# Crystal and Molecular Structure and Determination of Absolute Configuration of Two Enantiomers of Methoxycarbonylmethyl Carboxymethyl Sulfoxide

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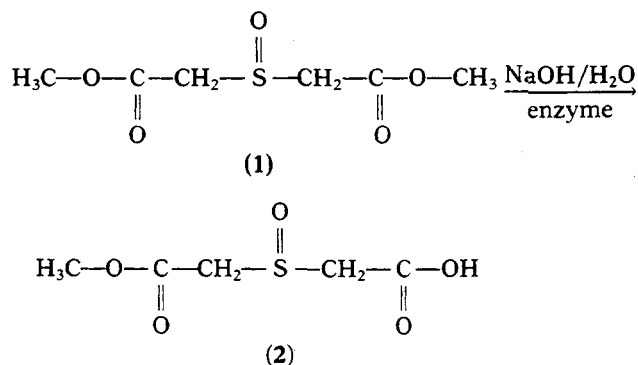
Received 5 October 1993; revised 24 January 1994

## ABSTRACT

*Crystal and molecular structures of two enantiomers of methoxycarbonylmethyl carboxymethyl sulfoxide 2 (2(−) and 2(+)) have been determined by X-ray methods. Crystals of 2 are orthorhombic, space group $P2_12_12_1$, Z = 4, with a = 5.1900(4) Å, b = 8.7960(7) Å, and c = 18.489(2) Å in 2(−) and a = 5.1897(7) Å, b = 8.787(1) Å, and c = 18.520(2) Å in 2(+). Structures 2(−) and 2(+) were refined to R factors equal to 0.041 and 0.052, respectively. The absolute configuration at the sulfur atom in enantiomer 2(−) with $[\alpha]_D^{20}$ = −20° (MeOH) is $R_S$. (In 2(+), where $[\alpha]_D^{20}$ equals +20° (MeOH), the absolute configuration at S atom is $S_S$.) In compounds 2(−) and 2(+), a strong intermolecular hydrogen bond O3–H3 . . . O1 occurs.*

## INTRODUCTION

Organic sulfoxides are very important substrates in asymmetric synthesis of organic compounds, in particular, in synthesis of biologically active compounds. Information about their absolute or relative configuration is necessary for proper planning of synthesis, or other chemical reactions. In this article, we present structural studies of two enantiomers of the compound 2 which are produced by enzymatic hydrolysis of prochiral dimethyl sulfinyl-diacetate (1) [1] (Scheme 1).

$$H_3C-O-\overset{\overset{\displaystyle O}{\|}}{C}-CH_2-\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle O}{\|}}{S}}-CH_2-\overset{\overset{\displaystyle O}{\|}}{C}-O-CH_3 \xrightarrow[\text{enzyme}]{\text{NaOH}/H_2O}$$

(1)

$$H_3C-O-\overset{\overset{\displaystyle O}{\|}}{C}-CH_2-\overset{\overset{\displaystyle O}{\|}}{S}-CH_2-\overset{\overset{\displaystyle O}{\|}}{C}-OH$$

(2)

