Optional Formation of "Parallel or Antiparallel" β-Sheet-like Structures in (*R*)-(1-Naphthyl)glycyl-(*R*)-phenylglycine Crystals

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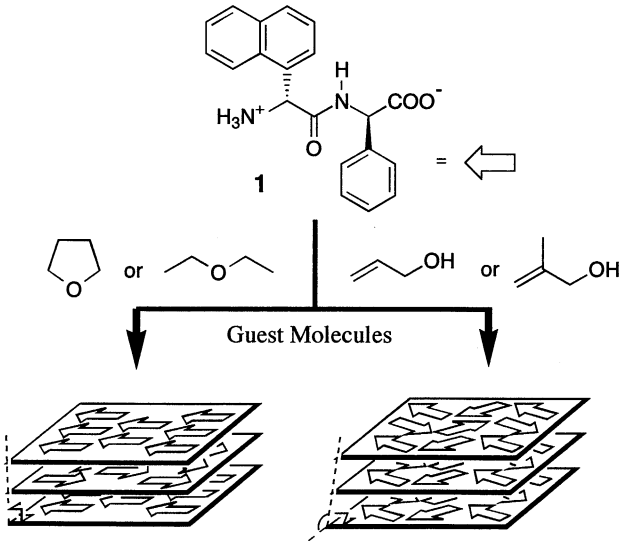
(*R*)-(1-Naphthyl)glycyl-(*R*)-phenylglycine forms inclusion compounds with ethers (tetrahydrofuran and diethyl ether) or allylic alcohols (2-propen-1-ol and 2-methyl-2-propen-1-ol). X-ray crystallographic study showed that the dipeptide has the ability to optionally form "parallel or antiparallel" β-sheet-like structures by the choice of ethers or allylic alcohols, respectively, as the guest molecules.

From a standpoint of the partial structures of proteins, the crystal structures of oligopeptides have been investigated and classified into α-helices, β-sheets, and β-turns.[1] However, the assembly and orientation modes of the oligopeptide depend so much on their primary structures that it is extremely difficult to control their secondary ones. In order to force them to aggregate in parallel or antiparallel β-sheets, "molecular scaffolds" have been employed as a useful tool to orientate hydrogen bonding between peptide backbones.[2] Since it is well known that, in usual inclusion compounds, the arrangement of host molecules is changeable by host-guest interactions,[3] our attention was focused on whether β-sheet structures of dipeptides can be controlled by guest molecules which are accommodated in their voids.[4] Here we report that inclusion compounds of (*R*)-(1-naphthyl)glycyl-(*R*)-phenylglycine (**1**)[5] with ethers or allylic alcohols have the ability to optionally form "parallel or antiparallel" β-sheet-like structures by the included molecules (Scheme 1). This is regarded as a prototype that the guest molecules control β-sheet structures.



(A) parallel mode (B) antiparallel mode

Scheme 1.

THF-included compound **2** formed on crystallization of **1** from a mixed solvent of tetrahydrofuran (THF) and methanol. X-ray crystal analysis (Figure 1)[6] shows that the dipeptide molecules were arranged in a parallel β-sheet-like structure which is constructed by ionic pairing of carboxyl and amino groups *via* a hydrogen bonding network: one terminal COO^- bridged two $^+NH_3$ of adjacent dipeptides, and the $^+NH_3$ also bound two adjacent COO^- groups (O•••N bond distances: 2.71 and 2.81 Å). The neighboring naphthyl and phenyl rings stacked each other with the aid of the edge-to-face interaction to form a wall.[7] Interestingly, a typical intermolecular hydrogen bonding among amide groups, which is essential to the formation of oligopeptide crystals,[1] did not contribute to the parallel β-sheet formation.[8] THF molecules were linked to $^+NH_3$ of dipeptide *via* hydrogen bonding (O•••N distance; 2.81 Å) and accommodated in the void between the walls of the naphthyl and phenyl groups. Similarly, diethyl ether-included compound was prepared by the same procedure, its X-ray crystal structure showed the parallel mode similar to that mentioned above.[9]

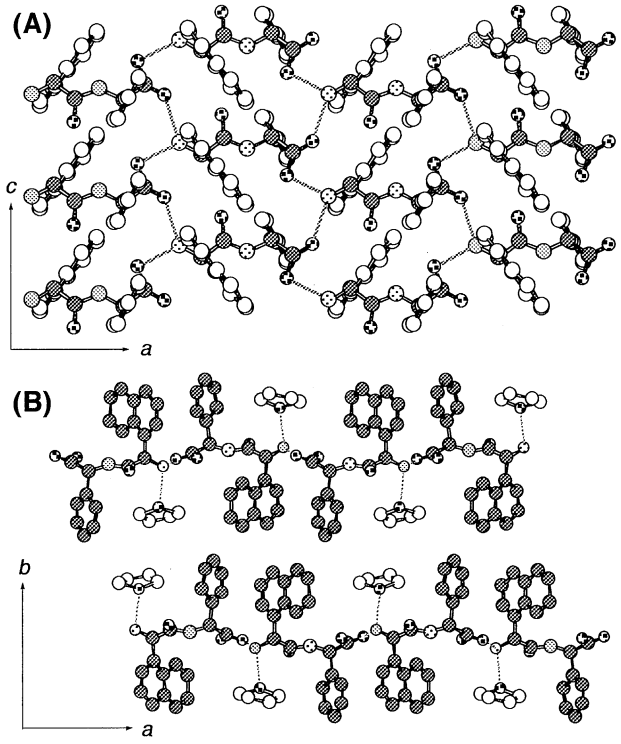


Figure 1. Parallel β-sheet-like structure of **2**. To improve clarity, all hydrogen atoms are omitted. (A) a-c face. THF is omitted, and the naphthyl and phenyl groups are colored white. (B) a-b face. The carbons of THF are colored white.

