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TETRAHEDRON: *ASYMMETRY*

Chiral crystalline salts from achiral biphenylcarboxylic acids and tryptamine

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Abstract

Chiral crystals of quaternary ammonium salts **5–7** were prepared by crystallization of achiral biphenylcarboxylic acids **1–3** and achiral tryptamine **4**. Molecular chirality is defined by chiral conformations of the biphenyl group and crystal chirality by a helical arrangement of the molecules in the lattice. The enantiomorphous crystals were easily discriminated by measuring their solid state (powder) CD spectra.

The generation of optically active compounds from achiral reactants in the absence of deterministic chiral influences is known as absolute asymmetric synthesis.[1,2] Absolute asymmetric syntheses in the solid state takes advantage of prochiral reactions that occur under the influence of the homochiral environment given by crystals lacking symmetry elements of the second order such as inversion centers, glide and mirror planes.[3] Although several interesting examples of absolute asymmetric syntheses are known, in order to design reliably absolute asymmetric syntheses in the solid state it will be necessary to prepare and predict the formation of chiral crystals from achiral compounds.[4] Since our recent finding of a chiral two-component molecular crystal formed with diphenylacetic acid and acridine,[5] we have prepared several other two-component chiral crystals composed of two achiral molecules. These include molecules that crystallize in propeller conformations such as diphenylacetic acid and phenanthridine,[6] and molecules that crystallize in helical conformations such as 3-indolepropionic acid and phenanthridine.[7] The induction of crystal chirality in those cases takes advantage of the frozen conformational chirality that results when a conformationally flexible compound assembles with a second achiral molecule. With that in mind, we decided to explore a set of biphenyl containing carboxylic acids and an amine base such as tryptamine. Although rapid racemization of biphenyl-containing compounds in solution renders them achiral (optically inactive), and even though biphenyl itself crystallizes with the two phenyl groups in a planar conformation in the achiral space group $P2_1/a$,[8] in analogy with previous

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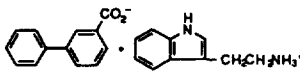
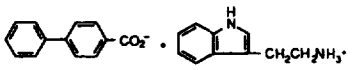
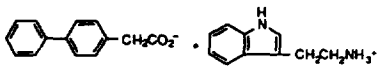
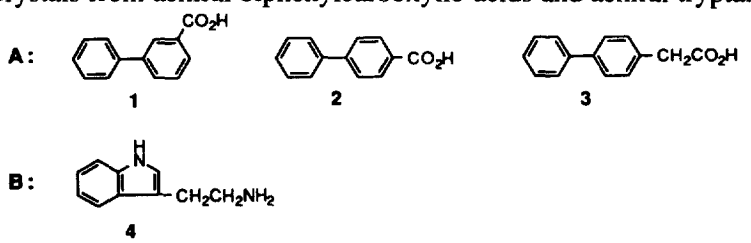
Table 1
Dihedral angles and distance data of the chiral salt crystals **5–7**

Chiral salt crystal		Space group	Dihedral angle (°)	Torsion angle (°)	Distance (Å)	
					Salt	H-Bonding
			Ph/Ph	InC–C–C–N	$CO_2^-\cdots{}^+H_3N$	$CO_2\cdots HN$-In
	Chiral 5	$P2_12_12_1$	29.53	175.92	1.70, 1.75, 1.81	1.99
	Chiral 6	$P2_12_12_1$	32.95	171.95	1.77, 1.85, 1.86	1.87
	Chiral 7	$P2_1$	–51.00(A)	–59.41(C)	1.73, 2.03, 2.16	1.91
			31.61(B)	–58.26(D)	1.82, 2.00, 2.12	1.91

A, B, C, and D correspond to the molecules in Figure 2b.

examples it may be expected that conformational chirality induced upon salt formation may result in the formation of chiral crystals from achiral biphenylcarboxylic acids and achiral tryptamine.



