Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 61 (2005) 1107–1113

Molecular recognition of L-leucyl-L-alanine: enantioselective inclusion of alkyl methyl sulfoxides

Motohiro Akazome,[a,*] Atsushi Hirabayashi,[b] Kousuke Takaoka,[a] Satoru Nomura[a] and Katsuyuki Ogura[a,b,*]

[a]*Department of Materials Technology, Faculty of Engineering, Chiba University, 1-33 Yayoicho, Inageku, Chiba 263-8522, Japan*
[b]*Graduate School of Science and Technology, Chiba University, 1-33 Yayoicho, Inageku, Chiba 263-8522, Japan*

Received 14 October 2004; accepted 19 November 2004

Available online 10 December 2004

Abstract—A simple aliphatic dipeptide, L-leucyl-L-alanine (Leu-Ala), includes several alkyl methyl sulfoxides enantioselectively to form inclusion crystals. From single-crystal X-ray analyses of three inclusion compounds of dimethyl sulfoxide (DMSO), isobutyl methyl sulfoxide, and benzyl methyl sulfoxide, it was elucidated that Leu-Ala molecules self-assemble to form layer structures and the sulfoxides are included via hydrogen bonding in a cavity between these layers. The inclusion cavity has methyl group and isobutyl group at its each side, and the guest sulfoxide is placed in such a manner that its methyl group faces toward the methyl of the Leu-Ala cavity. When the alkyl group of the sulfoxide is comparably large, it is located in the residual space of the cavity to attain effective crystal packing. Thus, the sulfoxides having a comparably large group such as isobutyl, butyl, and benzyl are included with a high (*R*)-enantioselectivity in Leu-Ala crystals.

1. Introduction

The chemistry of inclusion crystals has a long history, and one important aspect of this chemistry is to recognize the chirality of the included guest: for optical resolution of racemic compounds, enantioselective inclusion has emerged in the field of crystal engineering so that many artificial hosts have been developed for molecular recognition of organic guests.[1,2] For example, several chiral hosts were reported for asymmetric sulfoxides that have a chiral center on their sulfur atom. Toda has reported a practical separation of dialkyl sulfoxides using inclusion phenomena with chiral binaphthol[3a,b] or TADDOL derivatives.[3c] These host molecules have widely spread aromatic parts, which act as the walls of the chiral cavities. We have also demonstrated that a simple dipeptide host, (*R*)-phenylglycyl-(*R*)-phenylglycine, effectively forms inclusion crystals with various sulfoxides in a highly enantioselective manner.[4] The sulfoxides were included in the channel between the layers that were constructed by dipeptide backbones. In addition to hydrogen bonding, π–π interactions[5] and CH/π interactions[6] between the sulfoxide and two phenyl groups of the dipeptide play an essential role in recognizing the chirality of the sulfoxide. In a solution phase, chiral discrimination of sulfoxides has been realized by NMR chiral shift reagents such as binaphthol,[7a,b] α-methoxyphenylacetic acid,[7c] (*R*)-(−)-*N*-(3,5-dinitrophenyl)-α-phenylethylamine.[7d] From the facts mentioned above, the presence of benzene rings in the hosts and/or the guest seems to be crucial to the chiral recognition of the sulfoxides. Is this generally valid? With this question in mind, we started our investigation to realize that a host having no benzene ring can recognize the chirality of aliphatic sulfoxides to form an inclusion compound.

First, our attention was focused on the dipeptides that consisted of aliphatic amino acids. This is mainly because their backbones can be considered from our previous literatures[4,8] to construct a layer structure via salt formation and hydrogen bonding between their terminal amino and carboxyl groups. It is also likely that the inclusion cavities are produced by the alkyl side chains of the dipeptide that stand perpendicular to the layer. We synthesized several aliphatic dipeptides such as Leu-Gly, Leu-Ala, Ala-Leu, and Leu-Leu, which were subjected to a preliminary experiment to evaluate their recognition ability toward aliphatic sulfoxides: the solid dipeptides were simply stirred together with typical aliphatic sulfoxides such as methyl propyl sulfoxide and butyl methyl sulfoxide in hexane for 24 h. The formed inclusion compound was collected by filtration and washed with diethyl ether. Except for Leu-Leu, the aliphatic dipeptides examined here gave the expected inclusion

Keywords: Crystal engineering; Inclusion compounds; Peptides; Sulfoxides; Enantiomeric recognition.
* Corresponding authors. Tel.: +81 43 290 3388; fax: +81 43 290 3402; e-mail: katsuyuki@faculty.chiba-u.jp

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.11.058

compound that consists of the dipeptide and the sulfoxide in a ratio of approximatly 1:1. Among them, the inclusion compound of Leu-Ala and butyl methyl sulfoxide showed the highest chiral recognition ability (the enantiomeric excess of the included sulfoxide: 58%. Cf. Leu-Gly/^{n}PrSOMe 32%; Leu-Gly/^{n}BuSOMe 15%; Leu-Ala/^{n}PrSOMe 17%; Ala-Leu/^{n}PrSOMe 10%; Ala-Leu/^{n}BuSOMe 47%). Hence, we selected Leu-Ala as a host aliphatic dipeptide for further detailed investigation. It is noted that the crystal structure of Leu-Ala accompanied with water[9a] or dimethyl sulfoxide (DMSO)[9b] as solvation ligands have been reported from the standpoint of structural interest and conformational information of the dipeptide.