When allylic alcohols were used as a guest molecule instead of ethers (THF and diethyl ether), the arrangement of the dipeptide molecules was changed to an antiparallel β-sheet-like structure. By crystallization from methanol-methallyl alcohol (2-methyl-2-propen-1-ol), we obtained the single crystal of an inclusion compound **3**, which consisted of **1**, methanol, and methallyl alcohol.[10] The X-ray structure shows an antiparallel mode where two kinds of dipeptide ribbon structures are bound with one another by multiple hydrogen bonding (Figure 2). Both of the dipeptide ribbons are zigzagged with a binding angle of ca. 110°. The distances of the ionic pair ($COO^{-}\cdots{}^{+}NH_3$) are 2.68 and 2.71 Å, and four hydrogen bonding distances between two peptide ribbons are 2.82, 2.83, 2.86, and 2.94 Å. Thus four additional hydrogen bonds play an important role in the antiparallel mode. This is in sharp contrast with the parallel mode. Methanol and methallyl alcohol exist as two guest molecules in voids surrounded by naphthyl and phenyl groups that stand perpendicularly to the sheet.

In addition, the inclusion compound of 2-propen-1-ol (allyl alcohol) was also obtained and confirmed by the single-crystal X-ray crystallography to exhibit the same antipallarel mode.[9]

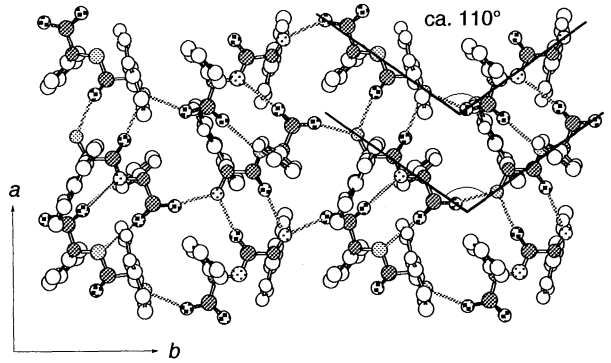


Figure 2. Antiparallel β-sheet-like structure of **3** (a-b face). To improve clarity, all hydrogen atoms and guest molecules are omitted, and the naphthyl and phenyl groups are colored white.

In conclusion, the dipeptide molecules **1** self-assemble to form β-sheet-like structures, which are piled up in crystals. The parallel or antiparallel mode of the sheet depends strongly on the shape of the guest molecule that are accommodated in the void between the sheets. This implies that *the guest molecules make it possible to control the secondary structure of dipeptides in crystals*. Further investigations are under way in our laboratory in order to define the factors to control the sheet structure of the dipeptide by the guest molecule.

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References and Notes

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6 A solution of **1** (0.08 mmol) in methanol (0.5 mL) was placed in an inside bottle of a double bottle, and THF was placed in the outside bottle equipped with a cap. The liquid surface was kept in contact with THF vapor at ambient temperature for several days to form single crystals of the inclusion compound **2**. X-ray data for **2** (sealed with mother liquor in a capillary because of unstable crystals): $C_{24}H_{26}N_2O_4$, FW = 406.48, orthorhombic, $P2_12_12_1$ with a = 15.918(2) Å, b = 23.857(4) Å, c = 5.5073(7) Å, V = 2091.5(5) Å^3, Z =4, D_c = 1.29 gcm^{-3}, temperature of data collection 173K, R = 0.101; Rw = 0.079; 641 unique reflections with I >3.00σ(I). D_m was not available for unstable crystals.

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8 The dipeptide backbones of the parallel mode are aligned with an interchain spacing of 5.51 Å, which corresponds to the c-axis length.[6] The value is larger than the interchain spacings of general parallel β-sheet structures (4.85 Å ideally, 4.90-5.08 Å observed).[1] Actually the N•••O distance from an amide group to the nearest one of the neighboring backbone is 3.91 Å and is outside the typical distances of N•••O (2.6~3.1Å), so hydrogen bonding among amide groups is obviously absent.

9 X-ray data for isostructural compounds will follow in a full paper.

10 A solution of **1** (0.05 mmol) in methanol (0.4 mL)-methallyl alcohol (0.5 mL) was placed in an bottle equipped with a cap. The bottle was left for several days at 15 ℃ to form single crystals of the inclusion compound **3**. X-ray data for **3** (sealed with mother liquor in a capillary because of unstable crystals): $C_{50}H_{60}N_4O_{10}$, FW = 877.04, monoclinic, $P2_1$ with a = 11.377(2) Å, b = 16.079(2) Å, c = 12.892(4) Å, β = 100.00(3)°, V = 2322.4(8) Å^3, Z = 2, D_c = 1.25 gcm^{-3}, temperature of data collection 173 K; R = 0.057; Rw = 0.064; 2063 unique reflections with I >4.00σ(I). D_m was not available for unstable crystals.