Optical Resolution, Characterization, and X-Ray Crystal Structures of Diastereomeric Salts of Chiral Amino Acids with (*S*)-(−)-1-Phenylethanesulfonic Acid

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Ten DL-Amino acids (AA), including neutral, and basic amino acids, and an imino acid, were optically resolved, without derivatization into their covalent compounds, by means of fractional crystallization of their diastereomeric salts with (−)-1-phenylethanesulfonic acid (PES) in various solvents. Several pairs of the diastereomeric crystalline salts formed during the resolutions were analyzed by DSC and spectroscopy, which showed that the successful resolutions were attributable to differences in various physicochemical properties between the more-soluble D-AA·(−)-PES and less-soluble L-AA·(−)-PES. Chiral recognition of the most successfully resolved species, DL-*p*-hydroxyphenylglycine (HPG) salt, was explored by comparing the X-ray crystal structures of D- and L-HPG·(−)-PES. The two crystal structures differed obviously in their hydrogen-bonding networks: the less-soluble L-HPG·(−)-PES only had strong hydrogen-bonded infinite chains of HPG in a "head-to-tail" arrangement through the *p*-hydroxyl group, the structure of which was more geometrically stable than that of the more-soluble D-HPG·(−)-PES. The differences in the two crystal structures related to striking differences in their solubilities and thermal properties.

Although recent advances in asymmetric synthesis and biotechnology are noteworthy, they do not completely satisfy the increasing demand for optically pure compounds, particularly where industrial applications are concerned. Traditional optical resolutions and physicochemical separations are still employed as useful procedures for the commercial preparation of optically pure compounds.[1,2]

We have been studying efficient resolution methods for the practical preparation of chiral amino acids. Generally, optical resolution of neutral DL-amino acids becomes possible after conversion into suitable salts or covalent derivatives (e.g., *N*-acyl, ester, etc.). Practically speaking, underivatized DL-amino acids are more favorable for resolution through the direct formation of their salts with the resolving agents. As suitable agents for this purpose, we have been studying strong acids, particularly sulfonic acids. Of these, various achiral aromatic sulfonic acids have been successfully used in the optical resolution of many DL-amino acids by the preferential crystallization procedure.[3] While chiral sulfonic acids are available for diastereomeric resolution, there are only a few at present, and these are mostly *d*-camphorsulfonic acid and its derivatives.[2,4] Recently, we reported that chiral 1-phenylethanesulfonic acid (PES) was an efficient resolving agent for the practical asymmetric transformation of both *p*-hydroxyphenylglycine (HPG)[5] and aspartic acid *β*-methyl ester.[6] These successful results led us to examine in more detail the optical resolving power of PES.

Though the number of such diastereomeric resolutions is quite large, information concerning the physicochemical properties of a pair of diastereomers, particularly the more-soluble one, is poor. We suggest that this information may provide important insights into the recognition mechanism during optical resolution. Such studies of diastereomeric pairs were energetically performed by Fogassy,[7] Arnett,[8] and Wynberg's[9] groups, but much more examples are required to generate useful common characteristics. In connection with the above work, we are extending our study in order to explore the characteristic differences between a diastereomeric pair because of interest in the optical resolution efficiency and the design of chiral resolving agents.

The present paper describes systematic resolutions of various DL-amino acids using (−)-PES and, subsequently, explores the relationships between the successful resolutions and physicochemical properties of the diastereomeric salt pairs by various analyses including X-ray crystallography.

Results and Discussion

Although racemic and optically active PES are known compounds,[10] their preparation and physicochemical properties have not yet been detailed. We found that (±)-PES[11] could be successfully resolved using D-HPG as a resolving agent.[5] While chiral PES is a useful agent due to its optical and chemical stability, the known example used as a resolving agent is quite rare.[4,12]

Optical Resolution of DL-Amino Acids with (−)-PES. The small-scale resolutions of twenty DL-amino acids, including neutral, acidic, and basic amino acids, and an imino acid, were carried out through the fractional crystallization of their diastereomeric salts formed with a 1 molar equivalent of (−)-PES in several solvents. The results showed that fourteen amino acids were crystallized through their diastereomeric salts, and ten of these were evidently resolved, as shown in Ta-

Table 1. Optical Resolution of DL-Amino Acids with (−)-PES

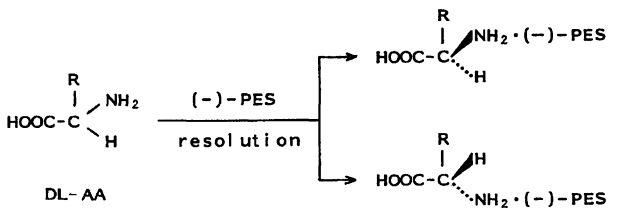
Fractional crystallization			Separated AA·(−)-PES			Optical
DL-AA·(−)-PES[a]	Solvent[b]	Temp	Yield[c]	$[\alpha]_D^{25}$/deg	Form	purity[d]
		°C	%	(*c*1, MeOH)		%
DL-Ala· (−)-PES	CH_3CN– (H_2O)	25	36.4	−4.5	L-· (−)	84
DL-ABA· (−)-PES	2-PrOH	25	48.4	−1.9	L-· (−)	95
DL-HPG· (−)-PES	H_2O	25	87.6	+74.8	L-· (−)	95
DL-Leu· (−)-PES	CH_3CN–(H_2O)	25	62.8	−15.2	D-· (−)	61
DL-Leu· (−)-PES	CH_3CN– (MeOH)	25	57.8	−2.9	L-· (−)	71
DL-*n*-Leu· (−)-PES	CH_3CN– (MeOH)	25	30.2	−0.7	L-· (−)	69
DL-PG· (−)-PES	*n*-BuOH	25	98.4	+44.6	L-· (−)	66
DL-Pro· (−)-PES	CH_3CN	5	38.4	−23.9	L-· (−)	91
DL-Ser· (−)-PES	CH_3CN–(MeOH)	25	68.4	−6.2	L-· (−)	91
DL-Val· (−)-PES	CH_3CN–(H_2O)	25	78.8	+2.3	L-· (−)	90
DL-Lys· (−)-PES	MeOH	25	66.0	+2.5[e]	L-· (−)	83

a) ABA: 2-aminobutyric acid, *n*-Leu: norleucine, PG: phenylglycine. b) See: Solubility in Table 2. ( ): A slight amount of the solvent was used. c) Based on 1/2 DL-AA·(−)-PES. d) Optical purities of free amino acids obtained by salt decomposition of AA·(−)-PES. e) *c*1, H_2O.

ble 1. In particular, HPG, serine, valine, and lysine could be successfully resolved. These diastereomeric salts (optical purity ca. 90%) could be completely optically purified by recrystallization from the corresponding solvent.

