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Spontaneous Resolution of Aromatic Sulfonamides: Effective Screening Method and Discrimination of Absolute Structure

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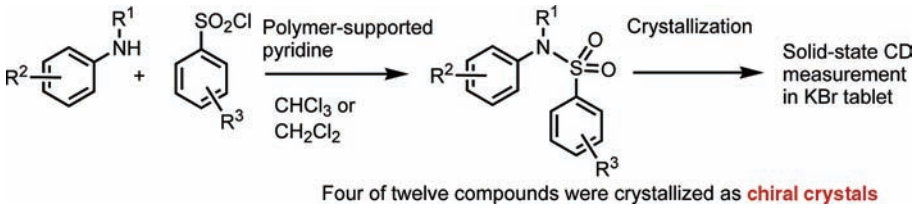
ABSTRACT



An effective screening method combining parallel synthesis and solid-state CD measurements was established to identify achiral aromatic sulfonamides that show spontaneous resolution with rapidity. We found that 4 of the 12 achiral sulfonamides crystallized as chiral crystals through this method. The chirality of each sulfonamide was discriminated by solid-state CD spectra and Flack parameter in an X-ray analysis. Correspondence between the observed Cotton effect and the absolute configuration could be confirmed by time-dependent DFT calculations.

The spontaneous resolution of an achiral compound (total asymmetric transformation) has been of great interest in connection with the origin of life.[1] This phenomenon also holds potential in that the spontaneously resolved chiral crystals could find application as chiral sources in asymmetric synthesis to produce compounds with fixed chirality. In this point of view, several approaches have been successful. For example, a photoreaction in the chiral crystalline state of achiral compounds produced high enantioselectivities.[2] Conformational chirality, which is retained when chiral crystals are dissolved at low temperature, has been utilized in

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diastereoselective syntheses.[3] Another approach is to utilize the spontaneously resolved chiral crystals as catalytic ligands to produce chiral compounds with fixed chirality.[4] Such an approach, however, is limited mainly because the spontaneous resolution of an achiral compound does not occur so frequently. During the course of our study on the stereochemistry of aromatic amides or sulfonamides,[5,6] we found that several groups of compounds with a common skeleton showed spontaneous resolution more frequently than other achiral compounds.[6] In this context, the development of a rapid screening method for spontaneous resolution would provide new insights into the field of asymmetric or diastereoselective synthesis. In this paper, we report an effective screening method for spontaneous resolution of aromatic sulfonamides, which relies on parallel syntheses and solid-state CD measurements. Furthermore, we also determined the absolute structures of several sulfonamides by X-ray crystallographic analysis, and showed that the corresponding CD spectra calculated from the absolute structures with the time-dependent DFT method[7] were consistent with the observed solid-state CD spectra.[8]

A schematic representation of the screening method for spontaneous resolution of aromatic sulfonamides is shown in Figure 1. Substituted anilines (0.1 mmol), substituted sulfonyl chlorides (0.1 mmol), and polymer-supported pyridine (5 equiv) in 1.0 mL of solvent (dichloromethane or chloroform) were mixed together and stirred until the reaction was complete. The polymer-supported pyridine was filtered off and the filtrate was evaporated to give single crystals, or slowly evaporated with stirring to give powder-like microcrystals of the corresponding sulfonamides. The sulfonamide crystals were ground together with KBr and pressed under reduced pressure to give a transparent discotic tablet (10-mm diameter). Then, solid-state CD spectra of the discotic tablets were measured.

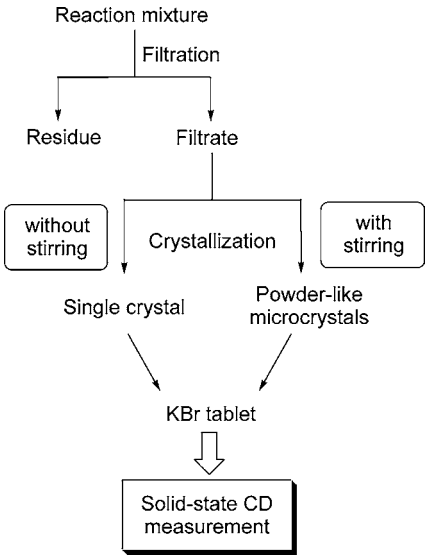

Figure 1. Procedure for rapid screening of sulfonamides showing spontaneous resolution.

