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Artículo científico

Synthesis, Crystal and Molecular Structure, and Hydrogen-bonding Patterns in Hydantoin-L-Aspartic Acid

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Resumen:

La hidantoina del ácido L-aspártico, $C_5H_6N_2O_4$, cristaliza en el sistema ortorrómbico con grupo espacial $P2_12_12_1$ (Nº19), Z=4, y parámetros de celda unidad *a*= 7,597(1) Å, *b*= 8,591(1) Å, *c*= 9,447(1) Å, V= 616,6(2) Å^3. En la estructura cristalina de este compuesto, las moléculas están unidas por enlaces de hidrógeno del tipo N---H···O y O---H···O, creando estructuras en cadenas y ciclos con grafos C(4), C(6), C(8), $R^3_3(15)$, $R^4_4(20)$ que forman una red tridimensional

Palabras clave: Estructura cristalina por difracción de rayos-X; enlaces de hidrógeno; hidantoinas

Abstract

Hydantoin-L-aspartic acid, $C_5H_6N_2O_4$, crystallize in the orthorhombic system with space group $P2_12_12_1$ (Nº19), Z=4, and unit cell parameters *a*= 7.597(1) Å, *b*= 8.591(1) Å, *c*= 9.447(1) Å, V= 616.6(2) Å^3. In the crystal structure of the title compound the molecules are joined by N---H···O and O---H···O hydrogen bonds into chain and cyclic structures with graph-set C(4), C(6), C(8), $R^3_3(15)$, $R^4_4(20)$ forming a three-dimensional network.

Keywords: X-ray diffraction crystal structure; hydrogen bonding; hydantoin

Introduction

The hydantoin or imidazolidine-2,4-dione heterocycle is a common 5-member ring containing a reactive cyclic urea core[1,2]. This heterocycle is present in a wide range of biologically active compounds including therapeutic drugs for the treatment of seizures and antitumor compounds[3]. Phenytoin (5,5-diphenylhydantoin, Dilantin®) is one of the oldest non-sedative antiepileptic drugs, which is employed in cases of generalized neural seizures (epilepsy) and focal motor seizures[4,5].

Moreover, this heterocycle represents a significant molecular template in combinatorial chemistry libraries[6-8], due principally to the four possible points of substitutions.

For the other hand, the biocatalitic conversion of 5-subtituted hydantoins to amino acids has received considerable attention recently for their potential applications in the industrial productions of optically pure amino acids[9,10], and for these reasons, there has been greatly interest in the search of new synthetic routes to preparing hydantoin derivatives[11-15].

As complexation to a metal ion usually modifies the biological activity of a ligand, the coordination properties of hydantoins could produce promising biologically active substances. However, to the best of our knowledge only few metal complexes with hydantoins are known in the literature[16-18].

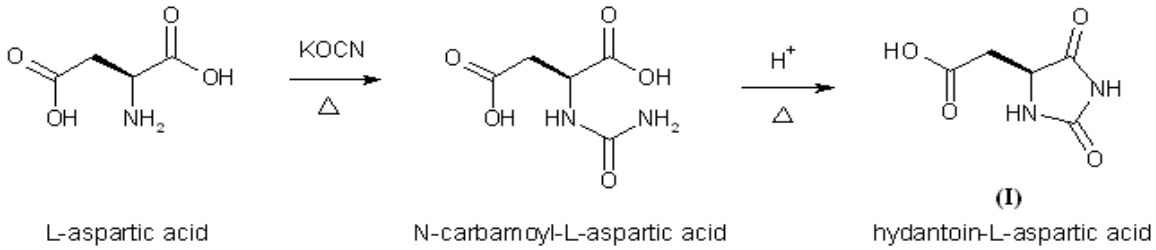
In continuation of our previous investigation on N-carbamoyl, hydantoin and thiohydantoin natural α-amino acids derivative compounds[19-27], the present work is focused on the synthesis, crystal and molecular structure of hydantoin-L-aspartic acid, a new derivative of the α-amino acid L-aspartic acid. The absolute structure for this compound is reported using data collected with a Cu source, and the analysis of the hydrogen bond patterns is also discussed.

