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Supramolecular assembly in the chiral N-carbamoyl compound 2-ureido-pentanedioic acid

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ABSTRACT
The compound 2-ureido-pentanedioic acid was synthesized and characterized by FT-IR and NMR spectra. Its molecular structure was solved by single crystal X-ray diffraction. In the title compound, $C_6H_{10}N_2O_5$, the chiral structure is stabilized by intermolecular O–H···O and N–H···O hydrogen bonds in a supramolecular assembly formed by infinite chains parallel to the **bc** plane with graph set C(4) connected by amide-acid dimers $R^2_2(8)$ into a three-dimensional network.

KEYWORDS
Crystal structure; hydrogen bonds; N-carbamoyl

1. Introduction

Ureido carboxylic acids, or N-carbamoyl amino acids, are organic compounds bearing both carboxylic (−COOH) and ureido (−NH–CO–NH_2) functional groups. These types of materials are closely related to biochemical and metabolic process because of their application as precursors to amino acids, hydantoins, and N-carboxyanhydride compounds, which are well-known precursors of peptides [1–3]. In addition, in recent years there has been an increasing interest in the industrial use of N-carbamoyl compounds, since natural and nonnatural amino acids can be obtained through an enantioselective enzymatic reaction [4,5]. Moreover, these compounds can display pharmaceutical and biological activity with a variety of applications. For instance, N-carbamoyl-glycine causes sedative and anticonvulsant effects [6], N-carbamoyl-β-alanine has antidiabetic properties [7], N-carbamoyl-methionine is used in insulin analogs design [8], N-carbamoyl-γ-aminobutyric acid is a weak GABA antagonist [9], and N-carbamoyl-L-glutamic acid is used in the treatment of acute hyperammonemia due to N-acetylglutamate synthase deficiency [10].

Additionally, the N-carbamoyl molecules containing ureido and acid groups are susceptible to form excellent supramolecular architectures through hydrogen bonds, which play a key role in molecular recognition and crystal engineering [11]. Studies of such interactions are also of current interest because of their applications in drug and pharmaceuticals design [12,13].

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We are currently investigating the synthesis and structural characterization of N-carbamoyl and hydantoin α-amino acids derivatives [14–20], and as part of ongoing studies, in this work we report the crystal structure of a chiral compound 2-ureido-pentanedioic acid, also namely N-carbamoyl-L-glutamic acid.

2. Experimental

2.1. *Synthesis*

4 mmol of L-glutamic acid was dissolved in 20 mL of water and the solution was acidified with concentrated HCl (37% v/v). Then, 12 mmol of potassium thiocyanate (KOCN) was added to this solution. The mixture was warmed up, with agitation, to 333 K, during 4 hr. The resultant solution was cooled at room temperature into a glass vial sealed with parafilm, which was perforated with a needle to allow slow evaporation until the precipitation of a white solid. Crystals of (I) suitable for X-ray analysis were obtained by slow evaporation of an ethanol solution at room temperature (Scheme 1). Yield 62%, mp 170°C–171°C. This experimental procedure correspond with a modified and improved methodology previously reported [14,15].

2.2. *Spectral studies*

The synthesized compound was characterized by spectroscopic data. The Fourier transform infrared spectroscopy (FT-IR) absorption spectrum was obtained as KBr pellet using a Perkin-Elmer 1600 spectrometer. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker Avance 400 model spectrometer in DMSO-d_6 solution.

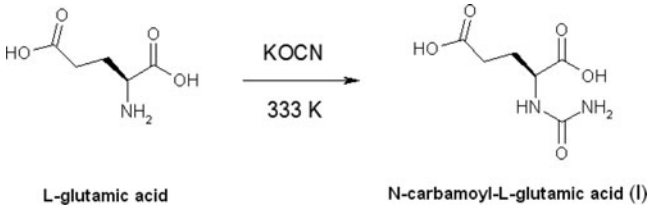
FT-IR: 3440 cm^{-1} (*t*, N–H), 3226 cm^{-1} (*t*, C–N), 3180 (*t*, O–H), 1710 cm^{-1} (*t*, C=O), 1728 cm^{-1} (*t*, C–O), and 1450 cm^{-1} (*t*, C–N).