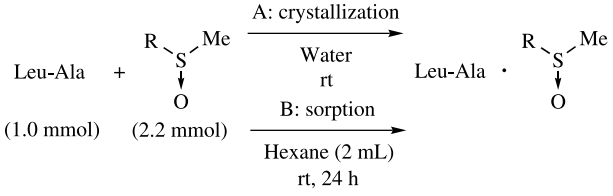
2. Results and discussion

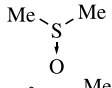
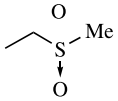
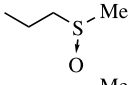
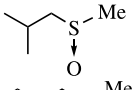
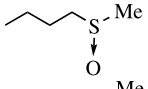
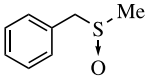
Since the present Leu-Ala shows good solubility in water, an inclusion compound was prepared by two methods: (a) Leu-Ala was crystallized from water in the presence of an alkyl methyl sulfoxide [method A: 'crystallization'] and (b) Leu-Ala and the sulfoxide were simply stirred in hexane for 24 h because Leu-Ala is insoluble in hexane [method B: 'sorption']

The results for enantioselective inclusion of several alkyl methyl sulfoxides are summarized in Table 1. Efficiency (Ef. in Tables 1 and 2) means 'mol percentage' of the guest molecule based on Leu-Ala molecule in the inclusion compound, which was determined by ^{1}H NMR spectra and elemental analyses. Interlayer distances (LD in Table 1) were gained by powder X-ray diffraction (PXRD) of the inclusion compounds, which showed diffraction peaks at lower 2θ range. This assignment of the interlayer distance was confirmed by the single-crystal structure (vide infra). Clearly, these results showed the formation of a 1:1 complex. The included alkyl methyl sulfoxide was recovered from the inclusion crystals and its enantiomeric excess was estimated by its optical rotation and the Kusumi's NMR method that transforms the sulfoxide into a diastereomeric mixture of its *N*-(methoxyphenylacetyl)-sulfoximine derivatives in order to estimate the enantiomeric excess.[10] We also examined the inclusion of benzyl methyl sulfoxide, a typical dialkyl sulfoxide having one phenyl group, whose result is also shown in Table 1 (entry 6).

In all entries of Table 1, both methods A and B gave comparable results for molecular recognition, though method A is often superior to method B in terms of the enantiomeric excess of the included sulfoxide. Small sulfoxides such as dimethyl sulfoxide and ethyl methyl sulfoxide formed the inclusion compounds with narrow interlayer distances (LD=9.3 and 9.4 Å). The stereochemistry of the preferably included enantiomer of ethyl methyl sulfoxide was *S*-form (8% ee by method A and 14% ee by method B in entry 2). In contrast, (*R*)-enantiomer was preferably recognized in the inclusion compound of methyl propyl sulfoxide though its enantioselectivity was low (13% ee by method A and 17% ee by method B in entry 3). Interestingly, other (*R*)-alkyl methyl sulfoxides bearing isobutyl, butyl, and benzyl groups were included with a high enantioselectivity (94, 94, and 93% ee by method A, respectively), and their interlayer distances were similar to each other within the range of 11.0–11.2 Å (entries 4–6). The efficient chiral recognition of benzyl methyl sulfoxide

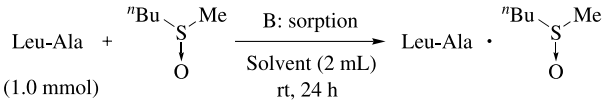
Table 1. Enantioselective inclusion of alkyl methyl sulfoxides by Leu-Ala



Entry	Sulfoxide	A: crystallization		B: sorption		LD[a]/Å
		ee/%	Ef.[b]/%	ee/%	Ef.[b]/%	
1		—	100	—	103	9.4
2		8(*S*)	98	14(*S*)	98	9.3
3		13(*R*)	97	17(*R*)	99	10.4
4		94(*R*)	100	60(*R*)	98	11.2
5		94(*R*)	100	58(*R*)	104	11.2
6		93(*R*)	93	44(*R*)	97	11.0

[a] LD is an interlayer distance measured by PXRD.
[b] Ef. means mol% of the guest based on the dipeptide in the inclusion complex.

Table 2. Enantioselective inclusion of butyl methyl sulfoxide by Leu-Ala



Entry	Solvent	Equiv of guest	ee/%	Ef.[a]/%
1	Hexane	2.2	58 (*R*)	104
2	Hexane	4.0	69 (*R*)	86
3	Hexane	8.0	75 (*R*)	99
4	Diethyl ether	2.2	59 (*R*)	98
5	Toluene	2.2	57 (*R*)	102

[a] Ef. means mol% of the guest based on the dipeptide in the inclusion complex.

by Leu-Ala is in marked contrast with that by (*R*)-phenylglycyl-(*R*)-phenylglycine, which formed the inclusion crystals containing both enantiomers of benzyl methyl sulfoxide to result in the racemic recognition.[4a]

As shown in Table 2, the replacement of hexane with diethyl ether or toluene as a dispersion solvent in method B did not affect the enantioselectivity and the Ef. significantly (entries 4 and 5). As the amount of the guest increased, the enantioselectivity was raised up to 75% ee with 8 equiv of sulfoxide (entries 2 and 3).

