Crystal Structures of the Salts of Chiral Primary Amines with Achiral Carboxylic Acids: Recognition of the Commonly-Occurring Supramolecular Assemblies of Hydrogen-Bond Networks and Their Role in the Formation of Conglomerates

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Abstract: X-ray crystallographic studies were carried out for seven conglomerates, seventeen racemic compounds, and four enantiomerically pure salts of chiral primary amines with achiral monocarboxylic acids. The crystal structures of the conglomerate salts revealed that these crystals can be regarded as being an assembly of a characteristic columnar hydrogen-bond network in which the ammonium cations and the carboxylate anions are aligned around a 2-fold screw axis (2_1-column). On the other hand, the crystal structures of the racemic-compound salts could be broadly classified into two types. One type is a crystal consisting of 2_1-columns; the other type is a crystal consisting of a different type of columnar hydrogen-bond network in which the ammonium cations and the carboxylate anions are related by inversion centers (*i*-column). Our results suggest that both the formation and the assembly of 2_1-columns are essential in the formation of conglomerates from these salts, and that the difference in the packing of 2_1-columns between conglomerate salts and racemic-compound salts is governed by van der Waals interaction between the 2_1-columns.

Introduction

Crystalline racemates can be classified into three categories:[1] (a) *racemic compounds*, in which both enantiomers are present in equal quantities in a well-defined arrangement within the crystal lattice, (b) *conglomerates*, mechanical mixtures of crystals of both pure enantiomers, and (c) *pseudoracemates*, in which the two enantiomers coexist in a disordered manner in the crystal lattice in any portion, or in a specified concentration range. Conglomerates and pseudoracemates are rarely found among racemates, which most frequently crystallize as racemic compounds. The first example of a conglomerate was reported by Pasteur in 1848 for sodium ammonium tartrate.[2] Subsequently, Gernez demonstrated that conglomerates could be used in an effective optical resolution; one of the enantiomers of a racemate could be preferentially crystallized upon seeding a supersaturated solution of the racemate with a small amount of that enantiomer when the racemate is a conglomerate.[3] This method is called preferential crystallization.

Preferential crystallization has been drawing much attention as a promising method for obtaining enantiomerically pure compounds.[4] However, its most serious limitation arises from the facts that it can be applied only to a conglomerate and that rather few racemates are known to exist as such. Although the frequency of occurrence of conglomerates has been estimated to be in the range of 5−10% of all racemates,[4] actually, most conglomerates have been adventitiously discovered; their actual frequency is rather less than this estimated value. Hence, the prediction and/or design of derivatizing reagents for conglomerate formation is a matter of importance. However, even now, the mechanism of conglomerate formation is insufficiently understood. In particular, hardly any studies on the characteristics of the crystal structure of conglomerates have been carried out, except for those dealing with limited types of compounds.[5]

During the course of our study of organic solid-state chemistry, we recently found that a characteristic, columnar hydrogen-bond network was formed in the salt crystals of primary amines with carboxylic acids.[6] Moreover, our previous study also showed that a similar characteristic columnar hydrogen-bond network was formed in the salt crystals of both 1-phenylethylamine and 1-(4-isopropylphenyl)ethylamine with cinnamic acid, which precipitate as conglomerates upon crystallization.[5a] These results strongly suggest that the pattern of hydrogen bonds plays a significant role in the formation of conglomerates.

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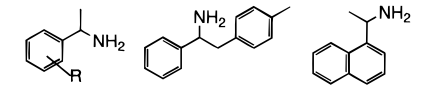
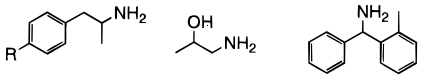
Chart 1

Chiral Amines



1a: R = H
1b: R = 2-Me
1c: R = 4-Me
1d: R = 4-OMe
1e: R = 4-Pr^i

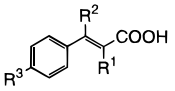
2 **3**



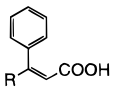
4a: R = H
4b: R = CF_3

5 **6**

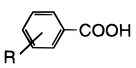
Achiral Acids



7a: $R^1 = R^2 = R^3 = H$
7b: R^1 = Me, $R^2 = R^3 = H$
7c: $R^1 = R^2 = H$, R^3 = Cl
7d: $R^1 = R^3 = H$, $R^2 = Pr^i$
7e: $R^1 = R^3 = H$, R^2 = cyclohexyl
7f: $R^1 = H$, R^2 =Et, $R^3 = H$
7g: $R^1 = H$, R^2 =Et, R^3 = Me
7h: $R^1 = H$, R^2 =Et, R^3 = Cl
7i: $R^1 = H$, R^2 =Et, $R^3 = Bu^t$



8a: R = Et
8b: R = Pr^i



9a: R = H
9b: R = 2-Cl
9c: R = 3-NO_2
9d: R = 4-Bu^t
9e: R = 4-OH
9f: R = 3-Cl
9g: R = 4-Cl
9h: R = 3,4-Me_2

10a: $R^1 = R^2 = H$
10b: $R^1 = H$, R^2 = Ph
10c: $R^1 = H$, $R^2 = PhCH_2$
10d: $R^1 = R^2$ = Cl
10e: $R^1 = R^2$ = Ph

Since the conglomerate salts of amines with carboxylic acids have been applied to the resolution of a wide variety of racemic amines and acids,[7] it is quite important to extract and understand the common features of conglomerate salts at the crystallographic level. To achieve this, we have studied a number of crystal structures (28) of salts of chiral primary monoamines with achiral monocarboxylic acids, in the expectation that the results would afford some statistical information about the characteristics of the crystal structure of conglomerate salts.

Herein, we report on the crystal structures of various salts of chiral primary monoamines with achiral monocarboxylic acids, including both conglomerates and racemic compounds, and describe statistical results on the basis of the supramolecular structures found in these salt crystals.

Results

Crystal Structures of Conglomerate Salts of Chiral Primary Monoamines with Achiral Monocarboxylic Acids.

Table 1. Summary of Conglomerate Salts of Chiral Primary Monoamines with Achiral Monocarboxylic Acids

amine	acid	crystal structure	ref no.
1a	**7a**	known[a]	5a
	7b	this study	
	9b	unknown	8
	9c	unknown	8
	9d	this study	9
1b	**7a**	this study	
1c	**9e**	unknown	10
1d	**10a**	unknown	11
1e	**7a**	known[b]	5a
2	**7a**	unknown	12
3	**10b**	this study	7
4a	**10b**	unknown	7
4b	**10c**	unknown[c]	13
	10b	known[d]	14
5	**9c**	unknown	15

[a] CSD REFCODE: FUSJAE. [b] CSD REFCODE: FUSJEI. [c] Only cell parameters were reported. [d] CSD REFCODE: GEYLIF.

