JOC Article

Sheet Structure of an L,D-Dipeptide Aggregate: Inclusion Compounds of (*S*)-Phenylglycyl-(*R*)-phenylglycine with Amides

Motohiro Akazome, Kyoko Senda, and Katsuyuki Ogura*

Department of Materials Technology, Faculty of Engineering, Chiba University, 1-33 Yayoicho, Inageku, Chiba 263-8522, Japan

katsu@galaxy.tc.chiba-u.ac.jp

Received July 2, 2002

A simple dipeptide, (*S*)-phenylglycyl-(*R*)-phenylglycine (*S*,*R*-**1**), formed inclusion compounds with a small amide such as formamide, acetamide, *N*,*N*-dimethylformamide (DMF), or *N*,*N*-dimethylacetamide. By single-crystal X-ray analysis, the inclusion compounds were shown to have a wavy layer structure. The molecules of *S*,*R*-**1** are arranged in parallel via ionic pairing of the carboxyl and amino groups to construct the wavy layers. The guest molecules were accommodated in a channel cavity between the layers by means of hydrogen bonding with $^{+}NH_3$ of *S*,*R*-**1**. The cavity is surrounded by the phenyl groups of *S*,*R*-**1** that conformationally rotate so as to make the cavity size fit the guest amide.

Introduction

In recent years, peptides, oligopeptides, and polypeptides with a regular sequence of enantiomeric residues (L and D) along the chain have received considerable attention because their conformational behavior somehow differs from that of homoconfigurational peptides or polypeptides. Most interestingly, they form intriguing structures[1] such as double-stranded helices[2] and nanotubes.[3] The structures of these peptides seem to come from the favorable conformation of the D,L-dipeptide unit that is different from that of L,L-dipeptides.

Hitherto we have reported that simple homoconfigurational D,D-dipeptide, (*R*)-phenylglycyl-(*R*)-phenylglycine [*R*,*R*-**1**], and its naphthyl analogue construct a layered structure, and guest molecules are included between the layers as illustratively depicted in Figure 1a.[4,5] In all of the crystals investigated, the dipeptide backbone adopts a linear extended conformation. This is in accordance with the observation that homoconfigurational dipeptides favor an extended conformation in solution.[6] Since the L,D-dipeptides are shown to adopt a more compact, intramolecularly hydrogen-bonded structure in water,[6] we were interested to see whether a diastereomer of *R*,*R*-**1**, namely (*S*)-phenylglycyl-(*R*)-phenylglycine (*S*,*R*-**1**), can form an inclusion compound with an appropriate guest and, if so, what conformation *S*,*R*-**1** adopts in the inclusion crystals. Molecular orbital calculation with a PM3 method suggested that the most stable conformation of *S*,*R*-**1** is an extended one (**A** in Figure 1b).[7] In this conformation, two phenyl groups face one another. When a zwitterion form is considered for *S*,*R*-**1**, a cyclic form (**B**) is more stable than an expanded form (**C**). Here, we wish to report that *S*,*R*-**1** forms an inclusion compound with an appropriate amide that is accommodated in the cavity between the layers of *S*,*R*-**1**.

Results and Discussion

Inclusion of Amides. Quite different from *R*,*R*-**1**, which easily forms crystals, *S*,*R*-**1** is poor in crystallinity. Actually, *S*,*R*-**1** is more soluble in methanol (up to 23.4 mM) than *R*,*R*-**1** (4.6 mM). This seems to result from their conformational difference based on the stereochemistry of the dipeptides. During our examination of the solubility of *S*,*R*-**1** in various solvents, it was found that, when *S*,*R*-**1** was dissolved in DMF, an inclusion compound of DMF was formed. This finding encouraged us to investigate the formation of inclusion compounds of *S*,*R*-**1** with amides.

First, we recrystallized *S*,*R*-**1** from methanol involving various amides. Formamide, *N*,*N*-dimethylformamide,

(1) Recent reviews on peptide helices and tubes: (a) Bong, D. T.; Clark, T. D.; Granja, J. R.; Ghadiri, M. R. *Angew. Chem., Int. Ed.* **2001**, *40*, 988. (b) Karle, I. L. *Acc. Chem. Res.* **1999**, *32*, 693.

