

Chiral Bimolecular Crystallization of Tryptamine and Achiral Carboxylic Acids

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Received July 30, 1998

Although tryptamine (**1**), 2-thiophenecarboxylic acid (**2**), and 3-indoleacetic acid (**4**) are achiral compounds, chiral crystalline salts **1·2** and **1·4** were prepared by recrystallization from solutions of the two components. The crystal chirality is generated by the formation of a 2-fold helix in only one direction between the two molecules through the salt interaction and hydrogen bonding in the lattice. Two enantiomorphous crystals (*P* and *M*) of **1·2** and **1·4** were obtained by spontaneous crystallization and were easily discriminated by the measurement of solid-state CD spectra. The absolute configuration of *P*-**1·2** was determined with high certainty by the Bijvoet method based on the anomalous dispersion of the sulfur atom during X-ray analysis.

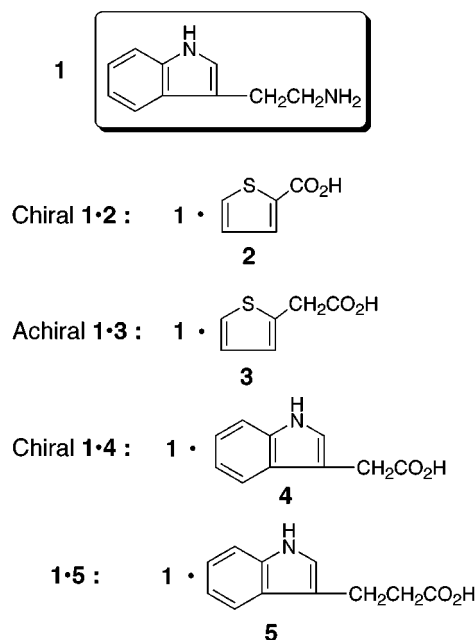
Introduction

Absolute asymmetric synthesis that prepares optically active compounds from achiral reactants in the absence of any external chiral agents is a challenging research subject.^{1–3} Several interesting examples of absolute asymmetric syntheses are known by the solid-state reaction of chiral crystals self-assembled from achiral molecules.^{1,3–6} To design absolute asymmetric syntheses with high reliability, it is necessary to prepare reactant chiral crystals from achiral compounds and predict such chiral crystallization. Since our recent finding of a chiral two-component molecular crystal of diphenylacetic acid and acridine,⁶ we have prepared several new chiral two-component crystals based on the idea of connecting an achiral flexible molecule with a second achiral molecule through hydrogen bonding.^{7–9} These include propeller-type chiral crystals from diphenylacetic acid and aza aromatic compounds such as phenanthridine⁷ and helical-type chiral crystals from 3-indolepropionic acid and phenanthridine,⁸ as well as biphenylcarboxylic acids and tryptamine.⁹ Here we report on the chiral crystals of quaternary ammonium salts of tryptamine and achiral carboxylic acids.

Results and Discussion

The salt crystals incorporate tryptamine (**1**) as a torsional base and four achiral carboxylic acids: 2-thio-

Scheme 1



phenecarboxylic acid (**2**), 2-thiopheneacetic acid (**3**), 3-indoleacetic acid (**4**), and 3-indolepropionic acid (**5**) (Scheme 1). Recrystallization from equimolar solutions of these two components in methanol gave four salt crystals. The high melting points (around 180 °C) and IR spectral patterns found in the Experimental Section show the salt formation in the crystals. Three crystals (**1·2**, **1·3**, and **1·4**) were submitted to X-ray crystallographic analysis to confirm the chiral nature of **1·2** and **1·4**, both of which had the space group *P2*₁. Crystal **1·3** was achiral, and its space group was *P2*₁/*n*. The crystal structure of **1·5** could not be determined due to the difficulty of preparing a high quality sample of the single crystal. Quaternary ammonium salt (NH₃⁺·CO₂⁻) interaction between the aminoethyl group of **1** and the carboxyl group and hydrogen bonding (N–H···O–C) between the indole N–H of **1** and the carboxyl group occurs in **1·2**, **1·3**, and **1·4**. The values of distance and angle estimated from the X-ray crystal data are summarized in Table 1.

