Specific Inclusion of 1,2-Dimethoxybenzene Derivatives by Crystalline (*R*)-Arylglycyl-(*R*)-phenylglycines and Its Structure

Motohiro Akazome, Yukiko Yanagita, Ryo-ichi Sonobe, and Katsuyuki Ogura*

Department of Applied Chemistry, Faculty of Engineering, Chiba University, 1-33 Yayoicho, Inageku, Chiba 263

(Received July 7, 1997)

The crystallization of (*R*)-arylglycyl-(*R*)-phenylglycine (**1**, aryl = phenyl; **2**, aryl = 1-naphthyl) in the presence of 1,2-dimethoxybenzene or its derivatives affords an inclusion compound. A single-crystal X-ray analysis has shown that, in a 1,2-dimethyoxybenzene inclusion compound, dipeptide molecules arrange in a sheet and the 1,2-dimethoxybenzene lies at the end in a void between the sheets by being anchored to an ammonio hydrogen on the sheet via three-center hydrogen bonding. The distance between the sheets was found to be variable according to the length of the guest 1,2-dimethoxybenzene derivatives, as if they were pillars that support the sheets.

Although crystal engineering to design and control the crystal packing arrangement has emerged as one of the most active fields in chemistry, no general theory is yet available to systematically predict how a given molecule will pack in the solid state.[1,2] In order to solve this problem, many kinds of organic host molecules that construct a three-dimensional rigid network or two-dimensional framework in a crystal have been designed to include guest molecules.[3,4] However, there are only a few reports on organic host molecules used to form a precise two-dimensional network (sheet structure) followed by the inclusion of a guest molecule.[5] Recently, Ward and his co-workers developed pillared two-dimensional hydrogen-bonded networks comprising guanidinium ions and disulfonate ions, in which the disulfonate ions act as pillars that connect opposing H-bonded sheets with adjustable porosity.[6]

We have also presented a new strategy to construct precise two-dimensional sheet structures from (*R*)-arylglycyl-(*R*)-phenylglycine molecules (**1**, aryl = phenyl; **2**, aryl = 1-naphthyl) (Chart 1). The dipeptide molecule adopts a relatively straight structure because of its central peptide linkage, which scarcely rotates. An intermolecular interaction (salt formation) works between the amino group of each dipeptide molecule and the carboxyl group of other peptide molecule to form a one-dimensional ribbon structure. When the ribbon structures are combined through hydrogen-bonding, a two-dimensional sheet is constructed. In the case of peptides **1** and **2**, phenyl and naphthyl groups are placed perpendicular to the sheet to form a cavity that can include an appropriate guest molecule. We have already reported on an efficient inclusion of some guest molecules by crystalline **1** or **2** in the cavity between the layers.[7,8] Here, we wish to report on the inclusion of 1,2-dimethoxybenzene and its derivatives (guests) between the layers in crystalline **1** and **2**, in which the guest molecules act as pillars to change the layer distance according to their length.

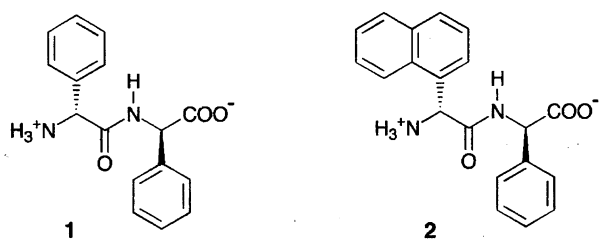


Chart 1.