Fortunately, we obtained good-quality single crystals for the inclusion compound of isobutyl methyl sulfoxide, DMSO, and benzyl methyl sulfoxide, which could be analyzed by single-crystal X-ray crystallography. Figure 1 shows the top view of the sheet structure of the inclusion compound, where the dipeptide backbones are colored in black, guest sulfoxides in gray, and alkyl groups of Leu-Ala in white. The space-filling models reveal that, in all of these inclusion crystals, the guest molecules are similarly arranged in the cavity of Leu-Ala, though dimethyl sulfoxide is disordered (Fig. 1b). As mentioned previously, the inclusion crystal of DMSO was reported in the literature.[9b] The result obtained here is similar to the literature one: the guest DMSO has the disordered structure of a trigonal-bipyramidal geometry having the sulfur atom that occupies two coordination sites (6:4). Our result is shown in Figure 1b: the ratio (S1/S2= 62:38) is reproducible and the disordered site occupancy is statistic.

In the present inclusion compounds, the dipeptide molecules have a straight glycylglycine backbone to construct a two-dimensional layer. In Figure 2, the intermolecular distances of hydrogen bonding in crystals are summarized. A set of the hydrogen bonding distances is similar to each other in all of the Leu-Ala inclusion compounds. The Leu-Ala backbones are arranged into a parallel motif to construct a sheet by ionic pairing of the carboxyl and amino groups via hydrogen bonding network: one terminal COO^- links two $^+NH_3$ of adjacent dipeptides and the $^+NH_3$ also binds two adjacent COO^- groups. Here, two characteristic distances, the repetition of glycylglycine backbone (*L*) and the distance between dipeptides arranged side by side (*W*), are introduced, and then the area occupied by glycylglycine backbone is estimated by $L\times W$. By comparison of three crystal structures of Leu-Ala, it was found that the values of $L\times W$ increased as the guest sulfoxides became larger.

It is worthy to note that these dipeptide backbone arrangements are quite similar to those of the inclusion compounds of (*R*)-phenylglycyl-(*R*)-phenylglycine.[4] Although the chiral cavity of Leu-Ala possesses no benzene ring, isobutyl methyl sulfoxide is included with a high enantioselectivity. Careful insight into the X-ray structure of the inclusion cavity suggests the reason why the chiral discrimination is achieved. Although the layer structure of Leu-Ala is similar in all of the inclusion compounds mentioned herein, these dipeptide sheets are arranged

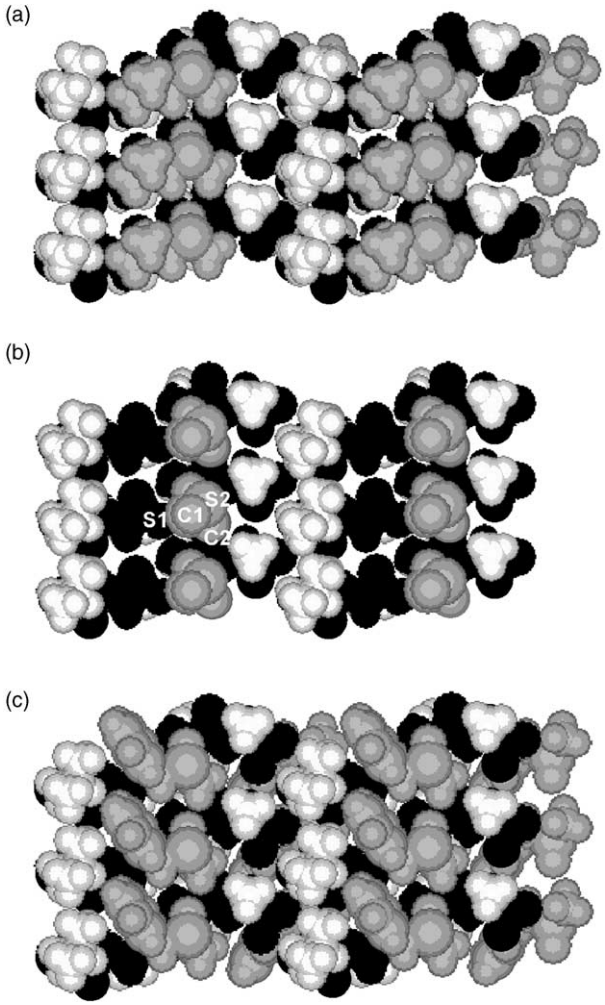
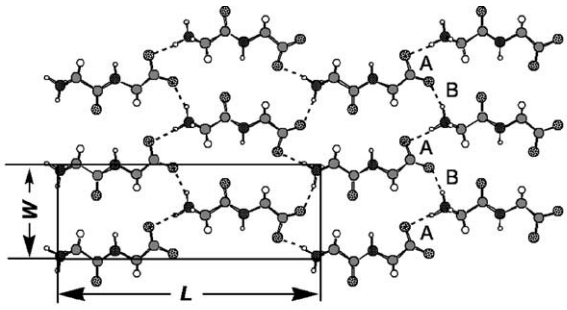


Figure 1. Top views of sheet structure of inclusion crystals (CPK model). (a) Leu-Ala with (*R*)-isobutyl methyl sulfoxide. (b) Leu-Ala with dimethyl sulfoxide. Hydrogens of the sulfoxide were omitted for its disordered structure. (c) Leu-Ala with (*R*)-benzyl methyl sulfoxide.



	host-host / Å		host-guest / Å
	A N---O	B N---O	N---O(G)
Leu-Ala · ^{t}BuSOMe	2.76	2.75	2.84
Leu-Ala · BnSOMe	2.78	2.75	2.81
Leu-Ala · MeSOMe	2.88	2.75	2.79

	L / Å	*W* / Å	*L* X *W* / Å^2
Leu-Ala · ^{t}BuSOMe	15.94	5.40	86.08
Leu-Ala · BnSOMe	15.88	5.57	88.45
Leu-Ala · MeSOMe	16.10	5.21	83.88

Figure 2. Atomic distances of intermolecular hydrogen bonds and dipeptide backbones.

differently depending on the guest structure, as shown in Figure 3.