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Table 1. Distance and Angle Data of the Crystals

	<i>P</i> -1·2	1·3	1·4
space group	<i>P</i> 2 ₁	<i>P</i> 2 ₁ / <i>n</i>	<i>P</i> 2 ₁
salt distance (Å) NH ₃ ⁺ ⋯CO ₂ ⁻	1.83, 1.87, 1.97	(A) ^a 1.72, 2.19, 2.59 (B) ^a 1.91, 1.97, 2.26	1.80, 2.18, 3.04
H-bonding distance (Å) (indole)NH⋯O-C	2.02	(A) ^a 2.07 (B) ^a 2.16	1.90
torsion angle (deg) tryptamine (indole)C-C-C-N	170.2	(A) ^a 61.6 (B) ^a 62.1	-67.8
carboxylic acid C-C-C-O	178.3	(A) ^a -145.4 (B) ^a -17.0	25.6

^a A and B correspond to the molecular pairs in Figure 2.

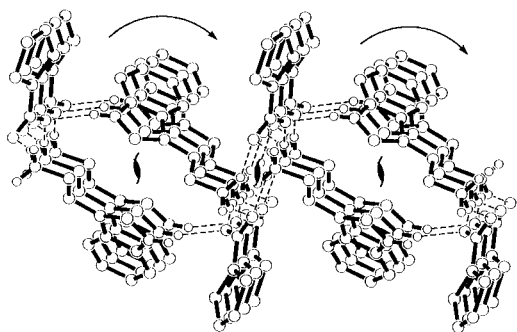
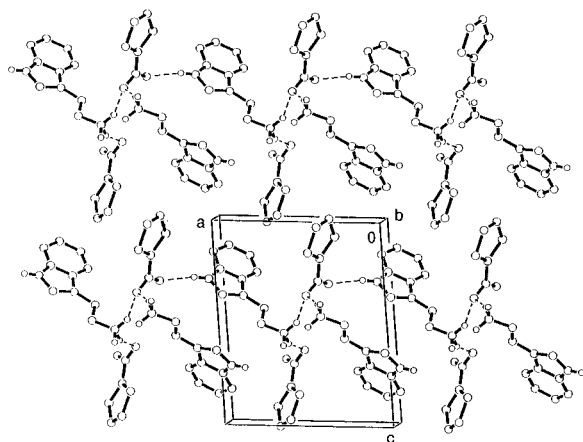


Figure 1. Molecular arrangement of *P*-1·2 viewed along *b* axis. The figure expresses its correct absolute configuration.

The determination of the absolute configuration of this kind of chiral crystal is an important subject. A single crystal **1·2** obtained by spontaneous crystallization was cut into two pieces. One half was submitted to measure the solid-state CD spectra (curve b in Figure 4). The second half was subjected to X-ray structure analysis followed by absolute configuration determination which was confirmed as *P*-1·2 with a high degree of certainty by using the Bijvoet method based on the X-ray anomalous dispersion of the sulfur atom.

Figure 1 shows the molecular arrangement of *P*-1·2 whose absolute configuration is correct. A two-fold helix along the *b* axis in a clockwise direction and, further, a hydrogen bond chain along the *c* axis are formed between the molecules of **1** and **2**. It is understandable that the crystal chirality is defined by the helical arrangement of

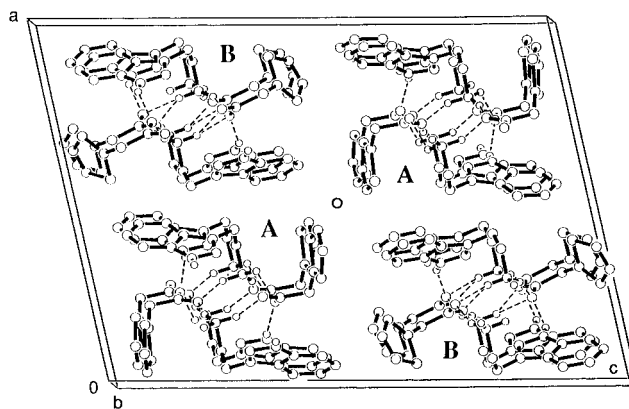


Figure 2. Molecular arrangement of achiral **1·3** viewed along *b* axis.

