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Molecular Recognition in the Formation of Conglomerate Crystal. The Role of Cinnamic Acid in the Conglomerate Crystals of 1-Phenylethylamine and 1-(4-Isopropylphenyl)ethylamine Salts

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The Crystal structures of (+)-1-phenylethylamine·cinnamic acid salt and (+)-1-(4-isopropylphenyl)-ethylamine·cinnamic acid salt were determined by X-ray analysis. The crystal structures of these two salts provided for the first time some insights into the mechanism of the formation of a conglomerate crystal. In each crytal, two amine components and two acid components form a helical column by hydrogen bonds. On the basis of this similarity in the molecular arrangements, the role of cinnamic acid, an achiral acid, is discussed, and the criteria for the choice of an achiral acid in the transformation of the racemic modification of an amine into a conglomerate crystal is proposed.

The optical resolution of the racemic modification of an amine or a carboxylic acid is usually carried out by the diastereomeric salt method.[1)] But, in this resolution, a stoichiometric amount of an optically pure enantiomer is required as a resolving agent, and it is difficult to get both enantiomers of the racemic modification by a simple operation. This difficulty can be solved by the preferential crystallization method. Despite the practical importance, the technique is known to be applicable for the optical resolution of only about 300 racemic modifications, since only conglomerates can be resolved by the method.[1)] Moreover, rational explanation has not been proposed for the experimental results. Then, the successful resolution by the preferential crystallization method can only be achieved by a time-consuming trial-and-error procedure.

In the previous papers, we reported that the cinnamic acid salts of α-substituted benzylamine derivatives such as 1-phenylethylamine,[2)] 1-phenyl-2-(*p*-tolyl)ethylamine,[2)] *erythro*-2-amino-1,2-diphenylethanol,[3)] and 1-(4-isopropylphenyl)ethylamine[4)] are conglomerates and that these salts can be resolved into pairs of enantiomers by the preferential crystallization. These results seem to suggest the presence of some structural relationship between the chiral amines and the achiral acid. We report here the crystal structures of two conglomerates, 1-phenylethylamine·cinnamic acid salt and 1-(4-isopropylphenyl)ethylamine·cinnamic acid salt that provide considerable insight into the mechanism of the formation of a conglomerate.

Table 1. Crystal Data and Details of Refinement

	1	**2**
Formula	$C_8H_{11}N\cdot C_9H_8O_2$	$C_{11}H_{17}N\cdot C_9H_8O_2$
M	269.35	311.43
Crystal system	orthorhombic	orthorhombic
Space group	$P2_12_12_1$	$P2_12_12_1$
a/Å	9.368 (1)	13.868 (1)
b/Å	26.703 (2)	20.457 (1)
c/Å	6.043 (1)	6.471 (1)
V/Å^3	1511.8 (5)	1835.7 (6)
Z	4	4
D_c/g cm^{-3}	1.183	1.127
μ(Cu $K\alpha$)/cm^{-1}	5.808	5.158
Crystal size/mm^3	0.45×0.40×0.30	0.30×0.30×0.40
Number of unique reflections	1701	2015
Number of observed reflections	1433	1565
Number of parameters	258	309
$\Delta\rho_{max}$/e Å^{-3}	+0.14	+0.18
$\Delta\rho_{min}$/e Å^{-3}	−0.15	−0.13
$(\Delta/\rho)_{max}$	0.29	0.24
R_w	0.049	0.059
R	0.036	0.042

Experimental

Materials. (+)-1-Phenylethylamine[3)] and (+)-1-(4-isopropyl)ethylamine[4)] were obtained by the optical resolution of the corresponding racemic modifications according to the

Table 2. Fractional Atomic Coordinates and Equivalent Isotropic Thermal Parameters for **1**

