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Absolute Helical Arrangement of Sulfonamide in the Crystal

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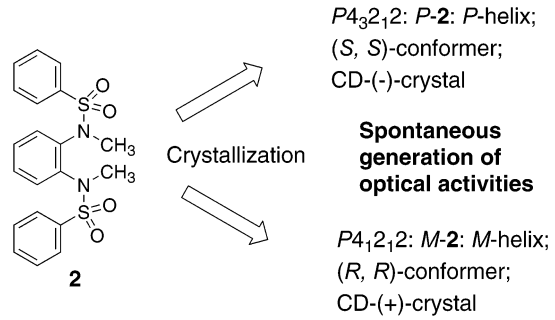
ABSTRACT



1,2-Bis(*N*-benzenesulfonyl-*N*-methylamino)benzene (2), which has no fixed asymmetric element, was crystallized from ethyl acetate as chiral crystals belonging to space group $P4_12_12$ (No. 92) or $P4_32_12$ (No. 96). The array of molecules built by the CH–π interaction along the *c*-axis forms an enantiomeric helical superstructure in each individual crystal. The absolute configurations of the chiral crystals of 2 were determined by X-ray crystal structure analysis using the Flack parameter method. The solid-state CD spectra of the chiral crystals in KBr were mirror images. The equilibrium between the two enantiomers in solution is fast during crystallization at ambient temperature, and the energy barrier ($\Delta G^{\ddagger}$) is estimated to be 11.7 ± 0.3 kcal/mol (233 K).

The spontaneous resolution of an achiral compound on crystallization in the absence of any chiral source is of great interest, for example, in the field of absolute asymmetric synthesis in the solid state[1] and especially in connection with the origin of homochirality of life.[2] Formation of chiral crystals of a compound without any stereogenic element (chiral center, axis, or face) is rare. However, some compounds having various functional groups or analogous bimolecular combinations do crystallize as chiral crystals in high ratio.[3] In the course of our investigation of such spontaneous resolution of various amides, we found that *o*-phenylenediamine derivatives such as 1,2-bis(*N*-benzoyl-*N*-methylamino)benzene (**1**)[4] afford chiral crystals in an unusual ratio. In this paper, we report that 1,2-bis(*N*-benzenesulfonyl-*N*-methylamino)benzene (**2**) afforded chiral crystals which consisted of a single enantiomer arranged in

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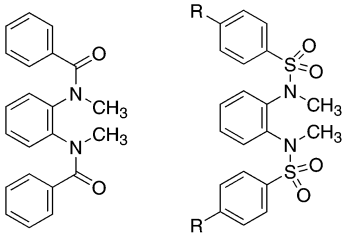
Table 1. Crystal Data for *M*-**2**, *P*-**2**, and **3**

crystal	*M*-**2**	*P*-**2**	**3**
formula	$C_{20}H_{20}O_4N_2S_2$	$C_{20}H_{20}O_4N_2S_2$	$C_{22}H_{24}O_4N_2S_2$
mol wt	416.51	416.51	444.56
crystal system	tetragonal	tetragonal	orthorhombic
space group	$P4_12_12$	$P4_32_12$	*Pbcn*
a (Å)	8.478(1)	8.475(1)	11.994(3)
b (Å)	8.478(1)	8.475(1)	11.904(3)
c (Å)	27.182(2)	27.185(1)	15.388(3)
V (Å^3)	1953.6(5)	1952.7(4)	2197.2(9)
$D\chi$ (Mg m^{-3})	1.416	1.417	1.344
Z	4	4	4
no. reflns used	1144	1217	2178
$R[I > 0.00\sigma(I)]$	0.050	0.051	0.073
$Rw[I > 0.00\sigma(I)]$	0.072	0.062	0.084
Flack param for $P4_12_12$	0.000698 (0.041448)	1.063694 (0.042455)	–
Flack param for $P4_32_12$	0.999296 (0.041448)	−0.063699 (0.042455)	–
CCDC No.	217006	217005	217007

a helical manner, in contrast to the racemic crystal of 1,2-bis(*N*-4-toluenesulfonyl-*N*-methylamino)benzene (**3**).