Experimental

Synthesis

The title compound was synthesized from the pure α-amino acid using a methodology previously reported[19,20], 4.3 mmol of L-aspartic acid were dissolved in 20 mL of

water and the solution was acidified with concentrated HCl (37% v/v) to pH= 5. Then, 12.9 mmol of KOCN were added to this solution. The mixtures were warmed up, with agitation, to 60 °C, during 4 h. The resultant solutions were acidified with HCl to pH= 2 and agitated during 4 h, until the precipitation of a white solid en each case (see scheme 1). The solid was filtered and washed with cool water. Colorless crystals suitable for X-ray diffraction analysis were obtained by slow evaporation in a 1:1 methanol-water solution (m.p. 487-488K).



Scheme 1: Synthesis of hydantoin-L-aspartic acid from the pure amino acid

FT-IR and NMR analysis

FT-IR (KBr) ν cm^{-1}, 3360 [t, O-H], 3202 [t, N-H], 1759 [t, C=O], 1707 [t, C=O], 1434 [t, C-N].

^{1}H NMR (400 MHz, DMSO-d_6) δ =12.52 (s, H8), 10.64 (s, H3), 7.89 (s, H1), 4.20 (t, H5), 2.64 (s, H6B), 2.63 (s, H6A).

^{13}C NMR (100.6 MHz, DMSO-d_6) δ =175.44 (C4), 171.04 (C7), 157.70 (C2), 54.40 (C5), 35.43 (C6).

X-ray powder diffraction

X-ray powder diffraction pattern was collected, at room temperature, in a Phillips PW-1250 goniometer using monocromatized CuKα radiation. A small quantity of hydantoin-L-aspartic acid was ground mechanically in an agate mortar and pestle and mounted on a flat holder covered with a thin layer of grease. The specimen was scanned from 10-60° 2θ, with a step size of 0.02° and counting time of 15s. Silicon was used as an external standard. X-ray powder pattern is show in Figure 1. The 20 first measured reflections were completely indexed using the program Dicvlo04[28], which gave a unique solution in an orthorhombic cell with parameters a = 7.60 Å, b = 8.59 Å, c = 9.44 Å in a P-type cell. In order to confirm the unit cell parameters, a Le Bail refinement[29] of the whole diffraction pattern without structural was carried out using the Fullprof program[30]. Figure 1 shows a very good fit between the observed and calculated patterns.

X-ray single-crystal crystallography

Colorless rectangular crystal of hydantoin-L-aspartic acid with dimensions 0.52×0.21×0.20 mm3 was used for data collection. This compound crystallizes in the orthorhombic system (space group $P2_12_12_1$) Diffraction data were collected at 296(2) K by ω-scan technique on a Bruker SMART APEX II CCD diffractometer[31] equipped with CuKα radiation (λ = 1.5418 Å).

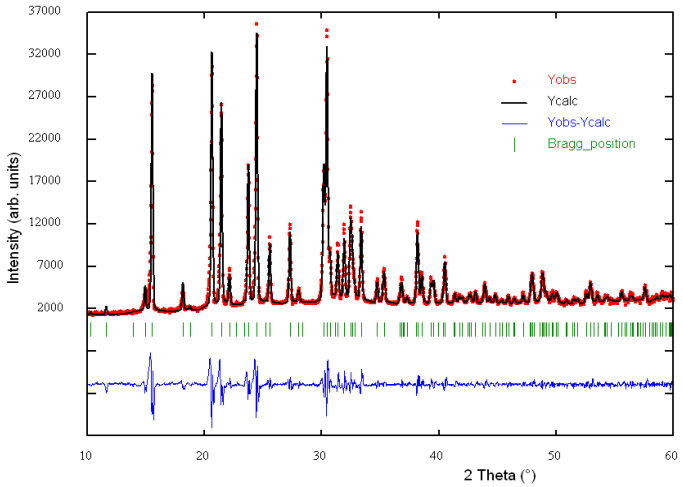


Figure 1: X-ray powder diffraction data for hydantoin-L-aspartic acid. The powder pattern was refined without structural model to confirm the unit cell parameters.

