

## The Crystal Structure of L-Methionyl-L-methionine

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L-Methionyl-L-methionine,  $C_{10}H_{20}N_2O_3S_2$ , crystallizes in the orthorhombic space group,  $P2_12_12_1$ , with  $a=16.177$  (3),  $b=16.431$  (3),  $c=5.071$  (1) Å,  $Z=4$ . Analysis of the Patterson function led to the structure solution, and refinement on intensities of the 20 hydrogen and 17 nonhydrogen atoms with isotropic and anisotropic temperature factors respectively gives an  $R_I$  ( $=\sum|I_o - I_c|/\sum|I_o|$ ) of 0.051 for all 1821 reflections to a maximum  $\sin \theta/\lambda$  of  $0.650$  Å<sup>-1</sup>. The peptide is planar;  $\omega=179.9$  (2)°. The molecules pack with the carboxyl and amine groups of adjacent molecules connected by hydrogen bonds and with some interaction between the carbonyl and amide groups of the peptide unit. This hydrogen bonding scheme leads to sheets of polar groups parallel to the  $xz$  plane separated by layers of aliphatic side chains. A comparison of the conformations of the side chains in this structure is made with previous structure determinations of the methionine residue.

### Introduction

Recent biochemical research (Lis, Crampton & Matthews, 1972) using L-methionyl-L-methionine has shown that the dipeptide is absorbed through the intestine walls of rats much faster than the equivalent amount of amino acid, suggesting that the mechanisms for uptake of amino acids and peptides differ. The bacterioidal activity of the dipeptide has been investigated (Shankman, Higo & Gold, 1961) as well as its biosynthesis (Brenner & Vetterli, 1957) and chemical synthesis (Dekker, Taylor & Fruton, 1949; Milne & Peng, 1957).

The structure determination was undertaken not only to provide parameters for this dipeptide, but also to provide additional information concerning the con-

formations of the peptide unit and methionine side chains.

### Data collection

L-Methionyl-L-methionine purchased from Schwarz/Mann Chemical Co. was crystallized by evaporation of an ethanol-water solution of the material. Oscillation photographs indicated that crystals grown in this manner were generally split and unsuitable for data collection. A satisfactory specimen was obtained by trimming away the extraneous part of a split crystal with the solvent lathe described by Stout & Jensen (1968). The solvent used was water, and a long human hair served as the cutting fiber. Table 1 lists pertinent data concerning the crystal and data collection. Neither coincidence loss nor absorption corrections were applied since the crystal was small and the absorption coefficient,  $\mu$ , was  $3.85$  cm<sup>-1</sup>.

Table 1. Crystal and data collection information

Space group $P2_12_12_1$	Crystal dimensions 0.1 × 0.06 × 0.5 mm
Systematic absences: $h00$ , $h$ odd $0k0$ , $k$ odd $00l$ , $l$ odd	Data collected on 4-circle diffractometer Mo $K\alpha$ radiation, $\lambda=0.71069$ Å, Nb filter $\mu=3.853$ cm <sup>-1</sup> Maximum $\sin \theta/\lambda=0.650$ Å <sup>-1</sup> Scan range 1.0° with adjustment of $\alpha_1$ - $\alpha_2$ 20 s backgrounds at limits of scan
$a=16.177$ (3) Å $b=16.431$ (3) $c=5.071$ (1)	4 monitor reflections every 200 reflections 1821 unique reflections 1637 reflections with $I$ greater than $\sigma(I)$
Unit-cell volume $1347.9$ Å <sup>3</sup>	Observational variances based on counting statistics plus $(0.025 N_{pk})^2$ where $N_{pk}$ is the net peak count.
4 molecules per unit cell	
$F_{000}=600.0$	
Formula $C_{10}H_{20}N_2O_3S_2$	
M.W. 280.4	

