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Preparation and Structure of Chiral Two-component Molecular Crystals from 3-(3-Indolyl)propanoic Acid and Aza Aromatic Compounds

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Despite 3-(3-indolyl)propanoic acid (1) and aza aromatic compounds such as phenanthridine (2), phenazine (3), and 3-bromoquinoline (4) being achiral molecules, chiral two-component molecular crystals 1 • 2, 1 • 3, and 1 • 4 were obtained by crystallization from solutions of both components. The crystal chirality of 1 • 2 is generated through the formation of a unidirectional two-fold hydrogen bonded helix between the two components. Two enantiomorphous crystals of *M*-1 • 2 and *P*-1 • 2 were obtained by spontaneous resolution and easily discriminated by the measurement of solid state CD spectra (powder) as Nujol mulls. The absolute configuration of *M*-1 • 2 was determined very carefully by the Bijvoet method based on the X-ray anomalous dispersion due to the oxygen atom. In the case of 1 • 3 and 1 • 4, a hydrogen bonded helix is not formed, but the crystal chirality is generated by the non-centrosymmetric arrangement of the symmetrical pairs of 1 and 3, and the two enantiomeric pairs of 1 and 4 in the lattice, respectively.

Keywords: Chiral two-component molecular crystals, achiral molecules, chirality generation, X-ray crystal structures

INTRODUCTION

Chiral crystallization whereby achiral molecules form chiral crystals through self-assembly received little attention from organic chemists [1, 2]. However, the preparation and prediction of such chiral crystals are important for achieving absolute asymmetric synthesis with high reliability by solid state reactions [3, 4]. Furthermore chiral crystallization is relevant to the origin of chiral compounds on our earth [5]. Since our discovery of a chiral two-component molecular crystal of diphenylacetic acid and acridine [6], we have prepared several new chiral two-component crystals using different achiral molecules [7-10]. These chiral crystals involve propeller-type crystals of diphenylacetic acid and aza aromatic compounds [6, 7], and helical-type crystals such as 3-(3-indolyl)propanoic acid and

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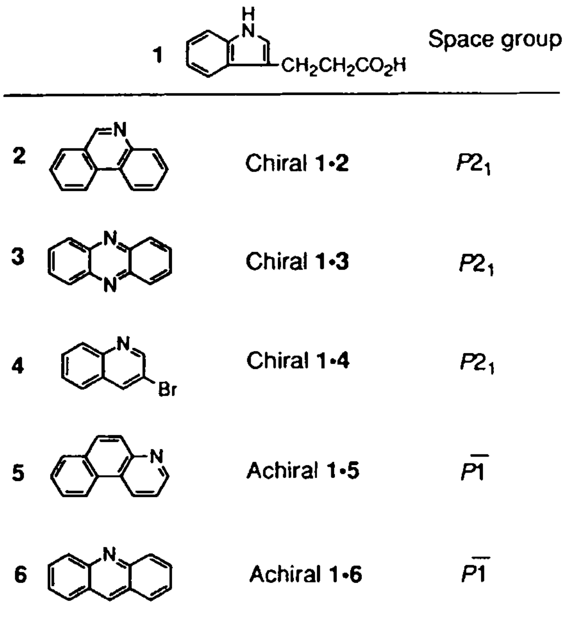
*Corresponding author. Tel.: +81-89-927-8523, Fax: +81-89-927-9944, e-mail: koshima@en3.ehime-u.ac.jp phenanthridine, as well as tryptamine {3-(2-aminoethyl)indole} with several achiral carboxylic acids [9, 10]. The chirality of the helical-type crystals was generated by formation of a helical hydrogen bonded chain between the two molecules in the lattice. The flexible 3-(3-indolyl)propanoic acid molecule in the helical-type crystal with phenanthridine played an important role in this helix formation [8]. Therefore, two-component crystals of 3-(3-indolyl)propanoic acid with several aza aromatic compounds have been investigated more thoroughly to extend the range of these new chiral crystals.

RESULTS AND DISCUSSION

The two-component molecular crystals investigated here incorporate 3-(3-indolyl)propanoic acid (**1**) as a flexible molecule and five aza aromatic compounds: phenanthridine (**2**), phenazine (**3**), 3-bromoquinoline (**4**), benzo[*f*]quinoline (**5**), and acridine (**6**) as hydrogen bonding connectors (Scheme 1). Crystallization from solutions of both components gave five two-component molecular crystals. The molar ratios of **1** and the aza aromatic compound are 1 : 1 for **1**•**2**, **1**•**4** and **1**•**5**, 2 : 1 for **1**•**3**, and 1 : 3 for **1**•**6**. The melting points and IR spectra are summarized in the Experimental Section.