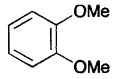
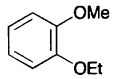
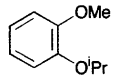
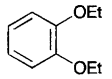
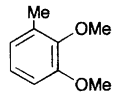
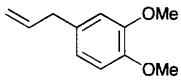
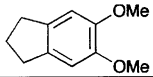
Results and Discussion

After 1,2-dimethoxybenzene was added to a dipeptide solution (see Experimental section), the resulting solution was allowed to stand for a few days to deposit crystals of a 1 : 1 inclusion compound. The present inclusion phenomenon is restrictive to 1,2-dimethoxybenzene derivatives. Thus, 1,3-dimethoxybenzene, 1,4-dimethoxybenzene, and anisole were not included at all. Table 1 summarizes representative results for the inclusion of various 1,2-dialkoxybenzenes by crystalline **1** or **2**.

Fortunately, a single crystal suitable for X-ray analysis was obtained by the crystallization of **2** and 1,2-dimethoxybenzene (Entry 1 in Table 1). An ORTEP drawing of this inclusion compound is shown in Fig. 1. 1,2-Dimethoxybenzene is anchored to an ammonio hydrogen of the dipeptide via three-center hydrogen bonding.[9] The distances of H(4B)···O(6) and H(4B)···O(7) are 2.14 and 2.55 Å, respectively. Noteworthily, two methoxy groups and the benzene ring lie almost on the same plane: The torsion angles of the C(22)–O(6)–benzene ring and the C(25)–O(7)–benzene ring are 1.59° and 1.43°, respectively.

Packing views of the crystal structure are illustrated in Figs. 2 and 3. As can be seen, the inclusion compounds have a layer structure, where the dipeptide molecules are arranged so as to adopt a parallel β-sheet-like structure. This is similar

Table 1. Inclusion of 1,2-Dialkoxybenzenes by Crystallization of Dipeptides[a)]

Entry	Guest	1		2	
		Efficiency[b)]/%	L. D.[c)]/Å	Efficiency[b)]/%	L. D.[c)]/Å
1		98	13.5	100	13.7
2		83	13.4	78	13.8
3		42	13.4	N. I.[d)]	—
4		N. I.[d)]	—	N. I.[d)]	—
5		N. I.[d)]	—	N. I.[d)]	—
6		94	15.2	90	15.2
7		78	15.7	88	15.0

a) Crystallization from a solution containing **1** (or **2**) and the guest in the ratio of 1 : 2. b) Efficiency means mol% of the included guest based on the dipeptide in the inclusion compound. Determined by ^{1}H NMR. c) L. D. means the layer distance measured by PXRD. d) N. I. means no formation of the inclusion compound.

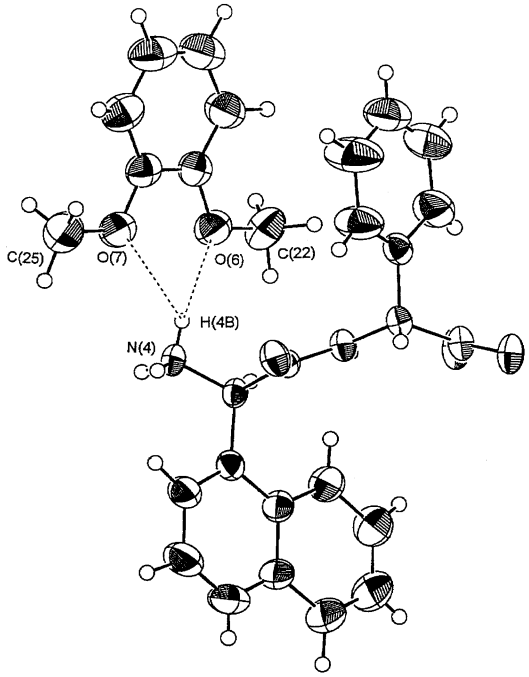


Fig. 1. ORTEP drawing of the inclusion compound of **2** and 1,2-dimethoxybenzene.