**SCHEME 1**

Together with studies published earlier [2–4] on the absolute configuration of α-phosphoryl sulfoxides (3, 4, and 5; Figure 1), the present investigations may augment the knowledge about the structure of sulfoxides with different substituents.
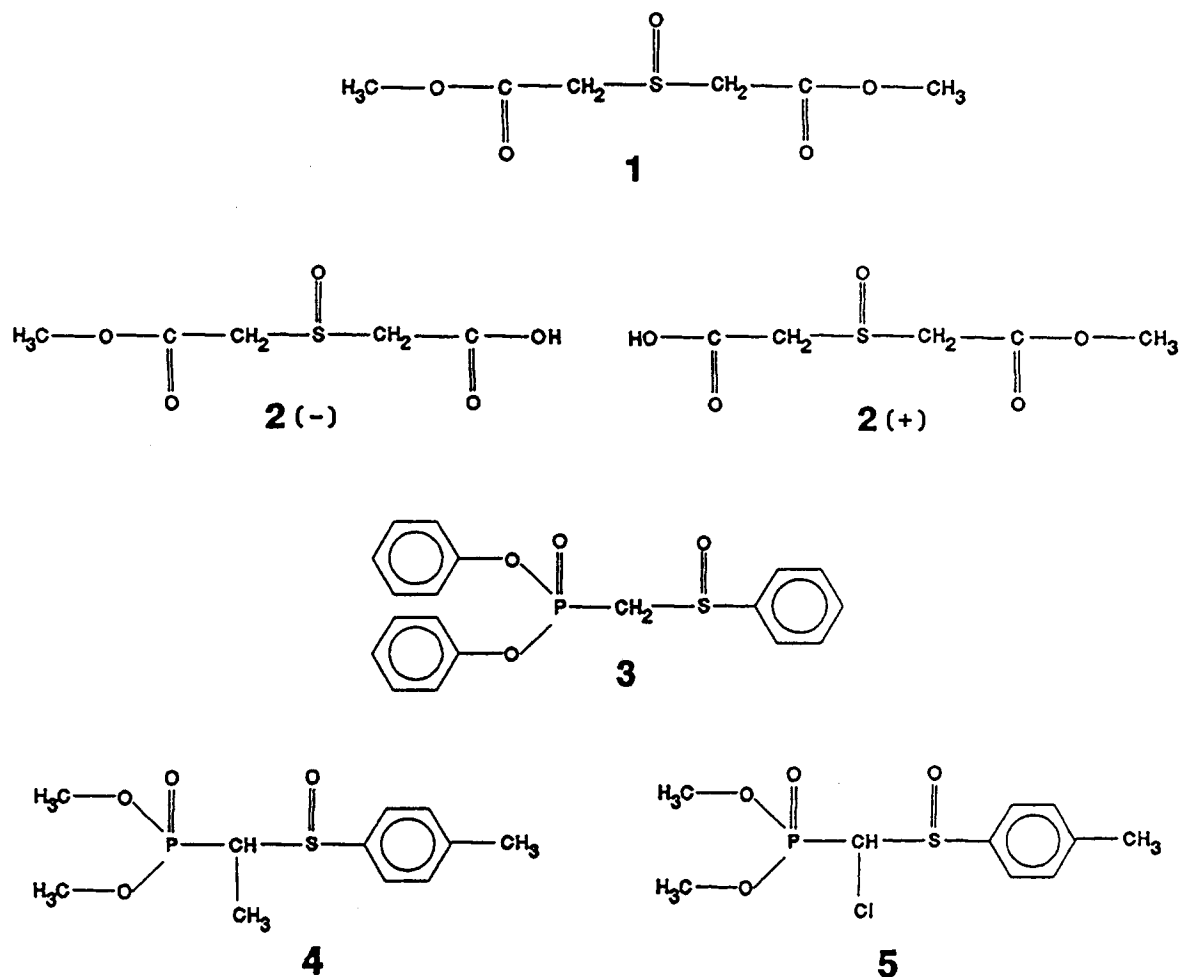
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**1**

**2 (−)**          **2 (+)**

**3**

**4**          **5**

**FIGURE 1**   Structures of α-phosphoryl sulfoxides investigated.

## RESULTS AND DISCUSSION

Atomic coordinates of examined compounds 2(−) and 2(+) are presented in Table 1. Table 2 shows bond lengths and angles of nonhydrogen atoms. The full crystallographic data (anisotropic displacement coefficients, torsional angles, least-squares planes, and values of $F_{obs}$ and $F_{calc}$) are deposited at Cambridge Crystallographic Data Centre [8].

Compound 2 is optically active possessing two enantiomers: with $[\alpha]_D^{20} = -20°$ (compound 2(−)) and with $[\alpha]_D^{20} = +20°$ (compound 2(+)). Both enantiomers were studied. The absolute configuration was determined by two methods: the first method by calculation of the ETA ($\eta$) parameter for 2(−) and 2(+), respectively, with uninversed and with inversed atomic coordinates [5]; the second one was the Hamilton test [6], analogically for "uninversed" and "inversed" structures.

The dextrorotatory enantiomer, the crystal of which was not ideally suitable for X-ray studies (dimensions, irregular external shape), was refined

to an $R$ factor of 0.0515 (with extinction parameter) and has the $S_S$ absolute configuration at the sulfur S atom. The calculated ETA parameter was 0.975(70), and after inversing of atomic coordinates, the ETA parameter was −0.975(70).