Interestingly, as shown in Table 1, all the resolutions of DL-amino acids (AA) with (−)-PES led to less-soluble salts, L-AA·(−)-PES, and more-soluble salts, D-AA-(−)-PES, in the prescribed solvents, without regard to their α-substituent groups (R) (Scheme 1). In the first resolution of DL-leucine with (−)-PES, however, D-Leu·(−)-PES preferentially crystallized from aqueous acetonitrile. In contrast, when acetonitrile–methanol was used as a solvent, L-Leu·(−)-PES crystallized as the less-soluble salt. Such a phenomenon is occasionally encountered through solvation or association of diastereomeric salts in a solvent.[13] This result proved that D-Leu·(−)-PES preferentially crystallized as the less-soluble monohydrate (H_2O) from aqueous acetonitrile (see solubility in Table 2). This solvation was also observed for L-Pro·(−)-PES.

Thus, optically active PES was a valuable resolving agent for underivatized DL-amino acids. No other such advantageous resolving agents exist. Even the resolving power of well-known *d*-camphorsulfonic acid is only useful for DL-phenylglycine.[14] Since there are only a few chiral organic strong acids, new chiral sulfonic acids containing the substituted PES are expected to become useful resolving agents for either racemic amino acids



Scheme 1.

or amines.

Properties of D- and L-AA·(−)-PES. In order to explore the characteristics of the successful resolutions of DL-AA·(−)-PES shown in Table 1, the physicochemical properties of their diastereomeric salt pairs were examined. Optically pure D- and L-AA·(−)-PES, prepared by the salt formation of equimolar amounts of the corresponding D- and L-amino acids with (−)-PES, were analyzed with several instruments. The results are shown in Table 2.

The ^{1}H NMR spectra (see Experimental Section) of the two diastereomeric salts agreed within experimental error. Such a result was also obtained for other diastereomeric pairs in our studies[5,6] and in the literature.[15] This is presumably responsible for the fact that counterions of a diastereomeric salt dissociated in ^{1}H NMR solvent were determined as independent ions without influencing each other.

On the other hand, the melting points, enthalpies of fusion, optical rotations, solubilities, and infrared spectra of the salts differed remarkably. Among these data, the great difference in the solubility between the two diastereomeric salts led to the high resolution yields, as shown in the resolution of HPG, serine, valine, and lysine. In particular, the solubility of D-HPG·(−)-PES in water at 25°C is 88 times greater than that of L-HPG·(−)-PES, which resulted in the highest resolution efficiency.

It is also notable that the melting points and enthalpies of fusion of L-AA·(−)-PES were relatively larger than those of D-AA·(−)-PES. In such thermodynamic studies of resolution, these values are known to be closely associated with the solubilities, for instance, as expressed by the applied form of the Schröder–Van Laar equation.[16] However, examples are scarce in the literature.[17] It is generally recognized that both the melting point and the enthalpy of fusion of a less-soluble diastereomer are larger than those of a more-sol-

Table 2. Crystal Properties of D- and L-AA·(−)-PES

[D- and L-AA·(−)-PES]

AA·(−)-PES	Form of AA	Mp °C	ΔH^{f} a) kJ mol^{-1}	Solubility d) g/100 g solv.	$[\alpha]_D^{25}$/deg (*c* 1,MeOH)	IR (cm^{-1}) f) C=O
Ala· (−)-PES	D	135	19.1	45.1(A)	+18.2	1750
	L	173	29.8	7.0(A)	−4.6	1740
ABA· (−)-PES	D	160	26.2	15.9(B)	−21.9	1765
	L	182	31.4	4.2(B)	−0.5	1745
HPG· (−)-PES	D	226	37.1	96.8(C)	−98.6	1740
	L	262	95.3 b)	1.1(C)	+78.9	1720
Leu· (−)-PES	D	172	7.0, 22.8 c)	3.7(D)	−18.1	1740
·H_2O	D	172	6.5, 56.2 c)	1.7(A)	−20.2	1740
	L	223	10.9, 28.1 c)	0.9(D),4.0(A)	−0.2	1750
n-Leu· (−)-PES	D	113	22.6	6.2(D)	−23.6	1740
	L	196	25.2	0.7(D)	+3.4	1750
PG· (−)-PES	D	191	30.8	9.9(E)	−89.2	1745
	L	199	26.0	0.5(E)	+72.7	1715
Pro· (−)-PES	D	Oil	—	—	—	—
·H_2O	L	93	53.2	—	−25.8	1740
Ser· (−)-PES	D	138	22.3	38.7(F)	−15.7	1760
	L	163	39.8	8.1(F)	−5.7	1745
Val· (−)-PES	D	140	19.4	38.6(A)	−24.4	1710
	L	191	37.1	2.9(A)	+3.6	1750
Lys· (−)-PES	D	190	17.6	20.1(G)	−9.2 e)	1610
	L	233	37.4	1.1(G)	+3.0 e)	1620

a) ΔH^{f}: Enthalpy of fusion. b) Fusion process accompanied with decomposition. c) Leu·(−)-PES has two peaks of fusion. d) At 25°C. Solvent (v/v): A = CH_3CN/H_2O (95/5), B = 2−propanol, C = H_2O, D = CH_3CN/MeOH (95/5), E = 1−butanol, F = CH_3CN/MeOH (8/2), G = MeOH. e) *c*1, H_2O. f) ^{1}H NMR: see Experimental Section.