### Structure solution and refinement

Positions of the two sulfur atoms were derived from the interpretation of the Patterson function and the other nonhydrogen atoms were found in a  $\Delta F$  map phased from the sulfur atoms. Least-squares refinement on  $|F|$  of the heavy atoms with isotropic thermal parameters gave a model sufficiently good to show the hydrogen atoms in a  $\Delta F$  map. Continued refinement by block-diagonal least-squares with isotropic thermal factors for the hydrogen atoms and anisotropic ones for the nonhydrogen atoms reduced  $R$  ( $=\sum||F_o| - |F_c||/\sum|F_o|$ ) to 0.043 for the reflections with  $|F_o| \geq 2\sigma(F)$ . To avoid any questions associated with the use of a threshold and the definition of  $\sigma(F)$  for weak intensities, the final refinement cycles were on  $I$  with all reflections included. The final  $R_I$  ( $=\sum|I_o - I_c|/\sum|I_o|$ ) is 0.051 and the average shift/error for the last cycles of

refinement was 0.14.\* The data set showed some extinction effects on the largest reflections, about 10%, but because of the small number of reflections affected no corrections were made. The measures of the quality of the structure determination are given in Table 2 and the atomic coordinates and thermal parameters are in Table 3. IUPAC nomenclature (IUPAC-IUB Commission on Biochemical Nomenclature, 1971) is used for this report.

### Discussion

Fig. 1 is a view of the molecule showing the 50% probability thermal ellipsoids along with the bond lengths, bond angles, and torsion angles for the nonhydrogen atoms, uncorrected for thermal motion. The largest thermal parameters are those of the terminal methyl groups of the side chains as has been found in previous methionine structure determinations (Mathieson, 1952; Aubry, Marraud, Protas & Néel, 1971; Torii & Iitaka, 1973; Stenkamp & Jensen, 1974). The thermal motion of the methyl C atoms notwithstanding, overall the molecule exhibits relatively moderate motion, a fact reflected by the overall  $B$  of  $3.0 \text{ \AA}^2$  evaluated from the Wilson plot and used to sharpen the Patterson function.

The bond lengths and bond angles of the molecule are all close to expected values. The  $C\alpha(1)-N(1)$  distance of  $1.500(4) \text{ \AA}$  is consistent with the molecule being in the zwitterionic form in the crystal although the  $C(2)-O'$  and  $C(2)-O''$  bond lengths differ by  $0.02 \text{ \AA}$ . Both oxygen atoms participate in hydrogen bonds; and on the basis of the  $N-O$  and  $O \cdots H$  distance in Table 4,  $O'$  participates in a slightly weaker interaction, accounting for the difference in bond lengths.

\* The table of structure factors has been deposited with the British Library Lending Division as Supplementary Publication No. SUP 30760 (14 pp., 1 microfiche). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester, CH1 1NZ, England.

The average C-H bond length is  $0.96(6) \text{ \AA}$  where the number in parentheses is the standard deviation

Table 2.  $R$  values

(a) $R$ values on $I$ for model refined on all $I$			
NVAR <sup>1</sup>	234	234	
Threshold	$0\sigma(I)$	$2\sigma(I)$	
NREF <sup>2</sup>	1821	1530	
$R_I = \frac{\sum  I_o - I_c }{\sum  I_o }$	0.051	0.050	
$R_{wI} = \sqrt{\frac{\sum 1/\sigma^2(I) ( I_o - I_c )^2}{\sum 1/\sigma^2(I) I_o^2}}$	0.076	0.071	
$GOF^3 = \sqrt{\frac{\sum 1/\sigma^2(I) ( I_o - I_c )^2}{NREF - NVAR}}$	1.19	1.22	
(b) $R$ values on $F$ for model refined on all $I$			
NVAR <sup>1</sup>	234	234	234
Threshold	$0\sigma(F)$	$2\sigma(F)$	$4\sigma(F)$
NREF <sup>2</sup>	1821	1646	1530
$R = \frac{\sum   F_o  -  F_c  }{\sum  F_o }$	0.051	0.042	0.038
$R_w = \sqrt{\frac{\sum 1/\sigma^2(F) (  F_o  -  F_c  )^2}{\sum 1/\sigma^2(F)  F_o ^2}}$	0.038	0.038	0.037
$GOF^3 = \sqrt{\frac{\sum 1/\sigma^2(F) (  F_o  -  F_c  )^2}{NREF - NVAR}}$	1.19	1.25	1.26
Cutoff <sup>6</sup>	$0\sigma(F)$	$2\sigma(F)$	$4\sigma(F)$
NREF <sup>5</sup>	1821	1665	1550
$R = \frac{\sum   F_o  -  F_c  }{\sum  F_o }$	0.051	0.043	0.039
$R_w = \sqrt{\frac{\sum 1/\sigma^2(F) (  F_o  -  F_c  )^2}{\sum 1/\sigma^2(F)  F_o ^2}}$	0.040	0.039	0.038
$GOF^3 = \sqrt{\frac{\sum 1/\sigma^2(F) (  F_o  -  F_c  )^2}{NREF - NVAR}}$	1.26	1.30	1.31