For the opposite enantiomer (i.e., with $[\alpha]_D^{20} = -20°$), the absolute configuration at the sulfur atom was established as $R_S$. The respective ETA values were ETA = 1.004(70) and $ETA_{inv}$ = −1.003(70); the $R$ factor was 0.0413 with refinement of the extinction parameter.

The determination of the absolute configuration by the Hamilton test gave the following results: for compound 2(−), $\mathfrak{R}_{ratio}$ = 1.01246, $N$ = 1020 − 103 = 917, $\alpha \leq 10^{-9}$, which confirms the $R_S$ configuration; for 2(+), the values were $\mathfrak{R}_{ratio}$ = 1.06260, $N$ = 892 − 103 = 789, $\alpha \leq 10^{-9}$, which proves the $S_S$ configuration. Thus, both methods unequivocally confirmed the established configuration.

The Newman projections of all theoretically possible conformations of molecule 2 are shown in Figure 2.

**TABLE 1** Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Coefficients ($\text{Å}^2 \times 10^3$) for **2(−)** and **2(+)**

| | x | y | z | U(eq) |
|---|---|---|---|---|
| | | Compound **2(−)** | | |
| S | 9302(1) | 7292(1) | 1072(1) | 47(1) |
| O1 | 11693(5) | 6499(3) | 1344(2) | 65(1) |
| O2 | 10200(9) | 9712(5) | 2094(2) | 126(2) |
| O3 | 7069(6) | 9237(3) | 2851(2) | 74(1) |
| C1 | 7332(6) | 7642(4) | 1855(2) | 53(1) |
| C2 | 8393(8) | 8982(4) | 2262(2) | 59(1) |
| O2′ | 9918(7) | 5922(4) | −345(2) | 81(1) |
| O3′ | 7505(9) | 3894(3) | −139(2) | 81(1) |
| C1′ | 7319(7) | 5792(4) | 717(2) | 52(1) |
| C2′ | 8455(8) | 5241(4) | 24(2) | 56(1) |
| C3′ | 8411(15) | 3258(6) | −824(3) | 107(2) |
| | | Compound **2(+)** | | |
| S | 698(1) | 2706(1) | 8928(1) | 47(1) |
| O1 | −1707(5) | 3494(3) | 8658(1) | 65(1) |
| O2 | −230(9) | 295(5) | 7907(2) | 119(2) |
| O3 | 2932(7) | 768(4) | 7144(2) | 74(1) |
| C1 | 2663(7) | 2350(4) | 8141(2) | 54(1) |
| C2 | 1614(9) | 1026(5) | 7734(2) | 59(1) |
| O2′ | 85(8) | 4075(4) | 10344(2) | 80(1) |
| O3′ | 2497(10) | 6104(3) | 10138(2) | 81(1) |
| C1′ | 2671(7) | 4218(4) | 9283(2) | 52(1) |
| C2′ | 1554(9) | 4754(4) | 9975(2) | 56(1) |
| C3′ | 1683(14) | 6753(6) | 10830(2) | 99(2) |

Equivalent isotropic *U* is defined as one third of the trace of the orthogonalized $U_{ij}$ tensor.

The calculations performed with molecular mechanics methods [13] (see Figure 3) confirm that the best energetically stable conformations are A, B, and C, as shown in Figure 2. The stable enantiomers in the solid state are **2(−)** and **2(+)** which correspond well with the theoretical 2-B conformation presented in Figure 2 (and its mirror image). The Newman projection of a sulfoxide moiety is presented in Figure 4.

Figures 2 and 4 reveal that both enantiomers (i.e., **2(−)** and **2(+)**) have the antiperiplanar arrangement of the -CH₂-group and the esterified carboxyl group. The difference is in the different location of the free electron pair which is synclinal to the esterified carboxyl group (but can be situated to the left or to the right of COOCH₃).

The bond lengths and angles in the compounds **2(−)** and **2(+)** correspond well with those presented in the literature [7]. Comparison of some interesting geometrical parameters is shown in Table 2. The selected torsional angles of compounds **2(−)** and **2(+)** are given in Table 3. The central plane is defined by the atoms O1, C1, C1′. The sulfur atom lies outside that plane, which suggests that it is pseudotetrahedral. Two other planes, i.e., the one defined by the carboxyl group (C1, C2, O2, O3) and the one defined by the ester group (C1′, C2′, O2′, O3′), lie at different angles to that plane. The values of these angles are 55.6(1)° and 42.4(1)°, respectively. The distances of the S and C3 atoms from these planes are given in Table 4. This table also presents the dihedral angles between respective planes in the molecules of **2(−)** and **2(+)**.