uble diastereomer, but only in the complicated case of polymorphism and solvation; that is, a crystalline solid of the less-soluble diastereomer is more thermodynamically stable than that of the more-soluble one because of the differences in their lattice and surface energies. In Tables 1 and 2, the results approximately satisfy the above concept. For instance, the enthalpy difference of ca. 20 kJ mol^{-1} in the diastereomeric salt pairs of serine, valine, and lysine is sufficiently large, which relates reasonably to the large differences in solubility; this led to efficient optical resolutions. Unfortunately, the enthalpy of fusion of the HPG pair could not be accurately compared, owing to the decomposition of L-HPG·(−)-PES. Strangely, D-PG·(−)-PES had a lower melting point and a larger enthalpy of fusion than L-PG·(−)-PES. This may cast some doubt on the idea that polymorphism is a cause of the change in the fusion process, but the details are still vague.

Another interesting phenomenon is the inversion in the relative solubility of D- and L-Leu·(−)-PES by solvation. This substantiates the important role of water molecules in selective crystallization during the resolution of DL-Leu·(−)-PES, and suggests that the crystal packing mode of D-Leu·(−)-PES·H_2O is more structurally stabilized by hydrogen bonding to water molecules. Unfortunately, such solvation of other diastereomeric pairs is not apparent and sometimes perplexes investigators in this field. In the near future, the solvation problem of the Leu salts could be clarified by their X-ray crystal structure analyses.

X-Ray Study of a Diastereomeric Salt Pair.[7—9,18] To obtain information on the crystal structures of diastereomeric salts of amino acids with (−)-PES, we carried out X-ray crystallographic analyses of both more-soluble D-HPG·(−)-PES and less-soluble L-HPG·(−)-PES. (We chose this pair because of the great solubility difference.)

Crystals of the two salts are colorless needles in the rhombic $P2_12_12_1$ space group. The fractional coordinates, bond lengths, and bond angles are given in Tables 3, 4, and 5, respectively. Perspective drawings of these salts are shown in Fig. 1 along with the atomic numbering scheme. The absolute configuration of (−)-PES was elucidated to be (*S*) by correlation with the known configuration of D-(*R*)-HPG.

In the two crystal structures, hydrogen-bonding networks are particularly noteworthy: The HPG cations and PES anions are linked by normal or strong hydrogen bonds involving the oxygen atom of the SO_3 group as the acceptor, and the carboxyl, *p*-hydroxyl, and ami-

Table 3. Fractional Coordinates ($\times 10^4$, S$\times 10^5$) and Thermal Parameters (Å^2) of Non-H Atoms with esd Values in Parentheses

Atom	x	y	z	B_{eq}	Atom	x	y	z	B_{eq}
D-HPG·(−)-PES					L-HPG·(−)-PES				
S1	70048(8)	75968(8)	54322(25)	2.69	S1	22311(4)	81034(5)	59178(2)	1.84
O2	6297(2)	7964(2)	5020(7)	3.48	O2	1473(1)	8226(2)	5784(5)	2.72
O3	7566(2)	8167(2)	4702(7)	3.43	O3	2606(1)	8864(1)	5030(6)	2.71
O4	7094(2)	7324(2)	7776(7)	4.12	O4	2484(2)	7871(2)	8321(5)	3.46
C5	7062(4)	6687(4)	3654(12)	4.08	C5	2445(2)	7272(2)	3825(7)	2.11
C6	6454(3)	6092(3)	4056(12)	3.60	C6	2015(2)	6478(2)	4279(7)	1.95
C7	6397(4)	5620(4)	6007(14)	4.93	C7	2123(2)	5968(2)	6287(8)	2.81
C8	5831(4)	5067(4)	6303(15)	4.85	C8	1733(2)	5223(3)	6603(9)	3.50
C9	5332(4)	4984(4)	4640(16)	6.13	C9	1228(2)	4996(3)	4893(9)	3.52
C10	5398(4)	5448(5)	2715(17)	6.69	C10	1119(2)	5505(3)	2934(10)	3.51
C11	5945(4)	5996(4)	2380(13)	7.76	C11	1507(2)	6247(3)	2610(8)	2.82
C12	7813(4)	6296(5)	3978(20)	5.40	C12	3237(2)	7109(3)	3831(10)	3.66
C1′	6767(3)	936(3)	4268(10)	2.78	C1′	1170(2)	231(2)	5244(7)	1.85
N2′	7451(2)	1279(3)	5207(8)	3.14	N2′	1928(1)	483(2)	5440(6)	1.99
C3′	6666(3)	66(3)	5242(10)	3.01	C3′	1083(2)	−259(2)	2877(7)	1.98
O4′	6894(2)	−133(2)	7102(7)	3.89	O4′	1522(1)	−302(2)	1315(5)	2.89
O5′	6313(2)	−421(2)	3839(8)	3.84	O5′	463(1)	−632(2)	2769(6)	2.90
C6′	6155(3)	1515(3)	4797(11)	2.88	C6′	707(2)	1019(2)	5381(7)	1.67
C7′	5776(3)	1464(4)	6852(10)	3.33	C7′	239(2)	1114(2)	7279(7)	2.10
C8′	5219(3)	2021(4)	7268(12)	3.81	C8′	−174(2)	1845(2)	7450(7)	2.37
C9′	5038(3)	2619(3)	5679(12)	3.78	C9′	−109(2)	2471(2)	5713(7)	2.17
C10′	5426(4)	2675(4)	3623(13)	4.39	C10′	350(2)	2380(2)	3774(8)	2.53
C11′	5979(3)	2126(4)	3226(11)	3.66	C11′	758(2)	1645(2)	3612(7)	2.32
O12′	4471(2)	3137(3)	5915(9)	5.51	O12′	−493(1)	3214(2)	5809(6)	3.33

$B_{eq}=4/3(B_{11}a^2+B_{22}b^2+B_{33}c^2+B_{12}ab\cos c+B_{13}ac\cos b+B_{23}bc\cos a)$.

