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The Crystal and Molecular Structure of 3-Hydroxyphenylalanine (*m*-Tyrosine)

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The crystal structure of 3-hydroxyphenylalanine has been determined by X-ray diffraction methods using 1690 observed reflections collected on a counter diffractometer. The crystals are monoclinic, space group $P2_1$, with cell dimensions $a = 5.95_6$ Å; $b = 5.29_9$ Å; $c = 13.86_6$ Å; $\beta = 104.3_6°$. The structure was refined to a conventional R-factor of 0.041, the standard deviations for bond lengths and angles involving non-hydrogen atoms are 0.002 Å and 0.1°, respectively.

The compound forms crystals each containing one enantiomer from solutions of the racemate. Both regarding molecular geometry and crystal packing of *m*-tyrosine the similarity to L-DOPA is pronounced.

3-Hydroxyphenylalanine (*m*-tyrosine) is a natural product occurring in certain plants [1] and also in mammals where the metabolic pathway from phenylalanine to L-DOPA partly may proceed through L-*m*-tyrosine.[2,3] The shift of the hydroxyl group from the 4-position in tyrosine to the 3-position in *m*-tyrosine gives rise to altered chemical as well as biological properties. L-*m*-Tyrosine behaves thus in some cases more like phenylalanine than like L-tyrosine [4] and it has been reported to act as a growth inhibitor.[5] Several of the biological activities of L-*m*-tyrosine have been shown to be analogous to those of L-DOPA [6,7] and the compound or its metabolically formed amines seem to interfere with the normal action of the neurotransmitters dopamine and noradrenaline.[8–10]

We have examined the crystal structure of 3-hydroxyphenylalanine as a part of a series of hydroxyphenyl- and pyridonalanines in order to study the variation in molecular conformation with varying crystal environment and to collect information useful for studies of relationships between structure and biological activity.

EXPERIMENTAL

A concentrated solution of oxalic acid in cold water was heated with an excess of 3-hydroxyphenylalanine and filtered. The solution was cooled down to room temperature and after a couple of weeks crystals of the pure compound appeared.

Oscillation and Weissenberg photographs showed the crystals to be monoclinic. The only condition for the presence of reflections was k even for ($0k0$). The number of molecules per unit cell being *two*, the only space group possible is $P2_1$ since $P2_1/m$ would require the molecule to exhibit mirror- or centrosymmetry.

Unit cell dimensions were calculated from diffractometer measurements of 28 reflections using CuKβ-radiation ($\lambda = 1.3922$ Å). The intensity data were recorded on an automatic Picker diffractometer using MoK-radiation monochromated by means of a graphite crystal. The specimen had approximate dimensions $0.2 \times 0.2 \times 0.5$ mm. Reflections with $\sin\theta/\lambda < 0.8$ were scanned in the $\theta - 2\theta$ mode at a rate of 1° min^{-1} in 2θ; the scan range was from 0.8° below $2\theta(\alpha_1)$ to 0.8° above $2\theta(\alpha_2)$. The background was measured 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.

A total of 2010 independent reflections were measured of which 1690 were considered observed with intensities greater than 2.0 standard deviations. The standard deviations for the intensities were taken as $\sigma(I) = (c_T + (0.02\ c_N)^2)^{\frac{1}{2}}$ where c_T is the total number of counts and c_N the scan count minus background count. The data were corrected with Lorentz and polarization factors, but not for absorption ($\mu = 0.12$ mm^{-1}).

Atomic form factors used were those of Hanson *et al.*[11] for oxygen, nitrogen and carbon and of Stewart *et al.*[12] for hydrogen. Calculations during the structure investigation were performed by means of computer programs described in Ref. 13. The full-matrix least-squares refinement program minimizes $\sum w(\Delta F)^2$ where $w = \sigma^{-2}(F_o)$.

Table 1. Observed and calculated structure factors. The columns are h, k, l, $10 \times F_o$ and $10 \times F_c$.

Table 1. Continued.