^{1}H-NMR (400 MHz, DMSO d_6): δ 11.0 (s, 2H; H1, H3), 6.0 (s, 3H; H1a, H2a, H2b), 4.46 (m, 1H; H10a), 2.23 (m, 2H; H12a,H12b), and 2.05 (m, 2H; H13a, H13b).

^{13}C-NMR (100 MHz, DMSO d_6): δ 177.3 (C11), 174.9 (C8), 162.7 (C1), 56.3 (C10), 30.0 (C12), and 26.5 (C13).

2.3. *X-ray powder diffraction*

The X-ray powder diffraction patterns of L-glutamic acid and N-carbamoyl-L-glutamic acid were collected at room temperature in a Phillips PW-1250 goniometer using monochromatized Cu*K*α radiation. A small quantity of each compound was ground mechanically in an agate mortar and pestle and mounted on a flat holder covered with a thin layer of grease. The samples were scanned from 10°–60° 2, with a step size of 0.02° and counting time of 10 s.



L-glutamic acid N-carbamoyl-L-glutamic acid (I)

Scheme 1. Synthesis of N-carbamoyl-L-glutamic acid from L-glutamic acid (I).

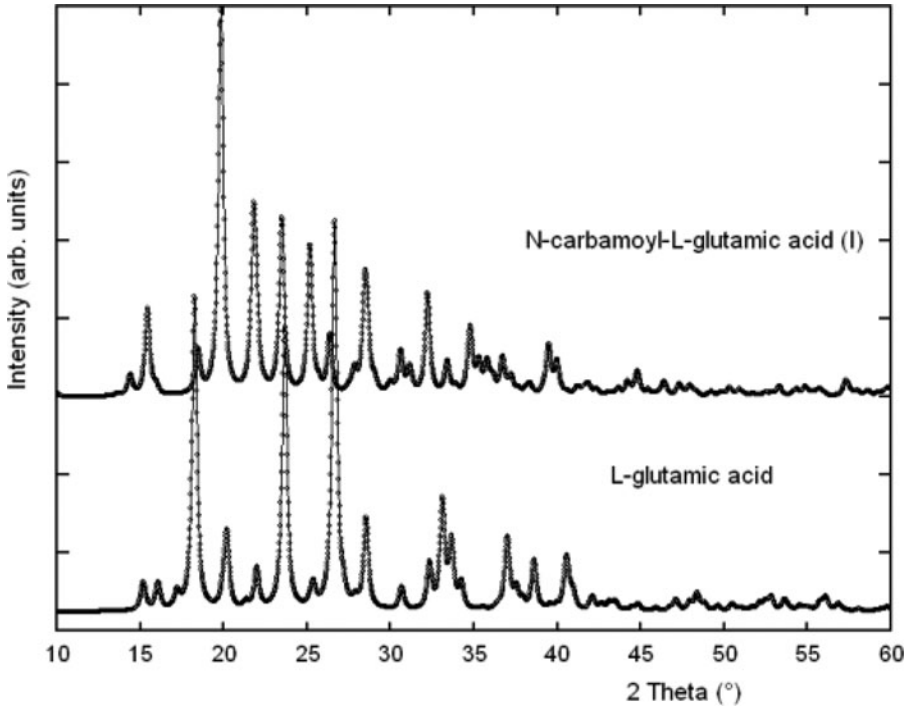


Figure 1. X-ray powder diffraction patterns of L-glutamic acid and N-carbamoyl-L-glutamic acid (I).

Silicon was used as an external standard. X-ray powder patterns showed in Fig. 1 evidences the formation of a new compound.

For the N-carbamoyl (I) powder pattern, the 20 first measured reflections were completely indexed which gave a unique solution in an orthorhombic cell with parameters $a = 5.20$ Å, $b = 12.30$ Å, $c = 12.97$ Å in a P-type cell. This cell was confirmed by means of single-crystal analysis.

