Crystal Structure of Thiamin Tetrahydrofurfuryl Disulfide

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The crystal structure of thiamin tetrahydrofurfuryl disulfide, one of the ring-opened derivatives of thiamin, has been determined by the X-ray diffraction methods. The crystal is monoclinic with cell dimensions of a = 8.704 (1), b = 11.207 (2), c = 21.260 (3) Å and β = 92.44 (2)°, space group P2₁/c and Z = 4. The structure was solved by direct methods and refined to R = 0.076 for 1252 observed reflections measured on a diffractometer. The molecule assumes a folded conformation in which the pyrimidine and the tetrahydrofurfuryl rings are on the same side of the ethylenic plane. The pyrimidinyl, N-formyl and ethylenic planes are mutually perpendicular to each other and the N(3)-C(4) bond retains a single bond character. The structure is stabilized by an intramolecular N(4′α)-H···O(2α) hydrogen bond. The molecules are connected via N(4′α)-H···(N3′) and O(5γ)-H···(N1′) hydrogen bonds, forming a two-dimensional hydrogen-bonding network. The tetrahydrofurfuryl ring is dynamically disordered. The overall conformation as well as the packing mode is very similar to that of thiamin propyl disulfide.

Introduction

Thiamin (vitamin B₁) is labile against acid, alkali and heat.[1] The thiazolium ring in thiamin is easily hydrolized in mildly alkaline solution to give various thiol or disulfide derivatives which, in turn, can be easily converted to thiamin upon acidification.[2] Some thiamin disulfide derivatives such as thiamin tetrahydrofurfuryl disulfide (TTFD) and thiamin propyl disulfide (TPD) have been used as therapeutic provitamins due to high absorptivity in the gastrointestinal tract.[3] Among many thiamin disulfide derivatives, only the crystal structure of TPD has been reported to date.[4] X-ray analysis of TTFD has been undertaken to obtain information on the structural characteristics of this class of compounds.

Experimental

Transparent, prismatic crystals of TTFD were obtained by slow evaporation of a methanol solution at room temperature. A crystal having dimensions of 0.3×0.4×0.5 mm was used in the experiment. Oscillation and Weissenberg

photographs, which showed systematically absent reflections for 0kl when k is odd and h0l when l is odd, unequivocally indicated the crystals were monoclinic with space group symmetry P2₁/c. The unit cell parameters were determined by least-squares fit to observed 2θ angles for 25 centered reflections (24°≤2θ≤49°) measured with Cu Kα radiation on an automated Rigaku AFC diffractometer. The 2θ value used for each reflection was the average of the values for the Friedel pair. The crystal data are as follows.

C₁₇H₂₆N₄O₃S₂; mol.wt. 398.56; F(000) = 848
space group P2₁/c; Z = 4; μ(Cu Kα) = 23.99 cm⁻¹
a = 8.704 (1), b = 11.207 (2), c = 21.260 (3) Å, β = 92.44 (2)°
V = 2071.9 Å³ ; D_c = 1.285 gcm⁻³
D_m = 1.29 gcm⁻³ by floatation in CH₃I/(CH₃CH₂)O

The intensity data were collected with graphite-monochromated Cu Kα radiation using the 2θ-ω scan technique over a scan range of (1.0 + 0.5 tanθ)° in ω at a scan rate of 4°/min. The background was counted for 10 sec on either side of the peak. Three standard reflections were monitored every 50 reflections throughout the data collection and showed random varitions of ± 1.8 % with no significant trends. After Lorentz and polarization effects appropriate for graphite-monochromated (2θ_m = 26.5°) radiation were corrected for, the intensity data were converted to relative structure factor amplitudes. Of the 2149 independent reflections measured

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within the range of $2\theta \leqslant 105°$, 897 (41.7 %) were considered unobserved as defined by F<5 σ(F). No correction for the absorption and extinction effects was made.

