

Discovery of a Solid Solution of Enantiomers in a Racemate-Forming System by Seeding

Jun Huang,[†] Shuang Chen,[†] Ilia A. Guzei,[‡] and Lian Yu^{*†}

Contribution from the School of Pharmacy, University of Wisconsin—Madison, Madison, Wisconsin 53705, and Department of Chemistry, University of Wisconsin—Madison, Madison, Wisconsin 53706

Received May 17, 2006; E-mail: lyu@pharmacy.wisc.edu

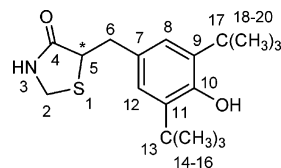
Abstract: A racemic liquid of opposite enantiomers usually crystallizes as a racemic compound (racemate), rarely as a conglomerate, and even more rarely as a solid solution. We discovered a Type II solid solution (mixed crystal) of the enantiomers of the chiral drug tazofelone (TZF) by seeding its racemic liquid with enantiomerically pure crystals (enantiomorphs). Without seeding, the racemic liquid crystallized as a racemic compound. The crystal structure of this solid solution resembles that of the enantiomorph but has static disorder arising from the random substitution of enantiomers. This solid solution is a kinetic product of crystallization made possible by its faster growth rate compared to that of the competing racemate (by 4- to 40-fold between 80 and 146 °C). The free energy of the solid solution continuously varies with the enantiomeric composition between those of the conglomerate and the racemates. The existence of the TZF solid solution explains the absence of eutectic melting between crystals of different enantiomeric compositions. The ability of TZF to simultaneously form racemate and solid solution originates from its conformational flexibility. Similar solid solutions of enantiomers may exist in other systems and may be discovered in similar ways. The study demonstrates the use of cross-nucleation for discovering and engineering crystalline materials to optimize physical properties.

Introduction

Crystals of chiral molecules are important for understanding chiral resolution by crystallization and structure–property relations in molecular solids.^{1–3} According to how its racemic liquid crystallizes, a chiral molecule can be described as a racemate-former, if the product is a crystal containing both enantiomers in the unit cell related by symmetry (racemic compound or racemate); a conglomerate-former, if the product is a physical mixture of enantiomerically pure crystals; or a solid-solution-former, if the product is a crystal in which the enantiomers are randomly distributed. For reasons still poorly understood, most chiral molecules are racemate-formers, few are conglomerate-formers, and even fewer are solid-solution-formers.¹ We report here that tazofelone (5-[(3,5-di-*tert*-butyl-4-hydroxyphenyl)methyl]-1,3-thiazolidin-4-one, TZF, Chart 1), a chiral drug for treating inflammatory bowel diseases and a racemate-former,⁴ can crystallize from a racemic liquid as a solid solution if seeded with enantiomerically pure crystals.

The racemic liquid of TZF crystallizes spontaneously as one of two racemates, RCI and RCII, which are related enantiotropically (RCII is more stable below 138 °C and RCI is more stable above 138 °C).⁴ An enantiomerically pure liquid of TZF

Chart 1. Tazofelone with Atom Numbering



(*R* or *S*) crystallizes as an enantiomorph (AR or AS). RCI and RCII are more stable than a conglomerate of AR and AS at any temperature. The building unit of RCI and RCII is an amide–amide hydrogen-bonded dimer (Figure 1a), and that in AR or AS is an amide–phenol hydrogen-bonded chain (Figure 1b). To form these different structures, the TZF molecules adopt different conformations: “folded” in RCI and RCII and “extended” in AR and AS.

This study found that, although a racemic liquid of TZF crystallized spontaneously as a racemate, it crystallized as a solid solution when seeded with an enantiomorph. Despite being metastable to the racemates, the solid solution could dominate the crystallization product because it grew faster. This solid solution provides a higher-solubility alternative to the racemate for formulating and delivering TZF. Similar solid solutions may exist in other systems, and perhaps can be discovered in a similar way. The manner in which the TZF solid solution was discovered (seeding racemic liquid with enantiomorph) is a variation of cross-nucleation between polymorphs^{5–7} and suggests that seeding can be used to discover and engineer crystal forms.

[†] School of Pharmacy.

[‡] Department of Chemistry.

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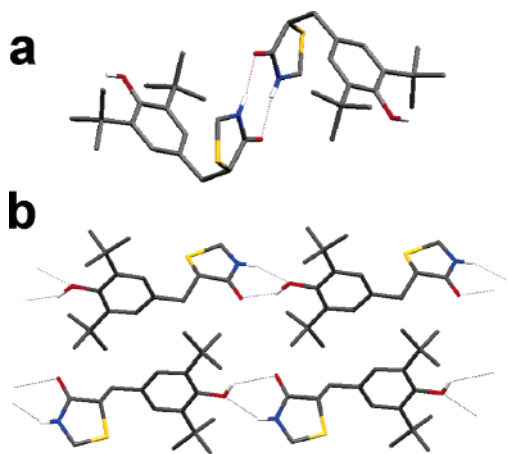


Figure 1. Building units of TZF crystals. (a) Head-to-head H-bonded dimer in RCI and RCII. (b) Head-to-tail H-bonded chains in AR and AS.

Experimental Section

Materials. The racemates and enantiomorphs of TZF were obtained from Lilly Research Laboratories (Indianapolis, IN). Solid solutions of TZF were crystallized by seeding melts of desired compositions with AR at 146 °C. For each run of seeded crystallization, ca. 5 mg of TZF was melted on a microscope cover glass on a hot stage (Linkam THMS 600). The liquid was cooled to a desired temperature and seeded. In top seeding, 0.2–0.3 mg of seeds was sprinkled evenly onto the melt. In side seeding, ca. 0.1 mg of seeds was preheated to the crystallization temperature (equilibrated for 1–2 min on the hot stage next to the liquid) and pushed to the melt with a spatula.

Differential scanning calorimetry (DSC) was performed with a TA Instruments DSCQ1000 calorimeter under a 50 mL/min N₂ purge. Samples were scanned at 0.5, 1, 2, 5, or 10 °C/min in crimped Al pans. The temperature and heat flow were calibrated against indium melting. The data reported were the averages of two or three measurements unless otherwise noted. Estimated standard errors were ±0.05 °C for temperatures and ±0.1 kJ/mol for heats.