The three chiral crystal salts **5**, **6**, and **7** incorporate 3-biphenylcarboxylic acid **1**, 4-biphenylcarboxylic acid **2** and 4-biphenylacetic acid **3** with tryptamine **4**. Recrystallization from 1:1 solutions of two components in methanol gave crystals **5–7**. High melting points for **5**, **6**, and **7** (198°C, 198°C, and 201°C, respectively) are consistent with the partially ionic structures of quaternary ammonium salts. Crystals submitted to X-ray crystallographic analysis confirmed the chiral nature of **5**,[9] **6**,[10] and **7**[11] whose space groups are $P2_12_12_1$, $P2_12_12_1$, and $P2_1$, respectively. Ionic interactions between CO_2^- and NH_3^+ and hydrogen bonding between indole N–H and CO_2^- groups are observed in all three crystals. Distances calculated from the X-ray structure are listed in Table 1.

Figure 1a shows the molecular arrangement in a crystal of salt **5**. The two phenyl planes of molecule **1** have a twisted conformation with a dihedral angle of 29.53° (Table 1). The ethylamino group of **4** has also torsional conformation with the (indole)C–CH_2–CH_2–NH_3 torsion angle of 175.92°. An important feature in **5** is that only one absolute configuration of **1** and **4** are represented in the crystal lattice to form a two-fold helix along axis *c* through the salt with hydrogen bonding. As shown in Fig. 1a, not only the torsional ethylamino group but also the imino group of the molecule **4** play an important role in the formation of a helical hydrogen bond chain. It is similar to the role of the 3-indolepropionic acid molecule in the helical type chiral crystal with phenanthridine as we previously reported.[7]

The crystal structure of **6**[10] is very similar to that of **5**[9] in terms of unit cell dimensions, the conformations of molecules **2** and **4** (Table 1), and the helical structure in the crystal lattice. This is understandable from the small difference in molecular structure between **1** and **2**. Due to formation of centrosymmetric carboxylic acid dimers, crystals of **1** and **2** alone are achiral with space groups $C2/c$[12] and $P2_1/c$,[13] respectively. However, as speculated, the axial chirality of the biphenyl group may be frozen by self-assembling with tryptamine **4**.

Crystals **7** have a different packing arrangement from those of **5** and **6** (Fig. 1b). Two different

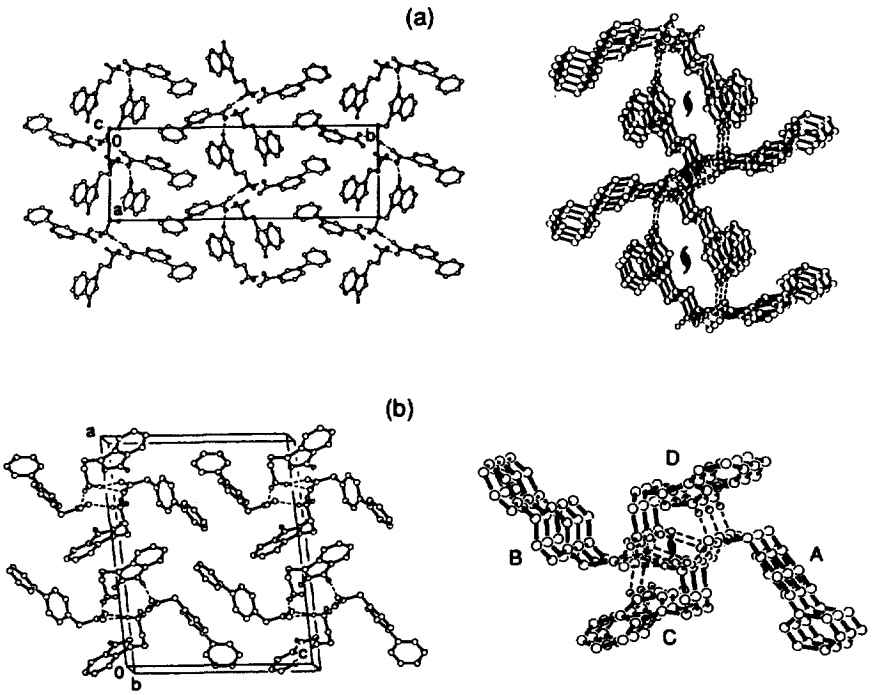


Fig. 1. Molecular packing arrangements of the chiral crystalline salts **5** (a) and **7** (b)

