Generation and amplification of optical activity of axially chiral *N*-(1-naphthyl)-2(*1H*)-pyrimidinethione by crystallization†

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X-Ray crystallographic analysis of *N*-(1-naphthyl)-2(1*H*)-pyrimidinethione revealed that the space group was tetragonal and chiral $P4_3$. The rate of racemization due to the C–N bond rotation was considerably influenced by the solvent properties. A nonpolar solvent lowers the $\Delta G^{\ddagger}$ value by about 3.0 kcal mol^{-1} relative to the value in a polar or a protic solvent. The crystallization of racemic axially chiral pyrimidinethione at high temperature led to the chiral breaking of symmetry up to 91% ee.

Introduction

The atropisomerism of biaryl molecules has been studied extensively from both theoretical and synthetic perspectives. A rotationally hindered and thus stereogenic biaryl axis is the structurally and stereochemically decisive element of a steadily growing number of natural products, chiral auxiliaries, and catalysts.[1] Much research has prepared optically active biaryl molecules, because axially chiral biarylic auxiliaries and catalysts exhibit especially excellent chirality transfer properties.[2]

In 1971 Pincock *et al.* discovered an elegant methodology in which 1,1′-binaphthyl underwent crystallization induced enantiomer transformation (CIET), the so-called total spontaneous resolution, to generate optically active *S* or *R* enantiomers when crystallized from the melt (Fig. 1).[3]

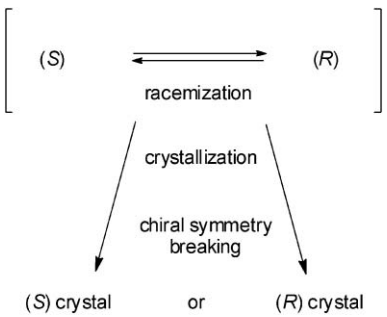


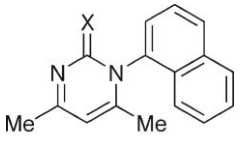
Fig. 1 Generation and amplification of chirality by crystallization of conglomerate crystals.

In 2003, we reported the first example of the chiral symmetry breaking of C–N axial chirality for *N*-aryl-2(*1H*)-pyrimidinones by CIET without any outside chiral source.[4] These *N*-aryl-2(*1H*)-pyrimidinones have stable axial chirality and do not racemize in the solution at room temperature. Now we have found that *N*-(1-naphthyl)-2(*1H*)-pyrimidinethione also gives conglomerate and broke the symmetry of the axial chirality by spontaneous crystallization with higher ees.

Enantioselective symmetry breaking of racemic conglomerates by crystallization has recently emerged as an alternative to the separation of enantiomers. The combination of resolution by crystallization and racemization in solution allows enantiopure compounds to be obtained in quantitative yields. Although many successful examples using the racemization of the α-position of carbonyl or imino groups have been reported,[5] these examples of symmetry breaking for axial chirality are still quite rare, and finding other examples would provide much crucial information for the generation and the amplification of chirality by spontaneous crystallization.[6,7]

Results and discussion

To resolve racemate by CIET, axially chiral materials must crystallize as conglomerates. X-Ray crystallographic analyses of *N*-(1-naphthyl)-2(*1H*)-pyrimidinone **1** and *N*-(1-naphthyl)-2(*1H*)-pyrimidinethione **2** (Fig. 2) revealed that the space group of pyrimidinethione **2** was tetragonal and chiral $P4_3$; but pyrimidinone **1** gave monoclinic and centrosymmetric space group $P2_1/n$ (Fig. 3–5). Each single crystal of **1** is composed of both enantiomers, but pyrimidinethione **2** is conglomerate and a single enantiomer forms each single crystal. This was also confirmed by HPLC analysis using a CHIRALCEL-OD-H column (Daicel Ind.). When one single crystal of pyrimidinone **1** was analyzed by HPLC, two peaks appeared in a 50 : 50 ratio; however, analysis of each single crystal of pyrimidinethione **2** exhibited only one peak of two enantiomers. The polar or the less polar peak appeared randomly. The crystal determined as (*R*)-configuration (Fig. 3(b)) by X-ray analysis showed a polar peak. The $[\alpha]_D^{20}$ value of (*R*)-**2** exhibited +587 ($c = 0.5$ in MeOH).



1: X = O
2: X = S

Fig. 2 Pyrimidinone **1** and pyrimidinethione **2**.

