CRYSTAL STRUCTURE OF L-PROLYL-L-METHIONINE MONOHYDRATE

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ABSTRACT

L-prolyl-L-methionine monohydrate $C_{10}H_{18}N_2O_3S,H_2O$, crystallises in the monoclinic space group $P2_1$ with $Z=2$ and $a=19.381(9)$, $b=5.472(4)$, $c=6.411(5)$A, $\beta=93.1(2)$, $D_{obs}=1.29(4)$, D_{cal} 1.29 g cm^{-3}, and $\mu=8.2$ cm^{-1} (for Cu K_α). The structure was solved by MULTAN and refined to an R index of 0.088 for 812 diffractometer data. C^ν of the pyrrolidine ring is statistically situated on both sides of $NC^\alpha C^\beta C^\delta$ plane. The peptide group is significantly non-planar with a torsion angle ω of 168.5°. The side chain group atoms sulphur and terminal carbon of methionine show large thermal vibration parameters. The side chain conformation at C^α-C^β, C^β-C^ν and C^ν-S bond is gauche-trans-gauche.

INTRODUCTION

PEPTIDES containing proline residues have been the subject of intensive study[1] because of the widespread occurrence of pro-residues in proteins, the possibility of *cis-trans* isomerisation about *x*-pro bond and the variations in pyrrolidine geometries[2]. As the cyclic aminoacid is regarded as a helix breaker, it will be also interesting to follow the effects in the neighbouring groups along the polypeptide chain, before and after the proline residue so as to come to some conclusions on protein conformation.

EXPERIMENTAL

Crystals of the title compound (Sigma Chemicals, USA) were grown from an aqueous solution. Elemental analysis indicated the presence of one water molecule. Preliminary Weissenberg photographs showed the crystal to be monoclinic. All measurements from a crystal $0.20\times0.20\times0.25$ mm were made on the computer controlled Trombay four-circle diffractometer[3] with Ni-filtered CuK_α radiation ($\lambda=1.5417$Å). The cell parameters were determined by least squares from the setting angles of 25 reflections. The intensities were

TABLE 1

The positional parameters (10^4) with e.s.d. in parenthesis and B_{eq}

Atom	x	y	z	B_{eq}(A2)
N_1	3271(4)	3075(7)	3456(4)	2.73(12)
C_1^α	3035(5)	2599(12)	5583(8)	2.78(12)
C_2^β	3718(6)	2046(16)	6683(9)	4.39(14)
C_3^ν	4178(6)	945(12)	5367(12)	3.85(10)
$C_3^{\nu'}$	4249(10)	2907(16)	5722(13)	6.12(10)
C_4^δ	4014(6)	2477(12)	3369(12)	4.49(8)
C_5	2704(5)	4948(12)	6254(10)	2.91(6)
O_1	2853(4)	6865(12)	5399(9)	3.97(8)
N_2	2325(4)	4631(10)	8058(8)	3.23(10)
C_6	2085(5)	6738(12)	9113(6)	3.39(8)
C_7	2687(4)	9266(12)	185(6)	2.15(10)
O_2	2530(3)	403(8)	588(8)	3.44(8)
O_3	3238(3)	7254(10)	601(10)	3.55(10)
C_8^β	1606(5)	5962(7)	830(8)	3.94(6)
C_9^ν	955(6)	42(7)	734(8)	6.34(10)
S	352(2)	438(1)	2050(7)	8.36(17)
C_{10}^δ	768(8)	2128(10)	3685(7)	9.25(18)
O_W	5328(6)	2208(8)	9979(4)	5.03(16)

measured by θ–2θ step scan mode. The data were corrected for Lorentz, polarization and absorption effects. Out of the 872 measured reflections ($\sin\theta/\lambda < 0.50$), 812 reflections with $I > 3\ \sigma(I)$ were used in calculations. The structure was solved with MULTAN.