(2) (a) Di Blasio, B.; Benedetti, E.; Pavone, V.; Pedone, C.; Spiniello, O.; Lorenzi, G. P. *Biopolymers* **1989**, *28*, 193−201. (b) Di Blasio, B.; Benedetti, E.: Pavone, V.; Pedone, C.; Gerber, C.; Lorenzi, G. P. *Biopolymers* **1989**, *28*, 203. (c) Benedetti, E.; Di Blasio, B.; Pedone, C.; Spiniello, O.; Lorenzi, G. P.; Tomasic, L.; Gramlich, V. A. *Nature* **1979**, *282*, 630.

(3) (a) Hartgerink, J. D.; Granja, J. R.; Milligan, R. A.; Ghadiri, M. R. *J. Am. Chem. Soc.* **1996**, *118*, 43. (b) Ghadiri, M. R.; Granja, J. R.; Milligan, R. A.; McRee, D. E.; Khazanovich, N. *Nature* **1993**, *366*, 324. (c) Pavone, V.; Benedetti, E.; Di Blasio, B.; Lombardi, A.; Pedone, C.; Tomasic, L.; Lorenzi, G. P *Biopolymers* **1989**, *28*, 215.

(4) (a) Akazome, M.; Ueno, Y.; Ooiso, H.; Ogura, K. *J. Org. Chem.* **2000**, *65*, 68. (b) Akazome, M.; Noguchi, M.; Tanaka, O.; Sumikawa, A.; Uchida, T. Ogura, K. *Tetrahedron* **1997**, *53*, 8315. (c) Ogura, K.; Uchida, T.; Noguchi, M.; Murata, A.; Fujita, M.; Ogata, K. *Tetrahedron Lett.* **1990**, *31*, 3331.

(5) (a) Akazome, M.; Takahashi, T.; Sonobe, R.; Ogura, K. *Supramol. Chem.* **2001**, *13*, 109. (b) Akazome, M.; Takahashi, T.; Ogura, K. *J. Org. Chem.* **1999**, *64*, 2293. (c) Akazome, M.; Yanagita, Y.; Sonobe, R.; Ogura, K. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 2823. (d) Akazome, M.; Sumikawa, A.; Sonobe, R.; Ogure, K. *Chem. Lett.* **1996**, 995.

(6) Barrett, G. C. In *Comprehensive Organic Chemistry*; Barton, S. D., Ollis, W. D., Eds.; Pergamon Press: Oxford, 1979; Vol. 5, p 367.

(7) With MOPAC (Ver. 6): Stewart, J. J. P. *QCPE Bull.* **1989**, *10*, 209−220 and 221−264.