(1) NVAR = number of variables refined. (2) NREF = number of reflections contributing to sums.  $|I_o| \geq$  threshold. (3) GOF = goodness of fit. (4)  $\sigma(F)$  defined by  $\sigma(F) = \sigma(F^2)/2F$ . For computation, if  $I_o \leq 0.0$ ,  $I_o$  set equal to 0.01. (5) NREF = number of reflections contributing to sums.  $|F_o| \geq$  threshold. (6)  $\sigma(F)$  defined by  $\sigma(F) = \sqrt{[F^2 + \sigma(F^2)]} - F$ . For computation, if  $I_o \leq 0.0$ ,  $I_o$  set equal to 0.01.

Table 3. Atomic parameters

(a) Atomic parameters for carbon, nitrogen, oxygen and sulphur atoms. Thermal parameters are defined by the expression  $\exp[-2\pi^2(U_{11}h^2a^{*2} + U_{22}k^2b^{*2} + U_{33}l^2c^{*2} + 2U_{12}hka^*b^* + 2U_{13}hla^*c^* + 2U_{23}k lb^*c^*)]$ . Values are  $\times 10^4$ .

	$x$	$y$	$z$	$U_{11}$	$U_{22}$	$U_{33}$	$U_{12}$	$U_{13}$	$U_{23}$
N(1)	5453 (1)	7027 (2)	8200 (5)	199 (11)	338 (13)	296 (14)	16 (10)	-6 (11)	-0.4 (11.5)
$C\alpha(1)$	6105 (2)	7581 (2)	7101 (6)	187 (11)	355 (14)	269 (14)	5 (11)	11 (12)	-17 (12)
$C\beta(1)$	5830 (2)	8460 (2)	7591 (7)	263 (14)	381 (16)	349 (18)	46 (11)	-5 (14)	1 (15)
$C\gamma(1)$	6337 (2)	9072 (2)	6050 (8)	431 (20)	350 (15)	417 (19)	15 (13)	27 (17)	2 (15)
$S\delta(1)$	6108 (0.6)	10085 (0.5)	7281 (2.0)	575 (5)	356 (4)	565 (6)	-64 (4)	169 (5)	-16 (4)
$C\epsilon(1)$	6796 (3)	10675 (2)	5238 (10)	711 (29)	384 (21)	801 (33)	34 (20)	177 (27)	-53 (22)
O(1)	6916 (2)	7395 (2)	8522 (6)	202 (12)	291 (13)	290 (15)	4 (11)	5 (12)	-17 (12)
O(1)	6933 (1)	7338 (1)	10946 (4)	240 (10)	628 (14)	235 (10)	34 (9)	15 (9)	-11 (11)
N(2)	7576 (1)	7311 (2)	6990 (5)	200 (11)	429 (15)	177 (12)	-54 (10)	14 (10)	4 (12)
$C\alpha(2)$	8396 (1)	7134 (2)	8034 (5)	190 (12)	321 (14)	232 (14)	-18 (10)	7 (11)	-33 (12)
$C\beta(2)$	8518 (2)	6211 (2)	8420 (6)	260 (13)	334 (14)	281 (15)	13 (13)	44 (14)	22 (13)
$C\gamma(2)$	8550 (2)	5754 (2)	5809 (6)	391 (16)	348 (15)	350 (17)	-3 (15)	37 (17)	-26 (14)
$S\delta(2)$	8523 (0.6)	4658 (0.5)	6184 (2.0)	492 (4)	315 (4)	581 (5)	-93 (4)	-90 (5)	103 (4)
$C\epsilon(2)$	9412 (4)	4515 (3)	8246 (10)	1280 (48)	493 (25)	536 (30)	340 (28)	233 (31)	10 (22)
C(2)	9075 (2)	7502 (2)	6341 (6)	252 (13)	277 (13)	285 (15)	30 (11)	-14 (12)	-81 (13)
O'(2)	8898 (1)	7794 (1)	4156 (4)	312 (10)	575 (13)	334 (12)	29 (10)	-17 (10)	156 (11)
O''(2)	9800 (1)	7451 (1)	7236 (4)	190 (9)	621 (14)	357 (11)	62 (9)	19 (10)	-59 (12)

Table 3 (cont.)

