Bull. Chem. Soc. Jpn., *71*, *1109—1116 (1998)* 1109

The Role of Water-Solvation in the Optical Resolution of DL-Leucine with (*S*)-(−)-1-Phenylethanesulfonic Acid. Characterization and X-Ray Crystal Structures of Their Diastereomeric Salts

Ryuzo Yoshioka,* Kimio Okamura,† Shin-ichi Yamada, Ken-ichi Aoe,† and Tadamasa Da-te†

Pharmaceutical Development Research Laboratory, Tanabe Seiyaku Co., Ltd.,
16-89, Kashima 3-Chome, Yodogawa-ku, Osaka 532

†Analytical Research Laboratory, Tanabe Seiyaku Co., Ltd., 16-89, Kashima 3-Chome, Yodogawa-ku, Osaka 532

(Received October 9, 1997)

In the optical resolution by diasteromeric salt formation of DL-leucine with (*S*)-(−)-1-phenylethanesulfonic acid (PES), the less-soluble L-Leu·(−)-PES salt preferentially crystallized from acetonitrile–methanol and, in contrast, the same resolution from acetonitrile–water afforded the monohydrated D-salt [D-Leu·(−)-PES·H_2O]. The role of the water of crystallization formed during this resolution system has been explored through a comparison of the crystalline characteristics of D-, monohydrated D-, and L-Leu·(−)-PES by thermoanalysis (DSC) and spectroscopy. The DSC indicated that D-Leu·(−)-PES had a polymorphic form with the water of crystallization; that is, D-Leu·(−)-PES·H_2O was thoroughly dehydrated at 60—90 °C and simultaneously converted into the D-Leu·(−)-PES form. However, L-Leu·(−)-PES does not have the water of crystallization even in 75% relative humidity. Detailed comparisons among the X-ray crystal structures of three salts have revealed that in all of the salts the conformations of the PES anion and the Leu cation, respectively, were approximately the same, and their crystal structures comprised specific interaction modes having characteristic hydrogen-bond networks. In particular, in D-Leu·(−)-PES·H_2O the PES and Leu ions are cross-linked to each other through water molecules. These observations suggested that the water of crystallization, together with the formation of a stable crystal-packing mode by cross-linking the PES and Leu ions, presumably plays an important role in the selective crystallization in the resolution.

Even now, classical optical resolution via crystallization, particularly diastereomeric salt formation, has been widely utilized in both laboratory and industrial techniques.[1] A main task on this diastereomeric procedure is to find a useful resolving agent for racemates through fractional crystallization. Regrettably, searching for a resolution system is still an empirical trial-and-error approach. For the present, a research examination using a number of resolving agents favorably leads to a successful resolution.[2]

We have been very interested in rational information for diastereomeric resolution efficiency as well as in the design of chiral resolving agents, especially chiral sulfonic acids. Our previous report revealed that 1-phenylethanesulfonic acid (PES) is an efficient resolving agent for a wide variety of racemic amino acids.[3] Interestingly, in the resolution of DL-leucine (Leu) with (−)-PES, the Leu configuration of the precipitated salts was reversed by the two solvents used (Chart 1); when acetonitrile–methanol was used, the L-Leu·(−)-PES salt was fractionally crystallized as the less-soluble salt, whereas acetonitrile–water gave the monohydrated D-salt, D-Leu·(−)-PES·H_2O. Such solvation of diastereomers is occasionally encountered and has great effect on the resolution efficiency.[4] However, studies of this solvation have been rare, and its role in most resolution systems is not apparent, particularly for the crystalline salts of chiral organic compounds. This situation motivated us to explore

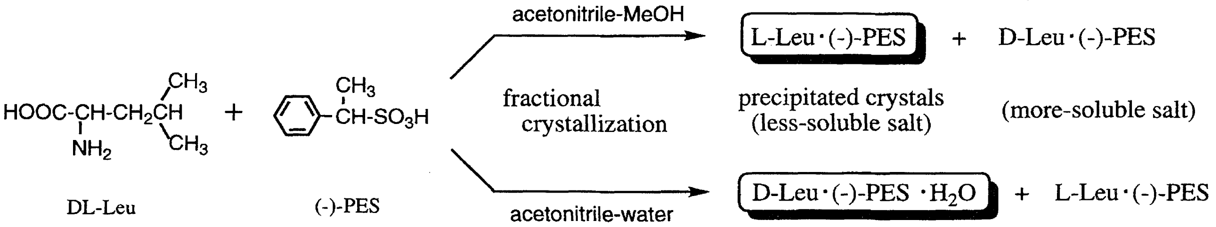


Chart 1.

how crystal solvation is related to chiral recognition in the resolution.

Recently, chiral recognition in diastereomeric resolutions has gradually been investigated through comparisons of the physicochemical properties and crystal structures between a pair of diastereomeric salts.[5] Previously, we also showed an interesting result: The successful resolution of DL-*p*-hydroxyphenylglycine with (−)-PES could be attributed to the characteristic differences between the more- and less-soluble salts.[3] The present paper is a part of our structural study concerning diastereomeric resolutions of various amino acids with PES, and explores the role of the water of crystallization formed during the resolution of DL-leucine with (−)-PES through comparing the physicochemical properties and crystal structures of their three diastereomeric salts determined by various analyses, including X-ray crystallography.

Results and Discussion

Optical Resolution of DL-Leucine with (−)-PES. The resolution of DL-Leu with a 1 molar equivalent of (−)-PES was carried out in the two solvent systems. When acetonitrile–methanol was used as a solvent, L-Leu·(−)-PES was preferentially crystallized at a resolution efficiency of 39%.[6] Alternatively, when acetonitrile–water was used, D-Leu·(−)-PES·H_2O was given in 64%. Although these two resolutions were repeatedly examined under several conditions (such as the amounts of solvents and crystallization temperatures), the resolution yields of D-Leu·(−)-PES·H_2O in acetonitrile–water were constantly greater than those of L-Leu·(−)-PES in acetonitrile–methanol.

