# X-ray Analysis of L-Pyroglutamic Acid. A Marked Case of Structural Pseudosymmetry

By E. van Zoeren, H. A. J. Oonk and J. Kroon*

*Laboratorium voor Structuurchemie, Rijksuniversiteit, Padualaan 8, Utrecht, The Netherlands*

L-Pyroglutamic acid, $C_5H_7NO_3$, is orthorhombic, space group $P2_12_12_1$, with $a = 9.018$ (8), $b = 13.495$ (8), $c = 14.662$ (4) Å, $Z = 12$. The structure was refined from 1612 counter intensities to $R = 0.049$. A high degree of pseudosymmetry in the structure explains the occurrence of a false, but structurally acceptable, solution obtained by direct methods. The structure consists of polymeric chains in which the carboxyl groups are connected to the keto O atoms through hydrogen bonding. Hydrogen bonding is also found as a result of $N-H \cdots O$ interactions between the chains. In all three independent molecules the bonds of the N atoms are found to be coplanar.

## Introduction

The structure of the racemic form of pyroglutamic acid ($C_5H_7NO_3$), a substance which is of psychopharmaceutical importance, has been determined by Pattabhi & Venkatesan (1974). In our laboratory CNDO calculations were performed on the pyroglutamic acid molecule in the context of a study of the packing of amino acids and related compounds. We report here the crystal structure of the optically active (−) form of this substance.

## Experimental

Transparent orthorhombic rod-shaped crystals of L-pyroglutamic acid (2-pyrrolidone-5-carboxylic acid) are obtained by crystallization from a mixture of methanol and acetone. Systematic absences determine uniquely the space group $P2_12_12_1$. Cell dimensions and intensities were measured on a three-circle CAD-3 diffractometer (Nonius), with Ni-filtered Cu $K\alpha$ radiation ($\lambda = 1.5418$ Å): $a = 9.018$ (8), $b = 13.495$ (8), $c = 14.662$ (4) Å, $V = 1784$ Å³; three molecules in the asymmetric unit; $D_x = 1.440$ (FW 129.11), $D_m = 1.45 \pm 0.01$ g cm⁻³. For the intensity measurements the $\omega$-scan technique was used; the variable scan angle was $(0.98 + 0.32 \tan \theta)°$. 3600 reflexions (two independent Friedel-related sets) were recorded. Averaging of equivalent data produced 1872 independent intensities, 1612 of which had $I > 2.5\sigma(I)$. All calculations were carried out with the XRAY system (Stewart, 1976) modified and extended by the Dutch X-ray system group.

## Structure determination and refinement

The Patterson synthesis shows a large peak at $0,\frac{1}{3},0$, two-thirds of the height of the origin peak, indicating an extremely high degree of pseudosymmetry. This fact correlates with the number of independent molecules in the asymmetric unit and evidently hampered initial trials to solve the structure with *MULTAN* (Main, Woolfson & Germain, 1971). To make a better start we calculated some universal structure invariants $[\cos(\varphi_{h_1} + \varphi_{h_2} + \varphi_{h_3}); h_1 + h_2 + h_3 = 0]$ with programs written by Weeks, Pokrywiecki & Edmonds (1973). The only triple products considered were those that contained either merely projectional reflexions or symmetry-related reflexions. This enabled us to determine with a high degree of reliability the phases of three projectional reflexions, whose phases are fixed in combination with the phases assigned to the origin-defining reflexions. At the same time the triple-product estimates allowed the inclusion of the signs of four structure seminvariants in the starting set. After application of *MULTAN* the phase set with the highest combined figure of merit resulted in an electron density distribution which at first sight seemed very promising, since molecules could be discerned fulfilling reasonable packing conditions. However, after least-squares refinement $R$ did not fall below 0.30. Moreover, the bond distances and angles deviated by up to 0.15 Å and 5° from expected values. Afterwards an error in the PSI ZERO test was found. The phase set, whose combined figure of merit was influenced disadvantageously by that test and which was the second in rank as regards the combined figure of merit, now produced a Fourier map from which a refinable model could be obtained.

