MOLECULAR-CRYSTAL STRUCTURE OF DL-β-(5-BROMO-1-URACILYL)-α-ALANINE

A. F. Mishnev, Ya. Ya. Bleidelis,
V. É. Krishane, R. A. Paégle,
and M. Yu. Lidak

UDC 548.737:547.854.4'466

The molecular-crystal structure of DL-β-(5-bromo-1-uracilyl)-α-alanine was determined by x-ray diffraction analysis. It was established that, in contrast to the free amino acids, this compound does not have a zwitterion structure in the crystalline state. Shortened distances, which may correspond to two intramolecular hydrogen bonds, are observed in the molecule.

For a number of years we have been engaged in the synthesis and study of 1-pyrimidinyl-α-alanines [1]; particular attention has been devoted to the elucidation of these peculiarities that distinguish them from natural amino acids. The differences in the corresponding characteristics could have been explained by the sparse distribution of 1-uracilyl-α-amino acids in nature, despite the fact that their components, viz., uracil and α-alanine, are encountered in many vital compounds.

In order to ascertain the structural peculiarities of β-(1-uracilyl)-α-alanine derivatives we determined their protolysis constants [2]. We found that the $pK_{NH_3^+}$ values are ∿1.4-2.0 units lower than their values for such amino acids as tryptophan (9.39), tyrosine (9.11), and α-alanine (9.97). We regarded the difference in the β-(1-uracilyl)-α-alanine series as a consequence of the formation of an intramolecular hydrogen bond between the closely located NH_3^+ and $C_7{=}O$ groupings. In addition, during a study of the chemical properties of β-(5-bromo-1-uracilyl)-α-alanine we discovered its unusual behavior upon reaction with amines, viz., intramolecular cyclization to give an imidazo[1,2-c]pyrimidine system [3].

To study the structure of DL-β-(1-uracilyl)-α-alanines in the crystalline state we subjected DL-β-(5-bromo-1-uracilyl)-α-alanine to an x-ray diffraction study.

A model of the molecule with designation of the atoms and its geometry are given in Fig. 1. The accuracy in the determination of the interatomic distances and bond angles was ±0.03 Å

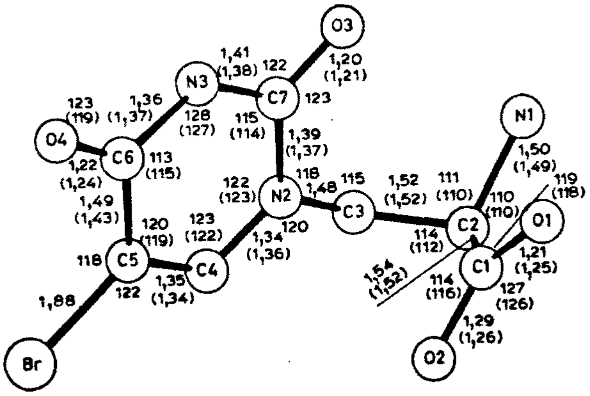

Fig. 1. Model of the DL-β-(5-bromo-1-uracilyl)-α-alanine molecule. The bond lengths and bond angles in the L-alanine [4] and uracil [5] molecules are given in parentheses.

Institute of Organic Synthesis, Academy of Sciences of the Latvian SSR, Riga 226006. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 3, pp. 398-401, March, 1981. Original article submitted June 17, 1980.

