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The Crystal and Molecular Structure of (2-Hydroxyphenyl)alanine (*o*-Tyrosine)

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The crystal structure of D,L-(2-hydroxyphenyl)-alanine has been determined by X-ray methods using 1971 observed reflections. The crystals are monoclinic, space group $P2_1$, with four molecules in the unit cell of dimensions $a=6.32_5$ Å; $b=26.48_9$ Å; $c=5.36_7$ Å, and $\beta=98.1_8°$. The structure was solved by direct methods and refined to a conventional R-factor of 0.048; estimated standard deviations in bond lengths not involving hydrogen are 0.002—0.004 Å and in angles 0.1—0.2°.

Bond lengths and angles are in accordance with those found in tyrosine. Owing to an *intra*-molecular hydrogen bond between the ammonium group and the ring hydroxyl oxygen atom, however, the conformational angles differ from those found in several other phenylalanine derivatives. There are non-crystallographic centres of symmetry between pairs of enantiomeric molecules.

(2-Hydroxyphenyl)alanine (*ortho*-tyrosine) is the third of the monohydroxyphenylalanines to be examined in this laboratory in order to study the conformation of tyrosine and related compounds in different crystalline environments.[1-3] In *o*-tyrosine there is an additional opportunity to study possible interactions between the *ortho* phenolic group and the side chain; such interactions could be of importance for the biological and chemical activity of the molecule.

Even if the existence and activity of *o*-tyrosine in biological systems has been reported,[4] this compound seems to be far less involved in biological processes than *m*-tyrosine and tyrosine. *o*-Tyrosine does not seem to be a substrate for phenylalanine hydroxylase, whereas both phenylalanine and *m*-tyrosine are hydroxylated in the *para* position by this enzyme.[5] This may be explained by the presence of an *ortho* substituent or a different conformation of the molecule due to an interaction between the substituents and the side chain.

EXPERIMENTAL

o-Tyrosine is only sparingly soluble in methanol but dissolves readily when small amounts of aqueous ammonia are added. When the solution is left standing the ammonia evaporates and a slow crystallization of the compound is attained. This crystallization procedure yielded well formed single crystals of the title compound and has also been successfully employed for crystal formation of other amino acids when other methods have failed.

The specimen used for the X-ray experiments had the dimensions $0.6\times0.5\times0.2$ mm³.

Oscillation and Weissenberg photographs showed the crystal to be monoclinic; systematically absent reflections are k odd for ($0k0$) indicating the space group $P2_1$ or $P2_1/m$. Unit cell dimensions were obtained from a least-squares fitting of diffractometer 2θ values for 40 centered reflections with 2θ in the range 23 to 40° using Mo$K\alpha$ radiation ($\lambda=0.71069$ Å). The intensity data were recorded with the use of a SYNTEX P $\bar{1}$ diffractometer with graphite crystal monochromated Mo$K\alpha$ radiation. The $\omega-2\theta$ scanning mode was employed with the 2θ scan speed varying from 2 to 8° min^{-1} depending on the intensity. Reflections with $2\theta>40°$ were measured only if a quick scan gave an intensity larger than a preset value. The scan range was from 1° below $2\theta(\alpha_1)$ to 1° above $2\theta(\alpha_2)$ and background counts were taken for 0.35 times the scan time at each of the scan range limits. Two standard reflections were measured after every 50 reflections; the data set was adjusted according to a slow decrease in the intensity of the standard reflections during the data collection. The estimate of the standard deviation of the measurements was based on counting statistics with an additional term of 2 % of the intensity. 2685 reflections with $2\theta<75°$ were measured; of these 1971 were found to

have intensities larger than three times their estimated standard deviation and were regarded as observed. The remaining reflections were excluded from the refinement procedure. The data set was corrected for Lorentz and polarization effects, no absorption correction was carried out.

A description of the computer programs used is given in Refs. 6 and 7. In the full-matrix least-squares program the quantity minimized was $\sum w\Delta F^2$ where w is the inverse of the variance of the observed structure factors; for reflections with $\sin\theta/\lambda < 0.5$ w was multiplied by $(2 \sin\theta/\lambda)^2$ to give less weight to low-order reflections. Atomic form factors applied were those of Doyle and Turner [8] for oxygen, nitrogen, and carbon atoms and of Stewart, Davidson and Simpson [9] for hydrogen.