Atom	x	y	z	B_{eq}[6)]/Å^2
O(1)	0.5697(2)	0.42478(6)	0.4982(3)	6.77(4)
O(2)	0.6843(2)	0.44281(5)	0.8082(3)	4.58(3)
N(1)	0.9024(2)	0.50408(5)	0.6814(3)	3.68(3)
C(1)	0.6018(2)	0.41643(6)	0.6939(4)	3.86(3)
C(2)	0.5356(2)	0.37105(7)	0.7927(4)	4.18(4)
C(3)	0.5608(2)	0.35539(7)	0.9950(4)	4.06(4)
C(4)	0.5050(2)	0.30988(6)	1.1025(3)	4.08(4)
C(5)	0.5639(3)	0.29638(8)	1.3022(4)	5.29(5)
C(6)	0.5207(3)	0.25344(9)	1.4126(4)	6.23(6)
C(7)	0.4170(3)	0.22367(8)	1.3212(5)	6.53(6)
C(8)	0.3567(3)	0.23651(9)	1.1243(5)	6.31(6)
C(9)	0.3993(2)	0.27997(8)	1.0130(4)	5.14(5)
C(10)	1.0466(2)	0.48095(7)	0.6639(3)	3.61(3)
C(11)	1.1530(2)	0.52163(7)	0.6005(4)	4.55(4)
C(12)	1.0496(2)	0.43768(6)	0.5022(3)	3.59(3)
C(13)	0.9633(2)	0.43453(7)	0.3193(4)	4.56(4)
C(14)	0.9771(3)	0.39551(8)	0.1686(4)	5.34(5)
C(15)	1.0807(3)	0.35967(7)	0.1984(4)	5.36(5)
C(16)	1.1688(3)	0.36256(8)	0.3802(5)	5.69(5)
C(17)	1.1526(2)	0.40086(8)	0.5330(4)	4.76(4)

methods in the literatures.

Crystal Structure Determination. Colorless crystals **1** and **2** were grown from a saturated solution of an equimolar mixture of the amine and cinnamic acid in methanol, respectively. The specimen used was a fragment of a plate. Data were collected up to $2\theta=140°$ on an Enraf-Nonius CAD-4 diffractometer using graphite-monochromated Cu $K\alpha$ (1.5418 Å) radiation by ω—2θ scan. Standard reflections showed no

Table 3. Fractional Atomic Coordinates and Equivalent Isotropic Thermal Parameters for **2**

Atom	x	y	z	B_{eq}[6)]/Å^2
O(1)	0.1563(2)	0.3929(1)	0.1739(3)	5.96(5)
O(2)	0.1974(1)	0.4288(1)	0.4829(3)	5.26(4)
N(1)	0.3393(1)	0.5147(1)	0.3670(3)	3.96(4)
C(1)	0.1507(2)	0.3916(1)	0.3665(4)	3.98(5)
C(2)	0.0843(2)	0.3424(2)	0.4530(5)	5.16(6)
C(3)	0.0883(2)	0.3184(1)	0.6391(5)	4.91(6)
C(4)	0.0203(2)	0.2704(1)	0.7306(5)	4.75(6)
C(5)	0.0337(3)	0.2519(2)	0.9316(6)	5.96(7)
C(6)	−0.0295(3)	0.2108(2)	1.0291(6)	7.21(9)
C(7)	−0.1097(3)	0.1875(2)	0.9314(7)	6.97(9)
C(8)	−0.1244(3)	0.2047(2)	0.7290(7)	6.67(9)
C(9)	−0.0598(2)	0.2456(2)	0.6311(6)	5.87(7)
C(10)	0.4261(2)	0.4720(1)	0.3692(5)	4.40(5)
C(11)	0.4405(2)	0.4462(2)	0.5870(6)	6.40(7)
C(12)	0.5135(2)	0.5070(1)	0.2826(4)	3.94(5)
C(13)	0.5500(2)	0.5638(1)	0.3730(5)	4.33(5)
C(14)	0.6303(2)	0.5943(1)	0.2901(5)	4.34(5)
C(15)	0.6769(2)	0.5692(1)	0.1179(5)	4.51(6)
C(16)	0.6408(2)	0.5129(2)	0.0307(5)	5.93(7)
C(17)	0.5603(2)	0.4823(2)	0.1111(5)	5.34(6)
C(18)	0.7651(2)	0.6018(2)	0.0205(5)	5.82(7)
C(19)	0.8151(2)	0.6501(2)	0.1580(7)	6.90(9)
C(20)	0.7381(3)	0.6332(2)	−0.1884(6)	8.5 (1)

Table 4. Bond Distances (l/Å)

	1	**2**
O(1)-C(1)	1.241(2)	1.249(3)
O(2)-C(1)	1.253(2)	1.251(2)
N(1)-C(10)	1.489(2)	1.488(3)
C(1)-C(2)	1.486(2)	1.475(3)
C(2)-C(3)	1.314(3)	1.302(4)
C(3)-C(4)	1.473(2)	1.485(3)
C(4)-C(5)	1.375(3)	1.367(4)
C(4)-C(9)	1.383(3)	1.381(4)
C(5)-C(6)	1.387(3)	1.367(5)
C(6)-C(7)	1.372(4)	1.366(5)
C(7)-C(8)	1.361(4)	1.371(5)
C(8)-C(9)	1.399(3)	1.379(4)
C(10)-C(11)	1.523(2)	1.519(4)
C(10)-C(12)	1.514(2)	1.514(3)
C(12)-C(13)	1.372(2)	1.395(3)
C(12)-C(17)	1.390(2)	1.381(3)
C(13)-C(14)	1.390(3)	1.386(3)
C(14)-C(15)	1.375(3)	1.386(3)
C(15)-C(16)	1.376(3)	1.377(3)
C(16)-C(17)	1.386(3)	1.382(3)
C(15)-C(18)		1.529(3)
C(18)-C(19)		1.500(5)
C(18)-C(20)		1.543(5)