Results and Discussion

It was evident in the early stages of refinement that the C^{ν} atom of the pyrrolidine ring was disordered. There were deviations from the expected geometry of the pyrrolidine ring and large thermal parameters of C^{ν}. A difference synthesis excluding C^{ν} showed two maxima consistent with the pyrrolidine ring. With the occupancy factors as 0.6 and 0.4 for the two positions, the structure was refined. The R factor at the present stage of refinement with anisotropic temperature factor for all atoms (without hydrogens) was 0.088. The quantity minimised was $\Sigma\omega(|F_0| - K|F_c|)^2$ where ω is the weight factor obtained from the counting statistics. The fractional coordinates and B_{eq} for the atoms are listed in table 1. (The F_0 and F_c tables are available from the authors).

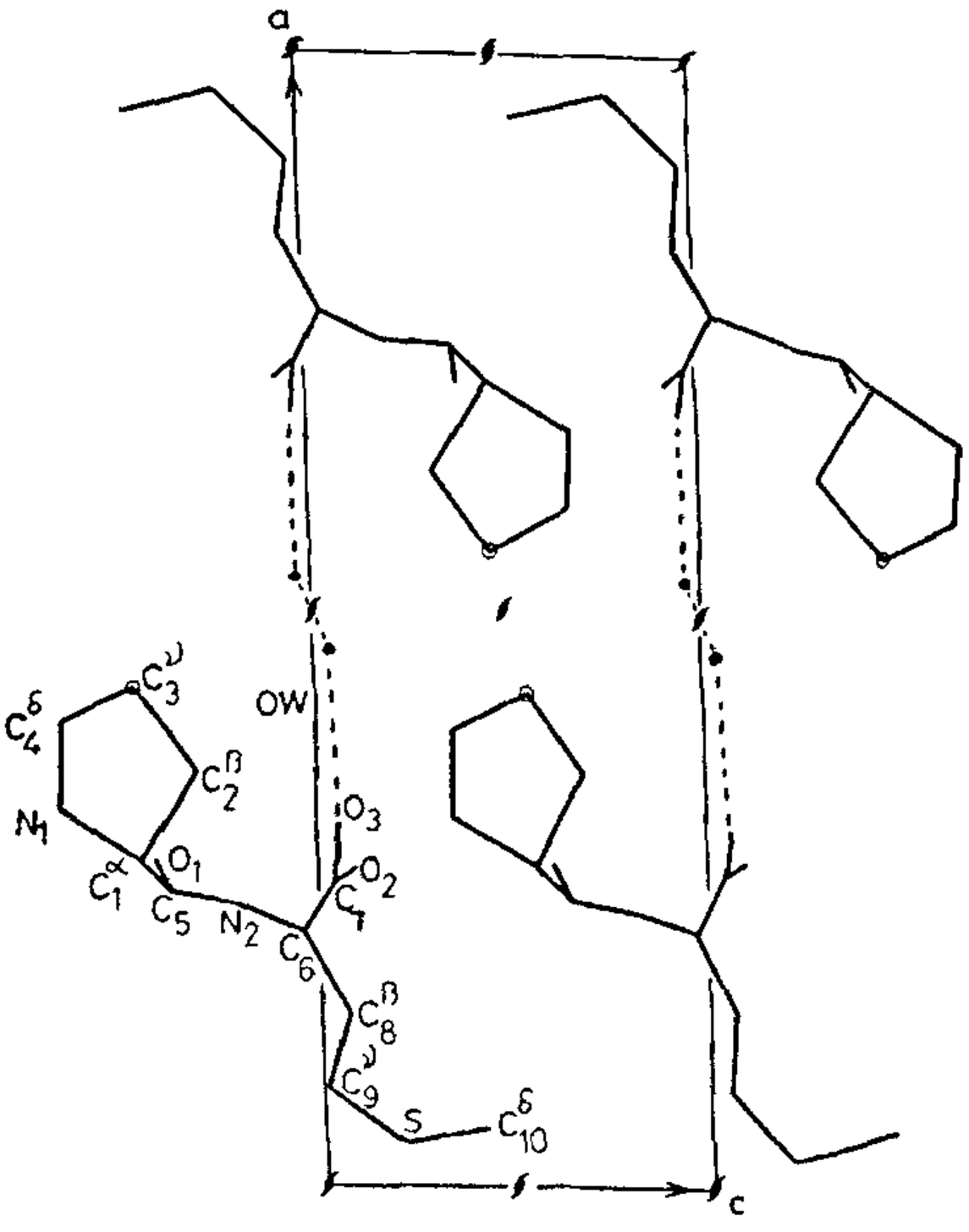

Figure 1. Molecular packing viewed down *b*-axis. Circle around C_3^{ν} indicates disordered atom. Broken line is the hydrogen bonding from water molecule.

TABLE 2

Bond lengths (Å) and angles (Å). The range of the e.s.d.'s are 0.006–0.010 Å in bond distances and 0.2–0.6° in angles (for all data)

N_1–C_4^{α}	1.482	C_5–N_2	1.338
C_1^{α}–C_2^{β}	1.547	N_2–C_6	1.481
C_2^{β}–C_3^{ν}	1.488	C_6–C_7	1.558
C_2^{β}–$C_3^{\nu'}$	1.402	C_7–O_2	1.219