CRYSTAL DATA

D,L-(2-Hydroxyphenyl)alanine (*o*-tyrosine), $C_9H_{11}NO_3$, monoclinic, $a=6.325(1)$ Å; $b=26.489(3)$ Å; $c=5.367(1)$ Å; $\beta=98.18(1)°$. ($t=18$ °C) $V=890.13$ Å^3; M = 181.19; $F(000)=384$; $Z=4$; $D_{calc}=1.352$ g cm^{-3}; $\mu(MoK\alpha)=1.1$ cm^{-1}. Absent reflections: $(0k0)$ for k odd. Space group $P2_1$.

STRUCTURE DETERMINATION

The crystals were formed from a solution of the racemate and contain four molecules per

Table 1. Fractional atomic coordinates and thermal parameters with estimated standard deviations ($\times 10^5$). The temperature factor is given by $\exp-(B11h^2+B22k^2+B33l^2+B12hk+B13hl+B23kl)$.

	x	y	z	$B11$	$B22$	$B33$	$B12$	$B13$	$B23$
O1	4198	29377	87093	1881	203	3422	207	191	−341
	22		27	37	3	60	17	72	21
O2	36977	36435	59415	2146	154	1403	281	344	105
	20	5	21	36	2	35	15	58	15
O3	68759	32795	61797	1847	159	2096	94	997	−43
	20	5	22	34	2	41	15	61	17
N1	35837	36221	108298	2414	151	1342	293	790	32
	26	6	25	44	3	40	19	71	18
C1	34697	24595	81752	2100	97	2558	−21	612	184
	30	7	35	51	3	62	19	90	22
C2	13407	25735	74002	2076	129	2722	−80	721	−4
	31	7	36	54	3	68	21	97	24
C3	1800	23262	53585	2704	171	3505	−254	251	−134
	36	9	44	66	4	86	26	121	31
C4	11440	19604	40874	4133	149	3870	−476	739	−336
	48	9	47	92	4	95	31	151	31
C5	32423	18341	48505	4202	110	4705	−35	3021	−255
	48	8	51	93	3	105	28	166	30
C6	43883	20825	68640	2808	107	4368	101	1475	140
	37	8	47	64	3	94	24	129	28
C7	47980	27329	103272	2048	127	2290	114	116	302
	31	7	34	51	3	61	20	92	22
C8	52218	32967	98847	1563	130	1358	62	52	43
	26	7	27	44	3	45	18	71	19
C9	52701	34177	71078	1742	101	1390	−64	326	−54
	27	6	28	44	3	43	18	75	18

Table 2. Fractional atomic coordinates ($\times 10^4$) and B-values with estimated standard deviations for hydrogen atoms.

	x	y	z	B
HC3	−1439	2438	4876	6.6
	51	11	53	7
HC4	358	1808	2596	6.2
	51	11	62	8
HC5	3884	1619	3982	6.0
	45	10	53	7
HC6	5829	1985	7415	3.1
	38	8	40	5
H1C7	6174	2565	10666	4.0
	39	8	41	5
H2C7	4129	2727	11879	3.6
	37	8	44	5
HC8	6618	3394	10934	2.7
	36	8	40	5
H1N1	2131	3503	9989	7.2
	66	15	73	1.1
H2N1	3666	3939	10344	4.9
	44	11	50	6
H3N1	3681	3625	12651	3.3
	45	10	54	7
HO1	−835	3048	8022	7.4
	47	11	54	7

unit cell. It would thus seem natural to assume the space group to be the centric $P2_1/m$ rather than the non-centric $P2_1$. Intensity statistics calculations seemed also to indicate a centric structure. Nevertheless, a Patterson synthesis gave no indication of the presence of a mirror plane normal to b in the unit cell and we therefore decided to solve the structure assuming the space group to be the lower symmetric $P2_1$.

