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CRYSTAL AND MOLECULAR STRUCTURES OF RACEMIC AND CHIRAL 4-PHENYL-1,3-THIAZOLIDINE-2-THIONES

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Abstract – The crystal and molecular structures of (*rac*)- and (*S*)-4-phenyl-1,3-thiazolidine-2-thiones (4-PTT) have been studied by X-Ray diffraction and *ab initio* MO calculations at the level of HF/6-31G*. In racemic crystals, the thioamide groups of the enantiomeric (*R*)- and (*S*)-4-PTT pairs are hydrogen-bonded around a crystallographic center of symmetry to form a planar cyclic dimer. On the other hand, in (*S*)-4-PTT crystals, a cyclic dimer through the hydrogen bonding is formed between the two independent molecules (molecules A and B) in the asymmetric unit and its geometry is distorted.

INTRODUCTION

Homochiral 1,3-oxazolidine- and 1,3-thiazolidine-2-thiones have been used as versatile and efficient auxiliaries.[1,2] Our research interest has been focused on the optical resolution of racemic 2-thioxo-1,3-heterocycles through crystallization. In the course of this study, we have recognized that there is a difference of 46 K in melting points between racemic and (*R*)-4-phenyl-1,3-oxazolidine-2-thione (4-POT) crystals.[3] Observation of the higher melting temperature of (*rac*)-4-POT compared to that of (*R*)-4-POT seems to be consistent with Wallach's rule,[4] which states that racemic crystals tend to be denser than their chiral counterparts. However, recent survey of the Cambridge Crystallographic Database done by Brock *et al.* has suggested that there are many exceptions for this rule.[5] Variety of intra- and intermolecular interactions may play roles in controlling the physical properties in an individual crystal system. Recently, we have analyzed single crystal X-Ray structures of (*rac*)- and (*R*)-4-POTs in order to get insight into the molecular and packing characteristics leading to a different melting temperature.[3] (*rac*)- and (*R*)-4-POTs are shown to have a different inter-molecular hydrogen bonding pattern to each other, although their molecular geometries are similar.

4-Phenyl-1,3-thiazolidine-2-thione (4-PTT) is a chalcogenic analog of 4-POT; *i.e.*, PTT carries a sulfur atom in the thiazolidine ring instead of an oxygen atom in the oxazolidine ring of 4-POT. Due to differences in atomic size, atomic polarizability and electronegativity of the O and S atom, the thiazolidine ring may have different molecular conformation and crystal properties from the oxazolidine ring. In the present study, we have analyzed the X-Ray structures of (*rac*)- and (*S*)-4-PTTs crystals in order to understand differences in the intermolecular interactions in the two crystal systems. The *ab initio* MO calculations at the HF/6-31G* level are performed and the optimized geometrical parameters are compared with those obtained from X-Ray diffraction.

EXPERIMENTAL

Materials

(*R*)- and (*S*)-4-PTTs were prepared from chiral phenylglycinol by using the published procedure.[6] The reaction products were recrystallized from chloroform several times. (*rac*)-4-PTT was prepared by mixing equimolar (*R*)- and (*S*)-4-PTTs in chloroform. The purities of these compounds were checked by the elemental analyses and ^{1}H NMR spectra. (*R*)- and (*S*)-phenylglycinols were purchased from Aldrich Chemical Co. Solvents and other chemicals were of reagent grade.

Spectral Measurements

The IR spectra were recorded on a Perkin Elmer 1650 FT-IR spectrophotometer by averaging 64 scans with a resolution of 4 cm^{-1}. The spectra of solid samples were measured as KBr pellets and nujol mulls. The FT-Raman spectra were obtained on a Perkin-Elmer 2000R spectrophotometer equipped with a quartz beam splitter and InGaAs detector. The 1064 nm line of a Spectron Laser System SL300 Nd:YAG laser was used as the exciting source with an output power of about 200 mW at the sample position. All spectra were accumulated for 60 scans with a resolution of 4 cm^{-1}.