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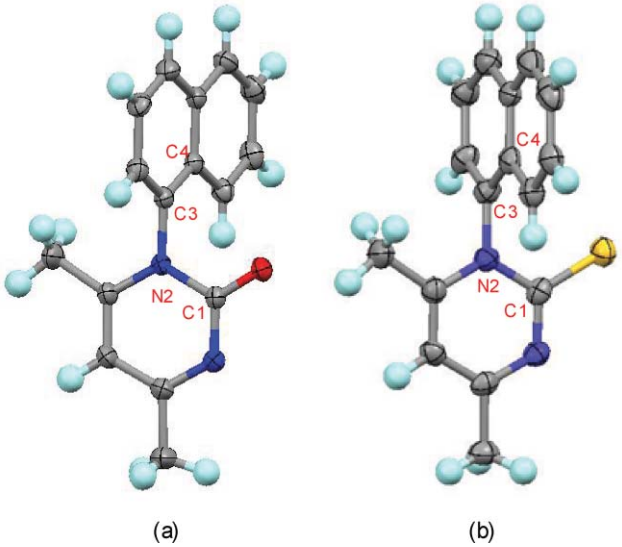


Fig. 3 ORTEP drawing of (a) (*S*)-conformer of *N*-(1-naphthyl)-2(*1H*)-pyrimidinone **1** and (b) the absolute conformation of (*R*)-(+)-*N*-(1-naphthyl)-2(*1H*)-pyrimidinethione **2**. The ellipsoids were presented in 50% probability.

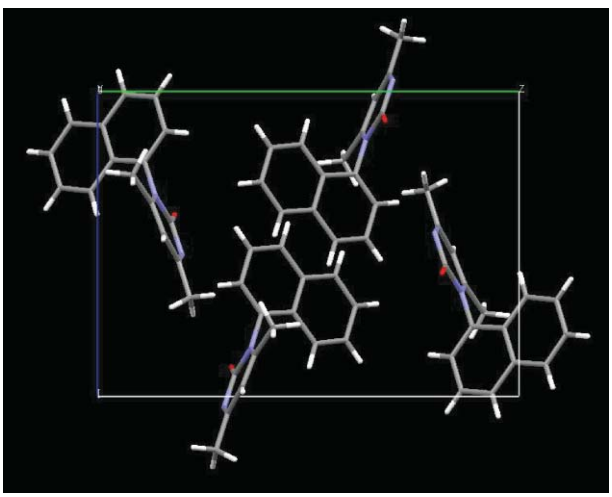


Fig. 4 Packing diagram of **1** in $P2_1/n$ crystal system and a view from the *a* axis.

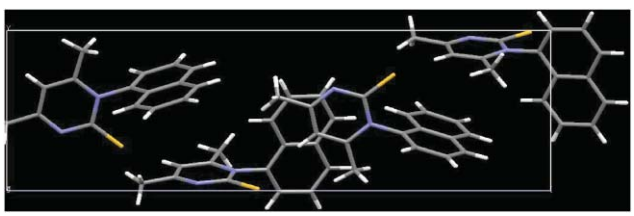


Fig. 5 Packing diagram of **2** in $P4_3$ crystal system and a view from the *b* axis.

The X-ray analyses also revealed the differences of the molecular conformations of **1** and **2**. The two arene planes are almost perpendicular to each other (inter-ring dihedral C1–N2–C3–C4: 70.27° for **1** and 89.14° for **2**) in both cases (Fig. 3). The bond lengths for C═O, C1–N2, and N2–C3 are 1.224, 1.420, and 1.449 Å for **1**, and the bond lengths for C═S, C1–N2, and N2–C3 are 1.683, 1.402, and 1.461 Å for **2**. These crystallographic data suggest that both materials have stable axial chirality, and that racemization due to bond rotation will occur at high temperature (Fig. 6).

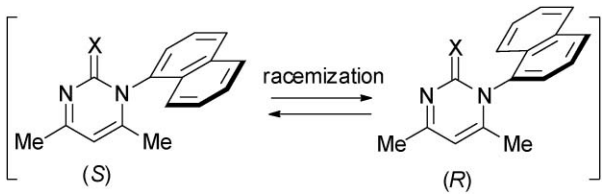


Fig. 6 Racemization of *N*-aryl-2(*1H*)pyrimidinone **1** and pyrimidinethione **2** owing to the C–N bond rotation.

To achieve chiral breaking by crystallization, fast enantiomerization must occur in the crystallization conditions. To estimate the conformational stability of these materials, the rate constants (k_{rot}) and the activation parameters for racemization have been studied.

