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Thiaminium bis(bisulfate) monohydrate

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Key indicators

Single-crystal X-ray study
T = 293 K
Mean σ(C–C) = 0.004 Å
R factor = 0.037
wR factor = 0.106
Data-to-parameter ratio = 12.7

For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

In the title compound, $C_{12}H_{18}N_4OS^{2+}\cdot 2HSO_4^{-}\cdot H_2O$, the protonated thiamine cation exhibits the frequently observed F conformation with respect to the methylene bridge atom. The value of the torsion angle $\varphi_{5\alpha}$ formed by the side chain is quite different from the frequently observed range, possibly because of the packing specificity/hydrogen bonding of the crystal structure. The thiazolium and pyrimidine rings interact with the anions through intermolecular/electrostatic contacts. The thiamine cations form 'head-to-head' hydrogen-bonded dimers. The bisulfate anions are dimerized themselves and an extensive three-dimensional network of classical hydrogen bonds is observed through the anionic dimers. The anions occupy positions close to the 'anionic holes' of the thiamine cation, leading to a host–guest structure.

Comment

Thiamine (vitamin B1) plays an important role in energy metabolism especially at the level of the heart muscle. Wet beri-beri is the characteristic vitamin B1 deficiency disease, which, besides others, is also characterized by heart failure. Evidence suggests that administering vitamin B1 can avoid the heart failure. Older individuals under a chronic diuretic therapy should obtain an oral vitamin B1 supplement (Suter, 2004). Thiamine (Th^+), as its pyrophosphate ester, is a cofactor for a number of metabolic enzymes (Krampitz, 1969). It is well established that the substrate (*e.g.* pyruvate anion) reacts with the coenzyme at the C12 site of the thiazolium ring to form a reaction intermediate, hydroxylethylthiamine pyrophosphate (Breslow, 1958). Thiamine itself exists as the inorganic acid (chloride/nitrate) salt of an organic cation with a quaternary N atom in the thiazolium ring, and may in turn have another proton added to produce a doubly charged acid form. Structural studies of Th^+ derivatives in the solid state began in 1962, when the crystal structure of thiamine chloride hydrochloride monohydrate ($ThCl\cdot HCl\cdot H_2O$) was reported (Kraut & Reed, 1962). Since then, several thiamine derivatives have been reported as monovalent cations (Th^+) or protonated divalent cations (HTh^{2+}). The crystal structures of thiamine chloride monohydrate (Pletcher, Sax *et al.*, 1972), thiamine free base (Shiro *et al.*, 1978), thiaminium tetrachlorocobaltate(II) monohydrate (MacLaurin & Richardson, 1983), thiamine nitrate (Ishida *et al.*, 1984), thiamine disulfide dinitrate (Shin & Chun, 1987), thiamine perchlorate monohydrate (Kozioł *et al.*, 1987), thiamine picrate (Kim *et al.*, 1988), thiamine acetate (Casas *et al.*, 1994) and oxythiamine hexafluorophosphate monohydrate (Hu *et al.*, 2000) have already been reported. This work on thiamine-related compounds led us to choose thiamine for part of our ongoing work on pharmacologically important compounds.

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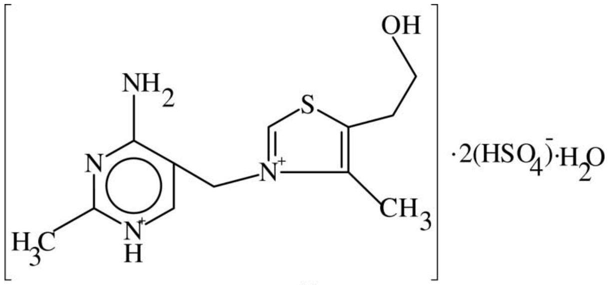

(I)