Table 2. Cell Dimensions of Conglomerate Salts of Chiral Primary Monoamines with Achiral Monocarboxylic Acids

salt	space group	*a*/Å	*b*/Å[a]	*c*/Å[a]	*β*/deg	*V*/Å^3	*Z*
1a·7a[5a]	$P2_12_12_1$	9.368(1)	26.703(2)	*6.043(1)*		1511.8(5)	4
1a·7b	$P2_12_12_1$	7.572(1)	34.424(6)	*6.321(1)*		1647.7(5)	4
1a·9d	$P2_1$	19.839(6)	*6.356(2)*	7.032(2)	90.13(2)	886.8(4)	2
1b·7a	$P2_12_12_1$	14.901(2)	18.377(2)	*5.970(1)*		1634.7(4)	4
1e·7a[5a]	$P2_12_12_1$	13.868(1)	20.457(1)	*6.471(1)*		1835.7(6)	4
3·10b[b]	$P2_12_12_1$	13.659(2)	20.024(3)	*6.357(1)*		1738.6(5)	4
4b·10d[14]	$P2_1$	13.359	*6.810*	8.447	107.55	732.7	2

[a] Italic cell axes are parallel to 2_1-columns. [b] A single crystal was prepared from (*R*)-**3·10b**.

To date, a number of chiral amines and chiral acids have been converted into conglomerates via salt formation with suitable achiral derivatizing agents. In the first stage of a study aimed at discerning common characteristics in the crystal structures of conglomerate salts, we initially restricted to looking at the conglomerate salts of chiral primary monoamines with achiral monocarboxylic acids. The chiral amines and achiral carboxylic acids considered in the present study are summarized in Chart 1.

A *Chemical Abstract* search showed that, up to the present, 13 salts of chiral primary monoamines with achiral monocarboxylic acids have been reported to be conglomerates. Table 1 shows these conglomerate salts (including **1a·7b** and **1b·7a** which were additionally found by us to be conglomerates during the current study). Among these, we addressed our attention to the crystal structures of those conglomerates having no hydrogen-donating nor -accepting group other than an ammonium group and a carboxylate group. The cell parameters of the conglomerates for which the crystal structures were determined are summarized in Table 2.

Perusal of the crystal structures of the conglomerates given in Table 2 revealed that a rather characteristic hydrogen-bond network was present, common to all of these salt crystals; Figure 1 shows an example (**1a·9d**) of the crystal structures, and a schematic representation of the characteristic hydrogen-bond network is given in Figure 2. Two ammonium cation/carboxylate anion pairs form a unit through three kinds of hydrogen bonds between the ammonium hydrogens and the carboxylate oxygens. This unit also has hydrogen bonds with translational units, forming an infinite columnar structure around a 2-fold screw axis along the shortest cell axis, *b* or *c*. The mode of this helical hydrogen-bond columns (2_1-column) is represented as $C_2^1(4)C_2^2(6)[R_4^3(10)]$ using the graph sets proposed by Etter

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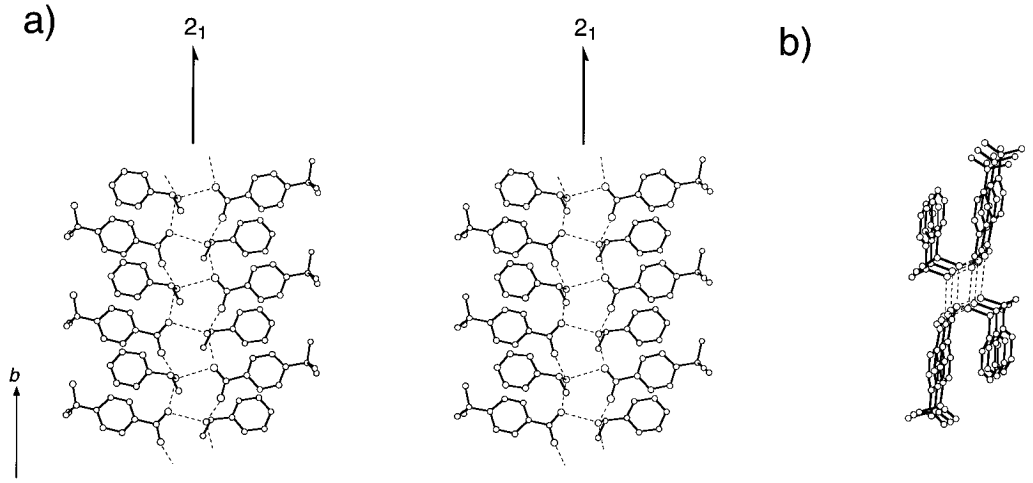

Figure 1. Hydrogen-bond network in the crystal of **1a·9d**. The dashed lines show hydrogen bonds. (a) Stereodrawing. (b) Viewed down the axis of the 2_1-column (*b* axis).

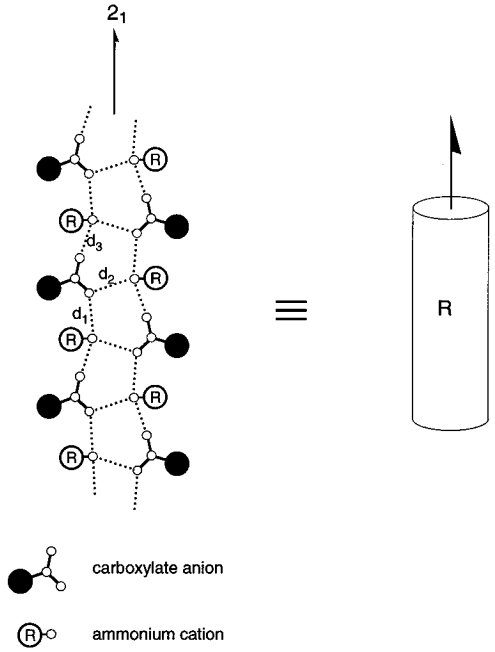

Figure 2. Schematic representation of a 2_1-column formed in conglomerate salts of chiral primary monoamines with achiral monocarboxylic acids. The dotted lines show hydrogen bonds.

Table 3. Type of Hydrogen-Bond Network and Distances between Ammonium Nitrogens and Carboxylate Oxygens in Conglomerate Salts

salt	space group	hydrogen-bond network	d_1/Å[a]	d_2/Å[a]	d_3/Å[a]
1a·7a[5a]	$P2_12_12_1$	2_1-column	2.727(2)	2.785(2)	2.709(2)
1a·7b	$P2_12_12_1$	2_1-column	2.740(6)	2.762(7)	2.742(7)
1a·9d	$P2_1$	2_1-column	2.77(1)	2.80(2)	2.70(1)
1b·7a	$P2_12_12_1$	2_1-column	2.773(4)	2.789(4)	2.682(4)
1e·7a[5a]	$P2_12_12_1$	2_1-column	2.787(3)	2.743(2)	2.741(3)
3·10b	$P2_12_12_1$	2_1-column	2.804(4)	2.827(4)	2.745(4)
4b·10d[14]	$P2_1$	2_1-column	2.840	2.789	2.788

[a] Defined as illustrated in Figure 2.

and MacDonald.[16] The distances between the carboxylate oxygens and the ammonium nitrogens are summarized in Table 3. In most cases, these distances are approximately 2.7−2.8 Å, suggesting that quite strong hydrogen bonds are formed between the ammonium and carboxylate groups. The alignment of the 2_1-columns results in the three-dimensional crystal structure. Since there is no significant interaction between these 2_1-columns except for van der Waals interaction, it is considered that the alignment mode of the 2_1-columns in the crystal is determined mainly by the latter, and that the 2_1-columns align so as to realize the closest packing, in which van der Waals interaction is most effective. When the directionality of the 2_1-columns is taken into account, they have two packing modes. One is a parallel packing corresponding to the space group $P2_1$ (Figure 3); the other is an antiparallel packing corresponding to the space group $P2_12_12_1$ (Figure 4).