molecules in the lattice. We previously reported that similar helices were formed in the chiral salt crystals of **1** with 3- and 4-biphenylcarboxylic acid.⁹

Achiral crystal **1·3** has a molecular arrangement different from that of chiral **1·2** (Figure 2). Two kinds of molecular pairs (A and B) of **1** and **3** are packed centrosymmetrically in a unit cell (*Z* = 8), not inducing crystal chirality. The molecular conformations of **1** in A and B are similar; the (indole)C-C-C-N torsion angles of 61.6° and 62.1°, respectively (Table 1). But the molecular conformations of **3** in A and B are very different, the (thiophene)C-C-C-O torsion angles being -145.4 and -17.0°, respectively. The A and B pairs each form 2-fold helices along the *b* axis in alternate clockwise and anticlockwise directions. Whether such helices are frozen into centrosymmetry or noncentrosymmetry in the crystallization depends on the small molecular structure difference that only one -CH₂- unit is between the carboxyl group of **2** in chiral **1·2** and the acetic acid group of **3** in achiral **1·3**. We already found a similar example: the crystal from 3-indolepropionic acid **5** and phenanthridine was chiral (*P*2₁), but the crystal from 3-indoleacetic acid **4** and phenanthridine was achiral (*P*1̄).⁸

Chiral crystal **1·4** also forms a 2-fold helix of a single absolute configuration along the *b* axis, inducing the chirality (Figure 3). The indole N-H of **1** is connected with **4** by the hydrogen bonding (N-H⋯O-C), while the indole N-H of **4** is free. The IR absorption band at 3415 cm⁻¹ was assigned to be the free indole N-H because of the similarity to the N-H band (3388 cm⁻¹) of the crystal of **4** alone. Other IR bands at 3259 and 3055-2642 (broad) cm⁻¹ are attributed to the quaternary ammonium

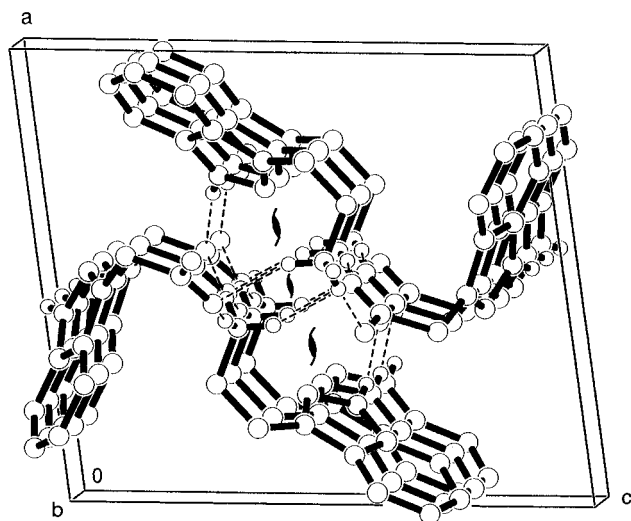


Figure 3. Molecular arrangement of chiral **1·4** viewed along *b* axis. The figure does not express its absolute configuration.

salt and the hydrogen bonding, respectively. In the case of **1·5**, a similar IR spectral pattern was observed at 3421, 3288, and 3089–2519 (broad) cm^{-1} .

The reason such a helical structure is easily formed may be explained as follows. Leiserowitz et al. have reported that if an acid molecule in a one-component crystal contains two groups such as NH, CONH, OH, etc., 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.¹⁰ A similar explanation may be applicable for **1·2**, **1·3**, and **1·4** because of the coexistence of NH_2 and NH of **1** and the CO_2H groups. In addition, the torsional conformations of $-\text{CH}_2-\text{CH}_2-\text{NH}_2$ of **1** in Figures 1–3, for which the (indole)C–C–C–N torsion angles are shown in Table 1, suggest that the flexible group may help to arrange the molecule into a helical structure.