(b) Atomic parameters for hydrogen atoms. Thermal parameter defined by the expression  $\exp[-8\pi^2 U^2 \sin^2 \theta/\lambda^2]$ . Values are  $\times 10^3$ .

	x	y	z	U
H1(1)	565 (2)	653 (2)	829 (6)	26 (8)
H2(1)	525 (2)	716 (2)	1006 (7)	57 (11)
H3(1)	491 (2)	710 (2)	706 (7)	56 (10)
H $\alpha$ (1)	617 (2)	747 (2)	517 (6)	22 (7)
H $\beta$ 1(1)	525 (2)	850 (2)	707 (6)	31 (8)
H $\beta$ 2(1)	589 (2)	858 (2)	946 (6)	29 (8)
H $\gamma$ 1(1)	690 (2)	898 (2)	634 (7)	37 (9)
H $\gamma$ 2(1)	616 (2)	903 (2)	415 (8)	67 (12)
H $\epsilon$ 1(1)	739 (2)	1048 (2)	538 (7)	63 (12)
H $\epsilon$ 2(1)	654 (3)	1067 (2)	335 (9)	84 (15)
H $\epsilon$ 3(1)	677 (3)	1122 (3)	588 (10)	103 (17)
H(2)	755 (2)	736 (2)	563 (5)	6 (7)
H $\alpha$ (2)	846 (2)	739 (2)	966 (6)	26 (7)
H $\beta$ 1(2)	900 (2)	614 (2)	948 (6)	34 (9)
H $\beta$ 2(2)	806 (2)	600 (2)	955 (7)	38 (9)
H $\gamma$ 1(2)	810 (2)	586 (2)	473 (7)	51 (11)
H $\gamma$ 2(2)	908 (2)	589 (2)	490 (7)	51 (11)
H $\epsilon$ 1(2)	951 (2)	402 (2)	830 (9)	72 (14)
H $\epsilon$ 2(2)	989 (3)	482 (3)	729 (13)	117 (22)
H $\epsilon$ 3(2)	930 (3)	465 (3)	983 (10)	87 (18)

derived from the sample by the formula  $\sigma = [\sum(\bar{l} - l)^2/m - 1]^{1/2}$  where  $l$  is the bond length,  $\bar{l}$  the mean, and  $m$  the number of observations. The average N-H distance, including the short N(2)-H(2) distance of 0.69 Å is 0.91 (16) Å. Omitting the short N-H length, the average is 0.99 (9) Å. H(2) refined satisfactorily but the temperature factor as seen in Table 3 is unreasonably small. Inspection of the  $\Delta F$  map based on a model omitting the atom suggested that its position was consistent with least-squares refinement. There were some residual noise peaks in the vicinity of the atom which may have caused the short bond length and small thermal parameter.

Each molecule participates in three hydrogen bonds, see Table 4. The N(1)-H2(1)···O'' and N(1)-

H3(1)···O' interactions are hydrogen bonds, but there may be doubt concerning the two other close distances given in Table 4. The N(1)-H3(1)···O'' contact, while having a suitable N···O distance, has an N-H···O angle of 128.3°, but this value is not unusual since H3(1) is involved in a bifurcated hydrogen bond. The fourth hydrogen bond listed in Table 4 is long at 3.234 Å and has the short N-H distance of 0.69 Å, but the angles associated with the contact are reasonable for a weak hydrogen bond.

A comparison of the two methionine side chains shows the bond lengths and bond angles for the non-hydrogen atoms to be essentially the same except for the bond angle,  $\tau(\gamma)$ , which differs by over 4.5°, a significant amount. Both side chains show the short bond of 1.515 Å and 1.523 Å between C $\beta$  and C $\gamma$ . The major difference in the side chains is in the torsion angles,  $\chi_1^1$  and  $\chi_2^1$ , as can be seen in Fig. 2.