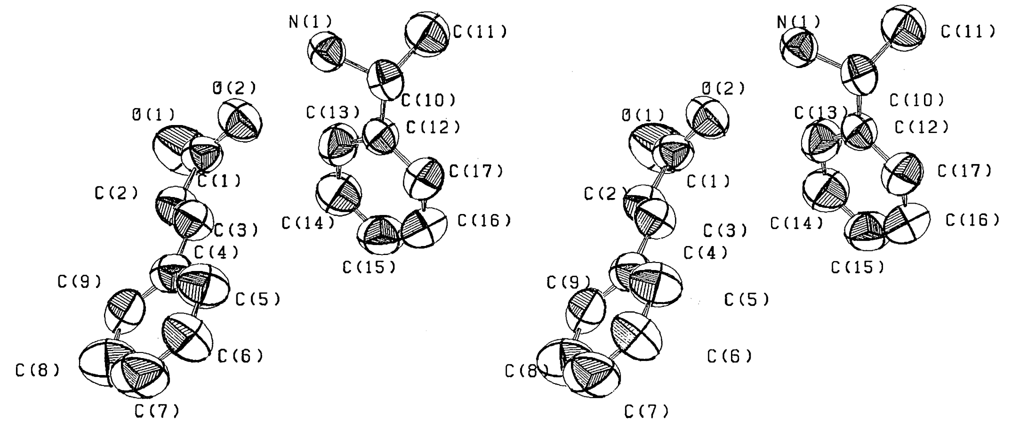


Fig. 1. Labeled Stereoscopic Drawing of **1**.

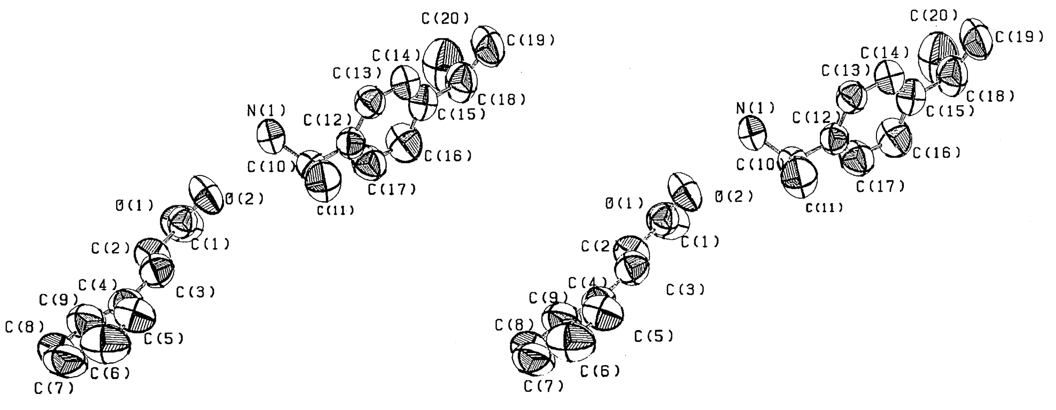


Fig. 2. Labeled Stereoscopic Drawing of **2**.

significant intensity change. Of unique reflections measured, those as observed with $I > 3\sigma(I)$ were used. The intensities were corrected for Lorentz, polarization, and extinction but not for absorption. The structure was solved by the direct method (MULTAN 11/82) and was refined by the full-matrix least-squares. Scattering factors were taken from "International Tables for X-Ray Crystallography (1974)." Computations were performed by using Enraf-Nonius SDP v3.0. Crystal data and details of refinement are summarized in Table 1.

Results and Discussion

Fractional coordinates for the crystals of (+)-1-phenylethylamine·cinnamic acid salt (**1**) and (+)-1-(4-isopropylphenyl)ethylamine·cinnamic acid salt (**2**) are given in Tables 2 and 3, respectively.[5] Labeled stereoscopic drawings of cinnamic acid and (+)-1-phenylethylamine in the crystal of **1** and those of cinnamic acid and (+)-1-(4-isopropylphenyl)ethylamine in the crystal of **2** are given in Figs. 1 and 2, respectively. Bond distances of **1** and **2** are given in Table 4.