We encounter here a marked case of homometric sets. The false solution can be interpreted as a structure whose coordinates stem from an origin which is not compatible with space-group symmetry. However, this

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* To whom correspondence should be addressed.

Table 1. *Fractional coordinates* ($\times 10^4$ *for* C, N *and* O, *and* $\times 10^3$ *for* H)

|        | x         | y          | z          |
|--------|-----------|------------|------------|
| O(11)  | 2423 (4)  | 8787 (2)   | 1879 (2)   |
| O(12)  | 3469 (3)  | 10260 (2)  | 2052 (2)   |
| O(13)  | 3476 (3)  | 10797 (2)  | 5258 (2)   |
| N(1)   | 3752 (3)  | 10006 (2)  | 3894 (2)   |
| C(11)  | 3022 (4)  | 9486 (3)   | 2356 (2)   |
| C(12)  | 3105 (4)  | 9213 (3)   | 3359 (2)   |
| C(13)  | 3069 (4)  | 10171 (3)  | 4692 (2)   |
| C(14)  | 1786 (4)  | 9479 (3)   | 4761 (2)   |
| C(15)  | 1577 (4)  | 9087 (3)   | 3795 (2)   |
| H(O11) | 240 (3)   | 900 (2)    | 126 (2)    |
| H(N1)  | 453 (3)   | 1029 (2)   | 380 (2)    |
| H(C12) | 361 (3)   | 854 (2)    | 341 (2)    |
| H(C14) | 91 (3)    | 982 (2)    | 500 (2)    |
| H'(C14)| 203 (3)   | 896 (2)    | 520 (2)    |
| H(C15) | 88 (3)    | 949 (2)    | 350 (2)    |
| H'(C15)| 127 (3)   | 842 (2)    | 381 (2)    |
| O(21)  | 1771 (4)  | 2468 (2)   | 1578 (2)   |
| O(22)  | 3537 (3)  | 3576 (3)   | 1831 (2)   |
| O(23)  | 4073 (2)  | 3741 (2)   | 4986 (2)   |
| N(2)   | 3849 (3)  | 2970 (3)   | 3613 (2)   |
| C(21)  | 2764 (4)  | 2885 (3)   | 2082 (2)   |
| C(22)  | 2787 (5)  | 2471 (3)   | 3037 (2)   |
| C(23)  | 3322 (4)  | 3299 (3)   | 4408 (2)   |
| C(24)  | 1729 (5)  | 3037 (3)   | 4464 (2)   |
| C(25)  | 1333 (5)  | 2647 (4)   | 3545 (3)   |
| H(O21) | 189 (4)   | 273 (2)    | 101 (2)    |
| H(N2)  | 467 (3)   | 301 (2)    | 350 (2)    |
| H(C22) | 304 (3)   | 173 (2)    | 297 (2)    |
| H(C24) | 116 (3)   | 356 (2)    | 470 (2)    |
| H'(C24)| 174 (4)   | 260 (2)    | 488 (2)    |
| H(C25) | 72 (3)    | 322 (2)    | 323 (2)    |
| H'(C25)| 59 (4)    | 228 (2)    | 344 (2)    |
| O(31)  | 3581 (3)  | 4306 (2)   | −3382 (2)  |
| O(32)  | 1337 (3)  | 3643 (2)   | −3287 (2)  |
| O(33)  | 1127 (3)  | 3046 (2)   | −35 (2)    |
| N(3)   | 1379 (3)  | 3809 (3)   | −1411 (2)  |
| C(31)  | 2385 (4)  | 4046 (3)   | −2944 (2)  |
| C(32)  | 2452 (4)  | 4345 (3)   | −1947 (2)  |
| C(33)  | 1878 (4)  | 3500 (3)   | −600 (2)   |
| C(34)  | 3459 (4)  | 3815 (3)   | −516 (2)   |
| C(35)  | 3910 (4)  | 4106 (3)   | −1471 (2)  |
| H(O31) | 354 (3)   | 409 (2)    | −396 (2)   |
| H(N3)  | 42 (3)    | 376 (2)    | −156 (2)   |
| H(C32) | 221 (3)   | 501 (2)    | −196 (2)   |
| H(C34) | 401 (4)   | 330 (2)    | −27 (2)    |
| H'(C34)| 357 (3)   | 435 (2)    | −11 (2)    |
| H(C35) | 447 (3)   | 351 (2)    | −186 (2)   |
| H'(C35)| 472 (3)   | 459 (2)    | −146 (2)   |

