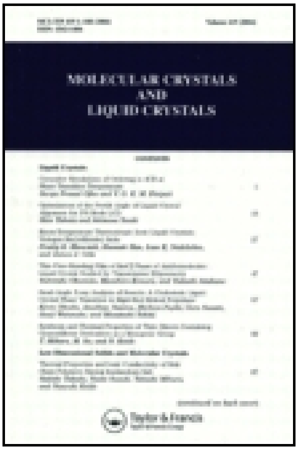

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Chiral Bimolecular Crystallization of Achiral Molecules

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Chiral Bimolecular Crystallization of Achiral Molecules

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Preparation, structure and discrimination of chiral two-component molecular crystals are described by connecting flexible achiral molecules such as diphenylacetic acid indole-3-propionic acid with aza aromatic compounds through hydrogen bonding. The chirality generation mechanisms are discussed.

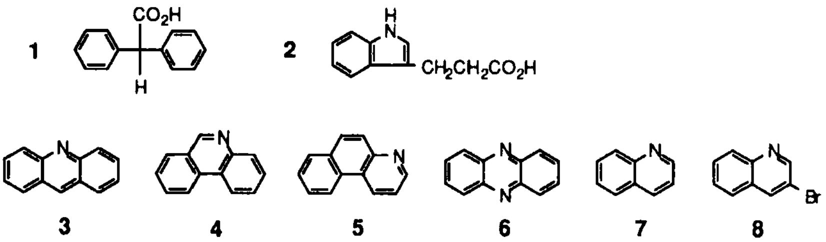
Keywords: chiral two-component crystals, crystal chirality generation mechanism, diphenylacetic acid, indole-3-propionic acid, aza aromatic compounds, solid-state CD spectrometry

INTRODUCTION

Chiral molecules never form achiral crystals, but the inverse is not true. In fact, a number of achiral molecules are already known to form chiral one-component crystals[1]. Our finding of a chiral two-component molecular crystal formation from acridine and diphenylacetic acid and successful absolute asymmetric synthesis by its solid state photoreaction have prompted us to prepare chiral two-component crystals by the self-assembly of achiral compounds and to elucidate their chirality generation mechanism[2]. Such a study will make possible to design absolute asymmetric syntheses, which have ever been attributed to the accidental findings[3,4]. Furthermore, this type of chiral crystallization is relevant to the prebiotic origin of chirality[5].

However, only a few chiral bimolecular crystals have been known[2,3,6]. How can chirality be induced in the spontaneous crystallization of achiral molecules? The fact that every chiral molecule crystallizes into chiral space groups suggests that freezing of achiral molecules such as glycine[7] and benzophenone[8] into chiral conformations can lead to the formation of chiral crystals. Our strategy for the preparation of new chiral two-component crystals based on the idea that connects an achiral flexible molecule with a second achiral molecule through hydrogen bonding by the self-assembly led to finding two series of chiral two-component crystals. A series is the chiral crystals composed of diphenylacetic acid and aza aromatic compounds, whose chirality is generated by virtue of the propeller-like conformation of two phenyl planes and a carboxyl plane of the diphenylacetic acid molecule self-assembled in the crystal lattice[2,9]. Another series is the chiral crystals constructed from indole-3-propionic acid and aza aromatic compounds whose chirality is generated by the formation of helical hydrogen bonding chain in the crystal lattice[10].

Chiral crystallization of achiral molecules necessarily gives the two enantiomorphous crystals such as the left and right handed quartz crystals. Solid-state circular dichroism (CD) spectrometry is shown to be easily applicable for the discrimination of two enantiomorphous crystals[9-11].