Table 4. Bond Lengths (Å) for D- and L-HPG·(−)-PES with esd Values in Parentheses

	D-HPG·(−)-PES	L-HPG·(−)-PES
S1–O2	1.473(4)	1.463(2)
S1–O3	1.458(4)	1.473(3)
S1–O4	1.449(4)	1.453(4)
S1–C5	1.791(6)	1.786(4)
C5–C6	1.504(9)	1.510(5)
C5–C12	1.556(10)	1.533(5)
C6–C7	1.372(10)	1.380(6)
C6–C11	1.379(10)	1.384(6)
C7–C8	1.394(10)	1.395(6)
C8–C9	1.359(12)	1.393(7)
C9–C10	1.355(13)	1.357(7)
C10–C11	1.364(11)	1.390(6)
C1′–N2′	1.502(7)	1.504(4)
C1′–C3′	1.513(8)	1.521(5)
C1′–C6′	1.509(8)	1.520(5)
C3′–O4′	1.213(7)	1.202(5)
C3′–O5′	1.311(7)	1.321(4)
C6′–C7′	1.401(9)	1.383(5)
C6′–C11′	1.381(8)	1.386(5)
C7′–C8′	1.396(9)	1.394(5)
C8′–C9′	1.376(9)	1.375(5)
C9′–C10′	1.410(10)	1.388(6)
C9′–O12′	1.357(7)	1.377(4)
C10′–C11′	1.381(9)	1.393(5)

no groups as donors (Fig. 2). The lengths of these hydrogen bonds are given in Table 6. In less-soluble L-HPG·(−)-PES [Fig. 3(b)], the hydroxyl O(5′) atom of the carboxyl group forms a strong hydrogen bond (2.673 Å) with the phenyl hydroxyl O(12′) atom of the adjacent HPG molecule. This bond forms an infinite chain of HPG molecules in a "head-to-tail" arrangement. The PES molecules are attached to this infinite chain through a strong hydrogen bond (2.648 Å) between the phenyl hydroxyl O(12′) and the sulfonium O(2) atom.

On the other hand, in more-soluble D-HPG·(−)-PES [Fig. 3(a)], the phenyl hydroxyl O(12′) atom forms a usual hydrogen bond with the sulfonium O(2) atom, and the hydroxyl O(5′) atom forms a strong hydrogen bond (2.672 Å) with the sulfonium O(2) atom.

Consequently, the strong hydrogen-bonded infinite chain [O(5′)–O(12′)] of HPG molecules, observed in L-HPG·(−)-PES, does not exist in D-HPG·(−)-PES. Additionally, in L-HPG·(−)-PES, the sulfonium O(3, 4) atoms are usually three-hydrogen-bonded with N(2′, 2′) atoms, while in D-HPG·(−)-PES, the sulfonium O-(3,4) atoms and the carbonyl O(4′) atom are usually two-hydrogen-bonded with the N(2′) atom. These observations reveal that the crystal structure of less-soluble L-HPG·(−)-PES, stabilized by the strong hydrogen-bonded infinite chains of HPG, is more geometrically stable than that of more-soluble D-HPG·(−)-PES. Such differences between the two crystal structures could be attributed to the differences in their physicochemical properties shown in Table 2, which could be responsi-

Table 5. Bond Angles (°) D- and L-HPG·(−)-PES with esd Values in Parentheses

	D-HPG·(−)-PES	L-HPG·(−)-PES
O2–S1–O3	110.8(2)	111.0(1)
O2–S1–O4	112.3(3)	114.0(2)
O2–S1–C5	106.4(3)	106.8(2)
O3–S1–O4	112.4(2)	110.1(2)
O3–S1–C5	107.1(3)	105.4(2)
O4–S1–C5	107.4(3)	109.1(2)
S1–C5–C6	112.1(5)	111.7(3)
S1–C5–C12	108.0(5)	110.2(3)
C6–C5–C12	114.6(5)	113.5(3)
C5–C6–C7	122.4(6)	121.9(3)
C5–C6–C11	119.1(6)	119.1(3)
C7–C6–C11	118.5(6)	118.9(3)
C6–C7–C8	120.8(7)	120.4(4)
C7–C8–C9	120.0(8)	119.9(4)
C8–C9–C10	118.6(7)	119.5(4)
C9–C10–C11	122.7(8)	120.8(4)
C6–C11–C10	119.6(7)	120.5(4)
N2′–C1′–C3′	107.8(4)	107.4(3)
N2′–C1′–C6′	110.7(4)	110.1(3)
C3′–C1′–C6′	112.9(4)	112.9(3)
C1′–C3′–O4′	122.3(5)	124.3(3)
C1′–C3′–O5′	111.8(5)	111.1(3)
O4′–C3′–O5′	125.9(5)	124.6(4)
C1′–C6′–C7′	121.9(5)	120.1(3)
C1′–C6′–C11′	118.6(5)	119.9(3)
C7′–C6′–C11′	119.4(5)	119.9(3)
C6′–C7′–C8′	119.6(5)	120.4(3)
C7′–C8′–C9′	120.7(6)	119.2(3)
C8′–C9′–C10′	119.6(5)	121.2(3)
C8′–C9′–O12′	123.3(6)	121.9(3)
C10′–C9′–O12′	117.0(6)	116.9(3)
C9′–C10′–C11′	119.5(6)	119.2(3)
C6′–C11′–C10′	121.2(6)	120.1(4)

Table 6. Interatomic Distances (Å) in the Crystal with esd Values in Parentheses

	Atom1–Atom2	(SM)[a]	Translation			Distance
			x	y	z	
D-HPG·(−)-PES						
	O2–O5′	(1)	0	0	0	2.672(5)
	O2–O12′	(4)	0	0	0	2.798(7)
	O3–N2′	(2)	0	0	0	2.776(6)
	O4–N2′	(2)	0	0	1	2.781(6)
	N2′–O4′	(2)	0	0	0	2.859(6)
L-HPG·(−)-PES						
	O2–O12′	(4)	0	0	0	2.648(4)
	O3–N2′	(1)	0	1	0	2.857(4)
	O3–N2′	(2)	0	0	0	2.867(4)
	O4–N2′	(2)	0	0	1	3.045(4)
	O5′–O12′	(4)	0	0	−1	2.673(4)

a) (SM): Symmetry (1) $x\ y\ z$, (2) $0.5-x\ -y\ 0.5+z$, (3) $0.5+x\ 0.5-y\ -z$, (4) $-x\ 0.5+y\ 0.5-z$.

