Generation of Chirality in Two-Component Molecular Crystals of Tryptamine and Achiral Carboxylic Acids

Hideko Koshima,* Shinji Honke, and Junko Fujita

Department of Applied Chemistry, Faculty of Engineering, Ehime University, Matsuyama 790-8577, Japan

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Preparation of chiral two-component molecular crystals was studied by the self-assembly of tryptamine with various achiral carboxylic acids. Ten chiral two-component crystals were obtained by crystallization from solutions of both components. A 2-fold helix is formed between the molecules of tryptamine and acid through salt interaction and hydrogen bonding in the lattice. The crystal chirality is generated through the formation of one direction of helicity in the crystals. The torsional ethylamino group of the tryptamine molecule and the carboxylic acid group play an important role in producing this helical structure. Two enantiomorphous crystals were obtained by spontaneous crystallization from the solutions and easily discriminated by the measurement of solid-state CD spectra as Nujol mulls.

Introduction

Synthesis of chiral compounds from achiral reactants in the absence of any external chiral agents is known as absolute asymmetric synthesis. More than 10 successful examples of absolute asymmetric synthesis have been reported by utilizing the reaction of chiral crystals obtained from achiral molecules.[1−3] To achieve absolute asymmetric synthesis with high reliability, it is necessary to predict and prepare chiral crystals through the self-assembly of achiral molecules.[4,5] This type of chiral crystallization is also useful for the development of new chiral materials for applications such as nonlinear optics[6] and has further relevance to the prebiotic origin of chirality.[7] We have prepared several new chiral two-component crystals,[3,8−11] based on the working hypothesis that crystal chirality can be induced by freezing a flexible molecule into a chiral conformation when undergoing self-assembly with another molecule through hydrogen bonding and salt formation. These chiral crystals comprise helical-type crystals formed from tryptamine and several achiral carboxylic acids.[9,10] The molecular packing diagrams from X-ray structure analysis suggested that the tryptamine molecule played an important role in formation of the helical structure in these crystals. Therefore, we tried to prepare a more extensive range of two-component crystals from tryptamine and various achiral carboxylic acids to produce a family of helical-type crystals.

Results and Discussion

The two-component crystals incorporate tryptamine (**1**) as the flexible base molecule and 20 achiral carboxylic acids **2**−**21** as bonding connectors (Scheme 1). The acid compounds are simple molecules having a phenyl group (**3**−**6**, **13**−**18**), biphenyl group (**7**−**9**), naphthyl group (**10**, **20**), thienyl group (**2**, **12**), or indolyl group (**11**, **21**). Several acids containing heavy atoms such as sulfur (**2**, **6**, **12**) and chlorine (**3**, **15**) were selected in order to determine accurately the absolute configuration by X-ray anomalous dispersion. Crystallization from 1:1 solutions of both components in methanol by evaporation at room temperature gave 20 two-component molecular crystals **1·2**−**1·21**. The results of their characterization by measurement of melting points and IR spectroscopy are summarized in Table 1. The relatively high melting points (around 200 °C) and IR spectral patterns suggest the formation of salt bonding in the crystals.

This type of chiral crystal should have inherent optical activity. Therefore, solid-state CD spectra were measured in the form of a Nujol mull[12] to determine whether the crystals are chiral or not. The CD spectra of 10 crystals **1·2**−**1·11** were observed to exhibit crystal chirality (Scheme 1). The two enantiomorphous crystals were obtained by spontaneous crystallization from the solutions of both components. Figure 1 shows the CD spectra of five crystals **1·3**−**1·6** and **1·10**; those of **1·2**, **1·7**−**1·9**, and **1·11** were previously reported.[9,10] The CD curves of two enantiomorphous crystals are in a good mirror image relationship, giving easy discrimination of their handedness. On the other hand, no significant solid-state CD spectra for **1·12**−**1·21** were observed, suggesting that these crystals are most probably achiral.

