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Two Closely Related Structures: (–)-(7a*S*)-2,3,7,7a-Tetrahydro-7a-phenylthio-1*H*-indene-1,5(6*H*)-dione and its Racemic Compound

BY CAROLYN PRATT BROCK, STEFAN KWIATKOWSKI* AND DAVID S. WATT

Department of Chemistry, University of Kentucky, Lexington, KY 40506-0055, USA

AND ASFAQ SAYED

Enraf–Nonius, 390 Central Avenue, Bohemia, NY 11716, USA

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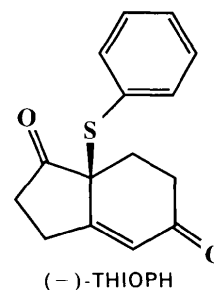
Abstract

$C_{15}H_{14}O_2S$, $M_r = 258.34$. Racemic compound: $T_{fus} = 397–399$ K (124–126 °C), monoclinic, $P2_1/c$, $a = 7.349$ (1), $b = 7.203$ (2), $c = 24.729$ (4) Å, $\beta = 91.27$ (1)°, $V = 1308.7$ (4) Å³, $Z = 4$, $D_x = 1.311$ g cm⁻³, $\lambda(Mo K\alpha) = 0.7107$ Å, $\mu = 2.27$ cm⁻¹, $(\sin\theta/\lambda)_{max} = 0.650$ Å⁻¹, $F(000) = 544$, $T = 297$ (1) K, $R = 0.038$ for 219 variables and 2228 observed reflections [$I > 3\sigma(I)$]. Chiral crystals: $T_{fus} = 350–351$ K (77–78 °C), orthorhombic, $P2_12_12_1$, $a = 7.3342$ (8), $b = 7.3587$ (4), $c = 24.613$ (6) Å, $V = 1328.4$ (4) Å³, $Z = 4$, $D_x = 1.292$ g cm⁻³, $\lambda(Cu K\alpha) = 1.5406$ Å, $\mu = 20.43$ cm⁻¹, $(\sin\theta/\lambda)_{max} = 0.497$ Å⁻¹, $F(000) = 544$, $T = 295$ (1) K, $R = 0.027$ for 220 variables and 1318 observed reflections [$I > 3\sigma(I)$], absolute configuration determined at the 0.001 confidence level so that the molecule is identified as the (S)-(–)-enantiomer. The common motif in these very closely related structures is a double layer of molecules; adjacent double layers are related by inversion centers in the racemic compound and by 2_1 screw axes in the chiral crystals. The conglomerate of the chiral crystals is very unstable relative to the racemic compound. The chiral crystals are also 1.5% less dense; the root-mean-square atomic displacements are ca 17% larger in the $P2_12_12_1$ than in the $P2_1/c$ crystals. Calculation of an idealized phase diagram suggests that attempts to grow well formed chiral crystals are unlikely to succeed unless the solution contains less than ca 1% of the 'wrong' enantiomer.

* On leave from the Warsaw Institute of Technology, Noakowskiego 3, 00-664 Warsaw, Poland.

Introduction

Samples of 2,3,7,7a-tetrahydro-7a-phenylthio-1*H*-indene-1,5(6*H*)-dione (hereafter, THIOPH) enriched



in the (–)-enantiomer (see below) were synthesized as described previously (Kwiatkowski, Syed, Brock & Watt, 1989) by application of the Hajos–Parrish asymmetrically biased aldol condensation to achiral 2-(3-oxobutyl)-2-phenylthio-1,3-cyclopentanedione using (+)-(R)-proline as a catalyst. A ¹H NMR analysis using a chiral shift reagent showed that the resulting product was obtained in greater than 95% enantiomeric excess. Preliminary estimates suggested that it would be possible to determine the absolute configuration of the product from an X-ray structure determination if Cu radiation were used ($\Delta f'' = 0.56$ e for the S atom, *i.e.*, 0.4% of the scattering power of the molecule). Some of the product was therefore dissolved in warm methanol, and the solution was allowed to cool and evaporate until a small crop of good-looking crystals had been obtained. One of the resulting lath-like crystals was mounted in

air on a diffractometer equipped with an Mo-target X-ray tube. The plan was to solve and refine the structure to find out whether there was any disorder that would interfere with the determination of the absolute configuration before arranging for data to be collected with Cu $K\alpha$ radiation.

The crystal was found, unexpectedly, to be racemic. Careful inspection of the whole batch of crystals suggested that only one crystal form was present, so the crystals of this batch were redissolved in methanol. The specific rotation of the resulting solution was near zero.

After the original product had been purified further a new crop of crystals was produced. At first glance the crystals in this second batch looked exactly like those in the first, but their melting point was more than 45 K lower (350–351 *versus* 397–399 K) and their solutions were optically active. A preliminary study, also with Mo $K\alpha$ radiation, showed that the unit-cell dimensions of the chiral and racemic crystals are very similar, and that their structures are closely related. Identification of the crystal faces confirmed that the crystal habits of the racemic compound and the chiral material are much alike (see Fig. 1).

Experimental

Data for the racemic compound were collected at the University of Kentucky with graphite-monochromated Mo $K\alpha$ radiation. The S atom was located from the Patterson function; the remaining non-H atoms were located using the program package *DIRDIF* (Beurskens *et al.*, 1983). H atoms were located in difference Fourier maps and refined isotropically. The structure was refined using programs and procedures described previously (Brock & Attig, 1980) to R and wR factors of 0.038 and 0.049 respectively (2228 observations; 219 variables).

