

# The Crystal and Molecular Structure of DL-2-Hydroxyphenylalanine (*o*-Tyrosine) Hydrochloride

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The crystal structure of the title compound has been determined by X-ray methods using 2524 reflections obtained by counter methods. The crystals are orthorhombic, space group  $Pca2_1$ , with unit cell  $a = 16.667(5)$  Å,  $b = 7.438(2)$  Å, and  $c = 16.659(5)$  Å,  $Z = 8$ . The structure was solved by Patterson methods and refined to a conventional  $R$ -value of 0.035. The estimated standard deviations in bond lengths not involving hydrogen atoms are 0.003–0.004 Å and in angles 0.2°; when hydrogen atoms are involved e.s.d. are about 10 times those given above.

There are only minor differences in the geometry of the two nonequivalent ions and the molecular structure agrees well with those found for salts of several other phenylalanine analogues. In the present structure neither all potential hydrogen donors nor acceptors have actually been used for hydrogen bonding.

The crystal structure of DL-2-hydroxyphenylalanine showed the molecule to exist in a conformation different from that usually found for amino acids with aromatic  $\beta$ -substituents.<sup>1</sup> The exceptional conformation is caused by an intramolecular hydrogen bond between the  $\alpha$ -amino group and the hydroxyl group on the phenyl ring. In order to examine the influence on the molecular conformation from a different crystalline environment we have determined the crystal structure of the corresponding hydrochloride.

## EXPERIMENTAL

Crystals were formed by slow diffusion of diethyl ether into a solution of racemic 2-hydroxyphenylalanine hydrochloride in 96 % ethanol at 0 °C. The crystal used for the X-ray experiments was cut to approximate dimensions 0.2 × 0.4 × 0.4 mm<sup>3</sup>.

Oscillation and Weissenberg photographs showed the crystals to be orthorhombic. Reflections were systematically absent for  $(0kl)$ ,  $l$  odd and  $(h0l)$ ,  $h$  odd indicating one of the space groups  $Pca2_1$  or  $Pbcm$  of which the former turned out to be correct.

Unit cell dimensions were calculated from diffractometer measurements of 30 reflections using  $CuK\beta$  radiation ( $\lambda = 1.3922$  Å). The intensity data were recorded on an automatic Picker four-circle diffractometer with graphite crystal monochromated  $MoK\alpha$  radiation. The  $\omega-2\theta$  scanning mode was employed with a  $2\theta$  scan speed of 1° min<sup>-1</sup>; the scan range was from 0.6° below  $2\theta(\alpha_1)$  to 0.6° above  $2\theta(\alpha_n)$ . The background counts were taken for 30 s at each of the scan range limits. Three standard reflections were measured after every 100 reflections; they showed no significant change in intensity during the data collection. The estimate of the standard deviation for the intensities was based on counting statistics with an additional term of 2 % of the net intensity. A total of 2968 unique reflections with  $2\theta < 60^\circ$  were measured; of these 2524 were considered observed with intensities larger than  $2.5\sigma(I)$  and used for the structure determination. Absorption corrections were applied ( $\mu = 3.55$  cm<sup>-1</sup>).

Atomic form factors used were those of Doyle and Turner<sup>2</sup> for the chlorine ion and the oxygen, nitrogen, and carbon atoms and of Stewart, Davidson and Simpson<sup>3</sup> for hydrogen atoms. Calculations for the structure investigation were performed by means of computer programs described in Ref. 4. The full-matrix least-squares refinement program minimizes the quantity  $\sum w(\Delta F)^2$  where  $w = \sigma^{-2}(Fo)$ .

## CRYSTAL DATA

DL-2-Hydroxyphenylalanine hydrochloride (*o*-tyrosine hydrochloride)  $C_9H_{11}NO_3 \cdot HCl$ , orthorhombic,  $a = 16.667(5)$  Å;  $b = 7.438(2)$

Table 1. Fractional atomic coordinates and thermal parameters ( $\times 10^5$ ) with estimated standard deviations. The temperature factor is given as  $\exp -(B_{11}h^2 + B_{22}k^2 + B_{33}l^2 + B_{12}hk + B_{13}hl + B_{23}kl)$ .

