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Abstract

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CRYSTALLOGRAPHY

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X-RAY DETERMINATION OF THE STRUCTURE OF PHENYLALANINE HYDROCHLORIDE

At present, the atomic structure is known for 17 amino acids out of the 22 principal ones. Here we present the results of a study of one more amino acid—phenylalanine—$C_6H_5CH_2CHNH_2COOH$.

The first X-ray data (space group and unit cell) for crystalline phenylalanine were obtained in 1931 by Bernal (^{1}). The structure of the phenylalanine residue in the tripeptide glycyl-phenylalanyl-glycine was established in (^{2}).

The crystals used by us for X-ray photography were grown from a saturated solution of the L-form of the amino acid in an aqueous solution of hydrochloric acid by slow evaporation of the solvent at a constant temperature of 25°. The space group of the crystals is $P2_12_12_1$, unit cell: $a = 27.68$; $b = 6.98$; $c = 5.34$; $z = 4$ ($C_6H_5CH_2CHNH_2COOHHCl$). On X-ray goniometric layer-line photographs and precession X-ray photographs, the intensities of 933 reflections (CuK_α radiation) were measured with the aid of blackening standards. A preliminary structural model was derived from a three-dimensional sharpened modified interatomic-distance function by the minimization method (^{3}). Refinement of the selected model was carried out using a series of projections (xy) and (xz) of the electron density, two three-dimensional electron-density distributions, and least-squares calculations taking into account the individual isotropic temperature vibrations of the atoms. In the refinement process, the scattering contributions of hydrogen atoms were also taken into account; their positions were determined from known values of interatomic distances and valence angles. On the final difference syntheses, peaks due to hydrogen atoms appeared distinctly (Fig. 1). As a result, a value of the discrepancy factor $R(hkl)$ equal to 14% over the entire three-dimensional set of intensities was attained. The values of the coordinates and isotropic temperature factors of the atoms of the structure are given in Table 1. The mean error in the determination of coordinates is $\sim \pm 0.015$ Å.

Table 1

Coordinates (in fractions of the axes a, b, c) and isotropic temperature factors of the basis atoms in the structure of phenylalanine hydrochloride

Atoms	x	y	z	B_j, Å^2	Atoms	x	y	z	B_j, Å^2
C_1	0.0645	0.7012	0.6812	3.23	$H_1(C_2)$	0.0474	0.6496	0.2988	4.56
C_2	0.0686	0.5819	0.4491	3.56	$H'_2(C_3)$	0.1374	0.6826	0.3038	4.21
C_3	0.1206	0.5449	0.3535	3.21	$H''_3(C_3)$	0.1188	0.4583	0.1816	4.21
C_4	0.1534	0.4398	0.5494	3.43	$H_4(C_5)$	0.1703	0.6957	0.7456	6.81
C_5	0.1765	0.5404	0.7322	5.81	$H_5(C_6)$	0.2282	0.5349	0.0434	7.57
C_6	0.2075	0.4543	0.9016	6.57	$H_6(C_7)$	0.2308	0.1758	0.0188	8.05
C_7	0.2134*	0.2588*	0.8866*	7.05	$H_7(C_8)$	0.1990	0.0046	0.6684	8.76
C_8	0.1888*	0.1544*	0.6946*	7.76	$H_8(C_9)$	0.1385	0.1656	0.3865	6.42
C_9	0.1587	0.2470	0.5276	5.42	$H'_9(N)$	0.0564	0.3467	0.6235	4.71
O_1	0.0860	0.8711	0.6412	4.93	$H''_{10}(N)$	0.0408	0.3323	0.3595	4.71
O_2	0.0457	0.6591	0.8684	3.69	$H'''_{11}(N)$	0.0112	0.4398	0.5430	4.71
N	0.0424	0.4027	0.5044	3.71	$H_{12}(O_1)$	0.0658	0.9166	0.7771	4.69
Cl	0.0561	0.1511	0.0232	3.76					

The interatomic distances and valence angles of the phenylalanine molecule, calculated from the coordinates given, are shown in Fig. 2. As is evident from the figure, the values of the lengths of single C—C bonds in the aliphatic part of the carbon chain of the molecule vary from 1.50 to 1.57 Å. Their average length (1.54 Å) coincides with the generally accepted value for the lengths of single C—C bonds (1.545 Å). The magnitudes of the valence angles are close to tetrahedral.

Fig. 1. Difference (xy)-projection of the electron density of hydrochloric phenylalanine. The contour lines are drawn through the levels: 0 el/Å^2 (dotted); 0.7 el/Å^2; 0.14 el/Å^2 ···(solid lines)

The average length of the C—C bonds of the benzene ring is 1.37 Å. This value is close to the average lengths of analogous bonds obtained in the structures of glycyl-phenylalanyl-glycine (1.38 Å) (^{2}) and L-tyrosine • HCl (1.387 Å) (^{4}). The values of the coordinates of atoms C_7 and C_8, given in Table 1 and marked with an asterisk, were obtained taking into account the symmetry of the benzene ring and differ from the coordinates given by the Fourier syntheses by approximately 0.03 Å. The larger errors in the coordinates of atoms C_7 and C_8 could have been caused by the relatively high values of their isotropic temperature factors (Table 1) and by neglect of the anisotropy of the thermal vibrations, which, as is evident from the overall structure (Fig. 3), should be manifested most strongly in them.