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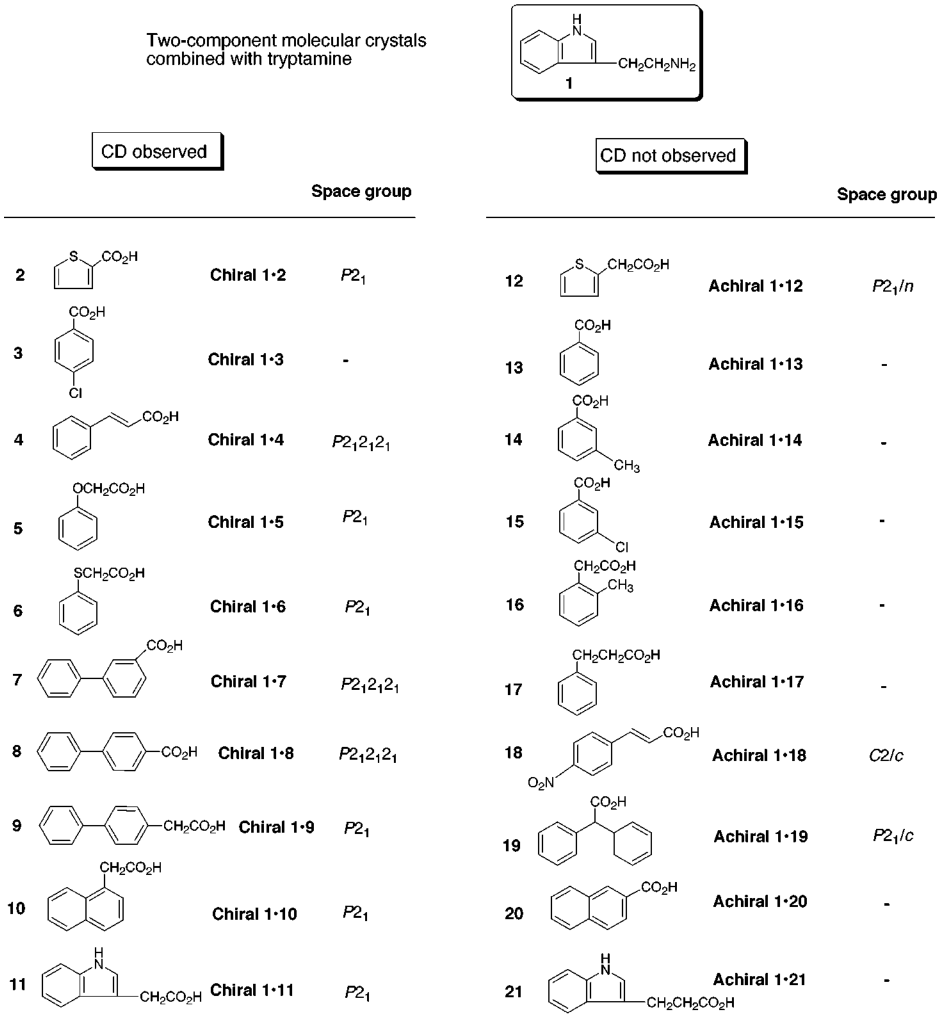
Scheme 1



- : X-ray crystal structure is not determined.

Table 1. Melting Points and IR Absorption Bands of the Two-Component Molecular Crystals

crystal	color	mp (°C)	IR (KBr) (cm^{-1})
chiral **1·2**[a]	colorless	182−183	3292, 2532−3005, 1549
chiral **1·3**	colorless	115−116	3282, 2503−3055, 1589
chiral **1·4**	colorless	176−177	3300, 2517−3080, 1637
chiral **1·5**	colorless	194−195	3212, 2557−3061, 1599
chiral **1·6**	colorless	184−185	3224, 2648−3120, 1565
chiral **1·7**[b]	colorless	197−199	3284, 2522−3037, 1529
chiral **1·8**[b]	colorless	197−199	3286, 2532−3021, 1504
chiral **1·9**[b]	colorless	200−202	3223, 2642−3078, 1521
chiral **1·10**	colorless	219−221	3228, 2582−3116, 1606
chiral **1·11**[a]	colorless	188−189	3415, 3259, 2642−3055, 1525
achiral **1·12**[a]	colorless	188−189	3226, 2667−3049, 1561
achiral **1·13**	colorless	199−200	3300, 2522−3055, 1630
achiral **1·14**	colorless	173−174	3259, 2519−3074, 1626
achiral **1·15**	colorless	202−203	3311, 2511−3115, 1622
achiral **1·16**	colorless	173−175	3277, 2519−3113, 1618
achiral **1·17**	colorless	152−153	2360−3226, 1622
achiral **1·18**	yellow	193−194	3290, 2503−3076, 1641
achiral **1·19**	colorless	191−192	3317, 2956−3128, 1624
achiral **1·20**	colorless	201−202	3294, 2507−3053, 1618
achiral **1·21**[a]	colorless	175−176	3421, 3288, 2519−3080, 1518

