Note

Crystalline Structure of N-(S)-2-Heptyl (1R,2R)-2-(2,3-Anthracenedicarboximido)cyclohexanecarboxamide That Differs from Its Preferred Conformation in the Solvent Used for Crystallization

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The crystalline structure of N-(S)-2-heptyl (1R,2R)-2-(2,3-anthracenedicarboximido)cyclohexamide (1), which was crystallized from methanol, was determined by an X-ray analysis and had a different conformation from its preferred one in CD3OD by a 1H-NMR analysis. Inter- and intra-molecular CH-π interaction in a crystal plays a very important role in crystal packing. The preferred conformation of the amide derivative in a solution allows us to exploit (1R,2R)-2-(2,3-anthracenedicarboximido)cyclohexanecarbonyl chloride as a conversion reagent to determine the absolute configuration of chiral amines by 1H-NMR.

Key words: crystalline structure; N-(S)-2-heptyl (1R,2R)-2-(2,3-anthracenedicarboximido)cyclohexanecarboxamide; chiral reagent; fluorescent reagent

The molecular structure determined in the crystalline state is often used to explain the properties of that molecule in the solution state. However, in some cases, the crystal structure is influenced by effects such as crystal packing. It is necessary to determine the structure independently in both the crystalline and solution states to make clear the relationship between the molecular structures in these two states. However, there are few reports about a combined study on the molecular structures in the two states.1,2) We describe in this paper an example showing the crystalline structure of a compound differs from its preferred conformation in the solvent used for crystallization.

We have developed both (1R,2R)- and (1S,2S)-2-(2,3-anthracenedicarboximido)cyclohexanecarboxylic acid as chiral conversion reagents.3,3) These reagents have proved very useful to separate by HPLC both chiral primary and secondary alcohols having a chiral methyl branch at a remote position from the hydroxyl group.3,4) The reagents have also been useful to discriminate the chirality of the secondary alcohol itself by HPLC and 1H-NMR.3) The acid chloride of the reagent also seemed to be useful as a conversion reagent for amines. Since the conformation of the derivative is a very important factor for chiral discrimination, a conformational analysis of its 2-heptyl amide derivatives was performed. (S)-2-Heptylamine was converted with (1R,2R)-2-(2,3-anthracenedicarboximido)cyclohexanecarbonyl chloride, which had been prepared by the reaction with an excess amount of oxalyl chloride in toluene at 50 °C for 1 h with subsequent evaporation of the solvent and excess oxalyl chloride in vacuo, in toluene in the presence of 4-dimethylaminopyridine at 50 °C for 5 h to give N-(S)-2-heptyl (1R,2R)-2-(2,3-anthracenedicarboximido)cyclohexanecarboxamide (1, Fig. 1). After purification by silica gel column chromatography [toluene/EtOAc (5:2, v/v), Rf = 0.49], 1 was crystallized from methanol to give crystals suitable for an X-ray analysis. The X-ray intensity data were measured with a Rigaku AFC8 Goniometer by using graphic monochromated MoKα (λ = 0.71070 Å). The crystal and experimental data for the crystals are listed in Table 1.

All the hydrogen atoms, except for NH, were calculated from the standard bond lengths and angles. The X-ray crystalline structures of 1 are shown in Fig. 1. The noteworthy points for the crystalline structure in Fig. 1A are as follows: (1) the C3–C7 alkyl chain is located over the anthracenedicarboximide group, (2) the conformation of H1′–C1′–C=O is s-cis, (3) the conformation of O=C–NH–C2–H2 is 1,3-syn, and (4) the conformation of H2′–C2′–N–C=O is 1,3-syn.

The conformations in points 3 and 4 are the preferred ones. Since the preferred conformation of H–C–C=O of cyclohexanecarboxylic acid in solution is s-trans, the s-cis conformation of crystal 1 is not the preferred one. These results prompted us to study the preferred conformation of 1 in methanol, because the conformation in solution is very important for chiral discrimination by this reagent.

Conformational analyses of both 1 and its diaster-
eomer, \( N\)-2-(R)-heptyl (1\( R\),2\( R\))-2-(2,3-anthracenedicarboximido)cyclohexanecarboxamide (2), which was prepared in the similar manner to that for 1, in CD\(_3\)OD were performed by \(^1\)H-NMR. In this case, 2 didn’t give crystals suitable for an X-ray analysis. \(^1\)H-NMR spectra were recorded with a Varian Unity Inova 500 spectrometer at 20 °C in CD\(_3\)OD, using Me\(_4\)Si as an internal standard. The \(^1\)H-NMR spectra of 1 and 2, and their preferred conformations in CD\(_3\)OD deduced from the \(^1\)H-NMR study are shown in Fig. 2.