10.1021/jo0204451 CCC: $22.00
Published on Web 11/09/2002

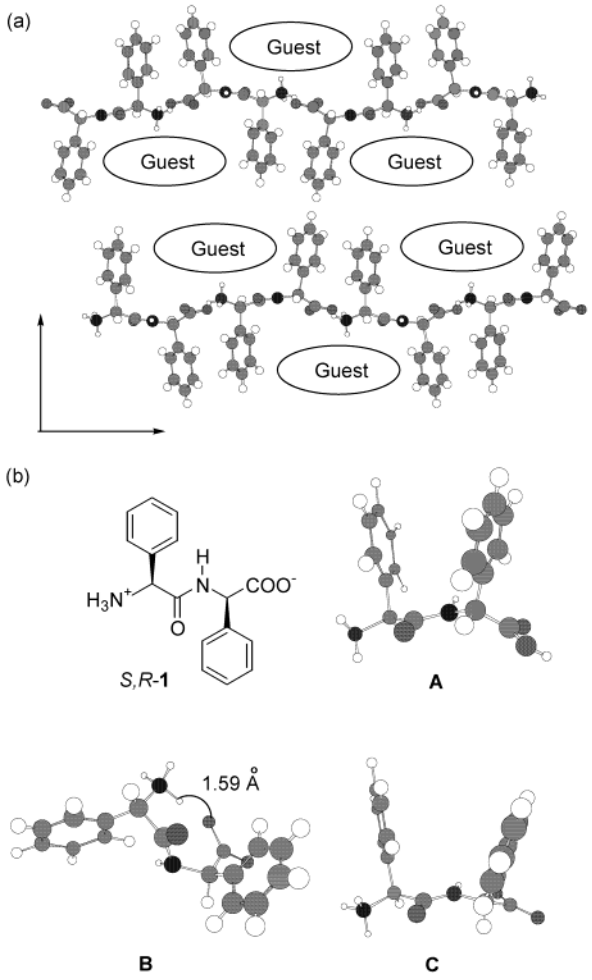


FIGURE 1. (a) Inclusion compounds of (*R*)-phenylglycyl-(*R*)-phenylglycine (*R*,*R*-**1**) with guests. (b) The most stable conformation of *S*,*R*-**1** calculated by the PM3 method: neutral one (A), cyclic zwitterion (B), expanded zwitterion (C) (relative energy to B, +17.4 kcal mol^{-1}).

TABLE 1. Inclusion of Amides with *S*,*R*-1

entry	amide	bp/°C[a]	host: guest[b]	dissoc/°C[c]	host dec/°C[d]	LD/Å[e]
1	H_2NCHO, **2**	210.5	1:1	155	193	10.9
2	Me_2NCHO, **3**	153	1:1	148	201	10.9
3	H_2NCOMe, **4**	222	1:1	161	204	10.9
4	Me_2NCOMe, **5**	163−165	1:1	133	197	11.0

[a] Reference 8. [b] Determined by TG and NMR. [c] "Dissoc" means dissociation temperature of the guest measured by TG-DTA. [d] "Host dec" means decomposition temperature of the host measured by TG-DTA. [e] LD is a layer distance measured by PXRD.

acetamide, and *N*,*N*-dimethylacetamide formed the expected 1:1 inclusion compounds with *S*,*R*-**1** (Table 1), but monoalkylamides such as *N*-methylacetamide and 2-pyridone were not included in crystals of *S*,*R*-**1**. The host: guest ratio of the inclusion compound was determined by ^1H NMR and TG-DTA, and the results are summarized in Table 1. TG-DTA curves showed that the volatile guests were removed from an inclusion cavity below their own boiling point.[8] This suggests that guest

(8) *Boiling points cited from Merck Index,* 13th ed.; Merck & Co., Inc.: Rahway, NJ, 2001.