In the title compound (I), the thiamine residue exists as a dication with a positively charged thiazolium ring and a protonated pyrimidine ring. This charge of +2 is balanced by two monovalent bisulfate anions. The molecular dimensions of thiamine in (I) agree well with those of thiamine dinitrate (Yang *et al.*, 1987). The protonation on the pyrimidine N1 atom is well confirmed by the C—N bond distances and C—N—C bond angle (Table 1). Both the pyridimine and thiazolium rings are virtually planar with r.m.s. deviations of 0.0043 and 0.0174 Å respectively. The pyrimidine and thiazolium planes make a dihedral angle of 78.1 (1)°. Generally, the conformation of the thiamine residue is classified in terms of the two torsion angles about the bonds formed by the methylene atom C7 with the rings, $\varphi_{\rm T}$ (C5—C7—N8—C12) and $\varphi_{\rm P}$ (C4—C5—C7—N8) (Pletcher & Sax, 1972). Three kinds of conformers have been observed in thiamine derivatives (Shin *et al.*, 1977): F($\varphi_{\rm T} = 0°$, $\varphi_{\rm P} = \pm 90°$), S($\varphi_{\rm T} = \pm 100°$, $\varphi_{\rm P} = \pm 150°$) and V($\varphi_{\rm T} = \pm 90°$, $\varphi_{\rm P} = \pm 90°$). From the Cambridge Structural Database (Version 5.26 of November 2004; Allen, 2002), it is observed that the F form occurs frequently when the thiazolium C12 atom is free of substituents. In the present structure, the thiamine is in the preferred F conformation with $\varphi_{\rm T} = 2.5\ (3)°$ and $\varphi_{\rm P} = 78.7\ (3)°$. The molecular conformation about the 5-(β-hydroxyethyl) side chain can be described by the two torsion angles $\varphi_{5\alpha}$ (S11—C10—C13—C14) and $\varphi_{5\beta}$ (C10—C13—C14—O15). The value of $\varphi_{5\alpha}$ in (I) is quite different from the most frequently observed range (±60 to ±90°) (Shin *et al.*, 1977). This disposition appears to be due to the required packing specificity/hydrogen bonding in the unit cell (Fig. 1).

The crystal packing is stabilized by an extensive hydrogen-bonding network (Fig. 2). A review of the literature disclosed that most thiamine complexes crystallize in a centrosymmetric space group with thiamine–thiamine interactions forming ‘head-to-head’ or ‘head-to-tail’ dimeric structures around the inversion centres of the unit cell (head: pyrimidine ring; tail: hydroxyethyl side chain). In the present structure, the thiamine cations dimerize through a pair of N41—H41*A*···N3$^{\rm ii}$ [symmetry code: (ii) $1 - x, 1 - y, -z$] hydrogen bonds forming a ‘head-to-head’ dimeric structure around the inversion centre at ($\frac{1}{2}, \frac{1}{2}, 0$) (Fig. 3). The thiamine cations and the S2/O21–O24 anions interact through O—H···O and C—H···O hydrogen interactions to form chains running along the [110] direction (Fig. 4).

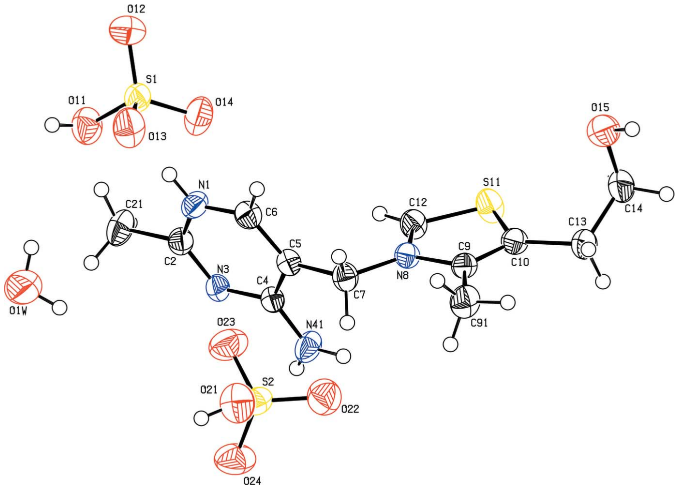

Figure 1
The molecular structure of title compound, with the atom-numbering scheme and 50% probability displacement ellipsoids.

Generally, pyrimidine and thiazolium rings interact with the anion through three kinds of non-bonded interactions: (i) C—H···O hydrogen bonds, (ii) S···O interactions and (iii) electrostatic interactions. The C—H···O interaction has been widely studied in all thiamine complexes because of the importance of the acidic proton (C12—H12) in hydroxyethylthiamine pyrophosphate reactions. In the present investigation, the acidic carbon makes a hydrogen bond with an O atom of the bisulfate anion and the anion further interacts with the pyrimidine ring, thus establishing interactions with the thiazolium and pyrimidine rings. This leads to a type I anion bridge, of the form C12—H12···anion···pyrimidine. The shortest distance between the O atoms of the anions and the thiazolium S atom is 3.198 (3) Å, which is significantly shorter than the sum of the van der Waals radii of 3.32 Å (Bondi, 1964). Combining this interaction with the N41—H41*B*···O14 hydrogen bond, the structure features the widely occurring type II anion bridge.