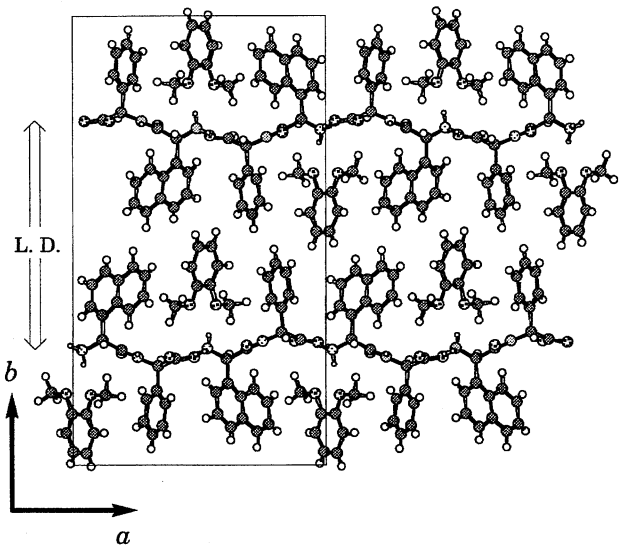


Fig. 2. Layer structure of the inclusion compound of **2** and 1,2-dimethoxybenzene (*a*–*b* plane). L. D. means the layer distance. An unit cell is shown using a box.

to that observed in the inclusion compound of **2** and THF.[8)] The layer distance is 13.7 Å (the half length of *b* axis). The sheet is constructed by ionic pairing of carboxyl and amino groups via a hydrogen bonding network: one terminal COO^- bridges two $^+NH_3$ of adjacent dipeptides and the $^+NH_3$ also

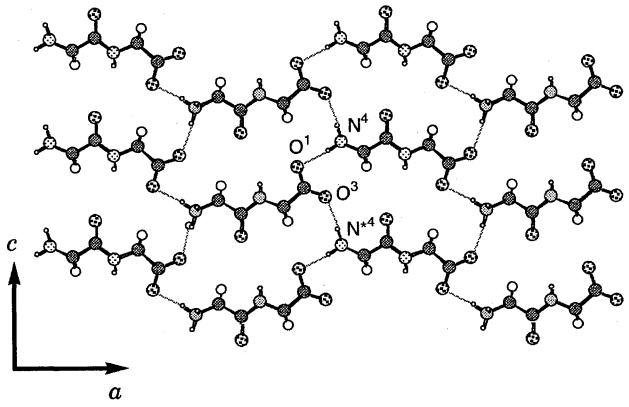


Fig. 3. Sheet structure of dipeptide backbone of the inclusion compound of **2** and 1,2-dimethoxybenzene (*a*–*c* plane). The naphthyl and phenyl groups of **2** and 1,2-dimethoxybenzene are omitted.

bound two adjacent COO^- groups ($O^1\cdots N^4$ bond distance; 2.73 Å and $O^3\cdots N^{*4}$ bond distance; 2.80 Å).

Powder X-ray diffraction analysis (PXRD) was performed on the single crystals at room temperature between 2° and 50° in the $2\theta/\theta$-scan mode. As shown in Fig. 4, a strong diffraction peak at a lower angle (13.7 Å) can be observed. This corresponds to the (020) plane, which is the layer distance (see Fig. 2). Hence, this fact encouraged us to use the PXRD technique in order to measure the layer distance for a series of the present inclusion compounds (Table 1; L.D./Å).

The CPK model of Fig. 5 indicated that the neighboring naphthyl and phenyl rings stacked one another with the aid of an edge-to-face interaction to form a wall.[10] Regarding the host–guest interaction, the benzene ring of the guest molecule is effectively stacked between the wall of the naphthyl and the phenyl groups of **2** in addition to three-center hydrogen bonding.

