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Hideko Koshima[a]; Masashi Miyauchi[a]; Motoo Shiro[b]
[a] Department of Applied Chemistry, Faculty of Engineering, Ehime University, Matsuyama, Japan [b] Rigaku Corporation, Tokyo, Japan

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Helicity Control in the Preparation of Chiral Co-crystals from Tryptamine and Achiral Carboxylic Acids by Pseudo-seeding

HIDEKO KOSHIMA[a,*], MASASHI MIYAUCHI[a] and MOTOO SHIRO[b]

[a]*Department of Applied Chemistry, Faculty of Engineering, Ehime University, Matsuyama 790-8577, Japan;* [b]*Rigaku Corporation, Matsubara 3-9-12, Akishima, Tokyo 196-8666, Japan*

Chiral crystals of tryptamine and achiral carboxylic acids such as *p*-chlorobenzoic acid, cinnamic acid, *p*-chlorocinnamic acid and *p*-methylcinnamic acid were prepared by crystallization from the solutions of both components. All the crystals belonged to typical chiral space group $P2_12_12_1$. The crystal chirality is generated through the formation of a unidirectional twofold helix between the two components through quaternary ammonium salt interaction and hydrogen bonding in the lattice. This kind of spontaneous crystallization necessarily gives crystals of both clockwise and counterclockwise helicites. Here, pseudo-seeding based on utilizing these crystals as seed crystals was examined, resulting in successful helicity control in crystallization from solutions of tryptamine and different carboxylic acids.

Keywords: Helicity control; Chiral bimolecular crystallization; Pseudo-seeding; Achiral molecules

INTRODUCTION

Solid state reaction of chiral crystals self-assembled from achiral molecules can lead to the success of absolute asymmetric synthesis [1–3]. It is necessary to prepare and predict such chiral crystals with high reliability for designing absolute asymmetric synthesis. Chiral crystallization of achiral molecules spontaneously gives mixtures of both enantiomorphous (left and right) crystals [4,5]. Therefore it is important to prepare only one-handed crystals, which is desired. Seeding has been commonly utilized in order to prepare selectively crystals with the same handedness as the seed. Amplification of the opposite-handed chirality by the addition of chiral inhibitors in crystallization was reported [6]. Since our study of the preparation of chiral co-crystals from different achiral compounds by self-assembly [7], we had already prepared a series of helical-type crystals from tryptamine and achiral carboxylic acids with a high probability of around 50% [8]. We reported in a preliminary communication that some of the helical-type crystals having similar crystal structures played the role of seed crystals in crystallization from solutions of tryptamine and different carboxylic

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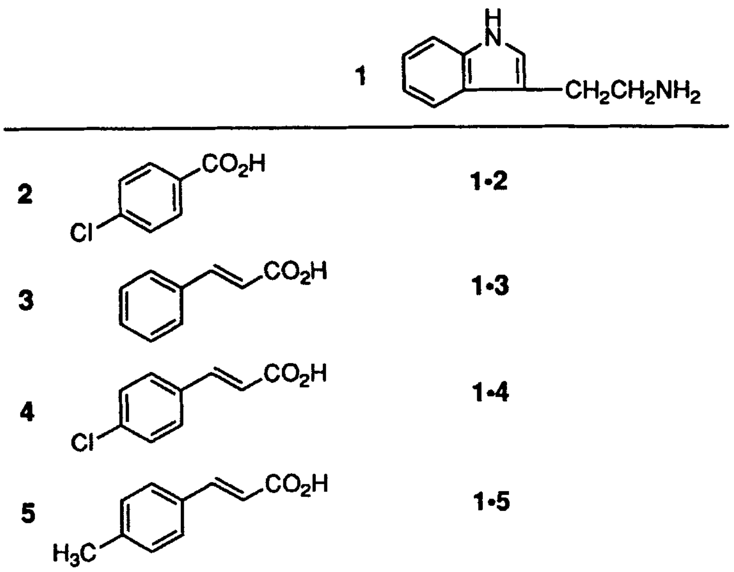
*Corresponding author. Tel.: (+81)-89-927-8523, Fax: (+81)-89-927-9923, e-mail: koshima@en3.ehime-u.ac.jp acids [9]. However, it was not yet clear whether helicity (clockwise and counterclockwise) control was achieved, because their absolute configurations could not be determined. Further combinations of tryptamine with other substituted carboxylic acids led to the finding of new chiral crystals followed by successful determination of the absolute configurations. Here, we achieved their helicity control by utilizing these crystals as the pseudo-seed crystals.