Thus, it was found that the crystals of those salts of chiral primary monoamines with achiral monocarboxylic acids which precipitated as conglomerates upon crystallization consisted of characteristic hydrogen-bond 2_1-columns, whose alignment in the crystal was stabilized only by intercolumnar van der Waals interactions; the crystal structures of these conglomerate salts can be regarded as being an assembly of the hydrogen-bond 2_1-column supramolecular structural units.

Crystal Structures of Racemic-Compound Salts of Chiral Primary Monoamines with Achiral Monocarboxylic Acids. In the next stage, we focused our attention on the crystal structures of racemic-compound salts of chiral primary monoamines with achiral monocarboxylic acids. Our previous X-ray crystallographic analyses of racemic compounds were performed for the salts of chiral amine **1a** with achiral β-substituted cinnamic acid derivatives (Table 4, entries 2−9),[6] the achiral acids being of limited types. To increase the generality of the present study, we prepared the racemic-compound salts of **1a** with more familiar acids (Table 4, entries 1 and 10−14). In addition, the racemic-compound salts of some chiral primary monoamines with acid **7a**, which has a high propensity for forming conglomerates with such amines (as shown in Table 1), were also prepared (Table 4, entries 15−17). The cell parameters of those racemic-compound salts for which the crystal structures were determined are summarized in Table 4.

As a result of these X-ray crystallographic analyses, it was found that the crystal structures of these racemic-compound salts (except for **3·7a**, entry 16) could be broadly classified into two types on the basis of their hydrogen-bond network (Table 5). The first type is a crystal constructed of 2_1-columns, which is similar to that found in the conglomerate crystals discussed above. This type of crystal structure was found for nine of the seventeen racemic compounds in Table 4. The 2_1-column of each racemic-compound salt is comprised of an achiral acid

(17) The crystal structure of **1a·7f** is an exceptional case, in which the carboxylate oxygens and the ammonium nitrogens align around a pseudo-2-fold screw axis so as to make a 2_1-column, although both enantiomers of the ammonium cation are included in a single column. This hydrogen-bond network is essentially identical with a 2_1-column, and classified as such in Table 5.

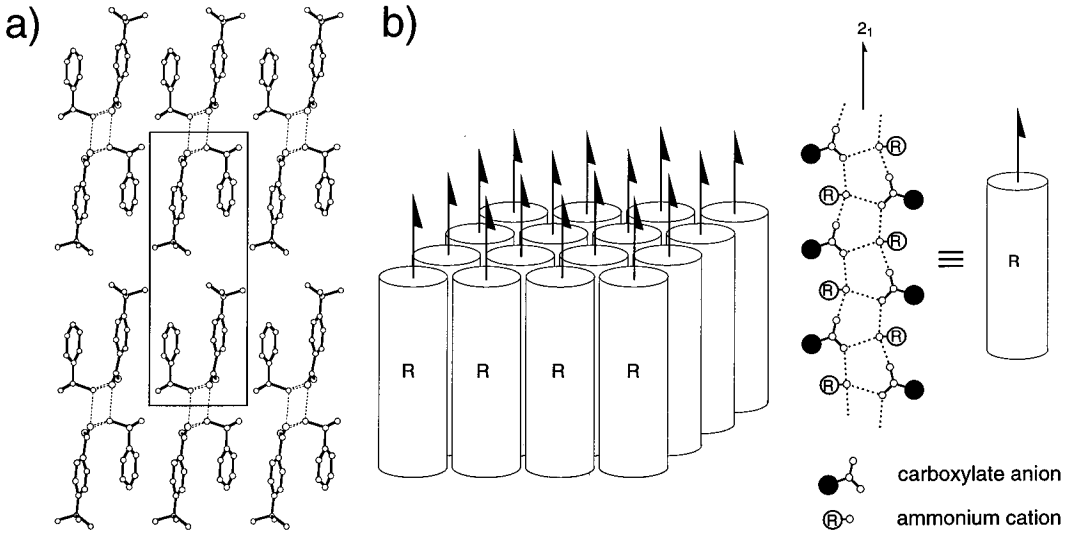

Figure 3. Crystal structure of **1a·9d**. (a) Viewed down the axis of 2_1-column (*b* axis). The dotted lines show the hydrogen bonds. The solid lines show the unit cell. (b) Schematic representation. The white rods represent 2_1-columns.

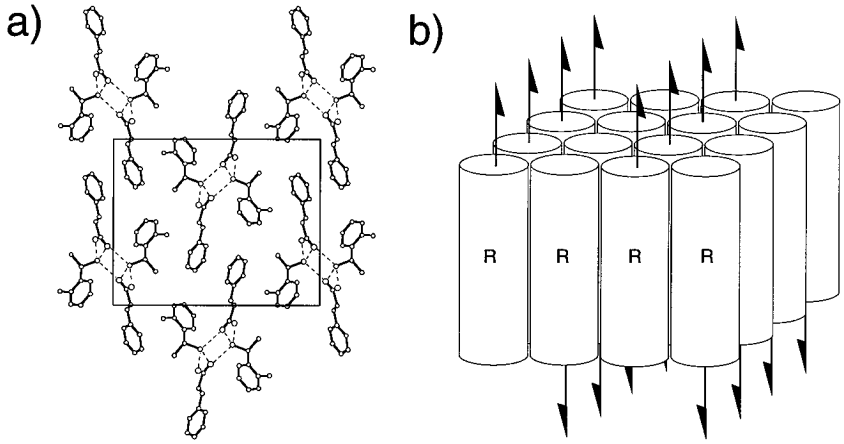

Figure 4. Crystal structure of **1b·7a**. (a) Viewed down the axis of the 2_1-column (*c* axis). The dashed lines show the hydrogen bonds. The solid lines show the unit cell. (b) Schematic representation. The white rods represent 2_1-columns.

and a chiral amine of uniform chirality, except in the cases of **1a·7f** and **1a·9a**, in which both enantiomers of chiral **1a** are alternatively[17] or randomly[19] aligned in a single 2_1-column, respectively. The whole crystal is formed by the packing of two kinds of homochiral 2_1-columns corresponding to the two enantiomers of a chiral amine, represented as an (*R*)-2_1-column and an (*S*)-2_1-column, in the same crystal lattice. The space group most frequently appearing for such cases is $P2_1/a$ (and its equivalents), in which the (*R*)-2_1-columns and (*S*)-2_1-columns pack alternately in an antiparallel manner (Figure 5). Another space group appearing less frequently is $Pbn2_1$, in which (*R*)-2_1-columns and (*S*)-2_1-columns align alternately in a parallel manner (Figure 6).

The second class of crystal found in racemic-compound salts is constructed of hydrogen-bond columns, which have no 2-fold screw axis, but rather inversion centers (*i*-column, Figure 7). This type of crystal structure was found for seven of the seventeen racemic compounds in Table 4. The pattern of hydrogen bonds in the *i*-column can be represented as $N_1 = C(4)R_4^2(4)$, $N_2 = R_4^4(8)$ using the graph sets.[16] In this case, each single column is comprised of the achiral acid and both enantiomers of the chiral amine; a single *i*-column is itself heterochiral. The whole crystal is formed by the packing of these heterochiral *i*-columns (Figure 7a). Two kinds of space groups appear in these cases, depending on the relationship between neighboring columns, $P\bar{1}$ and $P2_1/a$ (and its equivalents).