The two enantiomorphous crystals (*P* and *M*) of **1·2** and **1·4** were obtained by spontaneous crystallization from the methanol solutions. This kind of chiral crystal should have optical activity as a crystal, similar to that of a chiral molecule. The solid-state CD spectra were easily measured by using a Nujol mull of powder samples.¹¹ The two curves of enantiomorphous crystals are in a good mirror image relationship to give a simple discrimination of two enantiomorphous modifications (Figure 4). Although the crystal structure of **1·5** is not known, it is suggested that the crystal is likely achiral due to no CD curve.

Experimental Section

Preparation of Salt Crystals. Salt crystals **1·2**–**1·5** were prepared by recrystallization from equimolar solutions of **1** and **2**–**5** in methanol. The crystals were characterized by DSC and IR. Solid-state CD spectra using Nujol are shown in Figure 4.

1·2: colorless plate crystals; mp 182.0–183.0 °C; IR (KBr) 3292, 3005–2532 cm^{-1} .

1·3: colorless plate crystals; mp 188.0–189.0 °C; IR (KBr) 3250, 3226, 3049–2667 cm^{-1} .

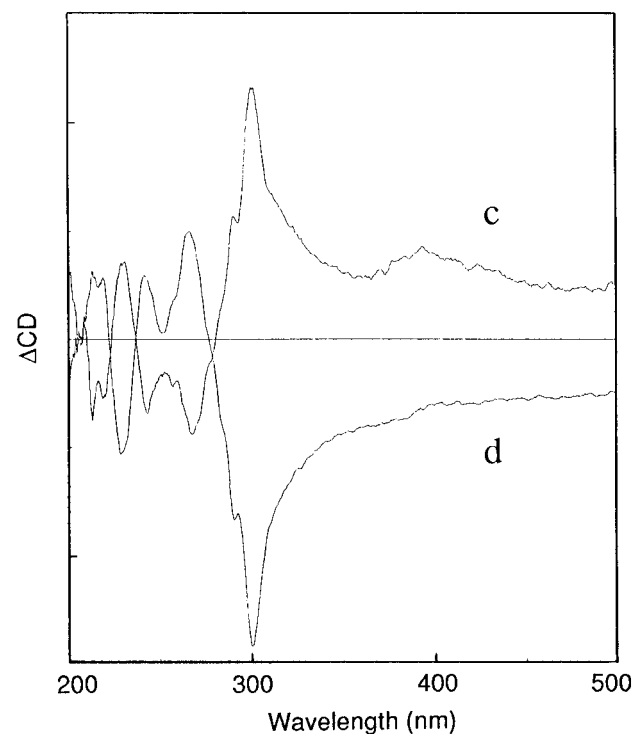
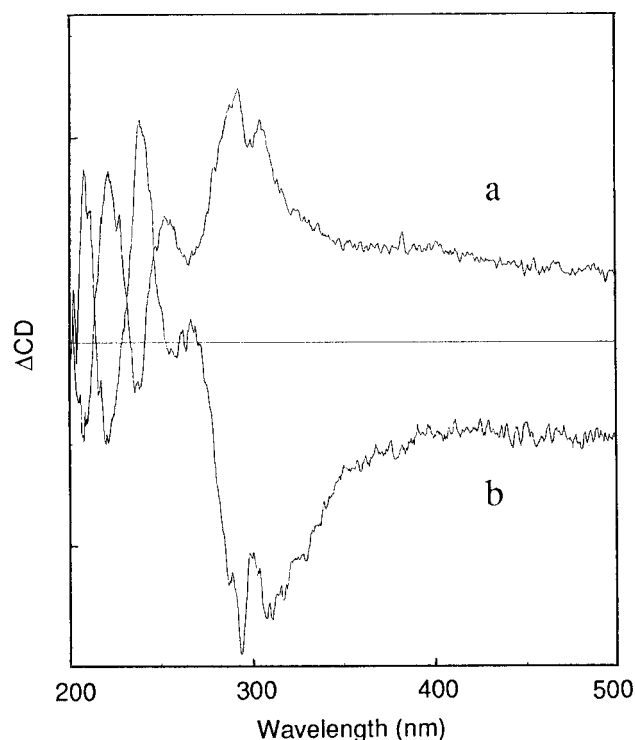


Figure 4. Solid-state CD spectra of the enantiomorphous crystals of (a) *M*-**1·2**, (b) *P*-**1·2**, (c) and (d) **1·4**. The curves c and d do not express their absolute configurations.