Table 5 contains the bond lengths, bond angles, and torsion angles for the methionine side chains in a number of amino acid and small peptide structures. The bond lengths and bond angles are in reasonable agreement for all the structures. Molecule II does not exhibit a short C $\beta$ -C $\gamma$  bond, and molecules IIIA and IIIB, when corrected for thermal motion by the original investigators, have C $\beta$ -C $\gamma$  lengths of 1.535 and 1.546 Å, respectively (Torii & Iitaka, 1973). IIIA and IIIB exhibited large thermal motion in the side chains while VA and VB do not, suggesting that thermal corrections would not cause the C $\beta$ -C $\gamma$  lengths in the latter to reach the C-C single-bond value.

The torsion angles for the residues show some variability (see Fig. 3). The general features of the behaviour of aliphatic side chains have been outlined previously (Lakshminarayanan, Sasisekharan & Ramachandran, 1967) but more information is available now that additional structures have been determined. Based on

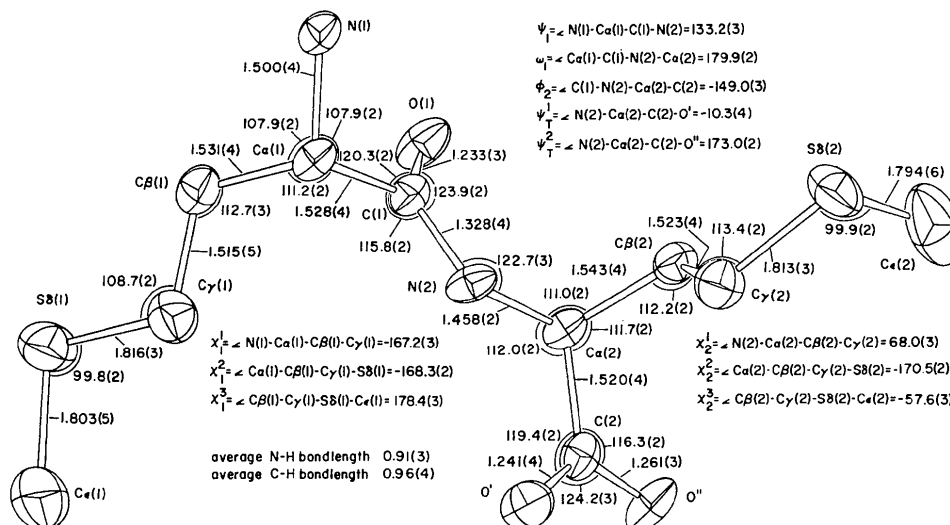


Fig. 1. View of molecule showing thermal ellipsoids, bond lengths, bond angles and major torsion angles.

a survey of amino acid structures known at the time, Lakshminarayanan and colleagues found that  $\chi_1^1$  could take values near  $60^\circ$ ,  $180^\circ$  and  $-60^\circ$  with  $-60^\circ$  being favored because the  $C_\gamma$  would be between the small N and H atoms. For similar reasons,  $\chi_1^1$  near  $60^\circ$  would be unlikely. For the methionine structures determined thus far,  $\chi_1^1$  of  $-60^\circ$  and  $180^\circ$  are equally populated. Moreover,  $\chi_1^1$  is not exactly equal to  $180^\circ$ , the distribution of values near  $180^\circ$  being shifted to the negative side of  $180^\circ$  because of the steric effect of the carboxyl group. The Madras workers also concluded that  $\chi_1^2$  and  $\chi_1^3$  tend strongly to  $180^\circ$  in order to maximize the distances between the nonhydrogen atoms. This is found to be the case for the structures in Table 5, but there are exceptions which can probably be ascribed to packing.