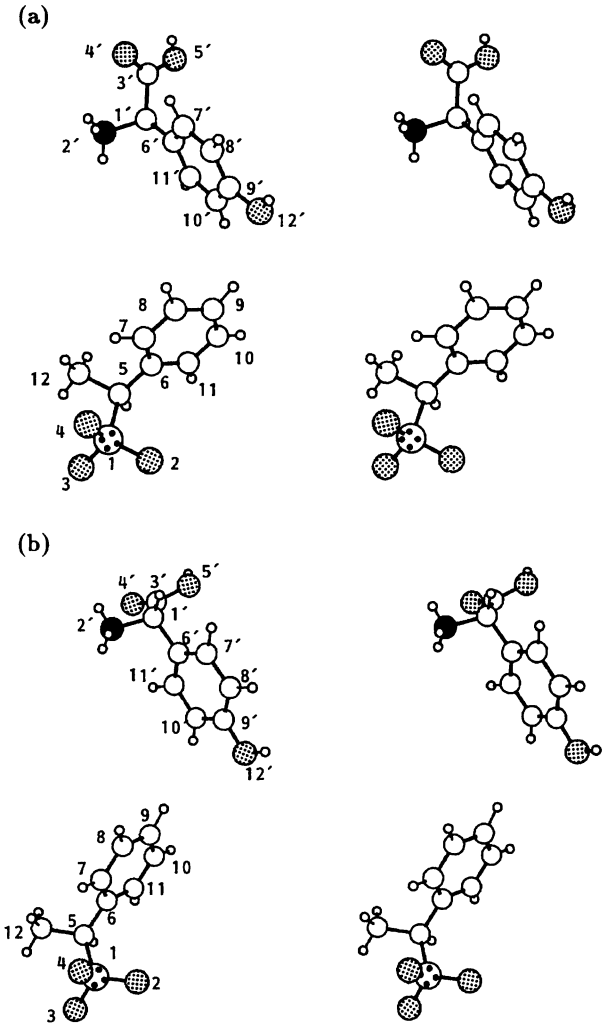


Fig. 1. Labeled stereoscopic drawings of diastereomeric salts. (a) D-HPG·(−)-PES; (b) L-HPG·(−)-PES. H, ○; C, ○; O, ◍; N, ●; S, ⊛.

Table 7. Torsion Angles (°) of D- and L-HPG·(−)-PES

	D-HPG·(−)-PES	L-HPG·(−)-PES
PES		
O2–S1–C5–C6	−54.65	−51.01
O3–S1–C5–C6	−173.23	−171.76
O4–S1–C5–C6	65.79	72.56
C12–C5–C6–C7	51.88	52.07
C12–C5–C6–C11	−126.28	−126.63
HPG		
C7′–C6′–C1′–N2′	−86.80	−119.90
C11′–C6′–C1′–N2′	91.47	59.52
C7′–C6′–C1′–C3′	34.13	118.45
C11′–C6′–C1′–C3′	−147.60	−62.13
C6′–C1′–C3′–O5′	87.43	−68.07
C6′–C1′–C3′–O4′	−92.86	111.99

ble for the great difference between the two solubilities.

The torsion angles are given in Table 7. While the conformations of the PES anions in both diastereomeric salts are approximately similar, those of the HPG cations are not mirror-related because of striking differences around the C(6′)–C(1′) bond. Consequently, PES is conformationally rigid, in contrast to flexible HPG. This rigid PES strongly stabilizes the flexible