Atom	<i>x</i>	<i>y</i>	<i>z</i>	<i>B</i> <sub>11</sub>	<i>B</i> <sub>22</sub>	<i>B</i> <sub>33</sub>	<i>B</i> <sub>12</sub>	<i>B</i> <sub>13</sub>	<i>B</i> <sub>23</sub>
O1	29306(11)	33952(25)	55155	250( 6)	1049(32)	594(11)	55(25)	-82(15)	-162(33)
O2	-9(11)	24072(25)	41963(19)	315( 7)	1822(43)	329( 8)	-548(28)	-175(14)	106(29)
O3	6358(12)	11062(26)	52235(20)	378( 8)	1319(38)	598(12)	-499(28)	-420(16)	482(35)
N1	9735(13)	51891(31)	41118(19)	339( 8)	1598(48)	230( 8)	-525(33)	21(14)	48(35)
C1	20405(14)	58473(32)	55534(21)	199( 8)	1115(43)	228( 9)	-172(32)	-12(14)	-21(33)
C2	28301(15)	52188(35)	55394(22)	244( 8)	1125(44)	262(10)	-13(33)	-33(16)	-80(39)
C3	34657(15)	64103(40)	55810(24)	202( 8)	1553(54)	369(12)	-172(36)	-24(17)	-74(45)
C4	33224(17)	82329(39)	56253(23)	314(11)	1425(54)	316(12)	-608(39)	-10(18)	4(41)
C5	25520(20)	88813(31)	56225(25)	400(11)	927(40)	369(13)	-185(42)	1(19)	-9(42)
C6	19135(16)	76831(35)	55890(22)	244( 8)	1239(46)	316(11)	104(35)	-18(16)	-109(40)
C7	13429(14)	45450(34)	55303(22)	196( 8)	1136(42)	284(10)	-80(31)	11(15)	35(39)
C8	11966(14)	37576(33)	47040(21)	184( 8)	1199(46)	289(10)	-144(30)	58(15)	-177(36)
C9	5416(14)	23454(35)	46742(23)	212( 8)	1117(45)	304(10)	-95(31)	49(15)	-205(37)
O11	55600(10)	115580(25)	24230(17)	223( 6)	1088(34)	632(13)	-73(24)	83(16)	-85(36)
O12	26124(12)	124069(27)	35984(21)	284( 7)	1951(40)	474(10)	439(28)	293(14)	226(34)
O13	33128(14)	139117(29)	26865(23)	444( 9)	1433(43)	792(14)	689(31)	559(19)	749(40)
N11	36424(12)	97269(30)	37073(18)	242( 7)	1394(41)	253( 9)	245(29)	-2(13)	70(32)
C11	46717(14)	91152(30)	22663(21)	208( 8)	1077(41)	196( 8)	53(29)	-13(14)	3(32)
C12	54624(14)	97388(35)	23320(23)	235( 8)	1039(44)	296(11)	-0(31)	74(17)	29(40)
C13	60958(15)	85555(38)	23065(24)	206( 8)	1577(53)	389(12)	237(35)	41(18)	34(45)
C14	59566(17)	67353(37)	22285(23)	344(11)	1511(53)	292(11)	595(39)	40(19)	59(42)
C15	51863(19)	60909(34)	21739(23)	416(12)	993(44)	299(12)	153(37)	20(19)	-95(39)
C16	45504(15)	72862(34)	21933(21)	289( 9)	1224(43)	234(10)	-55(34)	0(15)	4(37)
C17	39819(14)	104198(36)	22930(21)	207( 8)	1258(45)	246(19)	126(31)	5(15)	37(39)
C18	38473(13)	111742(30)	31262(21)	163( 7)	1081(41)	297(10)	-36(26)	-29(16)	-89(36)
C19	31776(14)	125595(33)	31738(22)	224( 8)	1134(48)	322(11)	91(30)	42(16)	-128(38)
C11	46720( 3)	22303( 9)	49496(15)	241( 2)	1145(11)	280( 3)	148( 8)	-75( 4)	-260(12)
C12	22694( 3)	71820( 8)	30385(15)	222( 2)	1091(10)	460( 3)	8( 7)	26( 4)	159(12)

Table 2. Fractional atomic coordinates ( $\times 10^3$ ) and *B*-values with estimated standard deviations for hydrogen atoms.