1

	R
2	H
3	CH_3

The sulfonamides **2** and **3** were prepared by condensation of *o*-phenylenediamine and the corresponding sulfonyl chloride, followed by *N*-methylation using CH_3I/NaH. Recrystallization of **2** from ethyl acetate afforded colorless prisms with space group $P4_12_12$ or $P4_32_12$ (orthorhombic), which are enantiomeric, in X-ray crystallographical analysis (Table 1). The absolute configuration in each crystal could be determined from the Flack parameter.[5] An ORTEP drawing of the sulfonamide **2** with a $P4_12_12$ unit cell is shown in Figure 1a. The chirality of the crystals of **2** was derived from the assembly of a single enantiomer of the molecule into the unit cell, and the conformational chirality was based on atropisomerism around two Ar−N bonds. The $P4_12_12$ or $P4_32_12$ crystals contain a folded C_2-symmetrical (*R*,*R*)- or (*S*,*S*)-conformer, respectively (Figure 2a). Compared to the planar cis (*E*) conformations of most aromatic *N*-methylated amide bonds, as observed in the crystal structure of **1** with (*R*,*R*)- or (*S*,*S*)-conformation, the sulfonamide bonds were chiral synclinal (Figure 2b), and the torsion angles of the sulfonamide moiety [C(Ar)−S−N−C(Ar)] are −78.0(3) ($P4_12_12$) and +78.1(2) ($P4_32_12$). Interestingly, the sulfonamide **3**, a tosyl analogue of **2**, was crystallized from ethyl acetate to give racemic crystals with space group *Pbcn* (Table 1, Figure 1b). The conformation of **3** in the racemic crystals is similar to that of **2**, and the two enantiomers (torsion angle

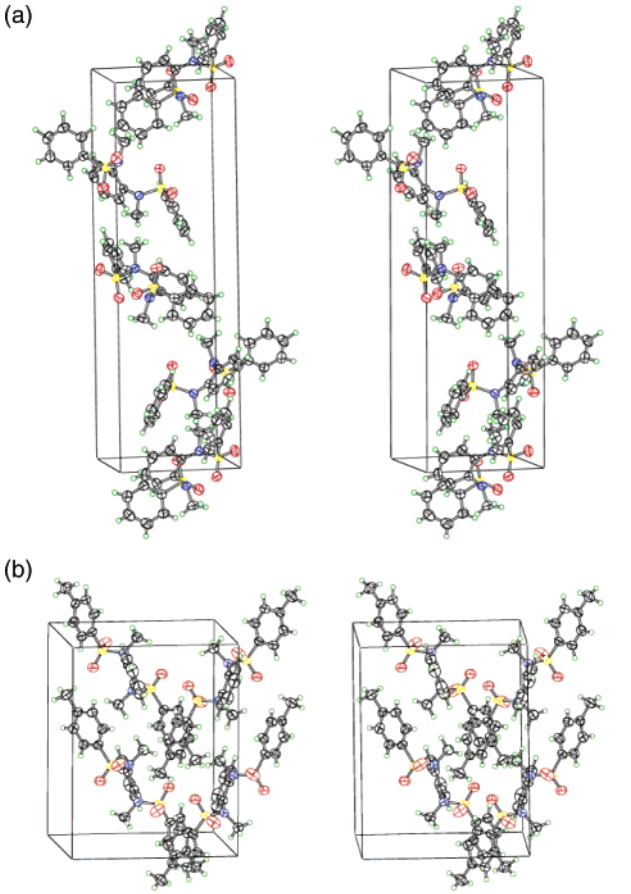


Figure 1. ORTEP stereoviews of the crystal structure of (a) compound **2** (*P*-**2**: $P4_32_12$, chiral) and (b) compound **3** (*Pbcn*, racemic). The thermal ellipsoids are drawn at the 50% probability level.

