Pergamon

Tetrahedron Letters, Vol. 38, No. 28, pp. 5009-5012, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)01072-1

Preparation, Structure and Discrimination of a Chiral Bimolecular Crystal by the Self-assembly of 3-Indolepropionic Acid and Phenanthridine

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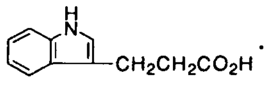
Abstract: Although 3-indolepropionic acid and phenanthridine are achiral molecules, a chiral bimolecular crystal is spontaneously formed; torsional conformation of the propionic acid group plays an important role in the helix formation through hydrogen bonding chain within the crystal lattice. © 1997 Elsevier Science Ltd.

Absolute asymmetric synthesis utilizing the solid state reaction of a chiral crystal self-assembled from an achiral molecule is a promising methodology for the asymmetric synthesis.[1,2] However, most of the successful examples have been attributed to the accidental findings, including our case by the photoreaction of a chiral bimolecular crystal of diphenylacetic acid and acridine.[1c] Although in the case of one-component crystals, a number of chiral crystals formed from achiral molecules are already known,[3] such a chiral crystallization phenomenon has scarecely drawn attention of organic chemists. On the other hand, chiral bimolecular crystals composed of different achiral compounds previously reported are few.[1,4] Challenge to the preparation of such chiral bimolecular crystals and the elucidation of chiral crystallization mechanism will not only make possible the design of absolute asymmetric synthesis but also contribute to the development of new materials such as crystal optics.[5] Furthermore, this type of chiral crystallization is relevant to the prebiotic origin of chirality.[6]

Flexible molecules such as glycine[7] and benzophenone[8] are fixed into chiral conformations in the spontaneous crystallization to give the chiral crystals. The chirality of a bimolecular crystal of diphenylacetic acid and acridine can be generated by virtue of the propeller-like conformation of two phenyl planes and a carboxyl plane of a diphenylacetic acid molecule in the crystal lattice.[1c] These examples suggest that torsional conformation of a flexible molecule is an important factor in the formation of chiral crystals. Here we tried to prepare new chiral bimolecular crystals, based on the idea that connects an achiral flexible molecule with the second achiral component through hydrogen bonding. We selected 3-Indolepropionic acid (**1**) as a flexible molecule and could prepare a chiral bimolecular crystal **3** by the combination with phenanthridine (**2**).

Chiral crystal **3**



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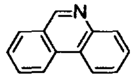

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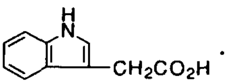
Achiral crystal **5**



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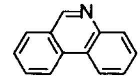

2

Recrystallization from an equimolar solution of **1** and **2** in acetonitrile gave a 1:1 chiral crystal **3**. The melting point is 113 °C, which is between those of **1** (132 °C) and **2** (107 °C). A single crystal (ca. 4 mg) was cut into two pieces. One piece was submitted to X-ray crystallographic analysis followed by absolute configuration determination, showing that the crystal has minus helicity (*M*-**3**) with high certainty by the Bijvoet method based on anomalous dispersion of the oxygen atom with Cu Kα radiation (Figure 1).[9] The second piece was subjected to measure a solid state CD spectrum to show the curve (b) in Figure 4.

In the crystal lattice of *M*-**3**, two hydrogen bondings are formed (Figure 1). One is the N–H•••O=C hydrogen bonding between the N–H of indole ring of **1** and the O=C group of a next molecule **1** 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 lattice leads to the generation of crystal chirality. Another O–H•••N hydrogen bonding between the residual OH group of **1** and the N atom of **2** 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.

Although the flexible propionic acid group can rotate in some extent around the –C–C–C– bonds in solution, the conformation is frozen by the crystallization into the torsional structure with the dihedral angle of 77.1° between the indole ring and the carboxyl group in Figure 1(b). In the helical chain, the dihedral angles between the two indole rings and between the indole ring and the carboxyl group connected with N–H•••O=C hydrogen bonding are 78.3° and 9.9°, respectively. Further, the dihedral angles between the indole ring and the phenanthridine ring and between the carboxyl group and the phenanthridine ring of the hydrogen bonding pair of **1** and **2** are 78.3° and 2.2°, respectively. Thus, the torsional confomation of the propionic acid group of **1** plays a key role in the helical chain formation in the crystal lattice.