SCHEME 1

The crystals were submitted to X-ray crystallographic analysis which confirmed the chiral nature of **1**•**2**, **1**•**3**, and **1**•**4**, all of which belonged to space group $P2_1$. Crystals **1**•**5** and **1**•**6** were achiral, and their space group was $P\bar{1}$. The details of their crystal data are listed in Table I. In the crystals of **1**•**2** – **1**•**5**, two kinds of hydrogen bonding patterns are formed in the lattice; O—H•••N between the hydroxyl group of **1** and the N atom of **2** – **5**, and N—H•••O = C between the indole imino group of **1** and the carbonyl group of the neighboring **1**. In the achiral crystal **1**•**6**, both hydrogen bonds and salt bridges are formed as explained below (Fig. 4). The distance data estimated from the X-ray crystallographic analyses are shown in Table II.

The determination of the absolute configuration of this kind of chiral crystal is important. A single crystal of **1**•**2** obtained by spontaneous resolution was cut into two pieces. One half was used for measurement of the solid state CD spectrum (curve a in Fig. 5). The second half was polished into a spherical form and subjected to absolute configuration determination. This showed it to be *M*-**1**•**2** with a high degree of certainty by the Bijvoet method based on X-ray anomalous dispersion due to the oxygen atom using Cu Kα radiation during the X-ray crystallographic analysis (Experimental Section).

The molecular arrangement of *M*-**1**•**2** in Figures 1a and b shows the correct absolute configuration ($P2_1$, $Z = 2$). The molecule of **1** is connected to its neighboring **1** through N—H•••O = C hydrogen bonding; the dihedral angle of the two indole planes is 78.27°. The molecule of **1** is also linked to **2** through O—H•••N hydrogen bonding; the dihedral angle between the indole and phenanthridine planes is 77.24°. An important feature of the

TABLE I Crystal data of the two-component crystals

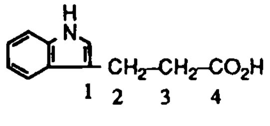
	M-**1•2**[a]	Chiral **1•3**	Chiral **1•4**	Achiral **1•5**	Achiral **1•6**
Crystal data					
formula	$C_{24}H_{20}N_2O_2$	$C_{34}H_{30}N_4O_4$	$C_{20}H_{17}N_2O_2Br$	$C_{24}H_{20}N_2O_2$	$C_{50}H_{38}N_4O_2$
Mr	368.43	558.64	397.27	368.44	726.88
color, habit	yellow prism	reddish yellow prism	colorless prism	colorless prism	colorless prism
crystal system	monoclinic	monoclinic	monoclinic	triclinic	triclinic
space group	$P2_1$	$P2_1$	$P2_1$	$P\bar{1}$	$P\bar{1}$
a(Å)	13.251(1)	5.29(4)	7.058(4)	9.4519(5)	13.15(1)
b(Å)	5.327(1)	11.92(2)	28.277(2)	14.3767(6)	13.43(1)
c(Å)	13.6091(9)	21.83(3)	8.884(2)	7.2012(4)	12.91(1)
α(°)	90.0	90.0	90.0	91.336(4)	102.01(9)
β(°)	104.779(7)	91.7(3)	91.39(3)	94.409(5)	109.02(7)
γ(°)	90.0	90.0	90.0	102.373	63.93(8)
Z	2	2	4	2	2
Dc (g cm^{-3})	1.317	1.347	1.489	1.285	1.250
F(000)	388.00	588.00	808.00	388.00	764.00
μ(cm^{-3})	6.74	0.90	32.89	6.57	0.77
Data collection					
crystal size (mm)	0.50 × 0.50 × 0.50	0.30 × 0.30 × 0.70	0.40 × 0.10 × 0.50	0.50 × 0.30 × 0.50	0.30 × 0.40 × 0.60
radiation	CuKα	MoKα	CuKα	CuKα	MoKα
$2\theta_{max}$(°)	120.0	50.1	120.1	120.1	50.0
no. of reflections measured	3244	2863	5868	3030	7131
Final refinement					
no. of observations, $I > 3.00\sigma(I)$	2708	1879	2222	2605	3364
no. of variables	334	391	452	260	512
R	0.033	0.037	0.066	0.053	0.067
R_w	0.052	0.062	0.099	0.110	0.096
$\Delta\rho_{max}$ (eÅ^{-3})	0.13	0.17	1.05	0.28	0.60
$\Delta\rho_{min}$ (eÅ^{-3})	−0.14	−0.20	−0.61	−0.15	−0.36

[a] Ref. [8].