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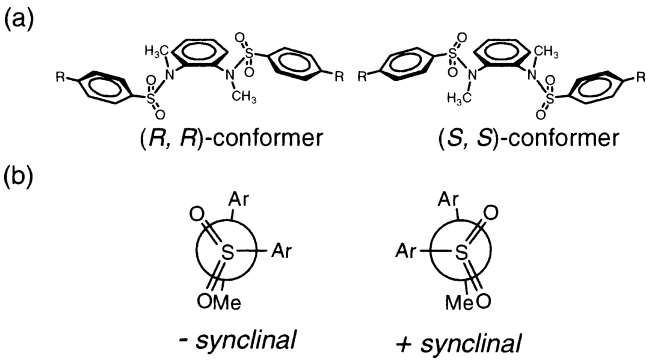

Figure 2. (a) Conformations of the two enantiomers of the sulfonamides and (b) ±synclinal conformations around the sulfonamide bond.

of C(Ar)−S−N−C(Ar) ±89.5(2)°) exist in a 1:1 ratio in the unit cell.

In the packing structures of **2**, one enantiomer was piled along the *c*-axis with successive rotations by one-fourth in the unit cell, and the molecular arrangement showed a beautiful left-handed (*M*-**2**) or right-handed (*P*-**2**) helix in the chiral crystal of $P4_12_12$ or $P4_32_12$, respectively (Figure 3). On the other hand, the two enantiomers of the sulfonamide **3** alternated linearly along the *c*-axis in the racemic

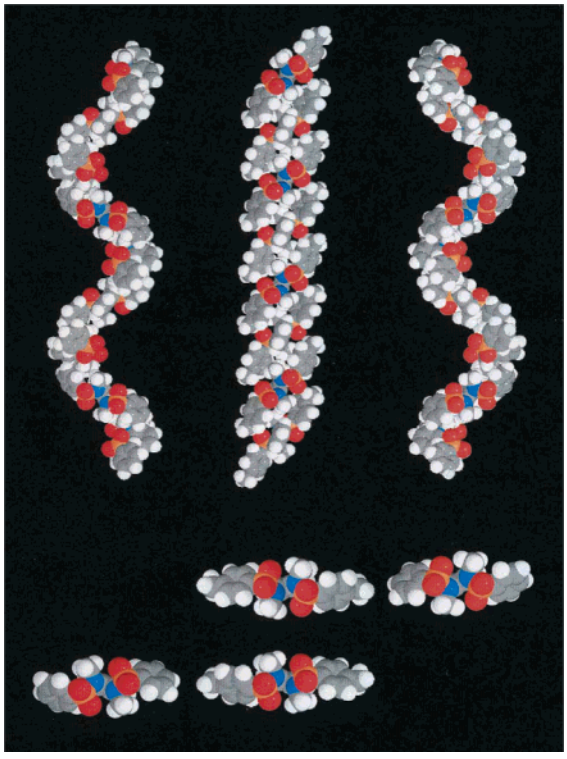

Figure 3. Space-filling plots of the molecular arrays along the *c*-axis in the crystal of *M*-**2** (left), *P*-**2** (right), and **3** (middle). The molecules at the bottom show the conformations of which each molecular array consists.

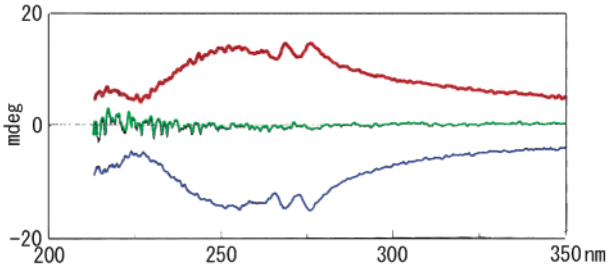

Figure 4. CD spectra of two enantiomeric crystals of **2** (*M*-**2**, red line; *P*-**2**, blue line) and **3** (green line) in KBr. A mixture of 8 μg of each crystal and 100 mg of KBr was ground well and formed into a transparent disk with a radius of 5 mm.

crystals. Since the distance between the terminal phenyl ring (*Ar*-SO_2) and the carbon atom of the *N*-methyl group in the adjacent molecule was 3.3 Å both for the chiral crystal of **2** and the racemic crystal of **3**, CH−π interaction between adjacent molecules may exist in both the helical and straight molecular arrangements.