Since the above-mentioned resolution-process result based on the difference in the solubilities of a diastereomeric salt pair in each solvent (Chart 1), optically pure D-, monohydrated D-, and L-Leu·(−)-PES were prepared, and their solubilities were determined (Table 1). These are fairly low in each solvent system, and the solubility ratio between more-soluble D-Leu·(−)-PES and less-soluble L-Leu·(−)-PES in acetonitrile–methanol is 3.5 times, which is slightly larger than 2.1 times between more-soluble L-Leu·(−)-PES and less-soluble D-Leu·(−)-PES·H_2O in acetonitrile–water. Nevertheless, the resolution yield in acetonitrile–water is superior to that in acetonitrile–methanol, which can not be understood based on the difference in both of the solubility ratios. This contradiction induced us to examine a factor in the selective crystallization of the hydrated D-salt during the resolution of DL-salt in acetonitrile–water.

Properties of D- and L-Leu·(−)-PES. In order to gain information about the three Leu·(−)-PES salts, the melting points, enthalpies of fusion, solubilities, and infrared spectra of their crystalline salts were examined (Table 1).

Figure 1 shows the thermal behavior of the three salts. The differential scanning calorimetry (DSC) of D-Leu·(−)-PES·H_2O displays two endothermic peaks due to fusion with maxima at 77.0 and 171.2 °C [Fig. 1(b)]. The former peak begins to be endothermic at about 60 °C, and the process completes at 90 °C. This endothermic process corresponds to the water of crystallization, which was identified to a single water based on the rate of decrease amount in thermogravimetry (TG) and elemental analysis. The latter peak and its enthalpy of fusion have been observed to be close to those of D-Leu·(−)-PES (unhydrate), which has only one endothermic peak at 171.5 °C [Fig. 1(a)]. Consequently, from Fig. 1(b) it can be presumed that the D-Leu·(−)-PES·H_2O form was dehydrated at 60—90 °C, and simultaneously thermal-transformed into the D-Leu·(−)-PES (unhydrate) form during the DSC measurement. In fact, when D-Leu·(−)-PES·H_2O was dried at 90 °C, the physicochemical properties of its obtained salt were confirmed to be identical with those of D-Leu·(−)-PES (unhydrate); conversely, this unhydrated form was easily monohydrated in a 75% humidity chamber or upon exposure to a wet atmosphere. Thus, D-Leu·(−)-PES has a polymorphic form containing the water of crystallization.

On the other hand, L-Leu·(−)-PES has only a single endothermic peak, with a maximum at 221.2 °C, which is immediately accompanied by decomposition [Fig. 1(c)]. Importantly, L-Leu·(−)-PES does not possess water of crystallization, even in a 75% humidity chamber or a wet atmosphere.

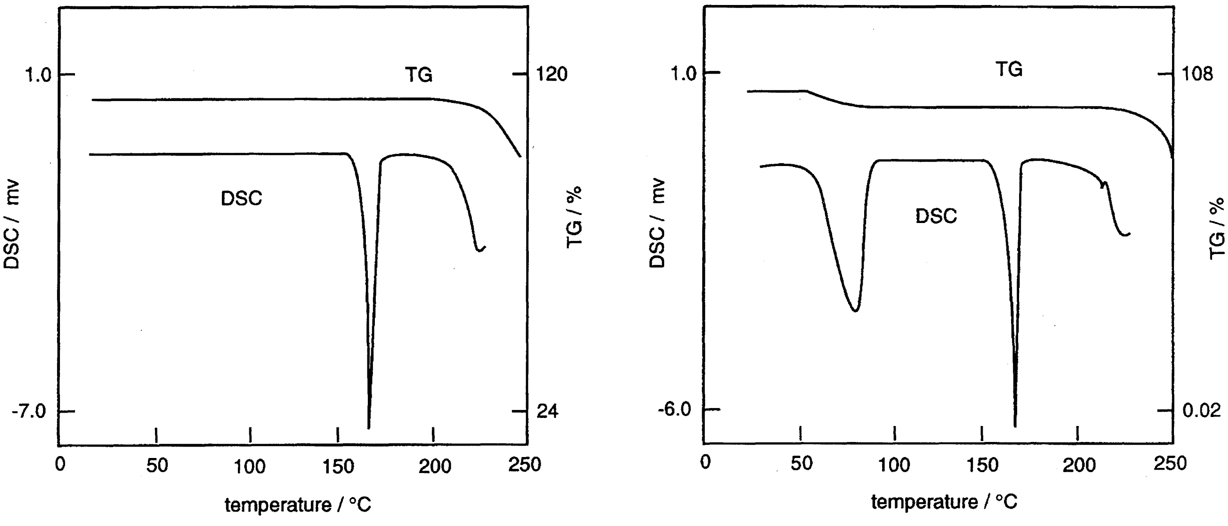
Consequently, these three DSC curves show that the thermal transitions of both the D- and L-Leu·(−)-PES crystals do not occur up to the decomposition points, whereas that of the D-Leu·(−)-PES·H_2O crystals is clearly observed from the thermal behavior.

