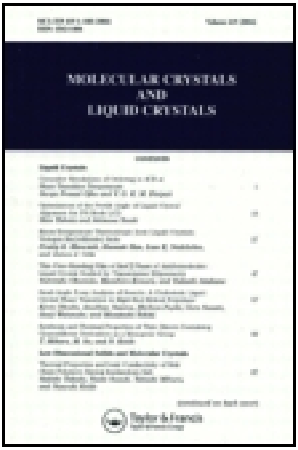

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# Preparation of Helical-Type Crystals from Tryptamine and Achiral Carboxylic Acids and their Enantiomorphous Control by Pseudo-Seeding

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# Preparation of Helical-Type Crystals from Tryptamine and Achiral Carboxylic Acids and their Enantiomorphous Control by Pseudo-Seeding

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A series of helical-type co-crystals of tryptamine and achiral carboxylic acids were prepared by the self-assembly. Their crystal chirality is generated through the formation of a unidirectional two-fold helix between the two components. Several crystals of them having similar crystal structures were found to play the role of pseudo-seed crystals in chiral crystallization.

*Keywords:* chiral two-component crystals; helical chain structure; enantiomorphous control; pseudo-seeding; solid state CD spectrometry; tryptamine; carboxylic acids

## INTRODUCTION

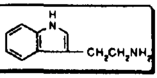
Formation of crystal into chiral space group from achiral molecule is known as chiral crystallization [1,2]. Since our finding of a chiral two-component crystal of diphenylacetic acid and acridine [3], we have prepared a number of new chiral two-component crystals by self-assembling two different molecules [4-9]. The chiral crystals comprise helical-type crystals of 3-indolepropionic acid and aza aromatic compounds [5,6] and tryptamine and achiral carboxylic acids [7-9], and propeller-type crystals of diphenylacetic acid and aza aromatic compounds [3,4]. In particular, helical-type crystals are the most imortant. Herein, a series of helical-type crystals of tryptamine and achiral carboxylic acids are reviewed.

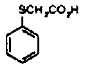
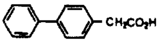
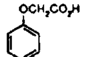
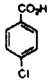
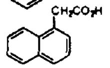
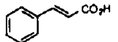
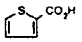
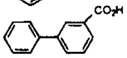
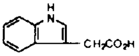
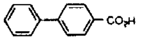
This kind of chiral crystallization of achiral molecules spontaneously gives both enantiomorphous (left and right) crystals. Seeding methods have been commonly utilized in order to prepare crystals with the same handedness as the seed on a large scale. Amplification of the opposite handed chirality has been also reported by crystallization in the presence of chiral additives as inhibitors [10]. Herein, enantiomorphous control in the preparation of the crystals was examine, based on utilizing crystals having similar crystal structures as the pseudo-seed crystals, to lead to the successful control.

## Helical-type Crystals of Tryptamine and Achiral Carboxylic Acids

The chiral two-component crystals incorporate tryptamine (**1**) as the flexible base molecule and ten achiral carboxylic acids **2** – **11** as bonding connectors (Table 1) [7-9]. The crystals were prepared by crystallization of both components in methanol. The crystals were submitted to X-ray crystallographic analysis to confirm the chiral nature, of which space groups belonged to $P2_1$ and $P2_12_12_1$.

Table 1. Chiral two-component crystals of tryptamine **1** and achiral carboxylic acids **2** – **11**

**1** 

| | Chiral crystal | | Space group | | Chiral crystal | | Space group |
|---|---|---|---|---|---|---|---|
| **2** |  | **1·2** | $P2_1$ | **7** |  | **1·7** | $P2_1$ |
| **3** |  | **1·3** | $P2_1$ | **8** |  | **1·8** | $P2_12_12_1$ |
| **4** |  | **1·4** | $P2_1$ | **9** |  | **1·9** | $P2_12_12_1$ |
| **5** |  | **1·5** | $P2_1$ | **10** |  | **1·10** | $P2_12_12_1$ |
| **6** |  | **1·6** | $P2_1$ | **11** |  | **1·11** | $P2_12_12_1$ |