The importance of the propionic acid group can be more easily understood in a comparison to an achiral crystal **5** (space group $P\bar{1}$),[10] of which the propionic acid group in **3** is replaced by an acetic acid group (Figure 2). Although

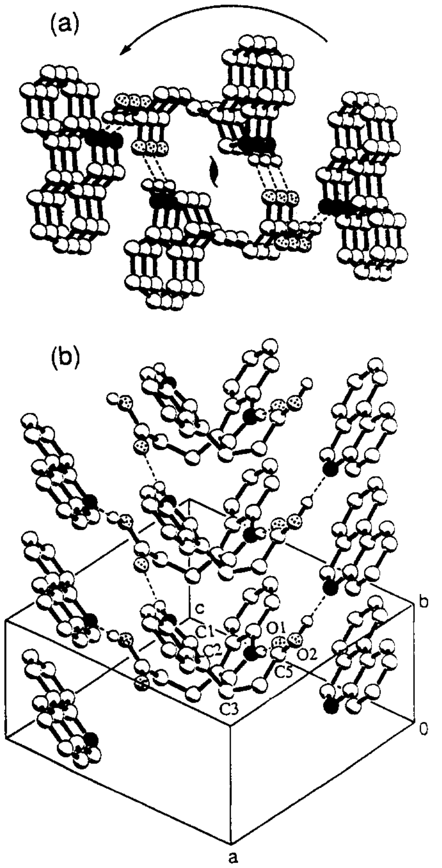

Figure 1. Packing diagrams of *M*-**3** (a) on *ac* face and (b) along *b* axis. Black and dotted atoms present N and O atoms, respectively. H atoms without H-bondings are omitted for clarity. Selected bond angles and torsion angles (°) C2–C3–C4 113.0, C3–C4–C5 114.5, O1–C5–O2 123.1, C1–C2–C3–C4 114.3, C2–C3–C4–C5 60.6, C3–C4–C5–O1 35.7, C3–C4-C5–O2 146.9.

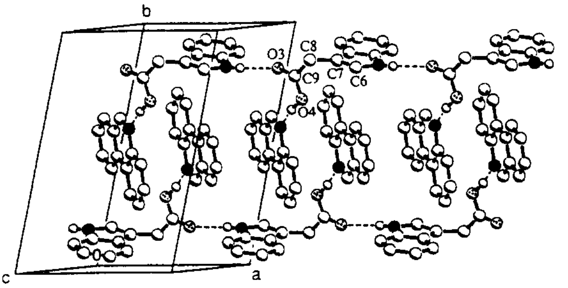

Figure 2. Packing drawing of the achiral crystal **5**. Black and dotted atoms present N and O atoms, respectively. H atoms without H-bondings are omitted for clarity. Selected bond angles and torsion angles (°) C7–C8–C9 113.3, O3–C9–O4 123.0, C6–C7–C8–C9 121.3, C7–C8–C9–O3 124.1, C7–C8–C9–O4 56.3.

similar two hydrogen bondings between 3-indoleacetic acid (4) and 2 are formed in the crystal lattice, the molecular arrangement is quite different. The molecules of 4 are connected through the N–H•••O=C hydrogen bonding with an H•••O distance of 2.09 Å and an N–H•••O angle of 155° to form a linear chain structure. Another O–H•••N hydrogen bonding between 1 and 2 with a distance of 1.57 Å and an O–H•••N angle of 170° forms a pendant-like structure. The molecules of 2 are stacked in head-to-tail and parallel manners with a centrosymmetry in the crystal lattice to lead to the formation of the achiral crystal. The perpendicular conformation of 4 with the dihedral angle of 89.89° between the indole ring and the acetic acid group cannot assemble a helical chain like 3.

Leiserowitz et al. reported that in the case of one-component cystals, achiral acid or amide molecule containing a second hydrogen bonding function such as OH and NH caused intermolecular interaction between the groups to lead more likely to the formation of a helical chain.[11] In fact, we found here that the crystal of 3-indolepropionic acid 1 alone was also chiral.[12] Although the two molecules of 1 form a hydrogen bonded carboxydimer, the dimers form also a helical structure through N–H•••O=C hydrogen bonding to afford a chiral crystal (Figure 3). 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 3 shown in Figure 1. Thus the flexible propionic acid group can change the conformation according to the packing environment in the crystal lattice.