Crystal Structures of Diastereomeric Salts. Since it is interesting to note that the thermal behavior of the water of crystallization in a diastereomeric salt reflects a difference in the crystal packing mode, we performed X-ray crystallo-

Table 1. Properties of D- and L-Leu·(−)-PES

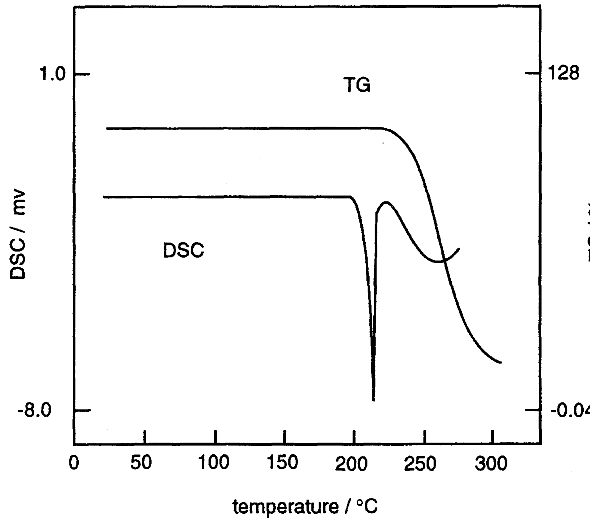
Leu·(−)-PES	Mp[a)]	ΔH^{f} [a)]	Solubility[b)]	$[\alpha]_D^{25}$/deg	IR (cm^{-1})
	°C	kJ mol^{-1}	g/100 g solv.	*c* 1, MeOH	C=O
D-Leu·(−)-PES	171.5	29.6	4.2 (A) 0.07 (B)	−19.8	1740
L-Leu·(−)-PES	221.2	(33.4)	1.2 (A) 0.03 (B) 4.2 (C)	−0.0	1750
D-Leu·(−)-PES·H_2O	77, 171.2	62.7, 27.6	2.0 (C)	−19.0	1740

a) DSC, ΔH^{f}: Enthalpy of fusion. ( ): Fusion process accompanied with decomposition. b) 25 °C. Solvent (v/v) : A = CH_3CN/MeOH (90/10), B = CH_3CN (100), C = CH_3CN/H_2O (95/5).



(a) D-Leu·(-)-PES

(b) D-Leu·(-)-PES·H_2O



(c) L-Leu·(-)-PES

Fig. 1. DSC and TG traces of the three diastereomeric salts.

graphic analyses of the three Leu·(−)-PES salts. Although suitable single crystals for this purpose of a diastereomeric salt pair, especially the more-soluble one, are generally difficult to obtain, we have fortunately succeeded in preparing and determining single crystals of all the three salts.

Crystals of D-Leu·(−)-PES·H_2O are colorless needles in the orthorhombic $P2_12_12$ space group, and those of D- and L-Leu·(−)-PES are colorless needles in the monoclinic $C2$ and $/P2_1$ space groups, respectively. The unit cell of L-salt contains two Leu cations and two PES anions, whereas those of both D-salts are four Leu cations and four PES anions. These crystal data are summarized in Table 2. The atomic-numbering scheme is according to Fig. 2. Complete lists of the fractional coordinates, bond lengths, bond angles, and coordinates of the calculated hydrogen positions have been deposited.[7)]

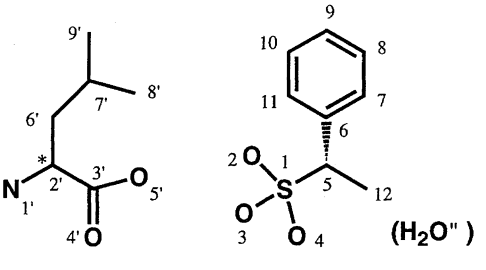
Additionally, the absolute configuration of (−)-PES was reconfirmed to be (*S*) by being correlated with the known configuration of L-(*S*)-Leu.

Stereochemistry of Diastereomeric Salts. The conformations of the PES and Leu molecules in D-, hydrated D-, and L-Leu·(−)-PES were examined by comparing their torsion angles (Table 3).

The molecular geometries of PES anions can mainly be correlated to the torsion angles of O2–S1–C5–C6, C12–C5–C6–C7, and S1–C5–C6–C7. The variations in the torsion angles among the three PES molecules, which do not differ by more than ca. 20°, are less different. These conformations are very similar to the previously reported species of a diastereomeric salt pair of PES with *p*-hydroxyphenylglycine (HPG).[3)] Thus, the PES molecule was reconfirmed to be conformationally rigid and stable. A further detailed comparison indicated that the differences in the torsion angles between the D- and hydrated D-salts are slightly

Table 2. Crystal and Experimental Data

	D-Leu·(−)-PES	L-Leu·(−)-PES	D-Leu·(−)-PES·H_2O
Formula	$C_{14}H_{23}NO_5S$	$C_{14}H_{23}NO_5S$	$C_{14}H_{25}NO_6S$
Formula weight	317.40	317.40	335.41
Crystal system	Monoclinic	Monoclinic	Orthorhombic
Space group	$C2$	$P2_1$	$P2_12_12$
Z	4	2	4
a/Å	21.096(3)	14.789(1)	10.173(1)
b/Å	5.505(2)	5.788(1)	27.763(3)
c/Å	20.667(3)	9.830(1)	6.137(1)
β/deg	137.35(1)	107.41(1)	90
V/Å^3	1626.3(5)	802.9(2)	1733.2(4)
D_x/g cm^{-3}	1.296	1.313	1.285
μ(Cu $K\alpha$)/mm^{-1}	1.952	1.977	1.902
No. of reflections used:	1364	1521	1736
No. of parameters:	193	193	208
R	0.058	0.035	0.033
wR	0.115	0.091	0.090
Goodness-of-fit	1.020	1.077	1.027
$\rho_{\mathrm{max/min}}$ (e Å^{-3})	0.203/−0.283	0.265/−0.372	0.299/−0.237



D- or L- Leu (-)-PES

Fig. 2. Atomic numbering for X-ray analysis.

larger than those between the D- and L-salts, particularly for one of the bond angles to the phenyl moiety (C5–C6). It would appear that this conformational difference is related to intermolecular interactions through the water molecules of crystallization.

The torsion angles of the L-Leu molecules are also shown in Table 3, compared with the corresponding values for a free L-Leu in the literature.[8] The conformations of the Leu molecules can be mainly represented through the torsion angles of N1′–C2′–C3′–C4′, N1′–C2′–C6′–C7′, and C2′–C6′–C7′–C8′. The variations in the torsion angles among the three Leu molecules do not differ by more than ca.