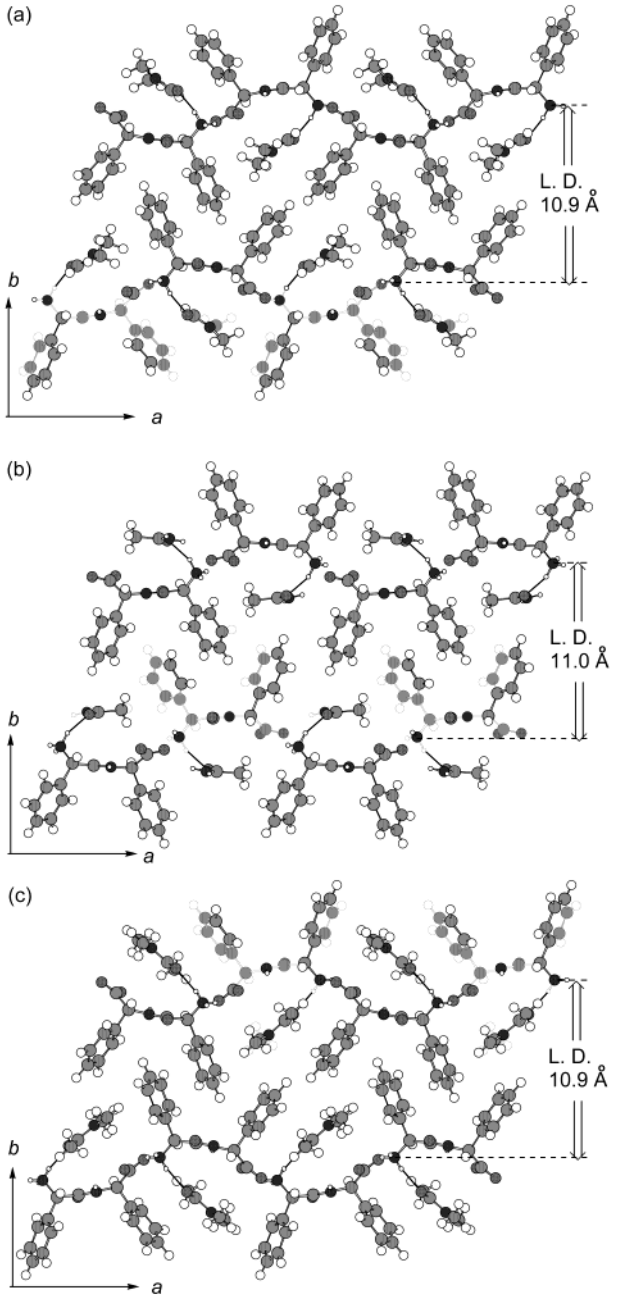
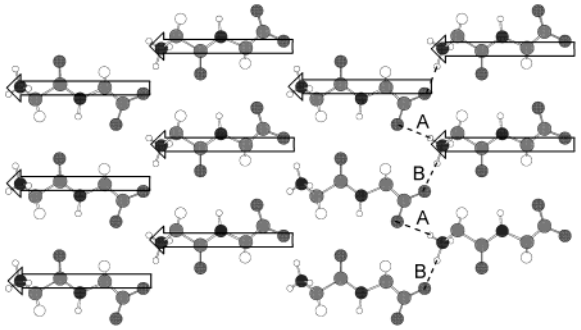


FIGURE 2. Layer structure of the inclusion compounds of *S*,*R*-**1** (the *a*−*b* plane): (a) with DMF, (b) with acetamide, (c) with *N*,*N*-dimethylacetamide.

molecules interact to a lesser extent intermolecularly in the cavities. After the guest was released, the remained apohost *S*,*R*-**1** decomposed around 200 °C to give a diketopiperazine by dehydration. Powder X-ray diffraction (PXRD) analysis revealed that these inclusion compounds have a strong diffraction peak at lower 2θ range (at 10.9−11.0 Å). These peaks correspond to the distance between the (020) planes (see Figure 2).

Crystal Structures of Inclusion Compounds. Three inclusion compounds (**3**, **4**, and **5** in Table 1) were obtained as single crystals suitable for X-ray analysis. All of the three inclusion crystals have a space group $P2_12_12_1$ and similar wavy sheet structure (Figure 2). The wavy sheet reflects the feature of *S*,*R*-**1**: Two phenyl



	A N---O	B N---O	H-G N---O
Me_2NCHO **3**	2.71	2.80	2.75
H_2NCOMe **4**	2.78	2.75	2.77
Me_2NCOMe **5**	2.76	2.84	2.71

FIGURE 3. Arrangement of *S*,*R*-**1** and atomic distances of hydrogen bonding.

groups of *S*,*R*-**1** are repulsive intramolecularly in its extended conformation, but they undergo an aromatic−aromatic interaction intermolecularly, especially between the layers. Not only supramolecular aggregates[9] but also natural proteins[10] utilize these aromatic−aromatic interactions. The small amide guests are accommodated via hydrogen bonding in the cavity between the layers.[11] The hydrogen-bonding distances of the inclusion compounds are summarized in Figure 3. The dipeptide backbones are arranged into a parallel motif to construct a sheet by ionic pairing of the carboxyl and amino groups via a hydrogen-bonding network: one terminal COO^- bridges two $^+NH_3$ of adjacent dipeptides and the $^+NH_3$ also binds two adjacent COO^- groups. This hydrogen-bonding motif of *S*,*R*-**1** is similar to that shown in the inclusion compound of *R*,*R*-**1** with sulfoxides[4] or ethers,[5c] where the guests also acted as a hydrogen acceptor for the ammonio hydrogen of *R*,*R*-**1**. Since the flat amides (**3**, **4**, and **5**) fall against the dipeptide backbone sheet, all of the inclusion compounds have the same layer distances (10.9−11.0 Å) along the *b* axis.