RESULTS AND DISCUSSION

The crystals incorporate from tryptamine (**1**) as base molecule and achiral carboxylic acids such as *p*-chlorobenzoic acid (**2**), cinnamic acid (**3**) [8c], *p*-chlorocinnamic acid (**4**) and *p*-methylcinnamic acid (**5**) (Scheme 1). Chiral crystals **1**·**2**–**1**·**5** were obtained by spontaneous crystallization from the solutions of both components in methanol, all of which belonged to chiral space group $P2_12_12_1$ (Tab. I). The melting points and the IR spectra are summarized in the Experimental section.

In all the crystals, quaternary ammonium salt bridges ($NH_3^+ \cdots CO_2^-$) and hydrogen bonding (In-NH$\cdots$O—C) are formed between the molecules of **1** and acids, whose distances estimated from the X-ray crystallographic analyses are very similar (Tab. II). The two kinds of intermolecular bondings form a twofold helical chain as shown in Figure 1. The crystal chirality is generated through the formation of unidirectional helicity in the lattice.

Both *P* (clockwise) and *M* (counterclockwise) crystals of **1**·**2**–**1**·**5** were obtained by spontaneous crystallization from the solutions of both components, and easily discriminated by the measurement of solid state CD spectra as Nujol mulls, giving a good mirror image relationship (Fig. 1). The absolute configurations of *P*-**1**·**2** and *M*-**1**·**4** were determined with a high degree of certainity from the Flack constants [10] (Experimental section). The solid state CD spectra of *P*-**1**·**2** and *M*-**1**·**4** correspond to the CD curves *P* and *M* in Figures 1a and c, respectively. However, the absolute configurations of **1**·**3** and **1**·**5** could not be determined because the oxygen atom ($\Delta f' = 0.032$) is not sufficiently heavy to obtain large X-ray anomalous dispersion using a



SCHEME 1

TABLE I Crystal data of the chiral crystals

	1·2	1·3[a]	1·4	1·5
Formula	$C_{17}H_{17}N_2O_2Cl$	$C_{19}H_{20}\ N_2O_2$	$C_{19}H_{19}N_2O_2Cl$	$C_{20}H_{22}N_2O_2$
Space group	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$
a(Å)	15.165(3)	9.681(3)	10.306(1)	10.244(3)
b(Å)	16.734(2)	29.00(1)	28.277(3)	28.584(8)
c(Å)	6.282(5)	5.931(4)	5.9269(5)	5.957(2)
β(°)	90.0	90.0	90.0	90.0
V(Å^3)	1594(1)	1664(1)	1727.3(3)	1744.4(8)
Dc(g cm^{-3})	1.320	1.230	1.318	1.228
Z	4	4	4	4

[a] Ref. [8c].

TABLE II Distance and angle data of the two-component crystals

			Torsion angle (deg)		
Crystal	Salt distance (Å) $NH_3^+\cdots CO_2^-$	H-bond distance (Å) In-NH···O—C	Tryptamine InC—C—C—N	Acid PhC—C=C—CO	Dihedral angle (deg) indole/phenyl
1·2	1.79, 1.80, 2.11	1.96	34(2)	–	3.0
1·3	1.75, 1.82, 2.01	1.99	73.7(6)	−179.2(5)	4.8
1·4	1.82, 1.83, 2.03	2.05	−73.3(2)	−179.3(2)	3.6
1·5	1.81, 1.82, 2.02	2.05	−73.4(2)	−179.3(2)	4.3

Cu target. Nevertheless, it can be indirectly assigned that the CD spectra of *P*- and *M*-crystals of **1**·**3** and **1**·**5** correspond to the CD curves (*P*) and (*M*) in Figures 1b and d, respectively, from the similarity to those of **1**·**4** due to the small molecular structure difference among the cinnamic acids **3**–**5**.

Next, pseudo-seeding was examined in order to prepare only one-handed crystals based on utilizing these chiral crystals as the seed crystals. For instance, a slightly supersaturated solution of **1** and **2** was divided into six glass vessels, and then a few pieces of small single crystals of *P*-**1**·**4** as seed crystals were added to the solution. The vessels were covered to prevent crystallization on the inner glass wall due to the vaporization of the solvents, and then allowed to stand at room temperature to give fine needle crystals in a radial manner on the surfaces of the pseudo-seed crystals. All the crystals in each vessel were filtered off to afford around 25% yield. Next, measurement of solid state CD spectra gave the CD curve *P* in Figure 1a for the crystals from all six vessels, which means the formation of *P*-**1**·**2** (entry 1 in Tab. III). Conversely, crystallization from the solutions of **1** and **2** in the presence of *M*-**1**·**4** gave *M*-**1**·**2** (CD curve *M* in Fig. 1a) for all six vessels (entry 2). For a comparison, when the crystals were spontaneously formed in the absence of seed crystals, *P*-**1**·**2** was obtained for the two vessels and *M*-**1**·**2** for the other four (entry 3). These results indicate that the pseudo-seed crystals of *P*-**1**·**4** and *M*-**1**·**4** provide successful helicity control in the preparation of chiral crystal **1**·**2** from the solution of **1** and **2**.

