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Structure of L-Lanthionine

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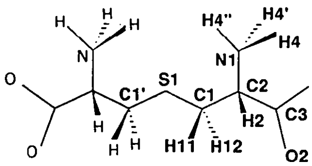
Abstract. $C_6H_{12}N_2O_4S$, $M_r = 208·24$, monoclinic, $C2$, $a = 9·748\ (2)$, $b = 5·187\ (1)$, $c = 10·584\ (2)$ Å, $\beta = 124·78\ (1)°$, $V = 439·5\ (1)$ Å^3, $Z = 2$, $D_x = 1·57$ g cm^{-3}, λ(Mo $K\alpha$) = 0·7108 Å, $\mu = 3·38$ cm^{-1}, $F(000) = 220$, $T = 273$ K, $R = 0·022$, $wR = 0·027$ for 526 independent observed reflections. The material was isolated from natural sources. Data were collected for Friedel pairs and the absolute configuration established. In the crystal, the molecule exists as a zwitterion and is bisected by a twofold axis. Molecules are connected by a three-dimensional network of N—H···O hydrogen bonds with each H atom forming a single hydrogen bond. A pair of carboxylate O atoms approach an S atom symmetrically and in a nucleophilic manner with S···O contacts of 3·561 (2) Å. The molecular structure resembles that of DL-lanthionine, while the crystal packing is somewhat similar to that found in L-cysteine.

Introduction. L-Lanthionine (3,3′-thiodialanine) is an uncommon amino acid whose mode of biosynthesis in either insect tissues or in mammalian systems is still unsettled. There has been a renewed interest in lanthionine as its metabolites have been detected in the human brain and urine under both normal and pathological conditions (Ricci, Nardini, Federici & Cavallini, 1986; Nardini, Ricci, Caccuri, Solinas, Vesci & Cavallini, 1988). For instance, thiomorpholine-3,5-dicarboxylic acid, which is formed from lanthionine, is found in brain tissues. This latter compound has structural features resembling the 1,4-diazepines, derivatives of which have considerable pharmacological significance as anti-anxiety agents. The crystal structures of *meso*-lanthionine dihydrochloride and of DL-lanthionine monohydrate have been determined (Rosenfield & Parthasarathy, 1974; Głowka & Parthasarathy, 1986). These structures are of interest because the S atom makes a very short intermolecular contact of 3·251 (2) Å to S (*meso*-lanthionine) and a contact of 3·238 (1) Å to O (DL-lanthionine). It has been suggested that such short heteroatom contacts to sulfur may be used in the deliberate design or crystal engineering of organic solids (Nalini & Desiraju, 1986, 1987). Accordingly, the crystal-structure analysis of the third naturally occurring isomer, L-lanthionine, was undertaken.



Experimental. The enantiomerically pure natural product was isolated by a previously reported procedure (Rao, Ennor & Thorpe, 1967) from the pupae of the silkworm *Bombyx mori*, collected from a silk filature in Channapatna, S. India. It was not easy to grow single crystals of the material. About 10 mg of the solid were taken in 0·5 mL water and heated over a water bath to 333 K. Another 0·5 mL of water were added and the temperature carefully raised to 343 K. Dissolution was completed by the addition of 3 drops of dilute ammonia solution (5 drops concentrated NH_4OH in 2 mL water). The solution was filtered and allowed to stand at 281 K (refrigerator) for a month, whereupon a small number of well formed colourless crystals were observed.

Intensity data were collected on a plate-like crystal 0·35 × 0·04 × 0·50 mm on a Syntex $R3$ diffractometer. Unit-cell parameters were obtained from 24 reflections in the range $4 \leq 2\theta \leq 55°$. The ω-scan method was used with a scan width of 1·30° ω and the scan speed was between 2·90 and 9·80° min^{-1}. A total of 1061 reflections were collected with $[(\sin\theta)/\lambda]_{\max} = 0·65$ Å^{-1} and in the range $-12 \leq h \leq 12$, $-6 \leq k \leq 6$, $-13 \leq l \leq 0$. Of these, 526 unique reflections were found to be non-zero with $I \geq$