Practically, the weight of crystal needed for solid-state CD measurement is 50−200 μg per KBr tablet (100 mg of KBr). When the weight of a single crystal is less than 50 μg, the overall mass of microcrystals obtained by slow evaporation of the solvent with stirring can be used. As a matter of course, all molecules in a spontaneously resolved single crystal have the same chirality. In addition to this, the entire number of microcrystals formed in a flask obtained by slow evaporation of the solvent with stirring tends to have high enantiomeric purity, because the chirality of the first generated crystal seed diffuses throughout the whole flask during stirred crystallization (see ref 9).

The developed procedure was performed for the following 16 combinations including aniline, *N*-methylaniline, 4-methoxyaniline, and 4-nitroaniline as amines, and benzenesulfonyl chloride, 4-methoxybenzenesulfonyl chloride, 4-nitrobenzenesulfonyl chloride, and mesitylenesulfonyl chloride as acid chlorides. 4-Nitroaniline did not react with sulfonyl chlorides because of the low nucleophilicity at the nitrogen atom, even when the reaction mixture was heated at reflux in chloroform. Four of the twelve sulfonamides (**1**, **2**, **3**, and **4**) revealed Cotton effects in the corresponding CD spectra (Table 1). Surprisingly, compound **4**, which showed Cotton effects, was previously reported to crystallize as achiral crystals by another group.[10b]

Next, those sulfonamides which showed spontaneous resolution were synthesized in large quantities by using a general method. Compounds **1**, **2**, and **3** were crystallized from chloroform to give prismatic single crystals. Each

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Table 1. Results of the Rapid Screening for Spontaneous Resolution (Optical Activity Seen in the CD Spectra) of Aromatic Sulfonamides

sulfonyl chloride / amine	SO_2Cl	SO_2Cl, OCH_3	SO_2Cl, NO_2	SO_2Cl
NH_2	**1** Active	**2** Active	Inactive	Inactive
H, N, CH_3	Inactive	Inactive	Inactive	**3** Active
NH_2, H_3CO	Inactive	**4** Active	Inactive	Inactive

crystal was then divided, and a single piece was ground with KBr to give discotic samples for solid-state CD analysis. Tablet preparation was repeated for each crystal until suitable mirror-imaged CD spectra of both enantiomeric crystals were obtained for each compound. Figure 2a−c shows the CD spectra of spontaneously resolved chiral crystals of sulfonamides **1**, **2**, and **3**. The crystals of compound **4** did not show any Cotton effect contrary to the result of our rapid screening method. Therefore, several recrystallizations under slow evaporation with stirring were performed in order to obtain both (+) and (−) CD spectra (Figure 2d).

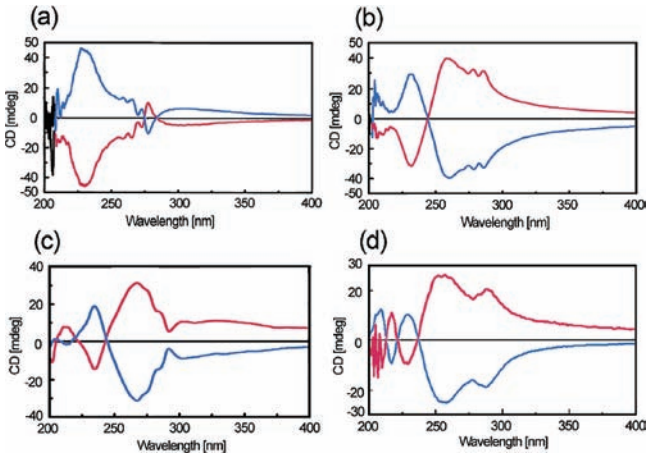

Figure 2. Solid-state CD spectra of enantiomeric crystals (in KBr) of sulfonamides (a) **1**, (b) **2**, (c) **3**, and (d) **4**.