2.4. *Single-crystal X-ray data collection and structure determination*

Colorless laminar crystal (0.40 0.30 0.20 mm) was used for data collection. Diffraction data were collected at 298(2) K by ω-scan technique on a Rigaku AFC7S Mercury diffractometer

Table 1. Crystal data, data collection, and structure refinement.

Chemical formula	$C_6H_{10}N_2O_5$	CCDC	1052742
Formula weight	190.16	Radiation (MoKα)	$\lambda = 0.71073$ Å
Crystal system	Orthorhombic	range (°)	2.3–28.0
Space group	$P2_12_12_1$ (N°19)	*hkl* range	−6, 4; −14, 14; −15, 15
a(Å)	5.1707(12)	Reflections Unique	1626
b(Å)	12.278(3)	Rint	0.039
c(Å)	12.959(3)	With $I > 2(I)$	1400
V(Å^3)	822.7(3)	Refinement method	Full-matrix least-squares on F^2
Z	4	Number of parameters	119
dx (g cm^{-3})	1.535	$R(F^2)$ [$I > 2(I)$]	0.0486
F(000)	400	$wR(F^2)$ [$I > 2(I)$]	0.1381
μ(mm^{-1})	0.135	Goodness of fit on F^2	1.09
Crystal size (mm)	0.40 0.30 0.20	Max/min (e Å^{-3})	0.30/−0.26

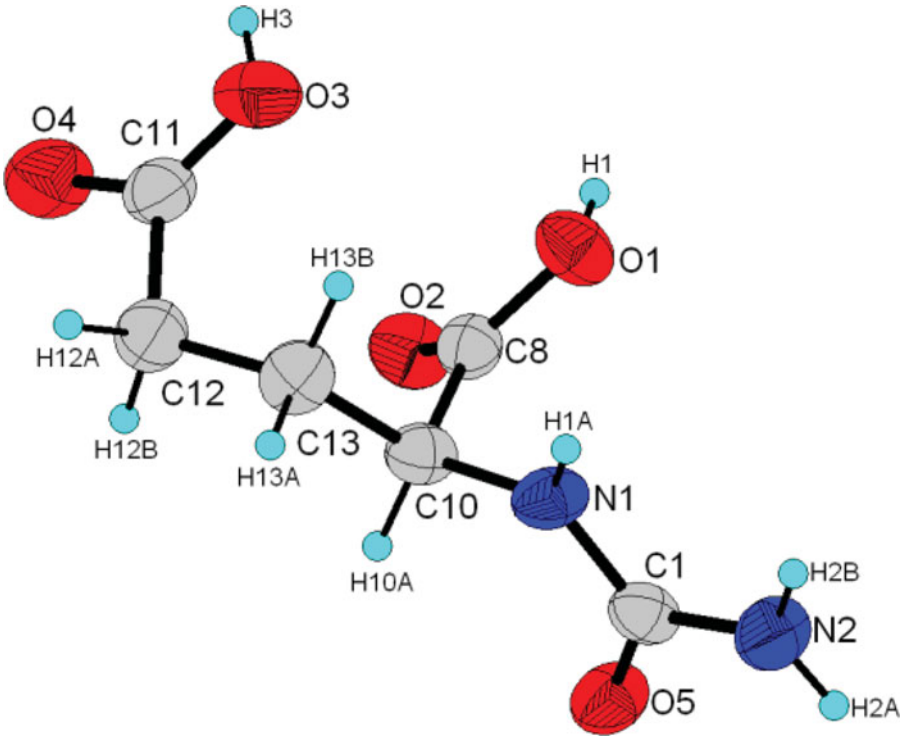


Figure 2. The molecular structure of N-carbamoyl-L-glutamic acid, showing the atomic-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown with an arbitrary radius.