1·4: colorless plate crystals; mp 188.0–189.0 °C; IR (KBr) 3415, 3259, 3055–2642 cm^{-1} .

1·5: colorless plate crystals; mp 174.5–176.0 °C; IR (KBr) 3421, 3288, 3080–2519 cm^{-1} .

X-ray Crystallographic Analysis of the Salt Crystals. Data collections were performed on a Rigaku AFC7R automatic 4-circle X-ray diffractometer with graphite monochromated $\text{Cu K}\alpha$ ($\lambda = 1.54178 \text{ \AA}$) radiation. Absorption correction was applied. The lack of degradation of the crystal by X-rays was ascertained in all cases by repeated monitoring of the 3

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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 Corp.

1·1·2: C₁₃H₁₆N₂O₂S; monoclinic; *P*2₁; *a* = 9.897(2) Å, *b* = 6.164(3) Å, *c* = 12.086(2) Å, β = 94.73(1)°; *V* = 734.7(3) Å³; *Z* = 2, *D*_{calc} = 1.303 g cm⁻³. The structure was solved by a direct method (SIR92) and refined by the full-matrix least-squares procedure to *R* = 0.065 and *R*_w = 0.092 for 1212 independent observed reflections [*I* > 3.00σ(*I*)] of the total 2099 reflections (Bijvoet method) with 2θ ≤ 120.1°.

The absolute configuration of **1·1·2** was determined very carefully, using half of a single crystal, by the Bijvoet method based on anomalous dispersion of the sulfur atom with Cu Kα radiation during X-ray crystallographic analysis. All of the 19 Bijvoet pairs of |Δ*F*_{*i*}|/σ(*F*₀) < 4 and 98 of the 100 pairs of 2.0 < |Δ*F*_{*i*}|/σ(*F*₀) ≤ 4.0 follow an incorrect trend. Therefore, *x*, *y*, and *z* axes were converted; the packing diagram in Figure 1 shows the correct absolute configuration of **1·1·2**. The second half was submitted to measurement of the CD spectrum (curve b in Figure 4).

1·3: C₁₈H₁₉N₂O₂S; monoclinic; *P*2₁/*m*; *a* = 18.527(4) Å, *b* = 6.772(5) Å, *c* = 25.668(4) Å, β = 102.68(1)°; *V* = 3141(2) Å³; *Z* = 8, *D*_{calc} = 1.283 g cm⁻³. The structure was solved by a direct method (SIR92) and refined by the full-matrix least-squares

procedure to *R* = 0.091 and *R*_w = 0.131 for 5135 independent observed reflections [*I* > 3.00σ(*I*)] of the total 2600 reflections with 2θ ≤ 120.0°.

1·4: C₂₀H₂₁N₃O₂; monoclinic; *P*2₁; *a* = 11.000(2) Å, *b* = 6.335(2) Å, *c* = 12.612(1) Å, β = 98.22(1)°; *V* = 869.8(2) Å³; *Z* = 2, *D*_{calc} = 1.281 g cm⁻³. The structure was solved by a direct method (SHELX86) and refined by the full-matrix least-squares procedure to *R* = 0.041 and *R*_w = 0.065 for 1436 independent observed reflections [*I* > 3.00σ(*I*)] of the total 1383 reflections with 2θ ≤ 120.0°.

Acknowledgment. We would like to thank Prof. F. Toda for kindly allowing us to use the CD spectrophotometer. This work was supported by the Hayashi Memorial Foundation for Female Natural Scientists in Japan.

Supporting Information Available: Tables giving full data-collection parameters and further details of refinement, atomic coordinates, anisotropic displacement parameters, bond lengths, and bond angles of **1·2**, **1·3**, and **1·4** (40 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO9815195