Two-component molecular crystals

Propeller type	Helical type
Chiral 1•3	Achiral 2•3
Chiral 1•4	Chiral 2•4
Achiral 1•5	Chiral 2•6
Achiral 1•6	Chiral 2•8
Achiral 1•7	

SCHEME 1

Propeller Type Chiral Two-component Molecular Crystals[2,9]

The two-component molecular crystals incorporate diphenylacetic acid (**1**) as a torsional molecule and five aza aromatic compounds, acridine (**3**), phenanthridine (**4**), benzo(f)quinoline (**5**), phenazine (**6**) and quinoline (**7**) as hydrogen bond connectors (Scheme 1). Recrystallization from the solutions of each two components gave five two-component crystals. The solvents, melting points, and X-ray crystallographic data are summarized in Table 1. The space groups of $P2_12_12_1$ and $P2_1$ confirmed the chiral nature of **1 · 3** and **1 · 4**, respectively. The other crystals **1 · 5**, **1 · 6** and **1 · 7** were achiral whose space groups are $P2_1/a$, $P2_1/c$ and $P2_1/n$, respectively. In all the crystals, O–H•••N hydrogen bonding is formed between the hydroxyl group of **1** and the N atom of aza aromatic compond.

TABLE I Characterization and X-ray crystal data of the two-component molecular crystals of diphenylacetic acid and aza aromatic compounds

Parameter	Chiral *M*-**1•3**	Chiral *P*-**1•4**	Achiral **1•5**	Achiral **1•6**	Achiral **1•7**
solvent	MeCN	MeOH	MeOH	MeOH	MeOH
mp (°C)	102	116	122	137	89
molar ratio	1:1	1:1	1:1	2:1	1:1
space group	$P2_12_12_1$	$P2_1$	$P2_1/a$	$P2_1/c$	$P2_1/n$
a (Å)	14.908(4)	12.837(4)	16.456(3)	5.824(1)	11.044(6)
b (Å)	25.367(6)	5.478(2)	6.106(4)	18.128(1)	19.484(2)
c (Å)	5.457(3)	14.592(2)	21.569(2)	15.194(2)	9.238(3)
α (°)	90.0	90.0	90.0	90.0	90.0
β (°)	90.0	92.80(2)	108.49(1)	97.99(2)	110.94(3)
γ (°)	90.0	90.0	90.0	90.0	90.0
V (cm^3)	2063(1)	1024.9(5)	2055(1)	1588(4))	1856(1)
Z	4	2	4	2	4
ρ_{calcd} (g cm^{-3})	1.260	1.268	1.265	1.264	1.221
radiation	Cu K_α	Cu K_α	Mo K_α	Cu K_α	Mo K_α
R	0.043	0.026	0.046	0.057	0.045
R_w	0.058	0.025	0.076	0.088	0.076

Each two enantiomorphous crystals of **1**·**3** and **1**•**4** could be obtained by spontaneous crystallization from the solutions of acetonitrile and methanol, respectively. The absolute configurations were determined to be *M*-**1**•**3** and *P*-**1**•**4** with a high degree of certainty[12] by using the Bijvoet method based on X-ray anomalous dispersion of the oxygen atom with Cu Kα radiation. The solid-state CD spectra of *M*-**1**•**3** and *P*-**1**•**4** correspond to the curves (a) and (d) in Figure 2. As shown in Figure 1, two phenyl planes and a carboxyl plane of the diphenylacetic acid molecule form a propeller-like conformation in each hydrogen bonding pair with aza aromatic compounds. An important feature of *M*-**1**•**3** and *P*-**1**•**4** is that only the molecular pairs of a single absolute configuration in Figure 1a and e, respectively, are packed in the crystal lattice, introducing chirality in the crystal. On the other hand, only the molecular pairs with opposite absolute configurations are packed in *P*-**1**•**3** and *M*-**1**•**4** (Figure 1b and c). The two kinds of molecular pairs (a and b, c and d) are in mirror image relationship to each other.

Here it is understandable that diphenylacetic acid molecule is achiral in the solution phase due to the free-rotation of planes but chiral in **1**·**3** and **1**·**4** due to freezing into the most stable conformation. Namely, this type of chiral crystallization is like a spontaneous resolution of racemic compounds. Thus, the flexible planes of diphenylacetic acid molecule play an essential role in the chiral bimolecular crystallization. However, the crystal of diphenylacetic acid alone is achiral (space group $P2_1/n$) due to the formation of an achiral carboxyl dimer of the antipodal molecules in the crystal lattice.[2] We have been aware that a chiral crystal of benzophenone[8] (space group $P2_12_12_1$) is in the similar situation. The two phenyl planes of benzophenone molecule have some torsions in the crystal. Although the two torsional conformations with mirror image relationship are possible, the molecules alone of a single absolute configuration are packed in a crystal.