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$3{\cdot}0\sigma(I)$. Three standard reflections $1\bar{3}\bar{1}$, $5\bar{1}\bar{3}$ and $1\bar{1}\bar{4}$ were measured every 97 reflections and showed less than 1% variation. The intensities of the $0\bar{4}\bar{1}$ reflection were measured to determine absorption effects. The minimum and maximum intensities were within 15% of each other, therefore no absorption corrections were applied. The structure was solved by direct methods using the program *MULTAN* (Germain, Main & Woolfson, 1971) and full-matrix least-squares refinement was performed on F_o using the program *SHELX*76 (Sheldrick, 1976). The H atoms, located from a difference map, were refined isotropically while the other atoms were refined anisotropically. Refinement converged at $R = 0{\cdot}022$, $wR = 0{\cdot}027$, $w = 1/\sigma^2(F_o)$, error-of-fit = 1·34, $\Delta/\sigma_{\max} = 0{\cdot}09$, the maximum peak in the final Fourier map $= 0{\cdot}34\ \text{e Å}^{-3}$ and the scattering factors were taken from *International Tables for X-ray Crystallography* (1974). Refinement was performed on all data (Friedel opposites) and the *R* values obtained for the two inversion-related sets of coordinates were 0·0217 and 0·0242. The absolute configuration of lanthionine is therefore established as the former and is as shown in Fig. 1.

Discussion. Atomic positions and equivalent isotropic temperature factors are listed in Table 1.* The bond lengths and angles are given in Table 2. The atom-numbering scheme is given in the structural formula in the *Introduction*. Atoms related by the crystallographic twofold axis are designated C(1)′ *etc.* in the following discussion. Fig. 1 depicts a pair of molecules translated along [010]. The molecule exists as a double zwitterion and is bisected by a twofold axis which passes through S(1) with the angle C(1)—S(1)—C(1)′ being 100·3 (1)°. Most of the intramolecular bond lengths and angles are in close agreement with those reported for DL-lanthionine (within 3σ). It was noted (Głowka & Parthasarathy, 1986) that the two C(2)—N(1) distances in the D (or L) molecule in that structure are significantly different, these distances being 1·478 (2) and 1·497 (2) Å. Curiously, the corresponding distance in the present structure is 1·485 (2) Å, which is the average of the two distances in the DL crystal. Unlike the DL structure, the two carboxyl distances C(3)—O(1) = 1·261 (2) Å and C(3)—O(2) = 1·242 (2) Å are significantly different (10σ).

Table 1. *Fractional coordinates and isotropic thermal parameters*

$$B_{\text{eq}} = (8\pi^2/3)\textstyle\sum_i\sum_j U_{ij}a_i^*a_j^*\mathbf{a}_i.\mathbf{a}_j.$$

	x	y	z	$B_{\text{eq}}/B_{\text{iso}}$(Å^2)
S(1)	0·5000	0·5000	0·5000	1·3 (1)
O(1)	−0·0349 (1)	0·1644 (2)	0·1331 (1)	1·6 (1)
O(2)	0·1073 (2)	−0·2001 (2)	0·2355 (2)	2·0 (1)
N(1)	0·2249 (2)	0·3957 (3)	0·1518 (1)	1·2 (1)
C(1)	0·3273 (2)	0·2769 (3)	0·4185 (2)	1·4 (1)
C(2)	0·2601 (2)	0·1768 (3)	0·2568 (2)	1·2 (1)
C(3)	0·0969 (2)	0·0314 (3)	0·2012 (2)	1·2 (1)
H(2)	0·3437 (25)	0·0604 (41)	0·2568 (23)	2·1 (4)*
H(4)	0·1479 (25)	0·3310 (41)	0·0518 (25)	2·1 (4)*
H(4′)	0·1776 (25)	0·5292 (51)	0·1689 (22)	2·0 (4)*
H(4″)	0·3146 (30)	0·4466 (47)	0·1674 (25)	2·5 (5)*
H(11)	0·3645 (27)	0·1482 (38)	0·4890 (26)	2·3 (5)*
H(12)	0·2368 (27)	0·3625 (38)	0·4134 (24)	2·1 (4)*

* Atoms refined isotropically.