The data were corrected for Lorentz-polarization and absorption effects[32]. The structure was solved by direct methods using the SHELXS97 program[33] and refined by a full-matrix least-squares calculation on F^2 using SHELXL97[33]. All H atoms were placed at calculated positions and treated using a riding model, with C-H distances 0.96-0.98 Å and $U_{iso}(H) = 1.2U_{eq}(C)$], N-H 0.86 Å and $U_{iso}(H) = 1.2U_{eq}(N)$]. The absolute structure of hydantoin-L-aspartic acid was assigned from the known configuration of the starting material L-aspartic acid. CuKα radiation used in this study improves the anomalous dispersion effects. Crystallographic data for the structure reported here have been deposited with the Cambridge Crystallographic Data Centre (Deposition No. CCDC-865398). The data can be obtained free of charge via http://www.ccdc.cam.ac.uk/perl/catreq.cgi (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: +44 1223 336033; e-mail: deposit@ccdc.cam. ac.uk).

Results and discussion

Hydantoin-L-aspartic acid crystallizes in a non-centro-symmetric space group preserved the L-configuration of the starting amino acid. Figure 2 shows the molecular structure and the atom-labeling scheme of the title compound, generated using DIAMOND program[34]. Table 1 summarizes the crystal data, intensity data collection and refinement details for the title compound. Selected geometrical parameters are given in Table 2. All geometrical calculations were done using the program PLATON[35]. Table 3 shows the hydrogen bonding geometry for the title compound.

Table 1: Crystal data, data collection and structure refinement

Crystal data	
Empirical formula	$C_5H_6N_2O_4$
Formula weight	158.12
Crystal system, space group	Orthorhombic, $P2_12_12_1$
Unit cell parameters	
a (Å)	7.597 (1)
b (Å)	8.591 (1)
c (Å)	9.447 (1)
Volume (Å^3)	616.6(2)
Z, calculated density (mg/m^3)	4, 1.703
Absorption coefficient (mm^{-1})	1.308
F000	328
Crystal size (mm^3)	0.52 x 0.21 x 0.20
Data collection	
Temperature (K)	296 (2)
Diffractometer	Bruker SMART APEX II CCD
Radiation (Å)	Cu Kα
θ range for data collection (°)	7.0-66.6
hkl range	-8≤h≤8, -10≤k≤9, -10≤l≤5
Reflections collected/unique	4346/987
R_{int}	0.040
Reflections observed [I > 2σ(I)]	947
Max. and min. transmission	0.780 and 0.550
Refinement	
Reflections/parameters	987/102
Goodness-of-fit on F^2	1.02
Final R indices [I > 2σ(I)]	R_1 = 0.036, wR_2 = 0.107
R indices (all data)	R_1 = 0.041, wR_2 = 0.116
Largest diff. peak and hole (e/Å)$^{-3}$	0.29 and -0.33
CCDC deposit no.	865398

Table 2: Selected geometrical parameters (Å, º)

O2-C2	1.227(4)	O4-C4	1.214(4)
N3-C2	1.383(4)	N3-C4	1.356(4)
N1-C2	1.334(4)	N1-C5	1.449(4)
C7-O7	1.208(4)	C7-O8	1.332(4)
N1-C2-O2	126.8(3)	N3-C2-O2	125.5(3)
N3-C4-O4	126.0(3)	C5-C4-O4	127.3(3)
C5-N1-C2-O2	175.7(3)	C4-N3-C2-O2	179.1(3)
C5-C6-C7-O8	166.4(3)	C4-C5-C6-C7	-53.0(4)

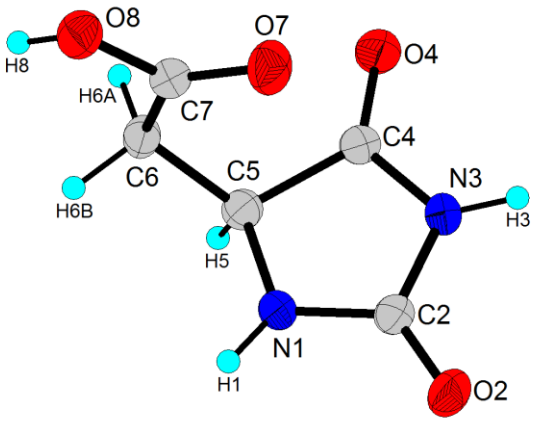


Figure 2: The molecular structure of (I), showing the atomic numbering scheme. Displacement ellipsoids are drawn at 35% probability level. H atoms are shown as spheres of arbitrary radii.