X-Ray Crystal Structure Analysis

(*rac*)- and (*S*)-4-PTT crystals suitable for X-Ray diffraction analysis were obtained by crystallization from chloroform and ethanol, respectively, at room temperature. The absolute configuration for the chiral crystals was determined based on the absolute stereochemistry established previously.[6] The preliminary cell dimensions and space group symmetry were determined photographically. X-Ray diffraction data were obtained on a Rigaku AFC-5R diffractometer with a graphite monochromated Cu Kα radiation (λ= 1.54178 Å). Intensity data were collected at room temperature (23 ±1 °C) with an ω-2θ scan mode. An empirical absorption correction, based on azimuthal scans of several reflections, was applied which resulted in transmission factors ranging from 0.85 to 1.00 for (*rac*)-4-PTT and 0.96 to 1.00 for (*S*)-4-PTT. The data were corrected for both Lorentz and polarization effects. Table 1 summarizes the crystal data and experimental conditions for the crystal structure determination.

The structures were solved by the direct method using SIR88.[7] Crystal structure analyses were performed by using the *teXsan* crystallographic software package.[8] Non-hydrogen atoms were refined anisotropically. All the H-atoms were located on a difference Fourier map, with the parameters of H-atom bonded to N-atom also being refined.

Computational procedure

Theoretical calculations were carried out for (*rac*)- and (*S*)-4-PTT molecules by using *ab initio* methods with GAUSSIAN98 program package.[9] Geometry optimizations were accomplished with the RHF

Table 1 Crystal Data and Structure Refinement

Compound	(*rac*)-4-PTT	(*S*)-4-PTT
Color / shape	Colorless / parallelepiped	Colorless / parallelepiped
Chemical formula	$C_9H_9NS_2$	$C_9H_9NS_2$
Formula weight	195.30	195.30
Temperature, K	296	296
Crystal system	monoclinic	orthorhombic
Space group	$P2_1/n$	$P2_12_12_1$
Unit cell dimensions		
a (Å)	11.681(2)	8.5020(8)
b (Å)	6.0858(3)	35.426(3)
c (Å)	12.871(2)	6.2857(5)
β (°)	90.77(1)	
Volume, Å^3	914.9(2)	1893.2(3)
Z	4	8
Dc, Mg/m^3	1.418	1.370
Absorption coefficient, mm^{-1}	4.7	4.6
Diffractometer / scan	Rigaku AFC-5R / ω-2θ	
θ range for data collection, deg	3.43-59.94	3.74-59.99
Reflections measured	1588	1704
Independent reflections	1508 (R_{int}=0.029)	1704(R_{int}=0.000)
Observed reflections	1508 [all data]	1704 [all data]
Data/ restrains/ parameters	1508 / 0 / 113	1704 / 0 /225
Goodness of fit	2.04	1.25
Final R indices [all data]	R=0.035,wR= 0.043	R=0.039,wR = 0.035
Largest diff. peak and hole, e/Å^3	0.20 -0.28	0.18 -0.22

approach using 6-31G* basis set in the GAUSSIAN98 suite of molecular electronic structure program (Gaussian Inc.). This program was run on Fujitsu GP400S-60 workstation until the default convergence criteria were satisfied. The initial geometries of the optimization procedure for the monomer were taken from that of the (*S*)-4-PTT molecule in the X-Ray data of (*rac*)- and (*S*)-4-PTT crystals. The calculation was also performed for the dimer to evaluate the effect of dimerization on the molecular structure and the conformation. The starting geometries for the (*S*)-/(*S*)- and the (*R*)-/(*S*)- cyclic dimers are also taken from the X-Ray data.