The two enantiomorphous crystals were obtained by spontaneous crystallization from the solutions of both components. Solid state CD spectra (powder) of both enantiomorphous crystals were measured as Nujol mulls to afford the CD curves in good mirror image relationship, giving easy discrimination of their handedness (Figure 1). The absolute configurations of *P*-**1**•**2**, *P*-**1**•**5**, and *P*-**1**•**8** were detemined with a high degree of certainty by the Bijvoet method based on X-ray anomalous dispersion of the sulfur or chlorine atom with Cu Kα radiation.

In all of the crystals, the quaternary ammonium salt bridge ($NH_3^+ \cdots CO_2^-$) between the aminoethyl group of **1** and carboxylate group, and the hydrogen bonding ($N\text{–}H \cdots O\text{–}C$) between the indole imino group and carboxylate group are formed to be self-assembled into a two-fold helix in the lattice. Figure 1 shows their representative helical arrangements. There involve two types of helices; an independent helix presented in the crystals such as **1**•**2** – **1**•**4**, **1**•**7** and **1**•**9**, and a helix linearly connected to the next helix in **1**•**5**. The crystal chirality is generated through the formation of one direction of helicity in the both type of helices.

## Enantiomorphous Control by Pseudo-seeding

For the study of pseudo-seeding, three crystals **1**•**2** – **1**•**4** were selected due to the same space group $P2_1$ (Table 1), the similar unit cell sizes (Table 2), and the very similar their helical arrangements (Figure 1). For instance, a slightly supersaturated 1:1 solution of **1** and **3** in methanol and acetonitrile (1:1) was divided into six glass vessels, and then small amounts of the needle crystals of *P*-**1**•**2** as pseudo-seed crystals were added to the solutions. The vessels with covers to prevent crystallization on the inner walls of vessels were allowed to stand on separate laboratory benches at room temperature to form fine needle crystals in a radial manner on the surfaces of the pseudo-seed crystals.

