

DL-Homoproline Tetrahydrate

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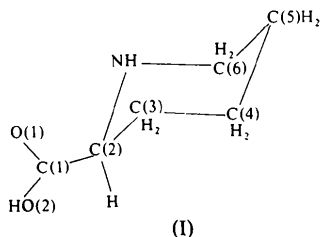
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Abstract

$C_6H_{11}NO_2 \cdot 4H_2O$, FW = 153.2, monoclinic, $P2_1/c$, $a = 13.404$ (7), $b = 6.510$ (4), $c = 12.962$ (8) Å, $\beta = 108.94$ (2)°, $Z = 4$, D_m (by flotation) = 1.23, $D_x = 1.222$ Mg m⁻³, $F(000) = 440$, Cu $K\alpha$ radiation ($\lambda = 1.54178$ Å, $\mu = 0.96$ mm⁻¹). The structure was refined to $R = 0.079$ for 1695 counter reflections. The molecule exists as a zwitterion. The piperidine ring has a chair conformation with the carboxyl group equatorial. There are four water molecules per asymmetric unit, which almost surround the amino acid. Two of the water molecules are coordinated to the homoproline by hydrogen bonds while the other two are hydrogen bonded to each other.

Introduction

Structure investigation of antagonists of biomolecules is one of the research projects of this laboratory. Several amino acid antagonists have been reported. They include thienyl-DL-serine (Swaminathan & Chacko, 1979a) which is an antagonist of serine and threonine, the hydrochlorides of *p*-nitrophenylalanine (Chacko, Swaminathan, Parthasarathy & Natarajan, 1978), an antagonist of phenylalanine, and crotylglycine (Swaminathan & Chacko, 1979b), an antagonist of methionine. The structure of L-thioprolin, an amino acid analogue of proline, has been reported (Chacko, 1974). Homoproline (I) or piperidine-2-carboxylic acid, another analogue of proline, has a six-membered piperidine ring instead of the five-membered pyrrolidine



ring of proline. (I) is an isomer of nipecotic acid (NA) which is a potent inhibitor of γ -aminobutyric acid. The structure of NA has been reported (Brehm, Krogsgaard-Larsen, Johnston & Schumburg, 1976).

Homoproline was obtained from Nutritional Biochemicals, Ohio, USA. Colourless, flat crystals were obtained from water. Cell dimensions were determined by a least-squares method from the 2θ values of 35 reflections on a Picker diffractometer. The measured density revealed that there were four water molecules per asymmetric unit.

A crystal of cross-section 0.2×0.3 mm and length 0.4 mm was used for data collection on the diffractometer with b parallel to the ϕ axis. The θ - 2θ scan mode was employed with scan speed 2° min⁻¹. The scan range was 2° with background measured on either side of the peak for 10 s. 1695 reflections with $2\theta \leq 130^\circ$ had $I > 2\sigma(I)$. The data were corrected for Lorentz and polarization factors and initially scaled by Wilson's method.

The structure was solved by the symbolic addition method (Karle & Karle, 1963) with a Σ_2 search program for E values calculated for 132 reflections with $E \geq 1.70$. The structure was seen in the E map computed with the phases of 128 reflections. The resulting R was 0.40. Block-diagonal least-squares refinement (Shiono, 1968) with isotropic temperature factors converged at $R = 0.15$. H atoms were located from a difference synthesis and included but not refined; anisotropic temperature factors were applied to the non-hydrogen atoms for further refinement. With a full-matrix least-squares refinement (Gantzel, Sparks & Trueblood, 1961), the refinement converged at a final R of 0.079. The function minimized was $\sum w(|F_o| - |F_c|)^2$ with $w = 1/(\sigma F)^2$ based on counting statistics (Stout & Jensen, 1968). Scattering factors were taken from *International Tables for X-ray Crystallography* (1962).

The final coordinates are given in Tables 1 and 2.‡

‡ Lists of structure factors and anisotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 34004 (11 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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Table 1. Positional parameters of non-hydrogen atoms with their e.s.d.'s

	x	y	z
C(1)	0.1126 (2)	0.4578 (4)	0.3502 (2)
C(2)	0.1840 (2)	0.5762 (4)	0.3003 (2)
C(3)	0.2401 (2)	0.7529 (5)	0.3747 (2)
C(4)	0.3126 (2)	0.8659 (5)	0.3244 (3)
C(5)	0.2496 (3)	0.9459 (6)	0.2122 (3)
C(6)	0.1907 (2)	0.7743 (5)	0.1389 (2)
N	0.1219 (2)	0.6598 (4)	0.1916 (2)
O(1)	0.0155 (1)	0.4834 (3)	0.3101 (2)
O(2)	0.1588 (2)	0.3488 (4)	0.4312 (2)
OW(1)	0.0530 (2)	0.2999 (4)	0.0704 (2)
OW(2)	0.4985 (2)	0.3549 (4)	0.3785 (2)
OW(3)	0.4133 (2)	0.4864 (4)	0.1612 (2)
OW(4)	0.3736 (2)	0.1772 (4)	0.0125 (2)