origin is situated at the particular position $0,\frac{1}{6},0$. This is a legitimate choice of origin as far as the subcell is concerned, for its *b* axis, as already indicated by the Patterson synthesis, is $\frac{1}{3}$ that of the real unit cell. A shift of the origin of the false solution over $\frac{1}{6}$ of *b* gives a starting set of parameters which is good enough to pursue the structure analysis successfully.

All H atoms were found in a difference map. A semi-full-matrix refinement was carried out in which those atoms related by the non-crystallographic translational symmetry operation $0,\frac{1}{3},0$ were assembled in one block. In addition to the coordinates the anisotropic thermal parameters of the heavy atoms were varied. The isotropic temperature coefficients of the H atoms were restricted to a value of 5 Å². The weighting scheme was $w^{-1} = \sigma^2(F)$. The final difference map did not show any

significant feature. The final $R_F = 0.048$ and $R_{wF} = 0.049$, omitting unobserved reflexions and four which were thought to be suffering from extinction. The final positional parameters are given in Table 1.* Scattering factors for C, N and O were those of Cromer & Mann (1968), for H those of Stewart, Davidson & Simpson (1965).

## Discussion of the structure

Bond distances and angles for the three independent molecules are listed in Table 2 together with those of the racemate (Pattabhi & Venkatesan, 1974). Atom numbering is given in Fig. 1. For clarity the first digit of the atomic numbering as used in Table 1 for reference to the serial number of the independent molecule is omitted.

All bond distances in the present study are found to be systematically smaller than those reported for the racemate. Pattabhi & Venkatesan found $D_m = 1.509$ g cm⁻³, which is appreciably larger than $D_x = 1.424$ g cm⁻³, and recorded $C(sp^3)–C(sp^2)$ bond distances which are significantly larger than usual (Table 2, column 5). We therefore redetermined the cell dimensions of the racemate. This resulted in $a = 7.974$ (1), $b = 8.751$ (2), $c = 9.123$ (2) Å and $\beta = 115.47$ (2)°. Simultaneously with the improvement in the agreement between calculated (1.492 g cm⁻³) and observed densities there was better agreement between the bond distances in the present study and those in the racemate.

A feature of the bonding is the coplanarity of H(N) with C(1), N and C(3). Torsion angles of the carboxyl groups with the plane through C(2), C(3) and N are 1.2, 1.4 and 18.4° respectively, with C=O nearly synplanar with the N atom.

There are two independent chains of hydrogen-bonded pyroglutamic acid molecules (Fig. 2). One chain is generated by a screw diad, the other contains two crystallographically independent molecules as a unit. In the present compound as well as in the racemate polymer formation (and not dimerization, as is more common) is found in which carboxyl groups and keto O atoms are linked. Hydrogen-bonded interchain interactions are also present and involve N–H···O bonds. For details of hydrogen bonding see Table 3. For N(2) no conclusive evidence for hydrogen-bond formation can be supplied. In this particular case a N(2)···O distance of 3.162 Å accompanies a N–H···O angle of 120°, while in a weak N(2)···O interaction with distance 3.611 Å the corresponding angle proves to be more favourable (162°). Combined

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Table 2. *Bond distances* (Å) *and angles* (°) *in pyro-glutamic acid*

The e.s.d.'s are in parentheses.