The rate of racemization of both materials was studied in three kinds of solvents: xylene (less polar and aprotic), dimethylformamide (DMF: polar and aprotic), and 1-propanol (polar and protic). To analyze the racemization of **1**, a resolved enantiomer by HPLC using a CHIRALCEL-OD-H column was used, and the rate of racemization was determined at 85, 90, 95, and 100 °C. On the other hand, an enantiomorphic crystal of **2** obtained from usual crystallization was dissolved in the solvent, and the rate of enantiomerization at 40, 50, 55, and 60 °C was also followed by HPLC. The Arrhenius and Eyring plots have excellent linear relationships. The activation parameters obtained from the plots are listed in Table 1.

The racemization of thione **2** is faster than that of pyrimidinone **1**. The $\Delta G^{\ddagger}$ value for the racemization of **2** was almost the same as that of 1,1′-binaphthyl;[8] however, **1** did not racemize at room temperature. Furthermore, the rate of racemization was considerably influenced by the solvent properties. The half-life ($t_{1/2}$) of **2** at 50 °C in xylene was 4 min but 225 min in DMF and 354 min in 1-propanol. In both cases, the free energy of the activation in a polar solvent is higher than that in a nonpolar solvent. Furthermore, a protic solvent like 1-propanol strongly controls enantiomerization; polarity, hydrogen bonding, and solvation by alcohol are important factors that influence the rate of racemization. A nonpolar solvent lowers the $\Delta G^{\ddagger}$ value by

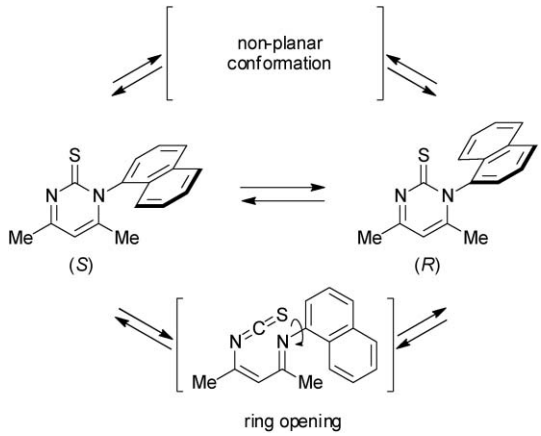
Table 1 Activation parameters for racemization of pyrimidinone **1** and pyrimidinethione **2** under various conditions[a]

Py	Solvent	$t_{1/2}$[b]	E_{rac}[c]	$\Delta G^{\ddagger}$[d]	$\Delta H^{\ddagger}$[e]	$\Delta S^{\ddagger}$[f]
1[g]	Xylene	27	42.8	27.5	42.1	40.0
1[g]	DMF	343	44.6	29.5	43.9	39.6
1[g]	1-PrOH	1562	40.1	30.5	39.4	24.6
2[h]	Xylene	4	28.7	23.1	28.0	15.2
2[h]	DMF	225	31.6	25.8	31.0	16.1
2[h]	1-PrOH	354	31.0	26.1	30.4	13.5

[a] All values include error limit within ±0.1. [b] Half-life in minutes. [c] Arrhenius parameter in kcal mol^{-1}. [d] Activation free energy in kcal mol^{-1}. [e] Activation enthalpy in kcal mol^{-1}. [f] Activation entropy in cal mol^{-1}K^{-1}. [g] Measured at 90 °C. [h] Measured at 50 °C.

about 3.0 kcal mol^{-1} relative to the value in a polar or a protic solvent.

As a mechanism of rotation, the following have been suggested in the literature: a pronounced C–N bond elongation for the transition states[9] and a 3,3-electrocyclic reaction with ring opening and closure. However, a different mechanism, the rotational barrier, was significantly lowered by a pronounced deplanarization of the central pyrimidinone ring, thereby bending the rotating naphthyl ring out of the plane (Scheme 1).[10] This mechanism involving non-planar conformation may contribute to the racemization of **1** and **2**, because the alcohol adduct from the open form could not be obtained. However, a mechanism involving open form could not be perfectly excluded.



Scheme 1 Plausible mechanism for racemization of pyrimidinethione **2**.

For the solvent effects, the solvent polarity may be attributable to the zwitterionic character of the pyrimidine ring, which increases the aromaticity of the pyrimidine ring, maintaining the transition state as more planar.

Next we attempted the induction of asymmetry by the crystallization of pyrimidinethione **2** (Fig. 7). The melting point of **2** is 178–180 °C, which is too high for crystallization without a solvent because **2** gradually decomposed above the melting point and could not be left for a long enough period for solidification at that temperature. Then asymmetric induction by crystallization was examined by removing the solvent from the solution at high temperature with fast racemization.