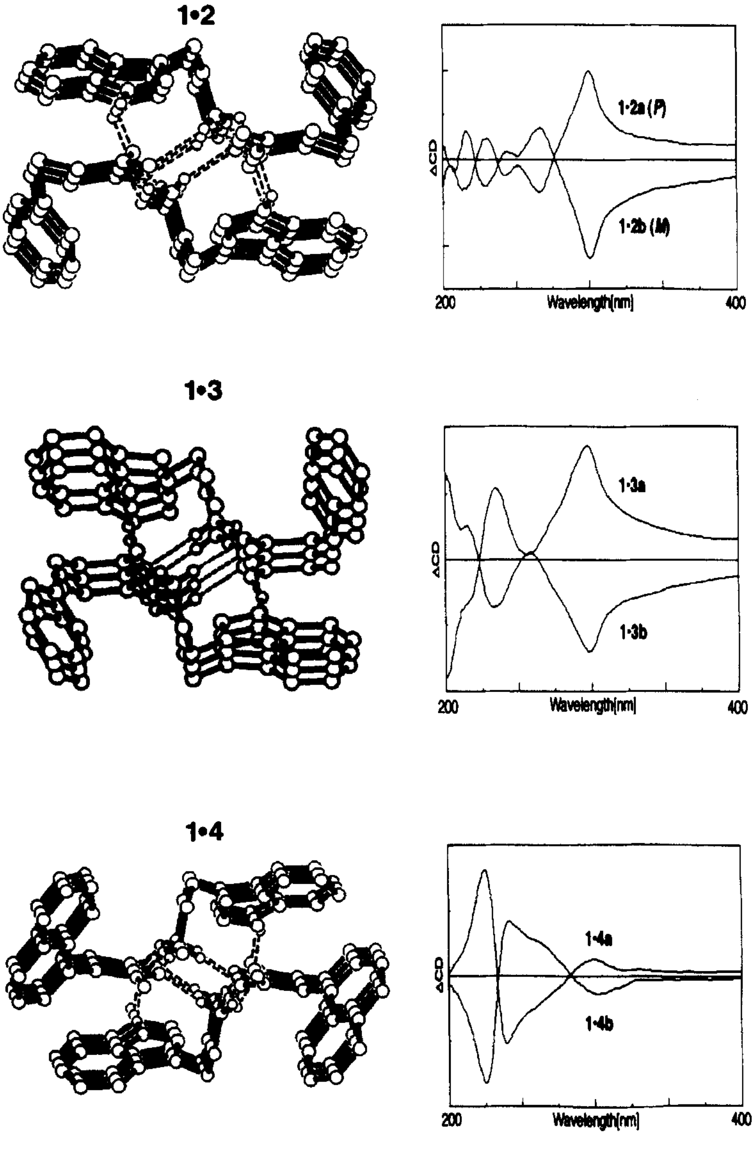


Figure 1. Helical molecular arrangemnets and solid state CD spectra in the chiral crystals.

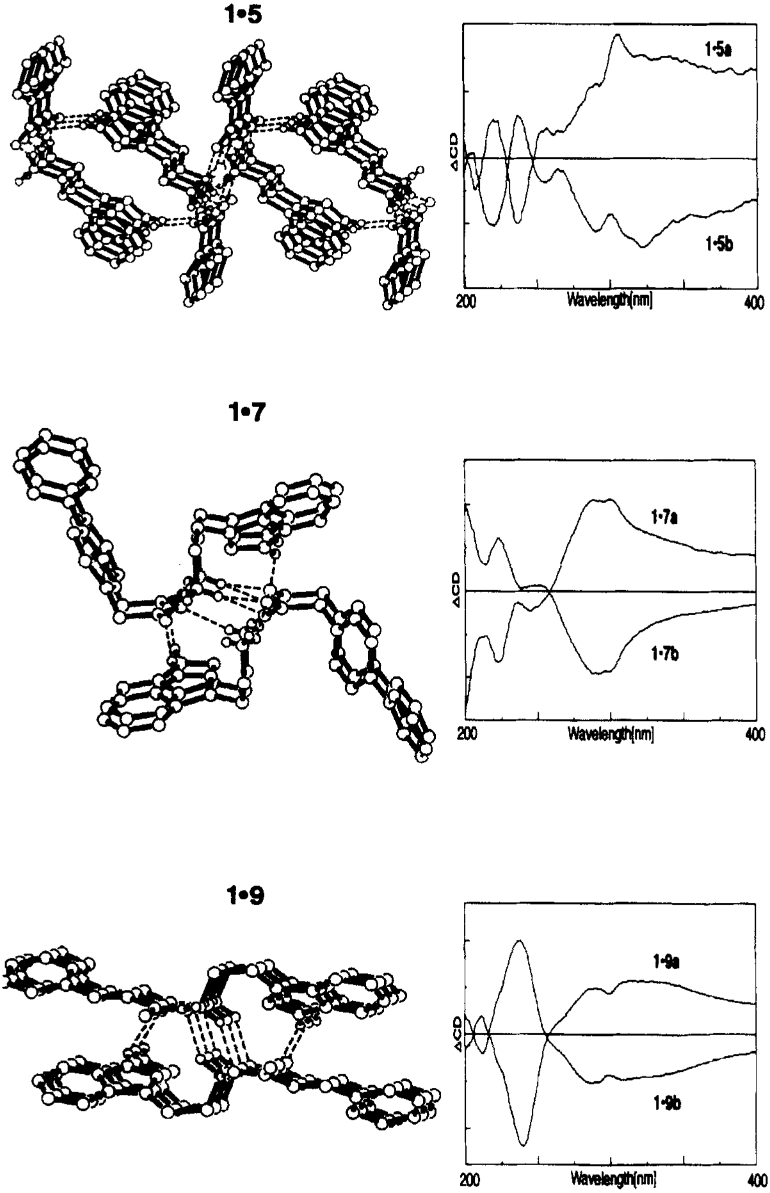


Figure 1. Continued.