| | Molecule 1 | Molecule 2 | Molecule 3 | Race-mate* |
|---|---|---|---|---|
| C(1)—O(1) | 1·293 (4) | 1·291 (5) | 1·304 (4) | 1·324 |
| C(1)—O(2) | 1·205 (4) | 1·221 (5) | 1·201 (4) | 1·232 |
| C(1)—C(2) | 1·518 (5) | 1·508 (5) | 1·517 (5) | 1·545 |
| C(2)—N | 1·450 (5) | 1·443 (5) | 1·442 (4) | 1·472 |
| C(3)—N | 1·341 (4) | 1·335 (4) | 1·339 (4) | 1·354 |
| C(3)—O(3) | 1·240 (4) | 1·239 (4) | 1·233 (5) | 1·258 |
| C(3)—C(4) | 1·491 (5) | 1·482 (6) | 1·492 (6) | 1·532 |
| C(4)—C(5) | 1·523 (5) | 1·490 (6) | 1·511 (5) | 1·554 |
| C(2)—C(5) | 1·529 (5) | 1·526 (6) | 1·523 (5) | 1·569 |
| O(1)—H(O1) | 0·95 (3) | 0·91 (3) | 0·90 (3) | – |
| N—H(N) | 0·81 (3) | 0·76 (3) | 0·89 (3) | – |
| C(2)—H(C2) | 1·01 (3) | 1·04 (3) | 0·93 (3) | – |
| C(4)—H(C4) | 0·98 (3) | 0·94 (3) | 0·93 (3) | – |
| C(4)—H'(C4) | 0·98 (3) | 0·85 (3) | 0·93 (3) | – |
| C(5)—H(C5) | 0·94 (3) | 1·05 (3) | 1·11 (3) | – |
| C(5)—H'(C5) | 0·94 (3) | 0·84 (3) | 0·97 (3) | – |
| | | | | |
| O(1)—C(1)—O(2) | 124·9 (3) | 123·8 (3) | 124·6 (3) | 123·9 |
| O(1)—C(1)—C(2) | 111·5 (3) | 112·3 (3) | 111·7 (3) | 112·4 |
| O(2)—C(1)—C(2) | 123·5 (3) | 123·7 (3) | 123·7 (3) | 123·6 |
| C(1)—C(2)—N | 111·4 (3) | 112·3 (3) | 111·4 (3) | 112·5 |
| C(1)—C(2)—C(5) | 112·8 (3) | 112·6 (3) | 114·8 (3) | 114·1 |
| C(5)—C(2)—N | 102·6 (3) | 102·3 (3) | 102·9 (3) | 103·2 |
| C(2)—N—C(3) | 114·2 (3) | 115·4 (3) | 114·5 (3) | 113·6 |
| O(3)—C(3)—N | 124·2 (3) | 124·3 (4) | 124·5 (4) | 124·6 |
| O(3)—C(3)—C(4) | 127·6 (3) | 127·4 (3) | 127·6 (3) | 126·0 |
| C(4)—C(3)—N | 108·2 (3) | 108·3 (3) | 107·8 (3) | 109·4 |
| C(3)—C(4)—C(5) | 104·5 (3) | 105·5 (3) | 104·8 (3) | 103·9 |
| C(4)—C(5)—C(2) | 103·8 (3) | 106·9 (3) | 104·3 (3) | 103·7 |
| C(1)—O(1)—H(O1) | 108 (2) | 106 (2) | 110 (2) | – |
| C(2)—N—H(N) | 127 (2) | 123 (2) | 124 (2) | – |
| C(3)—N—H(N) | 118 (2) | 121 (2) | 121 (2) | – |
| C(1)—C(2)—H(C2) | 108 (2) | 106 (2) | 103 (2) | – |
| C(5)—C(2)—H(C2) | 106 (2) | 112 (2) | 115 (2) | – |
| N—C(2)—H(C2) | 116 (2) | 111 (2) | 110 (2) | – |
| C(3)—C(4)—H(C4) | 111 (2) | 112 (2) | 109 (2) | – |
| C(5)—C(4)—H(C4) | 113 (2) | 118 (2) | 114 (2) | – |
| C(3)—C(4)—H'(C4) | 108 (2) | 101 (2) | 112 (2) | – |
| C(5)—C(4)—H'(C4) | 113 (2) | 114 (2) | 111 (2) | – |
| H(C4)—C(4)—H'(C4) | 107 (2) | 106 (3) | 106 (2) | – |
| C(2)—C(5)—H(C5) | 110 (2) | 111 (2) | 108 (2) | – |
| C(4)—C(5)—H(C5) | 108 (2) | 105 (2) | 114 (1) | – |
| C(2)—C(5)—H'(C5) | 112 (2) | 120 (2) | 121 (2) | – |
| C(4)—C(5)—H'(C5) | 110 (2) | 124 (2) | 111 (2) | – |
| H(C5)—C(4)—H'(C5) | 112 (3) | 86 (3) | 99 (2) | – |