[a] Reference 10. [b] Reference 9.

The solid-state CD spectra of chiral **1·2**−**1·11** may be derived from the exciton coupling of the chromophores such as indolyl and phenyl groups in the crystals. However, the relationship between the CD spectral pattern and the molecular arrangement cannot be elucidated because solid-state CD spectrometry is not yet very developed. Nevertheless, solid-state CD spectrometry is a powerful tool for determining whether a given crystal is chiral or not and also whether it is (+) or (−).

X-ray crystallographic analyses of 12 crystals were performed in order to reveal the molecular packing arrangement and elucidate the chirality generation mechanism. The nine crystals of **1·2** and **1·4**−**1·11** belonged to the typical chiral space groups $P2_1$ and $P2_12_12_1$ (Scheme 1). The crystal structure of **1·3** could not be determined due to difficulties in obtaining high-quality single crystals. The achiral nature of **1·12**, **1·18**, and **1·19** was confirmed from their achiral space groups of $P2_1/n$, $C2/c$, and $P2_1/c$, respectively. The detailed crystal data are summarized in Table 2. The absolute configurations of *P*-**1·2**[10] and *P*-**1·6** were determined with a high degree of certainty by the Bijvoet method based on X-ray anomalous dispersion of the sulfur atom (Experimental Section). However, absolute configuration of the other chiral crystals could not be determined because the oxygen atom is not sufficiently heavy to obtain large X-ray anomalous dispersion using a Cu target.

Table 2. Crystal Data of the Two-Component Crystals

	chiral P-**1·2**[a]	chiral **1·4**	chiral **1·5**	chiral P-**1·6**	chiral **1·7**[b]	chiral **1·8**[b]
formula	$C_{15}H_{16}N_2O_2$	$C_{19}H_{24}N_2O_2$	$C_{18}H_{20}N_3O_2$	$C_{18}H_{20}SN_2O_2$	$C_{23}H_{22}N_2O_2$	$C_{23}H_{22}N_2O_2$
M_w	288.36	312.41	312.37	328.43	358.44	358.44
color, habit	colorless prisms	colorless prisms	colorless prisms	colorless prisms	colorless prisms	colorless prisms
crystal size (mm)	0.50 × 0.40 × 0.50	0.50 × 0.50 × 0.50	0.40 × 0.30 × 0.50	0.50 × 0.50 × 0.60	0.50 × 0.40 × 0.50	0.40 × 0.30 × 0.50
crystal system	monoclinic	orthorhombic	monoclinic	monoclinic	orthorhombic	orthorhombic
space group, no.	$P2_1$, 4	$P2_12_12_1$, 19	$P2_1$, 4	$P2_1$, 4	$P2_12_12_1$, 19	$P2_12_12_1$, 19
T (k)	296	296	296	296	296	296
a (Å)	9.897(2)	9.681(3)	9.421(5)	9.285(1)	10.487(4)	6.213(7)
b (Å)	6.164(3)	29.000(1)	6.834(2)	6.874(1)	29.90(1)	9.80(1)
c (Å)	12.086(2)	5.931(4)	13.056(4)	13.988(1)	6.138(3)	32.33(3)
β (deg)	94.73(1)	90.0	102.89(3)	108.291(8)	90.0	90.0
V (Å^3)	734.7(3)	1664(1)	819.4(5)	847.6(2)	1925(1)	1969(3)
Z	2	4	2	2	4	4
D_c (g cm^{-3})	1.303	1.246	1.242	1.287	1.237	1.209
F(000)	304.00	672.00	332.00	348.00	760.00	760.00
μ (cm^{-3})	19.83	0.76	0.87	17.83	0.596	0.583
radiation	Cu Kα	Mo Kα	Mo Kα	Cu Kα	Cu Kα	Cu Kα
$2\theta_{max}$ (deg)	120.1	50.0	50.0	120.1	115.0	115.0
no. of reflections measured	2576	1734	1674	2956	1601	1635
no. of unique reflections	2527	1044	1574	1385	1159	1311
no. of observns, $I > 3.00\sigma(I)$	2099	1044	1388	2489	1159	1311
no. of variables	194	222	222	221	244	244
R	0.065	0.046	0.063	0.056	0.049	0.044
R_w	0.092	0.061	0.046	0.086	0.055	0.052
GOF	2.99	1.27	1.22	2.85	1.697	1.662
largest difference peak, hole (e Å^{-3})	0.92, −0.45	0.15, −0.12	0.09, −0.11	0.73, −0.65	0.013, 0.002	0.016, 0.002