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

Atom	x	y	z	B_{11}	B_{22}	B_{33}	B_{12}	B_{31}	B_{23}
O1	−5262	−18235	33277	1845	2511	492	−1000	902	15
	20		9	32	43	7	60	24	29
O2	68186	44618	961	1943	2841	307	25	846	−45
	19	35	8	29	44	5	63	19	26
O3	91707	57078	15259	1279	4099	475	−1529	833	−793
	18	39	9	26	55	7	66	22	35
N1	30236	45820	81395	996	2616	280	141	464	154
	18	37	8	24	44	5	61	18	29
C1	41770	21794	29090	1338	1813	249	185	414	272
	22	35	9	32	43	7	67	25	31
C2	25070	3046	27666	1504	1828	282	12	490	−14
	24	35	10	32	47	6	64	23	27
C3	11133	191	34404	1311	1865	317	142	477	324
	21	38	10	31	47	7	66	23	31
C4	13811	16531	42402	1853	2565	299	189	666	201
	25	41	10	38	58	7	80	27	35
C5	30309	35378	43720	2380	2707	284	−234	602	−244
	30	43	11	47	61	7	90	29	36
C6	44357	38154	37161	1925	2118	310	−727	468	−42
	27	39	11	40	52	7	77	27	32
C7	57707	24282	22171	1368	1862	326	484	617	300
	22	37	10	32	43	7	67	25	31
C8	53179	47597	15462	1033	1525	259	−96	500	13
	19	36	9	26	38	6	59	20	28
C9	72549	50061	10005	1227	1533	337	66	710	57
	21	36	10	30	41	7	61	23	28

CRYSTAL DATA

3-Hydroxyphenylalanine (*m*-tyrosine), $C_9H_{11}NO_3$, monoclinic, $a=5.956(0.002)$ Å; $b=5.2992(0.0004)$ Å; $c=13.866(0.002)$ Å; $\beta=104.36(0.02)°$, ($t=18$ °C). $V=424.0$ Å^3; $M=181.19$; $F(000)=192$; $Z=2$; $D_{obs}=1.42$ g cm^{-3} (flotation); $D_{calc}=1.419$ g cm^{-3}. Absent reflections: ($0k0$) for k odd; space group $P2_1$.

STRUCTURE DETERMINATION

The positions of the phenyl ring atoms and the carbon and oxygen atoms directly attached to it were deduced from a sharpened Patterson map. The remaining non-hydrogen atoms were located from subsequent Fourier syntheses. Two cycles of full-matrix least-squares refinement with isotropic temperature factors reduced R to 0.15; further refinement with anisotropic temperature factors brought R down to 0.07. The hydrogen atoms could all be located from a difference Fourier map at this stage. The refinement of all positional parameters (except for one origin defining y-parameter), anisotropic

Table 3. Fractional atomic coordinates ($\times 10^4$) and B-values with estimated standard deviations for hydrogen atoms.

Atom	x	y	z	B
HO1	−505	−2660	2830	2.7
	29	42	12	0.4
HN1	2900	3141	495	2.3
	29	38	12	0.3
HN2	2825	5774	329	2.9
	33	47	15	0.4
HN3	2044	4784	1114	3.3
	37	49	15	0.4
H2	2306	−748	2203	2.3
	29	36	12	0.4
H4	470	1407	4711	3.6
	33	44	13	0.5
H5	3207	4797	4934	3.0
	35	46	13	0.4
H6	5470	4958	3783	4.1
	35	52	15	0.5
H71	7337	2511	2599	3.3
	33	47	13	0.4
H72	5519	987	1762	2.8
	30	43	13	0.4
H8	5329	6229	1934	1.3
	25	36	11	0.3

Table 4. Interatomic distances (Å) and bond angles (°).

Bond	Length	Corrected	Bond angles		Bond angles	
C1–C2	1.385	1.389	C1–C6–C5	119.7	C4–C5–H5	121
C2–C3	1.403	1.406	C6–C5–C4	121.0	C5–C4–H4	121
C3–C4	1.385	1.388	C5–C4–C3	119.7	C3–C4–H4	119
C4–C5	1.381	1.385	C4–C3–C2	119.7	C3–O1–HO1	79
C5–C6	1.388	1.388	C3–C2–C1	120.3	C3–C2–H2	121
C1–C6	1.394	1.399	C2–C1–C6	119.5	C1–C2–H2	119
C1–C7	1.513	1.515	C6–C1–C7	119.5	C1–C7–H71	109
C7–C8	1.530		C2–C1–C7	120.9	C1–C7–H72	109
C8–N1	1.490	1.498	C1–C7–C8	114.3	C8–C7–H71	108
C8–C9	1.534	1.538	C7–C8–C9	109.1	C8–C7–H72	105
C9–O2	1.250	1.257	C4–C3–O1	118.5	H71–C7–H72	111
C9–O3	1.248	1.255	O1–C3–C2	121.8	C7–C8–H8	110
C3–O1	1.362	1.363	C8–C9–O2	118.7	N1–C8–H8	108
C6–H6	0.85		C8–C9–O3	115.3	C9–C8–H8	108
C5–H3	1.01		O2–C9–O3	125.9	C8–N1–HN1	110
C4–H4	0.96		C7–C8–N1	110.9	C8–N1–HN2	113
C2–H2	0.94		N1–C8–C9	110.1	C8–N1–HN3	108
O1–HO1	0.82		C1–C6–H6	118	HN1–N1–HN2	105
N1–HN1	0.91		C5–C6–H6	123	HN1–N1–HN3	113
N1–HN2	0.88		C6–C5–H5	118	HN2–N1–HN3	108
N1–HN3	0.80					
C7–H71	0.95					
C7–H72	0.98					
C8–H8	0.95					