The crystal structure of **3·7a** revealed that this salt has an exceptional hydrogen-bond network. Two ammonium cation/carboxylate anion pairs form an asymmetric unit. Unlike other racemic-compound salts, hydrogen bonds between the ammonium hydrogens and the carboxylate oxygens form a planar network (Figure 8). The formation of such a hydrogen-bond network has been reported for the salts of achiral amines with achiral carboxylic acids.[20] However, it is found for only one of the seventeen racemic compounds in Table 4.

Thus, it was found that the crystals of the racemic-compound salts of chiarl primary monoamines with achiral monocarboxylic acids have a tendency in most cases to pack in either a hydrogen-bond *i*-column or a 2_1-column, and that these two types occur with similar frequency, though the latter may be somewhat preferred. In addition, a quite different type of hydrogen-bond network, which appeared much less frequently than the other

(18) Salt **1a·9b** was found to afford both a conglomerate and a racemic compound, depending on the solvent used for crystallization; recrystallization from a tetrahydrofuran solution afforded a conglomerate,[8] while that from an aqueous solution afforded a racemic compound. We could determine the crystal structure of only the racemic compound.

(19) Although this crystal might be regarded as a pseudoracemate, it was treated as a racemic compound in the present study, since we could prepare this crystal only from 1:1 enantiomer mixtures.

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Table 4. Summary of Cell Dimensions of Racemic-Compound Salts of Chiral Primary Monoamines with Achiral Monocarboxylic Acids

entry	salt	space group	*a*/Å[a]	*b*/Å[a]	*c*/Å[a]	*β*/deg (α,*β*,γ)	*V*/Å^3	*Z*
1	**1a·7c**	$P2_1/a$	9.884(2)	29.104(4)	*5.750(1)*	106.45(1)	1586.3(5)	4
2	**1a·7d**[6]	$P\bar{1}$	*6.0014(6)*	10.824(1)	14.516(2)	93.30(1) 96.79(1) 103.43(1)	907.2(2)	2
3	**1a·7e**[6]	$P2_1/n$	20.794(6)	*6.507(2)*	15.844(4)	100.38(2)	2109(1)	4
4	**1a·7f**[6]	*Pn*	19.011(3)	*6.444(1)*	14.938(3)	110.30(1)	1716.3(5)	4
5	**1a·7g**[6]	$P2_1/a$	19.717(6)	*6.395(2)*	14.649(3)	91.07(2)	1846.7(7)	4
6	**1a·7h**[6]	$P2_1/n$	18.5291(5)	*6.854(1)*	14.728(5)	104.29(2)	1812.4(8)	4
7	**1a·7i**[6]	$P\bar{1}$	*6.707(1)*	9.954(2)	16.754(4)	90.42(2) 90.57(2) 102.55(1)	1091.7(3)	2
8	**1a·8a**[6]	$P\bar{1}$	*6.475(6)*	13.133(3)	20.896(5)	97.27(2) 91.67(4) 97.88(4)	1744(2)	4
9	**1a·8b**[6]	$P\bar{1}$	*6.448(3)*	13.770(4)	22.117(6)	106.55(2) 93.49(3) 81.83(3)	1863(1)	4
10	**1a·9a**	$Pbn2_1$	14.645(2)	15.402(5)	*6.142(2)*		1385.3(8)	4
11	**1a·9b**[18]	$P2_1/n$	12.796(1)	17.170(2)	*6.772(1)*	103.24(1)	1448.3(3)	4
12	**1a·9f**	$P2_1/a$	30.088(5)	*6.219(1)*	7.225(1)	92.61(1)	1440.4(4)	4
13	**1a·9g**	$P2_1/n$	24.116(4)	*6.056(1)*	9.856(1)	100.26(1)	1416.5(4)	4
14	**1a·10e**	$P2_1/n$	21.224(3)	*5.917(1)*	15.326(2)	102.76(1)	1877.1(5)	4
15	**1c·7a**	$Pbn2_1$	10.541(1)	26.326(3)	*5.8209(9)*		1618.1(4)	4
16	**3·7a**	$P\bar{1}$	11.122(1)	17.726(2)	9.2515(8)	98.827(8) 90.134(8) 81.084(9)	1780.2(3)	4
17	**6·7a**	$P2_1/n$	22.352(5)	*6.672(2)*	13.488(4)	105.56(2)	1937.7(8)	4

[a] Italic cell axes are parallel to hydrogen-bond columns.

Table 5. Type of Hydrogen-Bond Network and Distances between Ammonium Nitrogens and Carboxylate Oxygens in Racemic-Compound Salts

entry	salt	space group	hydrogen-bond network	d_1/Å[a]	d_2/Å[a]	d_3/Å[a]
1	**1a·7c**	$P2_1/a$	*i*-column	2.840(3)	2.839(3)	2.676(3)
2	**1a·7d**[6]	$P\bar{1}$	*i*-column	2.706(3)	2.790(3)	2.770(3)
3	**1a·7e**[6]	$P2_1/n$	*i*-column	2.720(3)	2.741(3)	2.718(3)
4	**1a·7f**[6]	*Pn*	2_1-column[b]	2.722(5)	2.790(5)	2.787(6)
				2.748(5)	2.748(5)	2.790(5)
5	**1a·7g**[6]	$P2_1/a$	2_1-column	2.745(5)	2.749(5)	2.775(5)
6	**1a·7h**[6]	$P2_1/n$	2_1-column	2.804(4)	2.786(4)	2.734(4)
7	**1a·7i**[6]	$P\bar{1}$	*i*-column	2.768(6)	2.754(8)	2.742(7)
8	**1a·8a**[6]	$P\bar{1}$	*i*-column[c]	2.767(3)	2.781(3)	2.733(3)
				2.749(3)	2.814(3)	2.706(3)
9	**1a·8b**[6]	$P\bar{1}$	*i*-column[c]	2.742(4)	2.718(4)	2.734(4)
				2.735(4)	2.758(5)	2.733(4)
10	**1a·9a**	$Pbn2_1$	2_1-column	2.756(5)	2.814(5)	2.727(6)
11	**1a·9b**[18]	$P2_1/n$	*i*-column	2.807(3)	2.774(3)	2.751(5)
12	**1a·9f**	$P2_1/a$	2_1-column	2.797(5)	2.751(4)	2.705(5)
13	**1a·9g**	$P2_1/n$	2_1-column	2.814(5)	2.732(4)	2.726(4)
14	**1a·10e**	$P2_1/n$	2_1-column	2.78(1)	2.792(7)	2.713(9)
15	**1c·7a**	$Pbn2_1$	2_1-column	2.768(6)	2.835(4)	2.719(4)
16	**3·7a**	$P\bar{1}$	planar			
17	**6·7a**	$P2_1/n$	2_1-column	2.71(1)	2.887(9)	2.75(1)

[a] Defined as illustrated in Figures 2 and 7. [b] See ref 17. [c] Two kinds of *i*-columns are included in the unit cell.

columnar structures, was found: a hydrogen-bond network stretching in two dimensions throughout the crystal lattice.