The CPK model consideration also implies that the channel cavity of **1** is wider than that of **2**.[7b] The channel cavity of **2** expands at one side upon replacing the naphthyl group by a phenyl group so as to include a larger guest molecule. In fact, **1** formed more easily an inclusion compound with 1-ethoxy-2-methoxybenzene and 1-isopropoxy-2-methoxybenzene than did **2** (Entries 1—3 in Table 1). Since another

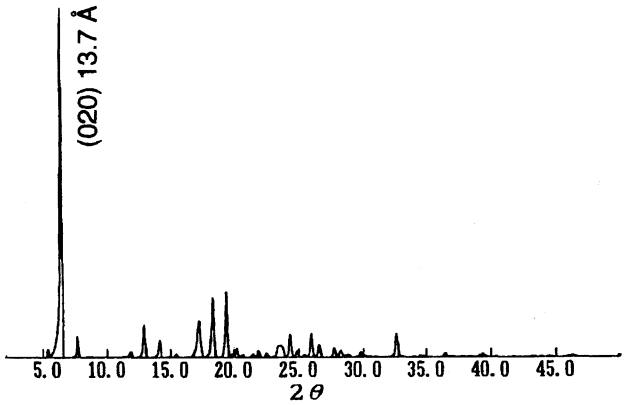


Fig. 4. Powder X-ray diffraction pattern for the inclusion compound of **2** and 1,2-dimethoxybenzene.

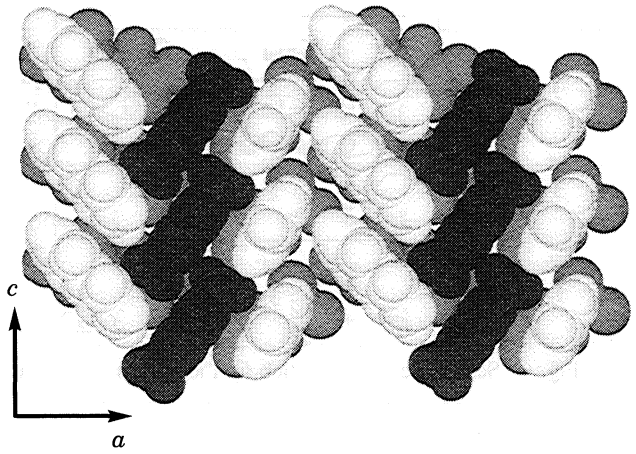


Fig. 5. CPK model of packing in the inclusion compound of **2** and 1,2-dimethoxybenzene (*a*–*c* plane). The naphthyl and phenyl groups of **2** and 1,2-dimethoxybenzene are colored white and black, respectively.

side of the cavity always terminates at the phenyl group, no inclusion of 1,2-diethoxybenzene by both **1** and **2** can be reasonably rationalized (Entry 4).

No inclusion was observed in the case of 1,2-dimethoxy-3-methylbenzene (Entry 5). This is probably due to the steric hindrance of the 3-methyl group, which repels the 2-methoxy group to adopt a conformation that disadvantages the three-center hydrogen bonding. Entries 6 and 7 of Table 1 show that the substituents at the 4- and/or 5-positions of 1,2-dimethoxybenzene did not hinder the inclusion. Indeed, 4-allyl-1,2-dimethoxybenzene and 5,6-dimethoxyindan afforded the corresponding inclusion compounds with high efficiency. It is noteworthy that the layer distances became larger in these inclusion compounds, which shows a sharp PXRD peak at 15.2 and 15.0 Å, respectively. As we have already reported, the layer distance of the THF-inclusion compound of **2** was 12.1 Å.[8,11] This value (12.1 Å) is likely to correspond to the distance between the peptide layers when the length of the guest molecule is shorter than the height of the 1-naphthyl (phenyl) groups.[12] Hence, the present results suggest that the guest molecules behave as pillars supporting the dipeptide layers and that the 4-allyl-1,2-dimethoxybenzene or 5,6-dimethoxyindan molecules lift up the layers by ca. 3 Å, as schematically illustrated in Fig. 6.