Figures 5 and 6 present the thermal ellipsoidal plots of the molecules of the compounds **2(−)** and **2(+)**; Figures 7 and 8 show the molecular arrangement in the unit cell with presentation of intermolecular hydrogen bonds O3–H3 ... O1, where the H3 ... O1 distances are 1.636(5) Å and 1.638(4) Å and the O3–H3 ... O1 angles are 158.8 (4)° and 159.2 (4)°, respectively.

## EXPERIMENTAL

Crystal and molecular structures of two enantiomers of carbomethoxymethyl carboxymethyl sulfoxide (**2(−)** and **2(+)**) were determined using data

**TABLE 2** Bond Lengths (Å) and Angles (°) of Nonhydrogen Atoms in Examined Structures **2(−)** and **2(+)**

| | 2(−) | 2(+) | | 2(−) | 2(+) |
|---|---|---|---|---|---|
| | | | Bond Lengths (Å) | | |
| S–O1 | 1.509(3) | 1.512(3) | O3′–C3′ | 1.462(6) | 1.465(6) |
| S–C1 | 1.799(3) | 1.806(3) | S–C1′ | 1.798(3) | 1.802(4) |
| O2–C2 | 1.178(6) | 1.196(6) | O2′–C2′ | 1.184(5) | 1.186(5) |
| O3–C2 | 1.307(5) | 1.309(5) | O3′–C2′ | 1.318(5) | 1.318(5) |
| C1–C2 | 1.503(5) | 1.488(6) | C1′–C2′ | 1.491(5) | 1.483(5) |
| | | | Bond Angles (°) | | |
| O1–S–C1 | 106.2(1) | 106.2(1) | O1–S–C1′ | 104.6(2) | 104.6(2) |
| C1–S–C1′ | 95.4(2) | 95.8(2) | C2′–O3′–C3′ | 115.0(4) | 116.3(4) |
| S–C1–C2 | 109.2(2) | 109.7(3) | S–C1′–C2′ | 109.0(2) | 109.1(3) |
| O2–C2–O3 | 123.0(4) | 123.2(4) | O2′–C2′–O3′ | 124.2(3) | 124.0(3) |
| O2–C2–C1 | 125.9(4) | 125.2(4) | O2′–C2′–C1′ | 125.8(3) | 126.1(4) |
| O3–C2–C1 | 111.0(3) | 111.5(4) | O3′–C2′–C1′ | 110.0(3) | 109.8(3) |
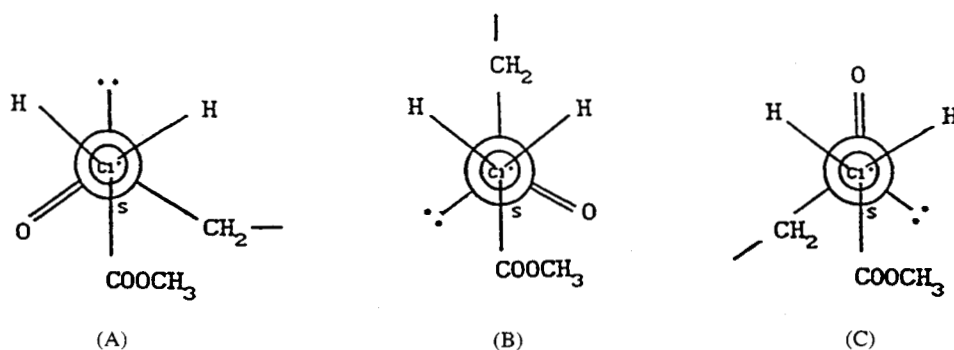
**FIGURE 2**   The Newman projections (A–C) of all theoretically possible conformations of the compound **2**.
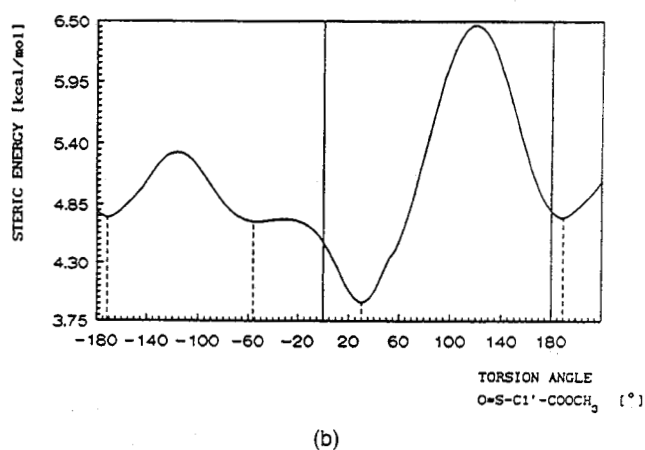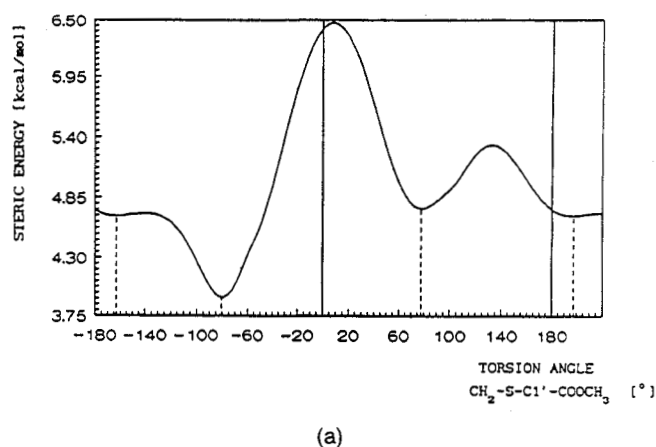


