Crystal Structure of *d*-Desthiobiotin

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The crystal structure of *d*-desthiobiotin was determined by the X-ray diffraction method. The crystals are orthorhombic, space group $P2_12_12_1$, with cell dimensions, $a=7.516(5)$, $b=29.100(8)$, $c=5.148(6)$Å, and $Z=4$. The structure was refined to $R=0.065$. The molecular conformation is characterized by the extended *trans* planar zig-zag conformation of the caproic acid chain. The ureido carbonyl oxygen forms a strong hydrogen-bond with the carboxyl group of a neighboring molecule (O···O distance, 2.649(7) Å). These structural features resemble those of *d,l*-desthiobiotin,indicating that the structure observed in *d*-desthiobiotin is characteristic of desthiobiotin.

Keywords *d*-desthiobiotin; vitamin H; *d*-biotin; crystal structure; X-ray analysis

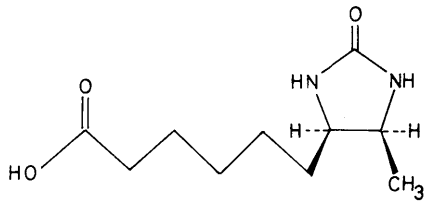
d-Desthiobiotin (I) is an intermediate in the biosynthesis of vitamin H (*d*-biotin) (II), and synthesized from 7,8-diaminopelargonate.[1] *d*-Biotin[2] has been known to act as a coenzyme in acetyl-Co A carboxylase, propionyl-Co A carboxylase, 3-methylcrotonyl-Co A carboxylase and pyruvate carboxylase in animals as well as microorganisms, and *d*-desthiobiotin also has a biotin-like function in microorganisms.[3–5] The conversion process of *d*-desthiobiotin (I) to *d*-biotin (II) is still unknown, although insertion of sulfur into desthiobiotin is a crucial step in the biosynthesis of *d*-biotin.[6] For these reasons, it is important to determine the actual structure of the biologically active *d*-desthiobiotin (I). To date, however, the structure of *d*-isomer of desthiobiotin has not yet been determined, although the structure of the racemic compound, *d,l*-desthiobiotin has been reported by Chen *et al.*[7] and Okabe *et al.*[8] The structure of racemic desthiobiotin determined by the two groups was almost the same except for a difference in the molecular packing scheme. In this study, we aimed to determine the structure of the biologically important enantiomorphic *d*-desthiobiotin in order to better understand the structural features of *d*-isomer itself.

Experimental

d-Desthiobiotin (I) was dissolved in 50% aqueous ethanol solution. Colorless platelet crystals were obtained by slow evaporation of the solution kept at 20 °C. A single crystal with the dimensions $0.4\times0.4\times0.1\,mm^3$ was used for the X-ray diffraction data collection. The intensities were measured with a Rigaku AFC 5R automated four circle diffractometer with graphite-monochromated MoK_α radiation ($\lambda=0.71069$ Å). Lattice parameters were determined from 2θ angles of 25 reflections ranging $9.6°<2\theta<14.1°$. The crystal density was measured by the floatation method using a C_6H_6/CCl_4 mixture. A total of 1573 reflections within $2\theta=55.0°$ were collected in the ω–2θ scan method with a peak range of $(0.88+0.30\tan\theta)°$ and a scan speed of $4.0°\,min^{-1}$ in ω; the ratio of peak counting time to background counting time was 2 : 1. The analysis was based on 779 reflections having intensities greater than 2.5 times their standard deviations. The data were corrected for Lorenz, polarization and absorption factors. An empirical absorption correction using the program DIFABS[9] resulted in the minimum and maximum transmission factors of 0.86 and 1.09, respectively. The structure was solved by direct methods with MITHRIL[10] and DIRDIF[11] and refined by a full-matrix least squares method with anisotropic thermal parameters for nonhydrogen atoms. The positions of hydrogen atoms were obtained from difference Fourier maps and were included in the subsequent refinement with isotropic thermal parameters. Refinement was carried out to minimize $\sum w(|F_o|-|F_c|)^2$, where $|F_o|$ and $|F_c|$ were observed and calculated structure amplitudes, respectively. The weight (w) used for the refinement was $w=4|F_o|^2/\sigma^2(|F_o|^2)$. The final $R(=\Sigma(|F_o|-|F_c|)/\Sigma|F_o|)$, $R_w(=[\Sigma w(|F_o|-|F_c|)^2/\Sigma w|F_o|^2]^{1/2})$ and $S(=[\Sigma w(|F_o|-|F_c|)^2/(M-N)]^{1/2})$, where M, the number of reflections, is 779, and N, the number of variables, is 136, were 0.065, 0.072 and 1.90, respectively. The H-atom positions were included for calculating R and R_w. The residual fluctuations on the difference Fourier map were in a range of -0.29 to $0.31\,e$Å^{-3}. Crystal data are given in Table I. Final atomic coordinates are listed in Table II.[12] The atomic scattering factors were taken from International Tables for X-Ray Crystallography.[13] All numerical calculations were performed using TEXSAN crystallographic software package.[14]