Data for the chiral crystals were collected at the University of Kentucky with Mo $K\alpha$ radiation, and the structure was solved and refined as described

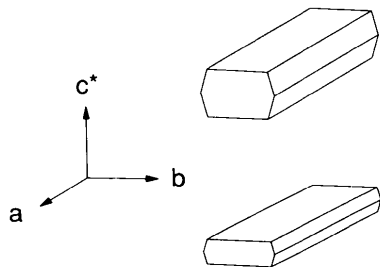


Fig. 1. Typical crystal habits of the $P2_1/c$ racemic compound (top) and $P2_12_12$, chiral crystals (bottom) of THIOPH; both crystals, however, are usually much more elongated parallel to a than is apparent in this drawing. The most prominent faces belong to the forms $\{001\}$ and $\{011\}$.

Table 1. Crystallographic data and experimental details of the structure determinations

	Racemic compound	Chiral crystals
Formula	C ₁₅ H ₁₄ O ₂ S	C ₁₅ H ₁₄ O ₂ S
Crystal shape	Colorless thin laths elongated parallel to a ; largest faces are $\{001\}$; bounding planes are $\{001\}$, $\{011\}$, $\{100\}$	
$F(000)$	$P2_1/c$ (No. 14)	$P2_12_12$, (No. 19)
Diffractometer	544 e (544.44 e)*	544 e (545.28 e)*
Scan type	Enraf Nonius CAD-4	Enraf-Nonius CAD-4
$\omega/2\theta$	$\omega/2\theta$	$\omega/2\theta$
Scan width (°)	$0.80 + 0.35 \tan \theta$	$0.90 + 0.35 \tan \theta$
Index range h	–9	–7
k	–9	0
l	–32–32	–24–24
2θ range (°)	4–55	2–100
Decay (%)	< 1.0 (no correction)	3.7
Absorption correction	None	Empirical; ψ scans
Data collected	3005	3332
Unique data collected	3005	1372
R factor for averaging	–	0.019
Data with $I > 3\sigma(I)$	2228	1318
No. of variables	219	220
Extinction coefficient	None	$1.21(3) \times 10^{-5}$
$R\ddagger$	0.038	0.027
$wR\ddagger$	0.049	0.034
Goodness of fit \ddagger	2.86	1.31
$(\Delta\sigma)_{\max}$	0.04	0.03
$\Delta\rho_{\max}$ (e Å ⁻³)	0.31	0.17

* Taking anomalous scattering into account.

† $R = (\sum |F_o| - |F_c|) / (\sum |F_o|)$; $wR = [\sum w(|F_o| - |F_c|)^2 / \sum wF_o^2]^{1/2}$, where $w = 4I / (\sigma^2(I) + 0.02I^2)$.

‡ G.o.f. = $[\sum w(|F_o| - |F_c|)^2 / (N_o - N_v)]^{1/2}$.

above. Data were then collected at the Enraf-Nonius Service Corporation using graphite-monochromated Cu $K\alpha$ radiation. All calculations for the Cu $K\alpha$ data set were carried out using the Enraf-Nonius *Structure Determination Package* (Frenz, 1978). An empirical absorption correction based on five ψ scans was applied to the data; correction factors were in the range 0.80–1.00 and averaged 0.92. H atoms were refined isotropically and an extinction parameter was included [final value: $1.21(3) \times 10^{-5}$]. The absolute configuration of the molecule was determined by comparing refinements (1318 observations; 220 variables) of the two enantiomeric structures. The agreement factors R and wR are 0.027 and 0.034 for the (*S*)-enantiomer, and 0.041 and 0.058 for the (*R*)-enantiomer. The R - and wR -factor ratios for the refinements of the two enantiomers are 0.66 and 0.59; the determination of the molecule as the (*S*)-(-)-enantiomer is therefore reliable at the 0.001 confidence level (Hamilton, 1965; Rogers, 1981).

Crystallographic data and the details of the structure determinations are given in Table 1, atomic coordinates and B values in Table 2, and bond lengths and angles in Table 3. The molecular structures and the atom-numbering scheme are displayed in Fig. 2.*

* Lists of structure factors, anisotropic displacement parameters and bond angles involving H atoms have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 55068 (34 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England. [CIF reference: CR0384]

Table 2. Positional parameters and isotropic or equivalent isotropic displacement parameters (\AA^2) for (-)-(7a*S*)-2,3,7,7a-tetrahydro-7a-phenylthio-1*H*-indene-1,5(6*H*)-dione

H atoms were refined isotropically; for S, O and C atoms $B_{\text{eq}} = (4/3)\text{Tr}(\beta \cdot G)$, where $\beta_{ij} = 2\pi^2 a_i^* a_j^* U_{ij}$.