In Figure 4, the sheet structures using a CPK model as well as the lengths of *a* and *c* axes are depicted.[12] The

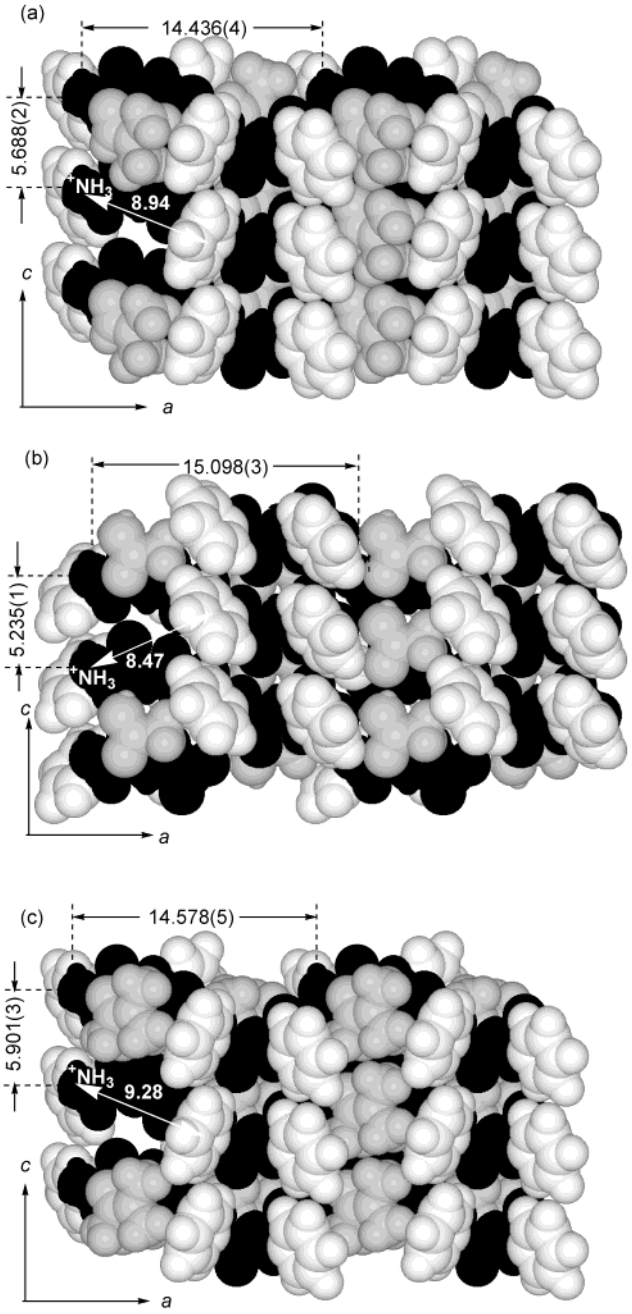


FIGURE 4. CPK model of recognition site of *S*,*R*-**1** (the *a*−*c* plane) showing the lengths (Å) of the *a* and *c* axes and the distances (Å) between the nitrogen of *S*,*R*-**1** and the center of benzene ring: (a) with DMF, (b) with acetamide, (c) with *N*,*N*-dimethylacetamide.

unit cell of the inclusion crystal expands along the *c* axis with the larger size of the guest. Hence, it is apparent that *N*,*N*-diethylformamide, acetylpyrrolidine, propionamide, isobutyramide, and benzamide are too large to be accommodated in the cavity. Thus, the size of amide guests is limited to the repetitious unit of the dipeptide framework in the inclusion crystal. To our surprise, a conformational change of the phenyl group of *S*,*R*-**1** was observed according to the size of the guest molecule. White arrows in Figure 4 show the distances between the nitrogen of $^+NH_3$ and the center of the phenyl ring of *S*,*R*-**1**, which are the critical value of the cavity to

(9) (a) Swift, J. A.; Pal, R.; McBride, J. M. *J. Am. Chem. Soc.* **1998**, *120*, 96. (b) Lewis, F. D.; Yang, J.-S.; Stern, C. L. *J. Am. Chem. Soc.* **1996**, *118*, 12029. (c) Hunter, C. A.; Sanders, J. K. M. *J. Am. Chem. Soc.* **1990**, *112*, 5525. (d) Dejuraju, G. R.; Gavezzotti, A. *J. Chem. Soc., Chem. Commun.* **1989**, 621.