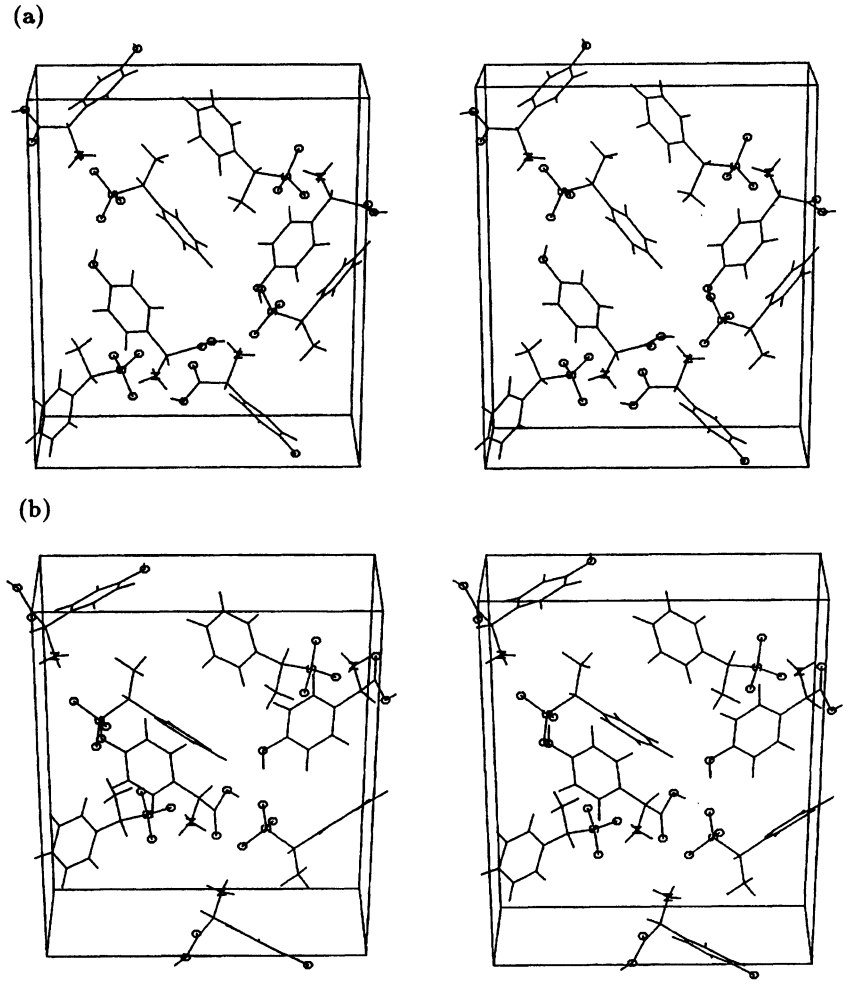


Fig. 2. Stereoscopic views of the crystal structures. (a) D-HPG·(−)-PES; (b) L-HPG·(−)-PES.

HPG through hydrogen bonds, which may be closely related to selective crystallization and crystal packing of the two diastereomeric salts. In particular, the strong infinite chains of HPG in the less-soluble L-HPG·(−)-PES could be strengthened by the action of rigid PES. Thus, a combination of the flexible DL-HPG and the rigid (−)-PES seems to be one of the favorable conditions for successful resolution.

As for the roles of the functional groups, it is also worth noting that the *p*-hydroxyl group of HPG forms different hydrogen bonds in the two crystal structures. This *p*-hydroxyl group, together with the conformational flexibility of HPG, presumably plays an important key role in chiral recognition for successful resolution. Interestingly, these characteristics of HPG have something in common with useful chiral resolving agents that have a hydroxyl group (e.g., tartaric acid,[19] ephedrine,[20] and 2-(benzylamino)-1-butanol[21]). DL-HPG is also known to be a very resolvable amino acid, as shown by the successful resolutions of the diastereomers[5,22] and the enantiomers.[23] This leads us to the assumption that optically active HPG and its analogues may be attractive as resolving agents for rigid racemic compounds.

Furthermore, X-ray crystallography studies of the other D- and L-AA·(−)-PES in Table 2 are now under way, which will clearly characterize the relationships between their physicochemical properties (especially the solubility) and their crystal structures.

Conclusions

Optically active PES was found to be a good resolving agent since ten free DL-amino acids could be successfully resolved directly. Comparison of the physicochemical properties of the diastereomeric pairs of the ten resolvable DL-AA·(−)-PES revealed that the less-soluble L-AA·(−)-PES are more thermodynamically stable than the more-soluble D-AA·(−)-PES. This related reasonably to other studies on the thermal behavior of diastereomeric pairs.[7—9] A worthwhile observation is that the successful resolution of DL-HPG·(−)-PES can be attributed to the striking differences in both the physicochemical properties and X-ray crystal structures of the more- and less-soluble salts. From these crystal structures, it is suggested that the combination of flexible DL-HPG and rigid (−)-PES is closely related to chiral recognition together with some role of the *p*-hydroxyl group of HPG in the hydrogen-bonding network.

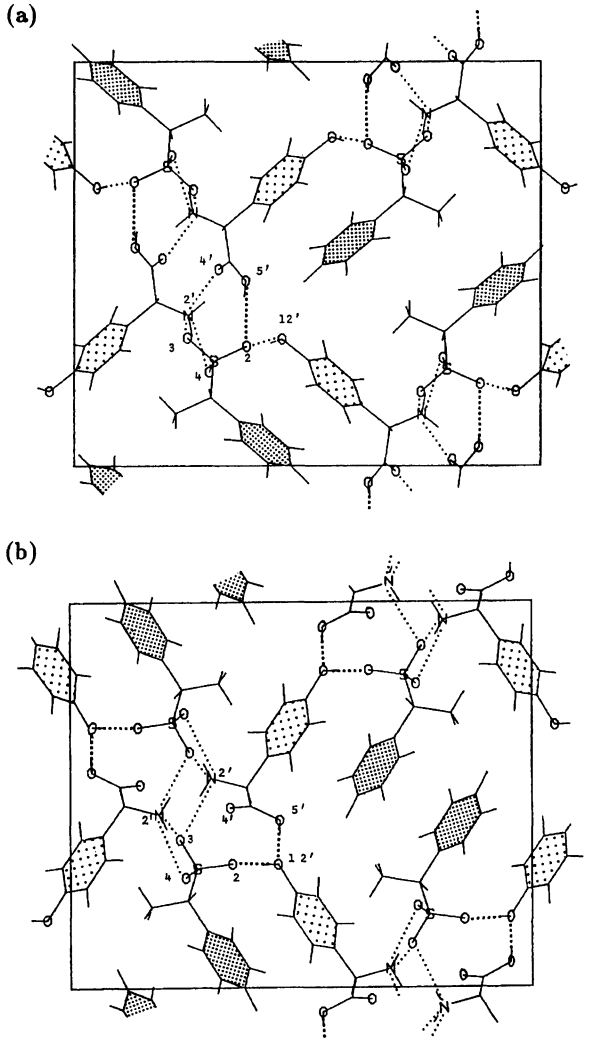


Fig. 3. Crystal structures of diastereomeric salts projected along the *c*-axis. Broken lines denote interionic hydrogen bonds. (a) D-HPG·(−)-PES; (b) L-HPG·(−)-PES.

Experimental

Melting points and enthalpies of fusion were taken with a Shimadzu DSC-50 differential scanning calorimeter at a heating rate of 5°C min^{-1} under N_2 gas. IR spectra were measured in nujol mulls with a Shimadzu IR-420 spectrophotometer. ^{1}H NMR spectra were recorded in DMSO-d_6 on a Hitachi Perkin–Elmer R-40 (90 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 240 elemental analyzer. Solubility was determined by approaching saturation equilibrium from both undersaturation and supersaturation. Solute concentrations were measured at 35°C with a Shimadzu LC-6A liquid chromatograph.

