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Structure of Thiamin Disulfide Dinitrate

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Abstract. 4,4′-Diamino-2,2′-dimethyl-5,5′-(dithiobis-{[2-(2-hydroxyethyl)-1-methylvinylene](formylimino)-methylene})dipyrimidinium dinitrate, $C_{24}H_{36}N_8O_4S_2^{2+}.2NO_3^-$, $M_r = 688·76$, monoclinic, $C2/c$, $a = 11·064\,(2)$, $b = 12·715\,(3)$, $c = 22·858\,(4)$ Å, $\beta = 96·03\,(1)°$, $V = 3198\,(1)$ Å^3, $Z = 4$, $D_x = 1·431$ g cm^{-3}, $\lambda(\mathrm{Cu}\,K\alpha) = 1·5418$ Å, $\mu = 19·87$ cm^{-1}, $F(000) = 1448$, $T = 295$ K, $R = 0·065$ ($wR = 0·068$) for 1366 reflections with $I > 3\sigma(I)$. Each half of the thiamin disulfide cation is related by a crystallographic twofold axis bisecting the disulfide bond. The two pyrimidine rings face each other with a dihedral angle of 4·1° so that the cation assumes a folded conformation. This conformation is stabilized in part by an intramolecular N(4′α)—H···O(2α) hydrogen bond [2·995 (6) Å]. The salt is stabilized by a hydrogen bond between O(5γ) and the nitrate O [2·801 (7) Å]. Hydrogen-bonding interactions form two-dimensional molecular layers and there are only C—H···O interactions between these layers. As observed in other ring-opened disulfide derivatives of thiamin, the *N*-formyl and ethylenic planes are perpendicular to each other so that the N(3)—C(4) bond remains an easily rotatable single bond.

Introduction. Thiamin (vitamin B_1) is labile against acid, alkali and heat (Dwidevi & Arnold, 1973). The thiazolium ring in thiamin is easily hydrolyzed in mildly alkaline solution to give various thiol or disulfide derivatives which, in turn, can easily be converted to thiamin upon acidification (Hopmann, 1982). Some thiamin disulfide derivatives such as thiamin tetrahydrofurfuryl disulfide (TTFD) and thiamin propyl disulfide (TPD) are used as therapeutic provitamins due to high absorptivity in the gastrointestinal tract (Suzuoki, Nishikawa & Numata, 1965). Thiamin disulfide is one of the open-ring derivatives which is frequently used as a starting material for syntheses of other thiamin derivatives. Among the many thiamin disulfide derivatives, only the crystal structures of TTFD (Shin & Kim, 1986) and TPD (Nishikawa, Kamiya, Asahi & Matsumura, 1969) have been reported to date. In an effort to obtain information on the structural characteristics of this class of compounds, the crystal structure of thiamin disulfide dinitrate (TDD) has been determined.

Experimental. Colorless tabular crystals obtained from an acetone–ethanol solution (1:1 *v*/*v*) of TDD (Sigma) by slow evaporation at room temperature; crystal *ca* 0·2 × 0·5 × 0·6 mm, Rigaku AFC diffractometer, graphite-monochromated Cu $K\alpha$ radiation, $2\theta < 122°$, ω–2θ scan, scan speed 4° min^{-1} in 2θ, ω-scan width $(1·3 + 0·4\tan\theta)°$, background measured for 12 s on either side of the peak; cell parameters by least-squares fit to observed 2θ values for 24 centred reflections with $22 < 2\theta < 50°$; intensity checks for three standard reflections showed little (±0·6%) variation; 2002 independent reflections (h −11 to 11, k 0 to 13, l 0 to 24), 1366 (68·2%) observed with $I > 3\sigma(I)$ and used in refinement; Lp corrections, no absorption or extinction corrections. Structure solved by direct methods with *MITHRIL* (Gilmore, 1984) and refined with *SHELX76* (Sheldrick, 1976) by full-matrix least squares on F with anisotropic thermal parameters; H atoms identified on a difference map and refined

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isotropically. $\sum w(|F_o| - |F_c|)^2$ minimized, with $w = k/[\sigma^2(F_o) + gF_o^2]$, $\sigma(F)$ from counting statistics, k and g optimized in the least-squares procedure ($k = 1{\cdot}00$, $g = 0{\cdot}0088$); $wR = 0{\cdot}068$ for 1366 observed reflections, 234 variables, $R = 0{\cdot}058$ for all data, $S = 0{\cdot}535$, $(\Delta/\sigma)_{\max} = 0{\cdot}255$ [thermal parameter of C(2′α)] in final refinement cycle, max. and min. heights in final difference map 0·34 and −0·35 e Å^{-3}, respectively. All calculations performed with *SHELX*76 on a VAX 11/780. Atomic scattering factors from *International Tables for X-ray Crystallography* (1974).