Table 2. Parameters of hydrogen atoms

Bonded to	x	y	z	B (Å ²)	
H(1)	C(2)	0.241	0.468	0.289	1.7
H(2)	C(3)	0.181	0.857	0.386	2.1
H(3)	C(3)	0.283	0.686	0.455	2.1
H(4)	C(4)	0.351	0.995	0.379	2.8
H(5)	C(4)	0.378	0.762	0.323	2.8
H(6)	C(5)	0.199	1.061	0.219	3.3
H(7)	C(5)	0.307	1.007	0.174	3.3
H(8)	C(6)	0.137	0.837	0.061	2.4
H(9)	C(6)	0.242	0.663	0.118	2.4
H(10)	N	0.064	0.766	0.203	1.6
H(11)	N	0.082	0.535	0.140	1.6
H(12)	OW(4)	0.389	0.300	0.078	2.9
H(13)	OW(3)	0.430	0.420	0.229	2.9
H(14)	OW(1)	0.011	0.200	0.111	3.5
H(15)	OW(1)	0.080	0.227	-0.010	3.5
H(16)	OW(4)	0.300	0.183	-0.011	3.6
H(17)	OW(2)	0.444	0.300	0.400	3.6
H(18)	OW(2)	0.556	0.467	0.400	2.9
H(19)	OW(3)	0.454	0.610	0.148	2.9

Discussion

Table 3 gives the bond lengths and angles which in general compare well with NA. The molecule exists as a zwitterion as does NA. The two C—O distances and the bond angles of the carboxyl group indicate its ionized state. C(2)—N, 1.488 (3) Å, agrees with the C^α—N distance, 1.487 Å (Marsh & Donohue, 1967). However, C(6)—N, 1.510 (4) Å, differs significantly from this value. The mean C—C length of 1.522 Å of the piperidine ring is the same as in NA. However, this is significantly different from the mean, 1.55 Å, of piperidine.HCl (Dattagupta & Saha, 1975). The average C—C—C angle of the ring is 110.6°, slightly larger than tetrahedral. However, it is smaller than the theoretically predicted 111.5° for the cyclohexane chair conformation (Bixon & Lifson, 1967). This angle is 111.1° in NA. The C(2)—N—C(6) angle of 111.9° is significantly larger than tetrahedral and compares with

Table 3. Bond lengths (Å) and angles (°) with their e.s.d.'s

C(1)—O(1)	1.246 (3)	C(1)—C(2)—C(3)	111.1 (3)
C(1)—O(2)	1.252 (3)	C(1)—C(2)—N	110.5 (2)
C(1)—C(2)	1.526 (4)	C(2)—C(1)—O(1)	115.7 (2)
C(2)—C(3)	1.532 (4)	C(2)—C(1)—O(2)	118.0 (2)
C(3)—C(4)	1.524 (5)	O(1)—C(1)—O(2)	126.2 (2)
C(4)—C(5)	1.517 (5)	C(2)—C(3)—C(4)	110.1 (3)
C(5)—C(6)	1.513 (5)	C(3)—C(2)—N	109.3 (2)
C(6)—N	1.510 (4)	C(2)—N—C(6)	111.9 (2)
N—C(2)	1.488 (3)	C(3)—C(4)—C(5)	110.0 (3)
		C(4)—C(5)—C(6)	111.3 (3)
		C(5)—C(6)—N	110.6 (3)

Table 4. Equation of and deviations (Å) from the best plane passing through C(1), C(2), O(1) and O(2)

$$0.6377x + 0.7692y + 0.0385z = 4.9432$$

C(1)	0.014	O(2)	-0.005
C(2)	-0.004	N	0.335
O(1)	-0.005		

112.5° in NA. However, it is significantly smaller than the 116.6° observed in piperidine.HCl. The N atom lies 0.335 Å from the plane of the carboxyl group (Table 4).