[21] equipped with graphite monochromatized Mo$K\alpha$ radiation ($\lambda = 0.71073$ Å). The data were corrected for Lorentz-polarization and absorption effects [21]. Three standard reflections were monitored every 100 reflections (intensity decay: none). The structure was solved by direct methods using the SHELXS program [22] and refined by a full-matrix least-squares calculation on F^2 using SHELXL [23].

All H atoms were placed at calculated positions and treated using the riding model, with C-H distances of 0.97–0.98 Å, N-H distances of 0.86 Å, and O-H distances of 0.82 Å. The Uiso (H) parameters were fixed at 1.2 Ueq (C, N, and O). The absolute structure of the title compound was assigned from the known configuration of the starting amino acid L-glutamic acid. All geometrical calculations were done using the program Platon [24]. Table 1 summarizes the crystal data, intensity data collection, and refinement details for the title compound.

Table 2. Selected geometrical parameters (Å, º).

O1-C8	1.310(3)	O2-C8	1.219(3)
O3-C11	1.218(4)	O4-C11	1.310(4)
N1-C1	1.347(3)	N2-C1	1.331(4)
O1-C8-O2	123.9(2)	O3-C11-O4	124.4(3)
N1-C1-N2	118.3(2)	O5-C1-N2	121.9(2)

Table 3. Hydrogen bonds geometry (Å, º). (D-donor; A-acceptor; H-hydrogen).

D–H···A	D—H	H···A	D···A	D–H···A
O1–H1···O5$^{(i)}$	0.820	1.800	2.564(3)	154.0
N2–H2A···O2$^{(ii)}$	0.860	2.310	3.114(3)	155.0
O3–H3···O4$^{(iii)}$	0.820	2.170	2.684(3)	121.0
N1–H1A···O2	0.860	2.210	2.941(3)	143.0
N2–H2B···O5	0.860	2.330	3.059(3)	142.0

Symmetry codes: $^{(i)}$ 2−x, $^1/_2$+y, $^3/_2$−z, $^{(ii)}$ $^3/_2$−x, −y, $^1/_2$+z, $^{(iii)}$ 2−x, −$^1/_2$+y, $^3/_2$−z.

3. Results and discussion

Figure 2 shows the molecular structure and the atom-labeling scheme of (I). This compound crystallizes in a neutral form, unlike the zwitterionic form of the amino acid parent L-glutamic acid [25], this is the result of a resonance effect in the ureido unit, which causes a diminution in