X-ray crystallographic analyses of a pair of enantiomeric crystals of compounds **1**−**3** were performed and each enantiomer was discriminated according to the Flack parameter method.[11] Thus, the sign of the Cotton effect could be related to the absolute structure for compounds **1**−**3** (red line: +synclinal; blue line: −synclinal in Figure 2a−c). Conformations of the enantiomers of sulfonamides **1**, **2**, and **3** in the crystals are shown in Figure 3. Both secondary and

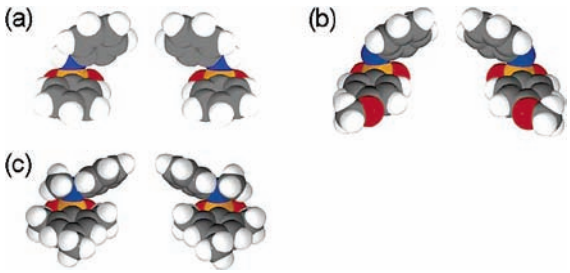

Figure 3. Conformations of each enantiomer (left: +synclinal; right: −synclinal) of sulfonamides (a) **1**, (b) **2**, and (c) **3** in the crystals.

tertiary sulfonamides exist in the synclinal conformation, as well as the related aromatic sulfonamide derivatives so far reported[6d,12] (Table 2). The +synclinal and −synclinal

Table 2. Torsion Angle (deg) of Ar−N−S−Ar in the Crystal of Compounds **1**−**3**

	1	**2**	**3**
+synclinal	58.15	72.52	83.09
−synclinal	−58.44	−72.44	−83.25

conformations are enantiomeric to each other. In the case of the spontaneous resolution of secondary sulfonamides (**1** and **2**), infinite chained structures were formed through hydrogen bonds between the conformers, with a single chirality along either the *b*-axis (compound **1**) or *a*-axis (compound **2**) observed in the crystal.

No remarkable intermolecular interaction was observed in the chiral crystal of the tertiary sulfonamide **3**, and the single enantiomeric conformer was just packed into the unit cell. The crystal of compound **4**, obtained through a typical recrystallization method, belongs to the achiral space group $P2_1/c$ and shows a melting point of 93 °C, properties which are intrinsically the same as those previously reported by other groups.[10] On the other hand, the crystal of compound **4** that showed Cotton effects in the solid-state CD spectra was observed to melt at 99 °C, which is apparently different from that of the achiral crystal. Moreover, crystals obtained through the melt-solidification of achiral crystals showed Cotton effects and revealed a melting point of 99 °C. This means that compound **4** exhibits crystal polymorphism, showing both chiral and achiral forms.[5f,13]