As described by Hu *et al.* (2001), thiamine in its F form leads to three well defined ‘anion holes’ between the thiazolium and pyrimidine rings. Because of electrostatic interaction, the anions are accommodated very close to these ‘anion holes’ and this leads to a ‘host–guest’ structure. The thiamine ‘host’ captures an anion ‘guest’ in an ‘anion hole’. The capture of the anion in ‘anion hole I’ is characterized by the hydrogen bond of the acidic carbon (C12) with the anion. The acidic nature of C12 and the S atom of the thiazolium ring make this site as prominent for anion (guest) capture. ‘Anion hole II’ is the position close to the quaternary N atom in the thiazolium ring and ’anion hole III’ is described by the C6—H6···anion hydrogen bond. Since the anion holes II and III are in very close proximity, only one anion guest will occupy these sites. ’Anion hole I’ is occupied by the S1/O11–O14 bisulfate dimer forming the C12—H12···O12$^{\rm vi}$ [symmetry code: (vi) $x - 1, y, z$] hydrogen bond. The other two anion holes II and III are occupied by another bisulfate (S2/O21—O24) dimer and the water molecule, leading to the C6—H6···O22$^{\rm vi}$ hydrogen bond (Table 2).

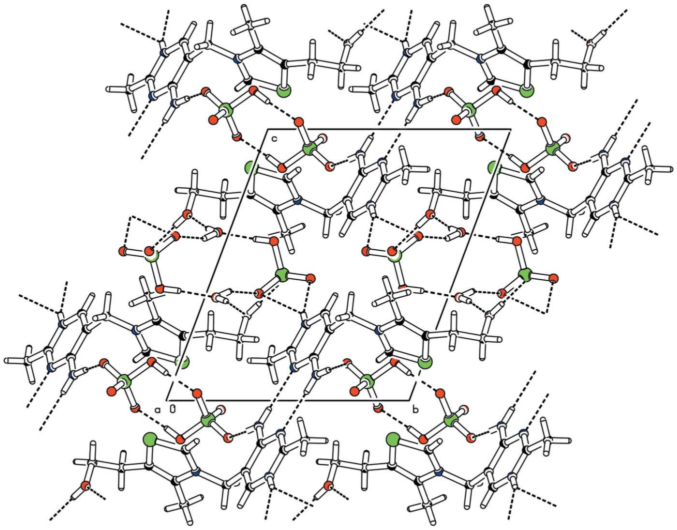

Figure 2
Packing diagram of the title compound viewed down the *a* axis. Hydrogen bonds are drawn as dashed lines.

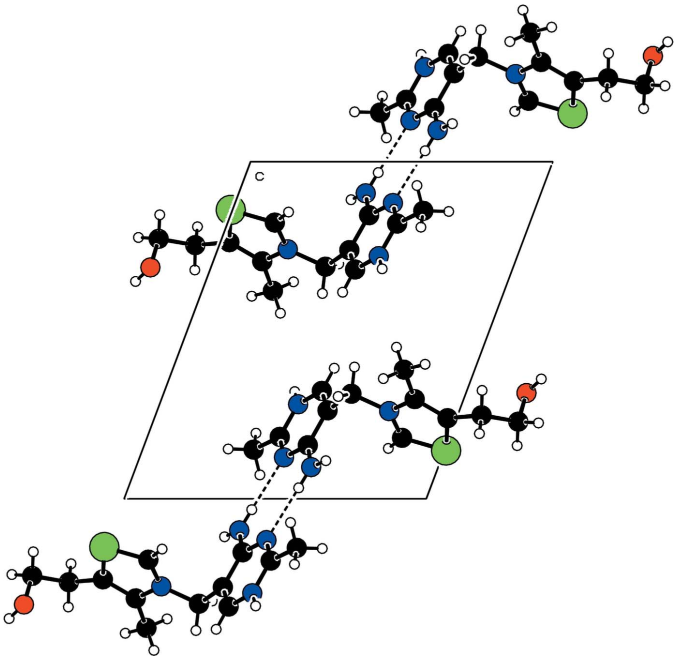

Figure 3
The centrosymmetric dimers formed by the cations. Hydrogen bonds are drawn as dashed lines.

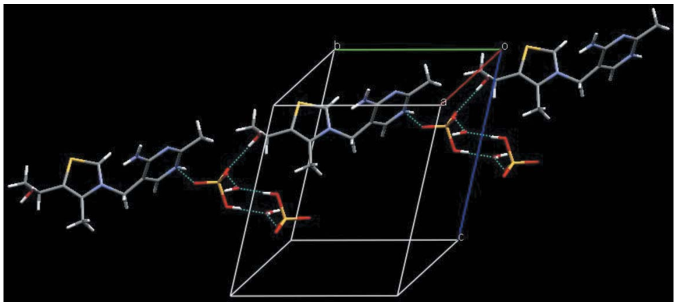

Figure 4
Chain of thiamine cations and bisulfate anions running along the [110] direction. Hydrogen bonds are drawn as dashed lines.