	x	y	z	$B_{\text{iso}}/B_{\text{eq}}$
Racemic compound ($P2_1/c$)				
S	-0.19769 (6)	-0.24977 (7)	-0.15085 (2)	3.42 (1)
O(1)	-0.6113 (3)	0.2821 (2)	-0.11375 (8)	6.92 (6)
O(2)	0.0666 (2)	-0.1983 (2)	-0.03834 (6)	4.92 (4)
C(1)	-0.3978 (2)	-0.1329 (2)	-0.06998 (7)	3.00 (4)
C(2)	-0.5277 (3)	-0.0060 (3)	-0.07829 (8)	3.72 (5)
C(3)	-0.4916 (3)	0.1661 (3)	-0.10749 (8)	4.25 (5)
C(4)	-0.3046 (3)	0.1921 (3)	-0.12933 (9)	4.55 (6)
C(5)	-0.1561 (3)	0.0956 (3)	-0.09635 (8)	3.80 (5)
C(6)	-0.2063 (2)	-0.1067 (2)	-0.08820 (6)	2.83 (4)
C(7)	0.0942 (3)	-0.2176 (3)	-0.04687 (7)	3.54 (5)
C(8)	0.2193 (3)	-0.3491 (4)	-0.01741 (11)	4.77 (6)
C(9)	-0.4108 (3)	-0.3125 (3)	-0.03972 (9)	3.93 (5)
C(10)	0.0261 (2)	-0.2218 (3)	-0.17460 (7)	3.18 (4)
C(11)	0.0658 (3)	-0.0735 (3)	-0.20786 (8)	4.49 (6)
C(12)	0.2359 (3)	-0.0587 (4)	-0.23015 (9)	5.42 (7)
C(13)	0.3654 (3)	-0.1925 (4)	-0.21969 (8)	5.01 (6)
C(14)	0.3273 (3)	-0.3397 (3)	-0.18681 (8)	4.48 (6)
C(15)	0.1582 (3)	-0.3555 (3)	-0.16398 (8)	3.72 (5)
H(2)	-0.651 (3)	-0.024 (3)	-0.0651 (9)	5.2 (5)
H(4A)	-0.282 (3)	0.314 (3)	-0.1309 (9)	5.8 (6)
H(4B)	-0.313 (3)	0.140 (3)	-0.1675 (9)	4.8 (5)
H(5A)	-0.036 (3)	0.108 (3)	-0.1127 (7)	3.5 (4)
H(5B)	-0.147 (2)	0.150 (3)	-0.0602 (8)	4.1 (4)
H(8A)	0.181 (3)	-0.471 (4)	-0.0223 (10)	6.2 (6)
H(8B)	0.209 (3)	0.310 (4)	0.0203 (11)	6.8 (7)
H(9A)	-0.503 (3)	-0.311 (3)	-0.0104 (9)	5.2 (5)
H(9B)	-0.444 (2)	0.409 (3)	0.0643 (8)	3.7 (4)
H(11)	-0.024 (3)	0.024 (3)	-0.2157 (9)	5.9 (6)
H(12)	0.258 (3)	0.060 (3)	-0.2516 (10)	6.5 (6)
H(13)	0.482 (3)	-0.192 (3)	-0.2353 (10)	6.2 (6)
H(14)	0.416 (3)	-0.433 (3)	-0.1789 (9)	5.6 (5)
H(15)	0.136 (3)	-0.451 (3)	-0.1413 (8)	4.4 (5)
Chiral crystals ($P2_1,2_1$)				
S	-0.21370 (6)	0.51054 (7)	-0.15365 (2)	4.38 (1)
O(1)	-0.6234 (3)	1.0316 (2)	-0.11493 (8)	9.24 (5)
O(2)	0.0274 (2)	0.5365 (3)	-0.03657 (7)	7.49 (4)
C(1)	-0.4264 (3)	0.6169 (2)	-0.07348 (7)	3.95 (4)
C(2)	-0.5519 (3)	0.7437 (3)	-0.08196 (9)	5.13 (5)
C(3)	-0.5080 (4)	0.9148 (3)	-0.10803 (9)	5.98 (6)
C(4)	-0.3149 (4)	0.9413 (2)	-0.1267 (1)	6.51 (6)
C(5)	-0.1766 (4)	0.8378 (3)	-0.09328 (9)	5.53 (5)
C(6)	-0.2315 (3)	0.6406 (2)	-0.08888 (7)	3.83 (4)
C(7)	-0.1312 (3)	0.5222 (3)	-0.04798 (7)	5.18 (5)
C(8)	-0.2655 (5)	0.3909 (3)	-0.0233 (1)	7.24 (7)
C(9)	-0.4505 (4)	0.4367 (3)	-0.04633 (9)	5.55 (5)
C(10)	0.0158 (3)	0.5338 (3)	-0.17564 (7)	4.13 (4)
C(11)	0.0636 (3)	0.6778 (3)	-0.20767 (9)	5.82 (5)
C(12)	0.2360 (4)	0.6857 (4)	-0.2300 (1)	7.13 (6)
C(13)	0.3585 (3)	0.5514 (4)	-0.22098 (8)	6.47 (6)
C(14)	0.3134 (3)	0.4087 (3)	-0.18931 (9)	5.60 (5)
C(15)	0.1414 (3)	0.3973 (3)	-0.16626 (8)	4.54 (4)
H(2)	-0.669 (3)	0.720 (2)	-0.0720 (8)	6.5 (5)
H(4A)	-0.296 (3)	1.063 (3)	-0.1253 (9)	7.5 (6)
H(4B)	-0.324 (3)	0.900 (3)	-0.1694 (9)	6.6 (5)
H(5A)	-0.062 (3)	0.848 (2)	-0.1090 (7)	5.4 (4)
H(5B)	-0.173 (3)	0.891 (2)	-0.0562 (8)	6.4 (5)
H(8A)	-0.241 (4)	0.266 (4)	-0.033 (1)	11.6 (8)
H(8B)	-0.271 (4)	0.408 (3)	0.011 (1)	8.8 (6)
H(9A)	-0.543 (4)	0.446 (3)	-0.019 (1)	8.3 (6)
H(9B)	-0.488 (3)	0.344 (2)	-0.0748 (8)	5.7 (5)
H(11)	-0.008 (4)	0.768 (3)	-0.2103 (9)	7.4 (6)
H(12)	0.260 (4)	0.781 (4)	-0.248 (1)	11.6 (9)
H(13)	0.482 (3)	0.563 (3)	-0.2361 (9)	6.7 (5)
H(14)	0.399 (3)	0.312 (3)	-0.1792 (8)	6.8 (5)
H(15)	0.111 (2)	0.304 (2)	-0.1442 (7)	4.5 (4)