Fig. 2. Interatomic distances (in Å) and valence angles in the phenylalanine molecule

Fig. 3. Packing scheme of molecules in the crystal of phenylalanine hydrochloride. View along the c axis (—ordinary hydrogen bonds; – • – “forked” hydrogen bonds)

Figure 1: Fig. 3. Packing scheme of molecules in the crystal of phenylalanine hydrochloride. View along the c axis (—ordinary hydrogen bonds; – • –“forked” hydrogen bonds)

The structural analysis made it possible to reveal a number of interesting features in the structure of the phenylalanine molecule. The carboxyl group COOH is clearly asymmetric. The hydrogen atom is attached to the oxygen atom O_1. In accordance with this, the bond length C_1–O_1 (1.34 Å) is close to the value of the length of a single C–O bond (1.395 Å) (^{5}), while the bond length C_1–O_2 (1.17 Å) is close to the length of a double C–O bond (1.185 Å) (^{5}).

The amino group of the molecule has the ionic form $(NH_3)^+$. Consequently, the amino-acid molecules in the crystal of hydrochloric phenylalanine are positively charged ions–$[C_6H_5CH_2CH(NH_3)^+COOH]$. The distance C_2–N, equal to 1.48 Å, is close to the “standard” value (1.47 Å) for the length of a single C–N bond and is somewhat lower than the average value of the lengths of C–N bonds (1.497 Å) obtained in the structures of other amino acids.

It should also be noted that in the phenylalanine molecule one can distinguish two planar groupings of atoms. One of them includes the atoms of the benzene ring and atom C_3; the mean deviation of the atoms from it is ∼ 0.016 Å. The other planar grouping is formed by the atoms of the carboxyl group and carbon atom C_2, which deviate from it by only ∼ 0.002 Å. The nitrogen atom is almost coplanar with the atoms of the carboxyl group. The bond C_2–N forms an angle of 2° with the plane of the carboxyl group, and the distan-

···from the nitrogen atom to this plane is 0.058 Å. Such coplanarity of the atoms of the carboxyl group and the nitrogen atom is characteristic of the structures of other amino acids (^{5}).

The conformation of the phenylalanine molecules in crystals of phenylalanine hydrochloride differs from the conformation of the phenylalanine residues in the tripeptide glycyl-phenylalanyl-glycine (^{2}), which points to the lability of the structure. One conformation can be transformed into the other by rotation of the peptide group about the single C_2–C_3 bond. The analysis showed that these two conformations are the most favorable.

Fig. 3. Packing scheme of molecules in the crystal of phenylalanine hydrochloride. View along the **c** axis (—ordinary hydrogen bonds; – • –“forked” hydrogen bonds)

In the packing of the amino-acid molecules in the crystal of phenylalanine hydrochloride, a saturated system of hydrogen bonds is formed (Fig. 3). Each phenylalanine molecule serves as a “donor” for four hydrogen bonds: three bonds are formed at the expense of the hydrogen atoms of the amino group $(NH_3)^+$, and one at the expense of the carboxyl hydrogen. Two bonds in which the amino nitrogen atom participates are formed with chlorine ions $N_M—H\ldots Cl_{\overline{M}}$ (3.13 Å); $N_M—H\ldots Cl_{\overline{M}001}$ (3.30 Å); the third hydrogen bond apparently has a "forked" character (6–8). The hydrogen atom belonging to it is directed both toward the chlorine ion $Cl_{\overline{B}}$ and toward the oxygen atom O_2 of molecule $B_{0\bar{1}1}$. In this case the angles $C_{2M}N_{MCl_{\overline{B}}}$ and $C_{2M}N_{MO_{2B011}}$ are respectively 87 and 155°, and the distances $N_M\ldots Cl_{\overline{B}}$ and $N_M\ldots O_{2B0\bar{1}1}$ are 3.23 and 3.06 Å. The hydrogen atom attached to the oxygen atom of the carboxyl group includes atom O_1 in a strong $O_{1M}—H\ldots Cl_{\overline{M}011}$ hydrogen bond (2.94 Å). As a result of the formation of such a system of hydrogen bonds, the phenylalanine molecules together with the chlorine ions prove to be linked into separate double layers (packets) parallel to the plane (100). The relative arrangement of the double layers in the crystal is determined only by the forces of van der Waals interaction (Fig. 3). This explains the good cleavage of the crystals along the planes (100).

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