TABLE II Hydrogen bond distance and torsion angle data

		M-**1•2**	**1•3**	**1•4**	**1•5**	**1•6**
H-bonding distance (Å)						
O—H•••NAr	A	1.48	1.94	1.87	1.50	
	B		1.93	1.91	1.50	
N—H•••O=C	A	2.09	1.99	1.94	2.02	
	B		2.20	2.19	2.02	
C—O$^-$•••$^+$H—N	A					1.64, 2.10
	B					1.64, 2.10
N—H•••NAr	A					1.97
	B					1.97
dihedral angle (deg)						
indole/NAr	A	77.24	3.59	65.78	98.33	90.61
	B		4.22	73.98	98.33	90.61
torsion angle[a] (DEG)						
C1—C2—C3—C4	A	60.0	178.0	−75.0	−70.1	173.3
	B		−179.6	55.0	70.1	−173.3

[a]



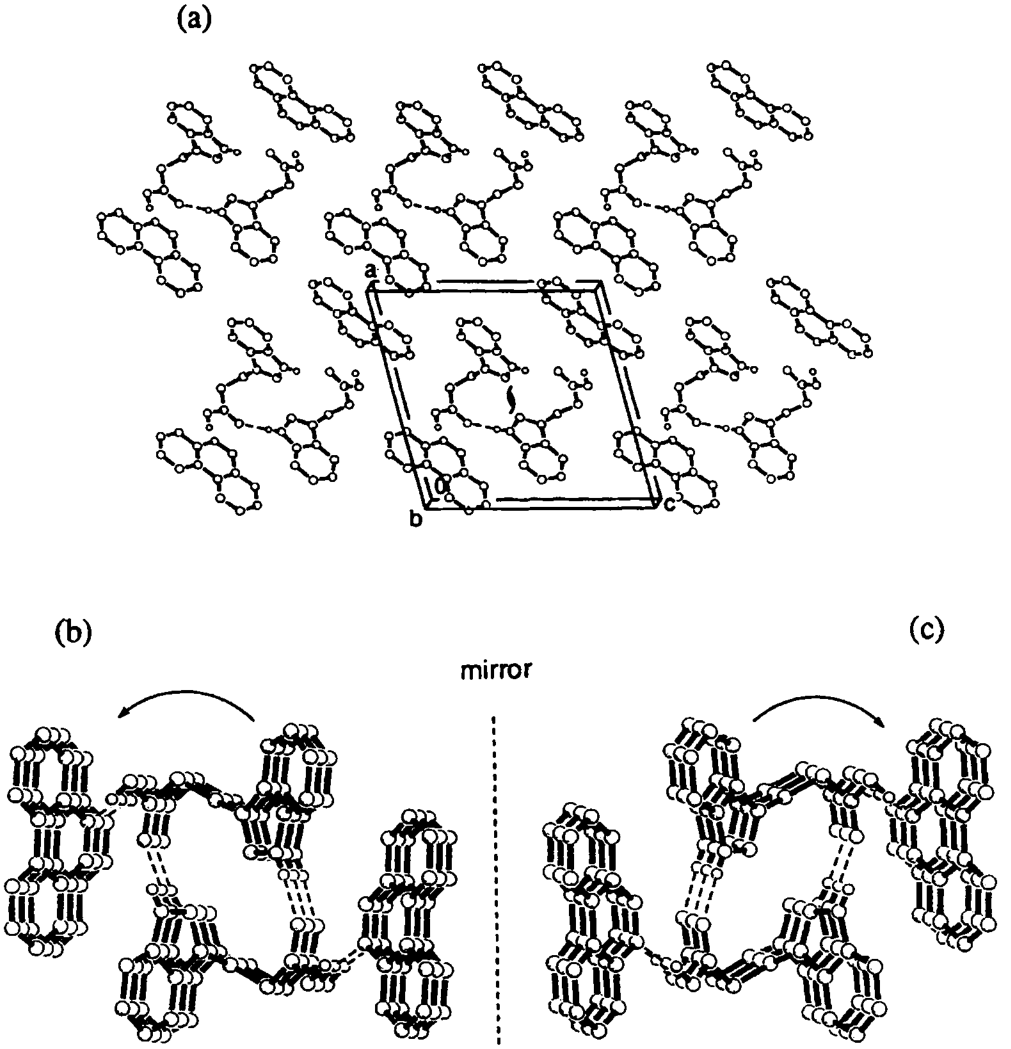


FIGURE 1 (a) Molecular packing arrangement of chiral *M*-**1**•**2**; (b) counterclockwise helix in *M*-**1**•**2**; and (c) clockwise helix in *P*-**1**•**2**. The figures express the correct absolute configuration.

molecular arrangement of *M*-**1**•**2** is that the $\mathrm{N{-}H \bullet\bullet\bullet O{=}C}$ hydrogen bonded chain between the molecules of **1** forms a counterclockwise two-fold helix along the *b* axis (Fig. 1b). This unidirectional helical structure induces the crystal chirality.

It can be seen in Figure 1 that the propanoic acid group plays an important role in formation of the helical hydrogen bonded chain. The flexible propanoic acid group of **1** can change its conformation according to the geometrical environment in the lattice; Table II shows the torsion angles observed. We have already reported the opposite combination whereby tryptamine having a flexible basic ethylamino group forms helical-type chiral crystals with several achiral carboxylic acids such as 2-thienylcarboxylic acid and 2-(3-indolyl) acetic acid [10]. Further, we have already reported that the crystal of **1** itself is also chiral ($P2_1$, $Z = 4$) [8]. In the lattice of **1**, two molecules form a carboxy dimer, but these dimers form a two-fold helix through intermolecular N—H • • • O = C hydrogen bonding to generate the crystal chirality [8]. As has been noted previously [4a, 11], if an acid molecule in a one-component crystal contains two functional groups such as NH, CONH, OH, *etc.*, then intermolecular interaction may occur, a helical chain is generally adopted instead of centrosymmetric pairs, and the resulting structure is more likely to be a chiral crystal.