Powder X-ray diffractometry (PXRD) was performed with a Bruker D8 Advance X-ray diffractometer, which was equipped with a Cu K α source ($\lambda = 1.54060$ Å) operating at a tube load of 40 kV and 40 mA. The divergence slit size was 1 mm, the receiving slit 1 mm, and the detector slit 0.1 mm. Data were collected by a solid-state (sol-X) detector. Each sample was scanned between 5° and 50° (2 θ), with a step size of 0.02° and a maximum scan rate of 1 s/step.

Crystal Structure Determination. Transparent plates were obtained by seeding racemic melts of TZF with AR at 146 °C. Most crystals examined were twinned. The crystal data were collected at 100 and 296 K on a Bruker CCD-1000 diffractometer with Mo K α radiation ($\lambda = 0.71073$ Å). The initial cell constants were obtained from three series of ω scans at different starting angles. Each series consisted of 30 frames collected at intervals of 0.3° in a 6° range about ω , with the exposure time of 10 s per frame. A total of 124 reflections were obtained. The reflections were successfully indexed by an automated indexing routine built in the SMART program.⁸ The highly redundant data sets were corrected for Lorentz and polarization effects. The absorption correction was based on fitting a function to the empirical transmission surface as sampled by multiple equivalent measurements.⁸ The systematic absences in the diffraction data were uniquely consistent for the space group $P2_1/n$ that yielded chemically reasonable and computationally stable results of refinement.⁸ A successful solution by direct methods provided most non-hydrogen atoms from the E -map. The remaining non-hydrogen atoms were located in an alternating series of least-

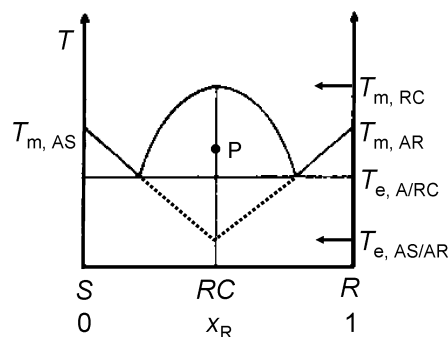


Figure 2. Phase diagram of R and S enantiomers for a racemate-former. P = point of seeding.

squares cycles and difference Fourier maps. All non-hydrogen atoms were refined with anisotropic displacement coefficients. All hydrogen atoms were included in the structure factor calculation at idealized positions and were allowed to ride on the neighboring atoms with relative isotropic displacement coefficients. Atoms C4, C5, and O4 were found to be disordered over two positions, designated (C4, C5, O4) and (C4A, C5A, O4A). The two sets of positions corresponded to the R and S enantiomers of TZF. In solving the structure at 100 K, the positions of the disordered atoms were refined under the following bond-length restraints: C5–S1 = C5A–S1, C5–C4 = C5A–C4A, C4A–O4A = C4–O4, C4A–N3 = C4–N3, C6–C5 = C6–C5A (tolerance = 0.002 Å). In addition, the anisotropic displacement parameters of O4, C4, and C5 were restrained to be the same as those of O4A, C4A, and C5A. The occupancies of the R and S enantiomers were allowed to vary, and they were refined to 56.89(15)% S and 43.11(15)% R . In solving the structure at 296 K, C4, C5, and O4 were refined isotropically, and the occupancies of R and S were constrained to 50%.

Crystal Growth Rate Measurement. Crystal growth rates were measured with a Nikon Optiphot2-Pol microscope equipped with a CCD camera. A 4–5 mg portion of TZF was melted between two cover glasses separated by 150 μ m. Crystal growth was initiated by side seeding. The growth rate was measured from the velocity of advance of the crystal front into the melt at a constant temperature.

Results and Discussion

Absence of Eutectic Melting. For a racemate-forming system, eutectic melting is expected between the racemate RC and the enantiomorph A (=AR or AS) (Figure 2). A mixture of RC and A should show eutectic melting at $T_{e,A/RC}$, below the melting points of RC ($T_{m,RC}$) and A ($T_{m,A} = T_{m,AR} = T_{m,AS}$). TZF is a racemate-former⁴ but showed no such eutectic melting. From standard equations,⁹ the eutectic melting points were estimated to be 142 °C (A/RCI) and 141 °C (A/RCII). But DSC showed no eutectic melting at these temperatures. The first melting endotherm of an RC/A mixture was at 150 °C, the enantiomorph's melting point. Similarly, eutectic melting is expected between AR and AS at $T_{e,AR/AS} = 110$ °C, but the first melting endotherm of their mixture appeared at 150 °C.

To help solve this puzzle, we seeded a racemic melt of TZF at 146 °C with crystals of AR. This temperature and liquid composition correspond to point P in Figure 2, which is above the liquidus lines of AR and AS and below the liquidus line of RC (=RCI or RCII). Under this condition, the AR seed should

(8) SADABS V.2.05, SAINT V.6.22, SHELXTL V.6.10, and SMART 5.622 Software Reference Manuals; Bruker-AXS, Madison, WI, 2000–2003.

(9) The T_e 's are the intersections of the melting-point depression curves of the enantiomorphs, $\ln x = \Delta H_{m,A}/R(1/T_{m,A} - 1/T)$, and of the racemates, $\ln 4x(1-x) = 2\Delta H_{m,RC}/R(1/T_{m,RC} - 1/T)$, where x ($0.5 \leq x \leq 1$) is the mole fraction of the more abundant enantiomer, $T_{m,A}$ and $T_{m,RC}$ are the melting points of A and RC, and $\Delta H_{m,A}$ and $\Delta H_{m,RC}$ are the heats of melting. See ref 1.