All other combinations between the solutions and the pseudo-seed crystals were also carried out to give always *P*-crystals in the presence of pseudo-seed *P*-crystals, oppositely *M*-crystals in the presence of pseudo-seed *M*-crystals, confirming the effectiveness of the psuedo-seeding. The results are summarized in Table III. The following explanation for successful helicity control by pseudo-seeding may be possible. The most

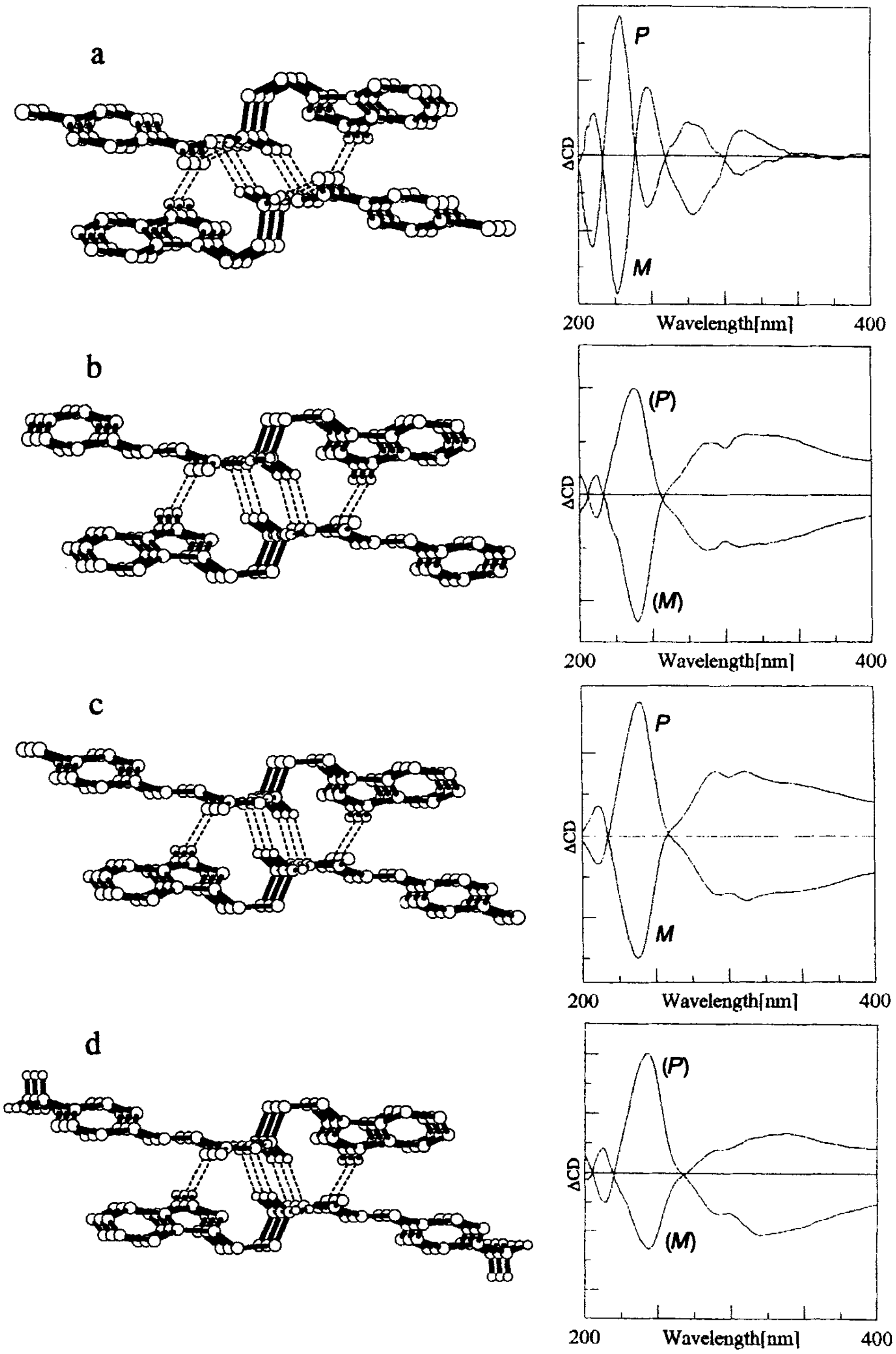


FIGURE 1 Helical molecular arrangements of *P*-crystals and solid state CD spectra of *P*- and *M*-crystals: (a) **1**·**2**, (b) **1**·**3**, (c) **1**·**4** and (d) **1**·**5**.