Results and Discussion

The crystal system and the space group of *d*-desthiobiotin (I) (orthorhombic, $P2_12_12_1$) are different from those of *d,l*-desthiobiotin (monoclinic, $P2_1/a$).[7,8] The bond lengths, bond angles for nonhydrogen atoms, hydrogen bonds and torsion angles for the molecular conformation are listed in Table III. A perspective view of *d*-desthiobiotin (I) is shown in Fig.1, the configuration of which is determined according to *d*-isomer of *d,l*-desthiobiotin,[7] and the absolute configuration of *d*-biotin.[2,15] The caproic acid chain of *d*-desthiobiotin (I) and *d,l*-desthiobiotin[7,8] has a fully extended nearly planar *trans* zig-zag conformation. The common extended *trans* conformation observed both in *d*- and *d,l*-desthiobiotin does not exist in *d*-biotin,[2] in which the chain is severely



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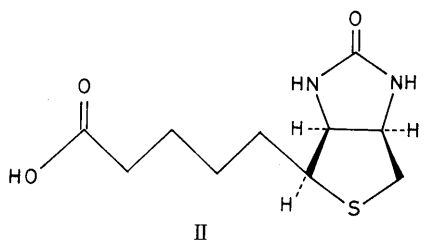

II

TABLE I. Crystal Data *d*-Desthiobiotin

Chemical formula	$C_{10}H_{18}N_2O_3$
Molecular weight	214.26
Space group	$P2_12_12_1$
a (Å)	7.516 (5)
b (Å)	29.100 (8)
c (Å)	5.148 (8)
V (Å^3)	5.148 (6)
Z	1126 (2)
	4
D (mesd) (g·cm^{-3})	1.263 (1)
D (calcd) (g·cm^{-3})	1.264
μ (MoK_α) (cm^{-1})	0.87
F (000)	464
T (K)	296

TABLE II. Atomic Coordinates for Non-H Atoms with e.s.d.s in Parentheses and in the Form of $B_{eq}=(8\pi^2/3)\Sigma_i\Sigma_j U_{ij}a_i^*a_j^*\boldsymbol{a}_i\cdot\boldsymbol{a}_j$

Atom	x	y	z	B_{eq} (Å^2)
O(2′)	0.7555 (7)	0.2066 (1)	1.453 (1)	3.6 (3)
O(10A)	0.9063 (8)	−0.1337 (2)	1.150 (1)	4.1 (3)
O(10B)	0.880 (1)	−0.0981 (2)	0.777 (1)	5.5 (4)
N(1′)	1.0402 (9)	0.2170 (2)	1.308 (1)	3.3 (3)
N(3′)	0.8711 (8)	0.1711 (2)	1.085 (1)	2.8 (3)
C(2)	1.117 (1)	0.1151 (2)	1.081 (2)	3.3 (3)
C(2′)	0.879 (1)	0.1988 (2)	1.296 (2)	2.6 (3)
C(3)	1.042 (1)	0.1612 (2)	0.984 (2)	3.1 (4)
C(4)	1.150 (1)	0.2040 (2)	1.081 (2)	2.9 (3)
C(5)	1.338 (1)	0.1980 (3)	1.140 (2)	4.7 (5)
C(6)	1.015 (1)	0.0739 (2)	0.976 (2)	3.2 (4)
C(7)	1.064 (1)	0.0292 (2)	1.110 (2)	3.2 (4)
C(8)	0.971 (1)	−0.0117 (2)	0.997 (1)	3.6 (4)
C(9)	1.011 (1)	−0.0572 (2)	1.123 (2)	3.5 (4)
C(10)	0.920 (1)	−0.0971 (2)	1.003 (2)	3.3 (4)

e.s.d.s: estimated standard deviations.