(10) In proteins, $\pi-\pi$ interactions on their side chains have already been investigated to reveal the edge-to-face interaction between benzene rings to be important: (a) Burley, S. K.; Petsko, G. A. *Science* **1985**, *229*, 23. (b) Gould, R. O.; Gray, A. M.; Taylor, P.; Walkinshaw, M. D. *J. Am. Chem. Soc.* **1985**, *107*, 5921. (c) Burley, S. K.; Petsko, G. A. *J. Am. Chem. Soc.* **1986**, *108*, 7995.

(11) IR spectra also suggested hydrogen bonding between the host and the guest. The amide I bands of DMF and formamide were shifted toward lower frequencies by 16 and 21 cm^{-1}, respectively, when these amides were included by hydrogen bonding. However, acetamimde and *N*,*N*-dimethylacetamide are ambiguous because *S*,*R*-**1** also has amide as the same functional group.

(12) Since the structural analysis of inclusion compound of DMF was preformed at 173 K, the lengths of the *a* and *c* axes are slightly short. At 298 K, the unit cell was measured: $a = 14.483(5)$ Å, $b = 22.049(5)$ Å, $c = 5.720(2)$ Å, $V = 1826.7(9)$ Å^3.

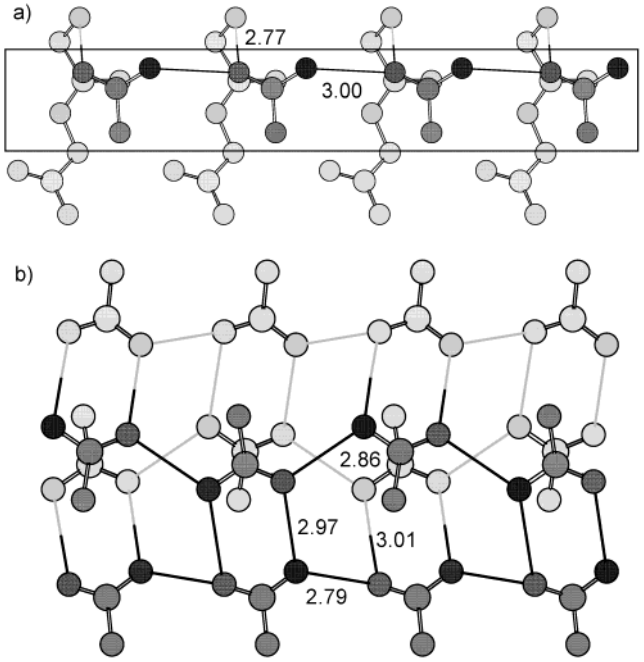


FIGURE 5. (a) Hydrogen bonding (Å) of acetamide (colored black) in the inclusion compounds. (b) Hydrogen bonding (Å) of acetamide crystals (ref 13).

contain the guest amide. In the case of acetamide, the distance (8.47 Å) is shorter than those of the inclusion compounds of DMF (8.94 Å) and *N*,*N*-dimethylacetamide (9.28 Å). Interestingly, the conformational change of the phenyl groups in the sidewall of the cavity happened to make the cavity space fit the small guest. In other words, the flipping of the benzene rings in the cavity induces favorable interactions of the guest with the phenyl groups of *S*,*R*-**1**. We have already reported a similar phenomenon in the inclusion of crystalline *R*,*R*-**1**, where the phenyl group rotates conformationally to accommodate various guests.[4a,b]

As shown in Figure 5a, the acetamide molecules in the inclusion compound are bonded not only to the hosts but also to the adjacent acetamide molecules. The guest molecules have infinite hydrogen bonding with each other to form a linear aggregate. This hydrogen-bonding pattern is also observed in acetamide crystals, as shown in Figure 5b. Acetamide molecules aggregate in a crystalline state to make cyclic dimers, and the dimers construct a three-dimensional network by hydrogen bonding.[13] Only one of these hydrogen-bonding patterns remains in the inclusion compound of *S*,*R*-**1** and acetamide. This seems to be the reason the inclusion crystals of acetamide have a rather high temperature of guest release (Table 1).