Results

The molecular conformations in the two structures are nearly the same; they differ only by a small displacement of the phenyl ring (see Fig. 3). All bond lengths and angles are normal (Allen, Kennard,

Table 3. Bond lengths (\AA) and angles ($^\circ$) in (-)-(7a*S*)-2,3,7,7a-tetrahydro-7a-phenylthio-1*H*-indene-1,5(6*H*)-dione

	$P2_1/c$	$P2_1,2_1$	Δ
S—C(6)	1.863 (2)	1.864 (2)	0.001
S—C(10)	1.770 (2)	1.777 (2)	0.007
O(1)—C(3)	1.221 (2)	1.218 (3)	-0.003
O(2)—C(7)	1.204 (2)	1.201 (3)	-0.003
C(1)—C(2)	1.334 (2)	1.327 (3)	-0.007
C(1)—C(6)	1.499 (2)	1.489 (3)	-0.010
C(1)—C(9)	1.499 (3)	1.495 (3)	-0.004
C(2)—C(3)	1.461 (3)	1.450 (4)	-0.011
C(3)—C(4)	1.500 (3)	1.501 (5)	0.001
C(4)—C(5)	1.516 (3)	1.511 (4)	-0.005
C(5)—C(6)	1.518 (2)	1.510 (3)	-0.008
C(6)—C(7)	1.525 (2)	1.521 (3)	-0.004
C(7)—C(8)	1.517 (3)	1.508 (4)	-0.009
C(8)—C(9)	1.523 (3)	1.509 (4)	-0.014
C(10)—C(11)	1.383 (3)	1.367 (3)	-0.016
C(10)—C(15)	1.388 (3)	1.382 (3)	-0.006
C(11)—C(12)	1.381 (3)	1.379 (4)	-0.002
C(12)—C(13)	1.375 (3)	1.354 (4)	-0.021
C(13)—C(14)	1.369 (3)	1.349 (4)	-0.020
C(14)—C(15)	1.381 (3)	1.386 (4)	0.005
C(2)—H(2)	0.98 (2)	0.91 (3)	-0.07
C(4)—H(4A)	0.89 (2)	0.91 (3)	0.02
C(4)—H(4B)	1.02 (2)	1.10 (3)	0.08
C(5)—H(5A)	0.98 (2)	0.93 (3)	-0.05
C(5)—H(5B)	0.98 (2)	0.99 (3)	0.01
C(8)—H(8A)	0.93 (3)	0.97 (4)	0.04
C(8)—H(8B)	0.97 (3)	0.84 (4)	-0.13
C(9)—H(9A)	1.00 (2)	0.95 (3)	-0.05
C(9)—H(9B)	0.95 (2)	1.01 (3)	0.06
C(11)—H(11)	0.98 (2)	0.85 (3)	-0.13
C(12)—H(12)	1.02 (3)	0.84 (4)	0.18
C(13)—H(13)	0.95 (2)	0.98 (3)	0.03
C(14)—H(14)	0.95 (2)	0.98 (3)	0.03
C(15)—H(15)	0.90 (2)	0.91 (2)	0.01
C(6)—S—C(10)	105.2 (1)	106.1 (1)	0.9
C(2)—C(1)—C(6)	122.7 (2)	122.9 (2)	0.2
C(2)—C(1)—C(9)	128.0 (2)	127.8 (2)	-0.2
C(6)—C(1)—C(9)	109.2 (1)	109.3 (2)	0.1
C(1)—C(2)—C(3)	121.3 (2)	121.8 (3)	0.5
O(1)—C(3)—C(2)	120.3 (2)	121.3 (3)	1.0
O(1)—C(3)—C(4)	122.2 (2)	121.4 (2)	-0.8
C(2)—C(3)—C(4)	117.5 (2)	117.2 (2)	-0.3
C(3)—C(4)—C(5)	113.8 (2)	113.7 (2)	-0.1
C(4)—C(5)—C(6)	109.7 (2)	110.1 (2)	0.4
S—C(6)—C(1)	103.3 (1)	103.0 (1)	-0.3
S—C(6)—C(5)	114.1 (1)	114.4 (2)	0.3
S—C(6)—C(7)	103.9 (1)	103.8 (1)	-0.1
C(1)—C(6)—C(5)	113.2 (1)	112.8 (2)	-0.4
C(1)—C(6)—C(7)	103.3 (1)	103.2 (2)	-0.1
C(5)—C(6)—C(7)	117.6 (1)	118.0 (2)	0.4
O(2)—C(7)—C(6)	124.8 (2)	125.0 (2)	0.2
O(2)—C(7)—C(8)	126.2 (2)	126.5 (2)	0.3
C(6)—C(7)—C(8)	109.0 (2)	108.5 (2)	-0.5
C(7)—C(8)—C(9)	106.4 (2)	107.0 (2)	0.6
C(1)—C(9)—C(8)	105.2 (2)	105.1 (2)	-0.1
S—C(10)—C(11)	119.7 (1)	119.6 (2)	-0.1
S—C(10)—C(15)	120.6 (1)	120.7 (2)	0.1
C(11)—C(10)—C(15)	119.5 (2)	119.3 (2)	-0.2
C(10)—C(11)—C(12)	120.1 (2)	119.8 (3)	-0.3
C(11)—C(12)—C(13)	120.0 (2)	120.8 (3)	0.8
C(12)—C(13)—C(14)	120.3 (2)	120.0 (3)	-0.3
C(13)—C(14)—C(15)	120.3 (2)	120.5 (3)	0.2
C(14)—C(15)—C(10)	119.8 (2)	119.6 (2)	-0.2