TABLE III. Bond Lengths (Å), Angles (°), Hydrogen-Bond Distances (Å) and Torsion Angles (°)

Bond	Distance (Å)	Bond	Distance (Å)
O(2′)–C(2′)	1.248 (9)	C(2)–C(6)	1.521 (9)
O(10A)–C(10)	1.310 (9)	C(3)–C(4)	1.567 (9)
O(10B)–C(10)	1.202 (9)	C(4)–C(5)	1.46 (1)
N(1′)–C(2′)	1.325 (9)	C(6)–C(7)	1.52 (1)
N(1′)–C(4)	1.48 (1)	C(7)–C(8)	1.498 (9)
N(3′)–C(2′)	1.359 (9)	C(8)–C(9)	1.507 (9)
N(3′)–C(3)	1.415 (9)	C(9)–C(10)	1.48 (1)
C(2)–C(3)	1.534 (9)		

Bond	Angle (°)	Bond	Angle (°)
C(2′)–N(1′)–C(4)	112.0 (6)	N(1′)–C(4)–C(5)	114.1 (8)
C(2′)–N(3′)–C(3)	112.1 (6)	C(3)–C(4)–C(5)	118.2 (7)
C(3)–C(2)–C(6)	113.0 (6)	C(2)–C(6)–C(7)	113.2 (6)
O(2′)–C(2′)–N(1′)	125.4 (7)	C(6)–C(7)–C(8)	113.0 (7)
O(2′)–C(2′)–N(3′)	126.5 (7)	C(7)–C(8)–C(9)	115.9 (7)
N(1′)–C(2′)–N(3′)	108.1 (7)	C(8)–C(9)–C(10)	114.4 (7)
N(3′)–C(3)–C(2)	113.0 (6)	O(10A)–C(10)–C(10B)	121.3 (8)
N(3′)–C(3)–C(4)	101.0 (6)	O(10A)–C(10)–C(9)	115.5 (7)
C(2)–C(3)–C(4)	113.8 (6)	O(10B)–C(10)–C(9)	122.6 (8)
N(1′)–C(4)–C(3)	99.7 (6)		

Donor (D) at x, y, z	Acceptor (A) at symmetry operation		Distance (Å) D------A
O(10A)	O(2′)	$-1/2-x$, $-y$, $1/2+z$	2.649 (8)
N(1′)	O(2′)	$3/2+x$, $1/2-y$, $-3-z$	3.013 (7)
N(3′)	O(10B)	$-1/2-x$, $-y$, $3/2+z$	3.007 (8)

Bond sequence	Angle (°)
C(4)–C(3)–C(2)–C(6)	−177.9 (7)
C(3)–C(2)–C(6)–C(7)	−169.1 (7)
C(2)–C(6)–C(7)–C(8)	−176.8 (7)
C(6)–C(7)–C(8)–C(9)	−178.8 (7)
C(7)–C(8)–C(9)–C(10)	−178.8 (7)
O(10A)–C(10)–C(9)–C(8)	−159.6 (7)
O(10B)–C(10)–C(9)–C(8)	29 (1)
C(2′)–N(3′)–C(3)–C(4)	−25.3 (8)
N(1′)–C(4)–C(3)–N(3′)	24.7 (7)
C(2′)–N(1′)–C(4)–C(3)	−18.6 (8)
N(3′)–C(2′)–N(1′)–C(4)	4.2 (8)
N(1′)–C(2′)–N(3′)–C(3)	14.8 (8)
N(3′)–C(3)–C(2)–C(6)	67.7 (8)

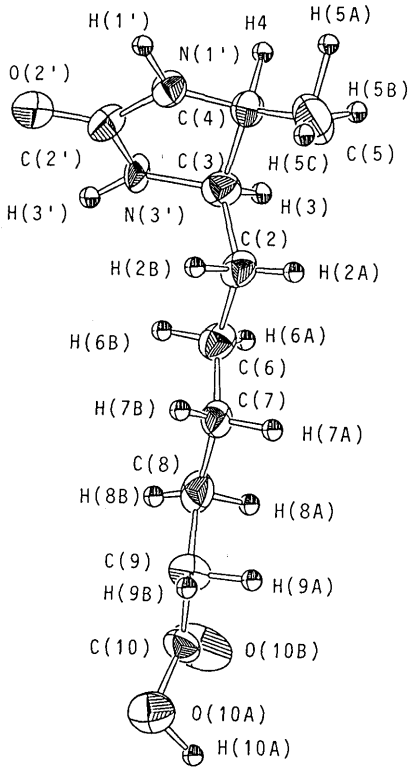

Fig. 1. A Perspective View of *d*-Desthiobiotin (I) Showing the Labelling of the Non-H Atoms

Thermal ellipsoids are shown at 50% probability levels.

twisted from the extended *trans* conformation; this is characterized especially by the torsion angle of 73.5° and 74.3° for C(2)–C(6)–C(7)–C(8) in the two independently analyzed structures of *d*-biotin.[2]