The guest sulfoxide in Leu-Ala crystals is bound to the dipeptide-backbone layer via hydrogen bonding between the sulfoxide oxygen and the ammonio proton of Leu-Ala with a N···O(G) distance of 2.79–2.84 Å. The inclusion compound of (*R*)-isobutyl methyl sulfoxide has $P2_12_12_1$ space group: the sheets piles up in the opposite direction (arrows in Fig. 3a). In this inclusion compound, the sulfinyl methyl group is faced toward the methyl group of Leu-Ala in the cavity. The larger area in the Leu-Ala cavity is filled with the isobutyl group. The such placement of isobutyl methyl sulfoxide in the inclusion cavity can diminish the space between the layers to make the host–guest packing effective. Consequently, (*R*)-enantiomer of the sulfoxide is recognized as the suitable guest. It should be noted that, in the inclusion compound of benzyl methyl sulfoxide, the sheets stacked in the same direction shown by the arrows to become the space group $P2_1$ (see Fig. 3c). In this case, the phenyl ring of the sulfoxide seems to contact with the Leu-Ala in the neighboring layer. Thus, the terminal proton of the Leu part is located 2.9 Å from the center of the benzene ring. This is within the distance that is capable of CH/π interaction.[6] This interaction would compel the dipeptide sheets to pile up in the same direction.

Since DMSO is too small to fill the inclusion cavity of Leu-Ala (Fig. 3b), another DMSO molecule belonging to the adjacent layer sticks the residual vacant space and, as a result, the layers interdigitate each other so as to make the interlayer distance smaller (9.4 Å). The PXRD pattern of the inclusion crystals with ethyl methyl sulfoxide showed the interlayer distance of 9.3 Å that is comparable with that of the DMSO inclusion crystal. This suggests that these crystals have the interdigitating structure similar to that of the DMSO inclusion compound. If the C1 (methyl) group of the disordered sulfoxide (Fig. 3b) is replaced with ethyl group, the stereochemistry of the included ethyl methyl sulfoxide would be *S*. Indeed, ethyl methyl sulfoxide was recognized with an enantioselectivity of 8–14% ee (*S*). While, methyl propyl sulfoxide and butyl methyl sulfoxide expanded the interlayer distance to 10.4 and 11.2 Å, respectively. From these facts, it seems to be suggested that the sulfoxide molecule itself is large enough to fill the cavity without the aid of another sulfoxide molecule. Since the (*R*)-form of these sulfoxides was preferably recognized by Leu-Ala crystal, it is likely that the structures of these sulfoxide inclusion crystals are analogous to that of (*R*)-isobutyl methyl sulfoxide inclusion crystal.

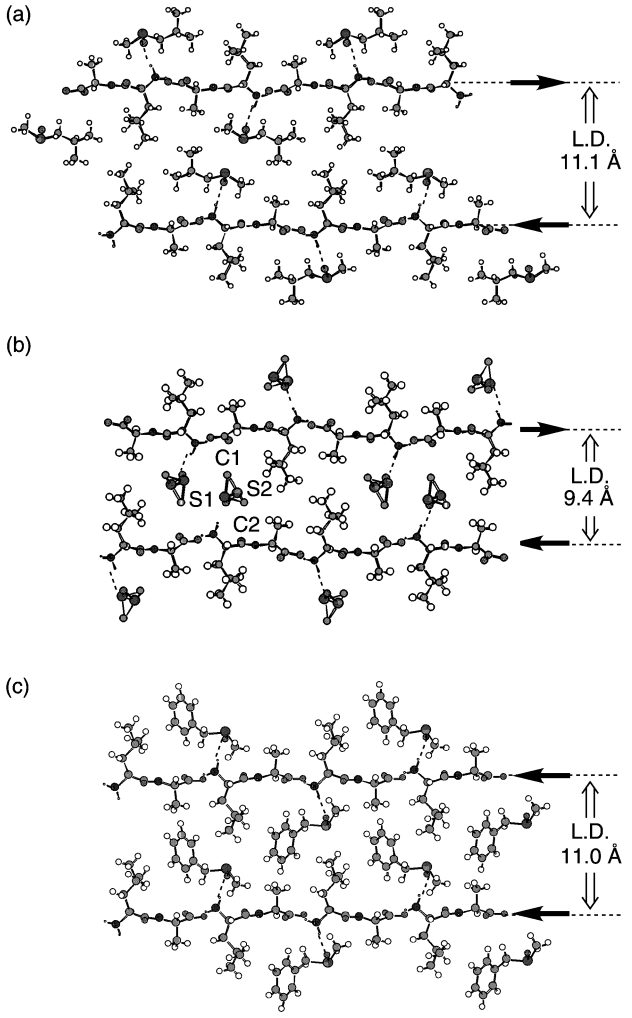


Figure 3. Layer structure of inclusion crystals. The arrows indicate the direction of the sheet from the *C*-terminal to the *N*-terminal. (a) Leu-Ala with (*R*)-isobutyl methyl sulfoxide. (b) Leu-Ala with dimethyl sulfoxide. (c) Leu-Ala with (*R*)-benzyl methyl sulfoxide.