Atom	<i>x</i>	<i>y</i>	<i>z</i>	<i>B</i> (Å <sup>2</sup> )
HC3	402(2)	592(4)	558(2)	4.1(0.7)
HC4	374(2)	904(5)	562(2)	5.5(1.0)
HC5	248(2)	1005(3)	571(2)	3.5(0.6)
HC6	139(2)	807(4)	562(2)	3.5(0.7)
H1C7	144(2)	371(4)	583(2)	3.0(0.6)
H2C7	87(1)	519(3)	567(1)	1.7(0.5)
HC8	168(2)	331(4)	445(2)	2.6(0.6)
H1N1	78(2)	465(4)	370(2)	4.1(0.7)
H2112	144(2)	599(5)	397(2)	6.3(0.8)
H3N1	56(2)	607(6)	434(3)	8.0(1.2)
HO1	344(2)	324(5)	539(3)	6.7(1.4)
HO3	29(2)	29(6)	506(2)	7.4(1.6)
HC13	660(2)	894(4)	237(2)	4.3(0.7)
HC14	636(2)	596(5)	220(2)	3.3(1.0)
HC15	507(2)	496(3)	219(2)	6.3(0.6)
HC16	401(2)	692(4)	218(2)	3.4(0.7)
H1C17	347(2)	985(4)	210(2)	3.3(0.6)
H2C17	409(1)	1139(3)	199(1)	2.6(0.5)
HC18	428(2)	1171(4)	332(2)	1.9(0.6)
H1N11	353(2)	1015(4)	419(2)	4.0(0.7)
H2N11	323(2)	908(5)	355(2)	4.7(0.8)
H3N11	402(2)	917(6)	377(3)	4.1(1.2)
HO11	606(2)	1172(5)	235(3)	3.5(1.4)
HO13	295(2)	1471(6)	272(2)	6.1(1.6)

Table 3. Interatomic distances (Å), bond angles and dihedral angles (°).

Bond	(A)		(B)		Angle	(A)	(B)
	Distance	Corrected	Distance	Corrected			
C1-C2	1.397(3)	1.405	1.401(3)	1.409			
C2-C3	1.383(4)	1.387	1.375(4)	1.379	C1-C2-C3	120.4	120.5
C3-C4	1.379(4)	1.386	1.379(4)	1.387	C2-C3-C4	120.0	120.1
C4-C5	1.372(4)	1.379	1.373(4)	1.380	C3-C4-C5	120.5	120.4
C5-C6	1.389(4)	1.393	1.384(4)	1.388	C4-C5-C6	119.5	119.5
C1-C6	1.383(4)	1.389	1.381(3)	1.387	C5-C6-C1	121.2	121.5
O1-C2	1.367(3)	1.372	1.371(3)	1.376	C6-C1-C2	118.4	118.1
C1-C7	1.514(3)	1.518	1.505(3)	1.509	O1-C2-C1	116.6	116.5
C7-C8	1.516(4)		1.514(4)		O1-C2-C3	122.9	123.0
C8-C9	1.516(3)		1.521(3)		C2-C1-C7	120.6	120.2
N1-C8	1.498(4)		1.488(3)		C6-C1-C7	121.0	121.7
O2-C9	1.201(3)		1.183(3)		C1-C7-C8	113.2	112.3
O3-C9	1.308(3)		1.312(4)		C7-C8-C9	114.4	114.1
					C7-C8-C1	111.3	111.3
C3-HC3	1.00		0.90		C8-C9-O2	122.4	123.4
C4-HC4	0.92		0.88		C8-C9-O3	112.3	111.2
C5-HC5	0.89		0.86		O2-C9-O3	125.4	125.5
C6-HC6	0.92		0.94		C6-C1-C7	121.1	121.6
C7-H1C7	0.82		1.00		N1-C8-C9	106.9	106.7
C7-H2C7	0.95		0.90				
C8-HC8	0.98		0.89		Dihedral angles		
N1-H1N1	0.86		0.87		(positive for a right-hand screw)		
N1-H2N1	1.01		0.89		C2-C1-C7-C8	-75.9	-72.1
N1-H3N1	1.02		0.76		C1-C7-C8-N1	-62.9	-61.7
O1-HO1	0.88		0.84		C1-C7-C8-C9	175.7	177.5
O3-HO3	0.88		0.84		N1-C8-C9-O2	+5.1	-1.2
Hydrogen bonds							
D-H...A			D-A	H...A	∠D-H...A	∠D-D(H)...A	
O3-HO3...Cl1	( $x-\frac{1}{2}, -y, z$ )		2.99	2.15	161	114	
O1-HO1...Cl1	( $x, y, z$ )		3.17	2.30	168	113	
N1-H3N1...Cl1	( $x-\frac{1}{2}, 1-y, z$ )		3.22	2.20	174	108	
N1-H2N1...Cl2	( $x, y, z$ )		3.17	2.26	150	122	
O13-HO13...Cl2	( $x, y+1, z$ )		3.06	2.23	164	113	
O11-HO11...Cl2	( $x+\frac{1}{2}, 2-y, z$ )		3.17	2.47	141	116	
N11-H2N11...Cl2	( $x, y, z$ )		3.17	2.29	173	112	
N11-H3N11...O2	( $x, \frac{1}{2}, 1-y, z$ )		2.88	2.13	168	114	