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Table 1. Crystallographic Data of SS-0.5 and Other Crystal Forms of Tazofelone^a

	SS-0.5 ^b	SS-0.5 ^c	AS ^d	RCI ^d	RCII ^d
<i>T</i> /K	100	296	293	293	295
space group	<i>P</i> 2 ₁ / <i>n</i> (No. 14)	<i>P</i> 2 ₁ / <i>n</i> (No. 14)	<i>P</i> 2 ₁ (No. 4)	<i>P</i> 2 ₁ / <i>c</i> (No. 14)	<i>Pbca</i> (No. 61)
crystal system	monoclinic	monoclinic	monoclinic	monoclinic	orthorhombic
<i>a</i> /Å	9.2106(7)	9.3882(14)	9.392	11.313	17.204
<i>b</i> /Å	10.9363(7)	10.9503(16)	10.962	17.082	11.287
<i>c</i> /Å	17.6476(8)	17.855(3)	17.823	19.324	18.860
β /°	93.331(2)	93.766(3)	94.29	101.11	90
<i>V</i> /Å ³	1774.64(19)	1831.6(5)	1829.8	3665	3662.2
<i>Z</i>	4	4	4	8	8
ρ_{calc} /g cm ⁻³	1.203	1.166	1.167	1.165	1.166

^a Formula, C₁₈H₂₇NO₂S; MW, 321.47. Error in the last digit is given in parentheses. ^b *R* = 0.0631, *wR* = 0.1542, GOF = 1.012. ^c *R* = 0.1208, *wR* = 0.2757, GOF = 1.408. ^d Ref 4.

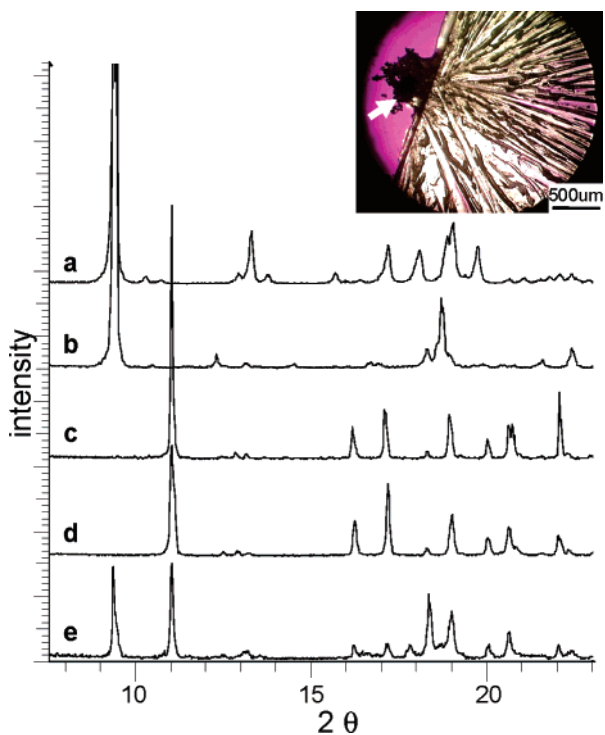


Figure 3. Picture: new growth from a racemic melt of TZF at 146 °C seeded with AR (arrow). PXRD patterns: (a) RCII, (b) RCI, (c) AR, (d) new growth in picture, and (e) new growth after 20 min at 125 °C.

dissolve; the liquid cannot crystallize as AR or AS but can crystallize as RCI or RCII. To our surprise, the AR seeds did not dissolve but induced a new growth (picture in Figure 3). Moreover, PXRD analysis showed that the new growth was not RCI or RCII but had a crystal structure similar to that of AR or AS (Figure 3a–d). After grinding and heating (125 °C/20 min), the new growth showed a PXRD pattern that contained new peaks (e.g., at 9.4° 2θ) assignable to RCI, RCII, or their mixture (Figure 3e). Thus, upon grinding and heating, the new growth converted partially to a racemate. The data did not definitively determine whether the product was RCI, RCII, or their mixture.

Single crystals were isolated from the new growth for analysis by X-ray diffraction. This analysis showed that the new growth was a racemic solid solution of the enantiomers of TZF with static substitutional disorder. We designate this solid solution SS-0.5. Table 1 shows the crystallographic parameters of SS-0.5 and those of AS, RCI, and RCII.⁴ The room-temperature cell constants of SS-0.5 are similar to those of AS, which explains their similar PXRD patterns (Figure 3c,d). The cell constants of SS-0.5 change slightly from 296 to 100 K.

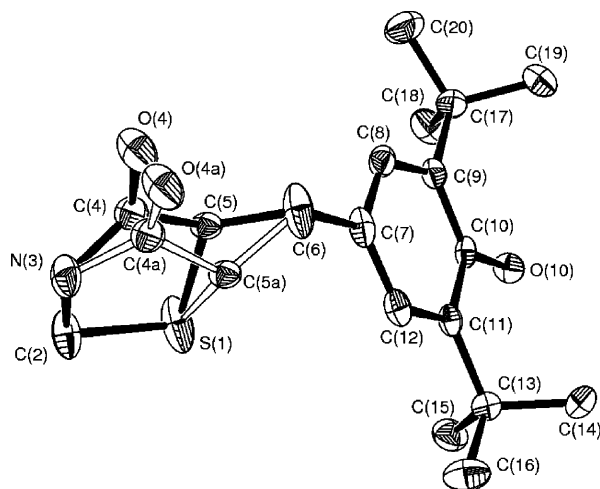


Figure 4. ORTEP drawing of tazofelone molecules in SS-0.5 (structure determined at 100 K, 50% probability ellipsoids). Disorder at C4, C5, and O4 results from random substitution of *R* and *S* enantiomers. The two conformers shown are *R*_A and *S*_B. H atoms are omitted.

Table 2. Torsion Angles (Degrees) and Hydrogen Bond Distances (Angstroms) for Conformers in SS-0.5 and AS^a

	SS-0.5 ^b		AS ^c	
	conformer <i>S</i> _A or <i>mR</i> _A	conformer <i>S</i> _B or <i>mR</i> _B	conformer A	conformer B
S1–C5–C6–C7	−50.1(2)	−33.8(3)	−62.6	−55.9
C5–C6–C7–C8	−90.1(2)	132.0(2)	−82.0	132.3
H-bond	<i>S</i> _A → <i>S</i> _A / <i>R</i> _B <i>R</i> _A → <i>R</i> _A / <i>S</i> _B	<i>S</i> _B → <i>S</i> _B / <i>R</i> _A <i>R</i> _B → <i>R</i> _B / <i>S</i> _A	A→A	B→B
<i>d</i> _{O...O}	2.80	2.64	2.81	2.65
<i>d</i> _{N...O}	2.87	2.87	2.94	2.92

^a *m* = mirror reflection operation. Arrows indicate conformers between which hydrogen bonds are formed. ^b 100 K structure. ^c 293 K structure from ref 4.