Solid-state CD spectra[6] were measured in a KBr matrix for *P*-**2** and *M*-**2** and **3** (Figure 4), as well as for compounds that crystallize as chiral crystals.[3,4] Mirror-image CD spectra were obtained for the two chiral crystals, and no CD peak was obtained for a racemic crystal of **3**. Characteristic vibration structures were observed at 275 and 268 nm and a broadened peak at around 245 nm in the CD spectra of *P*-**2** and *M*-**2**. A linear relation between the concentration and the intensity of ellipticity was seen at concentrations below 80 μg/100 mg KBr in the tablet.

The sign of the Cotton effect of the chiral sulfonamide **2** corresponded to the absolute configuration determined from the Flack parameter in X-ray analysis. The absolute configuration of the crystals with positive sign in the CD spectrum was (*R*,*R*), i.e., space group $P4_12_12$, and that of the crystals with negative sign was (*S*,*S*), which is $P4_32_12$. The sulfonamide was crystallized from various solvents (CH_2Cl_2, $CHCl_3$, ethyl acetate, ethanol, methanol, toluene) to give chiral crystals. Whereas the amide **1** afforded chiral and racemic crystals on recrystallization from dry and wet solvents, respectively,[4] the crystallization of **2** from water−saturated ethyl acetate or aqueous ethanol also gave chiral crystals.

The equilibrium between the two enantiomeric conformers is fast in solution, since no CD peak was observed when a chiral crystal of **2** was dissolved in various solvents. The ^{1}H NMR spectrum of **2** afforded a single set of peaks even at low temperature, and no separation of peaks corresponding to each enantiomeric conformation of **2** was observed when chiral 1,1-bi-2-naphthol was added as a chiral shift reagent.[4] To estimate the energy barrier to racemization of the sulfonamide **2** in solution, 2,3-bis(*N*-benzenesulfonyl-*N*-methylamino)-5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene (**4**) was synthesized and dynamic ^{1}H NMR measurement of **4** was performed. Compound **4** has two kinds of benzylic

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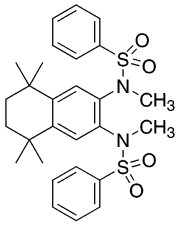
methyl groups that should be observed as different peaks if racemization between the two enantiomeric conformers is slow enough. Actually, coalescence of the peaks was observed at 233 ± 5 K and the energy barrier ($\Delta G^{\ddagger}$) calculated from the temperature and the chemical shift difference ($\Delta\nu$ = 20 Hz) of the peaks of methyl groups observed at lower temperature than T_c was 11.7 ± 0.3 kcal/mol (at T_c).[7] The energy barrier was lower than that of the chiral amide **1** ($\Delta G^{\ddagger}$ = 16.3 kcal/mol at 233 K).[4] This means the racemization is fast at ambient temperature and the chirality is fixed into the crystal only at the stage of crystallization.

We present an example of chiral transformation of a sulfonamide during crystallization. The molecules are arranged in a chiral helix with a single chirality in the crystal through CH-π interaction, though the molecule exists in fast equilibrium between the two enantiomers in solution. This phenomenon should shed light on the mechanisms involved in the initial stage of a chiral arrangement, that is, generation of optical activity by spontaneous resolution in crystals.



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Supporting Information Available: Spectral data for sulfonamides **2**−**4** and the synthetic procedure and dynamic ^{1}H NMR spectra of compound **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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