The protons of the C3–C7 alkyl chain of 2 are significantly shielded due to anisotropy by the anthracenedicarboximide group, and those of the C1-methyl appeared at the normal position. These results indicate that the C3–C7 alkyl chain exists in the deshielded region of anisotropy by the anthracenedicarboximide group and that the C1-methyl group is not in the preferred conformation of 2 in CD\(_3\)OD (Fig. 2B).

On the other hand, the protons of the C1-methyl group
of I are significantly shielded, while those of the C3–C7 alkyl chain are not (Fig. 2A). These results indicate that the C1-methyl group exists in the deshielded region of anisotropy by the anthracenedicarboximide group and that the C3–C7 alkyl chain is not in the preferred conformation of I in CD$_3$OD. The preferred conformations of I and 2 can be attained by the conformation of H1′−C1′−C=O as s-trans and of O=−C=−C2′−C2′ as 1,3-syn, the most stable conformation of N-secondary-alkylcyclohexanecarboxamide, as shown in Fig. 2.

CH−π interaction is one of the important factors to stabilize a conformation.$^6$–$^8$ If I had the same crystal structure as the preferred conformation in the solution, the C1 methyl group should be located over the aromatic ring. However, the crystalline structure of I differed from its preferred conformation in methanol. In this crystal structure, the C3–C7 alkyl chain was laid between two aromatic rings to stabilize the structure by both intra- and inter-molecular CH−π interactions (Fig. 1B). Although the three single bonds, C1′−CO, CO−NH and NH−C2′, of the amide part of I could rotate to provide the conformation for CH−π interaction, only the C1′−CO bond rotated in the crystalline structure. These results suggest that the 1,3-syn conformation at O=−C=−C2′(R,R′)=−H2 was more stable than the s-trans conformation at H1′−C1′−C=O. In the solution, inter-molecular CH−π interaction between the C3–C7 alkyl chain and the anthracene ring of another molecule may be too weak to form. This might be due to the difference of molecular structure in the solid state and in the solution for this system. The foregoing results suggest that CH−π interaction is one of the important factors causing structural differences in the two states.

In the solution, the stereochemistry of the amino group on a chiral secondary carbon atom determines which alkyl group on the chiral carbon atom is laid on the aromatic ring, because they form s-trans at H1′−C1′−C=O, 1,3-syn at O=−C=−C2′−H2, and 1,3-syn at H2′−C2′−N−C=O conformations as most preferred ones. This allows us to exploit 2-(2,3-anthracenedicarboximido)cyclohexanecarboxyl chloride as a chiral conversion reagent to determine the absolute configuration of chiral amines by $^1$H-NMR.

$N$-($R$)-2-Heptyl (1R,2R)-2-(2,3-anthracenedicarboximido)cyclohexanecarboxamide (I). Yellow crystals (76.1% from methanol), mp 207–208 C, [α]$^2$D −59.55° (c 0.22, CHCl$_3$); $^1$H-NMR δ: 0.638 (d, J = 6.3 Hz, 3H), 0.743 (t, J = 6.8 Hz, 3H), 1.13 (m, 6H), 1.24 (m, 2H), 1.36–1.54 (m, 2H), 1.56–1.66 (m, 1H), 1.79–1.98 (m, 4H), 2.15–2.24 (m, 1H), 3.34 (dt, J = 3.4 Hz, 11.7 Hz, 1H), 3.60 (m, 1H), 4.45 (dt, J = 3.9 Hz, 12.2 Hz, 1H), 7.62 (m, 2H), 8.12 (m, 2H), 8.51 (s, 2H), 8.75 (s, 2H); HRMS (FAB) m/z: calcd. for C$_{30}$H$_{35}$N$_2$O$_3$ [(M + H)$^+$], 471.2647; found, 471.2656. $N$-($R$)-2-Heptyl (1R,2R)-2-(2,3-anthracenedicarboximido)cyclohexanecarboxamide (2). Yellow crystals (40% from methanol), mp 223–224 °C, [α]$^2$D −75.33° (c 0.15, CHCl$_3$); $^1$H-NMR δ: 0.075 (d, J = 6.8 Hz, 3H), 0.44 (m, 4H), 0.70 (m, 2H), 0.931 (d, J = 6.3 Hz, 3H), 0.98 (m, 2H), 1.36–1.54 (m, 2H), 1.55–1.65 (m, 1H), 1.78–1.96 (m, 4H), 2.16–2.25 (m, 1H), 3.33 (dt, J = 3.4 Hz, 11.7 Hz, 3H), 3.60 (m, 1H), 4.47 (dt, J = 3.9 Hz, 12.2 Hz, 1H), 7.62 (m, 2H), 8.11 (m, 2H), 8.50 (s, 2H), 8.75 (s, 2H); HRMS (FAB) m/z: calcd. for C$_{30}$H$_{35}$N$_2$O$_3$ [(M + H)$^+$], 471.2647; found, 471.2651.

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References