Structure Determination and Refinement

The structure was solved by direct methods with the program MULTAN 78[5] using the largest 300 E's ($\geqslant 1.71$). From the initial E map calculated with the phase set having the highest reliability index, it was possible to identify the positions of 20 atoms among the 26 nonhydrogen atoms. After one cycle of isotropic refinement, the remaining atoms in the tetrahydrofurfuryl (THF) moiety were located in the subsequent difference Fourier map. However, further anisotropic refinements were hampered since the thermal parameters of the atoms in the THF moiety were ever increased indicating the presence of disorder. Numerous attempts to refine the structure using a statistically disordered model failed. Refinement could be finished satisfactorily only after the constraints of the fixed bond lengths for the atoms in the THF ring (C–C; 1.50 Å, C–O; 1.44 Å) were employed. The hydrogen positions in the THF moiety and the C(4a) methyl group were calculated geometrically and rided on the carbon atoms with a fixed bond length of 1.08 Å and the remaining hydrogen positions found in the difference Fourier map were refined. The refinement converged at R = 0.076 for 1252 observed reflections. The weighted R was 0.088. The function $\Sigma w(|Fo|-|Fc|)^2$ was minimized in the refinement. w, the weight of the reflection, was defined by $k/(\sigma^2(Fo)+gFo^2)$, where σ(F) was from counting statistics and k and g were optimized in the least-squares procedure (k = 0.50, g = 0.018). The final difference Fourier map revealed a maximum peak of 0.57 eÅ^{-3} in the vicinity of the C(6) atom. All of the calculations were done using the program SHELX 76.[6] Atomic scattering factors and the terms of the anomalous–dispersion correction were from the International Tables for X-ray Crystallography.[7]

Results and Discussion

Final atomic parameters are in Table 1.* The stereoscopic view of the molecule with numbering scheme is shown in Figure 1. Bond lengths and angles are listed in Table 2. Although critical evaluation of the molecular dimensions is
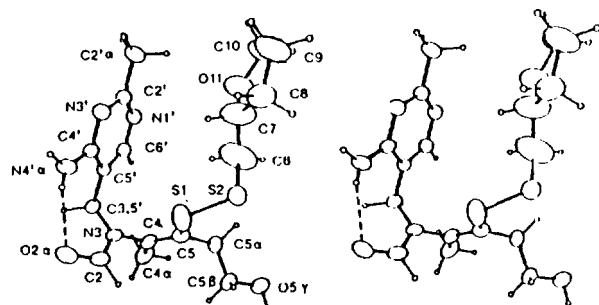

Figure 1. Stereoscopic ORTEP[8] drawing of the TTFD molecule, showing the thermal ellipsoids at 30 % probability.

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*Tables for anisotropic thermal parameters of the nonhydrogen atoms, coordinates of the hydrogen atoms, bond lengths and angles involving the hydrogen atoms and structure factors are available from the author.

Table 1. Atomic Coordinates ($\times 10^4$) and Thermal Factors (Å$^2 \times 10^3$) of TTFD

atom	x	y	z	Ueq
N(1')	3827 (9)	1903 (8)	3926 (4)	62
C(2')	4009 (11)	2465 (10)	4488 (5)	57
N(3')	4416 (9)	3609 (8)	4561 (3)	52
C(4')	4672 (10)	4283 (10)	4043 (4)	45
C(5')	4503 (10)	3750 (9)	3436 (4)	41
C(6')	4102 (11)	2587 (10)	3426 (5)	54
C(2'a)	3756 (21)	1742 (16)	5057 (7)	105
N(4'a)	5052 (12)	5397 (8)	4133 (4)	59
C(35')	4850 (12)	4417 (11)	2851 (4)	50
N(3)	3578 (9)	5198 (8)	2632 (3)	51
C(2)	3640 (16)	6403 (12)	2737 (5)	68
O(2a)	4683 (11)	6896 (7)	3025 (3)	80
C(4)	2290 (12)	4662 (9)	2283 (4)	54
C(5)	922 (13)	4621 (9)	2527 (4)	57
C(4a)	2649 (13)	4233 (11)	1629 (4)	82
C(5a)	-501 (13)	4186 (11)	2174 (5)	62
C(5β)	-1350 (13)	5183 (11)	1842 (6)	74
O(5γ)	-2718 (9)	4731 (7)	1568 (4)	85
S(1)	783 (4)	5236 (4)	3294 (1)	95
S(2)	-1174 (3)	4666 (3)	3637 (1)	81
C(6)	-922 (29)	3135 (9)	3822 (6)	205
C(7)	-630 (24)	2866 (10)	4495 (5)	158
C(8)	-1388 (17)	3475 (11)	5037 (5)	108
C(9)	-1518 (24)	2466 (12)	5506 (6)	139
C(10)	-1167 (23)	1309 (12)	5179 (6)	143
O(11)	-467 (13)	1621 (8)	4607 (4)	133