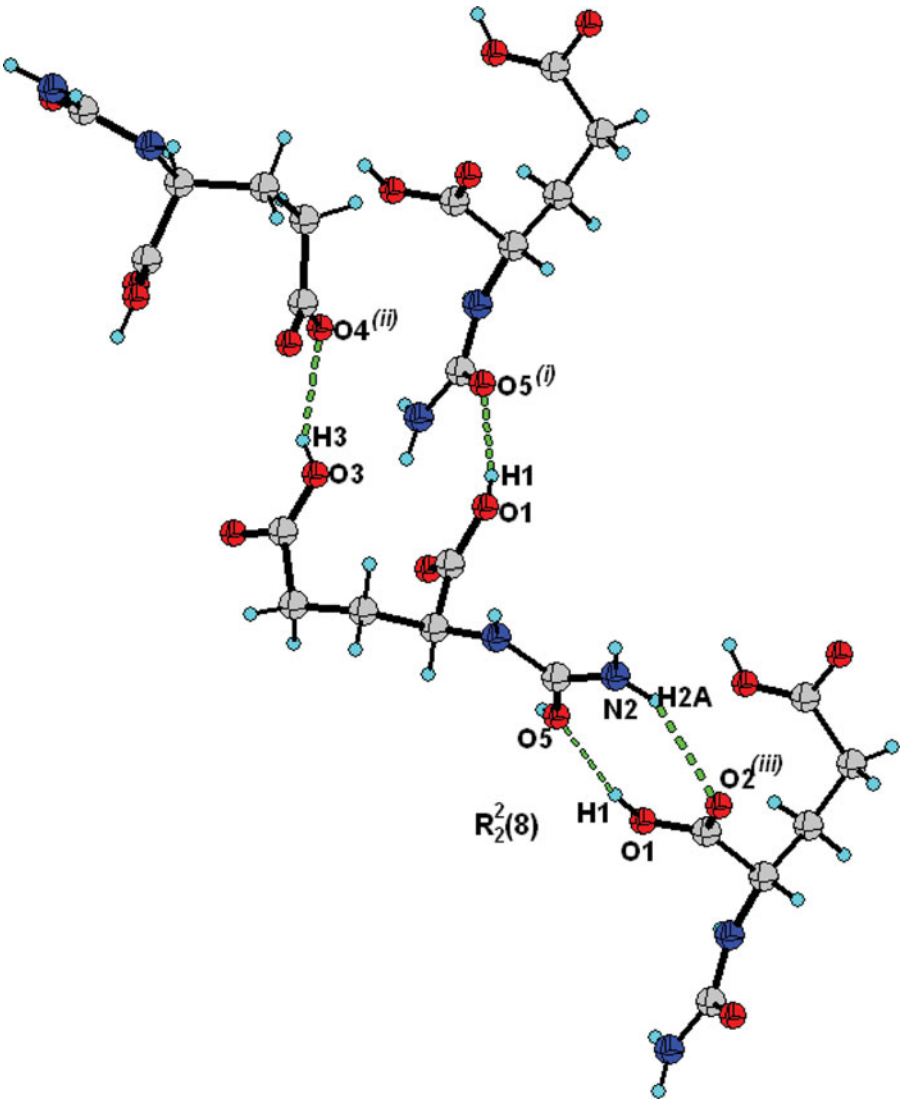


Figure 3. A portion of the crystal packing shows all hydrogen bonds formed (O–H···O and N–H···O). [symmetry codes: $^{(i)}$ 2−x, $^1/_2$+y, $^3/_2$−z, $^{(ii)}$ $^3/_2$−x, −y, $^1/_2$+z, $^{(iii)}$ 2−x, −$^1/_2$+y, $^3/_2$−z].