conformations of molecule **3** exist in the until cell of space group $P2_1$ (Z=4). The dihedral angles of the biphenyl group are −51.00° (A) and 31.61° (B), and the Ph–CH_2–CH_2–C=O torsion angles are 57.94° (A) and −44.90° (B) as shown in Fig. 1b and Table 1. Although molecules A and B are in nearly enantiomorphic conformations, two independent conformations of molecule **4** in the unit cell are very similar to one another. The (indole)C–CH_2–CH_2–NH_3 torsion angles are −58.26° for molecule C and −59.41° for D. The four molecules A–D form one structural unit through salt and hydrogen bonding. Further stacking along the *b* axis results in a helical structure which accounts for the crystal chirality.

The two enantiomorphous crystals of **5–7** were obtained by spontaneous crystallization from solution and either enantiomer can be obtained by chance. We could show that solid state CD spectra using a Nujol mull[14] offers a simple way to discriminate between the two enantimorphous modifications (Fig. 2). It indicates that solid state CD spectrometry may be a powerful tool in determining whether a given single crystal is chiral or not.

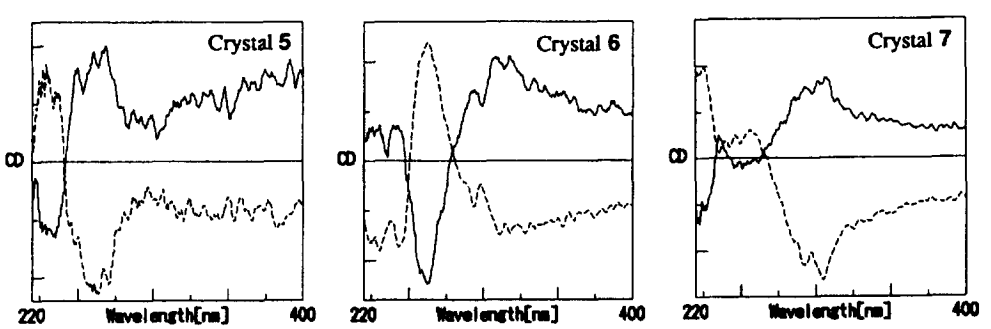


Fig. 2. Circular dichroism spectra of chiral crystals **5–7** using Nujol dispersions

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9. **5**: Colorless needle crystals; mp 198°C (from MeOH). Crystal data: $C_{23}H_{22}N_2O_2$; orthorhombic; $P2_12_12_1$; a=10.487(4) Å, b=29.90(1) Å, c=6.138(3) Å; Z=4; ρ_{calcd}=1.237 g cm^{-1}; R=0.049, R_w=0.055; GOF=1.697.
10. **6**: Colorless plate crystals; mp 198°C (from MeOH). Crystal data: $C_{23}H_{22}N_2O_2$; orthorhombic; $P2_12_12_1$; a=6.213(7) Å, b=9.80(1) Å, c=32.33(3) Å; Z=4; ρ_{calcd}=1.209 g cm^{-1}; R=0.044, R_w=0.052; GOF=1.662.
11. **7**: Colorless needle crystals; mp 201°C. Crystal data: $C_{24}H_{24}N_2O_2$; $P2_1$, a=19.329(9) Å, b=6.813(3) Å, c=15.298(7) Å, β=96.11(1)°, Z=4; ρ_{calcd}=1.235 g cm^{-1}; R=0.044, R_w=0.052; GOF=1.663.
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