	chiral **1·9**[b]	chiral **1·10**	chiral **1·11**[a]	achiral **1·12**[a]	achiral **1·18**	achiral **1·19**
formula	$C_{24}H_{24}N_2O_2$	$C_{21}H_{17}N_2O_2$	$C_{20}H_{21}N_3O_2$	$C_{16}H_{19}N_2O_2S$	$C_{19}H_{19}N_3O_4$	$C_{24}H_{24}N_2O_2$
M_w	360.37	329.38	335.40	303.40	353.38	372.47
color, habit	colorless prisms	colorless prisms	colorless prisms	colorless prisms	yellow prisms	colorless prisms
crystal size (mm)	0.40 × 0.30 × 0.50	0.30 × 0.10 × 0.50	0.15 × 0.10 × 0.50	0.30 × 0.10 × 0.50	0.40 × 0.30 × 0.50	0.30 × 0.40 × 0.50
crystal system	monoclinic	monoclinic	monoclinic	monoclinic	monoclinic	monoclinic
space group, no.	$P2_1$, 4	$P2_1$, 4	$P2_1$, 4	$P2_1/n$, 14	$C2/c$, 15	$P2_1/c$, 14
T (k)	296	296	296	296	296	296
a (Å)	19.329(9)	9.656(2)	11.000(2)	18.527(4)	36.586(8)	14.379(5)
b (Å)	6.813(3)	6.750(3)	6.335(2)	6.772(5)	6.077(2)	6.692(2)
c (Å)	15.298(7)	14.603(2)	12.612(1)	25.668(4)	18.314(4)	21.708(5)
β (deg)	96.11(1)	101.13(1)	98.22(1)	102.68(1)	118.66(1)	103.57(2)
V (Å^3)	2003(2)	933.8(4)	869.8(2)	3141(2)	3572(1)	2030(1)
Z	4	2	2	8	8	4
D_c (g cm^{-3})	1.235	1.171	1.281	1.283	1.314	1.218
F(000)	744.00	346.00	356.00	1288.00	1488.00	792.00
μ (cm^{-3})	0.588	0.71	6.77	18.78	0.94	6.17
radiation	Cu Kα	Mo Kα	Cu Kα	Cu Kα	Mo Kα	Cu Kα
$2\theta_{max}$ (deg)	115.0	50.0	120.0	120.0	50.0	120.2
no. of reflections measured	3115	1904	1517	5313	3186	3476
no. of unique reflections	2492	1904	1436	5135	3144	3337
no. of observns, $I > 3.00\sigma(I)$	2492	1189	1383	2600	2071	2425
no. of variables	504	248	242	404	566	275
R	0.044	0.039	0.041	0.091	0.065	0.086
R_w	0.050	0.052	0.065	0.131	0.093	0.148
GOF	1.663	1.18	1.94	2.95	2.13	3.85
largest difference peak, hole (e Å^{-3})	0.013, 0.002	0.14, −0.10	0.29, −0.15	0.38, −0.40	0.64, −0.28	0.80, −0.37

[a] Reference 10. [b] Reference 9.