Watson, Brammer, Orpen & Taylor, 1987) although the C(12)—C(13) and C(13)—C(14) bonds in the $P2_1,2_1$ structure appear to be a little short, probably as a consequence of the rather large thermal motion (see Fig. 2). The agreement of the bond lengths and angles between the two structures is excellent. The average and root-mean-square values of Δ , the difference between corresponding values in the two structures, are 0.006 and 0.010 \AA for the 20 bonds between S, O and C atoms, while the average e.s.d.

for an individual Δ value is 0.004 Å. For the 29 bond angles involving S, O and C atoms the average and r.m.s. values of Δ are 0.1 and 0.4°, and the average e.s.d. for an individual value is 0.3°. For the 14 bond lengths and 32 bond angles involving an H atom, the corresponding values are 0.02 and 0.08 Å (0.04 Å), and 0 and 3° (2°).

The shift of the phenyl ring between the two structures cannot be ascribed to differences in the torsion angles around the C(6)—S bond; corresponding angles differ by at most 0.4 (3)°. Rather, the most significant differences are found in the C(6)—S—C(10) bond angle [0.9 (2)°] and in the angle S—C(10)—C(13) [173.3 (2) — 175.1 (1) = -1.8 (2)°]. The S atom is displaced from the phenyl ring by 0.150 (1) Å in the $P2_1/c$ structure and by -0.206 (2) Å (*i.e.*, in the opposite direction) in the $P2_12_1$ structure.

As can be seen in Fig. 4, the arrangements of the molecules in the two structures are very similar;

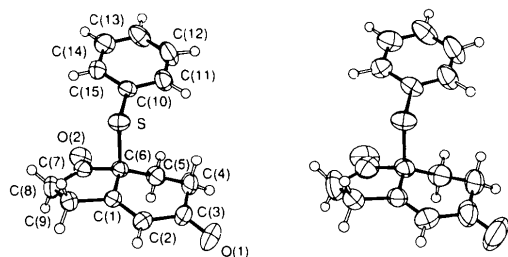


Fig. 2. Perspective drawing of the molecular structures of (-)-(S)-THIOPH determined in the (left) $P2_1/c$ racemic compound, and (right) $P2_12_1$ chiral crystals. The atom-numbering scheme, which is the same for both structures, is also shown. The shapes of the ellipsoids of the non-H atoms correspond to 50% probability contours of atomic displacement.

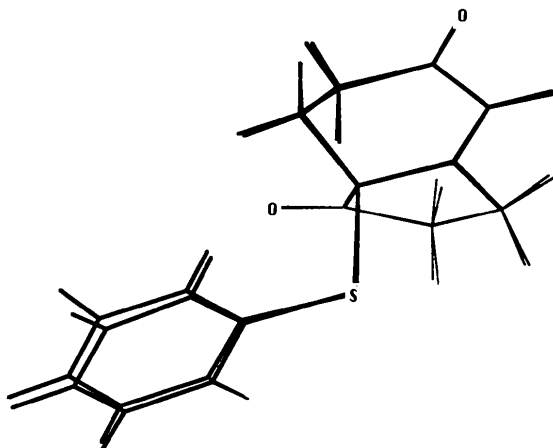


Fig. 3. Diagram in which the molecular structures found in the $P2_1/c$ and $P2_12_1$ structures are superimposed (Dobler, 1990). The sum of the squares of the distances between corresponding non-H atoms of the bicyclic ring system has been minimized.

Table 4. Model for the thermal motion of (-)-(7a*S*)-2,3,7,7a-tetrahydro-7a-phenylthio-1*H*-indene-1,5(6*H*)-dione

The inertial coordinate system is shown in Fig. 5.

	$P2_1/c$	$P2_12_1$	Ratio
$\langle \sigma^2(U_{ij}) \rangle^2$ (Å ²)	0.0010	0.001	
$\langle \Delta^2(A, B) \rangle^2$ (Å ²)			
Within bicyclic ring	0.0022	0.005	
Within phenyl ring	0.0019	0.006	
Between rings	0.0101	0.023	
wR^*	0.071	0.108	
Goodness of fit	4.1	7.4	
T (Å²)‡			
T^{11}	0.0337 (8)	0.0417 (18)	1.24 (6)
T^{22}	0.0302 (12)	0.0416 (24)	1.38 (10)
T^{33}	0.0406 (9)	0.0554 (17)	1.36 (5)
T^{12}	0.0012 (8)	-0.0017 (17)	
T^{13}	0.0022 (7)	0.0065 (15)	
T^{23}	0.0014 (8)	0.0022 (16)	
L (deg²)			
L^{11}	2.4 (5)	4.5 (9)	1.9 (5)
L^{22}	5.3 (6)	3.9 (10)	0.7 (2)
L^{33}	26.9 (13)	37.7 (27)	1.4 (1)
L^{12}	1.7 (4)	3.6 (8)	
L^{13}	3.2 (8)	3.3 (16)	
L^{23}	-0.3 (6)	1.9 (11)	
S (Å deg²)§			
S^{11}	0.050 (33)	0.092 (65)	
S^{12}	0.044 (13)	0.120 (23)	
S^{13}	-0.037 (16)	0.004 (31)	
S^{21}	0.025 (13)	0.012 (26)	
S^{22}	-0.045 (36)	-0.043 (73)	
S^{23}	-0.147 (17)	-0.286 (33)	
S^{31}	0.133 (22)	0.250 (43)	
S^{32}	-0.088 (21)	0.023 (45)	
S^{33}	-0.006	-0.048	
Internal vibrations (deg²)			
Torsion about C(6)—S	32. (5)	59. (10)	1.8 (4)
Bending of C(6)—C(7)—S	20. (6)	44. (11)	2.2 (8)
Bending of S—C(10)—C(15)	21. (8)	19. (16)	0.9 (8)

* $wR = \{ \sum w[(U_{ij})_o - (U_{ij})_c]^2 / \sum w(U_{ij})_c^2 \}^{1/2}$, where $w = (\sigma(U_{ij}))^{-2}$.

