

Refinement of the Crystal Structure of L-DOPA Hydrochloride and a Comment on the Structure of α -Amino Acids

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The crystal structure of L-DOPA hydrochloride has been refined by X-ray crystallographic methods using 2122 observed reflections with $0.3 < \sin \theta/\lambda < 0.8$. The final conventional R -factor is 0.030, standard deviations in bond lengths are less than 0.002 Å and in angles about 0.1°. The conformation of the carboxyl group has been shown to deviate from what is usually found in that the carbonyl oxygen atom is in *anti* position relative to the nitrogen atom about the C—C $_{\alpha}$ bond. The geometry of this particular conformation in α -amino acids is discussed.

The crystal structure determination of L-mimosine sulfate hydrate¹ demonstrated the presence of a conformation of the carboxylic group not commonly found in α -amino acids, *i.e.* an *anti*-planar arrangement of the atoms in the N—C—C=O group. A brief search in the literature yielded only one further example of this conformation in protonized α -amino acids, namely histidine hydrochloride,² although more examples may be found in some peptides and in other types of carboxylic acids. However, an indication of the same conformation was found in the report on the structure of L-DOPA hydrochloride.³ We have undertaken the refinement of the structure of the latter compound to an accuracy sufficient for establishing the geometry of the amino acid group.

EXPERIMENTAL AND REFINEMENT

Crystals of L-DOPA hydrochloride were formed by evaporation of a solution of the compound in hydrochloric acid. A single crystal ground to a sphere (radius 0.18 mm) was used in the X-ray experiments.

Unit cell dimensions were determined from diffractometer measurements of 12 general reflections using MoK $_{\alpha}$ radiation ($\lambda = 0.71069$ Å). In good agreement with the data given by Jandacek and Earle³ they were found to be: $a = 6.271(0.002)$ Å; $b = 5.835(0.001)$ Å; $c = 15.660(0.003)$ Å; $\beta = 112.65(0.02)^{\circ}$. The space group is $P2_1$.

Intensity data were recorded with the use of an automatic Picker diffractometer using graphite crystal monochromated MoK-radiation. The take-off angle was 4° and the temperature was 18 ± 1 °C during the data collection. The $\omega - 2\theta$ scan technique was used with a 2θ scan speed of $1^{\circ} \text{ min}^{-1}$ through the scan range from 0.6° below $2\theta(\alpha_1)$ to 0.6° above $2\theta(\alpha_2)$. Background counts were taken for 30 s at each of the scan range limits. The intensities of three standard reflections were measured at intervals during the intensity data measurements; they showed no systematic variations. The standard deviations were taken as $\sigma(I) = (C_T + (0.02C_N)^2)^{\frac{1}{2}}$ where C_T is the total number of counts and C_N the scan count minus background count. The measurements included 2408 unique reflections with $\sin \theta/\lambda$ less than 0.8. Of these 2265 had net intensity larger than $2.5 \sigma(I)$ and were regarded as observed reflections whereas the remaining reflections were excluded from the further calculations.

The intensity data were corrected for Lorentz, polarization, and absorption ($\mu = 0.4 \text{ mm}^{-1}$) effects.

Atomic form factors used were those of Doyle and Turner⁴ for the chloride ion and oxygen, nitrogen, and carbon atoms, and of Stewart, Davidson and Simpson⁵ for hydrogen. A description of the computer programs employed during the refinement procedure is given in Ref. 6.

The first attempt to refine the structure on the basis of the coordinates given by Jandacek and Earle was without success as it turned out that all negative signs for positional parameters were left out of their paper. The structure was redetermined using the position of the chlorine

Table 1. Fractional coordinates ($\times 10^5$ for heavy atoms and $\times 10^3$ for hydrogen atoms) and thermal parameters ($\times 10^5$ for heavy atoms, the temperature factor is given by $\exp(-B_{11}h^2 + B_{22}k^2 + B_{33}l^2 + B_{12}hk + B_{13}hl + B_{23}kl)$). Standard deviations (in parentheses) apply to the least significant figures.