Table 3. Selected Torsion Angles (°) of the Three Diastereomeric Salts

	D-Leu·(−)-PES	L-Leu·(−)-PES[a)]		D-Leu·(−)-PES·H_2O
PES				
O2–S1–C5–C6	−62.7	−49.7		−51.1
O3–S1–C5–C6	179.1	−171.1		−172.0
O4–S1–C5–C6	59.5	71.7		70.8
O2–S1–C5–C12	169.9	−176.7		−179.1
O3–S1–C5–C12	51.7	62.0		60.0
O4–S1–C5–C12	−67.9	−55.2		−57.2
S1–C5–C6–C7	−71.4	−80.1		−90.6
S1–C5–C6–C11	112.3	103.9		91.6
C12–C5–C6–C7	53.5	45.6		35.1
C12–C5–C6–C11	−122.9	−130.4		−142.7
Leu				
N1′–C2′–C3′–O4′	28.6	153.7	(154.3)	16.8
N1′–C2′–C3′–O5′	−154.5	−32.1	(−25.1)	−162.5
C6′–C2′–C3′–O4′	−91.4	−85.6	(−90.1)	−103.3
C6′–C2′–C3′–O5′	85.6	88.8	(90.5)	77.4
N1′–C2′–C6′–C7′	169.9	−175.9		172.3
C3′–C2′–C6′–C7′	−71.8	62.1		−69.4
C2′–C6′–C7′–C8′	−69.8	65.0		−60.6
C2′–C6′–C7′–C9′	167.7	−171.0		176.1

a) ( ): Torsion angles of the free L-Leu in the literature.[8]

13° and are almost similar, except for a difference (mirror image) in the D/L configuration on the chiral carbon atom (C2′). The torsion angles of these Leu molecules also agree moderately well with those of the free L-Leu. These observations show that the molecular geometries of the three Leu do not strikingly deform during optical resolution, although the previously reported HPG was somewhat flexible. Interestingly, the torsion angles of the D-Leu molecule in D-Leu·(−)-PES·H_2O, N1′–C2′–C3′–C4′, C6′–C2′–C3′–O4′, and C6′–C2′–C3′–C5′ depict slightly larger variations compared with those in D- and L-Leu·(−)-PES and the free Leu. This also seems to be due to intermolecular interactions through the water molecules of crystallization.

Thus, the torsion angles among the three PES and three Leu molecules, respectively, which were found to be slightly different, undeniably make a minor adjustment in the formation of a crystalline salt of PES with an amino acid.

Hydrogen Bonds and Crystal Packing. In crystal structures of the three salts, the carboxylate and ammonium groups of the Leu cations were mainly linked with the sulfonium group of the PES anions through hydrogen bonds as well as electrostatic and Van der Waals interactions. These ions are oriented in a definite parallel pattern of alternating Leu and PES molecules, the modes of which are hydrophobic layers comprising the PES phenyl and Leu methyl moieties and hydrophilic layers consisting of charged ions moieties. In particular, the characteristic hydrogen-bonding networks are noteworthy because they are strongly related to each other through hydrogen bonding, as listed in Table 4. Figures 3 and 4 show packing diagrams and stereodiagrams illustrating the three salts.

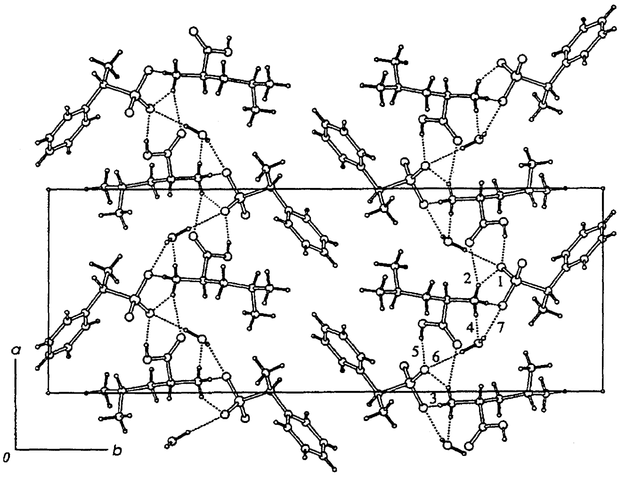
In the crystal packing of D-Leu·(−)-PES·H_2O [Fig. 3(a) and Fig. 4(a)], the Leu ammonium (N1′) group tightly forms several hydrogen bonds with the adjacent PES sulfonium oxygen, Leu carboxylate oxygen, and H_2O hydrogen. Additionally, the Leu carboxylate (O4′, O5′) bifurucately forms a short hydrogen bond (O5′–O4, 2.63 Å) with the sulfonium oxygen of the adjacent PES molecule and a normal hydrogen bond (N1′–O4′) with a carboxylate group of the other adjacent Leu molecule. The water molecule cross-links with one Leu and two PES molecules through three hydrogen bonds: N1′–O1″, O1″–O4, and O1″–O3. These hydrogen bonds form an asymmetric unit, which also links to both neighboring units related to a twofold screw axis; consequently, such tightly fixed hydrogen-bonding chain forms a helical zigzag-type column, elongating infinitely along the *a*-axis direction. Characteristically, the water molecules, through hydrogen-bonding bridges, probably play an important key role in the conformational stability among the molecules comprising the crystal.