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

D--H···A	D--H	H···A	D···A	D--H·A
N1--H1···O8$^{(i)}$	0.86	2.15	3.013 (4)	178
N3--H3···O4$^{(ii)}$	0.86	1.99	2.839 (3)	168
O8--H8···O2$^{(iii)}$	0.82	1.81	2.617 (3)	165

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

The hydantoin ring is essentially plane with a maximal deviations of 0.055 (1) Å in O2 and -0.028 (4) Å in N1. The dihedral angle between the hydantoin and the carboxylate plane is 88.8 (2)°. The organic molecule adopts a gauche conformation.

The N1--C2--O2 bond angle 126.8(2)° is slightly greater than the N3--C2--O2 angle 125.5 (3)° (Table 2). This difference is also observed in the 50 others hydantoin derivatives reported in the Cambridge Structural Database, CSD version 5.33 updates (August 2012)[36], including the hydantoin α-amino acid derivatives hydantoin-glycine[37] and hydantoin-L-phenylalanine[21], and the recently reported structure of hydantoin-L-proline[26].

The molecular structure and crystal packing of hydantoin-L-aspartic acid (I) is stabilized by intermolecular N--H···O and O--H···O hydrogen bonds (Table 3 and Figure 3).

The O7 atom is the only one not involved in hydrogen bonds. The three hydrogen bonds form infinite chains; N1--H1···O8 (-x, 1/2 + y, 1/2-z) form chains along the [001] direction, which can be described in graph-set notation as C(6) [29], N3---H3···O4 (1/2+x, 3/2-y, 1-z) form chains along the [001] direction with graph-set C(4) and O8---H8···O2 (-1+x, y, z) form chains along the [010] direction (Figure 3).

Additionally, these hydrogen bonds form different rings with graph-set $R^3_3(15)$[38] with 3 molecules involved, two N--H···O and one O--H···O hydrogen bonds, and graph-set $R^4_4(20)$ with two N--H···O and two O--H···O hydrogen bonds (Figure 2). The combination of these interactions produces a three-dimensional hydrogen bond network.