Hydrogen bonds	D···A	H···A	D–H	D–H···A
N1–HN1···O2 ($1-x,-\frac{1}{2}+y,-z$)	3.004	2.14	0.91	170
N1–HN2···O2 ($1-x,\frac{1}{2}+y,-z$)	2.889	2.07	0.88	150
N1–HN3···O3 ($-1+x,y,z$)	2.779	1.99	0.80	165
O1–HO1···O3 ($1-1+x,-1+y,z$)	2.786	1.97	0.82	171

thermal parameters for the non-hydrogen atoms and isotropic parameters for the hydrogen atoms was carried on until the shifts were negligible compared to the standard deviations. The final R-factor is 0.041 for 1690 reflections and R_w is 0.042. A difference Fourier synthesis showed electron densities between -0.2 eÅ^{-3} and $+0.3$ eÅ^{-3}.

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

A comparison of observed and calculated structure factors is given in Table 1; final parameters for non-hydrogen atoms are listed in Table 2 and for hydrogen atoms in Table 3. Interatomic distances and bond angles are given in Table 4. Standard deviations were calculated from the correlation matrix; standard deviations in distances were found to be 0.002 Å and in angles 0.1° when hydrogen atoms were not involved.

DISCUSSION

Bond lengths and angles are shown in Fig. 1 in which the numbering of the atoms is indicated.

The molecular geometry is remarkably similar to that of 3,4-dihydroxyphenylalanine (DOPA).[14] Neglecting the extra hydroxyl group in DOPA, none of the bond lengths differs by more than 0.01 Å, nor the bond angles by more than 0.7° except for the external angles at C3. In the present structure the external angles are found to be 118.5° and 121.8° with the greater angle

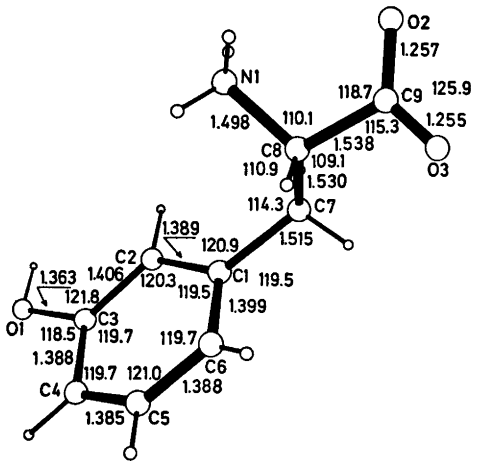

Fig. 1. Bond lengths (Å, corrected) and angles (°) in *m*-tyrosine.

cis to the phenol hydrogen atom which is situated in the phenyl ring plane. This feature is common for many phenol structures; the difference between the external angles in the present structure, 3,3° may be compared to that in L-tyrosine of 4.6°,[15] in DL-tyrosine of 4.4°,[16] and those in L-DOPA of 6.3 and 6.6°.

The similarity between *m*-tyrosine and DOPA applies also to the conformation of the molecules in the crystal. The following dihedral angles (°) were found:

	m-tyrosine	L-DOPA
C2 – C1 – C7 – C8	– 71.6	– 71.2
C1 – C7 – C8 – C9	171.6	175.2
N1 – C8 – C9 – O (*cis* to N)	– 16.0	– 14.4

The conformational angles are given as positive when progress along the atoms describes a clock-wise rotation.