On the other hand, two molecular pairs of left and right handed conformations coexist in achiral crystals of **1**·**5** (Figure 1e and f) and **1**•**7**. Therefore, the chirality is conpensated in the crystals to give the achiral crystals.

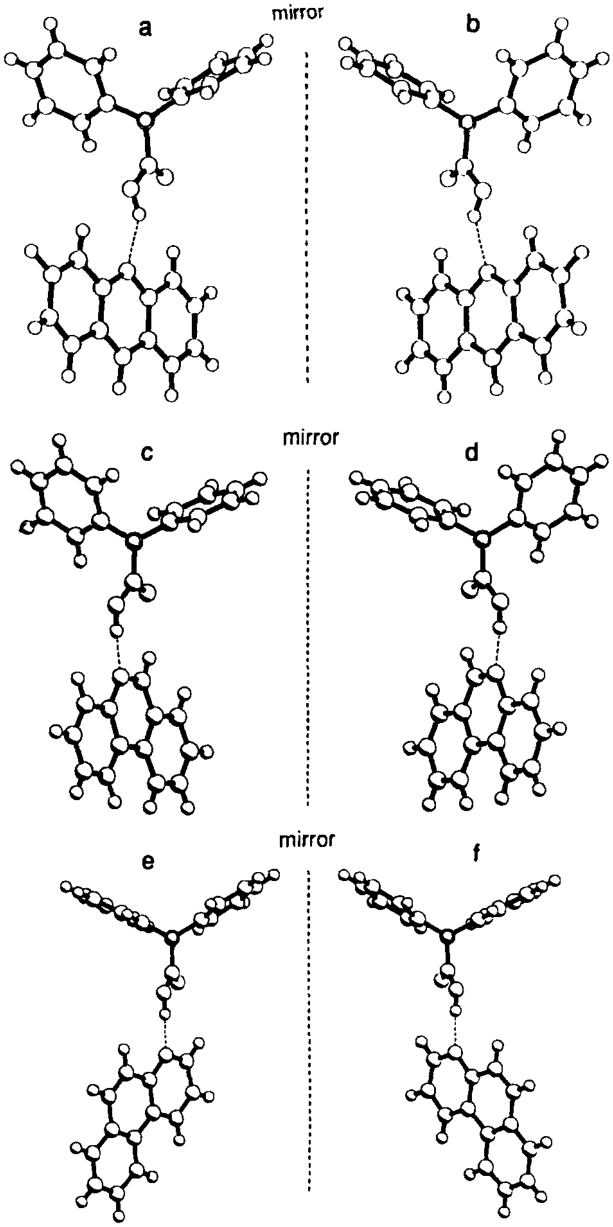
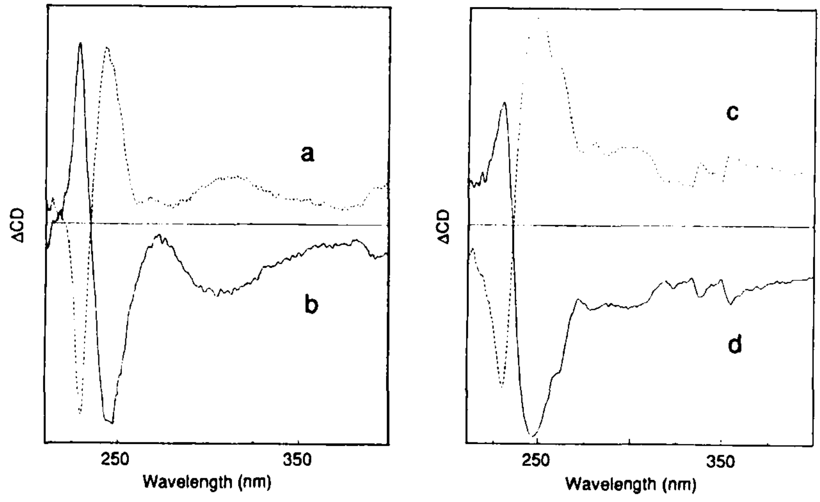


FIGURE 1 Hydrogen bonding pairs packed in the crystals. (a), (b), (c) and (d) exist separately in *M*-**1**•**3**, *P*-**1**•**3**, *M*-**1**•**4** and *P*-**1**•**4**, respectively. (e) and (f) coexist in achiral **1**•**5**.