In conclusion, (*R*)-arylglycyl-(*R*)-phenylglycines (aryl = phenyl and 1-naphthyl) forms a layer structure via intermolecular salt formation and aryl-phenyl stacking, and 1,2-dimethoxybenzenes (guests) are included in the void between the layers. *The layer distance of the inclusion compounds of dipeptide is changeable and is adjustable, depending on the size of the guest.* The primary driving force for the inclusion is three-center hydrogen bonding among an ammonio hydrogen and two methoxy groups; and also, the benzene ring contributes to the location of the methoxy groups at appropriate positions. A 1,2-dimethoxybenzene skeleton is often found in biologically active alkaloids[13] and artificial host compounds, such as cyclotriveratrylenes and

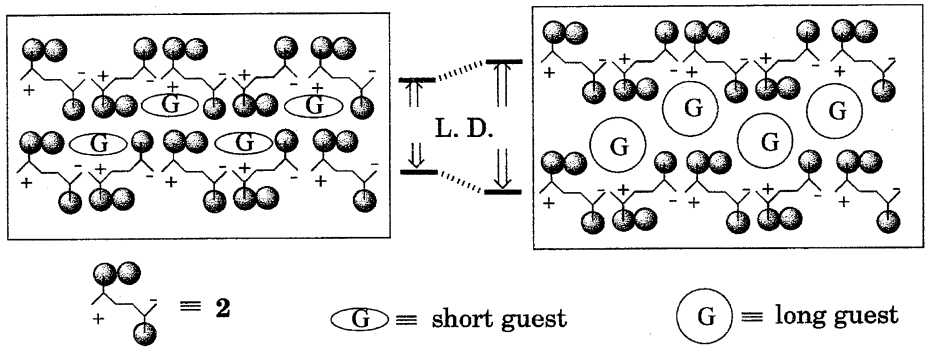


Fig. 6. Schematic representation for the expansion of layer structures depending on the length of guest molecules as pillars.

cryptophanes.[14] Therefore, the present elucidation of the nature of 1,2-dimethoxybenzene skeleton in molecular recognition seems to provide a clue to the useful design of new receptor molecules.

Experimental

General. ^{1}H NMR spectra were recorded on a JEOL JNM FX-270 or a JEOL GSX-400 spectrometer. The infrared spectra were recorded on a JASCO Herschel FT/IR-350. The melting points were measured on a hot-stage microscope apparatus (Yanagimoto) and are uncorrected. (*R*)-Phenylglycine (99% ee) was purchased from Tokyo Kasei Kogyo. (*R*)-(1-Naphthyl)glycine was prepared according to our previous literature.[15]

Synthesis of (*R*)-Phenylglycyl-(*R*)-phenylglycine (1). The preparation and spectral data were reported in our previous paper.[16]

Synthesis of (*R*)-(1-Naphthyl)glycyl-(*R*)-phenylglycine (2). (*R*)-(1-Naphthyl)glycine and (*R*)-phenylglycine were protected with CbzCl (benzyloxycarbonyl chloride) and benzyl alcohol, respectively. These protected amino acids were coupled with DCC (dicyclohexylcarbodiimide) and 1-BtOH (1-hydroxybenztriazole) to form the corresponding protected dipeptide. Final deprotection was performed by hydrogenation with Pd black under a hydrogen atmosphere to obtain **2**. All steps proceeded in excellent yields.

2: Colorless powder (amorphous); mp 140—147 °C (sintering); $[\alpha]_D^{25} = -162.0°$ (*c* 1.01, methanol); IR (KBr) 3400, 3061, 2961, 2925, 1671, 1656, 1623, 1604, 1564, 1546, 1512, 1375, 1260, 1096, 1027, 800, 780, 735, 698 cm^{-1}. ^{1}H NMR (D_2O, 270 MHz) δ=8.17—8.09 (m, 3H, Ar*H*), 7.80—7.64 (m, 4H, Ar*H*), 7.41—7.38 (d like, 5H, Ar*H*), 6.00 (s, 1H, H_2NCHCO), 5.19 (s, 1H, CONHC*H*). Found: C, 71.90; H, 5.57; N, 8.18%. Calcd for $C_{20}H_{18}N_2O_3$: C, 71.84; H, 5.42; N. 8.37%.