Table 2. Crystal data of the chiral crystals[a]

| | Chiral **1•2** | Chiral **1•3** | Chiral **1•4** |
|---|---|---|---|
| space group | $P2_1$ | $P2_1$ | $P2_1$ |
| $a$ (Å) | 9.285(1) | 9.421(5) | 9.656(2) |
| $b$ (Å) | 6.874(1) | 6.834(2) | 6.750(3) |
| $c$ (Å) | 13.988(1) | 13.056(4) | 14.603(2) |
| $\beta$ (deg) | 108.291(8) | 102.89(3) | 101.13(1) |
| $V$ (Å$^3$) | 847.6(2) | 819.4(5) | 933.8(4) |
| $Dc$ (g cm$^{-3}$) | 1.287 | 1.242 | 1.232 |
| $Z$ | 2 | 2 | 2 |

[a] Reference 9.

Table 3. Enantiomorphous crystals obtained in the presence and absence of pseudo-seed crystals

| entry | component | pseudo-seed crystal[a] | obtained crystal[a] number of vessels | |
|---|---|---|---|---|
| | | | **1•2a** | **1•2b** |
| 1 | **1** + **2** | **1•3a** | 6 | 0 |
| 2 | | **1•3b** | 0 | 6 |
| 3 | | **1•4a** | 6 | 0 |
| 4 | | **1•4b** | 0 | 6 |
| 5 | | **none** | 4 | 2 |
| | | | **1•3a** | **1•3b** |
| 6 | **1** + **3** | **1•2a** | 6 | 0 |
| 7 | | **1•2b** | 0 | 6 |
| 8 | | **1•4a** | 6 | 0 |
| 9 | | **1•4b** | 0 | 6 |
| 10 | | **none** | 2 | 4 |
| | | | **1•4a** | **1•4b** |
| 11 | **1** + **4** | **1•2a** | 6 | 0 |
| 12 | | **1•2b** | 0 | 6 |
| 13 | | **1•3a** | 6 | 0 |
| 14 | | **1•3b** | 0 | 6 |
| 15 | | **none** | 1 | 5 |

[a] The CD spectra are shown in Figure 1.

All of the crystals in each vessel were filtered off and ground up, followed by the measurement of solid state CD spectra to give the CD curve **1•3a** (Figure 1) for the crystals from all six vessels (entry 6 in Table 3). Conversely, crystallization from the solutions of **1** and **3** in the presence of *M*-**1•2** as the pseudo-seed crystals gave the CD curve **1•3b** (Figure 1) for all six vessels (entry 7).

For a comparison, when the crystals were spontaneously formed without any pseudo-seed crystals, the CD spectrum **1•3a** was obtained for the two vessels and **1•3b** for the other four (entry 10). These results indicate that the pseudo-seed crystals of *P*-**1•2** and *M*-**1•2** provide enantiomorphous control in crystallization from the solutions of **1** and **3**.

Further, all combinations between the solutions and the pseudo-seed crystals were carried out to confirm the effectiveness of the pseudo-seeding (Table 3). On the other hand, both handed crystals were formed in the absence of pseudo-seed crystals (entries 5, 10, and 15).

It is interesting whenever the pseudo-seed crystals of **a** were added, the crystals of **a** were formed; and conversely the crystals of **b** were always obtained in the presence of the pseudo-seed crystals of **b** (Table 3). Since it is confirmed that the CD curve **1•2a** is derived from the clockwise helix by the absolute configuration determination, it is suggested that the crystals **1•3a** and **1•4a** may be also arranged in clockwise helix from the similarity of their CD curves. In future, success of absolute configuration determination of **1•3** and **1•4** will make possible more precise discussion and usefulness of the pseudo-seeding process.

## Acknowledgement

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