ATOM	X	Y	Z	B ₁₁ , B	B ₂₂	B ₃₃	B ₁₂	B ₁₃	B ₂₃
CL	40733(6)	41180(8)	5867(2)	1744(9)	1266(8)	250(1)	78(17)	261(5)	-6(7)
O1	-22072(21)	-17729(26)	65147(10)	1720(30)	1806(32)	391(6)	-366(53)	339(21)	324(24)
O2	-43179(20)	11788(30)	52106(9)	1307(25)	2244(38)	318(5)	290(54)	129(18)	117(24)
O3	96490(19)	52124(31)	81029(9)	1305(26)	3438(49)	346(5)	-538(62)	542(20)	423(28)
O4	91286(18)	46751(37)	93730(7)	1312(24)	3264(41)	258(4)	-356(75)	221(16)	449(33)
N	46815(17)	41793(31)	86680(7)	1229(24)	1462(27)	234(4)	-40(63)	473(16)	-113(27)
C1	26797(23)	21090(27)	67876(9)	1304(30)	1760(37)	178(4)	62(57)	366(19)	-167(22)
C2	14546(24)	2662(28)	69458(9)	1410(31)	1581(36)	216(5)	369(57)	221(21)	4(23)
C3	-8944(24)	-2(28)	64119(9)	1466(32)	1485(33)	236(5)	67(57)	420(21)	-95(23)
C4	-26311(22)	15943(28)	57179(9)	1262(30)	1720(36)	200(5)	354(57)	312(20)	-86(22)
C5	-8359(26)	34356(31)	55704(10)	1627(35)	1971(39)	214(5)	224(63)	309(22)	223(24)
C6	15130(26)	36951(28)	61030(10)	1610(34)	2003(54)	220(5)	-284(60)	417(21)	178(23)
C7	92518(23)	23818(31)	73386(10)	1175(29)	2081(43)	227(5)	232(60)	575(21)	-254(26)
C8	58175(20)	44344(26)	79981(9)	1037(25)	1557(45)	209(4)	-43(51)	347(17)	22(22)
C9	84246(22)	46340(25)	85051(10)	1165(28)	1594(40)	248(5)	234(50)	331(20)	8(21)
HC2	219(5)	-84(7)	746(2)	3,1(,3)					
HC5	-165(4)	443(6)	503(2)	3,1					
HC6	247(5)	490(6)	598(2)	3,1					
H1C7	607(4)	266(6)	695(2)	2,9(,3)					
H2C7	567(5)	96(6)	768(2)	2,9					
HC8	535(5)	584(6)	767(2)	2,9					
H1N	514(6)	289(7)	901(2)	3,0(,3)					
H2N	319(5)	417(7)	845(2)	3,0					
H3N	499(6)	520(7)	903(3)	3,0					
H01	-153(7)	-248(9)	694(3)	4,3(,4)					
H02	-479(9)	213(9)	493(4)	4,3					
H04	1046(7)	422(10)	964(3)	4,3					

atom as the heavy atom, and the model was refined by the usual methods. The full-matrix least-squares refinement program applied minimizes $\sum w(F_o - F_c)^2$ where w is the inverse of the variance of the structure factor. The parameters varied were all positional coordinates

(except for one origin defining y coordinate), anisotropic thermal parameters for non-hydrogen atoms and isotropic thermal parameters for hydrogen atoms. The latter were constrained to be equal for groups of hydrogen atoms with presumably equal vibrations, *i.e.* hydrogen

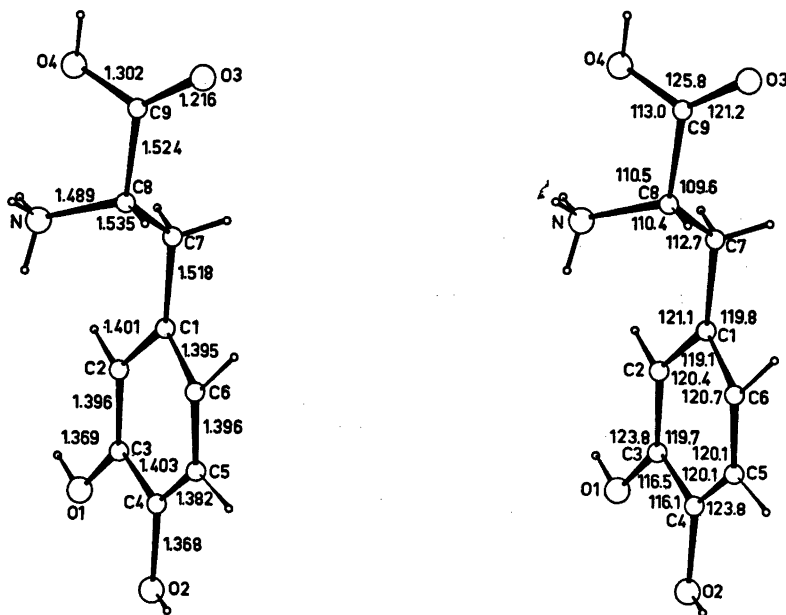


Fig. 1. a. Bond lengths (Å); b. bond angles ($^{\circ}$) in L-DOPA hydrochloride.