The static disorder in SS-0.5 can be represented by atoms C4, C5, and O4 having two possible positions, while the other atoms have single positions (Figure 4). The two sets of positions correspond to the *R* and *S* enantiomers of TZF. The occupancies of the *R* and *S* enantiomers were found to be 43% and 57%, which we took to signify random substitutions of *R* and *S* at each molecular site. The *R* and *S* enantiomers in Figure 4 are not mirror images of each other and are named *R*_A and *S*_B. Table 2 shows the torsion angles (S1–C5–C6–C7 and C5–C6–C7–C8) that distinguish the two enantiomers. By symmetry, a site equivalent to Figure 4 is occupied by *S*_A or *R*_B, where *S*_A is the mirror image of *R*_A and *R*_B is the mirror image of *S*_B. Table 2 shows that conformers *S*_A and *S*_B in SS-0.5 are similar

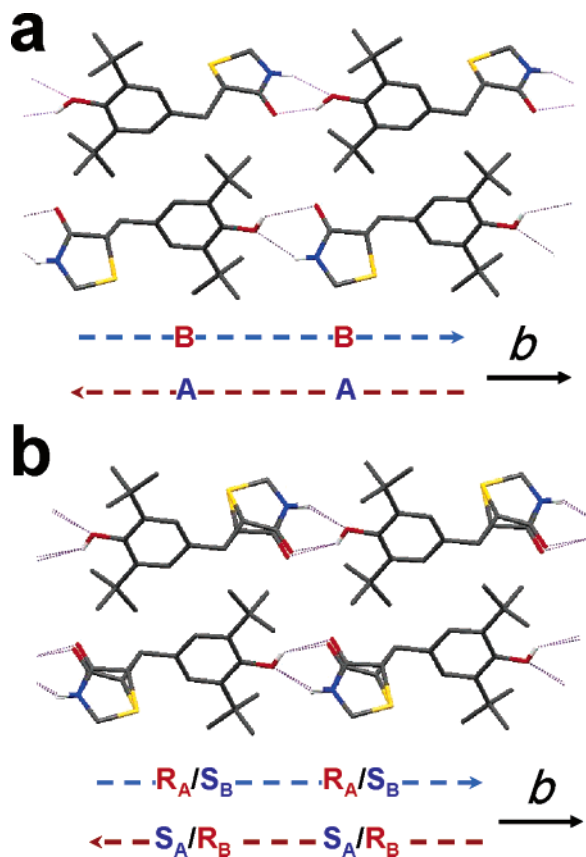


Figure 5. Hydrogen-bonded chains in (a) AS and (b) SS-0.5. The C–H hydrogen atoms have been omitted for clarity. Below each molecular model, a simplified schematic is shown to indicate the directions of H-bonded chains and the constituent molecules. R_A/S_B and S_A/R_B indicate interchangeable molecules at the same site. The opposite running chains are related by pseudo-inversion symmetry.

to (but slightly different from) conformers A and B in AS. By symmetry, conformers R_A and R_B in SS-0.5 are similar to (but slightly different from) the conformers in AR. It is noteworthy that the conformers in SS-0.5, AR, and AS differ significantly from those in the racemates RCI and RCII (Figure 1).⁴ Ab initio calculations showed that the conformers in RCI and RCII are more stable than those in AR and AS.⁴ Despite their conformational differences, the crystal forms of TZF have approximately the same densities at room temperature (Table 1).

It is convenient to describe the molecular packing of SS-0.5 in reference to AS. The AS structure contains opposite-running hydrogen-bonded chains along b (Figure 5a). Each hydrogen bond is an amide–phenol bidentate [graph set notation $R_2^2(6)$]. One chain contains conformer A; the opposite-running chain contains conformer B (Table 2). The SS-0.5 structure also contains opposite-running hydrogen-bonded chains of the same amide–phenol construction, but each chain contains both R and S enantiomers in a random distribution (Figure 5b). One chain contains conformers R_A and S_B ; the opposite-running chain contains conformers S_A and R_B . Despite this randomization of enantiomers, the hydrogen bonds are as efficiently formed in SS-0.5 as in AS (see hydrogen-bond parameters in Table 2). Conceptually, SS-0.5 can be constructed from AS as follows: (i) remove half of the molecules randomly; (ii) adjust the conformations of the remaining molecules to S_A if they reside in A-chains or to S_B if they reside in B-chains; (iii) fill the vacancies in A-chains with R_B in the same head–tail orientation;

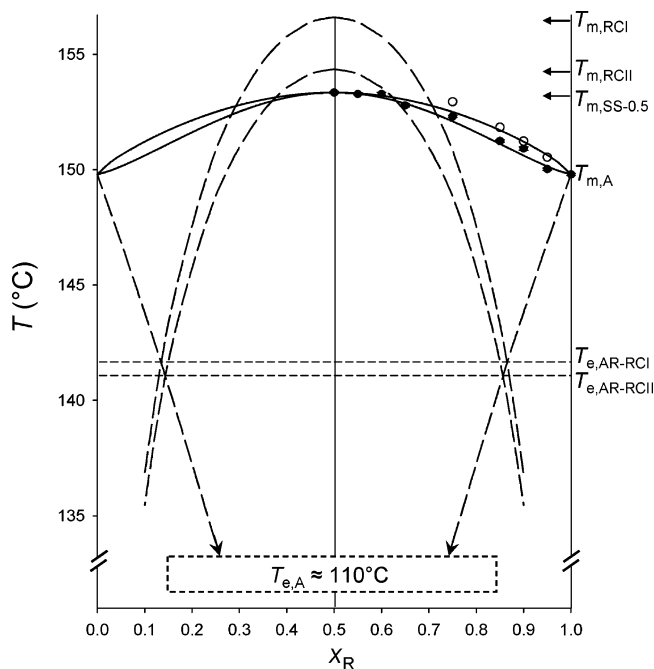


Figure 6. Phase diagram of TZF. Dashed lines: liquidus lines of the enantiomorphs (AR and AS) and racemates (RCI and RCII). Solid lines: melting onsets and ends of the solid solutions.

