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). 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 enantiotomerically 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 ΔG° 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 ΔG° 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.

With our interest in this gear molecule, we studied its physicochemical properties in detail to discover a crystallization-induced diastereomeric transformation (CIDT). Crystalization, 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.

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, 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). 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 (101.9 mg, trans/cis=54:46) was dissolved in AcOEt–hexane (1:2) and slowly recrystallized at 2°C for 12h. 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). From its mother liquor, a second recrystallization was performed at 2°C for 15h and yielded 195.5 mg of trans-1-enriched crystals (trans-1/cis-1=96:4). Furthermore, a third recrystallization from the second mother liquor (at 2°C for 14h) yielded 68.8 mg of trans-1-enriched crystals (trans-1/cis-1=98:2). These recrys-

![Fig. 1. Interconversion Path for Stereoisomers of 1](Image)

The authors declare no conflict of interest.

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Crystallization 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 crystals (10) 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, aR]-1, (trans, aS)-1, (cis, aR)-1, and (cis, aS)-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 (∆E 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 ∆G° 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.
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 (tR cis-isomer, 18.7 min for cis-isomer, tR trans-1, 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 (tR 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 CH2Cl2, in 1.5 mL of AcOEt, in 3.8 mL of Et2O, respectively. mp: 166–167°C.

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