Table 1. *Atomic coordinates* ($\times 10^4$) *and equivalent isotropic thermal parameters* (Å$^2 \times 10^3$) *of TDD*

$$U_{\rm eq} = \tfrac{1}{3}\textstyle\sum_i \sum_j a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j.$$

	x	y	z	$U_{\rm eq}$
S(1)	454 (1)	2007 (1)	2915 (1)	40
C(2)	−338 (6)	4356 (4)	3490 (3)	46
N(3)	768 (4)	3939 (3)	3650 (2)	37
C(4)	1635 (5)	3823 (4)	3227 (2)	38
C(5)	1577 (5)	2996 (4)	2862 (2)	38
O(2α)	−1138 (4)	4410 (3)	3816 (2)	63
C(4α)	2605 (7)	4661 (5)	3273 (4)	57
C(5α)	2503 (6)	2767 (6)	2438 (3)	49
C(5β)	3449 (6)	2001 (7)	2741 (4)	68
O(5γ)	4070 (5)	2546 (5)	3210 (2)	89
C(35′)	1119 (6)	3579 (5)	4251 (2)	38
N(1′)	2097 (4)	766 (4)	4229 (2)	41
C(2′)	1040 (5)	256 (4)	4252 (2)	37
N(3′)	21 (4)	735 (3)	4305 (2)	40
C(4′)	12 (5)	1809 (4)	4316 (2)	34
C(5′)	1098 (4)	2405 (4)	4299 (2)	33
C(6′)	2138 (6)	1830 (4)	4251 (2)	39
C(2′α)	1062 (7)	−911 (5)	4195 (4)	56
N(4′α)	−1050 (5)	2254 (4)	4345 (2)	46
N	5901 (5)	1388 (4)	4350 (3)	47
O(1)	6098 (4)	1603 (4)	3837 (2)	68
O(2)	6746 (4)	1106 (4)	4699 (2)	73
O(3)	4851 (4)	1457 (5)	4482 (2)	79

Table 2. *Bond lengths* (Å) *and angles* (°) *of TDD*

S(1)—C(5)	1·781 (5)	C(2)—N(3)	1·348 (7)
C(2)—O(2α)	1·218 (7)	N(3)—C(4)	1·439 (6)
N(3)—C(35′)	1·460 (7)	C(4)—C(5)	1·341 (7)
C(4)—C(4α)	1·508 (9)	C(5)—C(5α)	1·511 (8)
C(5α)—C(5β)	1·540 (11)	C(5β)—O(5γ)	1·396 (10)
C(35′)—C(5′)	1·497 (7)	N(1′)—C(2′)	1·344 (7)
N(1′)—C(6′)	1·355 (7)	C(2′)—N(3′)	1·299 (6)
C(2′)—C(2′α)	1·489 (9)	N(3′)—C(4′)	1·366 (6)
C(4′)—C(5′)	1·424 (7)	C(4′)—C(4′α)	1·312 (7)
C(5′)—C(6′)	1·376 (7)	S(1)—S(1)′	2·051 (3)
N—O(1)	1·246 (7)	N—O(2)	1·218 (7)
N—O(3)	1·233 (8)		

C(4)—N(3)—C(2)	120·5 (4)	C(4)—C(5)—S(1)	120·0 (4)
C(5)—C(4)—N(3)	120·5 (4)	O(2α)—C(2)—N(3)	123·7 (5)
C(4α)—C(4)—N(3)	113·6 (5)	C(4α)—C(4)—C(5)	125·8 (5)
C(5α)—C(5)—S(1)	115·6 (4)	C(5α)—C(5)—C(4)	124·0 (5)
C(5β)—C(5α)—C(5)	107·9 (5)	O(5γ)—C(5β)—C(5α)	106·8 (6)
C(35′)—N(3)—C(2)	121·5 (4)	C(35′)—N(3)—C(4)	118·1 (4)
N(3′)—C(2′)—N(1′)	123·0 (5)	C(4′)—N(3′)—C(2′)	118·6 (4)
C(4′)—C(5′)—C(35′)	123·5 (4)	C(5′)—C(35′)—N(3)	112·1 (4)
C(5′)—C(4′)—N(3′)	121·6 (4)	C(5′)—C(6′)—N(1′)	120·6 (5)
C(6′)—N(1′)—C(2′)	120·4 (5)	C(6′)—C(5′)—C(35′)	120·3 (4)
C(6′)—C(5′)—C(4′)	115·8 (4)	C(2′α)—C(2′)—N(1′)	117·1 (5)
C(2′α)—C(2′)—N(3′)	119·9 (5)	N(4′α)—C(4′)—N(3′)	116·1 (4)
N(4′α)—C(4′)—C(5′)	122·4 (5)	C(5)—S(1)—S(1)′	102·4 (2)
O(2)—N—O(1)	118·9 (5)	O(3)—N—O(1)	118·5 (5)
O(3)—N—O(2)	122·6 (6)		