Å;  $c = 16.659(5)$  Å. ( $t = 18$  °C)  $V = 2065.1$  Å<sup>3</sup>;  $M = 217.65$ ;  $F(000) = 912$ ;  $Z = 8$ ;  $D_{\text{calc}} = 1.400$  g cm<sup>-3</sup>;  $\mu = 3.55$  cm<sup>-1</sup>.

Absent reflections:  $(0kl)$  for  $l$  odd,  $(h0l)$  for  $h$  odd. Space group  $Pca2_1$ .

## STRUCTURE DETERMINATION

Statistical tests gave no definite conclusions as to the presence of a crystallographic center of symmetry. Space group  $Pca2_1$  was adopted for the structure determination; this turned out to be the correct choice. The structure was solved by Patterson methods and refined

by successive Fourier syntheses and least-squares calculations. All hydrogen atoms were localized from a difference Fourier map.

All positional parameters, anisotropic thermal parameters for the non-hydrogen atoms and isotropic thermal parameters for hydrogen atoms were varied; the overdetermination ratio was 7.2, the final conventional  $R$ -factor was 0.035 ( $R_w = 0.033$ ), and the goodness of fit  $S = [\sum w\Delta^2 / (n-m)]^{1/2} = 1.8$ .

Final parameters for non-hydrogen atoms are listed in Table 1 and for hydrogen atoms in Table 2. The structure factor list may be obtained from the authors upon request. In-

teratomic distances and bond angles are given in Table 3; estimated standard deviations were calculated from the correlation matrix and found to be 0.003–0.004 Å for distances and 0.2° for angles involving oxygen, nitrogen, and carbon atoms. A rigid-body analysis showed that the thermal motion of the hydroxyphenyl part of the molecules to a fair approximation could be interpreted in terms of translational and librational oscillations (r.m.s.  $\Delta U$  of 0.0023 Å<sup>2</sup> and 0.0017 Å for the two cations, respectively). The corrected bond lengths are also given in Table 3.

## DESCRIPTION OF THE STRUCTURE

The crystal packing of DL-2-hydroxyphenylalanine hydrochloride is illustrated in Fig. 1 in which the two independent molecules are labelled A and B, respectively. A stereoscopic view of an asymmetric unit is given in Fig. 2.