The structure was solved by application of non-centrosymmetric direct methods using the program assembly MULTAN.[7] All the non-hydrogen atoms of the two independent molecules appeared in the E-map based on the set of phases with the highest figure of merit, and the positions of the hydrogen atoms were calculated from stereochemical considerations after a preliminary refinement. Least-squares refinements yielded a conventional R-factor of 0.049 (R_w=0.050). The resulting bond lengths and angles were rather unsatisfactory, however, the distances deviating up to 0.08 Å from their expected values and corresponding distances in the chemically equivalent molecules being by as much as 0.12 Å different. Inspection of the correlation matrix revealed a very high correlation between corresponding parameters of the two molecules, and it became evident that there exists a non-crystallographic centre of symmetry between pairs of molecules. The centre of symmetry is situated in a general position and we have been unable to explain this in terms of space group symmetry. The existence of the extra symmetry was introduced as a constraining factor in the least-squares calculations which proceeded with only half the number of parameters. The refinement converged to a final conventional R-factor of 0.048 (R_w=0.052); the coordinates of the centre of symmetry are (0.6610,0.3899,0.8015).

The ratio of the weighted R-factors with and without the constraints is 1.03; the Hamilton test shows that the centrosymmetric model gives the best description of the structure.[10] The

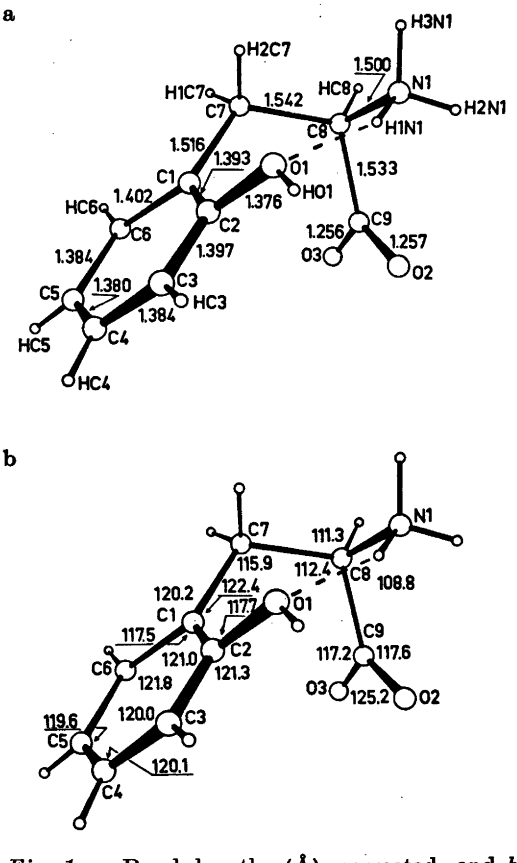

Fig. 1. a Bond lengths (Å), corrected, and *b* bond angles (°) in *o*-tyrosine.

Table 3. Bond lengths (Å) and angles (°).

Bond	Length	Corr.	Bond	Length
C1–C2	1.385(3)	1.393	HC3–C3	1.06
C2–C3	1.392(3)	1.397	HC4–C4	0.97
C3–C4	1.377(4)	1.384	HC5–C5	0.87
C4–C5	1.373(4)	1.380	HC6–C6	0.95
C5–C6	1.379(4)	1.384	H1C7–C7	0.97
C1–C6	1.395(3)	1.402	H2C7–C7	0.98
C1–C7	1.512(3)	1.516	HC8–C8	1.01
C7–C8	1.542(3)		H1N1–N1	1.01
C8–C9	1.529(2)	1.533	H2H1–N1	0.88
O1–C2	1.371(2)	1.376	H3N1–N1	0.97
N1–C8	1.491(2)	1.500	HO1–O1	0.88
O2–C9	1.249(2)	1.257		
O3–C9	1.250(2)	1.256		

	Angles		Angles
C1–C2–C3	121.0(2)	C7–C8–C9	112.4(1)
C2–C3–C4	120.0(2)	C7–C8–N1	111.3(1)
C3–C4–C5	120.1(2)	C9–C8–N1	108.8(1)
C4–C5–C6	119.6(2)	C8–C9–O2	117.6(1)
C5–C6–C1	121.8(2)	C8–C9–O3	117.2(1)
C2–C1–C6	117.5(2)	O2–C9–O3	125.2(1)
O1–C2–C1	117.7(2)	C2–O1–HO1	116
O1–C2–C3	121.3(2)	C8–N1–H1N1	107
C2–C1–C7	122.4(2)	C8–N1–H2N1	112
C1–C7–C8	115.9(1)	C8–N1–H3N1	114
C6–C1–C7	120.2(2)		

Table 4. Torsional angles and hydrogen bond data in *o*-tyrosine (°).