In all of the crystals, two kinds of intermolecular bonds are present; the quaternary ammonium salt ($NH_3^+\cdot CO_2^-$) between the aminoethyl group of **1** and the carboxylic acid group and hydrogen bonding (N−H···O−C) between the indole N−H of **1** and the carboxylic acid group. The distance and angle data estimated from the X-ray crystallographic analyses are summarized in Table 3.

Figure 2a shows the molecular arrangement in a chiral crystal of **1·4**. Four molecules of each component are present in the unit cell ($P2_12_12_1$, $Z = 4$). An important feature is that a single absolute configuration of **1** and **4** is present in the unit cell forming a 2-fold helix along the c axis through the salt and hydrogen bonding. Formation of the helical structure in one direction only induces the crystal chirality.

The crystal of P-**1·6** ($P2_1$, $Z = 2$) also forms a counterclockwise 2-fold helix. Figure 2b expresses the correct absolute configuration. The solid-state CD spectrum corresponds to the curve P in Figure 1d. The crystal structure of chiral **1·5** is very similar to that of **1·6** in terms of unit cell dimensions (Table 2) and helical arrangement (Figure 2b). This is understandable from

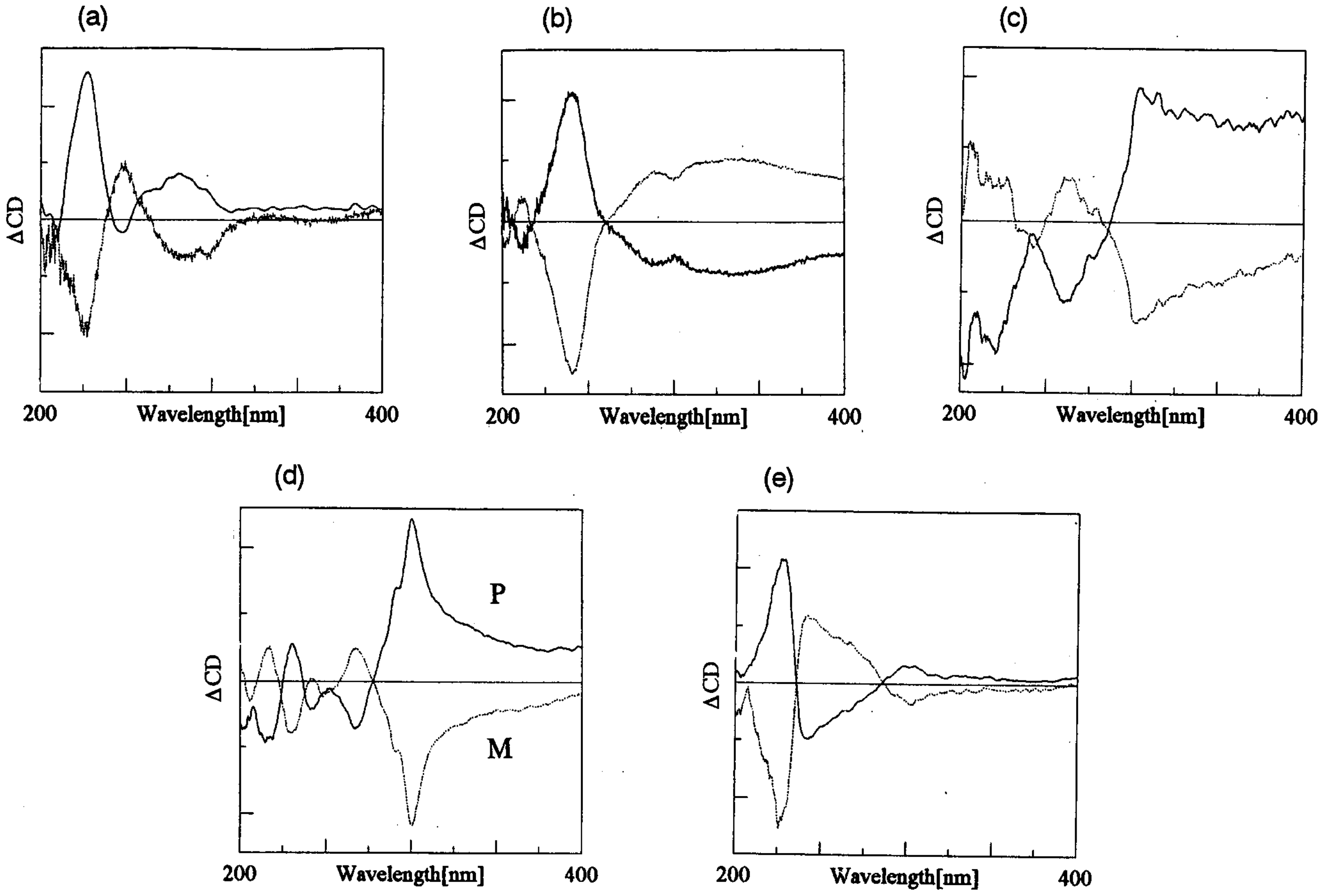


Figure 1. Solid-state CD spectra of the chiral crystals measured as Nujol mulls: (a)**1·3**, (b) **1·4**, (c) **1·5**, (d) **1·6**, (e) **1·10**.

Table 3. Distance and Angle Data of the Two-Component Crystals

	salt distance (Å) $NH_3^+\cdots CO_2^-$	H-bond distance (Å) In−NH···O−C	torsion angle (deg) tryptamine InC−C−C−N	carboxylic acid C−C−C−O