Discussion. Final atomic parameters are in Table 1.* The atomic labelling scheme is shown in Fig. 1. A stereoview of TDD is shown in Fig. 2. Bond lengths and angles are listed in Table 2.

All of the bond lengths and angles of the protonated pyrimidine ring are in good agreement with those of native thiamin (Cramer, Maynard & Ibers, 1981). The other molecular dimensions agree within 2σ with those of the related compounds such as TTFD, TPD and *N*-(*p*-bromophenylcarbamoyl)thiamin anhydrides (Nakai & Koyama, 1971, 1972). The S(1)—S(1) disulfide bond is relatively short [2·051 (2) Å]. It is consistent with the observation that the S—S bond length usually decreases as the magnitude of the C—S—S—C torsion angle [−87·4 (3)° in TDD] increases from 0 to 90° (Jones, Bernal, Frey & Koetzle, 1974; Neubert, Carmack & Huffman, 1977).

The pyrimidine ring is planar with a maximum deviation of 0·013 (5) Å. The five atoms around N(3) including the formyl group are also planar with a maximum deviation of 0·041 (5) Å. N(3) is only 0·006 (4) Å from the plane formed by C(2), C(4) and

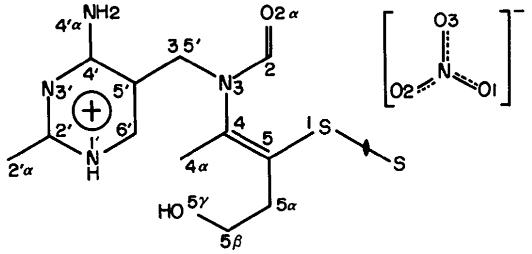

Fig. 1. Atomic numbering scheme for thiamin disulfide dinitrate.

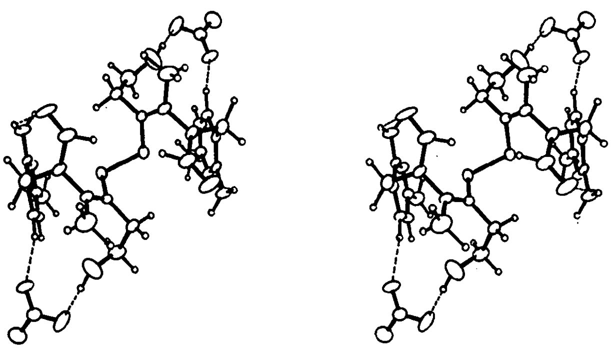

Fig. 2. Stereoscopic *ORTEP*II (Johnson, 1976) view of thiamin disulfide dinitrate approximately parallel to the twofold axis.

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* Lists of structure factors, anisotropic thermal parameters, coordinates of H atoms, bond distances and angles involving H atoms, least-squares planes, and a stereoscopic view of the crystal packing have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 44125 (12 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

C(35′), and the sum of the valence angles around N(3) is 360·0°. These results are indicative of an sp^2 hybridization of N(3). The bond lengths around N(3) indicate that the lone-pair electrons of N(3) are delocalized mainly through C(2)–N(3) [1·348 (7) Å] for conjugation with the formyl group, but only slightly through N(3)–C(35′) [1·460 (7) Å] or N(3)–C(4) [1·439 (6) Å]. The C(4)=C(5) ethylenic double bond and the four atoms attached to it are planar with a maximum deviation of 0·070 (8) Å. The nitrate ion is planar with a maximum deviation of 0·005 (5) Å.

Each half of the thiamin disulfide cation is related by a crystallographic twofold rotation axis bisecting the disulfide bond. The two pyrimidine rings are approximately parallel to the twofold axis with a dihedral angle of 4·1° between them. The overall folded conformation of thiamin disulfide is in part stabilized by the intramolecular N(4′α)–H···O(2α) hydrogen bond (Table 3) which has also been observed in TTFD and TPD. The TDD salt is stabilized by the hydrogen bond between O(5γ) and the nitrate oxygen O(1). There is also a close contact between C(6′) and O(3), which may be regarded as a weak C–H···O hydrogen bond.