Crystal **1** • **3** also crystallizes into a typical chiral space group $P2_1$ (Fig. 2, $Z = 4$). However, the molecular packing arrangement is very different from that of **1** • **2** which belongs to the same space group. Two antipodal molecules (A and B in Fig. 2b) of **1** connect to the two N atoms of a phenazine molecule to form a 2:1 hydrogen bonding pair with an inversion center in the center of the phenazine plane. These pairs are connected by bridging molecules of **1** through N—H • • • O = C hydrogen bonding to form an almost flat sheet structure. These sheets are arranged as a two-fold screw axis along the *b* axis to form a parallel layer structure with a sheet-to-sheet distance of 3.3 Å (Fig. 2a). The A antipodes line one edge of each sheet, and the B antipodes the other (Fig. 1b). Hence the crystal chirality is generated from the non-centrosymmetric arrangement, not from the formation of a hydrogen bonded helix like **1** • **2**.

In the case of chiral crystal **1** • **4** ($P2_1$, $Z = 4$), a molecular chain (A in Fig. 3a) of **1** is formed through the N—H • • • O = C hydrogen bonding, and further a molecule of **4** is connected to each **1** as a pendant molecule through the O—H • • • N hydrogen bonding. An almost antipodal molecular chain B of **1** linked with **4** is also formed. The dihedral angles between the indole and quinoline planes in the two chains are 65.78° and 73.98°, respectively (Tab. II). The chains are arranged in a head-to-tail manner along the *a* axis. However, even though the almost enantiomeric chains A and B coexist in the lattice, the crystal chirality is induced by their arrangement in a two-fold screw axis along the *b* axis. Here it becomes clear that there are two chirality generation factors for the chiral crystals belonging to $P2_1$; the formation of a hydrogen bonded helix of left- or right-handed molecular pairs in **1** • **2**, and the non-centrosymmetric arrangement of the symmetrical pairs in **1** • **3** and of the two enantiomeric molecular pairs in **1** • **4**.