C2–C1–C7–C8	66.1	C1–C2–O1–HO1	168
C1–C7–C8–N1	−92.8	C7–C8–N1–H1N1	55
C1–C7–C8–C9	29.5	C7–C8–N1–H3N1	−69
C7–C8–C9–O3	73.9	C9–C8–N1–H1N1	−69
N1–C8–C9–O2	18.1		
N1–C8–C9–O3	−162.4		

Hydrogen bonds D–H···A	D···A	H···A	Angle D–H–A
O1–HO1···O4	2.61	1.74	170
N1–H1N1···O1 (intramol.)	2.82	1.92	146
N1–H2N1···O2	2.73	1.76	177
N1–N3N1···O3	3.04	2.33	137

structural implications of the centre of symmetry are discussed together with the description of the crystal packing.

The anisotropic thermal parameters were analysed in terms of rigid-motion both for the whole molecule and for the hydroxyphenyl and alanine parts separately. The results indicated that the entire molecule does not behave as a rigid body, whereas separating the molecule into two parts gave better results. The latter description was adopted when correcting bond lengths for libration effects.

The structure factor list may be obtained from the authors upon request. Final parameters for

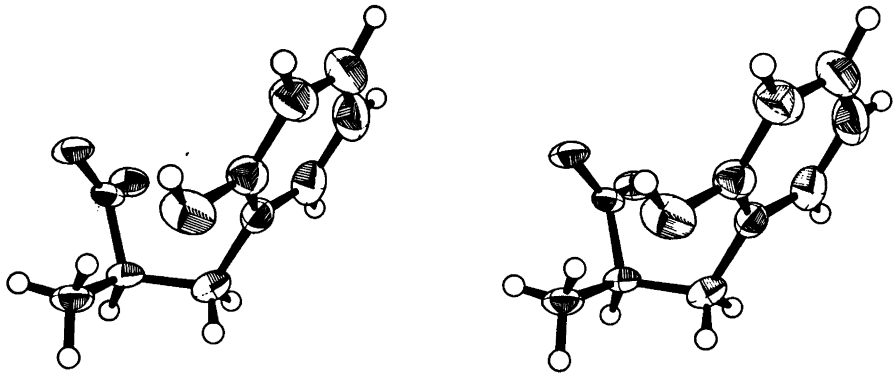

Fig. 2. Stereoscopic illustration of *o*-tyrosine.

non-hydrogen atoms are given in Table 1 and for hydrogen atoms in Table 2.

Standard deviations in interactomic distances and bond angles are calculated from the correlation matrix ignoring uncertainties in cell dimensions.

DISCUSSION

The bond lengths and angles are given in Table 3 as well as in Fig. 1 where the numbering of the atoms is also indicated. Conformational angles in the molecules and hydrogen bond data are given in Table 4. Dihedral angles are given as positive for a clockwise rotation and refer to the *R*-form.

The bond lengths found in *o*-tyrosine compare well with those in tyrosine [1,2] and *m*-tyrosine,[3] whereas there are some differences in some bond angles. Thus the angle C2—C1—C7 (122.4°) and C1—C7—C8 (115.9°) are significantly larger than the corresponding angles in the analogous compounds (120.4—120.9 and 114.0—114.4°, respectively). The C7—C8—C9 angle of 112.4° is larger than what is reported for this angle in L-DOPA [11] and *m*-tyrosine [3] but is close to that found in L- and D,L-tyrosine.[1,2] The cause of the opening of the angles may be found in the rather unusual conformation of the side chain brought about by an *intra*-molecular hydrogen bond between the *ortho* oxygen and the nitrogen atom. This hydrogen bond, in which the nitrogen