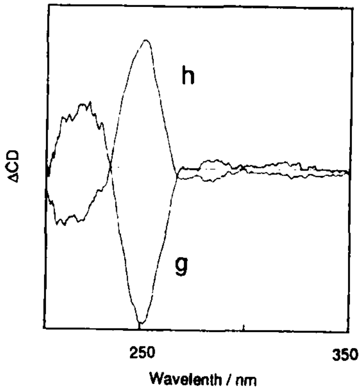


FIGURE 2 CD spectra of the enantiomorphous crystals of (a) *M*-**1•3**, (b) *P*-**1•3**, (c) *M*-**1•4**, (d) *P*-**1•4**, (g) *M*-**2•4**, (h) *P*-**2•4** by Nujol mull method

The prediction whether the molecular pairs are self-assembled in only one handed conformation or in both handed conformations in spontaneous crystallization remains difficult, depending on a small difference among the molecular structures of the aza aromatic compounds. We reached however a principal guideline that the torsional conformation such as a phenyl plane is effective for the induction of chirality in the formation of two-component crystals.

The discrimination of two enantiomorphous crystals is important. This type of chiral crystal has inherently optical activity. We succeeded to measure the solid-state CD spectra of **1**·**3** and **1**·**4** by Nujol mull method[11] (Figure 2). Reasonably, such CD spectra were not observed in solution state. The CD curves of *M*- and *P*-crystal are in mirror image relationship to each other. The plus and minus ellipticities of *M*-**1**•**3** and *P*-**1**•**3** are accordant with those of *M*-**1**•**4** and *P*-**1**•**4**, respectively, reflecting the similarity between the spatial arrangements of the molecular pairs in the two crystals. Further accumulation of a large number of experimental data and theoretical consideration will make possible to lead to the determination of absolute configuration of chiral crystal by the CD spectrometry. In addition, measurement of the optical rotations of *M*-**1**•**3** and *P*-**1**•**3** by HAUP (high-accuracy universal polarimeter)[13] using a single crystal is being undertaken.

Helical Type Two-component Molecular Crystals

We selected indole-3-propionic acid (**2**) as a flexible molecule because the molecules of **2** alone form a chiral crystal as shown in Table 2. Recrystallization from the solutions of **2** and aza aromatic compounds such as **3**, **4**, **6** and **8** followed by X-ray structure analysis to lead to finding three chiral two-component crystals of **2**•**4**, **2**•**6**, and **2**•**8**, whose space group belongs to $P2_1$ (Table 2).

The absolute configuration of **2**•**4** was successfully determined to be *M*-**2**•**4** by the anomalous dispersion of the oxygen atoms during X-ray analysis; the CD spectrum corresponds to the curve (g) in Figure 2. Figure 3 shows the molecular arrangement of two enantiomorphous crystals of *M*-**2**•**4** and *P*-**2**•**4**, which absolute configurations are correct. In the crystal lattice of *M*-**2**•**4**, two hydrogen bonds are formed (Figure 3g). One is the N–H•••O=C hydrogen bond between the N–H of indole ring of **2** and the O=C group of a next molecule **2** with an H•••O distance of 2.09 Å and an N–H•••O angle of 161°. This hydrogen bonding chain among the molecules of **1** forms a 2_1 helix in counterclockwise with a pitch of 5.33 Å, which corresponds to the length of *b* axis of the unit cell. Existence of only minus helix in the crystal

TABLE II Characterization and X-ray crystal data of the two-component molecular crystals of indole-3-propionic acid and aza aromatic compounds, and the component