The achiral crystal **1** • **5** also involves two enantiomeric molecular chains of **1** associated with **5** arranged in a head-to-tail manner, similar to the chiral crystal **1** • **4** in this point. However, their centrosymmetric arrangement leads to the formation of the achiral structure **1** • **5** ($P\bar{1}, Z = 2$).

The achiral crystal **1** • **6** (Fig. 4, $P\bar{1}, Z = 2$), with **1** and **6** in a 1:3 ratio, has a different packing arrangement from those of **1** • **2** – **1** • **5**. The carboxylic acid proton of **1** (A_0 in Fig. 4b) is transferred to the N atom of one acridine molecule A_1 to form a C—O$^-$ • • •$^+$H—N salt bridge. A second acridine molecule A_2 connects to the indole through N—H • • • N hydrogen bonding to complete a 1:2 molecular pair; the dihedral angle between the two acridine planes is 1.89°, almost parallel, with the indole ring almost perpendicular to both. The third unattached acridine molecule A_3 completes the 1:3 molecular unit A. Similarly, an antipodal unit B is also formed and these two enantiomeric units are centrosymmetrically arranged in the lattice (Fig. 4a).

The chiral crystals obtained here should exhibit optical activity in the solid state. In fact, we obtained easily the solid state CD spectra of **1** • **2** as a Nujol mull (Fig. 5) [8]. The CD curves of *M*-**1** • **2** and *P*-**1** • **2** gave a good mirror image relationship. Thus, CD spectrometry is a powerful tool for determining whether a given crystal is (+)- or (−)- [7 – 10, 12]. However, no significant solid state CD spectra for **1** • **3** and **1** • **4** were observed despite their chiral nature. This result means that conformation of whether a given crystal is chiral or not cannot necessarily be determined just by measurement of CD spectra. The reasons why meaningful CD spectra were