TABLE 1. Coefficients of the Equations of the Average Planes of the Fragments of the Molecule and Deviations of the Individual Atoms from Them

Plane	Atoms that form the plane	Deviations from the plane, Å	$A_x+\beta_y+C_z-D=0$			
			A	B	C	D
I	C4, N3	0,005	−0,6041	0,6508	−0,4599	−1,0925
	C5, C7	−0,005				
	N2*	−0,04				
	O4*	−0,02				
	O3*	0,01				
	C6*	0,01				
	Br*	0,05				
	C3*	0,06				
II	C2, C3, N2	—	−0,6843	−0,4780	−0,5506	−3,5702
III	C1	0,025	0,1244	0,1345	−0,9831	−6,4585
	C2	−0,007				
	O1	−0,010				
	O2	−0,010				
	N1*	0,054				

---

*These are the atoms that were disregarded in the calculation of the plane.

and ±2.0, respectively. The coefficients of the equations of the average planes of the fragments of the molecule and the deviations of the individual atoms from them are presented in Table 1.

Except for the C1—O1 and C1—O2 distances, the geometry of the amino acid residue of the molecule corresponds within the limits of accuracy of the measurements to the geometry of the L-alanine molecule [4] (see Fig. 1). The C1—O1 and C1—O2 distances in the L-alanine molecule are virtually identical, and their average value is 1.25 Å, which indicates its zwitterion structure. The C—O distances of the carboxy group in the alanine fragment of this molecule differ: The C1—O1 distance (1.21 Å) has typical double bond character, while the C1—O2 distance (1.29 Å) indicates protonation of the O2 atom.

A comparison of the geometry of the 5-bromouracil fragment of the β-(5-bromo-1-uracilyl)-α-alanine molecule with the geometry of the uracil molecule [5] (see Fig. 1) demonstrates their agreement within the accuracy limits, except for the interatomic C5—C6 distance and the exocyclic O4—C6—N3 bond angle, which as compared with uracil, are increased by 0.06 Å and 4°, respectively. However, the C5—C6 distance and the O4—C6—N3 angle correspond to the values in the 5-iodo-2'-deoxyuridine structure (1.49 Å and 121°) [6]. The change in these parameters is evidently a consequence of both the steric and electrostatic effects of the bromine atom.

It is apparent from the lengths of the C6—O4 (1.22 Å) and C7—O3 (1.20 Å) bonds that the uracil fragment in a crystal of this compound exists in the diketo form that is usual for it; the average value of the lengths of the C—O bonds (1.21 Å) corresponds to the length of the C=0 bonds double bond (1.2. Å) in ketone molecules [7].

Within the accuracy limits, the six-membered heteroring is planar (see Table 1). Plane I forms a dihedral angle of 69° with plane II.

The packing of the molecules in the crystal is basically realized at the van der Waals distances and is stabilized by strong intermolecular N1...O2 (2.67 Å) and N3—H...O2 (2.76 Å) bonds. An unsuccessful attempt at localization of the hydrogen atoms at the N1 atom did not make it possible to reliably establish the existence of intramolecular hydrogen bonds, the possibility of the existence of which was indicated in [2], although the nonvalence N1...O3 and N1...O1 distances of 2.86 and 2.67 Å, respectively, do not contradict this.

In the analysis of the character of the packing of the molecules in the crystal the short intermolecular O.3 ... Br contact of 2.90 Å is noteworthy, in addition to the van der Waals interaction and stabilization of the structure by two hydrogen bonds. This distance is considerably shorter than even the intermolecular distance calculated in accordance with [8] as the values $2\sqrt{R_{BR}\cdot R_O}$ (3.17 Å), to say nothing of the usually employed sum of the van der Waals radii of the corresponding atoms (3.24 Å). This specific halogen—oxygen interaction was also observed in the crystal structure of 5-iodo-2'-deoxyuridine [9]