chiral *P*-**1·2**[a]	1.83, 1.87, 1.97	2.02	170.2	178.3
chiral **1·4**	1.75, 1.82, 2.00	1.99	73.7	171.9
chiral **1·5**	1.81, 1.93, 2.18	1.90	58.3	172.9
chiral *P*-**1·6**	1.94, 1.96, 2.23	2.02	61.2	5.2
chiral **1·7**[b]	1.70, 1.75, 1.81	1.99	175.9	174.0
chiral **1·8**[b]	1.77, 1.85, 1.86	1.87	171.9	177.3
chiral **1·9**[b]	1.73, 2.03, 2.16	1.91	−59.1	57.9
	1.82, 2.00, 2.12	1.91	−58.3	−44.9
chiral **1·10**	1.65, 1.96, 2.06	2.06	59.4	175.6
chiral **1·11**[a]	1.80, 2.18, 3.04	1.90	−67.8	25.6
achiral **1·12**[a]	1.72, 2.19, 2.59	2.07	61.6	−145.4
	1.91, 1.97, 2.26	2.16	62.1	−17.0
achiral **1·18**	1.71, 1.83, 2.05	2.05	75.4	163.0
achiral **1·19**	1.70, 1.84, 1.95	2.24	63.6	4.9

[a] Reference 10. [b] Reference 9.

the small difference in molecular structure between **5** and **6** (Scheme 1). The similar helical structure of **1·10** ($P2_1$, Z = 2) is shown in Figure 1c. The diagrams of helical molecular arrangement in chiral crystals of **1·2**, **1·4**−**1·6**, and **1·11** were previously reported.[9,10]

In the achiral crystal of **1·18** ($C2/c$), 2-fold helical chains are also formed (Figure 3). However, two pairs of clockwise helices (A) and two pairs of anticlockwise helices (B) coexist centrosymmetrically in the unit cell. Therefore, the crystal chirality is nullified. The crystal of **1·12** ($P2_1/n$, $Z = 8$) is achiral also due to the coexistence of both directions of helices.[10] The achiral crystal of **1·19** does not form a helical chain but a symmetrical molecular unit of **1** and **19** through the quaternary ammonium salt bonding in the lattice, without induction of chirality.