somewhat meaningless due to the limited quality of the data associated with disorder in the THF moiety, none of the dimensions show significant deviations from those of the related compounds such as TPD[4] and N-(p-bromophenyl-carbamoyl)thiamin anhydride (BCTA)[9,10]. All of the bond lengths and angles of the pyrimidine moiety are in excellent agreement with those of unprotonated pyrimidine in thiamin.[11]

The pyrimidine ring shows a good planarity with a maximum deviation of 0.006 Å as listed in Table 3. The atoms around N(3) including the formyl group are also planar. The facts that N(3) is only 0.017 Å apart from the plane formed by C(2), C(4) and C(3.5') and the sum of the valence angles around N(3) is 359.8° indicate that N(3) adopts an sp^2 hybridization. The six atoms around the C(4)–C(5) ethylenic double bond are planar within 0.038 Å. These three planar groups are nearly perpendicular to each other with the dihedral angles listed in Table 3. It is interesting to note that the three π-electron clouds located in close proximity in a single molecule are in this arrangement. The bond lengths of the three bonds involving N(3) indicate that the lone pair electrons of N(3) are delocalized only through the C(2)–N(3) bond (1.370 (15) Å) for conjugation with the formyl group, but not through the N(3)– C(3,5') (1.472 (13) Å) or the N(3)–C(4) (1.448 (12) Å) bond. The interaction between the lone pair electrons of N(3) and the ethylenic π-orbital is practically forbidden due to perpendicular arrangement of the two planar groups. Thus the N(3)–C(4) bond can remain an easily rotatable single bond.

The TTFD molecule has a folded conformation in which

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Table 2. Bond Lengths (Å) and Angles (deg) of TTFD

N(1')–C(2')	1.354 (13)	N(1') –C(6')	1.341 (13)
C(2')–N(3')	1.338 (13)	C(2') –C(2'a)	1.480 (20)
N(3')–C(4')	1.362 (12)	C(4') –C(5')	1.424 (13)
C(4')–N(4'a)	1.304 (13)	C(5') –C(6')	1.349 (14)
C(5')–C(35')	1.494 (14)	C(35')–N(3)	1.472 (13)
N(3) –C(2)	1.370 (15)	N(3) –C(4)	1.448 (12)
C(2) –O(2a)	1.207 (15)	C(4) –C(5)	1.320 (14)
C(4) –C(4a)	1.516 (14)	C(5) –C(5a)	1.502 (15)
C(5) –S(1)	1.779 (10)	C(5a) –C(5β)	1.499 (16)
C(5β)–O(5γ)	1.398 (14)	S(1) –S(2)	1.987 (4)
S(2) –C(6)	1.772 (17)	C(6) –C(7)	1.474 (23)
C(7) –C(8)	1.514 (19)	C(7) –O(11)	1.421 (18)
C(8) –C(9)	1.515 (20)	C(9) –C(10)	1.509 (22)
C(10)–O(11)	1.427 (18)		