† G.o.f. = $\{ \sum w[(U_{ij})_o - (U_{ij})_c]^2 / (N_o - N_c) \}^{1/2}$, where $N_o - N_c = (6 \times 18) - 23 = 85$.

‡ The values of the components of the T and S tensors are origin dependent, but in each case the origin has been chosen at the center of mass of the molecule.

§ The value of S^{33} has been set equal to $-(S^{11} + S^{22})$.

indeed, if only the halves of the unit cells having $\frac{1}{2} < z < 1$ are considered, the arrangements are essentially superimposable. The cells can be thought of as being built from two double layers that are stacked perpendicular to *c*, one double layer being formed from molecules with S atoms having $0 < z < \frac{1}{2}$, and the other from molecules with S atoms having $\frac{1}{2} < z < 1$. The two double layers are related by an inversion center in the racemic compound, but by a 2_1 screw axis in the chiral crystals. Although there is no indication from the drawings that the intermolecular interactions are especially weak perpendicular to these double layers, identification of the crystal faces (see Fig. 1) shows that crystal growth is slowest in the *c* direction. Crystal growth is fastest parallel to *a*.

The $P2_1/c$ structure is *ca* 1.5% denser than the $P2_12_1$ structure; the ratio of the molecular volumes, V/Z , for the two cells is 0.985 (1). The relatively larger displacement parameters (or 'temperature-factor' parameters) found in the $P2_12_1$ structure are a manifestation of the less efficient packing in the

chiral crystals. The average of the ratios of the equivalent B values for corresponding atoms in the two structures, $\langle [(B_{\text{eq}})_{\text{chiral}}/(B_{\text{eq}})_{\text{racemic}}]_i \rangle$, is 1.37 (2) for the S, O and C atoms [1.36 (2) if the $P2_1/c$ refinement allows for isotropic extinction], and 1.41 (6) for the H atoms. A skeptic might suspect that this ratio is unreliable because data were collected to $(\sin\theta/\lambda)_{\text{max}} = 0.650 \text{ \AA}^{-1}$ for the $P2_1/c$ structure, but to only 0.497 \AA^{-1} for the $P2_12_1$ structure. Refinement, however, of the Mo $K\alpha$ data [$(\sin\theta/\lambda)_{\text{max}} = 0.650 \text{ \AA}^{-1}$] originally collected for the chiral structure [fixed H atoms; $R, wR = 0.056, 0.074$ for 163 variables and 1023 observations having $I > 3\sigma(I)$] gave the same value, 1.37 (3), for the non-H atoms as was obtained from the Cu $K\alpha$ data. That this average ratio of mean-square displacements is greater than the ratio of the reduced temperatures (T/T_{fus}) at which the structures were studied, 1.13, is another indication of the looser packing in the chiral crystals. The root-mean-square displacements are about 17% larger ($1.37^{1/2} = 1.17$) in the chiral crystals than in the racemic compound.

Calculation of r.m.s. $[\Delta^2(A,B)]$ values (Hirshfeld, 1976; Rosenfield, Trueblood & Dunitz, 1978), which measure both group rigidity and the quality of the U values, yielded the values shown in Table 4. The U values were determined more precisely in the racemic than in the chiral structure, but in both cases it is clear that there is significant motion between the

relatively rigid bicyclic [O(2), O(2), C(1)–C(9)] and phenyl [C(10)–C(15)] ring systems.

The anisotropic displacement parameters were analyzed in terms of the overall rigid-body motion (Cruickshank, 1956; Schomaker & Trueblood, 1968) together with the uncorrelated internal vibrations under the assumption that the molecule is composed of three rigid segments: the central group C(6)–S–C(10) and the groups of atoms on either side of the central segment. The analysis was performed according to the procedure of He & Craven (1992), which requires that the contribution of each internal vibration to the overall momentum of the molecule be zero; calculations were performed with He & Craven's program *EKRT*. The mechanical model that gave the lowest goodness of fit allowed torsional motion about the C(6)–S bond and bending of the angles C(7)–C(6)–S and S–C(10)–C(15) for a total of 23 variables determined by 108 observed U_{ij} values (see Table 4). The important conclusion of the many fits tried was that the increased displacements in the $P2_12_1$ crystals are not localized in any one translation, libration or molecular deformation, but are distributed approximately evenly over all the important degrees of freedom. The only apparent motions that are not larger in the chiral than in the racemic crystal are the libration associated with inertial axis y (see Fig. 5) and the bending of the S–C(10)–C(15) angle.