In D-Leu·(−)-PES [Fig. 3(b) and Fig. 4(b)], two Leu ammoniums and two PES sulfoniums form a unit through several normal hydrogen bonds; this unit also links systematically to both neighboring units through a short hydrogen bond pair (O5′–O4′, 2.66 Å) linking between both the carboxylate oxygens of the Leu···two-Leu mode. This hydrogen-bonding scheme extends parallel along the *c*-axis direction, the pattern of which seems to be somewhat coarse and unbalanced, due to a lack of densely packed columnar hydrogen-bonds, particularly for a forcible twisted linkage mode of Leu···two-Leu carboxylates. Such a relatively looser crystal structure is considered to be less stable than that of D-Leu·(−)-PES·H_2O, having a stable hydrogen-bonding pattern of a zigzag type column; this may be one of the factors why D-Leu·(−)-PES

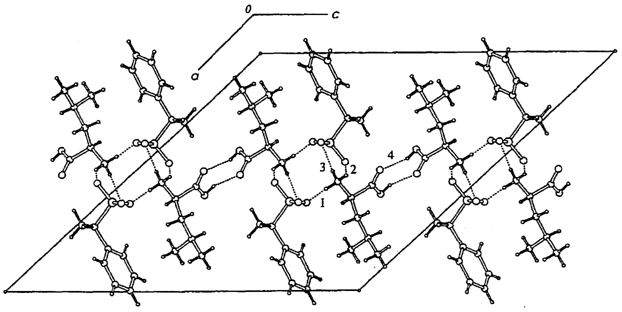
Table 4. Geometry of Interatomic Hydrogen Bonds (Å)

No	D–H···A	SYM	Distance	D–H	H–A	∠D–H···A (°)
	D-Leu·(−)-PES					
1	N1′–O4	1	2.821(13)	0.89	1.96	161
2	N1′–O3	2	2.836(11)	0.89	2.07	143
3	N1′–O2	2	2.923(7)	0.89	2.05	159
4	O5′–O4′	3	2.668(13)	0.82	1.88	159
	L-Leu·(−)-PES					
1	N1′–O3	5	2.907(5)	0.89	2.05	160
2	N1′–O4	1	2.831(5)	0.89	1.97	162
3	N1′–O4	6	2.874(4)	0.89	1.99	177
4	O5′–O3	7	2.758(4)	0.82	2.02	150
	D-Leu·(−)-PES·H_2O					
1	N1′–O4	1	3.102(4)	0.89	2.34	144
2	N1′–O4′	8	2.927(4)	0.89	2.24	134
3	N1′–O3	9	2.810(4)	0.89	1.95	163
4	N1′–O1″	1	2.833(5)	0.89	1.94	177
5	O5′–O4	8	2.633(4)	0.82	1.82	169
6	O1″–O4	8	3.055(5)	0.94	2.11	176
7	O1″–O3	1	2.890(5)	0.76	2.25	152

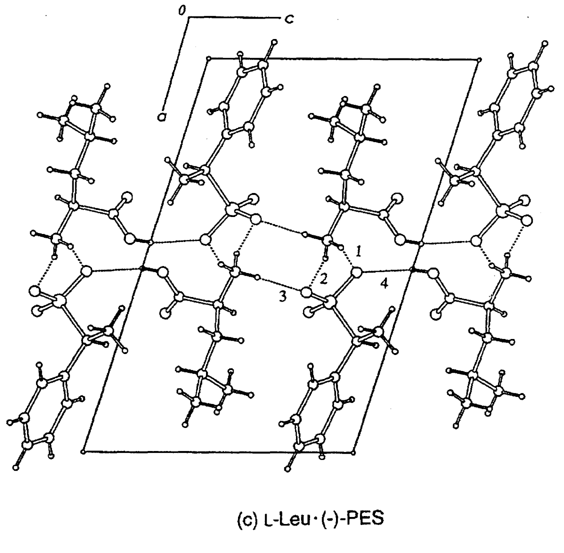
SYM: Symmetry cord
1: x, y, z. 2: $-x, y, -z$. 3: $0.5-x, 0.5+y, -z$. 4: $-x, 1+y, -z$. 5: $x, 1+y, z$. 6: $-x, 0.5+y, -z$. 7: $-x, 0.5+y, 1-z$. 8: $0.5+x, 0.5-y, -z$. 9: $x, y, 1-z$.



(a) D-Leu·(-)-PES·H_2O

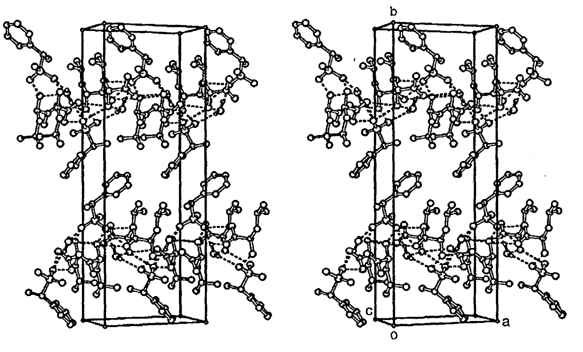


(b) D-Leu·(-)-PES

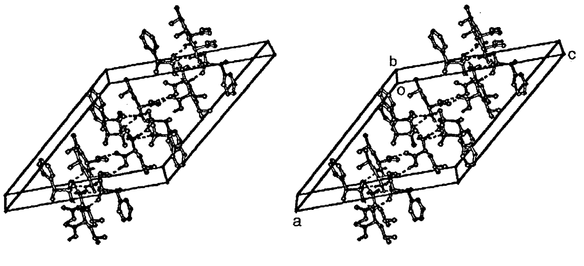


(c) L-Leu·(-)-PES

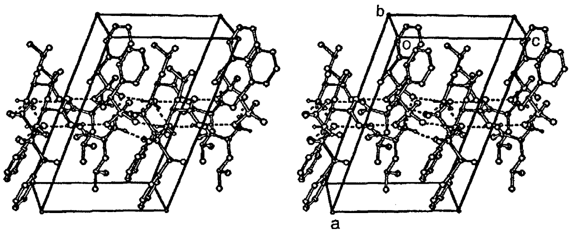
Fig. 3. Crystal structures of the three diastereomeric salts. Broken lines denote hydrogen bonds. The numbers indicate the interaction numbers shown in Table 4. The less-soluble (a) D-Leu·(−)-PES·H_2O and the more-soluble (c) L-Leu·(−)-PES in acetonitrile–water; the more-soluble (b) D-Leu·(−)-PES and the less-soluble (c) L-Leu·(−)-PES in acetonitrile–methanol.