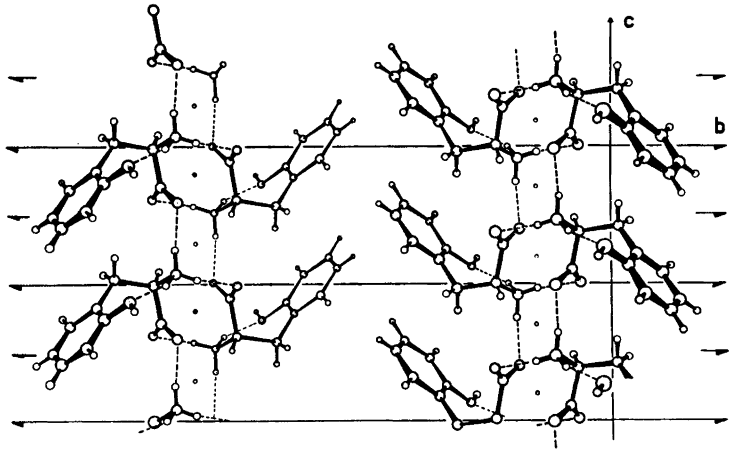

Fig. 3. The crystal structure of *o*-tyrosine as viewed down the *a* axis. The non-crystallographic centres of symmetry are drawn as small circles.

atom acts as the proton donor, is 2.82 Å with a H···O separation of 1.9 Å and a N—H···O angle of 146°. The existence of this hydrogen bond is probably also the reason for a considerable deviation from staggered conformation about the Cα—Cβ bond. The dihedral angle C1—C7—C8—C9 is 29.5° and the angle C1—C7—C8—N1 is 267.2°, whereas the corresponding torsional angles in L-tyrosine are 53.1 and 290.7°, respectively.[1] Furthermore, the torsion angle C2—C1—C7—C8 is 66° in the present compound as compared to 94° in tyrosine. The rotations about the Cα—Cβ and Cβ—Cγ bonds cooperate to bring a hydrogen atom of the ammonium group to a position favourable for the formation of the *intra*-molecular hydrogen bond to the phenolic oxygen atom. It is interesting to note, however, that there is practically no deviation from a staggered conformation about the C8—N1 bond nor in the usual features of the external angles at the C2 atom. The difference between the C3—C2—O1 and C1—C2—O1 angles is 3.6° with the larger angle on the same side of the C2—O1 bond as the phenolic hydrogen atom.

It seems reasonable that the special conformation of the molecule brought about by the *intra*-molecular hydrogen bond may account for the difference in biological activity as compared to that of the *meta* and *para* hydroxyphenylalanines.

The dihedral angle N1—C8—C9—O2 is 18.1°, the nitrogen atom being situated 0.43 Å out of the least-squares plane through the C8, C9, O2, and O3 atoms. This is the conformation usually found in amino acid groups. However, as distinct from the situation in most ionized amino acids [12] the two C—C—O angles are found to be equal in the present structure.

A stereo drawing of the molecule is presented in Fig. 2.

The packing of the molecules in the crystal is vizualized in Fig. 3. The hydrogen bonds are indicated in the figure, pertinent *inter*-molecular distances are listed in Table 4.

The four hydrogen atoms bonded to hetero atoms are all involved in hydrogen bonds, one of which is the *intra*-molecular hydrogen bond. Each molecule is donor in three and acceptor in three *inter*-molecular hydrogen bonds connecting each molecule to five neighbouring molecules through six such bonds. The N1—H3N1···O2 bonds produce chains of molecules in the *c* direction; these chains are connected through O1—HO1···O3 bonds to give layers parallel to the *a*—*c* plane. Each molecule of one layer is linked to a molecule of another layer by two N1—H2N1···O3 bonds related to each other by a non-crystallographic centre of symmetry. These centres of symmetry are operative within the double molecular layer only and have no effect on atoms outside these layers or on the two-fold screw axes. One layer is transferred to the next through the operation of the two-fold screw axes. The contacts between layers in the *b*-direction are only of the van der Waals type; the bonding is weak and the crystals have cleavage planes normal to the *b*-axis.

Owing to the *intra*-molecular hydrogen bond *o*-tyrosine is not as effectively packed as tyrosine and *m*-tyrosine. This results in a significantly lower density (1.352 g cm^{-3}) than that found for the other tyrosines (1.414—1.435 g cm^{-3}).

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