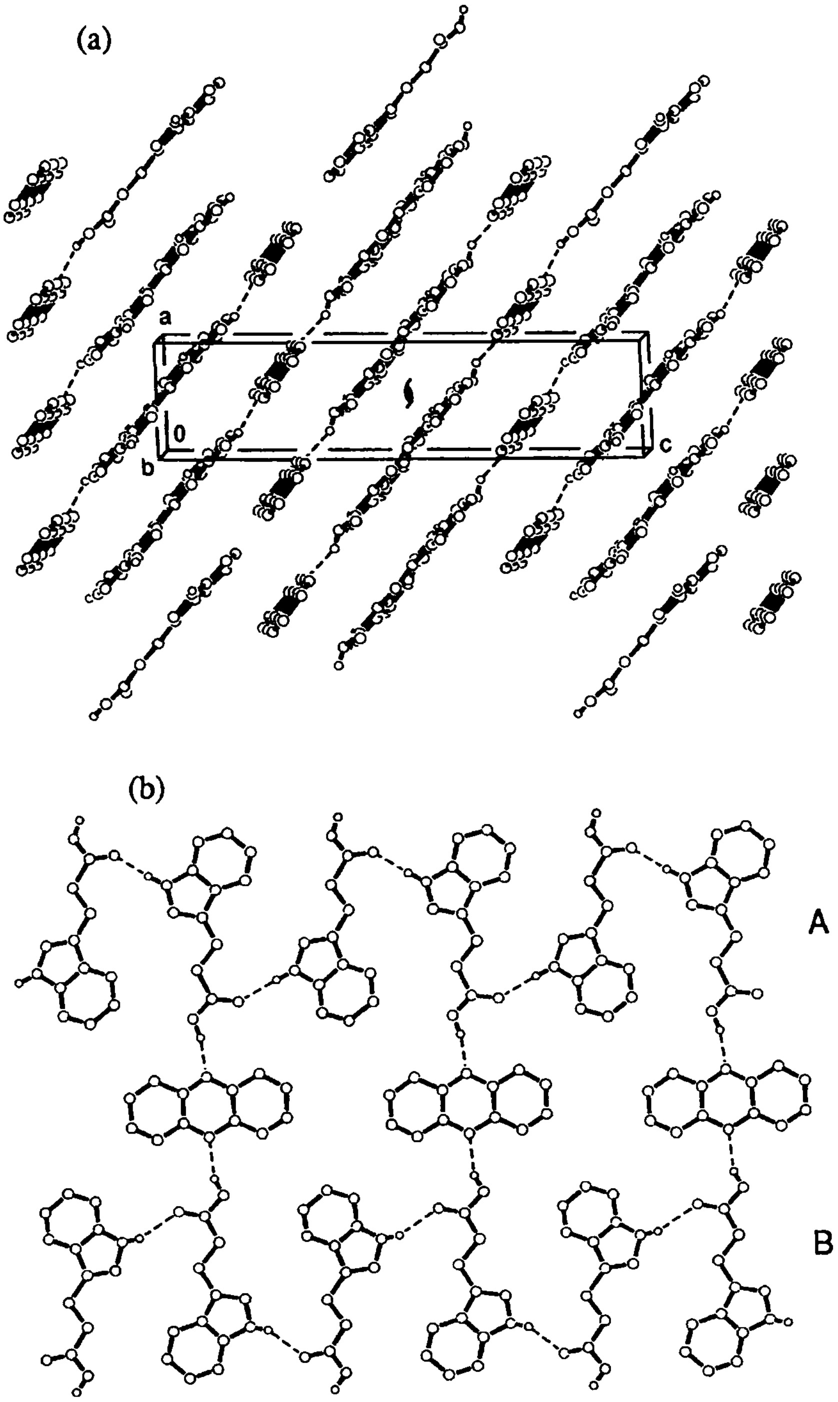


FIGURE 2 (a) Molecular packing arrangement; and (b) molecular sheet present in chiral **1** • **3**. The figures do not express the absolute configuration.