(iv) fill the vacancies in B-chains with R_A in the same head–tail orientation. The static substitutional disorder in SS-0.5 leads to an apparent centro-symmetry (space group $P2_1/n$), and this symmetry is traced to the pseudo-inversion symmetry of the enantiomorph.

Roozeboom Type. Solid solutions of enantiomers are classified into three types:¹ (I) the melting point of the solid solution, $T_{m,SS}$, is the same as that of the enantiomorph, $T_{m,A}$; (II) $T_{m,SS}$ is higher than $T_{m,A}$, being maximum at the racemic composition ($x_R = 0.5$); and (III) $T_{m,SS}$ is lower than $T_{m,A}$, being minimum at $x_R = 0.5$. Most known solid solutions of enantiomers are Type I, which are often derived from “globular” molecules capable of forming liquid crystals or plastic crystals prior to melting (dynamic disorder).^{1,10} Solid solutions of Types II and III are significantly rarer.^{1,11,12}

Figure 6 (solid lines) shows the phase diagram of the TZF solid solution, which features a maximum melting point $T_m = 153$ °C at $x_R = 0.5$. This solid solution is therefore Type II. For reference, Figure 6 also shows the calculated phase diagrams of the racemic compounds (dashed lines).⁹ The solid-solution phase diagram was constructed from the DSC melting endotherms of TZF solid solutions of different enantiomeric compositions (x_R) (Figure 7). For clarity, Figure 7 shows data for only selected x_R . Figure 6 was constructed from the full set of data. The solidus line was determined from the melting onsets of the solid solutions (solid circles) and the liquidus line from the melting ends extrapolated to zero heating rate (open circles). For the liquidus line, only data for $x_R \geq 0.75$ were used because the solid solution at near-racemic compositions

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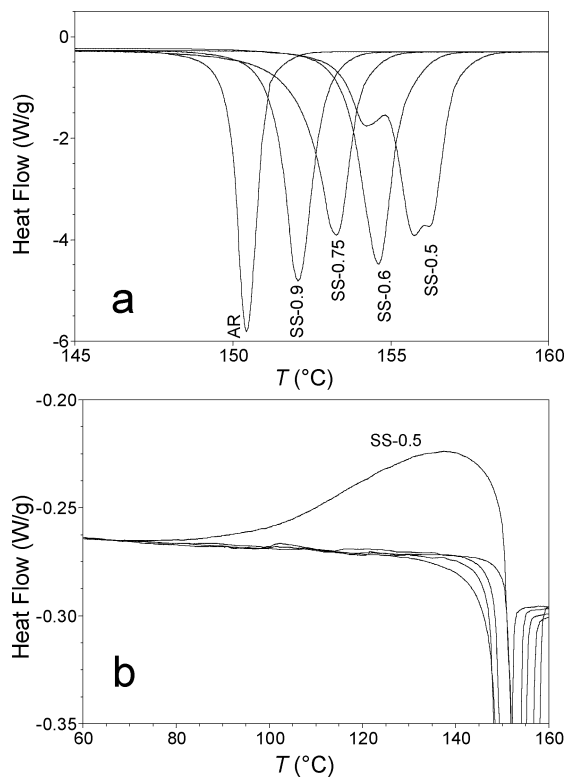


Figure 7. (a) DSC melting endotherms of TZF solid solutions of different compositions. (b) Enlarged view showing partial conversion of SS-0.5 prior to melting.

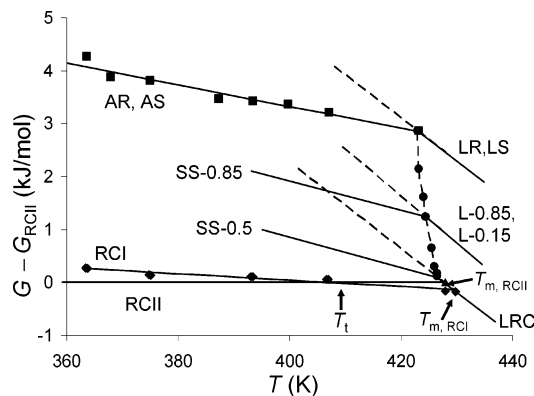


Figure 8. Free-energy differences between TZF phases. LR and LS, liquids of R and S; L- x_R , liquid of composition x_R ; SS- x_R , solid solution of composition x_R . For clarity, only SS-0.5 and SS-0.85 are shown. Circles indicate the $(G_{SS} - G_{RCII})$ values at the solid solutions' melting points.

did not melt congruently and converted partially to the racemates (Figure 7a). The phase diagram for the $0 < x_R < 0.5$ region was obtained by symmetry.

The relatively small difference between the melting points of SS-0.5 and A (3 °C) suggests that the solid solution of TZF enantiomers is approximately ideal, which is consistent with their similar crystal structures. Figure 7b shows that, except at near-racemic compositions, the solid solution was stable to heating (at 5 °C/min), showing its melting point without previously undergoing conversion. The conversion of SS-0.5 during heating (Figure 7b) yielded a racemate (RCI or RCII), as shown earlier (Figure 3e). In the DSC analysis, this conversion was only partial, so the melting point of SS-0.5 was still measurable (see the first endotherm of the SS-0.5 trace in Figure 7a). The conver-

sion was retarded in the presence of excess enantiomers, presumably because they must be removed from the site of conversion.