RESULTS AND DISCUSSION

Physical and spectroscopic properties of (rac)- and (S)-PTTs

Table 2 summarizes the physical and spectroscopic data of (*rac*)- and (*S*)-4-PTTs. (*rac*)-4-PTT crystals show a melting point of 192.0-194.0 °C, whereas (*S*)-4-PTT melts at 125.0-127.0 °C. This mp difference of 67 K is much larger than the 4-POT case. Furthermore, there is a large difference in solubility between (*rac*)- and (*S*)-4-PTT crystals; the latter is sixteen times more soluble in chloroform than the former. In spite of marked differences in the physical properties, the spectroscopic data of the two crystals are rather similar. In the IR spectra of (*rac*)- and (*S*)-4-PTT crystals, three intense peaks

Table 2 Physical and spectroscopic data of (*rac*)- and (*S*)-4-PTT

(*rac*)-4-PTT:

mp 192.0-194.0 °C; solubility (in $CHCl_3$ at 25 ℃, mol/l) : 0.055;

Anal. Calcd for $C_9H_9NS_2$: C 55.35, H 4.64, N 7.17 ; Found : C 55.45, H 4.64, N 7.11;

IR(KBr, cm^{-1}) : 3145(ν(N-H)), 1499(ν(C-N)+δ(N-H)), 1081(ν(C=S)) ; Raman(solid, cm^{-1}) : 3128(ν(N-H)), 1494(ν(C-N)+δ(N-H)), 1081(ν(C=S)); ^{1}H NMR($CDCl_3$): δ 3.50 (dd, *J*=8.2 and 11.2 Hz, 1H, CH_2), 3.85 (dd, *J*=8.2 and 11.2 Hz, 1H, CH_2), 5.32 (t, *J*=8.2 Hz, 1H, CH), 7.32-7.44(m, 5H, phenyl), 7.85 (s, 1H, NH).

(*S*)-4-PTT:

mp 125.0-127.0 °C; solubility (in $CHCl_3$ at 25 ℃, mol/l) : 0.875; $[\alpha]_D^{25}$: +158.57° (c 0.35, $CHCl_3$); Anal. Calcd for $C_9H_9NS_2$: C 55.35, H 4.64, N 7.17; Found : C 55.24, H 4.67, N 7.17;

IR(KBr, cm^{-1}) : 3123(ν(N-H)), 1491(ν(C-N)+ δ(N-H)), 1078(ν(C=S)); Raman(solid, cm^{-1}) : 3103(ν(N-H)), 1492(ν(C-N)+δ(N-H)), 1078(ν(C=S)); ^{1}H NMR($CDCl_3$): δ 3.51 (dd, *J*=8.2 and 11.2 Hz, 1H, CH_2), 3.85 (dd, *J*=8.2 and 11.2 Hz, 1H, CH_2), 5.32 (t, *J*=8.2 Hz, 1H, CH), 7.36-7.45(m, 5H, phenyl), 7.69 (s, 1H, NH).

characteristic of the 1,3-thiazolidine-2-thione ring are observed in the 3140, 1500, and 1080 cm^{-1} region. In the Raman spectra, these bands are observed at the corresponding frequencies, although the spectra are predominated by the benzene ring modes.

Crystal Structures of (rac)-4-PTT and (S)-4-PTTs

The final positional and thermal parameters, selected bond lengths, bond angles and torsion angles of (*rac*)-4-PTT and (*S*)-4-PTTs have been deposited with the Cambridge Crystallographic Database.[10] Table 3 summarizes selected bond lengths and hydrogen bonding geometries of the two crystals. As shown in Table 1, (*rac*)-4-PTT and (*S*)-4-PTT are crystallized in the monoclinic and orthorhombic forms with four and eight molecules, respectively, in a unit cell.