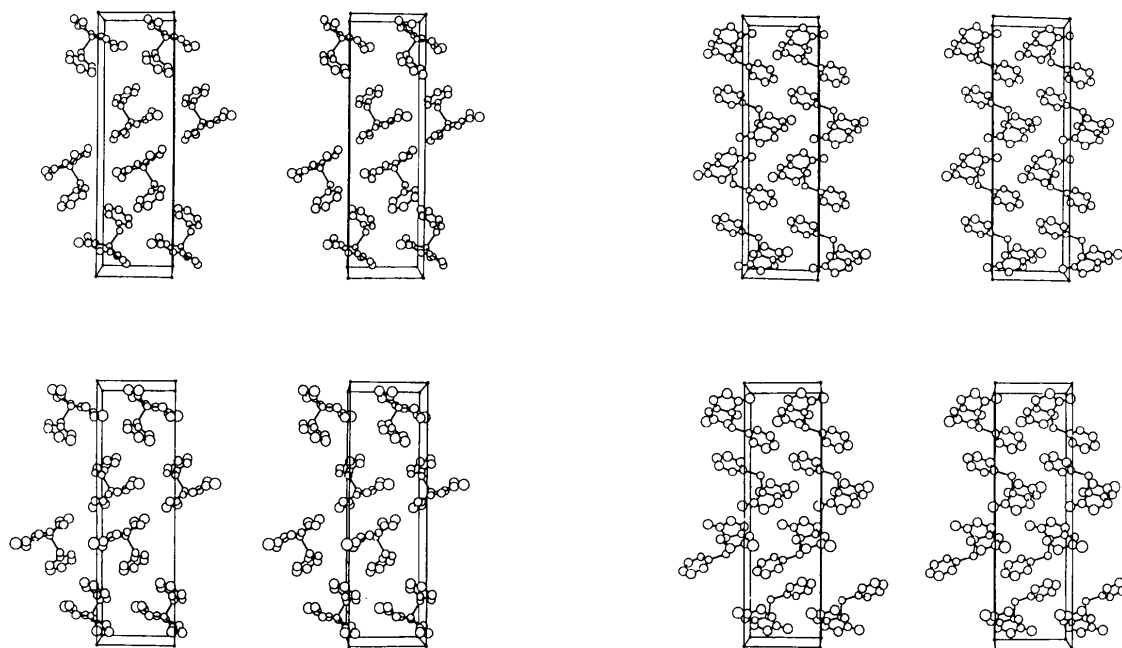


Fig. 4. Two stereoscopic views of the unit cells of the $P2_1/c$ racemic compound (top) and $P2_12_12_1$ chiral crystals (bottom) of THIOPH. In the stereopairs on the left the b axis points to the right, the c axis points upwards and the a axis points out of the plane of the paper. The stereopairs on the right have been rotated by 90° around c so that the a axis points to the right and the b axis points into the plane of the paper.

Discussion

How is it possible that recrystallization of a product with an enantiomeric excess of at least 95% gave a good crop of racemic crystals? The enantiomeric excess was determined from an NMR study using a chiral shift reagent (Kwiatkowski, Syed, Brock & Watt, 1989) and should be reliable. Racemization of the molecule under the conditions of the recrystallization is excluded.

Examination of an idealized binary solid-liquid phase diagram (see Fig. 6) calculated for the system reveals the problem: the racemic structure is so much more stable than the chiral structures that it dominates the phase diagram. As long as crystallization starts from a composition 'inside' the range defined by the two eutectic compositions (here, $ca\ 0.03 < x < 0.97$), the first crystals produced are racemic. When the composition of the melt reaches the eutectic composition (here, $x \approx 0.03$ or 0.97), the liquid solidifies as a fine-grained matrix. Well-formed chiral crystals cannot be obtained from the melt (as long as the system is in equilibrium) unless the enantiomeric excess is greater than the enantiomeric excess corresponding to the eutectic composition.

Crystallization in this case was not from the melt, but from a methanol solution, so the system must be described by a ternary, rather than a binary, phase diagram. The situation, however, is very similar [see pp. 167-177 of Jacques, Collet & Wilen (1981)]. It is well established, but perhaps not widely appreciated, that routine recrystallization of partially resolved mixtures of enantiomers may be counterproductive if the chiral solid is thermodynamically unstable relative to the racemic compound. If the relative stability of the chiral solid is very low, as is the case here, the

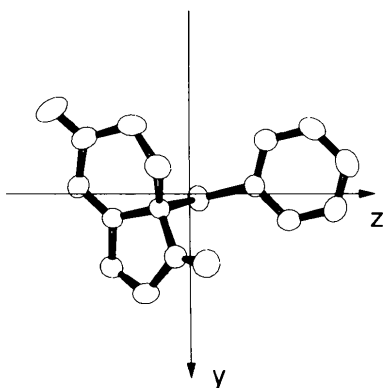


Fig. 5. Drawing showing the inertial axial system of (-)-(S)-THIOPH for the conformation observed in the $P2_1/c$ racemic compound. The system for the conformation observed in the $P2_12_1$ chiral structure differs only slightly (*cf.* Fig. 3); the moments of inertia are 2125, 1695 and 739 a.m.u. Å² for the former structure, and 2131, 1705 and 735 a.m.u. Å² for the latter (e.s.d.'s $ca\ 1$ a.m.u. Å²).

crop of crystals obtained may be racemic and the optical purity of the solution phase enhanced [see, *e.g.*, Downer & Kenyon (1939)].