Optically active and racemic amino acids were manufactured by Tanabe Seiyaku, Co., Ltd. (−)-1-Phenylethanesulfonic acid (PES) was prepared according to our previously reported procedure[5] [(−)-PES: pasty crystals or syrup; $[\alpha]_D^{25}$ −6.2° (*c*3, H_2O), Na salt; $[\alpha]_D^{25}$ −15.5° (*c*1, MeOH)].

General Procedure for the Optical Resolution of DL-Amino Acids. Unless otherwise noted, the resolution was carried out as follows: A solution of a DL-amino acid (AA, 10 mmol) and (−)-PES (free acid, 10×1.05 mmol) in 50% aqueous MeOH was evaporated to dryness, and the residue was further dried in vacuo at 50°C for 3 h. The resulting salt crystals were dissolved in the prescribed solvent (4—30 ml) with heating and then the solution was slowly cooled to 25°C with stirring. (Some solutions were further cooled, concentrated or added to a second solvent, when nothing or a few salt crystals appeared.) After stirring at the same temperature for 2 h, the crystals which precipitated were filtered by suction, washed with a small amount of cold solvent, and dried to give crude L- or D-AA·(−)-PES. The specific rotation was then measured. The optical purity and resolution degree were calculated from the specific rotation of the free amino acid obtained by the following salt decomposition: A part of the crude diastereomeric salt was dissolved in water, and the solution was passed through a column packed with Amberlite IR-120 (H^+ form). The column was then washed with water and eluted with 5% aqueous ammonia. The eluate was concentrated, treated with charcoal, and evaporated to dryness in vacuo to obtain the free amino acid, and its rotation was measured.

Table 1 indicates the results of the optical resolution of various DL-amino acids with (−)-PES by the above procedure.

Preparation of Pure L- and D-AA·(−)-PES. The title compounds were prepared by the salt formation of optically pure amino acids with (−)-PES: An L-amino acid (10 mmol) and (−)-PES (free acid, 10×1.05 mmol) were dissolved in 50% aqueous MeOH. The MeOH solution was treated with active charcoal and evaporated to well-dryness under reduced pressure. The resulting crude L-AA·(−)-PES was recrystallized from the prescribed solvent (water, MeOH, CH_3CN, etc., and mixed solvent) to give optically pure L-AA·(−)-PES. Optically pure D-AA·(−)-PES was prepared in a similar manner. The melting points, enthalpies of fusion, specific rotations, solubilities, and IR spectra of the two products are tabulated in Table 2. These ^{1}H NMR and elemental analyses are shown as follows (unless otherwise noted, characteristic ^{1}H NMR spectra of D-AA·(−)-PES were identical to that of L-AA·(−)-PES within experimental error).

D-Ala·(−)-PES: ^{1}H NMR δ=1.35 (d, 3H, J=7 Hz, CH_3), 1.47 (d, 3H, J=7 Hz, CH_3), 3.6—4.0 (m, 2H, CH ×2), 7.1—7.5 (m, 5H, Ar H), and 8.17 (brs, 3H, NH_3^+). Anal. Calcd for $C_{11}H_{17}O_5S$: C, 47.99; H, 6.22; N, 5.09; S, 11.64%. Found: C, 47.99; H, 6.19; N, 5.03; S, 11.58%.

L-Ala·(−)-PES: Found: C, 48.03; H, 6.23; N, 5.13; S, 11.76%.

D-ABA·(−)-PES: ^{1}H NMR δ=0.92 (t, 3H, J=7 Hz, CH_3), 1.47 (d, 3H, J=7 Hz, CH_3), 1.6—2.0 (m, 2H, CH_2), 3.5—4.0 (m, 2H, CH×2), 7.1—7.5 (m, 5H, Ar H), and 8.18 (brs, 3H, NH_3^+). Anal. Calcd for $C_{12}H_{19}NO_5S$: C, 49.81; H, 6.62; N, 4.84; S, 11.08%. Found: C, 49.77; H, 6.61; N, 4.79; S, 11.19%.

L-ABA·(−)-PES: Found: C, 49.93; H, 6.73; N, 4.83; S, 11.15%.

D-Val·(−)-PES: ^{1}H NMR δ=0.94 (d, 3H, J=2 Hz, CH_3), 1.02 (d, 3H, J=2 Hz, CH_3), 1.47 (d, 3H, J=7 Hz, CH_3), 2.0—2.4 (m, 1H, CH), 3.70 (m, 1H, CH), 7.1—7.5

(m, 5H, Ar H), and 8.2 (brs, 3H, NH_3^+). Anal. Calcd for $C_{13}H_{21}NO_5S$: C, 51.47; H, 6.98; N, 4.62; S, 10.57%. Found: C, 51.53; H, 7.01; N, 4.62; S, 10.49%.

L-Val·(−)-PES: Found: C, 51.53; H, 7.07; N, 4.71; S, 10.63%.

D-Leu·(−)-PES: ^{1}H NMR δ=0.90 (d, 6H, J=7 Hz, $CH_3\times2$), 1.47 (d, 3H, J=7 Hz, CH_3), 2.65 (m, 2H, CH_2), 3.5—3.9 (m, 2H, CH×2), 7.1—7.5 (m, 5H, Ar H), and 8.20 (brs, 3H, NH_3^+). Anal. Calcd for $C_{14}H_{23}NO_5S$: C, 52.98; H, 7.30; N, 4.41; S, 10.10%. Found: C, 52.92; H, 7.35; N, 4.46; S, 10.25%.

L-Leu·(−)-PES: Found: C, 53.06; H, 7.36; N, 4.40; S, 10.03%.

D-Leu·(−)-PES·H_2O: Anal. Calcd for $C_{14}H_{23}NO_5S\cdot H_2O$: C, 50.13; H, 7.51; N, 4.18; S, 9.56%. Found: C, 50.28; H, 7.62; N, 4.22; S, 9.46%.