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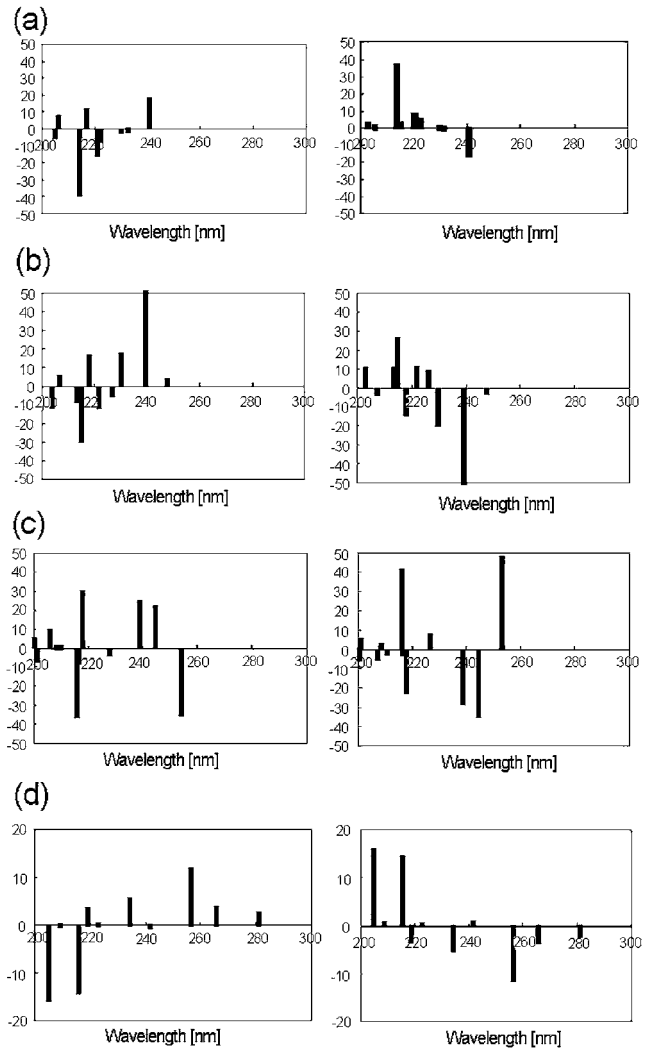

Figure 4. Predicted CD spectra (left: +synclinal; right: −synclinal) of compounds (a) **1**, (b) **2**, (c) **3**, and (d) **4**, calculated by the time-dependent DFT method (B3LYP/6-31G*), using the geometries obtained from the corresponding crystal structures (a−c) or B3LYP-optimized structures (B3LYP/6-31G*) based on typical synclinal conformations (d). Rotational strengths are given in cgs (10^{-40} erg esu cm/G).

Time-dependent (TD) DFT calculations were performed to predict the solid-state CD spectra of **1**−**4**. First, CD spectra of each enantiomer of sulfonamides **1**−**3** were calculated by using coordinate data determined by X-ray crystallographic analysis. Figure 4a−c shows the calculated CD intensities of compounds **1**−**3**. The sign of the Cotton effect in the predicted spectra correlated with that of the Cotton effect in the observed solid-state CD spectra, taking into account the general tendency of UV absorption red-shifts in the solid-state compared to that in the solvent.[14] For example, in both the +synclinal and −synclinal crystals of compound **1**, the Cotton effect sign occurred around 220 nm in the predicted spectra (Figure 4a), corresponding to that in the observed spectra (Figure 2a).

The TD-DFT calculations of compound **4**, the absolute structure of which was not determined by X-ray analysis, were performed on the basis of the structure of the B3LYP-optimized geometry constructed from the coordinates of the analogue. The Cotton effect sign occurred around 260 nm in the predicted spectra (Figure 4d), corresponding to that in the observed spectra (Figure 2d) in the +synclinal and −synclinal conformations. Thus, the red and blue CD spectra in Figure 2d are expected to correspond to the +synclinal and −synclinal conformations, respectively.

In conclusion, we established a rapid screening method for the spontaneous resolution of aromatic sulfonamides, and reported that four achiral sulfonamides gave chiral crystals, as confirmed by solid-state CD measurements and X-ray crystallographic analysis. In addition, we determined the absolute structure of these sulfonamides based on the Flack parameter method and a comparison of the observed solid-state CD spectra with the corresponding predicted spectra calculated with the TD-DFT method. We believe that our proposed method will help design asymmetric or diastereoselective syntheses with use of spontaneously resolved chiral crystals as a chiral source because it has become easy to find spontaneously resolved compounds which have a small or moderate energy barrier in racemization, that is, will be utilized as a chiral source, by being dissolved in a solvent at low temperature, in a two-phase reaction where the chiral crystals remain undissolved, or after UV irradiation to fix the chirality by covalent bonds.

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Supporting Information Available: Synthetic procedure, spectral data and crystallographic information for sulfonamides **1**−**4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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