Table 2. Observed and calculated structure factors (x 10).

Table with multiple columns containing numerical data representing observed and calculated structure factors for various h, k, l indices. The table is organized into a grid with rows and columns of numbers, some with subscripts or superscripts.

Table 3. Bond lengths (Å), bond angles (°) and hydrogen bond data for L-DOPA hydrochloride. Standard deviations in distances and angles involving only heavy atoms are 0.002 Å and 0.1°, respectively.

Bond	Corrected	Angle	Angle	
C1-C2	1.398	1.401	C6-C1-C2	119.1
C2-C3	1.395	1.396	C1-C2-C3	120.4
C3-C4	1.399	1.403	C2-C3-C4	119.7
C4-C5	1.379	1.382	C3-C4-C5	120.1
C5-C6	1.394	1.396	C4-C5-C6	120.1
C6-C1	1.391	1.395	C5-C6-C1	120.7
C1-C7	1.516	1.518	C2-C1-C7	121.1
C7-C8	1.531	1.535	C6-C1-C7	119.8
C8-C9	1.522	1.524	C1-C7-C8	112.7
C3-O1	1.367	1.369	C7-C8-C9	109.6
C4-O2	1.367	1.368	Dihedral angle	
C9-O3	1.213	1.216	C4-C3-O1-H	174
C9-O4	1.300	1.302	C3-C4-O2-H	171
C8-N	1.485	1.489	C6-C1-C7-C8	-70
			C1-C7-C8-C9	178
			N-C8-C9-O4	-13.3
Hydrogen bond		D...A	H...A	∠D-H...A
O1-HO1...O3	(-1+x, -1+y, z)	2.899	2.16	166
O2-HO2...O1	(-1-x, ½+y, 1-z)	2.992	2.41	142
O2-HO2...O2	(-1-x, ½+y, 1-z)	3.040	2.42	150
O4-HO4...C1	(1+x, y, 1+z)	2.947	2.18	169
N-H1N...C1	(1-x, -½+y, 1-z)	3.161	2.29	161
N-H2N...O3	(-1+x, y, z)	2.993	2.16	162
N-H3N...C1	(1-x, ½+y, 1-z)	3.094	2.33	152

deviations are given in Table 1, observed and calculated structure factors are listed in Table 2.

A rigid-body analysis showed that the thermal motion of the molecule to a fair approximation could be interpreted in terms of translational and librational oscillations; bond lengths were corrected for thermal libration.

Standard deviations in interatomic distances and bond angles were calculated from the correlation matrix ignoring uncertainties in unit cell parameters. Standard deviations in distances between non-hydrogen atoms are 0.002 Å and in angles 0.1°. If a hydrogen atom is involved the figures are 0.05 Å and 3-5°, respectively.

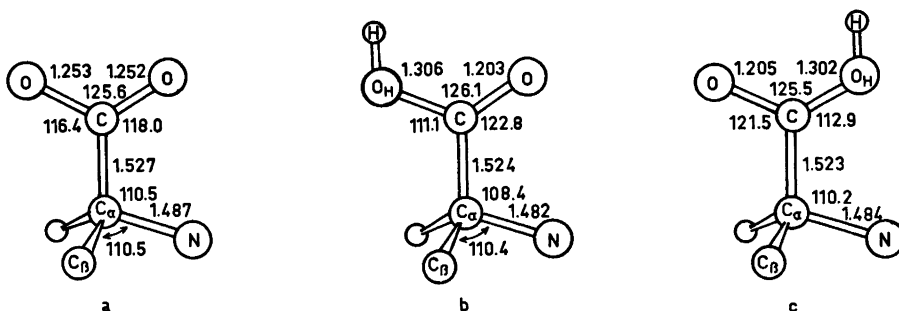


Fig. 2. Structural data for α -amino acids. a. The zwitterion (Marsh and Donohue⁸). b. Protonized group, carbonyl group *syn*-planar to nitrogen (Sundaralingam and Putkey⁹). c. Protonized group, carbonyl group *anti*-planar to nitrogen (present work).