As apparent from the diagrams in Figures 2 and 3, one of the reasons for the easy formation of the helical chains is that the flexible aminoethyl group of **1** and the carboxylic acid groups can be fixed into the torsional conformations according to the geometrical environment in the lattice. The (indole) C−C−C−N and C−C−C−O torsion angles of **1** and the various acids are shown in Table 3. Furthermore, the indole imino group of **1** plays an auxiliary role in the formation of the helical chains. However, it is still puzzling why such helices are packed in one direction or both directions during spontaneous

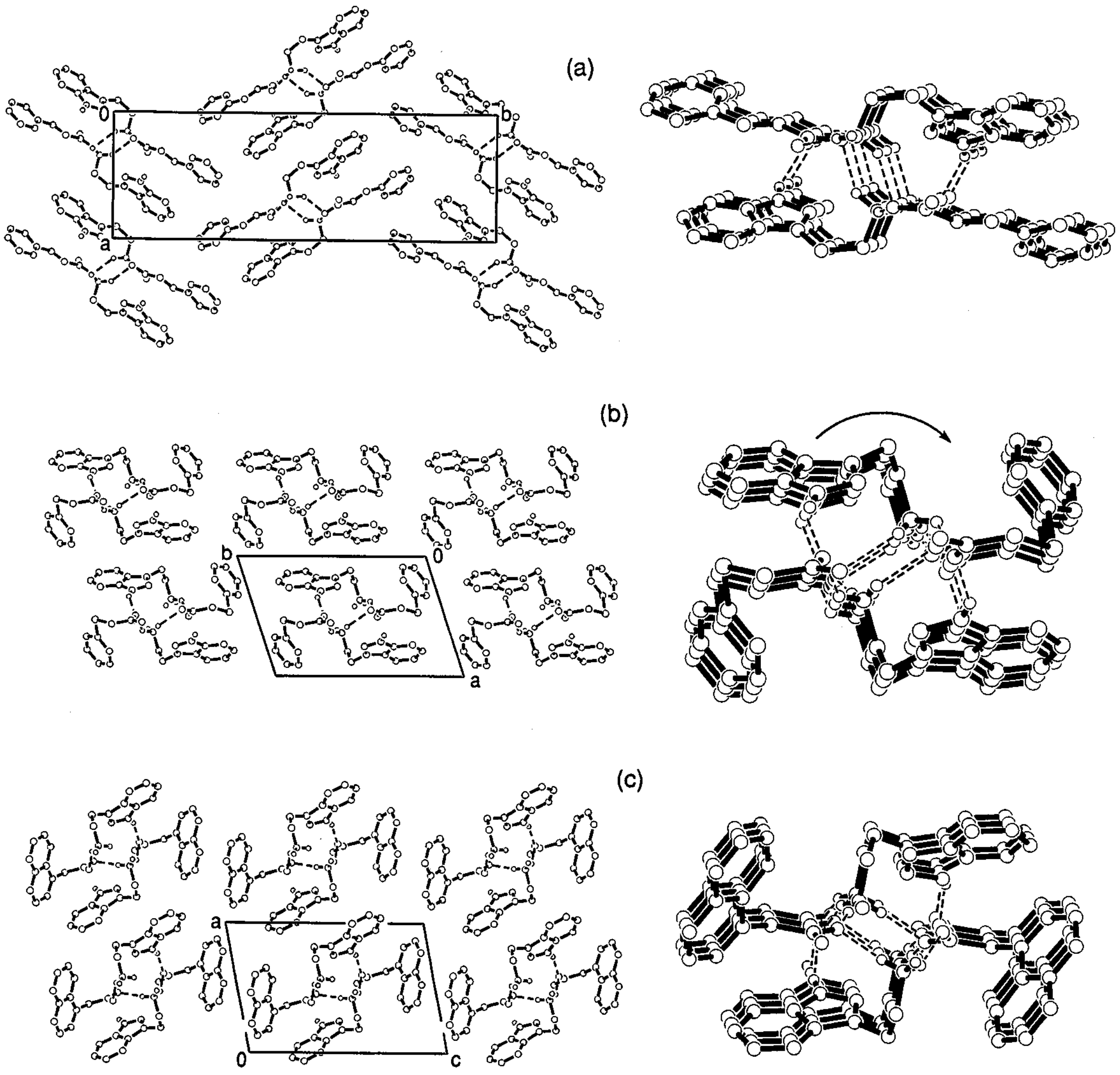


Figure 2. Helical molecular arrangement of the chiral crystals: (a) **1·4**, (b) *P*-**1·6**, (c) **1·10**. Part b expresses the correct absolute configuration of **P-1·6**.