Experimental

The title compound was crystallized by slow evaporation at room temperature, after mixing thiamine chloride and sulfuric acid in a 1:2 molar ratio.

Crystal data

$C_{12}H_{18}N_4OS^{2+}\cdot 2HSO_4^-\cdot H_2O$
$M_r = 478.52$
Triclinic, $P\bar{1}$
$a = 7.686$ (3) Å
$b = 10.801$ (7) Å
$c = 12.881$ (9) Å
$\alpha = 68.83$ (4)°
$\beta = 82.67$ (6)°
$\gamma = 83.23$ (5)°
$V = 986.0$ (11) Å^3
$Z = 2$
$D_x = 1.612$ Mg m^{-3}
$D_m = 1.601$ Mg m^{-3}
D_m measured by flotation using a mixture of carbon tetrachloride and bromoform
Mo $K\alpha$ radiation
Cell parameters from 25 reflections
$\theta = 11.1$–$14.2°$
$\mu = 0.44$ mm^{-1}
$T = 293$ (2) K
Block, colourless
0.25 × 0.20 × 0.12 mm

Data collection

Nonius MACH3 four-circle diffractometer
ω–2θ scans
Absorption correction: ψ scan (North *et al.*, 1968)
$T_{\min} = 0.911$, $T_{\max} = 0.954$
4297 measured reflections
3457 independent reflections
2898 reflections with $I > 2\sigma(I)$
$R_{\rm int} = 0.010$
$\theta_{\max} = 25.0°$
$h = -1 \rightarrow 9$
$k = -12 \rightarrow 12$
$l = -15 \rightarrow 15$
3 standard reflections frequency: 60 min intensity decay: none

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.037$
$wR(F^2) = 0.106$
$S = 1.06$
3457 reflections
273 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0485P)^2 + 1.0125P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{\max} = 0.001$
$\Delta\rho_{\max} = 0.43$ e Å^{-3}
$\Delta\rho_{\min} = -0.58$ e Å^{-3}

Table 1
Selected geometric parameters (Å, °).

N1—C2	1.339 (3)	N1—C6	1.348 (3)
C2—N1—C6	121.1 (2)		
C4—C5—C7—N8	78.7 (3)	S11—C10—C13—C14	36.0 (3)
C5—C7—N8—C12	2.5 (3)	C10—C13—C14—O15	66.8 (3)

Table 2
Hydrogen-bond geometry (Å, °).

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1—H1···O22[i]	0.86	2.06	2.864 (4)	155
N41—H41*A*···N3[ii]	0.86	2.18	3.039 (4)	178
N41—H41*B*···O14	0.86	2.04	2.877 (3)	164
O15—H15···O23[iii]	0.85	1.89	2.746 (3)	179
O11—H11···O13[iv]	0.82	1.79	2.604 (4)	176
O21—H21···O1*W*	0.82	1.70	2.519 (4)	176
O1*W*—H1*W*···O24[iii]	0.85 (6)	1.94 (6)	2.754 (4)	158 (5)
O1*W*—H2*W*···O15[v]	0.87 (7)	1.86 (7)	2.722 (4)	170 (6)
C12—H12···O12[vi]	0.93	2.43	3.346 (4)	169
C6—H6···O22[vi]	0.93	2.40	3.326 (4)	173

Symmetry codes: (i) $-x+1, -y+1, -z+1$; (ii) $-x+1, -y+1, -z$; (iii) $-x+2, -y+2, -z+1$; (iv) $-x+2, -y+2, -z$; (v) $x+1, y, z$; (vi) $x-1, y, z$.

The H atoms of the water molecule were located in a difference Fourier map and refined isotropically. All other H atoms were positioned geometrically and refined using a riding model, with C—H = 0.93–0.97 Å, O—H = 0.82–0.85 Å and N—H = 0.86 Å, and $U_{\rm iso}$(H) = 1.2–1.5$U_{\rm eq}$(parent atom). The displacement parameter of atom H15 was refined freely.

Data collection: *CAD-4 EXPRESS* (Enraf–Nonius, 1994); cell refinement: *CAD-4 EXPRESS*; data reduction: *XCAD4* (Harms & Wocadlo, 1995); program(s) used to solve structure: *SHELXTL*/*PC* (Bruker, 2000); program(s) used to refine structure: *SHELXTL/PC*; molecular graphics: *SHELXTL*/*PC* and *PLATON* (Spek, 2003); software used to prepare material for publication: *SHELXL97* (Sheldrick, 1997).

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