Individual bond distances and angles fall within normal ranges of non-substituted 1,3-thiazolidine-2-thione (TT)[11] and other substituted 1,3-thiazolidine-2-thione derivatives.[12-14] The C(1)=S(2) distances of 4-PTT [1.657(4)-1.664(2) Å] are intermediate between the values of 1.82 Å for a C-S single bond and 1.56 Å for a C=S double bond (Suton, 1965).[15] The C(1)-N(1) [1.305(5)-1.317(3) Å] and the C(1)-S(1) [1.738(2)-1.744(3) Å] distances are indicative of double bond character. Rather

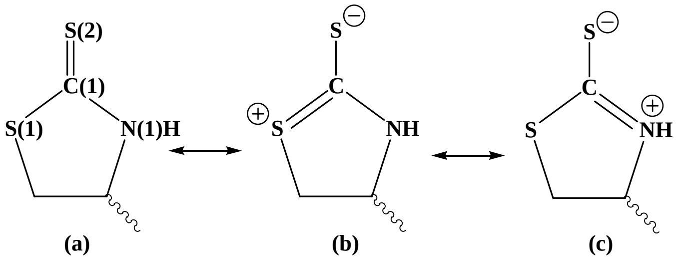


Figure 1 Canonical structures of 4-PTT

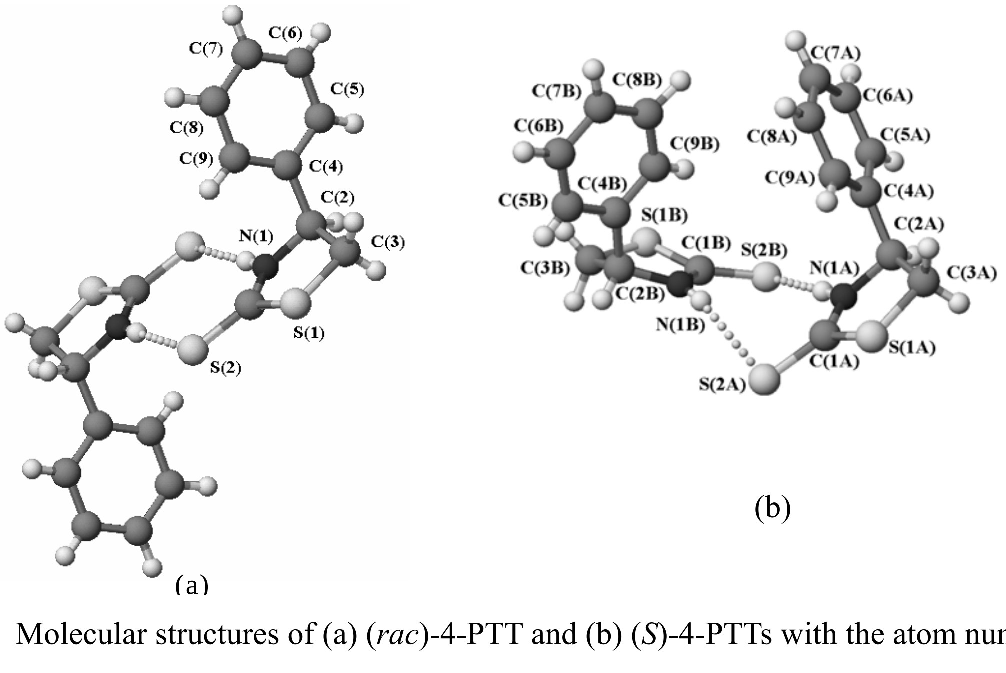


Figure 2 Molecular structures of (a) (*rac*)-4-PTT and (b) (*S*)-4-PTTs with the atom numbering.

long C=S bond and the short C-N bond distances suggest considerable conjugation and are due to contribution of canonical forms (b) and (c) shown in Figure 1.