(a)



(b)

**FIGURE 3**   Steric energy of molecule **2** as a function of torsion angles (a) $CH_2$–S–C1'–$COOCH_3$ and (b) O=S–C1'–$COOCH_3$ (MMX86 Molecular Mechanics Program [13]).



C1–S–C1'–C2'  = 179.0(3)            C1–S–C1'–C2'  = –178.4(3)
H11'–C1'–S–O1 = 164.7(10)           H11'–C1'–S–O1 = –145.5(10)

**Compound 2(–)**          **Compound 2(+)**

**FIGURE 4**   The Newman projection of the sulfoxide moiety of the compound **2**.

**TABLE 3**   Selected Torsional Angles (°) in Compounds **2(–)** and **2(+)**

|  | **2(–)** | **2(+)** |
| --- | --- | --- |
| S–C1–C2–O2 | 1.2(5) | –1.0(6) |
| S–C1–C2–O3 | –177.5(3) | 177.6(3) |
| S–C1'–C2'–O2' | –20.5(5) | 19.4(5) |
| S–C1'–C2'–O3' | 162.2(3) | –162.4(3) |
| O1–S–C1–C2 | 77.5(3) | –76.9(3) |
| O1–S–C1'–C2' | –72.7(3) | 73.1(3) |

**TABLE 4**   Distances of S and C3 Atoms (Å) from Least-Squares Planes and Interesting Dihedral Angles Between Planes (°) in **2**

| Atom/Plane | **2(–)** | **2(+)** |
| --- | --- | --- |
| S/O1 C1 C1' | 0.736(1) | 0.736(1) |
| C3/O3'C2'O2'C1' | 0.039(6) | 0.069(6) |
|  |  |  |
| Plane 1/Plane 2 |  |  |
| C1 C2 O2 O3/C1'C2'O2'O3' | 14.1(2) | 14.4(2) |
| C1 C2 O2 O3/C1 C1'O1 | 42.4(2) | 41.9(2) |
| C1'C2'O2'O3'/C1 C1'O1 | 55.6(2) | 55.4(2) |

collected on a CAD4 diffractometer. Compound **2** crystallizes in the orthorhombic system, space group $P2_12_12_1$. Crystal data and experimental details are shown in Table 5.