The piperidine ring exists in the stable chair conformation as in NA. The mean torsion angle 57.3° (Table 5) compares well with 56.1° calculated for NA. These values are, however, significantly larger than the theoretically expected 54.7° for cyclohexane (Bixon & Lifson, 1967) and hence the piperidine ring is more puckered. However, the puckering is significantly less than in piperidine.HCl which has a mean value of 63.3°. The bulkier carboxyl group is oriented in the favourable equatorial position with the H atom at C(2) axial, as in NA.

A projection of the structure down *b* is given in Fig. 1 with hydrogen bonds indicated. The N atom forms N—H...O hydrogen bonds with OW(1) and a symmetry-related O(1) at 2.80 and 2.79 Å respectively. The structure has 16 water molecules in the cell. Unusually, they occur in regions mainly about the hydrophobic side group of the amino acid. However, there are no C—H...O interactions in the structure. OW(2) and OW(3) form hydrogen bonds among

Table 5. Torsion angles (°) of the piperidine ring with their e.s.d.'s

N—C(2)—C(3)—C(4)	59.0 (3)
C(2)—C(3)—C(4)—C(5)	-57.8 (3)
C(3)—C(4)—C(5)—C(6)	56.1 (3)
C(4)—C(5)—C(6)—N	-55.1 (3)
C(5)—C(6)—N—C(2)	56.9 (3)
C(6)—N—C(2)—C(3)	-58.6 (3)

Mean torsion angle = 57.3

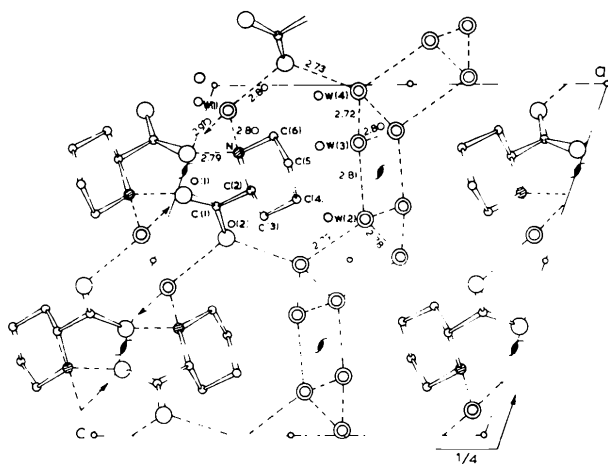


Fig. 1. Projection of the structure down *b*.

Table 6. Hydrogen-bond lengths (Å) and angles (°)

<i>D</i> —H... <i>A</i>	<i>D</i> ... <i>A</i>	H... <i>A</i>	∠H— <i>D</i> ... <i>A</i>
N—H(11)...OW(1)	2.80	1.75	10
N—H(10)...O(2 ⁱ)	2.79	1.75	12
OW(1)—H(14)...O(2 ⁱⁱ)	2.90	1.84	13
OW(1)—H(15)...O(1 ⁱⁱⁱ)	2.80	1.57	13
OW(2)—H(17)...OW(4 ^{iv})	2.79	1.98	26
OW(2)—H(18)...OW(4 ^v)	2.78	1.83	18
OW(3)—H(19)...OW(2 ^v)	2.80	1.79	7
OW(3)—H(13)...OW(2)	2.81	1.90	13
OW(4)—H(16)...O(1 ⁱⁱⁱ)	2.73	1.81	7
OW(4)—H(12)...OW(3)	2.72	1.59	3

Symmetry code

- | | |
|-------------------------------------------------|-----------------------------------------------|
| (i) $-x, \frac{1}{2} + y, \frac{1}{2} - z$ | (iv) $x, \frac{1}{2} - y, \frac{1}{2} + z$ |
| (ii) $-x, \frac{1}{2} + y - 1, \frac{1}{2} - z$ | (v) $1 - x, \frac{1}{2} + y, \frac{1}{2} - z$ |
| (iii) $x, \frac{1}{2} - y, \frac{1}{2} + z - 1$ | |

themselves as indicated in Fig. 1. OW(1) and OW(4) enter into O—H...O hydrogen bonds with the O atoms of the carboxyl group. Hydrogen-bond distances and angles are given in Table 6. Thus the structure has a network of O—H...O type hydrogen bonds, in addition to the piperidine moiety which is stabilized by N—H...O type hydrogen bonds. Except for OW(1), the other water molecules are arranged along a plane parallel to (100) and approximately situated as a broad hydrogen-bonded ribbon (~4 Å thick) at the centre of the cell.

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