Figure 2 shows molecular structure of (*rac*)-4-PTT and (*S*)-4-PTT in crystals with atom numbering. For both (*rac*)-4-PTT and (*S*)-4-PTT crystals, a pair of 4-PTT molecules forms a cyclic dimer through intermolecular N-H...S hydrogen bonds from the NH group of one molecule to the C=S group of an adjacent molecule. However, the hydrogen bonding geometry is quite different to each other. In (*rac*)-4-PTT crystals, an enantiomeric pair is hydrogen-bonded around a center of symmetry [N(1)...S(2)$^{(i)}$ 3.425(2) Å, N(1)-H...S(2)$^{(i)}$ 176(2)°] (symmetry code: (i) 2-x, -y, 2-z). On the other hand, in (*S*)-4-PTT crystals a cyclic dimer is formed between the two independent molecules (molecules A and B) and its geometry is considerably distorted [N(1A)...S(2B) 3.383(3) Å, N(1A)-H...S(2B) 177(4)°; N(1B)...S(2A) 3.411(3) Å, N(1B)-H...S(2A) 166(4)°]. Nakamoto *et al.* demonstrated that the N-H stretching band comes to be observed at lower frequency, as the N-H…X hydrogen bonding becomes stronger.[16] The associated NH stretching frequencies are observed at 3145 and 3128 cm^{-1}, respectively, in the IR and Raman spectra of (*rac*)-4-PTT crystals, whereas those of (*S*)-4-PTT are observed at 3123 and 3103 cm^{-1}. In view of the averaged values of the D...A distance, the D-H...A angle and the N-H stretching frequency, (*S*)-4-PTT crystals may have slightly stronger hydrogen bonding than (*rac*)-4-PTT crystals. However, this difference in the hydrogen bonding strength cannot account for the higher melting point and the lower solubility of (*rac*)-4-PTT crystals. Since densities of (*rac*)-4-PTT and (*S*)-4-PTT are calculated as 1.418 and 1.370 Mg m^{-3}, respectively, the large differences in physical properties may be more attributed to the difference in the crystal packing efficiency than in the strength of the intermolecular hydrogen bonding.

Table 3 Selected bond lengths (Å) and hydrogen bonding geometry (Å, °).

	Exp.			HF/6-31G*		
Parameter	(*rac*)-4-PTT	(*S*)-4-PTT(A)	(*S*)-4-PTT(B)	(*S*)-4-PTT	(*R*)/(*S*)-dimer	(*S*)/(*S*)-dimer
C(1)-S(1)	1.738(2)	1.744(3)	1.744(3)	1.757	1.756	1.756
C(1)-S(2)	1.664(2)	1.662(4)	1.657(4)	1.652	1.669	1.670
C(1)-N(1)	1.317(3)	1.305(5)	1.316(5)	1.330	1.316	1.316
SCF energy						
-E (a.u.)				1195.5338	2391.0825	2391.0826
ΔE (kcal/mol)				0.0	-9.35	-9.41

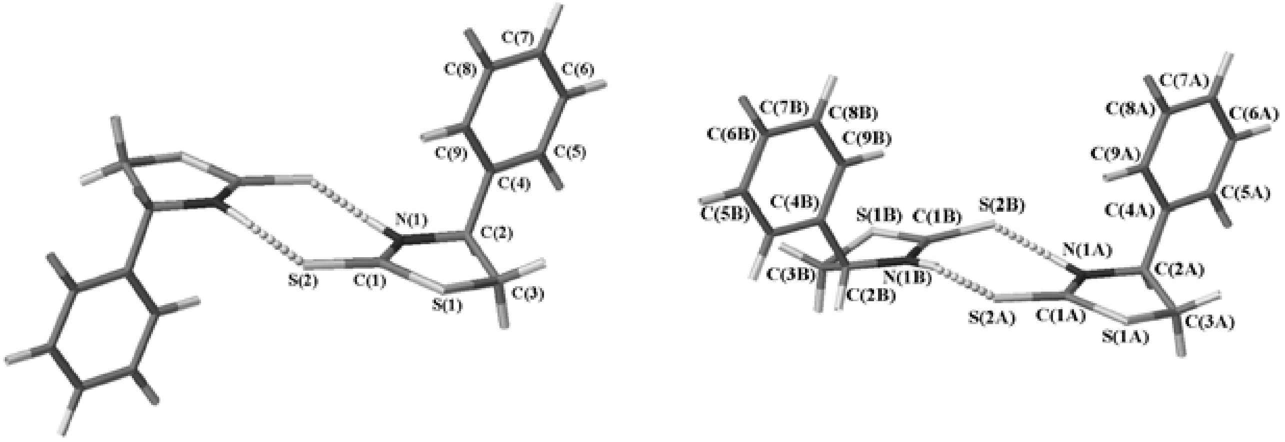
Compound		D-H...A	D-H	H…A	D…A	D-H…A
Obs.	(*rac*)-4-PTT	N(1)-H...S(2)^{i}	0.79(2)	2.63(3)	3.425(2)	176(2)
	(*S*)-4-PTT	N(1A)-H...S(2B)	0.84(3)	2.55(3)	3.383(3)	177(4)
		N(1B)-H...S(2A)	0.82(3)	2.61(4)	3.411(3)	166(4)
Calcd.	(*R*)/(*S*)-dimer	N-H...S	1.00	2.61	3.60	172
	(*S*)/(*S*)-dimer	N-H...S	1.00	2.61	3.60	170