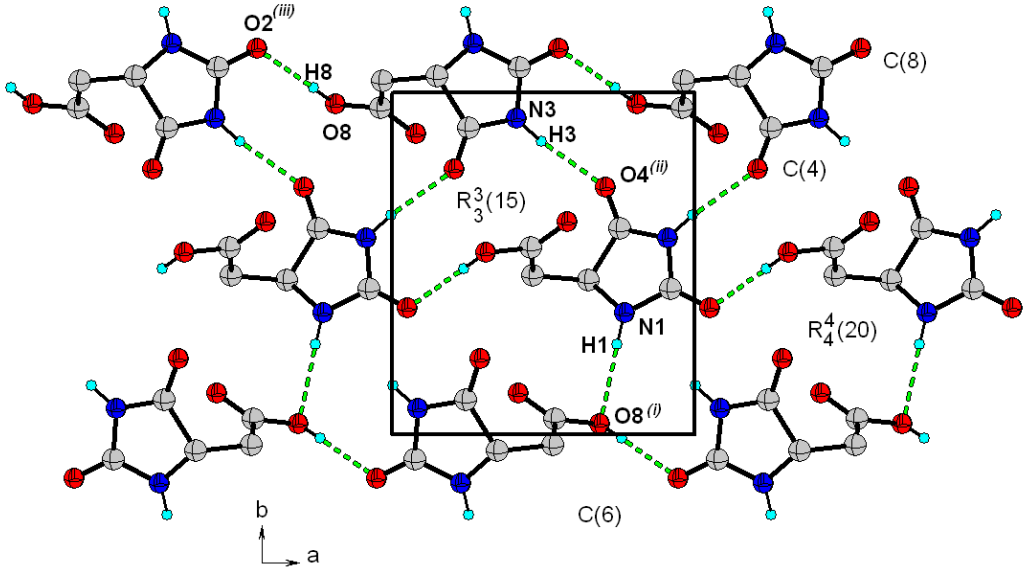


Figure 3: Packing view of (I). Intermolecular hydrogen bonds, N--H···O and O--H···O, are indicated by dashed lines. H atoms not involved in hydrogen bonding have been omitted for clarity.

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References

1. CA López, GG Trigo. The chemistry of hydantoins. **Adv. Heterocycl. Chem., 38,** 177-228 (1985).
2. M Meusel, M Gütschow. Recent developments in hydantoin chemistry. A review. **Org. Prep. Proced. Int., 36**, 391-443 (2004).
3. E Mutschler, H Derendorf. Drug Actions, Basic Principles and Therapeutic Aspects. Medpharm Scientific Publishers, Stuttgart (1995).
4. HH Merrit, TJ Putnam. A new series of anticonvulsant drugs tested by experiments on animals. **Arch. Neurol. Psychiatry, 39**, 1003-1015 (1938).
5. Y Yaari, ME Selzer, JH Pincus. Phenytoin: mechanisms of its anticonvulsant action. **Ann. Neurol., 20**, 171-184 (1986).
6. KH Park, J Ehrler, H Spoerri, MJ Kurth. Preparation of a 990-member chemical compound library of hydantoin- and isoxazoline-containing heterocycles using multipin technology. **J. Comb. Chem., 3**, 171-176 (2001).
7. MJ Lin, CM Sun. Microwave-assisted traceless synthesis of thiohydantoin. **Tetrahedron Lett., 44**, 8739-8742 (2003).
8. W Zhang, YM Lu, CHT Chen, L Zeng, DB Kassel. Fluorous mixture synthesis of two libraries with hydantoin-, and benzodiazepinedione-fused heterocyclic scaffolds. **J. Comb. Chem., 8**, 687-695 (2006).
9. B Wilms, A Wiese, C Syldatk, R Mattes, J Altenbuchner. Development of an Escherichia coli whole cell biocatalyst for the production of L-amino acids. **J. Biotechnol., 86**, 19-30 (2001).
10. SG Burton, RA Dorrington. Hydantoin-hydrolysing enzymes for the enantioselective production of amino acids: new insights and applications. **Tetrahedron Asymm., 15**, 2737-2741 (2004).
11. E Kleinpeter. The structure of hydantoins in solution and in the solid state. **Struc. Chem., 8**, 161-173 (1997).
12. A Ganesan. Cyclative cleavage strategies for the solid-phase synthesis of heterocycles and natural products. **Methods Enzymol., 369**, 415-434 (2003).
13. J Vázquez, M Royo, F Albericio. Re-evaluation of a solid-phase hydantoin synthesis. **Lett. Org. Chem., 1**, 224-226 (2004).
14. J Alsina, WL Scott, MJ O'Donnell. Solid-phase synthesis of α-substituted proline hydantoins and analogs. **Tetrahedron Lett., 46**, 3131-3135 (2005).
15. V Kumar, H Rana, R Sankolli, MP Kaushik. Highly efficient dialkylphosphate-mediated syntheses of hydantoins and a bicyclohydantoin under solvent-free conditions. **Tetrahedron Lett., 52**, 6148-6151 (2011).
16. X Hu, X Xu, D Wang and Y Qin Zhou. Bis(ethylenediamine-k^2N,N0)bis-(phenytoinato-kN)cobalt(II). **Acta Cryst., E65**, m1470 (2009).

17. M Puszynska-Tuszkanow, T Grabowski, M Daszkiewicz, J Wietrzyk, B Filip, G Maciejewska, M Cieślak-Golonka. Silver(I) complexes with hydantoins and allantoin. Synthesis, crystal and molecular structure, cytotoxicity and pharmaco-kinetics. **J. Inorg. Biochem., 105**, 17-22 (2011).