N(3') –C(2') –N(1')	124.7 (9)	C(4') –N(3') –C(2')	119.3 (8)
C(5') –C(4') –N(3')	119.1 (8)	C(5') –C(6') –N(1')	126.4 (9)
C(6') –N(1') –C(2')	114.6 (9)	C(6') –C(5') –C(4')	115.9 (9)
C(2'a)–C(2') –N(1')	116.8 (10)	C(2'a)–C(2') –N(3')	118.5 (10)
N(4'a)–C(4') –N(3')	117.5 (9)	N(4'a)–C(4') –C(5')	123.4 (9)
C(35')–C(5') –C(4')	121.9 (8)	C(35') –C(35') –C(6')	122.1 (9)
N(3) –C(35')–C(5')	112.6 (8)	C(2) –N(3) –C(35')	120.7 (9)
O(2a) –C(2) –N(3)	123.9 (11)	C(4) –N(3) –C(35')	118.0 (8)
C(4) –N(3) –C(2)	121.1 (8)	C(5) –C(4) –N(3)	120.3 (9)
C(4a) –C(4) –N(3)	114.6 (8)	C(4a) –C(4) –C(5)	125.0 (9)
C(5a) –C(5) –C(4)	123.6 (9)	C(5β) –C(5a) –C(5)	111.9 (9)
O(5γ) –C(2β) –C(5a)	108.7 (9)	S(1) –C(5) –C(4)	116.4 (8)
S(1) –C(5) –C(5a)	119.8 (7)	S(2) –S(1) –C(5)	107.7 (4)
C(6) –S(2) –S(1)	107.0 (6)	C(7) –C(6) –S(2)	115.3 (12)
C(8) –C(7) –C(6)	125.7 (13)	C(9) –C(8) –C(7)	102.2 (11)
C(10) –C(9) –C(8)	108.4 (12)	C(10) –O(11) –C(7)	109.9 (11)
O(11) –C(7) –C(6)	112.1 (12)	O(11) –C(7) –C(8)	111.0 (11)
O(11) –C(10) –C(9)	106.5 (12)		

Table 3. Least-Squares Planes and Dihedral Angles[*]

(1) Pyrimidinyl		(2) N–Formyl		(3) Ethylenic	
N(1')	–0.004	C(35')	–0.005	N(3)	0.031
C(2')	0.0	N(3)	0.012	C(4)	–0.026
N(3')	0.002	C(2)	–0.009	C(5)	–0.038
C(4')	–0.001	O(2a)	0.003	C(4a)	–0.001
C(5')	–0.004	C(4)	–0.002	C(5a)	0.033
C(6')	0.006	C(5)*	1.048	S(1)	0.0
C(2'a)*	0.021	C(4a)*	–1.309	C(35')*	–1.142
N(4'a)*	–0.011	S(1)*	2.443	C(2)*	1.161
C(35')*	0.070			S(2)*	–0.532

Equation of Planes

$$(1) \quad 0.9625\ x\ -\ 0.2655\ y\ +\ 0.0564\ z\ =\ -2.7723$$
$$(2) \quad -0.4941\ x\ -\ 0.1403\ y\ +\ 0.8580\ z\ =\ -2.5470$$
$$(3) \quad -0.1872\ x\ +\ 0.9052\ y\ -\ 0.3814\ z\ =\ -2.5711$$

Dihedral Angles between Planes (deg)

$$(1)/(2)\ =\ 113.0;\ (1)/(3)\ =\ 116.2;\ (2)/(3)\ =\ 111.2$$

[*]Atoms designated by an asterisk (*) were given zero weight in calculating the planes. The equation of the plane is in the orthogonal coordinates system.

Table 4. Comparison of Selected Torsion Angles (deg) for TTFD and TPD

	TTFD	TPD
C(4') –C(5') –C(35')–N(3)	–81.2	–81.2
C(5') –C(35')–N(3) –C(4)	–80.0	–74.2
C(35')–N(3) –C(4) –C(5)	115.0	117.6
N(3) –C(4) –C(5) –S(1)	–0.7	1.4
C(4) –C(5) –S(1) –S(2)	–164.4	–148.0
C(5) –S(1) –S(2) –C(6)	72.5	80.3
C(4) –C(5) –C(5a)–C(5β)	–91.4	–107.1
C(5) –C(5a) –C(5β) –O(5γ)	–175.2	67.0

Table 5. Hydrogen Bonds in TTFD

a	b	c	a–b (Å)	b–c(Å)	a–c (Å)	<abc (deg)
N(4'a)–H···O(2a)			0.80 (10)	2.16 (10)	2.900 (12)	154 (9)
N(4'a)–H···N(3')ⁱ			0.81 (10)	2.30 (11)	3.009 (12)	146 (10)
O(5γ)–H···N(1')ⁱⁱ			0.95 (12)	1.90 (12)	2.806 (12)	159 (10)

symmetry code: none (x, y, z); i (1–x, 1–y, 1–z); ii (1–x, 0.5+y, 0.5–z)

the pyrimidine and the THF rings are on the same side of the ethylenic plane. The dihedral angle between the best planes of the two rings is 31°. This folded conformation is very similar to that of TPD and the only difference is in the relative orientation of the hydroxyethyl groups, as can be seen in the comparison of the torsion angles listed in Table 4. The conformation is in part stabilized by the intramolecular N(4'a)-H···O(2a) hydrogen bond (see Table 5). Mutually perpendicular arrangement of the planar pyrimidinyl, N-formyl and ethylenic groups is also similar to that of BCTA and thus seems to be a characteristic conformation of the ring-opened thiamin derivatives that is not affected by the various substituents at S(1).