(a) D-Leu·(-)-PES·H_2O



(b) D-Leu·(-)-PES



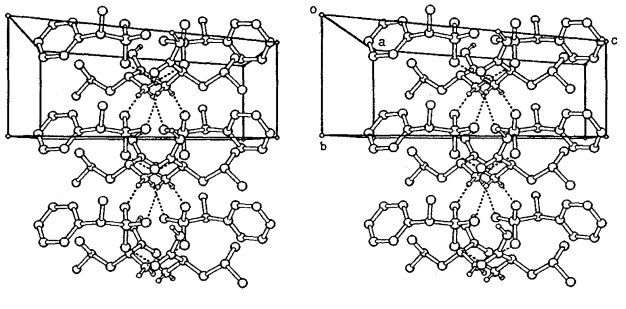
(c) L-Leu·(-)-PES

Fig. 4. Stereoscopic views of the three crystal structures. The less-soluble (a) D-Leu·(−)-PES·H_2O and the more-soluble (c) L-Leu·(−)-PES in acetonitrile–water; the more-soluble (b) D-Leu·(−)-PES and the less-soluble (c) L-Leu·(−)-PES in acetonitrile–methanol.

is easily transformed into the corresponding monohydrated salt by the approach of water molecules.

On the other hand, L-Leu·(−)-PES [Fig. 3(c) and Fig. 4(c)] has a unit comprising two pairs of Leu ammoniums and PES sulfoniums through several normal hydrogen bonds. This unit also links systematically to both neighboring units through a comparatively short hydrogen-bond pair (O5′–O3, 2.75 Å), characteristically observed between the Leu carboxylate oxygens and the adjacent PES sulfonium oxygens. Seemingly, though this unit is similar to that of D-salt as described above, both geometrical structures in more detail are moderately different, which is apparent from the characteristic difference in the partner molecules linking to each neighboring unit. Such a hydrogen-bonding scheme forms a pillar-type column structure around a twofold screw axis, which is parallel along the *c*-axis direction; this seems to be more dense and stable than that of the D-salt.

Consequently, these observations of hydrogen-bond networks indicate that the monoclinic *C*2 space group in the



D-Leu·(-)-PES

Fig. 5. Crystal packing structure of more-soluble D-Leu·(−)-PES observed from different direction.

crystals of D-Leu·(−)-PES is structurally transformed into the corresponding orthorhombic $P2_12_12$ space group by hydration. Such a space-group change, accompanying the formation of a twofold screw axis, is presumably strongly related to the density and stability of the whole crystal structure, which leads to the less solubility.

Relation between Structure and Thermodynamic Properties. Our final interest is in the role of the water of crystallization together with chiral recognition during optical resolution by a total comparison among the thermodynamical, physicochemical properties, and the crystal-packing structures of the three diastereomeric salts.

The differences between the crystal-packing structures of the more-soluble D- and the less-soluble L-Leu·(−)-PES could be attributed to the differences in their physicochemical properties, melting points and enthalpies of fusion, as shown in Table 1 and Fig. 1; these could be responsible for the difference between the two solubilities in acetonitrile–methanol. On the other hand, a similar comparison between the less-soluble D-Leu·(−)-PES·H_2O and the more-soluble L-Leu·(−)-PES is not simple, due to the existence of the water of crystallization. In D-Leu·(−)-PES·H_2O, however, the enthalpy of fusion for the dehydration DSC process is 62.7 kJ mol^{-1} (15 kcal mol^{-1}), which is large enough; this will be closely related to the difference between the two solubilities in acetonitrile–water.

Although a study of the role of solvation in a resolution system is very rare, Larsen et al. calculated the Gibbs free-energy (ΔG) values of the solvation reaction using the solubilities.[9] According to this method, the ΔG of the water-solvation reaction of D-Leu·(−)-PES is calculated to be ca. −8 kJ mol^{-1}; this minus value means that D-Leu·(−)-PES proceeds into the monohydrated form by a hydration reaction. Regretfully, this ΔG value may be considerably uncertain, because the solubilities of both D- and L-Leu·(−)-PES in each solvent, particularly in only the acetonitrile solvent, are very small.

In addition to these thermodynamic analyses, we noted in more detail the crystal-packing structure of D-Leu·(−)-PES observed from a different direction, as visualized in Fig. 5. This crystal structure seems to be alternating-crossing Leu and PES layers; also, the vacancy between both layers is moderately bigger. Such characteristic spaces, which are not observed in L-Leu·(−)-PES, appear to facilitate an invasion of water molecules, together with the relatively looser packing arrangement structure; consequently, the packing structure is transformed into a stable monohydrated form. As a tool, quantitative calculations of such a vacancy using computational techniques should furthermore help to clarify an answer to the plain question why D-Leu·(−)-PES is easily converted into the monohydrated salt in the presence of water.

Conclusions

The optical resolution of DL-Leu with (−)-PES preferentially crystallized L-Leu·(−)-PES from acetonitrile–methanol, whereas from acetonitrile–water D-Leu·(−)-PES·H_2O precipitated. This reversed-resolution result relates reasonably to the differences in the physicochemical properties between the less- and more-soluble salts in each solvent system, as well as to the differences in their X-ray crystal structures, consisting of the characteristic hydrogen-bonding networks. In particular, the more-soluble D-Leu·(−)-PES, consisting of a less-stable packing structure, was found to be structurally transformed into the less-soluble D-Leu·(−)-PES·H_2O having a more stable packing structure constructed through water molecules. The present work will supply some information that the water molecules of crystallization play an important role in chiral recognition together with selective crystallization during optical resolution.