Table 2. *Intramolecular bond lengths* (Å) *and angles* (°) *with e.s.d.'s*

S(1)—C(1)	1·806 (2)	N(1)—H(4″)	0·835 (24)
O(1)—C(3)	1·261 (2)	C(1)—C(2)	1·533 (2)
O(2)—C(3)	1·242 (2)	C(2)—C(3)	1·542 (2)
N(1)—C(2)	1·485 (2)	C(1)—H(11)	0·908 (22)
N(1)—H(4)	0·943 (21)	C(1)—H(12)	0·961 (23)
N(1)—H(4′)	0·906 (26)	C(2)—H(2)	1·014 (21)

C(1)—S(1)—C(1)′	100·3 (1)	O(1)—C(3)—C(2)	116·3 (1)
C(2)—N(1)—H(4)	105 (1)	O(2)—C(3)—C(2)	117·8 (1)
C(2)—N(1)—H(4′)	111 (1)	N(1)—C(2)—C(1)	110·2 (1)
C(2)—N(1)—N(4″)	109 (2)	N(1)—C(2)—C(3)	109·9 (1)
H(4)—N(1)—H(4′)	109 (2)	N(1)—C(2)—H(2)	107 (1)
H(4)—N(1)—H(4″)	114 (2)	C(1)—C(2)—C(3)	106·4 (1)
H(4′)—N(1)—H(4″)	108 (2)	C(2)—C(1)—H(11)	113 (1)
S(1)—C(1)—C(2)	116·0 (1)	C(2)—C(1)—H(12)	107 (1)
S(1)—C(1)—H(11)	105 (1)	C(1)—C(2)—H(2)	112 (1)
S(1)—C(1)—H(12)	108 (1)	C(3)—C(2)—H(2)	111 (1)
O(1)—C(3)—O(2)	125·6 (1)	H(11)—C(1)—H(12)	108 (2)

The conformation of the molecule is also similar to that of the L molecule in the DL structure and to that of L-cysteine (Harding & Long, 1968). The S(1) atom is −synclinal to the N(1) atom with χ^1[S(1)—C(1)—C(2)—N(1)] = −51·1 (2)° [−58·1 (2) and −63·8 (2)° in the DL structure]. The value of χ^2[C(1)—S(1)—C(1)′—C(2)′] = −85·2 (2)° [−81·9 (1) and −63·8 (2)° for the DL]. The conformation of the carboxyl group, ψ^2[N(1)—C(2)—C(3)—O(1)], is −31·0 (2)° [−17·0 (2) and −27·1 (2)° in the DL; −3·0 and −36·1° in L-cysteine]. These similarities suggest that the three crystal structures are closely related.

Not surprisingly, N—H···O hydrogen bonding is the dominant interaction in the crystal packing. The general pattern of molecules is similar to that found in the structure of L-cysteine. There is even some resemblance in the unit-cell dimensions (L-cysteine: $P2_1$, $Z = 4$, $a = 9{\cdot}517$, $b = 5{\cdot}240$, $c = 11{\cdot}51$ Å, $\beta = 109{\cdot}13°$, $V = 542{\cdot}4$ Å^3; L-lanthionine: $C2$, $Z = 2$, $a = 9{\cdot}748$, $b = 5{\cdot}187$, $c = 10{\cdot}584$ Å, $\beta = 124{\cdot}78°$, $V = 439{\cdot}5$ Å^3). Table 3 gives pertinent intermolecular contact distances. Ammonium and carboxylate groups alternate in a hydrogen-bonded network that is arranged around a twofold screw axis such that

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* Lists of structure factors and anisotropic thermal parameters have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 52422 (5 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

each carboxylate oxygen O(1) accepts hydrogen bonds from H(4) and H(4″) of different molecules. The two N···O distances are 2·755 (2) and 2·827 (2) Å while the corresponding H···O distances are 1·83 (2) and 2·04 (2) Å. The second carboxylate oxygen O(2) is also hydrogen bonded but to an H(4′) atom of a third neighbouring molecule translated along [010] (Fig. 1). This is a shorter hydrogen bond with an N···O distance of 2·767 (2) Å and an H···O distance of 1·87 (3) Å.