3. Conclusion

L-Leucyl-L-alanine molecules self-assemble by intermolecular salt formation and hydrogen bonding to form a layer structure. In the cavity between the layers, alkyl methyl sulfoxides (alkyl = methyl, ethyl, propyl, isobutyl, butyl, and benzyl) were included by the driving force of hydrogen bonding between the oxygen atom of the sulfinyl group and the ammonio proton of Leu-Ala. The included sulfoxide is placed in such a manner that the sulfinyl methyl group faces toward the methyl group of Ala part. When the sulfoxide such as DMSO or ethyl methyl sulfoxide is too small to fill the cavity, the layers are interdigitated to one another and, as a result, the cavity is filled by two sulfoxide molecules. In the case that the alkyl group is comparably large, it is placed in the residual space and, as a result, one molecule of the sulfoxide itself can fill the cavity. Thus, the alkyl methyl sulfoxide having a comparably large group as the alkyl was included with a high (*R*)-enantioselectivity.

4. Experimental

4.1. General methods

NMR spectra were recorded at 300 MHz for ^{1}H NMR. Elemental analyses were performed at the Chemical Analysis Center, Chiba University, Japan. Inclusion efficiency was determined by NMR measurements and elemental analyses. Melting points (decomposition) were measured on a TG-DTA. As a chiral shift reagent, (*S*)-α-methoxyphenyl acetic acid [(*S*)-MPAA] was purchased from Aldrich Chemical Co.

4.1.1. Synthesis of Leu-Ala. Protected amino acids, *N*-(benzyloxycarbonyl)-L-leucine and L-alanine benzyl ester *p*-toluenesulfonate, were prepared according to literature procedure.[11,12] These were coupled with DCC and HOBt to form the corresponding protected dipeptide.[13] Final deprotection was performed by hydrogenation with Pd black under hydrogen atmosphere. The Leu-Ala was dried over 3 h at 70 °C in vacuo. It contained 2.1 wt% water detected by elemental analysis and TG-DTA.[14] Leu-Ala·0.24H_2O: a colorless solid; dec 143.5 °C; $[\alpha]_D^{25} = +21.7$ (*c* 0.82, methanol); $[\alpha]_D^{25} = +22.9$ (*c* 5, methanol);[15] ^{1}H NMR (300 MHz, D_2O) δ (q, 1.0H, J=7.28 Hz), 4.01 (t, 1.0H, J=7.21 Hz), 1.84–1.68 (m, 3.0H), 1.38 (d, 3.0H, J=7.28 Hz), 0.99 (d, 3.0H, J=6.32 Hz), 0.97 (d, 3.0H, J=6.32 Hz); IR (KBr) 3057, 1664, 1589 1510 cm^{-1}. Powder X-ray diffraction [Å(I/I_0)] 12.8(1.00), 7.16(0.43), 5.80(0.28), 4.87(0.47), 4.14(0.64). Anal. Calcd for $C_9H_{18}N_2O_3\cdot 0.24H_2O$: C, 52.33; H, 9.02; N, 13.56. Found: C, 52.31; H, 9.11; N, 13.40.

4.2. Preparation of inclusion compounds of Leu-Ala and alkyl methyl sulfoxide

Method A. To a solution of Leu-Ala (1.0 mmol) in water (2 mL) was added a racemic sulfoxide (2.2 mmol). Inclusion compounds were formed by slow evaporation of a solution of the complex at an ambient temperature, then it was collected by filtration and washed with diethyl ether (20 mL).

Method B. Crystals of Leu-Ala are essentially insoluble in hexane. A suspension of Leu-Ala (1.0 mmol) in hexane (2 mL) was stirred together with a racemic sulfoxide (2.2 mmol) at an ambient temperature for 1 day. The formed inclusion compound was collected by filtration and washed with diethyl ether (20 mL).

4.2.1. Leu-Ala·ethyl methyl sulfoxide. A colorless solid; dec 127.2 °C; IR (KBr) 3350, 1664, 1587, 1510, 1005 cm^{-1}. Powder X-ray diffraction [Å(I/I_0)] 9.33(0.34), 9.14(0.31), 6.99(0.33), 4.98(1.00), 4.90(0.77), 4.01(0.61). Anal. Calcd for $C_9H_{18}N_2O_3\cdot 0.98C_3H_8OS$: C, 49.02; H, 8.90; N, 9.57. Found: C, 48.92; H, 9.11; N, 9.53.

4.2.2. Leu-Ala·methyl *n*-propyl sulfoxide. A colorless solid; dec 135.2 °C; IR (KBr) 3352, 1666, 1583, 1510, 1005 cm^{-1}. Powder X-ray diffraction [Å(I/I_0)] 10.4(0.93), 8.70(0.24), 5.27(0.90), 5.00(1.00), 3.73(0.69), 3.54(0.65). Anal. Calcd for $C_9H_{18}N_2O_3\cdot 0.97C_3H_8OS$: C, 50.68; H, 9.15; N, 9.18. Found: C, 50.42; H, 9.14; N, 9.03.

4.2.3. Leu-Ala·*n*-butyl methyl sulfoxide. A colorless solid; dec 130.2 °C; IR (KBr) 3354, 1669, 1581, 1507, 1009 cm^{-1}. Powder X-ray diffraction [Å(I/I_0)] 11.2(0.34), 10.7(0.38), 7.80(1.00), 5.53(0.18), 4.50(0.23), 3.66(0.79). Anal. Calcd for $C_9H_{18}N_2O_3\cdot 1.0C_5H_{12}SO$: C, 52.15; H, 9.38; N, 8.69. Found: C, 52.05; H, 9.44; N, 8.61.