$C_3^{\nu'}$–C_4^{δ}	1.547	C_7–O_3	1.239
$C_3^{\nu'}$–C_4^{δ}	1.565	C_6–C_8^{β}	1.543
C_4^{δ}–N_1	1.478	C_8^{β}–C_9^{ν}	1.502
C_1^{α}–C_5	1.512	C_9^{ν}–S	1.800
C_5–O_1	1.226	S–C_{10}^{δ}	1.778
N_1–C_1^{α}–C_2^{β}	103.5	N_2–C_6–C_7	109.8
C_1^{α}–C_2^{β}–C_3^{ν}	106.5	C_6–C_7–O_2	118.3
C_1^{α}–C_2^{β}–$C_3^{\nu'}$	104.8	C_6–C_7–O_3	114.3
C_2^{β}–C_3^{ν}–C_4^{δ}	102.7	N_2–C_6–C_8	112.9
C_2^{β}–$C_3^{\nu'}$–C_4^{δ}	105.6	C_6–C_8^{β}–C_9^{ν}	114.8
C_3^{ν}–C_4^{δ}–N_1	105.1	C_8^{β}–C_9^{ν}–S	111.9
$C_3^{\nu'}$–C_4^{δ}–N_1	101.3	C_9^{ν}–S–C_{10}^{δ}	101.3
C_4^{δ}–N_1–C_1^{α}	108.8	C_1^{α}–C_5–O_1	118.8
N_1–C_1^{α}–C_5	105.9	C_5–N_2–C_6	121.4

Hydrogen-bond distances (A)

$N_1 \ldots O_3^{(z+1)}$	2.908	$O_w \ldots O_3^{z-1}$	2.827
$N_1 \ldots O_2^{(y-1)}$	2.666	$O_w \ldots O_3^{II}$	3.017
$N_2 \ldots O_2^{(y-1)}$	2.851		

(The atom with superscript II is at x, $1/2+y$, z and those with $(y-1)$, $(z-1)$ and $(z+1)$ are in adjacent cells)

The molecular packing is illustrated in figure 1. The molecules linked by hydrogen bonds, form a spiral round the screw axis. Bond distances and bond angles are given in table 2. The lengths C_2^{β}–C_3^{ν}, 1.488 and C_2^{β}–$C_3^{\nu'}$, 1.402 (mean 1.445), C_3^{ν}–C_4^{δ}, 1.547 and $C_3^{\nu'}$–C_4^{δ}

TABLE 3

Torsion angles (°)