Symmetry codes: (i) 2-x, -y, 2-z

Estimated standard deviations in the least significant figure are given in parentheses.

MO calculations

The structure and conformation of the 4-PTT molecule are analyzed by the HF/6-31G* based *ab initio* calculations. The calculations are carried out for the (*S*)-4-PTT monomer, and the (*R*)-/(*S*)- and the (*S*)-/(*S*)- cyclic dimers. The starting geometries for MO calculations were taken from the present X-Ray results. The optimized conformations are depicted in Figure 3. Regardless of the starting geometry, i.e. (*S*)-4-PTT or (*rac*)-4-PTT crystals, the geometry optimization of a single (*S*)-4-PTT molecule leads to a practically identical conformation. The calculated bond distances of the C(1)-S(2) [1.652 Å] and the C(1)-N(1) [1.330 Å] are somewhat shorter and longer, respectively, than the observed value of (*rac*)- and (*S*)-4-PTT crystals. On going from the (*S*)-4-PTT monomer to the (*R*)/(*S*)-cyclic dimer, the former and the latter bond lengths are elongated and shortened, respectively, and come closer to the observed values. These observations indicate that the weakening of the C(1)-S(2) bond and the strengthening of the C(1)-N(1) bond occur on the dimer formation. These structure changes are due to increasing contribution of the canonical structure (c) in Figure 1 on formation of cyclic dimer. The SCF energy difference of 9.35 kcal/mol between the (*S*)-4-PTT monomer and the (*R*)/(*S*)-cyclic dimer corresponds to the hydrogen bonding enthalpy. The planar hydrogen bonding geometries were obtained for both the (*S*)-/(*S*)- and (*R*)-/(*S*)- cyclic dimers as shown in Figure 3. There is little difference (less than 0.1 kcal / mol) in SCF energies between the two dimers. This result suggests that both these cyclic dimers assume the planar hydrogen bonding geometry in gas phase and that a distorted hydrogen bonding geometry in (*S*)-4-PTT crystals results from the crystal packing effect.



(a) (b)

Figure 3 The 6-31G* optimized conformations of (*R*)/(*S*)- and (*S*)/(*S*)- dimers.

CONCLUSION

The crystal structures of (*rac*)- and (*S*)-4-PTTs have been determined. (*rac*)- and (*S*)-4-PTT crystals form cyclic dimers through the intermolecular hydrogen bondings between the thioamide moieties. The cyclic dimer of the former is planar and that of the latter is distorted. The melting point difference of 67

K between the two crystals is due to a difference in crystal packing rather than a difference in hydrogen bonding pattern. The results of the *ab initio* MO calculations predict that the rather distorted hydrogen bonding in (*S*)-4-PTT molecule also results from the crystal packing.

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