Conclusion

It was found that *S*,*R*-**1** aggregates together with a small amide such as formamide, DMF, or *N*,*N*-dimethylacetamide to form an inclusion compound. By single-crystal X-ray crystallography, the inclusion compound was shown to have a wavy layer structure and the amide guest is accommodated in the cavity between the layers. The phenyl groups of *S*,*R*-**1** stand perpendicular to the layer to form the wall of the cavity and change their conformation so as to make the cavity size fit the amide guest.

Experimental Section

General. Melting points (dec) are measured on a TG-DTA. NMR spectra were recorded at 300 MHz for ^{1}H NMR. Elemental analyses were performed at the Chemical Analysis Center, Chiba University, Japan. Both of (*S*)- and (*R*)-phenylglycine (99% ee) were purchased from Tokyo Chemical Industry.

X-ray Analyses. X-ray powder diffractions were obtained with a MAC Science MXP diffractometer using graphite-monochromated Cu *K*α radiation (40 kV, 300 mA). The spectra were measured at room temperature between 2° and 50° in the 2θ scan mode with steps of 0.01° in 2θ and 4°/min.

Crystallograpic Data for the Inclusion Compounds. To the solution of *S*,*R*-**1** was added a methanol solution of the guest directly, then the lid of the vial was loosely closed for evaporation of the solvent. The samples were allowed to stand for several days to form the desirable single crystals. Data collection was performed on a Mac Science MXC18 four-circle diffractmetor with graphite-monochromated Cu Kα (λ = 1.54178) radiation using the 2θ−ω scan technique, and the X-ray intensities were measured up to 2θ = 140°. The structures were solved by a direct method SIR-92[17] and refined by a computer program package, maXus ver. 1.1, from MAC Science Co. Ltd. Hydrogen atoms are calculated in the appropriate position.

Synthesis of (*S*)-Phenylglycyl-(*R*)-phenylglycine (*S*,*R*-1). According to the same method to prepare *R*,*R*-**1**,[4a] dipeptide *S*,*R*-**1** was also prepared. According to the DCC−HOBt method,[14] coupling between (*S*)-*N*-(benzyloxycarbonyl)phenylglycine[15] and (*R*)-phenylglycine benzyl ester *p*-toluenesulfonate[16] provided the protected dipeptide. The deprotection by hydrogenolysis proceeded in the presence of Pd black to afford *S*,*R*-**1**. *S*,*R*-**1** is amorphous, easily hydrated to give monohydrate, and has a better solubility in methanol (23.4 mM) than *R*,*R*-**1** (4.6 mM): white powder; mp (dec) 177 °C; $[\alpha]^{25}_{D} = -19.6$ (c = 0.94, MeOH); ^{1}H NMR (300 MHz, D_2O + DCl) 7.37 (m, 10H), 5.60 (s, 1H), 5.29 (s,1H); IR (KBr) 3379, 1685, 1589 cm^{-1}. Anal. Calcd for $C_{16}H_{16}N_2O_3 \cdot 0.80H_2O$: C, 64.33; H, 5.94, N, 9.38. Found C, 64.49; H, 5.85, N, 9.40.

Preparation of Inclusion Compound. *S*,*R*-**1** (28.4 mg, 0.10 mmol) was dissolved in MeOH (8 mL). After addition of amide (2.5−5.0 mmol), the solution stood for 3 days. Deposited crystals were collected and washed with chloroform (5 mL).

The inclusion compound of formamide (2): mp (dec) 155 °C; IR (KBr) 3321, 1664, 1577 cm^{-1}; powder X-ray diffraction [Å (I/I_o)] 10.9 (1.00), 7.47 (0.11), 5.20 (0.23), 4.52 (0.34), 3.79 (0.72).