The structure may be described as bimolecular layers parallel to (001). The aromatic rings are nearly parallel to the layer planes, the phenyl ring of A molecules lying on one of the layer surfaces and that of B molecules on the other. Between the layers there appear

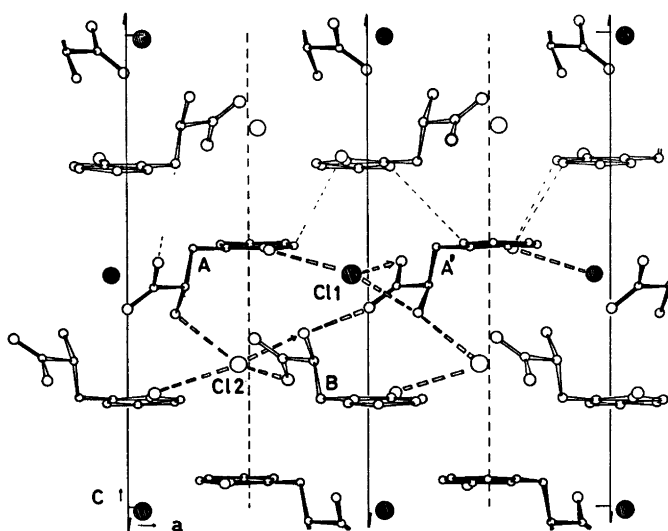


Fig. 1. The crystal structure of *o*-tyrosine hydrochloride as viewed down the *b* axis.

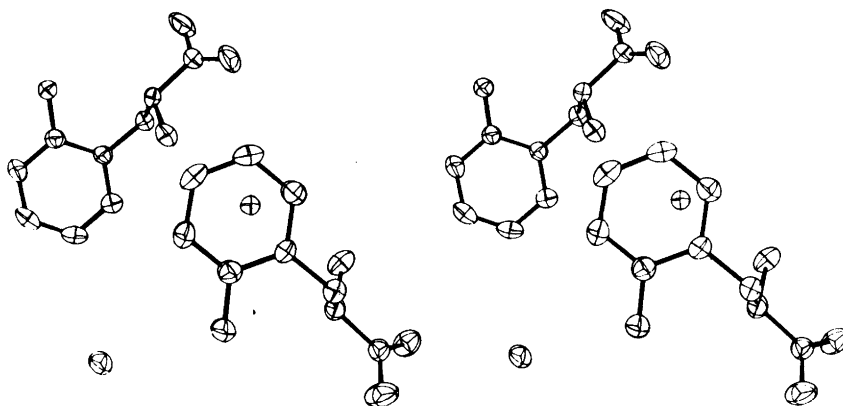


Fig. 2. Stereoscopic illustration of *o*-tyrosine hydrochloride.

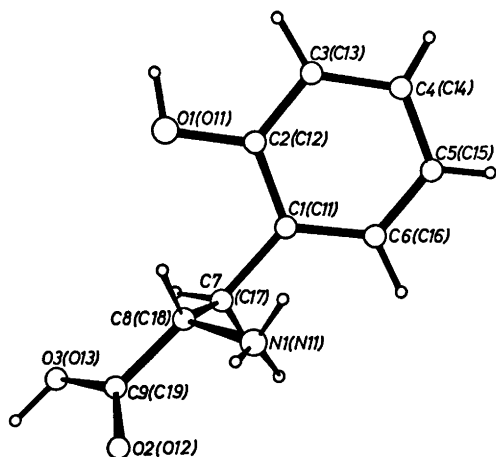


Fig. 3. Numbering of the atoms in the A and B molecules. The numbering of the B molecules in parentheses.

to be only van der Waals forces, the shortest interatomic distances being 3.40 Å (O1–C14), 3.69 Å (O1–C13), 3.54 Å (O3–C17), 3.53 Å (O11–C4) and 3.63 (C6–C16). In this way each molecule in one layer is in contact with four molecules in an adjacent layer. Pseudo centers of symmetry are situated between the layers giving symmetry relations between A molecules in one layer and B molecules in the next. Within the layers molecules are closely connected through hydrogen bonds also involving chloride ions. The formally independent A and B molecules within a layer are related through a pseudo glide plane.

However, the environment of the A molecules differ from that of the B molecules, as may be seen from the hydrogen bonding. A molecules are involved in five hydrogen bonds whereas the B molecules are engaged in only four.