D-*n*-Leu·(−)-PES: ^{1}H NMR δ=0.87 (m, 3H, CH_3), 1.3 (m, 4H, $CH_2\times2$), 1.47 (d, 3H, J=7 Hz, CH_3), 1.75 (m, 2H, CH_2), 3.5—4.0 (m, 2H, CH×2), 7.1—7.5 (m, 5H, Ar H), and 8.2 (S, 3H, NH_3^+). Anal. Calcd for $C_{14}H_{23}NO_5S$: C, 52.98; H, 7.30; N, 4.41; S, 10.10%. Found: C, 52.99; H, 7.40; N, 4.43; S, 10.18%.

L-*n*-Leu·(−)-PES: Found: C, 53.07; H, 7.33; N, 4.44, S, 10.21%.

D-Ser·(−)-PES: ^{1}H NMR δ=1.47 (d, 3H, J=7 Hz, CH_3), 3.55—4.05 (m, 3H, CH×2, CH_2), 7.1—7.5 (m, 5H, Ar H), and 8.17 (brs, 3H, NH_3^+). Anal. Calcd for $C_{11}H_{17}NO_6S$: C, 45.35; H, 5.88; N, 4.81; S, 11.01%. Found: C, 45.44; H, 5.92; N, 4.78; S, 11.04%.

L-Ser·(−)-PES: Found: C, 45.39; H, 5.87; N, 4.80; S, 11.09%.

L-Pro·(−)-PES·H_2O: ^{1}H NMR δ=1.47 (d, 3H, J=7 Hz, CH_3), 1.7—2.4 (m, 4H, $CH_2\times2$), 3.15 (m, 2H, CH_2), 3.77 (q, 1H, J=7 Hz, CH), 4.16 (t, 1H, J=7 Hz, CH), 6.3 (brs, 2H, H_2O), and 9.0 (brs, 2H, NH_3^+). Anal. Calcd for $C_{13}H_{19}NO_5S\cdot H_2O$: C, 48.89; H, 6.71; N, 4.39; S, 10.04%. Found: C, 48.97; H, 6.63; N, 4.47; S, 10.05%.

D-PG·(−)-PES: ^{1}H NMR δ=1.47 (d, 3H, J=7 Hz, CH_3), 3.67 (q, 1H, J=7 Hz, CH), 5.06 (s, 1H, CH), 7.1—7.6 (m, 10H, Ar H), and 8.73 (brs, 3H, NH_3^+). Anal. Calcd for $C_{16}H_{19}NO_5S$: C, 56.96; H, 5.68; N, 4.15; S, 9.50%. Found: C, 56.83; H, 5.65; N, 4.16; S, 9.66%.

L-PG·(−)-PES: Found: C, 56.86; H, 5.60; N, 4.18; S, 9.76%.

D-HPG·(−)-PES: ^{1}H NMR δ=1.47 (d, 3H, J=7 Hz, CH_3), 3.72 (q, 1H, J=7 Hz, CH), 4.97 (s, 1H, CH), 6.8—7.5 (m, 9H, Ar H), and 8.7 (brs, 3H, NH_3^+). Anal. Calcd for $C_{16}H_{19}NO_6S$: C, 54.38, H, 5.42; N, 3.96; S, 9.07%. Found: C, 54.35; H, 5.45; N, 3.94; S, 9.05%.

L-HPG·(−)-PES: Found: C, 54.34; H, 5.49; N, 3.98; S, 9.10%.

D-Lys·(−)-PES: ^{1}H NMR δ=1.1—1.9 (m, 12H, CH_3, $CH_2\times3$), 2.7 (m, 2H, CH_2), 3.28 (m, 1H, CH), 3.74 (q, 1H, J=7 Hz, CH), and 6.5—8.3 (m, 10H, Ar H, NH_2 and NH_3^+). Anal. Calcd for $C_{14}H_{24}N_2O_5S$: C, 50.58; H, 7.28; N, 8.43; S, 9.65%. Found: C, 50.40; H, 7.39; N, 8.55, S, 9.81%.

L-Lys·(−)-PES: Found: C, 50.50; H, 7.30; N, 8.48; S, 9.72%.

X-Ray Crystal Structure Determination. D-HPG·(−)-PES: $C_{16}H_{19}NO_6S$, Fw=353.39, space group $P2_12_12_1$, a=18.799(5), b=15.976(3), c=5.855(1) Å, U=1758.2(6) Å^3, Z=4, D_X=1.34 kg m^{-3}, μ=18.73 cm^{-1}. L-HPG·(−)-PES: $C_{16}H_{19}NO_6S$, Fw=353.39, space group $P2_12_12_1$, a=19.096(3), b=15.668(1), c=5.501(1) Å, U=1645.8(3) Å^3, Z=4, D_X=1.43 kg m^{-3}, μ=20.01 cm^{-1}. The unit cell dimensions were determined from the angular settings of 20 reflections in the range of $30°\leqq\theta\leqq60°$. Three-dimensional intensity data were measured on a four-circle diffractometer (AFC5, Rigaku). The measured unique reflections were 1661 for L-HPG·(−)-PES and 1745 for D-HPG·(−)-PES, of which 1578 and 1488, respectively, were used in the successive structure analyses.

The crystal structures of D- and L-HPG·(−)-PES were solved by the heavy atom method and by direct methods using MULTAN, respectively. The refinements of the atomic parameters of both compounds were carried out using the block-diagonal matrix least-square's method with anisotropic temperature factors for the non-hydrogen atoms and isotropic ones for the hydrogen atoms, all of which were located on the D-Fourier maps. The function $\sum w(|F_o|-|F_c|)^2$ was minimized in the refinement, and $\sqrt{w}=1/\sigma(F)$ were used in the final refinement stages.

The final R values were 0.062 (R_w=0.064) and 0.040 (R_w=0.045) for D- and L-HPG·(−)-PES, respectively. The ρ_{max} were 0.35 and 0.29 and ρ_{min} −0.32 and −0.33 e Å^{-3} for D- and L-HPG·(−)-PES, respectively.

The atomic scattering factors were taken from "International Tables for X-Ray Crystallography".[24]

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