Free Energies of TZF Solid Solutions Relative to Racemates. Figure 8 shows the free energies of the TZF solid solutions relative to the racemate RCII, $(G_{SS} - G_{RCII})$. SS- x_R indicates a solid solution of enantiomeric composition x_R . For clarity, only the results for SS-0.5 and SS-0.85 are shown, although other results were also obtained (for SS-0.55, -0.6, -0.65, -0.75, -0.9, and -0.95). For those not shown, only the $(G_{SS} - G_{RCII})$ values at the solid solutions' melting points are indicated. $(G_{SS} - G_{RCII})$ was calculated from eqs 1 and 2,

$$(G_{SS} - G_{RC})_{T_{m,SS}} = \Delta H_{m,RC}(T_{m,RC} - T_{m,SS})/T_{m,RC} + \Delta C_{p,RC}[T_{m,SS} - T_{m,RC} - T_{m,SS} \ln(T_{m,SS}/T_{m,RC})] + RT_{m,SS}[\ln 2 + x_R \ln x_R + (1 - x_R) \ln(1 - x_R)] \quad (1)$$

$$(S_{SS} - S_{RC})_{T_{m,SS}} = \Delta H_{m,RC}/T_{m,RC} - \Delta H_{m,SS}/T_{m,SS} + \Delta C_{p,RC} \ln(T_{m,SS}/T_{m,RC}) - R[\ln 2 + x_R \ln x_R + (1 - x_R) \ln(1 - x_R)] \quad (2)$$

where RC refers to RCII, $T_{m,RC}$ and $T_{m,SS}$ are the melting points of RC and SS, respectively, $\Delta H_{m,RC}$ is the heat of melting of RC, and $\Delta C_{p,RC}$ is the heat capacity change upon melting of RC. $\Delta C_{p,RC}$ can be measured by DSC or estimated from $\Delta C_p/\Delta H_m \approx 0.003/\text{K}$.¹³ Equation 1 was used to calculate $(G_{SS} - G_{RC})$ at $T_{m,SS}$, and eq 2 was used to calculate the temperature slope of $(G_{SS} - G_{RC})$ at $T_{m,SS}$ ($dG/dT = -S$ at constant P). Equations 1 and 2 are modified forms of the equations for calculating the free-energy and entropy differences between the racemate and the conglomerate of resolvable enantiomers.¹ They differ from the original equations only in the $[x_R \ln x_R + (1 - x_R) \ln(1 - x_R)]$ term. They are derived using the same method of thermodynamic cycle, except the new cycle contains an additional step that transforms a racemic liquid ($x_R = 0.5$) to a liquid with enantiomeric excess. As in the original derivation, ideal mixing is assumed between the liquids of the opposite enantiomers.

Together, eqs 1 and 2 provided a segment of the $(G_{SS} - G_{RC})$ vs T plot for each solid solution (Figure 8). Although we had carried out eutectic melting for other crystal forms (RCI, AR, and AS) to determine $(G - G_{RC})$ at lower temperatures,¹⁴ we did not do so here because the materials of AR and AS were scarce and because the previously obtained $(G - G_{RC})$ plots were approximately linear. Figure 8 shows that the solid solutions have higher free energies than RCI and RCII but lower free energies than the conglomerate of AR and AS. Among the solid solutions, SS-0.5 has the lowest free energy, and the free energy increases with an increase or decrease of x_R . By symmetry, SS- x_R and SS- $(1 - x_R)$ have the same free energy. The observed variation of the free energy of SS- x_R is well reproduced by the relationship appropriate for ideal solid solutions: $G_{SS} = G_A + RT[x_R \ln x_R + (1 - x_R) \ln(1 - x_R)]$, where G_A is the molar free energy of AR or AS. This near-ideality is in accord with the small change (3 °C) of the solid solution's melting point with x_R and its similar crystal structure as that of the enantiomorph (Figure 5).

Growth Rate of Solid Solution. Figure 9a shows the growth rate of SS-0.5 from a racemic liquid as a function of temperature.

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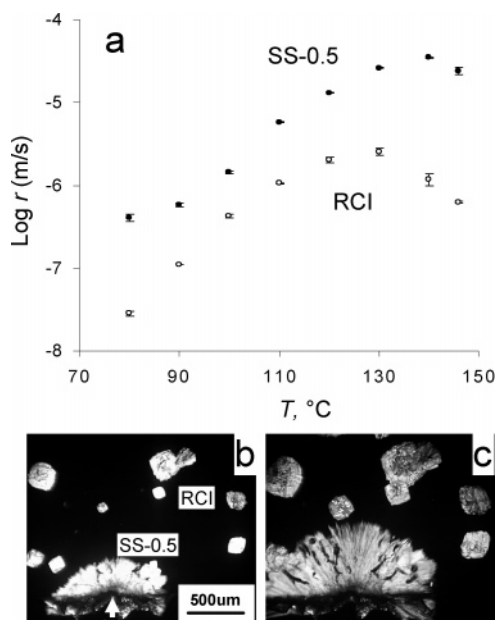


Figure 9. (a) Growth rates of SS-0.5 and RCI. (b,c) Results of seeded crystallization of SS-0.5 and spontaneous crystallization of RCI at 110 °C, (b) soon after seeding (arrow) and (c) 1.0 min after (b).

The growth was initiated by seeding a liquid between two cover glasses from the side (arrow in Figure 9b). For comparison, Figure 9a also shows the growth rate of RCI, which spontaneously crystallized from the same liquid. Throughout the temperature range of measurement, SS-0.5 grew significantly faster than RCI. It is noteworthy that SS-0.5 reached the maximum growth rate near its melting point, but RCI did so at larger undercooling. At 146 °C, SS-0.5 grew 40 times faster than RCI. This difference, combined with the slow spontaneous nucleation of RCI at 146 °C, ensured that we could grow pure SS-0.5 by seeding. At lower temperatures, SS-0.5 still grew faster than RCI, but the difference became smaller. From the limited experiments performed, we found no significant dependence of the solid solution's growth rate on the enantiomeric composition. Seeding at 146 °C was effective for producing a solid solution of any composition. In contrast, deviation from the racemic composition significantly slowed the growth of RCI.

The crystal of SS-0.5 contains hydrogen-bonded molecular chains along b (Figure 5b), which suggests that b is the fast-growing direction. This preferred growth direction was verified by X-ray diffraction. A sample of SS-0.5 grown from a liquid between two cover glasses showed fewer diffraction peaks than a sample of randomly oriented particles prepared by grinding (Figure 10). This showed that SS-0.5 grew along preferred crystallographic directions. The dominant reflections were (101), (202), and (303), which suggests that the preferred growth direction was parallel to (101). Single-crystal X-ray analysis found that SS-0.5 crystals were frequently twinned and the twin planes were parallel to b (Table 3). Thus, we assign the preferred growth direction of SS-0.5 as b . The SS-0.5 growth rates in Figure 9 were measured along b .