The disulfide bond lies approximately in the ethylenic plane and the THF moiety perpendicular to the plane. The S(1)-S(2) bond length of 1.987 (4) Å is abnormally shorter than the normal S-S bond length usually larger than 2.00 Å. Although the S-S bond length usually decreases as the magnitude of C-S-S-C torsion angle increases from 0 to 90°[12,13] (72.5° in TTFD), the short S-S bond in this structure seems to result from the foreshortening effects of large thermal motion. The

THF ring is disordered showing large thermal motion in a direction perpendicular to the ring plane.

Figure 2 shows the packing drawing of the structure. The crystal packing consists of the two unique intermolecular hydrogen bonds listed in Table 5. The molecules related by a center of symmetry at (½, ½, ½) are dimerized through the N(4'a)-H···N(3') hydrogen bonds. Same type of dimer formation has been frequently observed in other thiamin structures.[14-16] The molecules related by the screw axis sym-
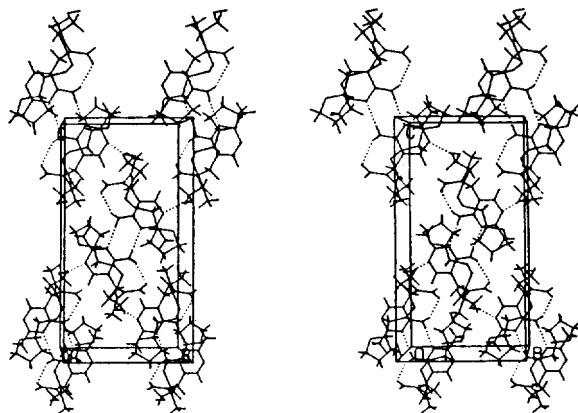
Figure 2. Stereoscopic view of the packing. Dotted lines indicate the hydrogen bonds.

metry are connected by the O(5y)-H···N(1') hydrogen bonds. These hydrogen bonds connect the molecules to form a hydrogen-bonded molecular layer. The flexible THF moieties lie between these layers and do not make close contacts with any parts of the other molecules. TPD also has a similar hydrogen bonding scheme and the propyl moiety is dynamically disordered.

The great reactivity of the ring-opened derivatives toward the formation of the thiazolium ring seems to result in part from flexibility of the substituent at S(1) and preserved capability of easy rotation about the N(3)-C(4) single bond as observed in this structure.

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Syntheses and Spectroscopic Studies of Metal–Metal Bonded Complexes (Zr–Fe)

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The preparation of the metal-metal bonded complex Cp₂ZrClFeCp(CO)₂ has been achieved by the reaction of Cp₂ZrCl₂ and strong nucleophile NaFeCp(CO)₂. The more soluble metal-metal bonded complexes Cp₂ZrRFeCp(CO)₂(R = CH₃, n-C₄H₉) have also been prepared through the reaction of Cp₂ZrRCl and NaCpFe(CO)₂. The complexes were characterized by IR, Raman, ¹H NMR and Mass spectra. The complete absorption (100–3800cm⁻¹) spectra for the three metal-metal bonded molecules are reported and the bands of each vibration were assigned.

Introduction

There is increasing evidence that binuclear transition metal complexes will play important roles in the development of organotransition metal chemistry. In one role, these simple compounds can serve as models for more complex systems. In a second role, bimetallic compounds containing early transition metal and late transition metal should prove unique and useful in their own right. This potential is suggested by recent studies revealing bimetallic mechanisms in reactions previously believed to take place at a single metal site.[1] Especially interesting are the recent applications of mixed-metal systems in organic synthesis.[2]

In view of the importance of biheterometallic compounds containing early and late transition metals, we have attempted to form metal-metal bonds containing zirconium. The first