The inclusion compound of DMF (3): mp (dec) 148 °C; IR (KBr) 3356, 1656, 1586 cm^{-1}; powder X-ray diffraction [Å (I/I_o)] 10.9 (1.00), 5.13 (0.29), 4.41 (0.26), 3.75 (0.72), 3.26 (0.22); $C_{19}H_{23}N_3O_4$, M = 357.40, crystal dimensions 0.30 × 0.20 × 0.15 mm, orthorhombic, $P2_12_12_1$, T = 173 K, a = 14.436(4) Å, b = 21.818(6) Å, c = 5.688(2) Å, V = 1791.6(9) Å^3, Z = 4, η_{calcd} = 1.325 g cm^{-3}, 2066 reflections measured, 1690 independent, R = 0.032, (1645 reflections with $I > 1.00\sigma(I)$), Rw = 0.033, 326 parameters, with heavy atoms refined anisotropically, residual electron density 0.38/−0.15. The unit cell at 298 K

(13) Hamilton, W. C. *Acta Crystallogr.* **1965**, *18*, 866−870.

(14) König, W.; Geiger, R. *Chem. Ber.* **1970**, *103*, 788.

(15) Doyle, F. P.; Fosker, G. R.; Nayler, J. H.; Smith, H. *J. Chem. Soc.* **1962**, 1440.

(16) Zervas, L.; Winitz, M.; Greenstein, J. P. *J. Org. Chem.* **1957**, *22*, 1515.

(17) Altomare, A.; Cascarano, G.; Giacovazzo, C.; Guagliardi, A.; Burla, M. C.; Polidori, G.; Camalli, M. *J. Appl. Crysatllogr.* **1994**, *27*, 435.

was determined: $a = 14.483(5)$ Å, $b = 22.049(5)$ Å, $c = 5.720(2)$ Å, $V = 1826.7(9)$ Å^3.

The inclusion compound of acetamide (4): mp (dec) 161 °C; IR (KBr) 3420, 3341, 1655, 1628, 1577 cm^{-1}; powder X-ray diffraction [Å (I/I_o)] 10.9 (0.59), 8.77 (0.22), 5.20 (0.20), 4.87 (0.38), 4.54 (0.27), 3.79 (1.00); $C_{18}H_{21}N_3O_4$, $M = 343.40$, crystal dimensions 0.35 × 0.10 × 0.05 mm, orthorhombic, $P2_12_12_1$, $T = 298$ K, $a = 15.098(3)$ Å, $b = 21.978(5)$ Å, $c = 5.235(1)$ Å, $V = 1737.2(7)$ Å^3, $Z = 4$, $\eta_{calcd} = 1.313$ g cm^{-3}, 2037 reflections measured, 1658 independent, $R = 0.058$, (1229 reflections with $I > 1.50\sigma(I)$), Rw = 0.055, 277 parameters, with heavy atoms refined anisotropically, residual electron density 0.23/−0.21.

The inclusion compound of *N,N*-dimethylacetamide (5): mp (dec) 133 °C; IR (KBr) 3371, 1684, 1634, 1587 cm^{-1}; powder X-ray diffraction [Å (I/I_o)] 11.0 (1.00), 5.51 (0.06), 5.30 (0.06), 3.27 (0.13); $C_{20}H_{25}N_3O_4$, $M = 371.40$, crystal dimensions 0.45 × 0.15 × 0.15 mm, orthorhombic, $P2_12_12_1$, $T = 298$ K, $a = 14.578(5)$ Å, $b = 22.104(8)$ Å, $c = 5.901(3)$ Å, $V = 1901(1)$ Å^3, $Z = 4$, $\eta_{calcd} = 1.297$ g cm^{-3}, 2194 reflections measured, 1800 independent, $R = 0.038$ (1725 reflections with $I > 1.00\sigma(I)$), Rw = 0.038, 317 parameters, with heavy atoms refined anisotropically, residual electron density 0.14/−0.16.

Supporting Information Available: Tables of atomic coordinates and thermal parameters, bond lengths and angles, and ORTEP views of inclusion compounds of *S,R*-**1** with **3**, **4**, and **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0204451