Experimental

IR spectra were measured with a Perkin–Elmer 1600-series FTIR spectrophotometer using KBr disks. ^{1}H NMR spectra were recorded in DMSO-d_6 on a Bruker AC-200 (200 MHz) spectrometer. Optical rotations were obtained on a Perkin–Elmer 243 automatic polarimeter using a 10 cm water-jacketed cell. Elemental analyses were performed by a Perkin–Elmer 2400 elemental analyzer. The solubilities were determined by approaching saturation equilibrium from both undersaturation and supersaturation. The solute concentrations were measured at 35 °C with a Shimadzu LC-9A liquid chromatograph.

Materials: Optically active and racemic leucine were obtained from Tanabe Seiyaku, Co., Ltd. (−)-1-Phenylethanesulfonic acid (PES) was prepared according to our previously reported procedure.[10] All of the reagents and solvents (the water content of both methanol and acetonitrile were less than 0.1%) were used commercial products without further purification.

Optical Resolution of DL-Leucine. A solution of DL-leucine (2.0 g, 15.2 mmol) and (−)-PES (free acid: 2.89 g, 15.2×1.02 mmol) in 50% aqueous MeOH was evaporated to dryness, and the residue was further dried in vacuo at 80 °C for 5 h. The resulting crude DL-Leu·(−)-PES (4.90 g); $[\alpha]_D^{25}$ +9.5° (*c* 1, MeOH) was resolved by the following two procedures:

(i) The crude DL-Leu·(−)-PES (4.90 g) was dissolved in water (2 ml)/acetonitrile (40 ml) with heating. The solution was cooled to 40 °C and then seeded with crystals of D-Leu·(−)-PES·H_2O. After stirring at 23 °C for 4 h, the precipitated crystals were filtered by suction, washed with a small amount of acetonitrile, and dried to give crude D-Leu·(−)-PES·H_2O (1.73 g, 33.8%), $[\alpha]_D^{25}$ −18.3° (*c* 1, MeOH). An enantiomeric excess (ee) of the salt (Leu moiety) was determined to be 94.6% by a chiral HPLC analysis with a Daicel

CHIRALPAK CR(+) column; aqueous $HClO_4$ (pH 2).

(ii) The crude DL-Leu·(−)-PES (4.90 g) was dissolved in MeOH (4 ml)/ acetonitrile (36 ml) with heating. The solution was cooled to 40 °C, and then seeded with crystals of L-Leu·(−)-PES. After stirring at 23 °C for 4 h, the precipitated crystals were filtered by suction, washed with a small amount of acetonitrile, and dried at <50 °C to give crude L-Leu·(−)-PES (1.38 g, 28.5%), $[\alpha]_D^{25}$ $-3.0°$ (c 1, MeOH), 68.2 %ee (chiral HPLC).

Preparation of Pure D- and L-Leu·(−)-PES. The title compounds were reprepared, according to our previously reported procedure,[3] by the salt formation of optically pure leucine with (−)-PES.

After the resulting crude D- and L-Leu·(−)-PES were recrystallized from MeOH/acetonitrile, the crystals were dried in vacuo at 80 °C for 5 h to give optically pure D- and L-Leu·(−)-PES, respectively. Optically pure D-Leu·(−)-PES·H_2O was prepared by recrystallization of the crude D-Leu·(−)-PES from aqueous acetonitrile; the crystals were then dried at <50 °C for 5 h. The melting points, enthalpies of fusion, specific rotations, solubilities, and IR spectra of the three products were measured by the above-mentioned and following apparatus. The results are tabulated in Table 1. These ^{1}H NMR and elemental analyses were identical to our previously reported values within the experimental error.

Thermoanalysis (DSC, TG) Measurements. Differential-scanning calorimetric (DSC) traces were recorded on a Shimadzu DSC-50 system. Samples (2—5 mg) were sealed in aluminum lid-perforated pans. The temperature ranges were from ambient to approximately the decomposition of the salts at a heating rate of 5 °C min^{-1} under N_2 gas (30 ml min^{-1}). The DSC temperatures cited in this paper correspond to the peak maxima. Thermogravimetric (TG) traces were recorded on a Shimadzu TGA-50 system under a similar condition.

X-Ray Crystal Structure Determination. The single crystals of each salt were grown from the same solvent system as that used in the optical resolution. All of the intensity data were collected on a AFC5R diffractometer (Rigaku) using graphite monochromated Cu $K\alpha$ ($\lambda = 1.5418$ Å) radiation by a ω–2θ scan technique. The unit-cell dimensions were determined by a least-squares refinement using the setting angles of 25 reflections in the range of $35° < \theta < 45°$. The range of data collection was within $0° < \theta < 65°$. Three standard reflections were monitored every 200 reflection intervals and showed insignificant fluctuations. The data were corrected for Lorentz and polarization effects, but not for absorption. The structures were solved by a direct method using SHELXS-86,[11] and structure refinements on F^2 were carried out using SHELXL-93[12] with anisotropic temperature factors for all non-hydrogen atoms. All hydrogen atoms were found in a difference Fourier map, and were refined riding with the atoms to which they were bonded. The crystal data and final results are summarized in Table 2.

The authors are grateful to Drs. Kazuo Matsumoto, Tadashi Sato, Takeji Shibatani, and Tetsuya Tosa, Managing Directors of Tanabe Seiyaku Co., Ltd., for their encouragement and interest in this study.

References

1) a) A. N. Collins, G. N. Sheldrake, and J. Crosby, "Chirality in Industry," John Wiley & Sons, England (1992); b) J. Crosby, *Tetrahedron*, **47**, 4789 (1991); c) S. Kotha, *Tetrahedron*, **50**, 3639 (1994).