A hydrogen-bonded molecular layer parallel to the *ab* plane is formed through the N(1′)–H···O(2α) and N(4′α)–H···O(2) hydrogen bonds. There are several short C–H···O contacts some of which may be regarded as, albeit very weak, hydrogen bonds, while N(3′), a potential acceptor, is not hydrogen bonded. Two of these weak interactions, namely, C(35′)–H···O(3) and C(2′α)–H···O(2), are the only close contacts between the two-dimensional molecular layers along the **c** direction.

Selected torsion angles in TDD, TTFD and TPD are listed in Table 4. In TTFD and TPD, the three planar pyrimidinyl, *N*-formyl and ethylenic moieties are approximately perpendicular to one another, each of the dihedral angles between the planes being about 110° (Shin & Kim, 1986). However, in TDD, only the *N*-formyl and ethylenic planes are nearly perpendicular with a dihedral angle of 98·1°. The dihedral angle between the pyrimidinyl and ethylenic planes is only 42·4° and that between the pyrimidinyl and *N*-formyl planes is 76·7°. The conformations of the hydroxyethyl moieties with respect to the ethylenic planes are different in the three structures. The disulfide bonds of TTFD and TPD lie approximately parallel to the ethylenic plane but it is more or less perpendicular to the plane in TDD. Therefore, the only common feature in the conformations of the three related compounds is a perpendicular arrangement of the *N*-formyl and ethylenic planes. Owing to this particular arrangement, the interaction between the lone-pair electrons of N(3) and the ethylenic π orbital is practically forbidden so that the N(3)–C(4) bond can remain an easily rotatable single bond. The high reactivity of the ring-opened derivatives toward the formation of the thiazolium ring seems to result from the preserved capability of easy rotation about the N(3)–C(4) single bond observed in these structures.

Table 3. *Hydrogen bonds and short contacts in TDD*

A–*B*···*C*	*A*–*B* (Å)	*B*···*C* (Å)	*A*···*C* (Å)	∠*ABC* (°)
N(4′α)–H(1)···O(2α)	0·79 (7)	2·29 (7)	2·995 (6)	150 (7)
N(1′)–H···O(2α$^{\text{i}}$)	0·97 (6)	1·92 (6)	2·840 (6)	158 (5)
O(5γ)–H···O(1)	0·83 (10)	1·98 (10)	2·801 (7)	170 (10)
N(4′α)–H···O(2$^{\text{ii}}$)	0·84 (6)	2·35 (6)	3·023 (7)	138 (6)
C(35′)–H(2)···O(2α)	0·93 (6)	2·44 (6)	2·796 (7)	102 (4)
C(35′)–H(2)···O(3$^{\text{iii}}$)	0·93 (6)	2·44 (6)	3·194 (8)	138 (5)
C(2′α)–H(3)···O(2$^{\text{iv}}$)	0·95 (7)	2·41 (7)	3·325 (9)	161 (6)
C(6′)–H···O(3)	0·96 (5)	2·41 (5)	3·030 (7)	121 (4)
C(4α)–H(3)···O(1$^{\text{v}}$)	1·08 (7)	2·56 (7)	3·314 (9)	126 (5)

Symmetry code: none x, y, z; (i) $\frac{1}{2}+x, -\frac{1}{2}+y, z$; (ii) $-1+x, y, z$; (iii) $\frac{1}{2}-x, -\frac{1}{2}-y, 1-z$; (iv) $1-x, -y, 1-z$; (v) $-\frac{1}{2}+x, \frac{1}{2}+y, z$.

Table 4. *Comparison of selected torsion angles* (°) *for TDD, TTFD and TPD*

	TDD	TTFD	TPD
C(4′)–C(5′)–C(35′)–N(3)	−78·3 (6)	−81·2	−81·2
C(5′)–C(35′)–N(3)–C(4)	−74·9 (5)	−80·0	−74·2
C(35′)–N(3)–C(4)–C(5)	96·9 (6)	113·0	117·6
N(3)–C(4)–C(5)–S(1)	−2·1 (4)	−0·7	1·4
C(4)–C(5)–S(1)–S(1)′	122·6 (5)	−164·4	−148·0
C(5)–S(1)–S(1)′–C(5)′	−87·4 (3)	72·5	80·3
C(4)–C(5)–C(5α)–C(5β)	94·2 (7)	−91·4	−107·1
C(5)–C(5α)–C(5β)–O(5γ)	−66·4 (6)	−175·2	67·0

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