In checking back through laboratory notebooks we found that the first sample of THIOPH isolated from the synthesis was described as a 'yellow crystalline product' with a specific rotation $[\alpha]_D^{20} \text{ } ^\circ\text{C} = -88.2^\circ$ (1,4-dioxane, 10 g dm⁻³). Recrystallization from methanol ultimately yielded colorless crystals with a melting point of 349 K and a specific rotation $[\alpha]_D^{20} \text{ } ^\circ\text{C} = -101.6^\circ$ (1,4-dioxane, 10 g dm⁻³), but the *first* crystals isolated, which, because they were the most attractive, were the crystals given to the crystallographer, had a much lower specific rotation, namely $[\alpha]_D^{20} \text{ } ^\circ\text{C} = -7.3^\circ$ (1,4-dioxane, 10 g dm⁻³). The yield of this first recrystallization was, of course, very low, and the material remaining in solution was recovered and purified further. After the mole fraction of the (*R*)-(+)-enantiomer had been reduced to essentially zero, it was possible to grow good crystals of the (*S*)-(-)-enantiomer. The specific rotation of the pure (*S*)-(-)-material was then determined to be $[\alpha]_D^{20} \text{ } ^\circ\text{C} = -103.0^\circ$ (1,4-dioxane, 10 g dm⁻³).

The greater stability of the $P2_1/c$ crystals is apparent from a comparison of the melting points; the melting point of the racemic compound is 48 (3) K higher than T_{fus} of the chiral crystals. Actually this comparison significantly underestimates the stability difference: all other things being equal, the melting point of a racemic compound formed from resolvable enantiomers is *ca* 20-30 K lower

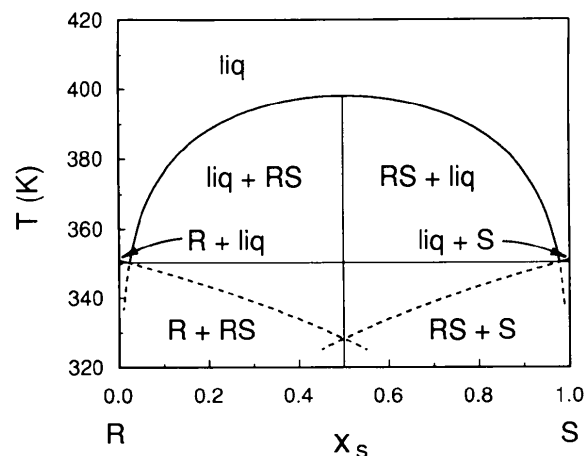


Fig. 6. Idealized solid-liquid phase diagram calculated for THIOPH from the melting points of the $P2_1/c$ racemic compound and the $P2_12_1$ chiral crystals assuming heats of fusion of 7.0 kcal mol⁻¹ (29 kJ mol⁻¹) [see pp. 94-95 of Jacques, Collet & Wilen (1981) and Brock, Schweizer & Dunitz (1991)]. The calculation is based on the Schröder-van Laar and Prigogine-Defay equations [see pp. 46-47 and 90-91 of Jacques, Collet & Wilen (1981)]. The predicted composition of the ($P2_12_1$)/($P2_1/c$) eutectic is relatively insensitive ($\pm 2\%$) to the ΔH_{fus} values if the latter are varied within reasonable limits [± 2 kcal mol⁻¹ (± 8 kJ mol⁻¹)].

than the melting point of chiral crystals composed of one of the enantiomers [see, *e.g.*, Brock, Schweizer & Dunitz (1991)]. It is more appropriate to compare the melting point of the racemic compound with the eutectic temperature of the D and L chiral crystals, which can be estimated from the simplified Schröder–van Laar equation [see pp. 46–47 of Jacques, Collet & Wilen (1981)]. Assuming a ΔH_{fus} of 7 kcal mol⁻¹ (29 kJ mol⁻¹), the eutectic temperature for (R)-(+)- and (S)-(-)-P₂₁2₁2₁ crystals is *ca* 328 K (55 °C), and the difference between this eutectic temperature and the melting point of the P₂₁/c crystals is *ca* 70 K (see Fig. 6).

A number of pairs of closely related chiral and racemic structures are known (see, *e.g.*, Pedone & Benedetti (1972) and Jacques, Collet & Wilen (1981, p. 24 *ff.*)) of which L- and D,L-alanine (Simpson & Marsh, 1966) is perhaps the classic example. As in the pair of structures described here layers of enantiomers can be identified, and the two crystal forms in each pair differ mainly in the stacking of the layers. A growing crystal might then be expected to twin or to incorporate layers of the 'wrong' enantiomer if growth occurs parallel to the layer normal [see, *e.g.*, the study by Freer & Kraut (1965) of a 'hybrid' crystal of D,L-homocysteine thiolactone hydrochloride]. The more energetically similar the two kinds of interlayer interactions, the more likely such mistakes. In the case of THIOPH the large {001} faces of the crystals (see Fig. 1) indicate that growth is slow perpendicular to the layer normal. The greater thickness parallel to *c* of the racemic crystals, as well as their much higher melting point, indicates that the stacking is more favorable in the P₂₁/c than in the P₂₁2₁2₁ crystals. We came across no indication of stacking disorder, probably because the mole fraction of the 'wrong' enantiomer in the solutions from which chiral crystals could be grown was so very low.

This system would seem to be an example of the widely held, but poorly documented, belief that crystals of racemic compounds are usually denser than their chiral counterparts. A recent study (Brock, Schweizer & Dunitz, 1991) has shown that if the enantiomers can be resolved (*i.e.*, if the racemic melt is a two-component system) and if both chiral and racemic crystalline forms are known, then *on average* the racemic crystals are about 1% denser than their chiral counterparts. In about 20% of the structure pairs, however, the chiral crystal is the more dense. Furthermore, the comparison of densities is affected by the fact that the sample includes pairs for which

the racemic crystal is much more stable than the chiral crystal (as is the case here), but no pairs for which that stability order is reversed. If the racemic compound is significantly less stable than the chiral material, it disappears from the phase diagram and cannot be isolated under equilibrium conditions.

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