The side-chain torsion angles in Table 5 do not correspond to the minimum energy conformations for methionine calculated by Ralston & DeCoen (1974). In their work, two backbone conformations ( $\varphi = -160^\circ$ ,  $\psi = 160^\circ$ ;  $\varphi = -80^\circ$ ,  $\psi = 80^\circ$ ) have substantially lower energies than the other four. The side-chain conformations corresponding to these have  $\chi_1^1, \chi_1^2, \chi_1^3$  values of  $60^\circ, 180^\circ, 60^\circ$  and  $-60^\circ, 180^\circ, -60^\circ$ . None of the side chains observed experimentally exhibits either of these conformations although one must have reservations in comparing the values from crystal structure analyses with those from energy calculations. Moreover, the calculations were for *N*-acetyl-*N*-methylamide blocked amino acids so the backbone torsion angles could be defined. The energy calculations had fixed backbone conformations corresponding to minima in the van der Waals or van der Waals-electrostatic energy map, but the crystal structures do not correspond exactly to those backbone conformations. However, the crystal structures have side chains with  $\chi_1^1$  near  $-60^\circ, 60^\circ, 180^\circ$ ;  $\chi_1^2 \simeq 180^\circ$  highly favored; and  $\chi_1^3 \simeq 180^\circ$  favored. The values for  $\chi_1^i$  are in contrast to the results of the energy calculations.

Fig. 4 is the packing diagram for L-methionyl-L-methionine (METMET). The hydrogen-bonding scheme gives sheets of polar groups parallel to the  $xz$  plane; the carboxyl and amine groups of molecules adjacent along  $x$  interact as do the peptide carbonyl and amide of molecules adjacent along  $z$ . The aliphatic side chains pack in layers between these hydrogen-bonded nets. Each molecule is similar to a small segment of parallel pleated sheet where adjacent side chains are on opposite sides of the sheet, and in fact the backbone torsion angles have values near those of the pleated sheet. Fig. 4 shows that this does not continue on to the next molecule; the next molecule in the

sheet being rotated  $180^\circ$ . Thus, the residues alternate pair-wise from side to side of the hydrogen bonded net.

This packing arrangement is very much like that of D-alanyl-L-methionine (ALMET) (Stenkamp & Jensen, 1974). In both structures, the peptide backbone is

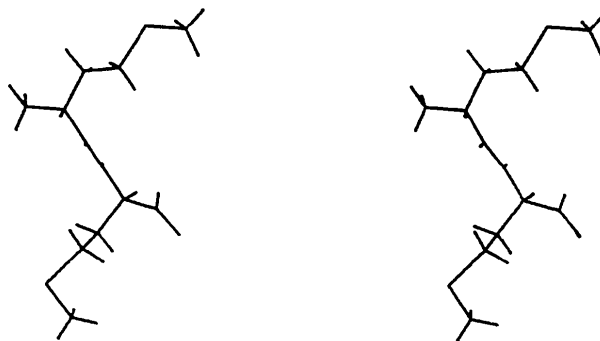


Fig. 2. Stereoscopic stick drawing of the molecule including hydrogens.

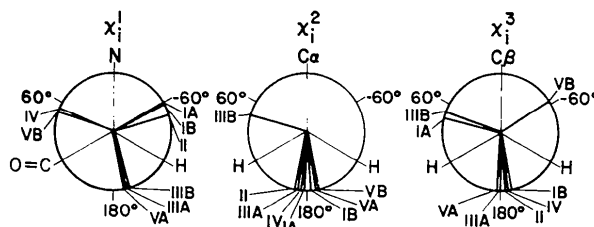


Fig. 3. The side-chain torsion angles.

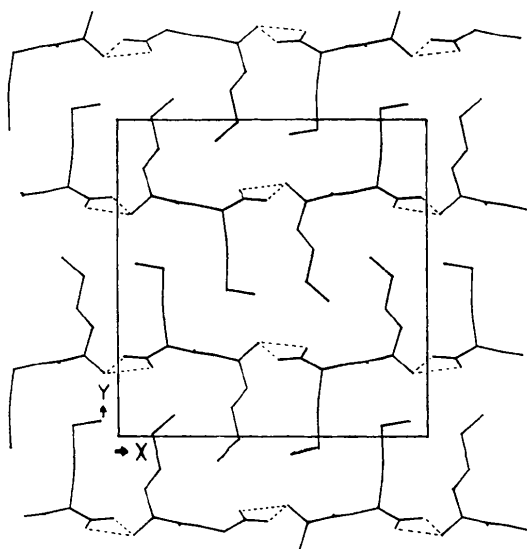


Fig. 4. Packing diagram viewed along  $z$ .