2) a) J. Jacques, A. Collet, and S. H. Wilen, "Enantiomers, Racemates, and Resolutions," Wiley-Interscience, New York (1981); b) N. L. Allinger and E. L. Eliel, *Top. Stereochem.*, **6**, 107 (1971); c) P. Newman, "Optical Resolution Procedures for Chemical Compounds," Optical Resolution Information Center, New York, Vol. 1 (1978) and Vol. 2 (1981).

3) R. Yoshioka, O. Ohtsuki, T. Da-te, K. Okamura, and M. Senuma, *Bull. Chem. Soc. Jpn.*, **67**, 3012 (1994).

4) a) W. H. Mills and K. A. C. Elliott, *J. Chem. Soc.*, **1928**, 1291; b) M. Matell, *Ark. Kemi.*, **3**, 129 (1951); c) R. R. Sealock, M. E. Speeter, and R. S. Schweet, *J. Am. Chem. Soc.*, **73**, 5386 (1951); d) B. Sjöberg, *Ark. Kemi.*, **9**, 295 (1956); e) L. Westman, *Ark. Kemi.*, **12**, 167 (1958); f) J. A. Berson and D. A. Ben-Efraim, *J. Am. Chem. Soc.*, **81**, 4083 (1959); g) M. J. Brienne, C. Ouannès, and J. Jacques, *Bull. Soc. Chim. Fr.*, **1967**, 613; h) D. Varech and J. Jacques, *Tetrahedron*, **28**, 5671 (1972); i) Y. Shimura and K. Tsutsui, *Bull. Chem. Soc. Jpn.*, **50**, 145 (1977); j) M. Kuramoto, Y. Kushi, and H. Yoneda, *Bull. Chem. Soc. Jpn.*, **51**, 3251 (1978); k) D. Kozma, Á. Nyéki, M. Ács, and E. Fogassy, *Tetrahedran: Asymmetry*, **5**, 315 (1994); l) S. Yamada, R. Yoshioka, and T. Shibatani, *Chem. Pharm. Bull.*, **45**, 1922 (1997).

5) For examples see: a) M. C. Brianso, *Acta Crystallogr., Sect. B*, **B37**, 618 (1981); b) R. O. Gould and M. C. Walkinshaw, *J. Am. Chem. Soc.*, **106**, 7840 (1984); c) R. O. Gould, R. Kelly, and M. C. Walkinshaw, *J. Chem. Soc., Perkin Trans. 2*, **1985**, 847; d) E. Fogassy, M. Ács, F. Faigl, K. Simon, J. Rohonczy, and Z. Ecsery, *J. Chem. Soc., Perkin Trans. 2*, **1986**, 1881; e) A. M. G. Kok, H. Wynberg, J. M. M. Smits, P. T. Beurskens, and V. Parthasarathi, *Acta Crystallogr., Sect. C*, **C43**, 1328, 1331, and 1336 (1987); f) S. P. Zingg, E. M. Arnett, A. T. McPhail, A. A. Bothner-By, and W. R. Gilkerson, *J. Am. Chem. Soc.*, **110**, 1565 (1988); g) A. D. van der Haest, H. Wynberg, F. J. J. Leusen, and A. Bruggink, *Recl. Trav. Chim. Pays-Bas*, **109**, 523 (1990); h) F. Faigl, K. Simon, A. Lopata, É. Kozsda, R. Hargitai, M. Czugler, M. Ács, and E. Fogassy, *J. Chem. Soc., Perkin Trans. 2*, **1990**, 57; i) F. J. J. Leusen, H. J. Bruins Slot, J. H. Noordik, A. D. van der Haest, H. Wynberg, and A. Bruggink, *Recl. Trav. Chim. Pays-Bas*, **110**, 13 (1991); j) S. Kuwata, J. Tanaka, N. Onda, T. Yamada, T. Miyazawa, M. Sugiura, Y. In, M. Doi, M. Inoue, and T. Ishida, *Bull. Chem. Soc. Jpn.*, **66**, 1501 (1993); k) K. Kinbara, K. Sakai, Y. Hashimoto, H. Nohira, and K. Saigo, *J. Chem. Soc., Perkin Trans. 2*, **1996**, 2615; l) M. R. Caira, R. Clauss, L. R. Nassimbeni, J. L. Scott, and A. F. Wildervanck, *J. Chem. Soc., Perkin Trans. 2*, **1997**, 763.

6) The efficiency of the optical resolution has been defined using the chemical yield (Y%) and the optical purity (OP% or ee%) as the following equation: $2Y \times \mathrm{OP}/100\%$.

7) These lists and $F_o - F_c$ tables have been deposited as Document No. 71025 at the Office of the Editor of Bull. Chem. Soc. Jpn.

8) M. Coll, X. Solans, M. Font-Altaba, and J. A. Subirana, *Acta Crystallogr., Sect. C*, **C42**, 599 (1986).

9) S. Larsen, D. Kozma, and M. Ács, *J. Chem. Soc., Perkin Trans. 2*, **1994**, 1091.

10) a) R. Yoshioka, M. Tohyama, O. Ohtsuki, S. Yamada, and I. Chibata, *Bull. Chem. Soc. Jpn.*, **60**, 649 (1987); b) E. J. Corey and J. I. Shulma, *Tetrahedron Lett.*, **1968**, 3655; c) A. M. Nazarov, V. D. Komissarov, and G. A. Tolstikov, *Zh. Org. Khim.*, **27**, 884 (1991); d) E. J. Corey and K. A. Cimprich, *Tetrahedron Lett.*, **1992**, 4099.

11) G. M. Sheldrick, "SHELXS-86: A Program for the Solution of Crystal Structures," University of Göttingen, Germany (1986).

12) G. M. Sheldrick, "SHELXL-93: A Program for Crystal Structure Refinement," University of Göttingen, Germany (1993).