The two enantiomer crystals *P*-3 and *M*-3 could be obtained by spontaneous crystallization from the solution. Solid state CD spectra of the enantiomers were easily measured by using Nujol[13] to give the mirror image spectra (Figure 4), in contrast to the difficulty caused by the opaque nature of KBr pellets. Such CD spectra were not observed in solution state as a matter of course. If a chiral crysal is reactive under certain reaction conditions to give a chiral product, the handedness can be discriminated from the plus or minus optical rotation of the obtained chiral product,[1] but such a method cannot be used for the crystal 3 due to no photoreactivity. Further the solid state CD spectrometry gives a simpler discrimination method whether a given crystal is chiral or not than time-consuming X-ray structure analysis. In future, the determination of absolute configuration of chiral crystal by the CD spectral pattern will become possible by the accumulation of a large number of experimental data and the theoretical considerations.

Finally, we show that this type of chiral bimolecular crystal is applicable for SHG (second-harmonic generation) materials. The effective SHG

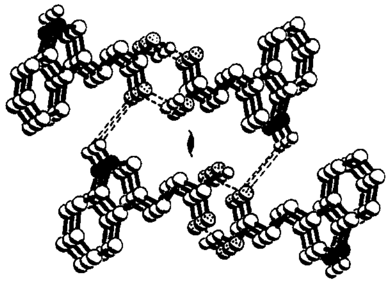

Figure 3. Packing drawing of the chiral crystal 1. Black and dotted atoms present N and O atoms, respectively. H atoms without H-bondings are omitted for clarity.

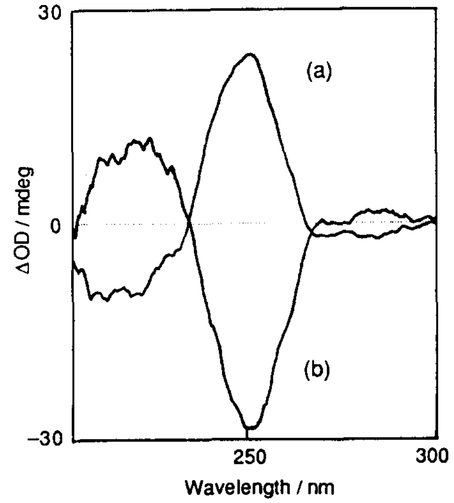

Figure 4. CD spectra of the two enantiomeric crystals (a) *P*-3 and (b) *M*-3 by Nujol mull method. A mixture of 2 mg of the crystal and 10 mg of liquid paraffin was well ground and placed between two NaCl plates into a thin layer. The peak intensities were reasonably reproduced under these conditions.

coefficient (d_{eff}) of the chiral crystal **3** was measured by the SHEW (second-harmonic wave generated with the evanescent wave) technique using the powder crystals[14] to give the d_{eff} of 1.4 pm/V, while the achiral crystal **5** showed no SHG activity. Although this d_{eff} value of **3** is low compared to d_{33} =14.9 pm/V for the maximum d component of *m*-nitroaniline,[15] the design of chiral bimolecular molecular crystals with a larger SHG coefficient would be possible by the combination of stronger π-electron donors and acceptors.

Acknowledgements: This research was partly supported by the Grant-in-Aid for scientific research from the Ministry of Education, Science, Sports and Culture, Japan.

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9. Crystal data for **3**: $C_{24}H_{20}N_2O_2$, M = 368.43, space group $P2_1$, a = 13.251(1), b = 5.327(1), c = 13.6091(9) Å, β = 104.779(7)°, Z = 2, D_c = 1.317 g cm^{-1}, R = 0.032, R_w = 0.052, GOF = 1.67. For the determination of absolute configuration, 25 reflections $\{1.06>|\Delta F_c|/\sigma(F_c)>0.32\}$ of the Bijvoet pairs were selected and the diffraction intensities of the spherical crystal were measured manually in a low speed to give opposite plus and minus signs of all the 25 reflections. Therefore, x, y and z axes were converted; Figure 1 shows correct absolute configuration of *M*-**3**.
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(*Received in Japan* 7 *May* 1997; *revised* 24 *May* 1997; *accepted* 30 *May* 1997)