Crystal Structures of Enantiomerically Pure Counterparts of Racemic-Compound Salts. We considered that the general features of conglomerate salts and racemic-compound salts would become clearer on comparison of the crystal structures of enantiomerically pure salts, of which the racemic forms deposit as racemic compounds, with those of the corresponding racemic salts. Therefore, we carried out crystal structure analyses of four enantiomerically pure salts of **1a** with achiral monocarboxylic acids (Table 6). The crystal structures of these enantiomerically pure salts revealed that all contained hydrogen-bond 2_1-columns, regardless of the pattern of the hydrogen-bond network formed in the corresponding racemates (Table 7); the structures of these homochiral crystals are quite similar to those of the conglomerates listed in Table 2.[21] This and the above-mentioned results indicate that the salt crystals of primary amines with achiral primary monocarboxylic acids are assemblies of supramolecular units, such as the hydrogen-bond 2_1- or *i*-column; when a salt crystallizes into a chiral space group, a 2_1-column is always formed, whereas when a salt crystallizes into an achiral space group, hydrogen bonds form either a 2_1-column or an *i*-column or, rarely, afford a planar network.[22]

Discussion

In order to confirm whether the above-mentioned hydrogen-bond networks found in chiral ammonium carboxylates are general, we next focused our attention on the hydrogen-bond networks formed between achiral primary ammonium groups and achiral carboxylate groups, making a search of the Cambridge Structural Database (CSD) (August 1995 version). Those salt crystals, including precisely three kinds of hydrogen bonds between ammonium nitrogens and carboxylate oxygens, were picked out, since we were interested in a hydrogen-bond network formed between a primary amine and a monocarboxylic

(21) Generally, it was quite difficult to prepare single crystals of enantiomerically pure salts of compounds for which the corresponding racemates were racemic compounds. In such cases, the crystals were usually thin needles or whiskers, suggesting the presence of a one-dimensional intermolecular interaction, i.e., a hydrogen-bond column.

(22) It should be noted that the crystal structures discussed here were solved only for compounds which afforded a single crystal having sufficient quality for an X-ray crystallographic analysis; we could not solve the crystal structures of salts containing aliphatic carboxylic acids, such as butyric acid. Hence, it is possible that the statistical analysis is biased to some extent. However, since we have chosen the target salts almost at random, we consider our results to be sufficient to represent the general features of the crystal structures of the salts of primary amines with monocarboxylic acids.

(23) Our study is concerned with hydrogen bonds between primary amines and monocarboxylic acids. Therefore, amino acids, the salts of diamines and/or dicarboxylic acids, and inclusion compounds, in which the entropical contribution was supposed to be quite different from that in the salts of primary amines with monocarboxylic acids, were excluded from this search. In addition, solvated crystals, in which the solvent molecules participated in the hydrogen-bond network, were also excluded.

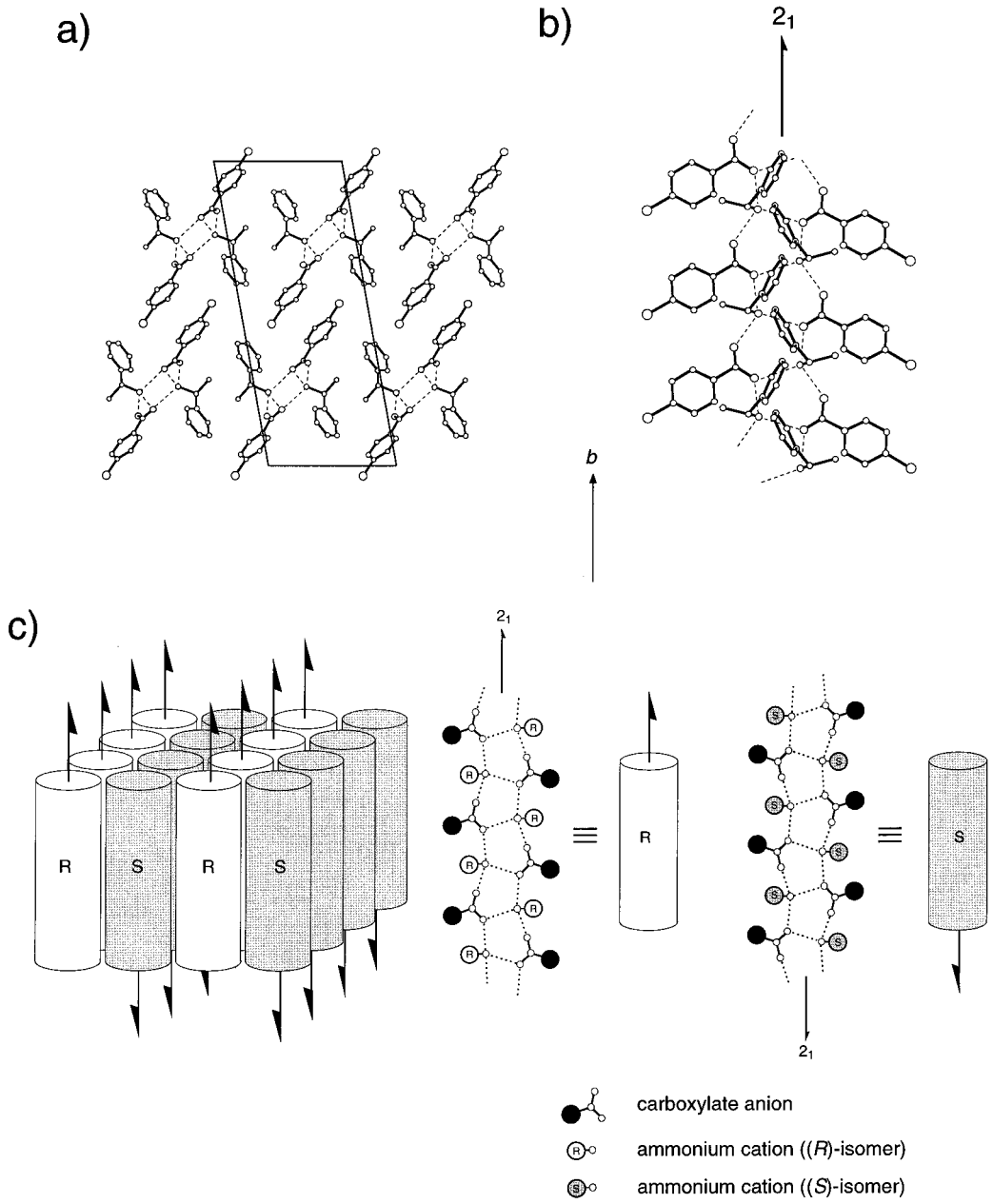

Figure 5. Crystal structure of **1a·9g**. (a) Viewed down the axis of the 2_1-column (*b* axis). The dashed lines show the hydrogen bonds. The solid lines show the unit cell. (b) Hydrogen-bond network in the crystal. The dashed lines represent hydrogen bonds. (c) Schematic representation. The white and shaded rods represent (*R*)-2_1-columns and (*S*)-2_1-columns, respectively.