C_4^{δ}–N_1–C_1^{α}–C_5	ϕ^1	125.6
N_1–C_1^{α}–C_5–N_2	ψ_1	166.3
N_1–C_1^{α}–C_5–O_1	ψ_2	–15.4
C_1^{α}–C_5–N_2–C_6	ω	168.3
C_5–N_2–C_6–C_7	ϕ_1	–70.5
C_5–N_2–C_6–C_8^{β}	ϕ_2	171.8
N_1–C_6–C_7–O_2	ψ_T^1	–28.9
N_1–C_6–O_7–O_3	ψ_T^2	160.5
N_2–C_6–C_8^{β}–C_9^{ν}	χ_1	–62.7
C_6–C_8^{β}–C_9^{ν}–S	χ_2	-168.4
C_8^{β}–C_9^{ν}–S–C_{10}^{δ}	χ_3	–71.8

(e.s.d. 0.2–0.6°)

TABLE 4

Comparison of torsion angles (°) in methionine side chain

Crystal	N_2–C^{α}–C^{β}–C^{ν}	C^{α}–C^{β}–C^{ν}–S	C^{β}–C^{ν}–S–C^{δ}
L-methionine[7] molecule A	-166.1	174.2	179.7°
L-methionine[7] molecule B	-165.6	73.6	73.6
D-alanyl-L-methionine[8]	67.3	175.0	-173.8
L-methionyl-L-methionine first residue[9]	-167.2	-168.3	-178.4
L-methionyl-L-methionine second residue[9]	68.0	-170.5	-57.6
L-prolyl-L-methionine (this work)	-62.7 χ_i^1	-168.4 χ_i^2	-71.8 χ_i^3

1.565 (mean 1.556), and C_4^{δ}–N_1, 1.478A in the pyrrolidine ring differ from the expected values, but these deviations appear to have no influence on the C_2^{β}–C_3^{ν}–C_4^{δ} and C_2^{β}–C_3^{ν}–C_4^{δ} angles. The disordered pyrrolidine ring exhibits two conformations which occur in the ratio 3:2. In the first conformation C_5 and C_3^{ν} are on the opposite side of the N C^{α} C^{β} C^{δ} plane (equation $0.1769x + 0.9660y + 0.1883z - 3.1656 = 0$) and deviate from it by 1.22 and −0.59Å. In the second they are on the same side and C_3^{ν} deviates by 0.56 Å. The distance between C_3 and C_3^{ν} is 1.103Å. A similar behaviour of C^{ν} in proline residue has been reported in DL-proline manganese dibromide[4].

The torsion angles are listed in table 3. Although ϕ_1 is -70.5°, the other two torsion angles ψ_1(166.3°) and ω (168.3°) indicate that the main peptide chain is in extended conformation. The peptide group is significantly non-planar with a torsion angle ω of 168.3°. The negative value of N_1–C_1^{α}–C_5–O_1 (-15.4°) indicates that prolyl-methionine belongs to α-helix type of proline compounds whereas collagen type prolines[5] exhibit positive ψ_2 values in the range +150 to 180°.

Methionine residue: The bond lengths and bond angles of the methionine residue of the present work are in reasonable agreement with the reported values[7-9]. The temperature factors for the sulphur and the terminal methyl carbon are large (table 1), but this is not unusual. The torsion angles for the residue show some variations. In table 4 the torsion angles for the methionine side chain from several methionine peptides are listed. The side chain conformation according to minimum energy calculations[6] should have χ_1^1, χ_1^2, χ_1^3 values of 60, 180, 60° or -60, 180, -60°. None of the side chains observed experimentally so far exhibited either of these conformations. However prolyl methionine has the torsion angles -62.7 -168.4, -71.8°, indicating that prolyl-methionine favours the theoretical predictions. The conformation is gauche-trans-gauche.

The hydrogen bonds are listed in table 2. Water molecule acts both as a donor and acceptor. The other relevant groups in the molecule (peptide and amino nitrogens) utilize their hydrogen bonding potential.

Further refinement (with hydrogen atoms included) is in progress and will be reported in due course.

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