddagger$ value of 103 kJ/mol, and no interconversion between any other pair [*i.e.*, (*trans*, *aS*)-**1**/(*trans*, *aR*)-**1**, (*trans*, *aS*)-**1**/(*cis*, *aS*)-**1**] was observed. It is clear that the rotation about the C7'–C1' axis must be in perfect concert with the rotation about the N–C7' axis at 37°C.¹⁾

With our interest in this gear molecule,^{2,3)} we studied its physicochemical properties in detail to discover a crystallization-induced diastereomeric transformation (CIDT).^{4–8)} Crystallization, where the pure isomer is crystallized from diastereomeric mixtures, could be cost-effective compared with conventional column chromatography. In particular, diastereomeric transformation allowing an isomer to be converted to the desired one through *in situ* isomerization and selective crystallization might be very practical. Such *in situ* isomerization and crystallization (CIDT) has been researched recently by many groups.^{4–8)}

Results and Discussion

In the course of the crystallization experiments on **1**, we discovered that the diastereoisomeric mixture **1** was crystallized through isomerization to give *trans*-isomer-enriched crystals in nearly quantitative yield (Fig. 2).

Following the established method,¹⁾ 2'-*t*-butyl-6'-iodo-substituted *N*-benzoyl-3-bromocarbazole **1** was prepared as a

crude solid. HPLC analysis using a nonchiral column showed two peaks corresponding to *trans*-**1** and *cis*-**1** (54:46).⁹⁾ In order to purify **1**, we examined recrystallization using various solvents and found that **1** was isomerized in a mixed solvent of AcOEt–hexane to produce crystals of *trans*-**1** preferentially. The crude solid of **1** (1.019 g; *trans/cis*=54:46) was dissolved in AcOEt–hexane (1:2) and slowly recrystallized at 2°C for 12 h. The crystals obtained (703.5 mg) were analyzed using nonchiral HPLC, and we found that the *trans*-isomer was selectively crystallized (*trans*-**1**/*cis*-**1**=97:3).⁹⁾ From its mother liquor, a second recrystallization was performed at 2°C for 15 h and yielded 195.5 mg of *trans*-**1**-enriched crystals (*trans*-**1**/*cis*-**1**=96:4).⁹⁾ Furthermore, a third recrystallization from the second mother liquor (at 2°C for 14 h) yielded 68.8 mg of *trans*-**1**-enriched crystals (*trans*-**1**/*cis*-**1**=98:2).⁹⁾ These recryst-

Fig. 1. Interconversion Path for Stereoisomers of **1**

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Fig. 2. Crystallization-Induced Diastereomeric Transformation (CIDT) of **1**

Fig. 3. Isomerization of *trans*-Enriched (*trans*-**1**/*cis*-**1**=97:3) **1** at 25°C in CDCl₃ Analyzed by ¹H-NMR

tallization procedures produced a total of 967.8 mg of *trans*-**1**-enriched crystals (*trans*-**1**/*cis*-**1** > 96:4) in 95% yield.

Although the first crystals of the *trans*-**1**-enriched (*trans*-**1**/*cis*-**1** = 97:3) mixture retained the ratio for weeks in the crystal state, the mixture reached an equilibrium state (*trans*-**1**/*cis*-**1** = 54:46) in CDCl₃ solution within 126 h (5.25 d) at 25°C (Fig. 3). When analyzed using a chiral column (CHIRALPAK IB), the *trans*-**1**-enriched crystals¹⁰ were shown to exist as a racemate.

We found it surprising that the 3-bromo-substituted carbazole derivative **1** showed a preference for the *trans*-isomer in the crystal state, which resulted in efficient CIDT. Therefore, we carried out *in silico* conformational analysis of **1** to confirm the advantage of the *trans*- over the *cis*-isomer. Using the density functional theory method, minimum energy conformations among the stereoisomers [(*trans*, a*R*)-**1**, (*trans*, a*S*)-**1**, (*cis*, a*R*)-**1**, and (*cis*, a*S*)-**1**] were explored at the B3LYP/LanL2DZ level. It was estimated that the energy difference between the *trans*- and *cis*-isomer was 1.01 kJ/mol (ΔE value, 25°C, gas phase) (Fig. 4).

Thus, a preference for the *trans*-isomer was theoretically

predicted. As mentioned above, HPLC and ¹H-NMR provided the information that **1** is in equilibrium (*trans*-**1**/*cis*-**1** = 54:46) in solution at 23°C, which means that the $\Delta G^\ddagger$ value should be 0.39 kJ/mol. Both the theoretical and experimental investigations suggested that the energy difference between *trans*- and *cis*-isomers is very small, which is insufficient to explain the unusual preference for the *trans*-isomer in the crystal state. We therefore conclude that CIDT, which provides *trans*-isomer-enriched crystals, should be attributed to the crystallization characteristics of **1**. Although we have only limited information on CIDT, we hope that this study will contribute to elucidating the physicochemical property of the *N*-acylated carbazoles.

Experimental

General Remarks NMR Spectra were recorded on a JEOL JNM-ECS 400 spectrometer at 400 MHz for ¹H-NMR. Melting points were taken on a Yanaco micro melting point apparatus and are uncorrected. High-pressure liquid chromatography (HPLC) was performed with a Shimadzu Prominence system. All solvents used were of analytical grade.

Fig. 4. Optimized Structures and Relative Energies of Stereoisomers of **1**

Procedure of Recrystallization The crude solid of **1** (*trans/cis*=54:46) weighing 1.019 g was dissolved in mixed solvents (AcOEt/hexane=1:2) and slowly recrystallized at 2°C for 12 h. The crystals obtained (703.5 mg) were analyzed using nonchiral HPLC. Its mother liquor was immediately analyzed to find the diastereomeric mixtures with a ratio of *trans-1/cis-1*=42:58. The second and the third recrystallizations followed the way mentioned above. Each mother liquor was analyzed in the same way to find the diastereomeric mixtures (*trans-1/cis-1*=40:60).

Determination of Diastereomer Ratio of **1 Using Non-chiral HPLC** Diastereomers of **1** were analyzed using non-chiral HPLC (YMC SIL-06 (0.6 cm×25 cm), flow rate 0.5 mL/min; temperature 23°C; detection 254 nm) with eluent hexane/ethyl acetate (20:1) to separate each diastereomer (t_R 18.7 min for *cis*-isomer, t_R 20.2 min for *trans*-isomer).

Analysis of *trans*-1-Enriched Crystals Using Chiral HPLC *trans*-1-enriched crystals (*trans-1/cis-1*=97:3) were analyzed using CHIRALPAK IB ((0.46 cm×25 cm), flow rate 0.5 mL/min; temperature 23°C; detection 254 nm) with eluent hexane/ethyl acetate (20:1) to separate each stereoisomer (t_R 14.6 min, 16.7 min, 19.7 min, 23.4 min).

Physical Property of *trans*-1-Enriched Crystals *trans*-1-enriched crystals (50 mg; *trans-1/cis-1*=97:3) were dissolved

in 0.5 mL of CH_2Cl_2 , in 1.5 mL of AcOEt, in 3.8 mL of Et_2O , respectively. mp: 166–167°C.

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References and Notes

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- 9) The ratio of *trans*- and *cis*-isomers was determined by HPLC analysis.
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