Table 4. Structural data for three α -amino acids with the hydroxyl group *syn*-planar with respect to the nitrogen atom. Standard deviations in bond lengths are 0.002 Å, 0.005 Å, and 0.003 Å, respectively.

	DOPA.HCl	Mimosine. H ₂ SO ₄	Histidine.HCl	Weighted mean
C=O	1.213 Å	1.202 Å	1.196 Å	1.205 Å
C-O(H)	1.300 Å	1.289 Å	1.313 Å	1.302 Å
C α -C	1.522 Å	1.524 Å	1.525 Å	1.523 Å
C α -N	1.485 Å	1.487 Å	1.482 Å	1.484 Å
O=C-O	125.8°	126.3°	124.9°	125.5°
O=C-C	121.2°	119.1°	123.4°	121.5°
O-C-C	113.0°	114.7°	111.6°	112.9°
C-C-N	110.5°	110.9°	109.2°	110.2°
Dihedral angle N-C-C-O(H)	-13°	6°	25°	

DISCUSSION

Bond lengths and angles are given in Table 3 and in Fig. 1, *a* and *b*. The numbering of the atoms is not the same as that given by Jandacek and Earle³ but corresponds to that given for L-DOPA.⁷ Compared to the original structure determination of L-DOPA. HCl the standard deviations of the present refinement are improved by factors between 7 and 10.

The geometry of the L-DOPA ion is nearly identical to that of the L-DOPA molecule as found in the crystals of the pure compound,⁷ the obvious deviation being that of the alanine moiety which contains a carboxylate group in L-DOPA and a carboxyl group in the hydrochloride. The similarities apply to both bond lengths and angles as well as to the conformation.

The C8-C9 bond is slightly shorter in the protonized group than in the carboxylate group. The difference is highly significant even if no such difference exists between the mean value of the corresponding bond length (1.527 Å) in α -amino acids given by Marsh and Donohue⁸ as compared to the value for protonized α -amino acids (1.524 Å) given by Sundaralingam and Putkey⁹ (*cf.* Fig. 2).

The main reason for taking up the present refinement was to determine the structure of the carboxyl group with this special conformation about the C-C α bond. As pointed out by several authors (*e.g.* Refs. 9, 10, 11) the conformation about this bond in α -substituted carboxylic acids is such as to bring the carbonyl oxygen atom in a *syn* planar arrangement with

respect to the α -substituent. As far as α -amino acids are concerned no exception to this rule has been reported until recently. However, in the present structure it is the hydroxyl group which is found *syn* relative to the nitrogen atom; the dihedral angle N-C-C-O(H) is equal to -13.3°. The same conformation has been found in mimosine sulfate¹ (dihedral angle 5.6°) and in histidine hydrochloride.²

The structural data for the α -amino acid group (not corrected for thermal motion) for the three compounds found to have this uncommon conformation are given in Table 4. The weighted mean values are given in Fig. 2 together with the corresponding values given by Marsh and Donohue⁸ for a zwitterionic group and those given by Sundaralingam and Putkey⁹ for protonized α -amino acids with the carbonyl group in the *syn*-planar conformation.

From the data given in Fig. 2 it appears that the 180° rotation about the C-C α bond has only a small, if any, influence on the C α -C-O angles. However, Table 4 indicates a consistent variation of the C-C-O angles with the torsion angle N-C8-C9-O as would be expected if a repulsion between the carboxyl oxygen atoms and the substituents on the C α carbon atom is postulated. Mean values such as those given in Fig. 2 should thus be used with caution.

The packing of ions in the crystals of L-DOPA hydrochloride has been discussed in detail by Jandacek and Earle.³ The hydrogen bond lengths found in the present refinement are listed in Table 3; they are in good agreement with those given in the original paper. It was

suggested, however, that the chlorine ion is hydrogen acceptor in *four* hydrogen bonds in a way involving a set of bifurcated hydrogen bonds. After having localized the hydrogen atoms of the ammonium group we believe that only *three* of the interactions referred to may be described as proper hydrogen bonds; the remaining short N—Cl contact is 3.171 Å, whereas the hydrogen atoms bonded to this nitrogen atom are situated 2.80 Å or more from the chlorine ion. This short contact is thus better classified as a short van der Waals contact rather than a weak hydrogen bond, in which case the bifurcated hydrogen bonds reduce to one normal N—H···Cl hydrogen bond.

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