4.2.4. Leu-Ala·isobutyl methyl sulfoxide. A colorless solid; dec 130.5 °C; IR (KBr) 3353, 1666, 1584, 1508, 1009 cm^{-1}. Powder X-ray diffraction [Å(I/I_0)] 11.2(0.65), 10.3(0.84), 5.37(0.47), 4.46(0.34), 3.70(1.00), 3.62(0.81). Anal. Calcd for $C_9H_{18}N_2O_3\cdot 1.0C_5H_{12}SO$: C, 52.15, H, 9.38; N, 8.69. Found: C, 51.78; H, 9.66; N, 8.59.

4.2.5. Leu-Ala·benzyl methyl sulfoxide. A colorless solid; dec 167.2 °C; IR (KBr) 3354, 1671, 1578, 1508, 1018 cm^{-1}. Powder X-ray diffraction [Å(I/I_0)] 11.0(0.10), 10.5(0.10), 8.53(0.33), 4.49(0.47), 4.40(1.00), 3.95(0.52). Anal. Calcd for $C_9H_{18}N_2O_3\cdot 0.93C_8H_{10}SO$: C, 57.12; H, 7.96; N, 8.10. Found: C, 56.85; H, 8.05; N, 7.81.

4.3. Determination of stereochemistry and enantiomeric excess in the inclusion

The included sulfoxide was isolated by dissolution of the inclusion compound in water (5.0 mL) and extraction with $CHCl_3$. In addition to comparison of the optical rotation to the value of the literature, absolute configuration and enantiomeric excess of recognized sulfoxides were determined by a Kusumi's NMR method (chiral sulfoximines), another NMR method with a chiral shift reagent [(*S*)-MPAA], or a chiral HPLC method. According to the Kusumi's methodology,[10] *N*-(methoxyphenylacetyl)-sulfoximines were obtained from sulfoxides by a one pot reaction (alkyl methyl sulfoxide/*O*-(mesitylsulfony)-hydroxylamine[16]/$CHCl_3$ then (*S*)-MPAA/PyBOP/HOBt/pyridine).

4.3.1. Ethyl methyl sulfoxide. $[\alpha]_D^{25} = +7.69$ (*c* 1.26, ethanol). 8.1% ee *S* by NMR;[10] *S*-ethyl methyl *N*-[(*S*)-methoxyphenylacetyl]sulfoximine: colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51–7.27 (m, 5.0H), 4.75 (s, 0.54H, *S*

major), 4.74 (s, 0.46H, *R* minor), 3.47–3.10 (m, 8.0H, *S* major and *R* minor), 1.31 (t, 1.38H, $J=7.42$ Hz, *R* minor), 1.18 (t, 1.62H, $J=7.49$ Hz, *S* major).

4.3.2. Methyl propyl sulfoxide. $[\alpha]_D^{25}=-17.8$ (*c* 0.94, ethanol); 13% ee *R* by [α]; (*R*)-(−)-methyl *n*-propyl sulfoxide: $[\alpha]_D^{25}=-139.0$ (*c* 0.83, EtOH).[17a] *S*-Methyl *n*-propyl *N*-[(*S*)-methoxyphenylacetyl]sulfoximine: colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 17% ee *R*) δ 7.51–7.27 (m, 5.0H), 4.75 (s, 0.42H, *S* minor), 4.73 (s, 0.58H, *R* major), 3.41–3.12 (m, 8.0H, *R* major and *S* minor), 1.79–1.55 (m, 2.0H, *R* major and *S* minor), 1.03 (t, 1.74H, $J=$ 7.42 Hz, *R* major), 0.94 (t, 1.26H, $J=7.42$ Hz, *S* minor).

4.3.3. Butyl methyl sulfoxide. $[\alpha]_D^{25}=-103.2$ (*c* 1.12, ethanol); 94% ee *R* by [α]; (*S*)-(+)-*n*-butyl methyl sulfoxide: $[\alpha]_D^{25}=+109.9$ (*c* 1.53, ethanol).[17a,b] *S*-*n*-Butyl methyl *N*-[(*S*)-methoxyphenylacetyl]sulfoximine: colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 90% ee *R*) δ 7.51–7.27 (m, 5.0H), 4.75 (s, 0.05H, *S* minor), 4.73 (s, 0.95H, *R* major), 3.48–3.12 (m, 8.0H, *R* major and *S* minor), 1.71–1.60 (m, 2.0H, *R* major and *S* minor), 1.40 (sext, 1.90H, $J=7.42$ Hz, *R* major), 1.30 (sext, 0.10H, $J=7.57$ Hz, *S* minor), 0.89 (t, 2.85H, $J=7.28$ Hz, *R* major), 0.81 (t, 0.15H, $J=7.32$ Hz, *S* minor).

4.3.4. Isobutyl methyl sulfoxide. $[\alpha]_D^{25}=-129.2$ (*c* 2.94, ethanol); 94% ee *R* by [α]; (*S*)-(+)-isobutyl methyl sulfoxide: $[\alpha]_D^{25}=+138.0$ (*c* 0.97, ethanol).[17a,b] *S*-Isobutyl methyl *N*-[(*S*)-methoxyphenylacetyl]sulfoximine: colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 88% ee *R*) δ 7.51–7.27 (m, 5.0H), 4.77 (s, 0.06H, *S* minor), 4.74 (s, 0.94H, *R* major), 3.47–3.00 (m, 8.0H, *R* major and *S* minor), 2.23 (sept, 0.96H, $J=6.71$ Hz, *R* major), 1.99 (sept, 0.04H, $J=$ 6.53 Hz, *S* minor), 1.07 (d, 2.88H, $J=6.73$ Hz, *R* major), 1.02 (d, 2.88H, $J=6.73$ Hz, *R* major), 0.96 (d, 0.12H, $J=$ 6.73 Hz, *S* minor), 0.83 (d, 0.12H, $J=6.87$ Hz, *S* minor).