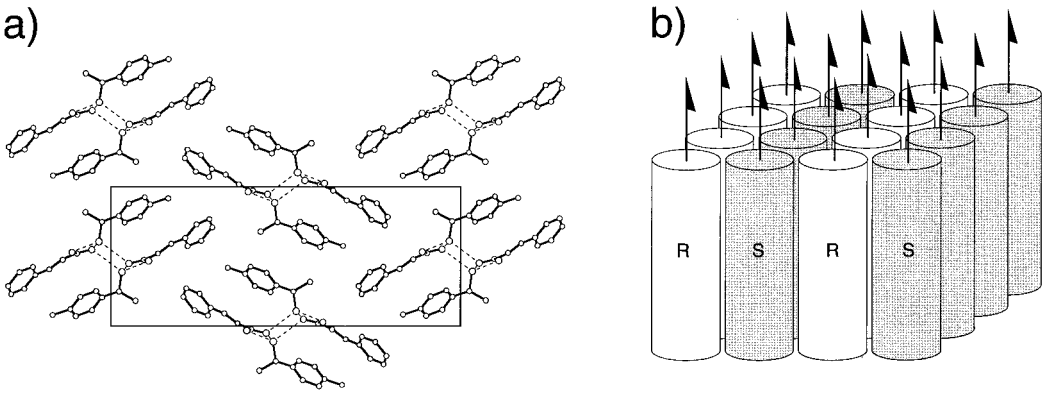

Figure 6. Crystal structure of **1c·7a**. (a) Viewed down the axis of the 2_1-column (*c* axis). The dashed lines show the hydrogen bonds. The solid lines show the unit cell. (b) Schematic representation. The white and shaded rods represent (*R*)-2_1-columns and (*S*)-2_1-columns, respectively.

acid.[23] Table 8 shows the result of the search, in which our own previous results are also included.[6] As can be seen from Table 8, these achiral salts also each contain one of the three types of hydrogen-bond networks: 2_1-column, *i*-column, and planar network.[24] A 2_1-column hydrogen-bond network was found for 11 of 22 achiral salt crystals (entries 1−11). Although

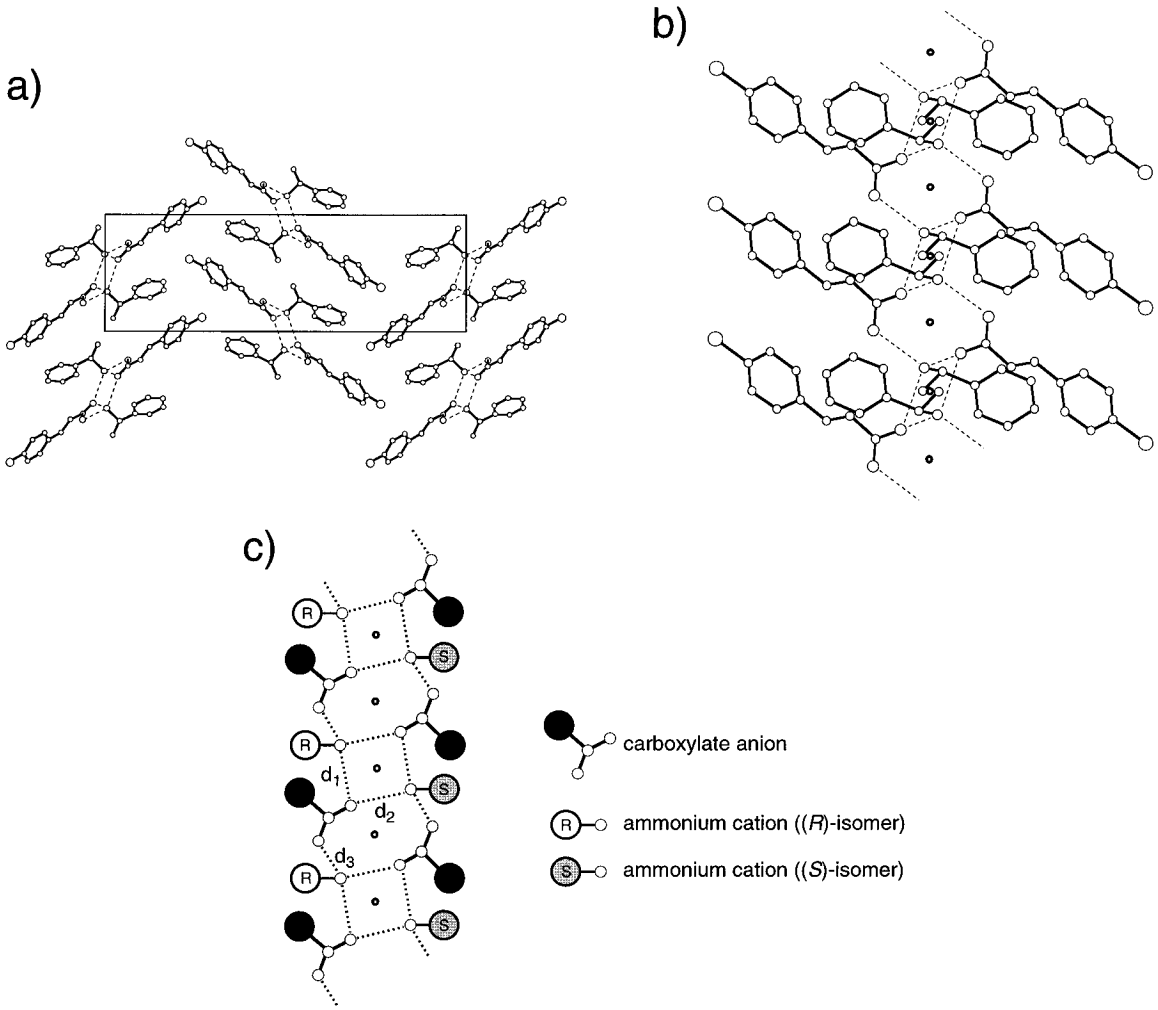

Figure 7. Crystal structure of **1a·7c**. (a) Viewed down the axis of the *i*-column (*c* axis). (b) Hydrogen-bond network in the crystal. The dashed lines show the hydrogen bonds. The circles show inversion centers. (c) Schematic representation of an *i*-column in racemic-compound salts of chiral primary monoamines with achiral monocarboxylic acids. The dotted lines show hydrogen bonds.

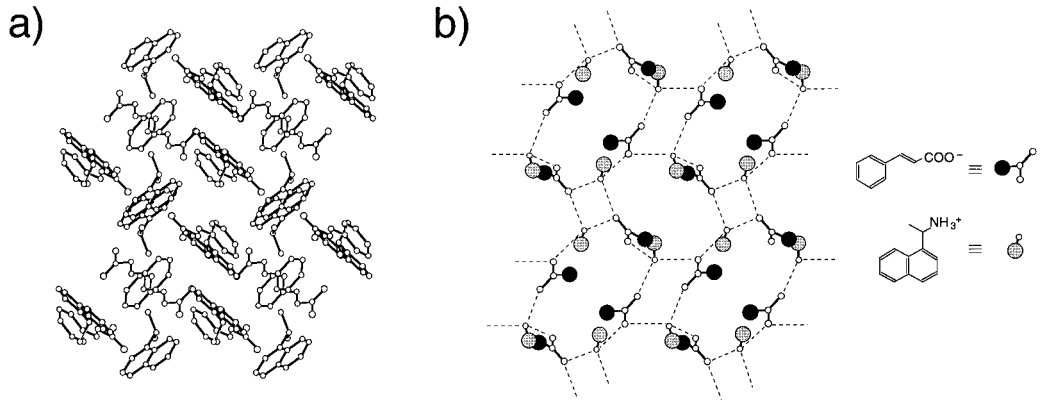

Figure 8. Crystal structure of **3·7a**. (a) Viewed down the *b* axis. (b) Schematic representation of the hydrogen-bond network. The dashed lines show the hydrogen bonds.