Table 4. Hydrogen bonds

	N...O	N-H	H...O	N-H...O	H-N...O
N(1)-H2(1)···O''	2.684 (3) Å	1.02 (4) Å	1.68 (4) Å	166.7 (3.1)°	8.3 (2.0)°
N(1)-H3(1)···O'	2.801 (3)	1.06 (3)	1.76 (3)	167.0 (2.9)	8.1 (1.8)
N(1)-H3(1)···O''	3.074 (3)	1.06 (3)	2.31 (3)	128.3 (2.3)	36.1 (1.8)
N(2)-H(2)···O(1)	3.237 (3)	0.69 (3)	2.58 (3)	158.9 (2.6)	16.7 (2.1)

Table 5. Methionine side chains

Bond lengths, bond angles and torsion angles calculated from published coordinates and standard deviations. Values are not corrected for thermal motion.

Identifier	$\tau(\beta)$	$\tau(\gamma)$	$\tau(\delta)$	$l(\alpha\beta)$	$l(\beta\gamma)$	$l(\gamma\delta)$	$l(\delta\epsilon)$	$\chi^2 = \chi(\alpha\beta)$	$\chi^2 = \chi(\beta\gamma)$	$\chi^2 = \chi(\gamma\delta)$
$\alpha$ Form, D,L-methionine (Mathieson, 1952)	111.0	111.7	99.1	1.55	1.51	1.79	1.77	-60.1	177.0	80.5
$\beta$ Form, D,L-methionine (Mathieson, 1952)	112.3	107.4	100.3	1.60	1.52	1.80	1.78	-61.0	-176.4	-169.6
N-Acetyl-methionyl-dimethylamide (Aubry, Marraud, Protas & Néel, 1971)	108.6 (1.0)	108.3 (9)	98.5 (6)	1.57 (2)	1.55 (2)	1.82 (1)	1.83 (1)	-72.3 (1.1)	173.4 (6)	-176.7 (8)
Molecule A, L-methionine (Torii & Iitaka, 1973)	111.0 (1.2)	107.3 (1.1)	99.8 (1.0)	1.52 (2)	1.51 (2)	1.83 (3)	1.80 (3)	-166.1 (1.1)	174.2 (8)	179.7 (1.1)
Molecule B, L-methionine (Torii & Iitaka, 1973)	117.9 (1.7)	113.3 (1.4)	101.8 (1.5)	1.53 (4)	1.51 (4)	1.79 (4)	1.71 (5)	-165.6 (1.7)	73.6 (1.7)	73.6 (1.7)
D-Alanyl-L-methionine (Stenkamp & Jensen, 1974)	113.9 (3)	110.0 (3)	99.1 (3)	1.527 (5)	1.508 (6)	1.811 (4)	1.792 (7)	67.3 (4)	175.0 (2)	-173.8 (3)
First residue, L-methionyl-L-methionine (this work)	112.7 (3)	108.7 (2)	99.8 (2)	1.531 (4)	1.515 (5)	1.816 (3)	1.803 (5)	-167.2 (3)	-168.3 (2)	178.4 (3)
Second residue, L-methionyl-L-methionine (this work)	112.2 (2)	113.4 (2)	99.9 (2)	1.543 (4)	1.523 (4)	1.813 (3)	1.794 (6)	68.0 (3)	-170.5 (2)	-57.6 (3)

connected in chains by hydrogen bonding, forming layers of polar groups in the crystal. These polar regions are separated by the packing of the aliphatic side chains, appearing as a ladder-like structure when viewed in projection.

The similarities of these packing schemes could explain a previous observation concerning the ALMET structure. In that case, the starting material supposedly consisted of all four possible D, L enantiomers, but the molecules in the crystals studied were D-alanyl-L-methionine and its enantiomer. There are two effects which could have kept the L-L (or D-D) molecules from crystallizing in the METMET or ALMET arrangement. First, the hydrogen-bonding network of the ALMET structure would be disrupted by two C $\alpha$  atoms in the same absolute configuration. This would cause the alanyl methyl group to take the position of the amine group involved in the hydrogen bonding. Second, replacement of the methionine side chain in the METMET structure by an alanyl side chain would leave a large void in the crystal, leading to an unstable packing arrangement.

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