In the crystal of **1**, two amine components and two acid components form a helical column by hydrogen bonds along the *c* axis (Fig. 3). The lengths of the hydrogen bonds are 2.727(2) Å for $O(2)^{i} \cdots N(1)^{i}$, 2.709(2) Å for $N(1)^{i} \cdots O(1)^{ii}$, and 2.785(2) Å for $O(2)^{i} \cdots N(1)^{ii}$. But, no hydrogen bond exists between the columns. Excluding the hydrogen bonds, the shortest intermolecular distance is 3.618(1) Å which is a little larger than the sum of ordinary van der Waals radii.

In the crystal of **2**, two amine components and two acid components are also arranged to form a helical column by hydrogen bonds along the *c* axis (Fig. 4). The lengths of the hydrogen bonds are 2.743(2) Å for $O(2)^{i} \cdots N(1)^{i}$, 2.741(3) Å for $N(1)^{i} \cdots O(1)^{ii}$, and 2.787(3) Å for $O(2)^{i} \cdots N(1)^{ii}$. There is no hydrogen bond between the columns. Other than the hydrogen bonds,

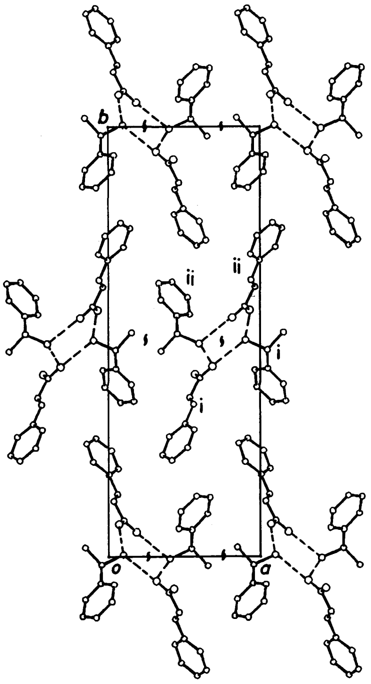


Fig. 3. The Crystal Structure of **1** viewed along the *c* axis. Hydrogen bonds are shown by dashed lines. The numbers i, ii denote the operations, i: *x*, *y*, *z*; ii: 3/2−*x*, 1−*y*, 1/2+*z*.

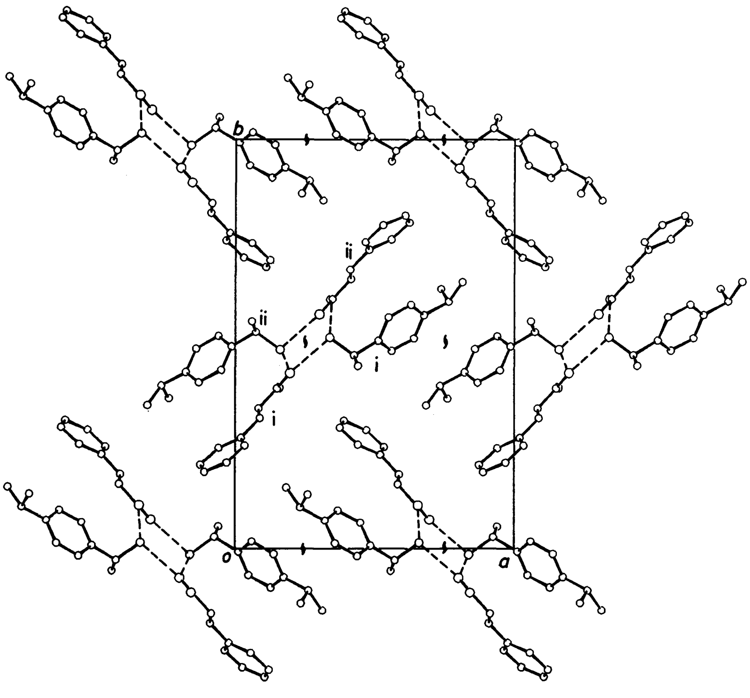
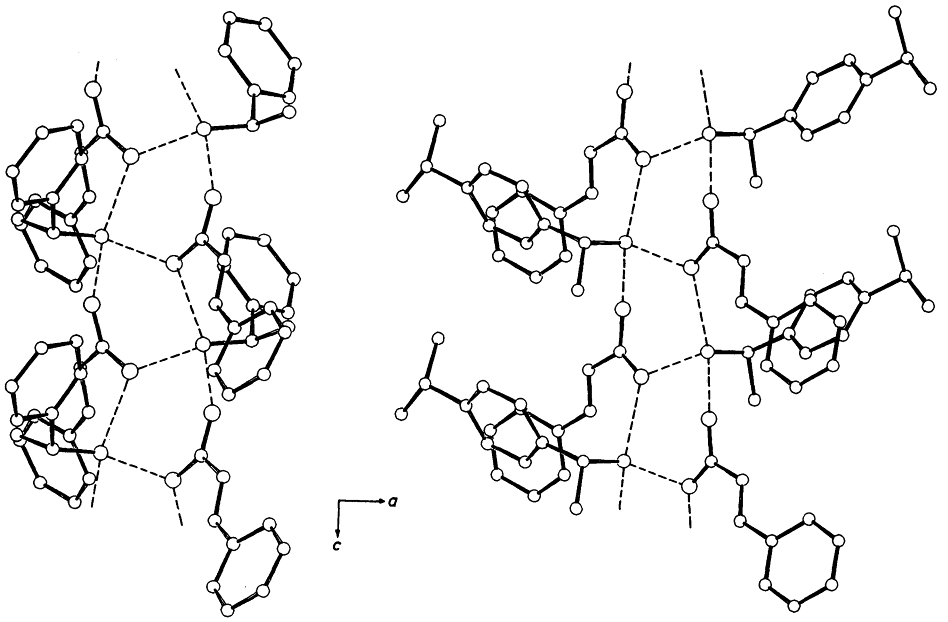