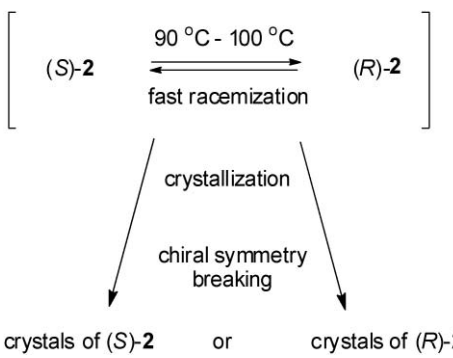


Fig. 7 Crystallization induced enantiomer transformation of **2**.

A mixture of a toluene solution of pyrimidinethione **2** in a test tube was warmed at the range of 90–100 °C with or without vigorous stirring; nitrogen was gradually induced to the top of the test tube. The solvent was gently removed while evaporating at the atmospheric pressure until all solvent was removed to solidify **2**. Then the enantiomeric excesses of the remaining solid were analyzed by HPLC. When a small amount of seed crystals, which powdered a single crystal obtained by standard recrystallization, was used during crystallization, chiral symmetry breaking of the solid was achieved up to 91% ee (Table 2, entry 1). However since it was reported that constant stirring in crystallization effectively produced a large enantiomeric excess,[11] the effect of stirring and seeding on enantiomeric excesses was also examined. Both effects are needed to achieve CIET with reproducible high ees (entries 2 and 3).

Table 2 Chiral breaking of racemic pyrimidinethione **2** by crystallization[a]

Entry	Seeding	Stirring	*ee* (%)
1	Yes	Yes	89–91[b]
2	No	Yes	41–88[c]
3	Yes	No	8–37[b]

[a] Crystallization was tried each five times. Each 50 mg of **2** and 0.5 ml of toluene was used for crystallization. Solvent was removed at the range of 90–100 °C. Pyrimidinethione **2** was quantitatively recovered after crystallization under these conditions. [b] Crystals was obtained with the same direction of optical rotation as the seed crystal. [c] Obtained crystals exhibited the optical rotation randomly.

Furthermore, when the crystals of **2** obtained by CIET were recrystallized from a mixture of ethanol and hexane, 100% ee of pyrimidinethione **2** was obtained. That is, enantiomerically pure, axially chiral **2** could be easily obtained without any chiral source by the twice crystallization process. If seed crystals are used in the crystallization, a large amount of desired enantiomorphic crystals can be prepared selectively (entries 1 and 3).

Conclusions

We provided a new example of symmetry breaking of C–N axially chiral atropisomers by crystallization by evaporating off the solvent at high temperature. Pyrimidinethiones are well-known not only as a derivative of a nucleic acid base but also as pharmacologically active materials. This axially chiral pyrimidinethione should be useful for precursors of various kinds of optically active heterocycles. Furthermore, we believe that this methodology can be applied to resolve many axially chiral compounds.

Experimental

General. NMR spectra were recorded on $CDCl_3$ solutions on a BRUKER 300 operating 300 MHz, respectively, for ^{1}H- and ^{13}C-NMR spectroscopy. Chemical shifts are reported in parts per million (ppm) relative to TMS as internal standards. IR spectra were recorded on a JASCO FT/IR-230 spectrometer as KBr disks. Pyrimidine-2(*1H*)-one **1** and thione **2** were prepared according to the reported procedure.[9]

4,6-Dimethyl-*N*-(1-naphthyl)-2(*1H*)-pyrimidinone (1)

Yellow prismatic crystal from a mixture chloroform and hexane; mp 195.0–195.5 °C; IR (cm^{-3}, KBr) 1658; ^{1}H-NMR: ($CDCl_3$)

δ 1.87 (s, 3H, CH_3), 2.47 (s, 3H, CH_3), 6.28 (s, 1H, –CH=C–), 7.38–7.60 (m, 5H, ArH), 7.91–7.97 (m, 2H, ArH), ^{13}C-NMR: ($CDCl_3$) δ 20.8, 25.9, 105.8, 121.8, 126.0, 126.1, 127.3, 128.2, 129.2, 129.7, 130.2, 134.6, 135.0, 157.4, 158.1, 176.8; HRMS (FAB-MS) m/z calcd for $C_{16}H_{15}N_2O$ (MH^+) 251.1184, found 251.1194.