Intensity data were collected at room temperature using a diffractometer with graphite mono-chromatized Cu $K_\alpha$ radiation. Lattice constants were refined by least-squares fit of 25 reflections in the
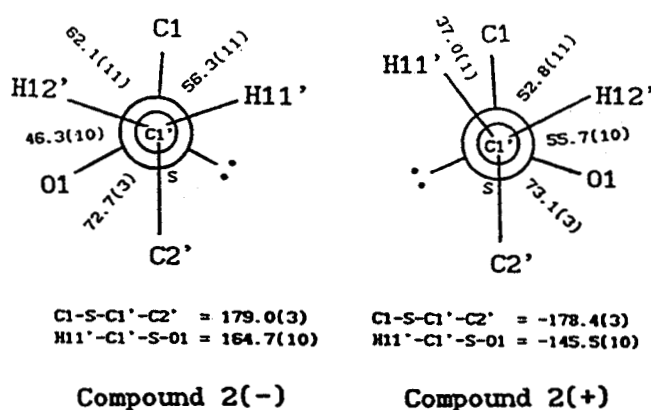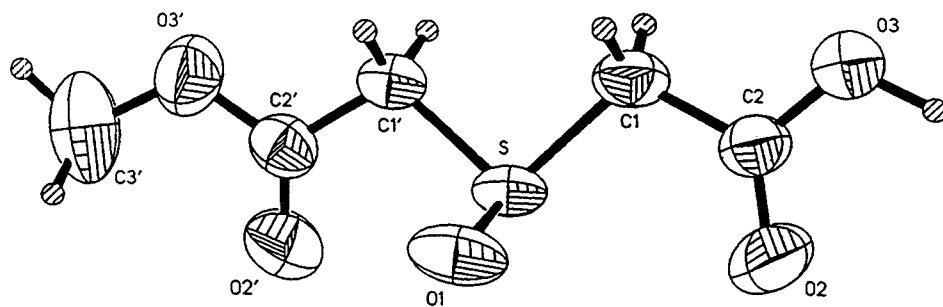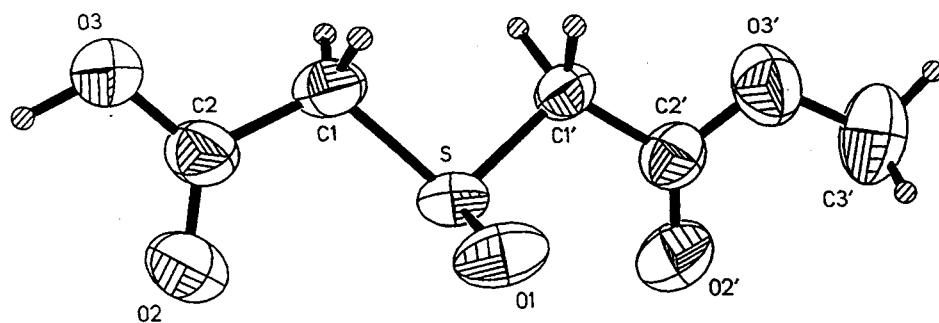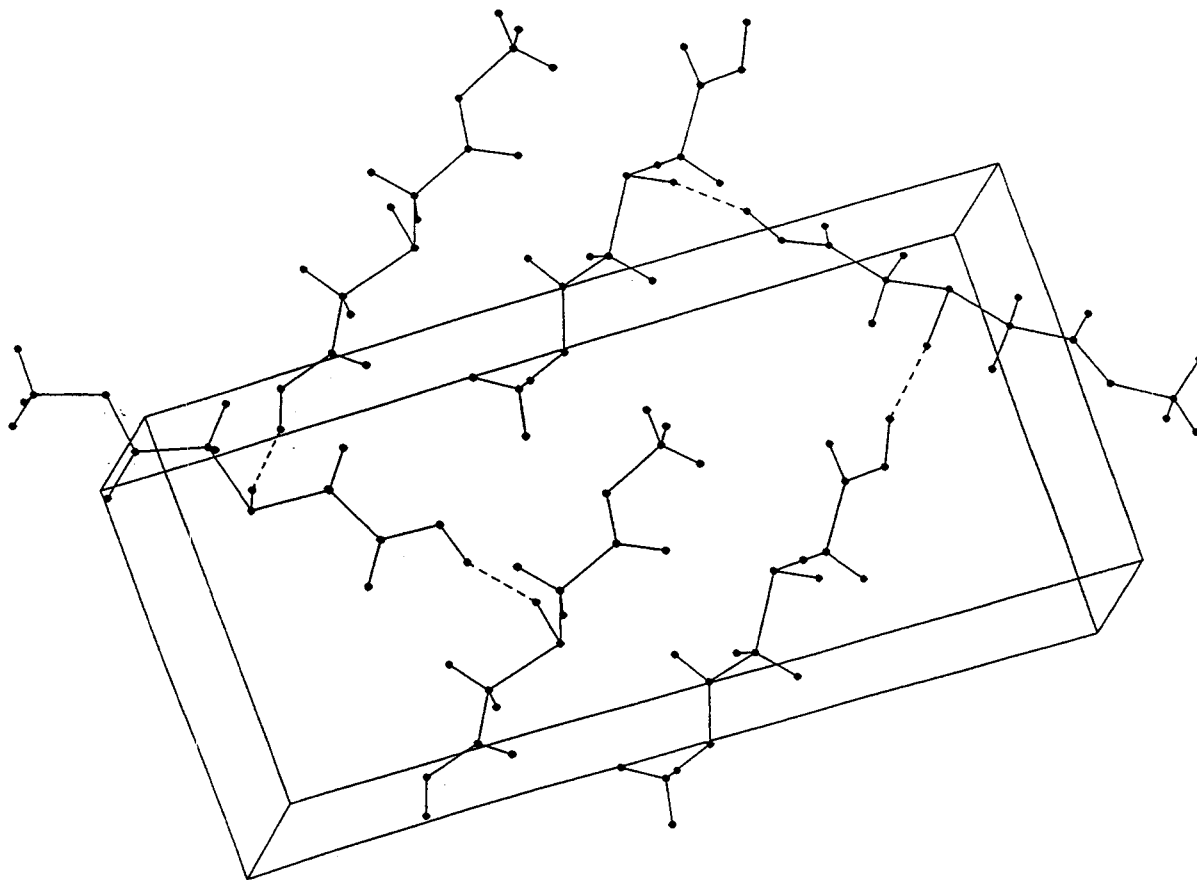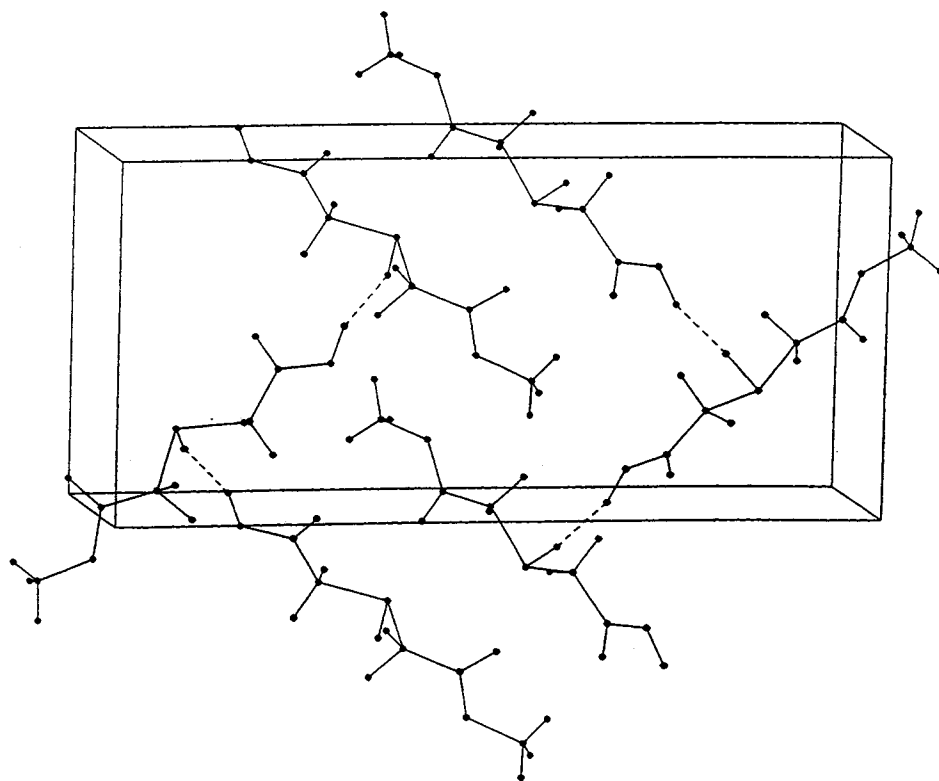
**FIGURE 5**   Thermal ellipsoidal plot of the molecule of 2(−) with atom numbering.