General Procedure of Inclusion. In Case of 1. Since **1** is essentially insoluble in methanol and water, we obtained an aqueous solution of **1** by carefully adjusting the pH. Thus, **1** was dissolved in 0.1 M HCl aq (1 M = 1 mol dm^{-3}) and then the pH was adjusted to about 6.5 by the addition of 0.1 M NaOH aq. After the addition of a guest compound (2 molar equiv) to the aqueous solution of **1**, the resulting mixture was allowed to stand at ambient temperature for several days. The deposited inclusion compound was collected by filtration and washed with water and CH_2Cl_2. After decomposition of the inclusion compound with a dilute solution of DCl in D_2O, the inclusion efficiency was determined by a NMR measurement.

In Case of 2. A methanolic solution of **2** is utilized because it slightly soluble in methanol. After the addition of a guest compound (2 molar equiv) to the methanolic solution of **2**, the resulting mixture was allowed to stand at ambient temperature for several days. The deposited inclusion compound was collected by filtration and washed with water and CH_2Cl_2. After decomposition of the inclusion compound with D_2O and/or d_4-methanol, the inclusion efficiency was determined by a NMR measurement.

Powder X-Ray Diffraction. All powder spectra were taken on a MAC Science MXP powder diffractometer using graphite-monochromated Cu $K\alpha$ radiation (40 kV, 300 mA). The spectra were measured at room temperature at between 2° and 50° in the $2\theta/\theta$-scan mode with steps of 0.01° in 2θ and 4° min^{-1}.

X-Ray Crystallography. A solution of **2** in methanol containing a small amount of water was prepared. The guest was directly added in a bottle equipped with a cap, and evaporation of the solution was controlled with the cap. The sample was allowed to stand for several days to form the desirable single crystals. Data collection was performed on a Mac Science MXC18 four-circle diffractometer with monochromated Cu $K\alpha$ (λ = 1.54178 Å) radiation using the 2θ–ω scan technique, and the X-ray intensities were measured up to 2θ = 140° at 298 K, respectively. Three standard reflections were monitored every 100 reflections; there were no significant variations in intensities.

Crystal Data for the Inclusion Compound of 2 and 1,2-Dimethoxybenzene: $C_{20}H_{18}N_2O_3 + C_8H_{10}O_2$, M = 472.50, orthorhombic ($P2_12_12_1$), a = 15.568(3), b = 27.485(5), c = 5.566(1) Å, V = 2381.8(8) Å^3, Z = 4, D_c 1.32 g cm^{-3}; crystal dimensions: 0.30×0.20×0.20 mm; 2634 reflections measured. 2184 used. The structure were solved by a direct method with SIR 92,[17] and refined by the full-matrix least-squares method using the Crystan GM program package (Mac Science). All of the none-hydrogen atoms were refined anisotropically. Hydrogens were localized from a deference Fourier synthesis and refined isotropically. R=0.0457; R_w=0.0454.

Tables of the coordinates, thermal parameters, bond lengths, and angles for the inclusion compound have been deposited as Document No. 70045 at the Office of the Editor of Bull. Chem. Soc. Jpn.

This work was supported by a Grant-in Aid for Scientific Research No. 07405041 from the Ministry of Education, Science, Sports and Culture and "Research for the Future" Program (JSPS-RFTF96P00304) from The Japan Society for the Promotion of Science.

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11) The inclusion compound of **2** and THF has been already reported in our previous paper.[8] Further details of the crystal structure investigation are available from the Cambridge Crystallographic Data Centre. Cambridge Crystallographic Data Centre, 12 Union Road, Cambride CB 1 EZ, UK.

12) The diethyl ether-included compound of **2** was also shown to adopt the similar structure, the layer distance of which was 12.1 Å.

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