Fig. 4. The Crystal Structure of **2** viewed along the *c* axis. Hydrogen bonds are shown by dashed lines. The numbers i, ii denote the operations, i: *x*, *y*, *z*; ii: 1/2−*x*, 1−*y*, 1/2+*z*.



1 **2**

Fig. 5. The Crystal Structures of **i** and **2** viewed along the *b* axis. Hydrogen bonds are shown by dashed lines.

the short intermolecular distances are 3.432(1) Å for C(3)^{i}-C(13)^{ii} and 3.489(0) Å for C(4)^{i}-C(14)^{ii}, which are nearly equal to the sum of van der Waals radii.

As mentioned above, the crystal structures of **1** and **2** are very close. Namely, the crystals of **1** and **2** are built up by the hydrogen bonds between two amine components and two acid components to form columns along the *c* axis. Figure 5 shows the hydrogen bond columns in **1** and **2**. The arrangements of the acid components are very similar to each other in the two columns, whereas those of the amine components are differed from one another. In the structure of **1**, the phenyl group of (+)-1-phenylethylamine is parallel to the axis of the column, whereas in the structure of **2** the isopropylphenyl group of (+)-1-(4-isopropylphenyl)ethylamine is nearly perpendicular to the column axis. Such different arrangements may be interpreted by steric requirement. The parallel arrangement of isopropylphenyl group would be unfavorable for the formation of the hydrogen bonds. In other words, unusually short contacts less than 2 Å appear between the isopropyl group and the methyl group of the neighboring amine in the hydrogen bond columns, if the phenyl group is replaced by the isopropylphenyl one. The formation of these rigid hydrogen bonds would result in the high selectivity for only one enantiomer of the chiral amine in the course of crystallization. On the other hand, the phenyl group and double bond of cinnamic acid play a significant role for crystal packing to offer suitable space for the amine molecules and to fix it well. In addition, a similar size between the molecules of the amine and cinnamic acid seems to be very important in order to form the column by the hydrogen bonds and to make it rigid.

On the basis of structural similarity of the two conglomerates it is suggested that an achiral acid satisfying the following structural requirement is favorable for the transformation of a racemic modification of an amine into a conglomerate crystal: (a) The achiral acid can form a helical column by hydrogen bonds with the amine; (b) the acid should be rigid and flat to limit the orientation of the amine; (c) the sizes of the amine and the acid are similar to each other.

These working hypotheses are the first insights for the structure of a conglomerate crystal, and they are regarded at the first step for the prediction of the transformation from a racemic modification into a conglomerate crystal.

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5) F_o—F_c Tables, anisotropic thermal temperature factors, fractional atomic coordinates of hydrogen atoms, and bond angles are deposited as Document No. 8757 at the Office of the Editor of Bull. Chem. Soc. Jpn.

6) The equivalent isotropic temperature factors were computed using the following expression; $B_{eq}=4/3(B_{11}a^2+B_{22}b^2+B_{33}c^2)$.