The three-dimensional structure of the complex of egg-white avidin with *d*-biotin has recently been determined using X-ray diffraction method at 2.7 Å resolution.[16] Avidin acts as an antibiotic protein inhibiting bacterial growth by binding *d*-biotin with $K_d=10^{-15}$ M and *d*-desthiobiotin with $K_d=5\times10^{-13}$ M.[17] In the avidin–*d*-biotin complex, the caproic acid chain of *d*-

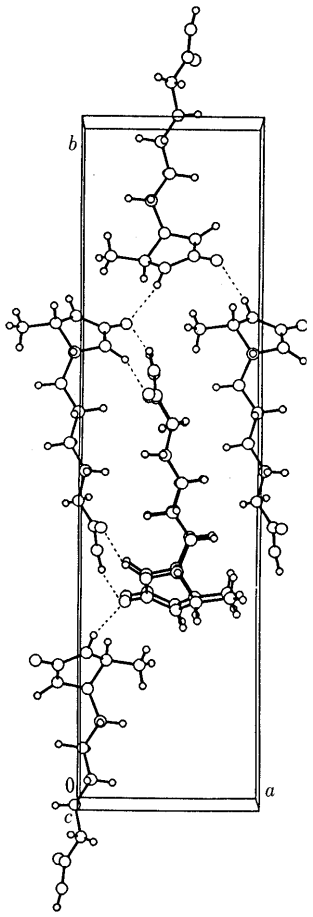

Fig. 2. Crystal Structure of *d*-Desthiobiotin (I) with the Hydrogen Bonding Scheme, Viewed along the *c*-Direction

biotin is also twisted from all-*trans* conformation at the same position about the C(6)–C(7) bond as the crystal structure of *d*-biotin.[2] The twist of *d*-biotin may be formed to avoid S···C(7) contact.[7] However, the direction of the twist in the avidin complex seems to be opposite that with *d*-biotin only. C(8) atom in the complex is apart from the sulfur atom of the tetrahydrothiophenic ring of *d*-biotin, and the terminal carboxylate group is fitted to the binding pocket hydrogen bonding to Ala 39, Thr 40, Ser 73 and Ser 75. The pronounced rotation about C(6)–C(7) occur easily and is a favorable characteristic of *d*-biotin. On the other hand, the nearly planar *trans* zig-zag conformation of caproic acid chain appearing in both *d*- and *d,l*-desthiobiotin[7,8] seems to be a predominant structure of desthiobiotin. This fully extended conformational feature of *d*-desthiobiotin (I) may be one of the reasons for the low affinity of *d*-desthiobiotin to avidin as compared with *d*-biotin.[1,7]

Molecular packing in the crystal structure is shown in Fig. 2. The crystal stability is due to van der Waals force between fully extended hydrocarbon chains,[7] and the hydrogen bonding network formed between 2-imidazolidone ring and terminal carboxylate group. Similar packing schemes are also observed in *d,l*-desthiobiotin crystal structures,[7,8] in which there are differences among molecular orientations. There are three hydrogen bonds in the *d*-desthiobiotin (I) structure, O(10A)–H···O(2′), N(1′)–H···O(2′) and N(1′)–H···O(10B). The hydrogen bond distance from the carboxyl group to the ureido carbonyl oxygen, 2.649(7) Å is shorter than the others indicating a strong hydrogen bond. The hydrogen bonding scheme of *d*-desthiobiotin (I) is the same as that in both *d,l*-desthiobiotin[7,8] and *d*-biotin.[2] The hydrogen bond O(10A)···O(2′) predicts participation of the carbonyl oxygen in the binding of *d*-desthiobiotin to avidin, as suggested in *d*-biotin crystal structure by DeTitta *et al.*[2] In fact, this seems to be true, since in the structure of avidine–*d*-biotin complex, the ureido carbonyl oxygen has strong interactions with Ser 16 and Tyr 33. The complex also includes participation of two NH groups of the 2-imidazolidone ring in the hydrogen bonding with Thr 35 and Asn 118. These facts suggest that the similar hydrogen bonding scheme identified in the crystal structure of *d*-desthiobiotin (I), *d,l*-desthiobiotin[7,8] and *d*-biotin[2] could result when these ligands bind to the related enzymes.

In conclusion, we were able to determine the structure of enantiomorphic *d*-desthiobiotin and learn that *d*-desthiobiotin maintains the same characteristic molecular structure and hydrogen bonding scheme as in *d,l*-desthiobiotin.[7,8]

References and Notes

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