All hydrogen atoms bonded to hetero atoms are involved in hydrogen bonds. Thus N1 and O1 act as hydrogen donors; the two carboxyl oxygen atoms are acceptors in four hydrogen bonds. In this way each molecule is connected to six neighbouring molecules through eight hydrogen bonds. The situation is illustrated in Fig. 2 which shows the crystal structure as seen along the *c*-axis. The pronounced similarity of the structures of *m*-tyrosine and L-DOPA may be seen from Fig. 3 where details of corresponding projections along *b* are visualized. Except for the *para* hydroxyl group in L-DOPA forming hydrogen bonds to corresponding groups in

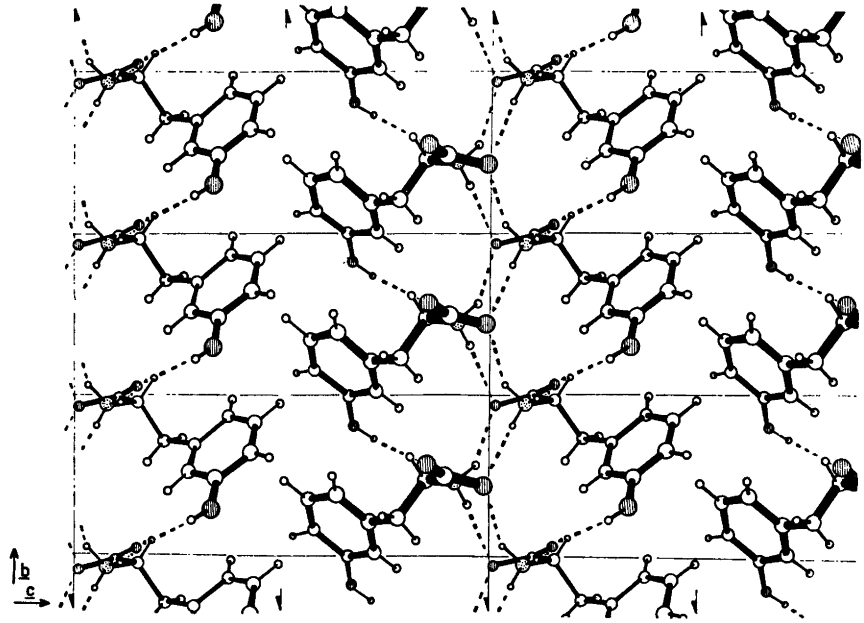

Fig. 2. The crystal structure as seen along the *a*-axis.

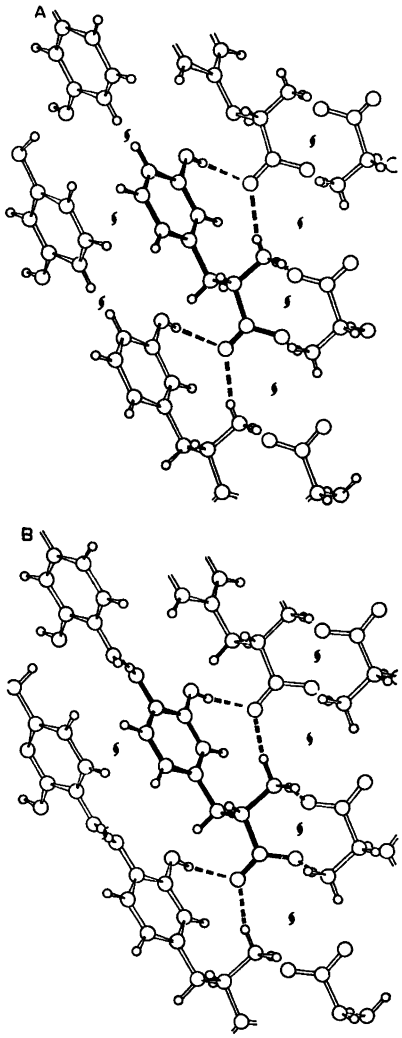

Fig. 3. The structure of *m*-tyrosine (A) and L-DOPA (B) as viewed along *b*.

molecules along a two-fold screw axis, the hydrogen system in the two structures is nearly identical. The N1–H···O3 bond of 2.78 Å (2.82 Å in L-DOPA) establishes chains of molecules along the *a*-axis. These chains are tied together through O1–H···O3 bonds of 2.79 Å (2.74 Å in L-DOPA) and through two N1–H···O2 bonds of 2.89 Å and 3.00 Å (2.87 Å and 3.02 Å in L-DOPA) to form double molecular layers normal to the (001) plane. Between the layers there are only weak van der Waals interactions.

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