TABLE III Enantiomorphous crystals obtained in the presence and absence of pseudo-seed crystals

Entry	Component	Pseudo-seed crystal	Obtained crystal[a] number of vessels	
			P-**1**·**2**	*M*-**1**·**2**
1	**1** + **2**	*P*-**1**·**4**	6	0
2		*M*-**1**·**4**	0	6
3		none	4	2
			(*P*)-**1**·**3**	(*M*)-**1**·**3**
4	**1** + **3**	*P*-**1**·**2**	6	0
5		*M*-**1**·**2**	0	6
6		*P*-**1**·**4**	6	0
7		*M*-**1**·**4**	0	6
8		none	3	3
			P-**1**·**4**	*M*-**1**·**4**
9	**1** + **4**	*P*-**1**·**2**	6	0
10		*M*-**1**·**2**	0	6
11		none	3	3
			(*P*)-**1**·**5**	(*M*)-**1**·**5b**
12	**1** + **5**	*P*-**1**·**2**	6	0
13		*M*-**1**·**2**	0	6
14		*P*-**1**·**4**	6	0
15		*M*-**1**·**4**	0	6
16		none	3	3

[a] The CD spectrum in Figure 1.

important and strongest core forming the helical structures is the $NH_3^+ \cdots CO_2^-$ salt interaction and the In-NH···O—C hydrogen bonding, which are basically common among the four crystals. At the initial crystallization process from the solutions, the similar helical bonds on the surface of the pseudo-seed crystals recognize with higher priority the amino and imino groups of the tryptamine molecule and the carboxylic acid group of acid molecules in the solution rather than the whole of the molecules, resulting in assembly into the same helicity as the pseudo-seed crystals. Thus the pseudo-seeding is interesting from the aspect of molecular recognition in the crystallization process.

EXPERIMENTAL SECTION

Preparation of Co-crystals

Two-component molecular crystals **1**·**2**–**1**·**5** were prepared by crystallization from solutions of **1** and **2**–**5** in methanol. The crystals were characterized by the measurements of their melting points and IR spectra. Solid state CD spectra were measured as Nujol mulls (Fig. 1).

1·**2**: colorless plate; mp 203–204°C (from MeOH); IR (KBr) 3282, 2503–3055, 1589 cm^{-1}.

1·**3**: colorless plate; mp 176–177°C (from MeOH); IR (KBr) 3300, 2517–3080, 1637 cm^{-1}.

1·**4**: colorless plate; mp 209–211°C (from MeOH); IR (KBr) 3300, 2511–3076, 1560 cm^{-1}.

1·**5**: colorless plate; mp 188–190°C (from MeOH); IR (KBr) 3288, 2513–3076, 1560 cm^{-1}.

Pseudo-seeding

Firstly, pure *P*- and *M*-crystals as seed crystals were prepared by spontaneous crystallization from the solutions of **1** and acids, and then purified by seeding. Next, a slightly supersaturated solution of **1** (1 mmol) and acid

(1 mmol) in methanol and acetonitrile (1 : 1) was prepared by gentle heating and divided into six glass vessels. Then a few pieces of other *P*- or *M*-crystals were added to the solutions as the seed crystal. The vessels were covered and allowed to stand at room temperature until the formation of crystals. All the crystals in each vessel were filtered and solid state CD spectra were measured as Nujol mulls for all six vessels. Table III lists the results of all the combinations of solutions and seed crystals.

X-ray Crystallographic Analysis

Data collections were performed on a Rigaku AFC5R automatic four-circle X-ray diffractometer with graphite monochromated Cu $K\alpha$ ($\lambda = 1.54178\,\text{Å}$) and Mo $K\alpha$ ($\lambda = 0.71069\,\text{Å}$) 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 using the teXsan crystallographic software packager from Molecular Structure Corporation. Table I summarizes the crystal data of **1**·**2**–**1**·**5**. The absolute configurations of *P*-**1**·**2** and *M*-**1**·**4** were determined with a high degree of certainty from the Flack constants [10] to give −0.018(0.038) and 0.024(0.050), respectively, with Cu $K\alpha$ radiation, which means that the obtained configurations are correct.

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