Table 6. Summary of Cell Dimensions of Enantiomerically Pure Salts

salt	space group	*a*/Å	*b*/Å[a]	*c*/Å[a]	*β*/deg	*V*/Å^3	*Z*
(*R*)-**1a·7c**	$P2_12_12_1$	9.376(1)	28.353(4)	*6.076(1)*		1615.3(4)	4
(*R*)-**1a·8a**	$P2_1$	13.326(4)	*6.172(2)*	11.885(3)	114.90(2)	886.6(4)	2
(*R*)-**1a·9f**	$P2_12_12_1$	7.182(1)	32.302(6)	*6.256(2)*		1451.4(5)	4
(*R*)-**1a·9g**	$P2_12_12_1$	10.0889(8)	23.117(2)	*5.9726(6)*		1393.0(2)	4

[a] Italic cell axes are parallel to hydrogen-bond columns.

the salts found by this CSD search were of restricted types, this suggests that the hydrogen-bond 2_1-column is a widespread supramolecular structural unit, even in achiral salt crystals; the formation of such 2_1-columns is an inherent characteristic of salts of a primary amine with a monocarboxylic acid, regardless of the presence or absence of chirality in the amine.

The components of those salts having the planar hydrogen-bond network shown in Table 8 are quite limited; namely, they

Scheme 1

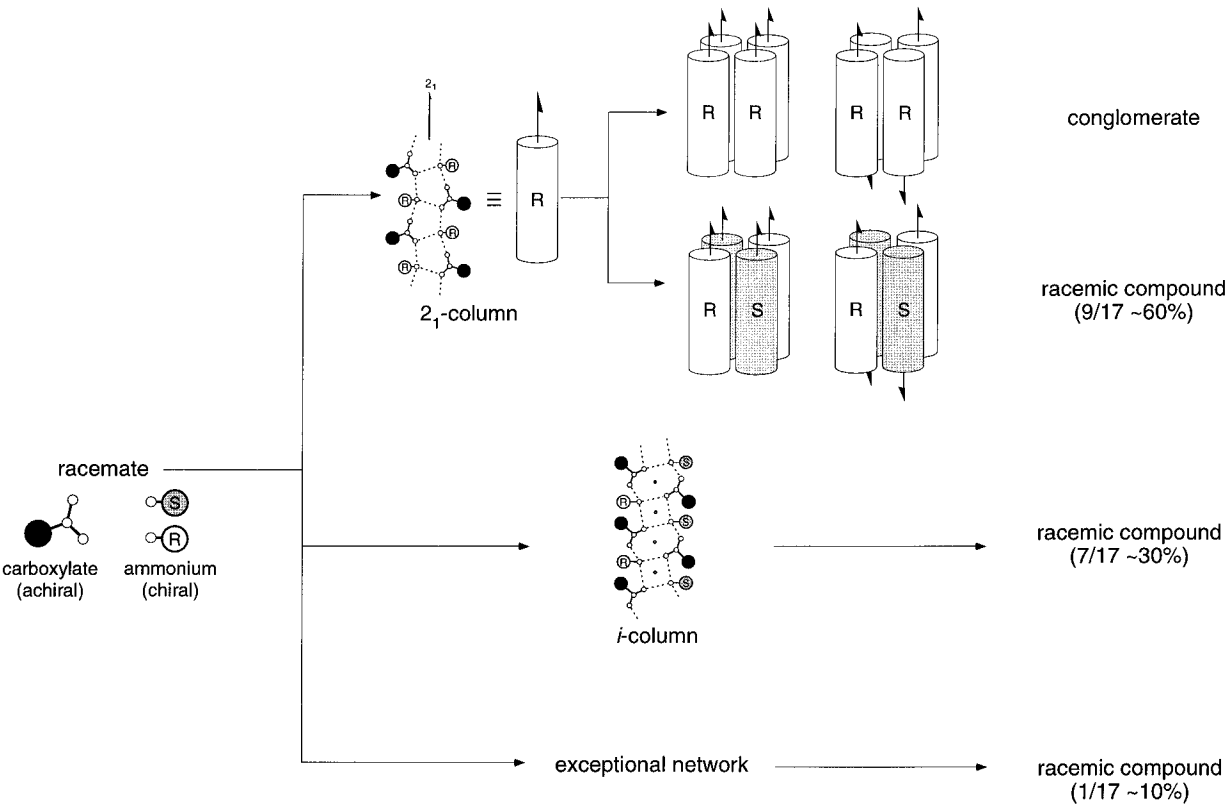

Table 7. Type of Hydrogen-Bond Network and Distances between Ammonium Nitrogens and Carboxylate Oxygens in Enantiomerically Pure Salts

salt	hydrogen-bond network	d_1/Å[a]	d_2/Å[a]	d_3/Å[a]	hydrogen-bond network of racemate
(*R*)-**1a·7c**	2_1-column	2.786(5)	2.727(5)	2.701(5)	*i*-column
(*R*)-**1a·8a**	2_1-column	2.78(1)	2.77(1)	2.72(1)	*i*-column
(*R*)-**1a·9f**	2_1-column	2.787(8)	2.744(6)	2.697(8)	2_1-column
(*R*)-**1a·9g**	2_1-column	2.802(5)	2.745(5)	2.723(6)	2_1-column

[a] Defined as illustrated in Figure 2.

all contain substituted anilines and chlorine-substituted acetic acids (entries 16−22). In all these salt crystals, a Cl···Cl interaction was observed in addition to the hydrogen-bonding interactions. This secondary interaction may stabilize the planar hydrogen-bond structure, and therefore we consider the general frequency of the planar network among the salts of a primary amine with a monocarboxylic acid is likely to be much lower than that found in the present survey.

When these salts having an additional Cl···Cl interaction are excluded, among the thirty-three kinds of racemic and achiral salts, the 2_1-column, *i*-column, and planar network, occur in total twenty, eleven, and two times, respectively. The high frequency of the 2_1-column in the salts of chiral primary amines with achiral monocarboxylic acids is ascribed to a characteristic of the hydrogen bonds between the primary ammonium and carboxylate groups.

This classification of the crystal structures of the salts of chiral primary amines with achiral monocarboxylic acids is summarized in Scheme 1. As is illustrated in this scheme, the formation of a 2_1-column is the primary requirement for conglomerate formation, and this supramolecular structure occurs in over 50% of the examples referred to in the present study. The higher frequency of conglomerates for salts compared to covalent compounds can be explained in terms of an inherent trend toward the formation of a chiral supramolecular structure in salt crystals. As can be seen from Tables 5 and 8, salts of a bulky amine or a bulky achiral carboxylic acid tend to form an *i*-column (Table 5, entries 2, 3, and 7−9; Table 8, entries 12−15),[25] while salts with a less-bulky achiral carboxylic acid is favorable for the formation of a 2_1-column; the relative stability of the 2_1-column and *i*-column, and hence the preference for one or the other, seems to be governed by steric congestion. When the difference in stability between the 2_1- and *i*-columns is not very large for a salt, the stability of not only the hydrogen-bond column itself but also of the packing of the columns needs to be taken into account; a hydrogen-bond column leading to closer packing in the crystal is more favorable. This interpretation is supported by the fact that the cell volumes of the racemates which form an *i*-column in the crystal are smaller than those of their chiral counterparts (compare **1a·7c** and (*R*)-**1a·7c**, and **1a·8a** and (*R*)-**1a·8a**); this phenomenon is in good agreement with the close-packing rule proposed by Wallach.[26]

The secondary requirement for conglomerate formation is as follows: Even when a homochiral 2_1-column is formed preferentially, the packing mode of these 2_1-columns is important. As mentioned above, it is considered that the alignment of 2_1-columns in a crystal is governed only by van der Waals interaction between them. Consequently, only when the stability of (*RR*)-packing (i.e., a single crystal consists of only (*R*)-2_1-columns) ((*SS*)-packing, vice versa) overcomes the entropical advantage of (*RS*)-packing (a single crystal consists of alternate (*R*)- and (*S*)-2_1-columns) will a conglomerate be formed. A rigid 2_1-column would be more favorable for conglomerate formation than a flexible one, since a rigid 2_1-column maximizes

(24) All kinds of hydrogen-bond network spreading in two dimensions are classified in this category.