* Pattabhi & Venkatesan (1974). The mean e.s.d.'s are 0·005 Å for bond distances and 0·3° for angles; bond distances involving H range from 0·86 to 1·04 Å, but they are not explicitly stated; bond angles involving H are not given.
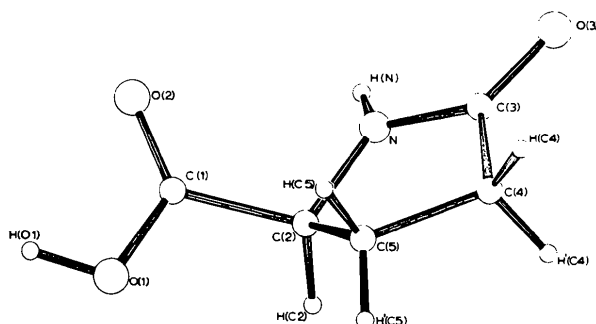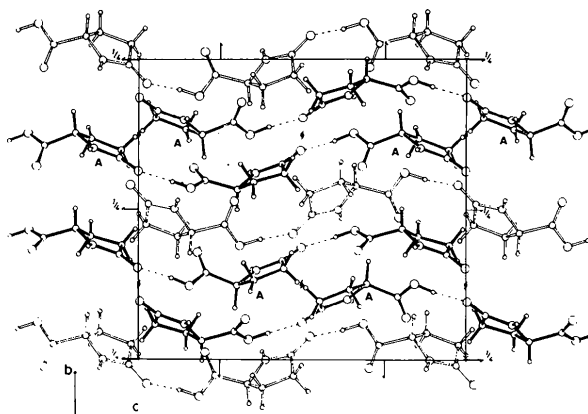
Fig. 1. Numbering of the atoms.

Fig. 2. Molecular arrangement viewed down [100]. Intrachain hydrogen bonds are represented by broken lines. The three independent molecules are represented by thin lines, thick lines and the letter 'A'.

Table 3. *Distances* (Å) *and angles* (°) *involving hydrogen bonds in* L-*pyroglutamic acid*

The e.s.d.'s are in parentheses.

| $D$–H$\cdots A$ | $D$–H | H$\cdots A$ | $D\cdots A$ | $D$–H$\cdots A$ |
|---|---|---|---|---|
| O(11)—H(O11)$\cdots$O(13ⁱ) | 0·95 (3) | 1·69 (3) | 2·573 (3) | 153 (3) |
| O(21)—H(O21)$\cdots$O(33) | 0·91 (3) | 1·73 (3) | 2·556 (4) | 149 (3) |
| O(31)—H(O31)$\cdots$O(23ⁱⁱ) | 0·90 (3) | 1·69 (3) | 2·550 (3) | 161 (3) |
| N(1)—H(N1)$\cdots$O(32ⁱⁱⁱ) | 0·81 (3) | 2·30 (3) | 3·090 (4) | 165 (3) |
| N(3)—H(N3)$\cdots$O(12ⁱᵛ) | 0·89 (3) | 2·32 (3) | 3·057 (4) | 141 (3) |

Symmetry code superscript: none $x,y,z$; (i) $\frac{1}{2} - x$, $2 - y$, $-\frac{1}{2} + z$; (ii) $x, y$, $-1 + z$; (iii) $\frac{1}{2} + x$, $1\frac{1}{2} - y$, $-z$; (iv) $-\frac{1}{2} + x$, $1\frac{1}{2} - y$, $-z$.

with the data in Table 3 this last observation indicates that the N—H$\cdots$O bonding scheme does not fit in with the overall characteristic of this structure, *viz* the marked pseudosymmetry in the **b** direction.

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