Crystallization Experiments. Tables 4 and 5 summarize crystallization experiments performed to characterize the conditions of solid-solution formation. In spontaneous crystallization (Table 4), a racemic melt crystallized only as a racemate, and never as the solid solution. Even with enantiomeric excess (e.g., $x_R = 0.75$), the first and major phase of spontaneous crystal-

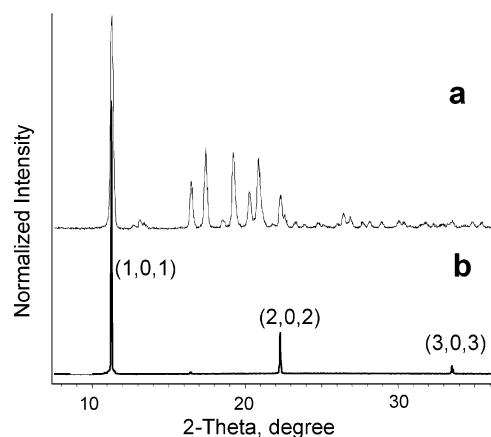


Figure 10. X-ray diffraction patterns of a powder sample (a) and a bulk sample (b) of SS-0.5 grown from a racemic melt at 146 °C. Peaks showing strongest intensities were indexed in (b).

Table 3. Crystal Data Characterizing the Twinning of SS-0.5 Grown from Racemic Melts at 140–150 °C

	T , K	a , Å/ b , Å/ c , Å/ β , °	twin law	rotation, °	twin composition ratio, %
1	100	9.21/10.94/17.65/93.33	$[\bar{1} 0 1]$	180.0	88:12
2	100	9.20/10.92/17.68/93.17	$[1 0 0.29]$	179.9	86:14
2	295	9.39/10.95/17.85/93.77	$[1 0 0.29]$	180.0	86:14
3	100	9.20/10.95/17.70/93.34	$[1 0 \bar{1}]$	179.8	N/A
4	100	9.22/10.94/17.67/93.42	$[1 0 0.29]$	179.9	N/A

Table 4. Products of Spontaneous Crystallization

x_R	T , °C	product ^a
0.5	80, 110, 135	RCI
0.75	60, 146	RCI (incomplete)
0.85	60	RCI, SS (incomplete)
0.85	135	SS
0.9	60	SS

^a Assessed by PXRD and microscopic observations.

lization was RCI, not the solid solution. Only at relatively high enantiomeric purity ($x_R \geq 0.85$) could the solid solution crystallize spontaneously. In seeded crystallization (Table 5), pure solid solutions resulted from liquids of any x_R ($0.5 \leq x_R < 1$) seeded with AR or AS above 140 °C. At 146 °C, seeding an R liquid with AR yielded AR, but seeding an R liquid with AS also yielded AR. Below 140 °C, a racemic liquid seeded with AR or AS yielded a mixture of SS-0.5 and RCI because of the spontaneous crystallization of RCI. Figure 11 shows this competition at 70 °C. Within each method of seeding (top or side), the fraction of SS-0.5 increased with increasing temperature. This temperature dependence resulted because higher temperature reduced the spontaneous nucleation of RCI and increased the difference between the growth rates of SS-0.5 and RCI (Figure 9). Seeding a racemic liquid with RCI or RCII yielded RCI. Excess enantiomers significantly slowed the crystallization of RCI and favored the solid solution (compare the products of the $x_R = 0.5$ and $x_R = 0.6$ liquids top-seeded with AR at 80 °C).

The existence of a solid solution explains the missing eutectic melting between RC and AR and between AR and AS of TZF. Figure 12 shows the DSC traces for a mixture of 50% RCII + 50% AR (bottom) and a mixture of 50% AR + 50% AS (top). No melting endotherm is observed below 150 °C for either

Table 5. Products of Seeded Crystallization

seeds	seeding method	$T, ^\circ\text{C}$	product ^a
$x_R = 0.5$			
AR	top	70	81% SS, 19% RCI
AR	top	80	79% SS, 21% RCI
AR	top	90	84% SS, 16% RCI
AR	side	80	37% SS, 63% RCI
AR	side	90	35% SS, 65% RCI
AR	side	110	53% SS, 47% RCI
AR	side	135	89% SS, 11% RCI
AR	side	140, 146, 150	SS
AS	top	80	80% SS, 20% RCI
RCII	side	80, 110, 146	RCI
RCI	side	110, 146	RCI
$x_R = 0.55, 0.65, 0.75, 0.85, 0.90, 0.95$			
AR	side	146	SS
$x_R = 0.6$			
AR	top	80	96% SS, 4% RCI
AR	side	146	SS
$x_R = 1.0$			
AR	side	146	AR
AS	side	146	AR

^a Assessed by PXRD and microscopic observations. Phase composition was calculated from the relative intensities of PXRD peaks and a one-point calibration using an equal-weight mixture of SS-0.5 and RCI.

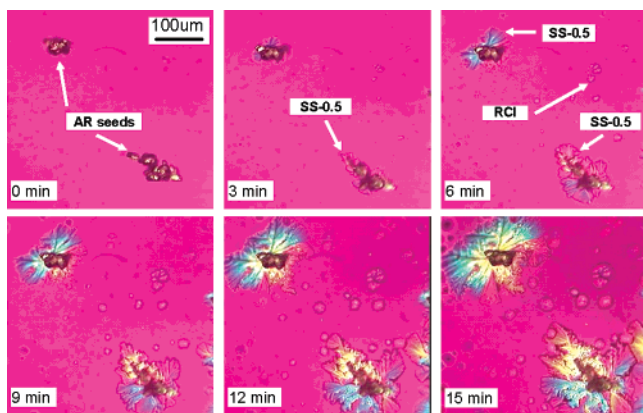


Figure 11. Growth of SS-0.5 from AR seeds at 70 °C. Spontaneous growth of RCI is also shown.