(25) There are some reports that molecules having a large dipole moment tend to crystallize in centrosymmetric crystals; see: Gavezzotti, A. *J. Phys. Chem.* **1990**, *94*, 4319. Whitesell, J. K.; Davis, R. E.; Saunders, L. L.; Wilson, R. J.; Feagins, J. P. *J. Am. Chem. Soc.* **1991**, *113*, 3267.

(26) Wallach, O. *Liebigs Ann. Chem.* **1895**, *286*, 90. Brock, C. P.; Schweizer, W. B.; Dunitz, J. D. *J. Am. Chem. Soc.* **1991**, *113*, 9811.

Table 8. Type of Hydrogen-Bond Networks in the Salts of Achiral Primary Amines with Achiral Monocarboxylic Acids

entry	amine	acid	hydrogen-bond network	REFCODE
1	1-adamantylamine	**7f**	2_1-column	ref 6
2	9-(2-aminoethyl)adenine	**10b**	2_1-column	BOYDUO
3	*tert*-butylamine	**7f**	2_1-column	ref 6
4		**8**	2_1-column	ref 6
5	4-chloroaniline	dichloroacetic acid	2_1-column	GARVAW
6	5-methoxytryptamine	indole-3-acetic acid	2_1-column	IAAMTA
7		5-methoxyindole-3-acetic acid	2_1-column	MIAMTA
8	tryptamine	**9h**	2_1-column	GONFOQ
9		**10b**	2_1-column	TRPPAC
10		thymine-1-acetic acid	2_1-column	TPATAA
11		adenine-9-acetic acid	2_1-column	TRADAA
12	1,1-diphenylmethylamine	**7f**	*i*-column	ref 6
13		**8a**	*i*-column	ref 6
14	1-naphthylamine	dichloroacetic acid	*i*-column	LECCIF
15		trichloroacetic acid	*i*-column	LECCOL
16	1,8-diaminonaphthalene	trichloroacetic acid	planar	LECCUR
17	2,3-dimethylaniline	dichloroacetic acid	planar	KUKCIC
18	2,4-dimethylaniline	chloroacetic acid	planar	KUKCOI
19		dichloroacetic acid	planar	KUKCUO
20	3,4-dimethylaniline	dichloroacetic acid	planar	YABVEC
21		trichloroacetic acid	planar	YABVIC
22	4-methylaniline	dichloroacetic acid	planar	YABVAY

the difference in the packing energy between (*RR*)- and (*RS*)-packings, while a flexible one has an energy difference lessened due to conformational changes of the molecules. In our previous paper, we proposed empirical rules for the choice of a derivatizing reagent for conglomerate formation as follows:[5b] (a) the derivatizing reagent should be rigid and flat; (b) the sizes of the derivatizing reagent and the racemate should be complementary. The above observations regarding the correlation between the molecular structure and the structure of the hydrogen-bond column suggest that our proposal is reasonable: A flat reagent is favorable for the formation of a 2_1-column, while the rigidity and complementary in size of the reagent assist in the realization of a rigid 2_1-column.

At the present stage, it is quite difficult to quantitatively estimate the stability of a 2_1-column or that of the packing of the 2_1-columns, although such an estimation is indispensable for predicting whether a salt of a chiral amine with an achiral acid will be a conglomerate or not. In order to solve this problem, computational studies concerning the differences in energy between 2_1- and *i*-columns and between (*RR*)- and (*RS*)-packings are now in progress.

Conclusion

The results of X-ray crystallographic analyses of the salts of chiral primary monoamines with achiral monocarboxylic acids existing as conglomerates and racemic compounds, and of their homochiral analogs, showed that almost all of these crystal structures can be regarded as being assemblies of a supramolecular unit of structure, such as a hydrogen-bond 2_1- or *i*-column. Of these two supramolecular structures, the 2_1-column is homochiral, implying that the assembly of 2_1-columns is essential for the formation of a conglomerate, although similar 2_1-columns occasionally afford a racemic compound. The alignment of 2_1-columns in these two cases is governed by van der Waals interaction between the columns.

(27) Kinbara, K.; Sakai, K.; Hashimoto, Y.; Nohira, H.; Saigo, K. Submitted for publication.

(28) CRYSTAL-GM, A Computer Program for the Solution and Refinement of Crystal Structures for X-ray Diffraction Data (MAC Science Corp.).

Experimental Section

The preparations of the chiral amines and achiral acids have been described in our previous papers.[6,27] Single crystals for X-ray analysis were prepared in all cases by slow evaporation of the solvent from a saturated solution of the compound in aqueous ethanol. The X-ray intensities were measured up to $2\theta = 130°$ with graphite-monochromated Cu Kα radiation ($\lambda = 1.5418$ Å) on a Mac Science MXC18 four-circle diffractometer by a $2\theta-\omega$ scan. All of the data were collected at room temperature, except for **1a·9a** (150 K). The cell dimensions were determined from about 20 reflections ($50° < 2\theta < 60°$). The intensities and orientation of the crystals were checked by three standard reflections every 100 reflections.

The structures were solved and refined by applying the CRYSTAN-GM package.[28] All of the non-hydrogen atoms were refined anisotropically. Hydrogen atoms were localized from a difference Fourier synthesis, except for those of **1a·7b**, **1a·9a**, **1a·9d**, **1a·10e**, **6·7a**, (*R*)-**1a·7c**, (*R*)-**1a·8a**, and (*R*)-**1a·9f**, which were located at calculated positions. The isotropic thermal parameters of the hydrogen atoms were fixed in the cases of **1a·7b**, **1a·9a**, **1a·9d**, **1a·10e**, **6·7a**, and (*R*)-**1a·8a**, and refined in all other cases. The details concerning the crystallographic analyses have been deposited as supporting information.

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Supporting Information Available: Complete tables of the atomic coordinates, thermal parameters, bond angles, bond lengths, and intermolecular distances between the ammonium nitrogens and the carboxylate oxygens for **1a·7b**, **1a·7c**, **1a·9a**, **1a·9b**, **1a·9d**, **1a·9f**, **1a·9g**, **1a·10e**, **1b·7a**, **1c·7a**, **3·7a**, **3·10b**, **6·7a**, (*R*)-**1a·7c**, (*R*)-**1a·8a**, (*R*)-**1a·9f**, and (*R*)-**1a·9g** (35 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

JA9539960