Parameter	Achiral **2•3**	Chiral ***M*-2•4**	Chiral **2•6**	Chiral **2•8**	Chiral **2**
solvent	MeCN	MeCN	AcOEt	MeOH	
mp (°C)	114	113	147	79	132
molar ratio	1:3	1:1	2:1	1:1	
space group	$P\bar{1}$	$P2_1$	$P2_1$	$P2_1$	$P2_1$
a (Å)	13.1581)	13.251(1)	5.29(4)	7.058(4)	12.332(1)
b (Å)	13.43(1)	5.327(1)	11.92(2)	28.277(2)	5.241(1)
c (Å)	12.91(1)	13.609(1)	21.83(3)	8.884(2)	14.342(1)
α (°)	102.01(9)	90.0	90.0	90.0	90.0
β (°)	109.02(7)	104.78(1)	91.7(3)	91.39(3)	94.793(7)
γ (°)	63.93(8)	90.0	90.0	90.0	90.0
V (cm^3)	1930(3)	928.9(2)	1377(10)	1772(1)	923.6(2)
Z	2	2	2	4	4
ρ_{calcd} (g cm^{-3})	1.250	1.317	1.347	1.489	1.361
radiation	Mo K_α	Cu K_α	Mo K_α	Cu K_α	Cu K_α
R	0.067	0.032	0.037	0.066	0.042
R_w	0.096	0.052	0.062	0.099	0.081

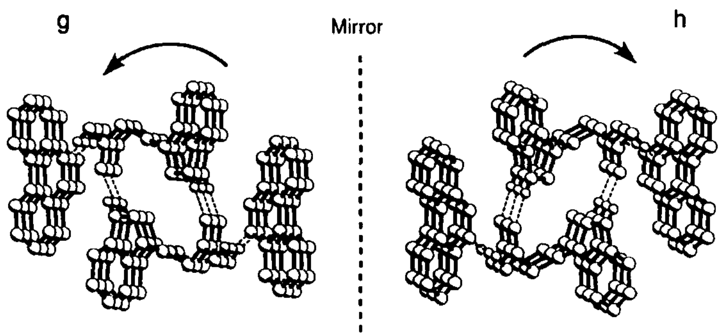


FIGURE 3 Helical hydrogen bonding chains formed in the crystals of (g) *M*-2•4 and (h) *M*-2•4

lattice leads to the generation of crystal chirality. Another O–H•••N hydrogen bond between the residual OH group of **2** and the N atom of **4** with a distance of 1.48 Å and an O–H•••N angle of 176° seems to act as an auxiliary for the helix formation.

The chiral crystals **2•6** and **2•8** also form helical hydrogen bonding chains in the crystal lattice, in the different torsional conformations of propionic acid group. Although in the case of the crystal of **2** alone, the two molecules of **2** form a hydrogen bonded carboxydimer, the dimers form also a helical structure through N–H•••O=C hydrogen bond to afford a chiral crystal (Figure 4). The molecular conformation of **1** with the dihedral angle of 2.7° between the indole ring and the propionic acid group is almost flat, very different from that in the crystal **2•4** in Figure 3. Although the flexible propionic acid group of **2** can rotate to some extent around the –C–C–C– bonds in solution, the torsional shape can be changed and frozen into the best fitted conformation according to the spatial environment in the crystallization. Thus, the torsional confomation of the propionic acid group plays a key role in the helix formation in the crystal lattice.

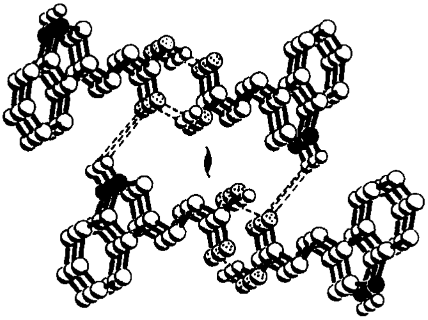


FIGURE 4 Helical hydrogen bonding chain formed in the crystal **2**

In concusion, propeller type and helical type of chiral two-component molecular crystals were prepared by using diphenylacetic acid and indole-3-propionic acid, and aza aromatic compounds as the components. The flexible phenyl group and propionic acid group play an essential role in the chiral bimolecular crystallization.

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