**FIGURE 6**   Thermal ellipsoidal plot of the molecule of 2(+) with atom numbering.



**FIGURE 7**   The unit cell of 2(−) with intermolecular O3–H3 ... O1 hydrogen bonding system (symmetry: 2 − x, 0.5 + y, 0.5 − z).

**FIGURE 8** The unit cell of **2(+)** with intermolecular O3–H3 . . . O1 hydrogen bonding system (symmetry: $-x$, $-0.5 + y$, $1.5 - z$).

**TABLE 5** Crystal Data and Experimental Details

|  | 2(−) | 2(+) |
|---|---|---|
| Molecular formula | $C_5H_8O_5S$ | $C_5H_8O_5S$ |
| $[\alpha]_D^{20}$ (°) | −20 | 20 |
| Space group | $P2_12_12_1$ | $P2_12_12_1$ |
| $a$ (Å) | 5.1900(4) | 5.1897(7) |
| $b$ (Å) | 8.7960(7) | 8.787(1) |
| $c$ (Å) | 18.489(2) | 18.520(2) |
| $V$ (Å³) | 844.1(1) | 844.5(2) |
| $Z$ | 4 | 4 |
| $D_c$ (g/cm³) | 1.418(2) | 1.417(2) |
| $\mu$ (cm⁻¹) | 32.3 | 32.3 |
| Crystal dimensions (mm) | 0.3, 0.4, 0.4 | 0.4, 0.4, 0.5 |
| Maximum $2\theta$ (°) | 150 | 150 |
| Radiation, $\lambda$ (Å) | Cu $K_\alpha$, 1.54178 | Cu $K_\alpha$, 1.54178 |
| Scan mode | $\omega/2\theta$ | $\omega/2\theta$ |
| Scan width (°) | 0.65 + 0.14 tan $\theta$ | 0.74 + 0.14 tan $\theta$ |
| $hkl$ ranges | $h = 0\ 6$ | $h = 0\ 6$ |
|  | $k = 0\ 11$ | $k = 0\ 11$ |
|  | $l = 0\ 23$ | $l = 0\ 23$ |
| EAC correction: |  |  |
| min | 0.9173 | 0.8078 |
| max | 0.9985 | 0.9998 |
| av | 0.9672 | 0.9325 |
| No. of reflections: |  |  |
| total | 1046 | 938 |
| with $I \geq 3\sigma$ $(I)$ | 1014 | 894 |
| Absolute configuration at S atom | R | S |
| R | 0.041 | 0.052 |

$\theta$ range of 20.3–29.3° for **2(−)** and 19.5–29.1° for **2(+)**. Decline in intensities of three standard reflections (−1, −1, 8; 1, −2, 7; 2, −2, −6 for **2(−)** and −2, −2, −4; 1, −4, 4; −3, −2, 2 for **2(+)**) was, respectively, 2.6% during 10.5 hours of exposure and 0.01% during 10 hours. An absorption correction was applied using the EAC program [9,10], where the minimum transmissions were 84.14 and 65.26%, max 99.71 and 99.97%, and av 93.55 and 86.95% (for **2(−)** and **2(+)**, respectively; see Table 5). A total of 1014 observed reflections for **2(−)** and 894 for **2(+)** [with $I \geq 3\sigma$ $(I)$] were used to solve the structures by direct methods [11] and to refine them by full matrix least-squares using $F$'s [12]. Hydrogen atoms were placed geometrically at idealized positions with fixed isotropic thermal parameters (except the H3 hydroxyl atom which was found on a difference Fourier map) and set as riding. Anisotropic thermal parameters were refined for all nonhydrogen atoms. The final refinement converged to $R = 0.041$ (in **2(−)**) and $R = 0.052$ (in **2(+)**) with the weighting scheme,

$$w = \frac{1}{\sigma^2(F) + 0.01\,F^2}$$

for 103 refined parameters, with inclusion of the extinction parameter into refinement (the obtained value of the extinction parameter in **2(−)** is 0.0509(87) and in **2(+)** is 0.0850(136)). Refinement without the extinction parameter gives $R = 0.052$ in **2(−)** and $R = 0.068$ in **2(+)**. The largest residual peak in the final difference Fourier map was 0.319 eÅ$^{-3}$ (**2(−)**) and 0.410 eÅ$^{-3}$ (**2(+)**). Data corrections were carried out with the Enraf–Nonius SDP crystallographic computing package [9], with structure solution and refinement on the SHELXTL

package [11]. Scattering factors were taken from the International Tables for X-ray Crystallography [12].

## ACKNOWLEDGMENT

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