18. M Puszynska-Tuszkanow, M Daszkiewicz, G Maciejewska, Z Staszak, J Wietrzyk, B Filip, M Cieslak-Golonka. HSAB principle and nickel(II) ion reactivity towards 1-methyhydantoin. **Polyhedron, 30**, 2016-2025 (2011).

19. LE Seijas, GE Delgado, AJ Mora, A Bahsas, J Uzcategui. Síntesis y caracterización de los derivados N-carbamoilo e hidantoina de L-prolina. **Av. Quím., 1**, 3-7 (2006).

20. LE Seijas, GE Delgado, AJ Mora, A Bahsas, A Briceño. (2S)-1-carbamoylpyrrolidine-2-carboxylic acid. **Acta Cryst., C63**, o303-o305 (2007).

21. GE Delgado, AJ Mora, J Uzcátegui, A Bahsas, A Briceño. (S)-5-benzylimidazolidine-2,4-dione monohydrate. **Acta Cryst., C63**, o448-o450 (2007).

22. ME. Sulbaran, GE Delgado, AJ Mora, A Bahsas, H Novoa de Armas, N Blaton. Hydrogen-bonding patterns in rac-1-acetyl-5-methyl-2-thioxoimidazolidine-4-one. **Acta Cryst., C63**, o543-o545 (2007).

23. MC Uzcátegui, GE Delgado, AJ Mora, T. González, A. Briceño. rac-1-acetyl-5-benzyl-2-thioxo-imidazolidin-4-one. **Acta Cryst., E65**, o104 (2009).

24. LE Seijas, AJ Mora, GE Delgado, M Brunelli, AN Fitch. Study of the conversion of N-carbamoyl-L-proline to hydantoin-L-proline using powder synchrotron X-ray diffraction. **Powder Diffr. 25**, 342-348 (2010).

25. GE Delgado, LE Seijas, AJ Mora, T González, A Briceño. Synthesis, crystal structure and hydrogen-bonding patterns in (RS)-1-carbamoyl pyrrolidine-2-carboxylic acid. **J. Chem. Cryst., 42**, 388-393 (2012).

26. GE Delgado, LE Seijas, AJ Mora. Synthesis and crystal structure determination of hydantoin-L-proline. **J. Chem. Cryst., 42**, 968-971 (2012).

27. GE Delgado, ME Sulbaran, AJ Mora. Synthesis, crystal structure and hydrogen-bonding patterns in rac-N-acetyl-2-thiohydantoin-leucine. **Int. J. Mater. Chem., 3**, 1-4 (2013).

28. A Boultif, D Löuer. Powder pattern indexing with the dichotomy method. **J. Appl. Cryst., 37**, 724-731 (2004).

29. A Le Bail. Whole powder pattern decomposition methods and applications: a retrospection. **Powder Diffr., 20**, 316-326 (2005).

30. J. Rodriguez-Carvajal, Fullprof, version 5.3, LLB, CEA-CNRS, France, 2012.

31. Bruker SAINT. Bruker AXS Inc., Madison, Wisconsin, USA, 2009.

32. Bruker APEX2. Bruker AXS Inc., Madison, Wisconsin, USA, 2010.

33. GM Sheldrick. A short history of SHELX. **Acta Cryst., A64**, 112-122 (2008).

34. Brandenburg K, DIAMOND, Crystal Impact GbR, Bonn, Germany, 1998.

35. AL Spek. Single-crystal structure validation with the program Platon. **J. Appl. Cryst., 36**, 7-13 (2003).

36. FH Allen. The Cambridge Structural Database: a quarter of a million crystal structures and rising **Acta Cryst., B58**, 380-388 (2002).

37. F Yu, CH Schwalbe, D Watkin. Hydantoin and hydrogen-bonding patterns in hydantoin derivatives. **Acta Cryst., C60**, 714-717 (2004).

38. MC Etter. Encoding and decoding hydrogen-bond patterns of organic-compounds. **Acc. Chem. Res., 23**, 120-126 (1990)