4.3.5. Benzyl methyl sulfoxide. $[\alpha]_D^{25}=-97.4$ (*c* 0.27, ethanol); 93% ee *R* by [α], (*R*)-(+)-benzyl methyl sulfoxide: $[\alpha]_D^{25}=-105$ (*c* 6.0, ethanol).[17c] HPLC (Daicel Chiralcel OB–H) eluent, hexane/2-propanal=9:1, flow rate=0.9 mL/min, $t_R(S)=31$ min, $t_R(R)=39$ min, 97% ee *R*. ^{1}H NMR (300 MHz, with (*S*)-MPAA (3 mol equiv) in $CDCl_3$, 94% ee *R*) δ 4.17 (d, 1.00H, $J=12.8$ Hz, *R* major and *S* minor), 3.99 (d, 0.03H, $J=13.2$ Hz, *S* minor), 3.98 (d, 0.97H, $J=12.9$ Hz, *R* major), 2.51 (s, 2.91H, *R* major), 2.49 (s, 0.09H, *S* major). Aromatic H could not be identified because of (*S*)-MPAA.

4.4. X-ray analyses

X-ray powder diffractions were obtained with a MAC Science MXP diffractometer using graphite-monochromated Cu Kα radiation (30 kV, 200 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.

4.5. Crystallographic data for the inclusion compounds

To the solution of Leu-Ala was added the guest (dimethyl sulfoxide, isobutyl methyl sulfoxide and benzyl methyl sulfoxide) directly in a vial, then a 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 diffractometer with graphite-monochromated Cu Kα ($\lambda=1.54178$) radiation using the $2\theta-\omega$ scan technique, and the X-ray intensities were measured up to $2\theta=140°$ at 298 K. The structures were solved by a direct method SIR97[18] and refined by a computer program package; maXus ver. 4.3.p2 from BrukerAXS. Hydrogen atoms were placed in calculated position with C–H= 0.96 Å. Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 250905-250907. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

The inclusion compound of Leu-Ala and isobutyl methyl sulfoxide: $C_{14}H_{30}N_2O_4S$, M_w 322.47, crystal dimensions $0.50\times0.50\times0.10$ mm^3, orthorhombic, $P2_12_12_1$, $a=$ 22.212(7) Å, $b=15.943(5)$ Å, $c=5.401(2)$ Å, $V=$ 1912.7(11) Å^3, $Z=4$, $d_{calcd}=1.120$ g cm^{-3}, 2237 reflections measured, 2157 independent, $R1=0.051$ (1541 reflections with $I>2.00\sigma(I)$), $Rw2=0.174$, $S=1.018$, 190 parameters, with heavy atoms refined anisotropically, residual electron density 0.25/−0.32.

The inclusion compound of Leu-Ala and benzyl methyl sulfoxide: $C_{17}H_{28}N_2O_4S$, M_w 356.49, crystal dimensions $0.40\times0.35\times0.10$ mm^3, monoclinic, $P2_1$, $a=10.983(8)$ Å, $b=15.878$ (12) Å, $c=5.569(4)$ Å, $\beta=96.22(6)°$, $V=$ 965.5(12) Å^3, $Z=2$, $d_{calcd}=1.226$ g cm^{-3}, 2010 reflections measured, 1932 independent, $R1=0.044$ (1746 reflections with $I>2.00\sigma(I)$), $Rw2=0.144$, $S=1.030$, 217 parameters, with heavy atoms refined anisotropically, residual electron density 0.28/−0.32.

The inclusion compound of Leu-Ala and dimethyl sulfoxide: $C_{11}H_{24}N_2O_4S$, M_w 280.39, crystal dimensions $0.45\times0.08\times0.08$ mm^3, orthorhombic, $P2_12_12_1$, $a=$ 5.208(3) Å, $b=16.095(3)$ Å, $c=18.7069(10)$ Å, $V=$ 1568.1(9) Å^3, $Z=4$, $d_{calcd}=1.188$ g cm^{-3}, 1911 reflections measured, 1782 independent, $R1=0.058$ (1120 reflections with $I>2.00\sigma(I)$); $Rw2=0.176$, $S=1.032$, 174 parameters, with heavy atoms refined anisotropically, residual electron density 0.31/−0.28.

Acknowledgements

This work was supported by a Grant-in-Aid for Scientific Research (C) (No. 16550120) from the Ministry of Education, Culture, Sports, Science, and Technology, Japan.

References and notes

1. Weber, E., Ed.; Molecular Inclusion and Molecular Recognition—Clathrates I and II; Springer: Berlin, 1987/1988; Vols. 140 and 149.