There is only one hydrogen bond between the two types of molecules (O2–N11); the others are directed to chloride ions. Accordingly there are differences also in the environments of the two chloride ions, one being coordinated to four of the hydrogen donor atoms in a distorted tetrahedral arrangement, the other to only three in an almost planar trigonal arrangement. The N1 atom has two of its hydrogen atoms directed to chloride ions whereas N11 has one hydrogen bond to a chloride ion and one to an oxygen atom (O2). It is interesting to note that both of the ammonium groups are involved in only two hydrogen bonds.

In the A molecules both oxygen atoms of the carboxyl group take part in hydrogen bonding, O3 as a donor to a chloride ion and O2 as an acceptor from N11. In the B molecules only one oxygen atom of the carboxyl group participates in hydrogen bonding, *i.e.* O13 as a donor to a chloride ion.

A drawing of the molecules is given in Fig. 3 where also the numbering of the atoms may be found. The drawing displays the *S*-form and the conformational angles are given accordingly in Table 3 where also bond lengths and angles are presented. In Table 3 only the numbering of molecule A appears. The respective values for molecule B are listed in column B.

### DISCUSSION

The lack of a conclusion from the intensity statistical tests may be explained by the presence of the pseudo symmetry elements. It may be noted that such pseudo symmetry elements also exist in the structure of *o*-tyrosine itself.<sup>1</sup> In both cases a racemate crystallizes in a noncentric space group, and it may

Table 4. The C–COO bond length (Å) for various  $\alpha$ -amino acids and some corresponding salts.

Compound	C $_{\alpha}$ –COO	Ref.	Compound	C $_{\alpha}$ –COO	Ref.
L-Tyrosine	1.529(2)	6	L-Tyrosine.HCl	1.520(2)	11
DL-Tyrosine	1.530(3)	7	<i>o</i> -Tyrosine.HCl	1.519(2)	(mean value)
<i>o</i> -Tyrosine	1.534(2)	1			
<i>m</i> -Tyrosine	1.534(2)	8	L-DOPA.HCl	1.522(2)	12
L-DOPA	1.539(2)	9			
$\alpha$ -Methyl tyrosine	1.538(2)	10			

not be uncommon to find pseudo symmetry in such cases.

A rather unusual feature in the present structure is that the protonated amino group in both A and B molecules is involved in only two hydrogen bonds. It seems possible that for both molecules a comparably small rotation about the C-N bond could lead to the formation of another contact without breaking the existing hydrogen bonds, but apparently a strictly staggered conformation about the C-N bonds is preferred.

In the crystals of *o*-tyrosine hydrochloride the molecules have a conformation close to that found in other phenylalanines but quite different from that of *o*-tyrosine in which the conformation is dominated by the intramolecular hydrogen bond between the ammonium group and the *ortho* hydroxyl group. In the structure of the hydrochloride, however, the conformational angle about the C1-C7 bond is rotated 180° bringing the *ortho* hydroxyl group away from the ammonium group and thus excluding any interaction between the groups.

As may be seen from Table 3 there is good agreement in bond lengths and angles found in A and B molecules; the agreement also applies to the conformational angles. The only significant difference in bond lengths namely between C9-O2 and C19-O12 may probably be explained by the difference in hydrogen bonding. The torsional angle N1-C8-C9-O2 is positive (+5.1°); this angle has usually a small negative value in amino acids.

According to Sundaralingam<sup>5</sup> the C<sub>α</sub>-COO bond length is 1.530 Å as a mean value for protonated as well as zwitterionic α-amino acids. In the present structure determination this bond was found to be 1.516 and 1.521 Å for the A and B molecules, respectively. It appears from studies of related molecular species that there may be a difference in this bond length for protonated and ionized carboxyl groups. The values found for this bond length in various structures determined with an e.s.d. of 0.003 or less are listed in Table 4. For protonated amino acids the C<sub>α</sub>-COOH bond length has a mean of 1.520(3) Å and for ionized compounds the mean C<sub>α</sub>-COO<sup>-</sup> distance is 1.533(4) Å.

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