Crystal data for 1

(Recrystallized from a mixture of EtOH and hexane): Monoclinic, space group $P2_1/n$, a = 7.3179(6) Å, b = 15.6561(13) Å, c = 11.4483(10) Å, β = 103.4610(10)°, V = 1275.60(19) Å^3, Z = 4, ρ = 1.303 Mg m^{-3}; 7048 reflections measured, 2913 unique, R_{int} = 0.0179, in the final least-square refinement cycles on F^2, the model converged to R_1 = 0.0443, wR_2 = 0.1196. CCDC 770678 contains crystallographic data.

(*R*)-(+)-4,6-Dimethyl-1-(1-naphthyl)-2(1*H*)-pyrimidinethione (2)

Yellow prismatic crystal from a mixture of ethanol and hexane; $[\alpha]_D^{20}$ = +563.8° (*S* isomer, 100% *ee*, c = 0.500%, chloroform); m.p. 178–180 °C; IR (cm^{-1}, KBr) 1257; ^{1}H-NMR: ($CDCl_3$) δ 1.92 (s, 3H, CH_3), 2.51 (s, 3H, CH_3), 6.60 (s, 1H, –CH=C–), 7.38–7.63 (m, 5H, ArH), 7.93–7.99 (m, 2H, ArH), ^{13}C-NMR: ($CDCl_3$) δ 22.1, 25.6, 111.4, 121.8, 125.7, 126.4, 127.4, 128.4, 128.5, 129.4, 130.2, 135.1, 138.1, 158.8, 170.4, 185.4; HRMS (FAB-MS) m/z calcd for $C_{16}H_{15}N_2S$ (MH^+) 267.0956, found 267.0962.

Crystal data for 2

(Recrystallized from a mixture of EtOH and hexane): Tetragonal, space group $P4_3$, a = 7.6223(3) Å, b = 7.6223(3) Å, c = 23.186(2) Å, V = 1347.09(14) Å^3, Z = 4, ρ = 1.313 Mg m^{-3}; 7568 reflections measured, 2928 unique, R_{int} = 0.0238, in the final least-square refinement cycles on F^2, the model converged to R_1 = 0.0384, wR_2 = 0.0892. CCDC 770679 contains crystallographic data.

Kinetic studies for racemization of 1 and 2

The rate of racemization of both materials was studied in three kinds of solvents: xylene (less polar and aprotic), dimethylformamide (DMF: polar and aprotic), and 1-propanol (polar and protic). To analyze the racemization of **1**, a resolved enantiomer by HPLC using a CHIRALCEL-OD-H column was used and determined at 85, 90, 95, and 100 °C. Optically active **1** resolved by HPLC using a CHIRALCEL-OD-H was dissolved into solvents at 85, 90, 95, and 100 °C, and the change of the ee value was monitored by HPLC. The activation parameters were obtained from the Eyring equation and the Arrhenius plots. The first-order kinetic plots of the decay profile of the ee value were shown as a plot of ln(*ee*) *versus* time (eqn (1)), and the rate of racemization (k_{rac}) was calculated from the slope of the line. The free energy barrier ($\Delta G^{\ddagger}$) for racemization was calculated based on the Eyring equation (eqn (2)). The value of ln(k_{rac}) *versus* 1/T was plotted (Arrhenius plots), and then E_a was determined. From the values of k_{rac} and E_a, $\Delta H^{\ddagger}$, $\Delta S^{\ddagger}$, and half-life were calculated based on equations (eqn (4))–(eqn (6)).

$$\ln(ee) = k_{rac}t \quad (1)$$

$$k_{rac} = (kT/h)\exp(-\Delta G^{\ddagger}/RT) \quad (2)$$

$$k_{rac} = A\exp(-E_{rac}/RT) \quad (3)$$

$$\Delta H = E_{rac} - RT \quad (4)$$

$$k_{rac} = (kT/h)\exp(-\Delta H/RT)\exp(\Delta S/R) \quad (5)$$

$$t_{1/2} = \ln 2/2k_{rac} \quad (6)$$

k_{rac}: rate of racemization, h: Planck constant, k: Boltzmann constant, R: gas constant, T: temperature

Chiral symmetry breaking of pyrimidinethione 2 by crystallization

Each 50 mg of **2** and 0.5 ml of toluene was used for crystallization. The solvent was removed at the range of 90–100 °C with vigorous stirring. All the solidified sample was dissolved in chloroform and the optical purity of **2** was determined by HPLC using a CHIRALCEL-OD-H column.

Acknowledgements

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