2. MacNicol, D., Toda, F., Bishop, R., Eds.; Comprehensive Supramolecular Chemistry; Pergamon: UK, 1996; Vol. 9.
3. (a) Toda, F.; Tanaka, K.; Nagamatsu, S. *Tetrahedron Lett.* **1984**, *25*, 4929–4932. (b) Toda, F.; Tanaka, K.; Mak, T. C. W. *Chem. Lett.* **1984**, 2085–2088. (c) Toda, F.; Tanaka, K.; Okuda, T. *J. Chem. Soc., Chem. Commun.* **1995**, 639–649.
4. (a) Akazome, M.; Ueno, Y.; Ooiso, H.; Ogura, K. *J. Org. Chem.* **2000**, *65*, 68–76. (b) Akazome, M.; Noguchi, M.; Tanaka, O.; Sumikawa, A.; Uchida, T.; Ogura, K. *Tetrahedron* **1997**, *53*, 8315–8322. (c) Ogura, K.; Uchida, T.; Noguchi, M.; Minoguchi, M.; Murata, A.; Fujita, M.; Ogata, K. *Tetrahedron Lett.* **1990**, *31*, 3331–3334.
5. (a) Hunter, C. A.; Lawson, K. R.; Perkins, J.; Urch, C. J. *J. Chem. Soc., Perkin Trans. 2* **2001**, 651–668. (b) Swift, J. A.; Pal, R.; McBride, J. M. *J. Am. Chem. Soc.* **1998**, *120*, 96–104. (c) Lewis, F. D.; Yang, J.-S.; Stern, C. L. *J. Am. Chem. Soc.* **1996**, *118*, 12029–13037. (d) Hunter, C. A.; Sanders, J. K. M. *J. Am. Chem. Soc.* **1990**, *112*, 5525–5534. (e) Desiraju, G. R.; Gavezzotti, A. *J. Chem. Soc., Chem. Commun.* **1989**, 621–623.
6. (a) Umezawa, Y.; Tsuboyama, S.; Honda, K.; Uzawa, J.; Nishio, M. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 1207–1213. (b) For a review of CH/π interaction: Nishio, M.; Umezawa, Y.; Hirota, M.; Takeuchi, Y. *Tetrahedron* **1995**, *51*, 8665–8701 and references therein.
7. (a) Drabowicz, J.; Duddeck, H. *Sulfur Lett.* **1989**, *10*, 37–40. (b) Toda, F.; Mori, K.; Okada, J.; Node, M.; Itoh, A.; Oomine, K.; Fuji, K. *Chem. Lett.* **1988**, 131–134. (c) Buist, P. H.; Marecak, D.; Holland, H. L.; Brown, F. M. *Tetrahedron: Asymmetry* **1995**, *6*, 7–10. (d) Deshmukh, M.; Duñach, E.; Juge, S.; Kagan, H. B. *Tetrahedron Lett.* **1984**, *32*, 3467–3470.
8. (a) Akazome, M.; Takahashi, T.; Sonobe, R.; Ogura, K. *Tetrahedron* **2002**, *58*, 8857–8861. (b) Akazome, M.; Senda, K.; Ogura, K. *J. Org. Chem.* **2002**, *67*, 8885–8889. (c) Akazome, M.; Takahashi, T.; Sonobe, R.; Ogura, K. *Supramol. Chem.* **2001**, *13*, 109–136. (d) Akazome, M.; Takahashi, T.; Ogura, K. *J. Org. Chem.* **1999**, *64*, 2293–2300. (e) Akazome, M.; Yanagita, Y.; Sonobe, R.; Ogura, K. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 2823–2827. (f) Akazome, M.; Sumikawa, A.; Sonobe, R.; Ogura, K. *Chem. Lett.* **1996**, 995–996.
9. (a) Görbitz, C. H. *Acta Crystallogr. Sect. C* **1997**, *53*, 736–739. (b) Mitra, S. N.; Govindasamy, L.; Subramanian, E. *Acta Crystallogr. Sect. C* **1996**, *52*, 2871–2873.
10. Yabuuchi, T.; Kusumi, T. *J. Am. Chem. Soc.* **1999**, *121*, 10646–10647.
11. Zervas, L.; Winitz, M.; Greenstein, J. P. *J. Org. Chem.* **1957**, *22*, 1515–1521.
12. Doyle, F. P.; Fosker, G. R.; Nayler, J. H. C.; Smith, H. *J. Chem. Soc.* **1962**, 1440–1444.
13. König, W.; Geiger, R. *Chem. Ber.* **1970**, *103*, 788–798.
14. Leu-Ala hydrate is supplied by Acros Organics and Sigma Chemical Co.
15. Polglase, W. J.; Smith, E. L. *J. Am. Chem. Soc.* **1949**, *71*, 3081–3084.
16. (a) Tamura, Y.; Minamikawa, J.; Sumoto, K.; Fujii, S.; Ikeda, M. *J. Org. Chem.* **1973**, *38*, 1239–1241. (b) Krause, J. G. *Synthesis* **1972**, 140.
17. (a) Andersen, K. K.; Bujnicki, B.; Drabowicz, J.; Mikolajczyk, M.; O'Brien, J. B. *J. Org. Chem.* **1984**, *49*, 4070–4072. (b) Drabowicz, J.; Bujnicki, B.; Mikolajczyk, M. *J. Org. Chem.* **1981**, *46*, 2788–2790. (c) Fernández, I.; Khair, N.; Llera, J. M.; Alcudia, F. *J. Org. Chem.* **1992**, *57*, 6789–6796.
18. Altomare, A.; Burla, M. C.; Camalli, M.; Cascarano, G.; Giacovazzo, C.; Guagliardi, A.; Moliterni, A. G. G.; Polidori, G.; Spagna, R. *J. Appl. Crystallogr.* **1999**, *32*, 115–119.