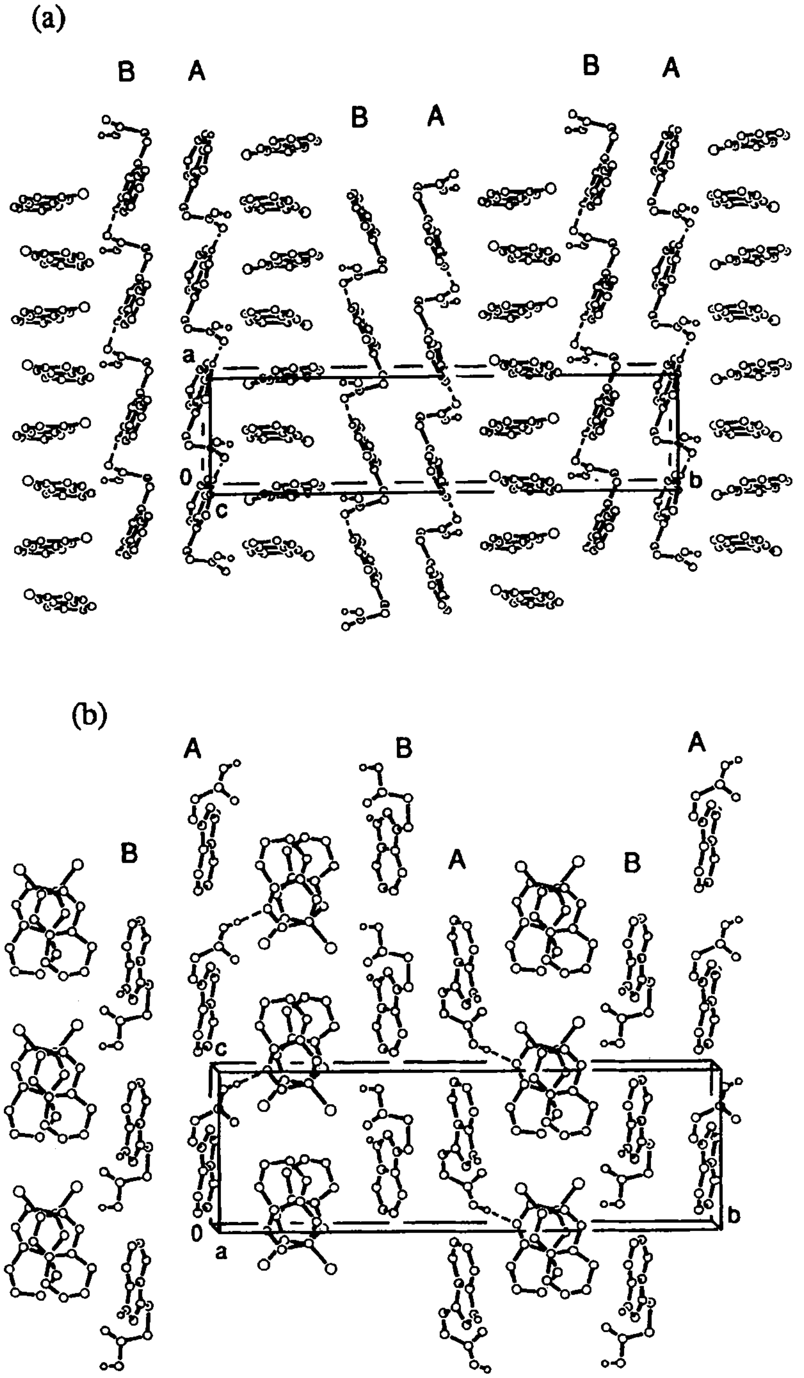


FIGURE 3 Molecular packing arrangement of chiral **1** • **4** on (a) *ac* face; and (b) *bc* face. The figures do not express the absolute configuration.

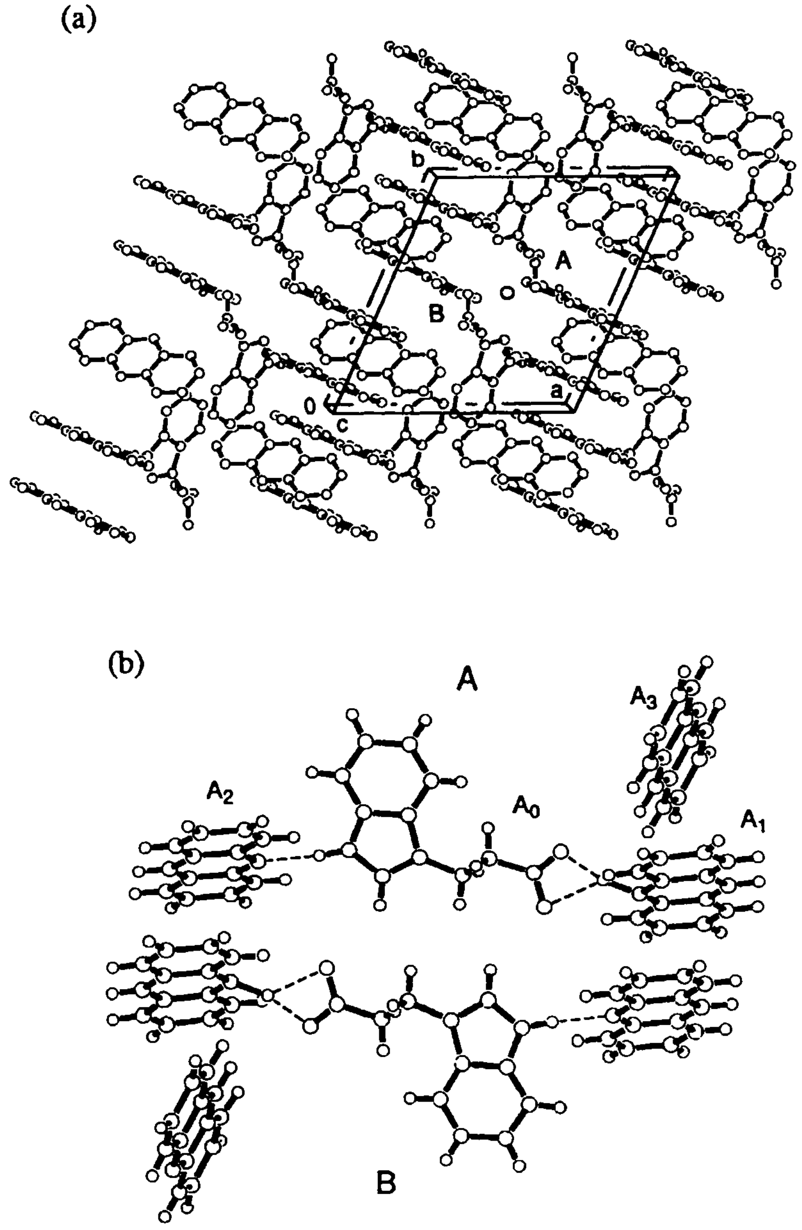


FIGURE 4 (a) Molecular packing arrangement; and (b) molecular units of the achiral **1**•**6**.

not obtained are not clear at this time, but this may be due to the large coexisting birefringence which masks small values of crystal optical activity [13]. Another reason may be due to the molecular packing arrangement. The existence of symmetrical molecular pairs in **1**•**3**, and the coexistence of almost enantiomeric pairs in **1**•**4**, lead to decreased or cancelled exciton couplings through the interaction of chromophores such as **3** and **4**, resulting in the disappearance of significant CD spectra. Therefore, it will be necessary to measure the accurate optical activity by HAUP [13] using single crystals in future work.