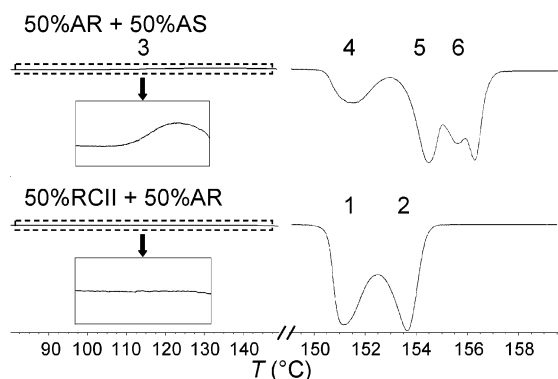


Figure 12. DSC traces of heating a mixture of 50% AR + 50% AS (top) and a mixture of 50% RCII + 50% AR (bottom). Visible thermal events are shown by numbers 1–6.

mixture, even though eutectic melting is expected at 141 and 110 °C, respectively. For the RCII/AR mixture, we interpret the DSC trace as follows. First, eutectic melting occurs near 141 °C at the interface of RCII and AR. The liquid formed is in contact with AR and quickly grows to a solid solution, which

prevents further eutectic melting from occurring. No thermal event is observable near 141 °C because the events of melting and crystallization cancel each other calorimetrically. The first visible event is the melting of AR at 150 °C (Event 1), and the next (Event 2) is the dissolution of RCII and the solid solution.

The DSC trace of 50% AR + 50% AS shows a weak exotherm from 110 to 150 °C (Event 3). We interpret Event 3 as a combined result of the eutectic melting at the AR/AS interface, the growth of the solid solution SS-0.5, and the conversion of the solid solution. The solid solution grows rapidly between AR and AS, blocking further eutectic melting. The conversion of SS-0.5 is already shown in Figure 7b. Event 3 is weak because the endotherm of melting is canceled by the exotherms of solid-solution crystallization and conversion. When the temperature reaches 150 °C ($T_{m,A}$), AR and AS melt (Event 4). From the melt, more solid solution may grow, and the racemates may crystallize. The next endotherm (Event 5) is the melting of the solid solution and conversion to the racemates. Finally, the two racemates melt (Event 6).

This study found that the crystal of a pure enantiomer can nucleate a racemic solid solution of enantiomers. In such a process, the seed and the new growth have different compositions. In most cases examined, the seed is thermodynamically unable to grow and should, in fact, dissolve. For example, as explained with Figure 2, an AR seed placed in a racemic liquid at 146 °C cannot grow as AR. Thus, the nucleation of the solid solution does not require exact compositional matching and may instead result from lattice matching or templating.¹⁵ For TZF, the lattice matching is evident between an enantiomorph and the solid solution of enantiomers from their crystal structures (Table 1).

The cross-nucleation just described is similar to (but distinct from) the cross-nucleation between polymorphs.^{5–7} The latter requires that the initial phase and the new phase have the same composition. One case of cross-nucleation between polymorphs was observed in this study: RCI grew from RCII seeds at 80, 110, and 146 °C. Previous studies^{6,7} identified two kinetic features of cross-nucleation between polymorphs: (i) for cross-nucleation to be observed while the initial polymorph grows, the new polymorph must grow faster than or at least as fast as the initial; (ii) certain polymorphs cannot nucleate without the aid of other polymorphs. These features also characterize the crystallization of the TZF solid solution by cross-nucleation: once nucleated, it can dominate the product because it grows faster than the competing racemate; without seeding, it cannot nucleate spontaneously from a racemic liquid or a liquid of moderate enantiomeric excess. The crystallization of the solid solution of TZF enantiomers on a pure enantiomorph is analogous to the crystallization of DL-alanine on the crystal of D-alanine,¹⁶ although in the alanine case, the DL-crystal is a racemic compound, not a solid solution. The crystallization of R TZF on the seed crystal of S TZF (Table 5, last entry) is reminiscent of chiral twinning,¹⁷ the crystallization of one enantiomorph on the opposite.

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It is rare for a racemic liquid of enantiomers to crystallize as both racemic compound and solid solution,¹ as TZF does. In this behavior, TZF is similar to 2-[4-(3-ethoxy-2-hydroxypropoxy)phenylcarbamoylethyl]dimethylsulfonium *p*-toluenesulfonate.¹² The latter system differs from TZF in that its racemic solution spontaneously crystallizes as a *mixture* of racemic compound and solid solution, whereas only with seeding can the racemic melt of TZF crystallize as solid solution. This seeding approach might be useful for discovering other solid solutions of enantiomers. The discovery of new crystal forms by crystallizing under new conditions is well documented.¹⁸ Solid solutions of enantiomers are potentially useful for drug formulation and delivery because they offer physical properties intermediate between racemic compounds and conglomerates. The ability of tazofelone to form solid solutions of enantiomers results from its conformational flexibility (Figure 1), the ability of an enantiomorph's structure to accommodate the opposite enantiomer (Figure 5), and the fast growth of the solid solution (Figure 9).

Conclusions

By seeding racemic liquids with chiral crystals, we discovered a rare example of a solid solution of enantiomers in a racemate-forming system (tazofelone). This solid solution has static

substitutional disorder and is derived from the enantiomorph's structure by randomly replacing the molecules with the opposite enantiomers while maintaining the hydrogen-bonding network. The free energy of the solid solution continuously varies with the enantiomeric composition between the values of the racemic compounds and the enantiomorphs. The solid solution is a kinetic product of crystallization made possible by its faster growth rate compared to that of the competing racemate RCI. Cross-nucleation between RCI and RCII (two true polymorphs) was observed. The existence of the solid solution explains the missing eutectic melting between TZF crystals of different enantiomeric compositions. Solid solutions of enantiomers are potentially useful for formulating and delivering chiral drugs. Similar solid solutions of enantiomers may exist in other racemate-forming systems and may be discovered in similar ways. This study demonstrates the use of cross-nucleation for discovering and engineering crystal forms to optimize physical properties.

Acknowledgment. We thank the University of Wisconsin–Madison and the Petroleum Research Fund for supporting this work.

Supporting Information Available: Crystallographic data for SS-0.5 (100 K) and SS-0.5 (296 K) (PDF, CIF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

JA063450L

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