TABLE 2. Coordinates of the Nonhydrogen Atoms*

	x	*y*	*z*
C1	−0,028 (4)	−0,287 (3)	1,022 (2)
C2	−0,271 (3)	−0,174 (2)	1,014 (2)
C3	−0,266 (4)	0,054 (3)	0,868 (2)
C4	0,094 (4)	0,240 (2)	0,678 (3)
C5	0,269 (4)	0,291 (3)	0,518 (2)
C6	0,275 (4)	0,189 (3)	0,342 (3)
C7	−0,084 (5)	−0,011 (3)	0,538 (3)
N1	−0,439 (3)	−0,320 (2)	0,963 (2)
N2	−0,072 (3)	0,091 (2)	0,695 (2)
N3	0,097 (3)	0,045 (3)	0,370 (2)
O1	−0,006 (6)	−0,473 (4)	1,003 (5)
O2	0,129 (3)	−0,173 (2)	1,063 (2)
O3	−0,236 (3)	−0,138 (3)	0,544 (3)
O4	0,430 (3)	0,223 (2)	0,194 (2)
Br	0,500 (0)	0,500 (0)	0,500 (0)

*The anisotropic temperature factors can be obtained from the authors.

and in the binary complex of 9-ethyladenine with 1-methyl-5-bromouracil [10] and was discussed in [11].

Thus the difference between DL-β-(5-bromo-1-uracilyl)-α-alanine and protein derived amino acids in the crystalline state is the fact that a protonated carboxy structure is characteristic for the former, while a zwitterion structure is characteistic for the latter.

EXPERIMENTAL

DL-β-(5-Bromo-1-uracilyl)-α-alanine was synthesized by bromination of DL-β-(1-uracilyl)-α-alanine [1]. Single crystals were obtained by crystallization at room temperature from an aqueous solution.

A three-dimensional set of intensities of reflections from a single crystal with the composition $C_7H_8BrN_3O_4$ was obtained with a Syntex P2₁ diffractometer from a 0.60 × 0.50 × 0.27 mm single crystal. The following crystallographic characteristics of the unit cell were found: $a = 5.775(1)$, $b = 6.277(1)$, $c = 6.809$ Å, $\alpha = 74.91(1)$, $\beta = 81.12(1)$, $\gamma = 87.29(1)°$, $V = 235.5(4)$ Å^3, $M = 278.06$, $d_{calc} = 2.08$ g-cm^{-3}, $Z = 1$, $\mu(\mathrm{Cu}\ K_\alpha) = 67.6$ cm^{-1}, space group P1, and $F_{000} = 147$. The intensities of 830 nonzero independent reflections were measured by $\theta/2\theta$ scanning with monochromatic copper emission (graphite monochromator) to $2\theta_{max} = 150°$. The structure was elucidated by the heavy-atom method and was refined within the total matrix anisotropic approximation to R = 0.06. The positions of the hydrogen atoms were obtained from geometrical considerations. The coordinates of the nonhydrogen atoms are presented in Table 2.

LITERATURE CITED

1. M. Yu. Lidak, R. A. Paégle, M. G. Plata, and Yu. P. Shvachkin, Khim. Geterotsikl. Soedin., No. 4, 530 (1971).
2. M. Yu. Lidak, I. V. Dipan, R. A. Paégle, and Ya. P. Stradyn', Khim. Geterotsikl. Soedin., No. 5, 708 (1972).
3. R. A. Paégle, I. Zh. Lulle, V. É. Krishane, I. B. Mazheika, É. É Liepin'sh, and M. Yu. Lidak, Khim. Geterotsikl. Soedin., No. 4, 538 (1980).
4. H. J. Simpson and R. E. Marsh, Acta Crystallogr., 20, 550 (1966).
5. R. Stewart and L. H. Jensen, Acta Crystallogr., 23, 1102 (1967).
6. N. Camerman and J. Trotter, Acta Crystallogr., 15, 203 (1965).
7. G. Glocker, J. Phys. Chem., 62, 1049 (1958).
8. Yu. V. Zefirov and P. M. Zorkii, Zh. Struk. Khim., 15, 118 (1974).
9. N. Camerman and J. Trotter, Science, 144, 1348 (1966).
10. L. Katz, K. Tomita, and A. Rich, Acta Crystallogr., 21, 754 (1966).
11. O. Hassel and C. Romming, Quart. Rev., 16, 1 (1962).