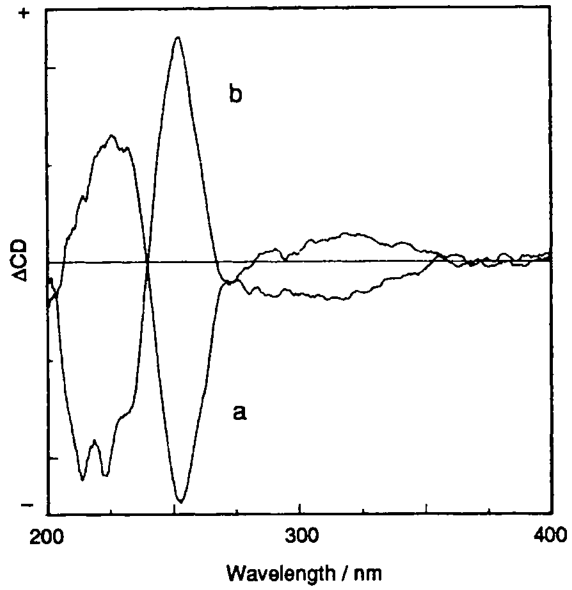


FIGURE 5 Solid state CD spectra of (a) *M*-**1** • **2**; and (b) *P*-**1** • **2** as Nujol mulls.

EXPERIMENTAL SECTION

Preparation of Two-component Molecular Crystals

Two-component molecular crystals **1** • **2**–**1** • **6** were prepared by crystallization from solutions of **1** and **2**–**6**. The crystals were characterized by DSC and IR. Solid state CD spectra of **1** • **2** were measured as Nujol mulls (Fig. 5).

1 • **2**: light yellow prisms; mp 112–114°C (from MeCN); IR (KBr) 3294, 3074–2364, 1697 cm^{-1}.

1 • **3**: reddish yellow prisms; mp 146–147°C (from AcOEt); IR (KBr) 3319, 3097–1934, 1705 cm^{-1}.

1 • **4**: colorless prisms; mp 78–80°C (from MeOH); IR (KBr) 3282, 3045–2360, 1915, 1687 cm^{-1}.

1 • **5**: colorless prisms; mp 94–95°C (from MeCN); IR (KBr) 3238, 3059–2362, 1923, 1676 cm^{-1}.

1 • **6**: yellow prisms; mp 112–114°C (from MeCN); IR (KBr) 3142–1940, 1709 cm^{-1}.

X-Ray Crystallographic Analysis

Data collections were performed on a Rigaku AFC7R automatic four-circle X-ray diffractometer with graphite monochromated Cu Kα(λ = 1.54178 Å) and Mo Kα(λ = 0.71069 Å) radiation. Absorption corrections were applied. No degradation of the crystal by X-ray was ascertained in all cases by repeated monitoring of the 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 I summarizes the crystal data of **1** • **2**–**1** • **6**.

The absolute configuration of *M*-**1** • **2** was determined very carefully by the Bijvoet method based on anomalous dispersion due to the oxygen atom during X-ray crystallographic analysis [8]. Despite oxygen being a light atom

($\Delta f = 0.032$ for Cu Kα radiation), its use as an anomalous scatterer was preferred, because even slight modification of *M*-**1** • **2** by the insertion of heavier elements such as sulfur and chlorine may cause changes in the initial crystal structure. A single crystal was cut into two pieces. The first was used to measure the CD spectrum (curve a in Fig. 5). The second piece was made spherical by gradually polishing the edge and then was submitted to absolute asymmetric determination with Cu Kα radiation. Further, the diffraction intensities of 25 reflections $\{0.32 < |\Delta F_c| / \sigma(F_o) < 1.06\}$ of the Bijvoet pairs which were selected in order of larger absolute value were measured manually at a low speed to give opposite plus and minus signs of all 25 reflections. Therefore, *x*, *y*, and *z* axes were converted; the molecular arrangement in Figures 1a and b shows the correct absolute configuration of *M*-**1** • **2**.

Acknowledgments

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