The topology of the hydrogen-bond network in this structure finds a close parallel in those of L-cysteine and L-leucine (Harding & Howieson, 1976). Network properties of hydrogen bonds in amino-acid structures have been recently classified (Głowka & Parthasarathy, 1986). L-Lanthionine corresponds to type-*A* hydrogen bonding as defined by these authors, in that all H atoms participate in an equal number of hydrogen bonds. Since the number of acceptor (O; four) and donor (H; six) atoms are unequal in lanthionine, this type-*A* packing may be achieved only if (as observed) two of the four O atoms receive *two* H atoms. It has been remarked by these above authors that several other amino acids with an acceptor/donor ratio of 2/3 (Ala, Gly, Ile, Leu, Met, Phe, Val) exist as zwitterions and further that the DL and L forms have almost identical crystal structures. In contrast, the DL and L forms of lanthionine have completely different hydrogen-bond patterns mainly because the DL form crystallizes as a monohydrate with an effective acceptor/donor ratio of 5/8. It is curious that the racemic and enantiomeric forms of lanthionine should exhibit this difference, especially since crystals of both forms were obtained under similar conditions. This example illustrates our relatively poor ability to predict hydrogen-bond patterns even in crystals of simple molecules.

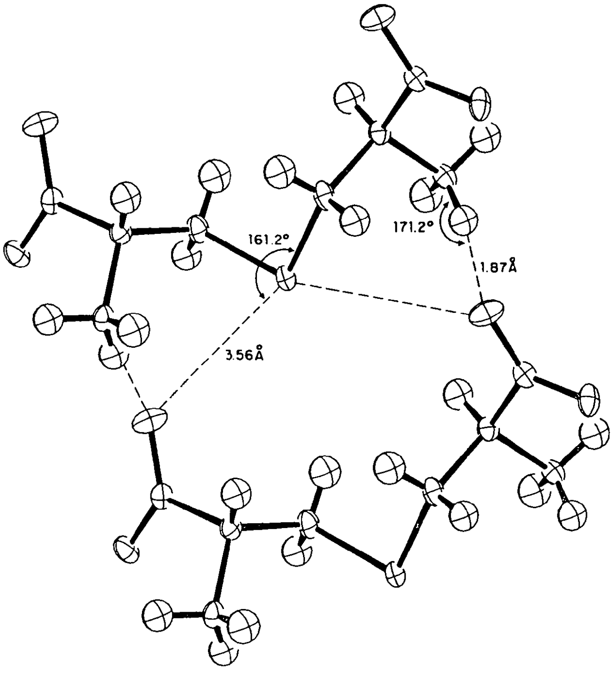

Fig. 1. Arrangement of molecules along [010] to show hydrogen bonding and S···O interactions.

Table 3. *Intermolecular distances* (Å) *with e.s.d.'s*

O(1)···N(1^{i})	2·755 (2)	O(2)···H(4′^{iii})	1·868 (26)
O(1)···N(1^{ii})	2·827 (2)	O(1)···H(4″^{ii})	2·041 (25)
O(2)···N(1^{iii})	2·767 (2)	O(2)···S(1^{iii})	3·561 (2)
O(1)···H(4^{i})	1·825 (22)		

Symmetry code: (i) $-x, y, -z$; (ii) $-\frac{1}{2}+x, -\frac{1}{2}+y, z$; (iii) $x, -1+y, z$.

Examination of Fig. 1 and Table 3 also shows that the S(1) atom is flanked by a pair of O(2) atoms belonging to the [010]-translated molecule such that the S···O contact distances are 3·561 (2) Å. While this distance is longer than the van der Waals distance (3·30 Å), the orientation of the O atom is almost exactly as predicted by the electrophile–nucleophile model (Rosenfield, Parthasarathy & Dunitz, 1977). The vector O(2)(x, $1+y$, z)···S(1)(x, y, z) makes an angle of 13·6 (1)° with the plane formed by S(1), C(1) and C(1)′ of the molecule (x, y, z) and an angle of 161·2 (1)° with the distant S—C covalent bond (Fig. 1). All this suggests that the angular preferences of some of these weak intermolecular contacts extend out to distances well beyond the so-called 'normal' van der Waals distances (Desiraju, 1989).

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