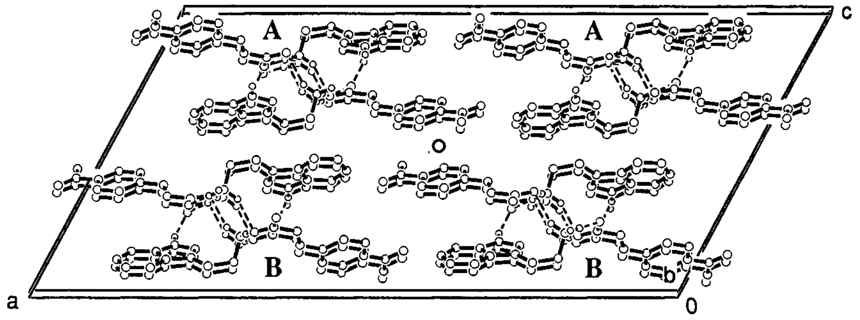


Figure 3. Molecular arrangement of the achiral crystal **1·18**.

crystallization. Probably, it depends on interaction between the helical chains in the lattice. For instance, the chiral **1·2** structure ($P2_1$) crystallizes with one helix direction, but the achiral **1·12** ($P2_1/n$) has both directions. This difference in packing direction is derived from the small molecular structure difference of only one $-CH_2-$ unit between **2** and **12**.[10] In conclusion, our success in preparing helical-type crystals from tryptamine and achiral carboxylic acids with relatively high probability provides many interesting possibilities for further study in the future.

Experimental Section

Preparation of Two-Component Crystals. Twenty two-component crystals **1·2**–**1·21** were prepared by dissolving separately the acid reagents **2**–**21** into 20 centrifuge tubes containing an equimolar solution of **1** in methanol followed by evaporation at room temperature. The crystals were separated by centrifugation or filtration and washed with a small amount of methanol. High-quality single crystals for X-ray structure analysis were prepared with greater care. The crystals were characterized by measuring their melting points, IR, and solid-state CD spectra as Nujol mulls. The melting points and IR absorption bands are listed in Table 1. The solid-state CD spectra of five chiral crystals are shown in Figure 1.

X-ray Crystallographic Analysis. Data collections were performed on a Rigaku AFC7R (or AFC5R) automatic four-circle X-ray diffractometer equipped with graphite-monochromated Cu Kα ($\lambda = 1.541\,78$ Å) or Mo Kα ($\lambda = 0.710\,69$ Å) radiation. Absorption corrections were applied. No degradation of the crystal by X-ray radiation was ascertained in all cases by repeated monitoring of three representative reflections every 150 reflections. These structures were solved by direct methods and expanded using Fourier techniques. The non-hydrogen atoms were refined anisotropically. Atomic parameters were refined by the full matrix least-squares method at the final stage. All the calculations were carried out on teXsan crystallographic software package, Molecular Structure Corporation. Table 2 summarizes the crystal data of **1·2**, **1·4**−**1·12**, **1·18**, and **1·19**.

The absolute configuration of *P*-**1·6** by using the half of a single crystal was determined very carefully by the Bijvoet method based on anomalous dispersion due to the sulfur atom with Cu Kα radiation during X-ray crystallographic analysis. All 25 and 128 Bijvoet pairs of $|\Delta F_c|/\sigma(F_o) < 4$ and $2.0 < |\Delta F_c|/\sigma(F_o) \leq 4.0$, respectively, resulted in incorrect trends. Therefore, *x*, *y*, and *z* axes were converted; the packing diagram in Figure 2c shows the correct absolute configuration of *P*-**1·6**. The second crystal half was used to measure the CD spectrum (curve P in Figure 1d). The determination of absolute configuration of *P*-**1·2** by the Bijvoet method was previously reported.[10]

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Supporting Information Available: Tables giving full data collection parameters and further details of refinement, atomic coordinates, anisotropic displacement parameters, bond lengths, and bond angles of **1·4**, **1·5**, *P*-**1·6**, **1·10**, **1·18**, and **1·19**. This material is available free of charge via the Internet at http://pubs.acs.org.

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