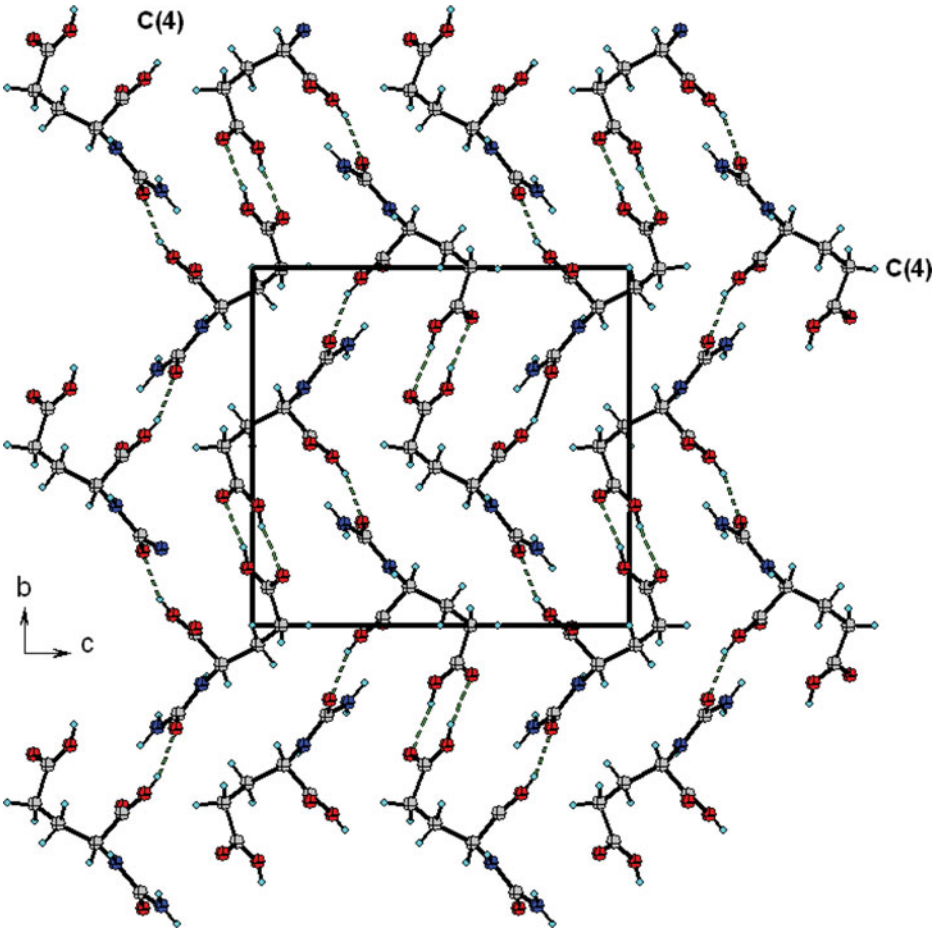


Figure 4. Packing view of N-carbamoyl-L-glutamic acid along the ***bc*** plane. Hydrogen bonds are shown as dashed lines.

the nucleophilic character of the N atoms, and makes it impossible for this atom to withdraw the acidic H atom of the carboxyl group. The neutral character of the compound is confirmed by the clear difference of the values for the O1-C8 and O2-C8, and O3-C11 and O4-C11 bond distances (Table 2). All bond distances and angles are normal for this type of compounds [26].

The dihedral angles between the carboxylates and the ureido group are 65.0(3)° and 83.1(2)°. These values agree with the intercepting angles of 79.08(9)° in N-carbamoyl-L-proline [15] and 86.62(8)° in N-carbamoyl-DL-proline [17], and differs from that observed in N-carbamoyl–L-asparagine [27] and N-carbamoyl-DL-aspartic acid [28], which have intercepting angles values of 155.0(3)° and 164.2(5)°, respectively. These four N-carbamoyl amino acid compounds are reported in the Cambridge Structural Database, CSD version 5.36 update Nov, 2014 [26].

The crystalline structure of (I) is stabilized by three hydrogen bonds, which involve the carboxyl and ureide groups in the molecule, serving as both acceptors and donors in a set of head-to-tail interactions, as depicted in Figs. 3 and 4. The geometrical parameters of these hydrogen bonds are summarized in Table 3.

The O1–H1···O5 (2-x, ½+y, $^3/_2$-z), N2–H2A···O2 ($^3/_2$-x, -y, ½+z), and O3–H3···O4 (2-x, -½+y, $^3/_2$-z) hydrogen bonds form infinite chains which run along the ***b*** and ***c*** axis described

by the graph set C(4) [29,30] (Fig. 4). Together, these hydrogen-bond patterns produces a 11-atom cycle described by $R^2_2(11)$, which are connected by typical amide-acid $R^2_2(8)$ dimers. The infinite chains are connected by head-to-tail interactions of carboxyl and ureido groups and the network is reinforced by the intermolecular N1–H1A···O2 and N2–H2B···O5 interactions, which play the role of keeping the extended chains together. The combination of these interactions produces a three-dimensional hydrogen bond network as depicted in Fig. 4.

4. Conclusions

The title compound was synthesized by a reaction of L-glutamic acid and potassium thiocyanate. The structure was unambiguously assigned by X-ray diffraction studies. The FT-IR and NMR results were consistent with the structural results. The structure of N-carbamoyl-L-glutamic acid is built up from self-assembly of molecules via O–H···O and N–H···O hydrogen-bonding interactions, forming chains and rings into a three-dimensional network.

Supplementary data

Crystallographic data for the structure reported here have been deposited with the Cambridge Crystallographic Data Centre (CCDC-1052742). These data can be obtained free of charge from CCDC, 12 Union Road, Cambridge CB21EZ, United Kingdom; fax: (+44)1223336033; e-mail: deposit@ccdc.cam.ac.uk.

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