

On the polymorphism of thiamine dichloride monohydrate (Vitamin B1)

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To date the structures of only *two* polymorphs of thiamine dichloride monohydrate have been reported in the literature.Received 21 October 2006
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Comment

The crystal structure of a new polymorph of Vitamin B1 has recently been described (Balasubramanian *et al.*, 2006). According to these authors, this is the *third* polymorphic form of this important biochemical to be identified and they note that 'two different forms [were] reported previously' by Kraut & Reed (1962) and Suh *et al.* (1982); similar statements appear in their *Abstract* and elsewhere in their text. These statements about the *number* of polymorphs require careful examination. The *reported* cell dimensions summarized in Table 1 clearly fall into two groups – firstly Cambridge Structural Database (CSD, Version 1.8; Allen *et al.*, 2002) refcodes THIAMC, THIAMC01 and THIAMC12, and then separately polymorph III (THIAMC13). In the first group, the values of *a*, *b* (unique) and unit-cell volume are very similar but the values of β and *c* differ, as do the assigned space groups. One immediately suspects that revised choices of β and *c* would give essentially the same unit cells and the same space group for all three members of the first group. This has been confirmed by transforming THIAMC12 to space group $P2_1/c$, as shown in Table 1. An alternative but equivalent method of demonstrating the equivalence of the group I structures is *via* the reduced cells, not reproduced here but given in the CSD. Suh *et al.* (1982, see p. 116) recognized that they and Kraut & Reed studied the same polymorph. For convenience, we designate the group I structure as the $P2_1/n$ polymorph and the THIAMC13 structure as the $P2_1/c$ polymorph; standard designations require knowledge of the thermodynamic relations between the polymorphs.

We note that the differences in cell dimensions for the various independent determinations are far larger than their

Table 1

Cell dimensions reported for Vitamin B1 (\AA , $^\circ$, \AA^3).

Measurements at nominal 300 K unless stated otherwise. Standard uncertainties as in publications; those of III were measured 'from 25 reflections'.

Refcode	Polymorph designation	<i>a</i>	<i>b</i> / β	<i>c</i>	Unit cell volume	Z	Reported space group	Reference
Group I results								
THIAMC	I	6.99 (1)	20.59 (2) 114.0 (1)	12.73 (2)	1673.8	4	$P2_1/c$	Kraut & Reed (1962)
THIAMC01 [†]	II	6.975	20.555 98.78	11.727	1661.16	4	$P2_1/n$	Suh <i>et al.</i> (1982)
THIAMC12 296K	Not given	6.9928 (2)	20.6631 (10) 98.699 (2)	11.7695 (5)	1681.0 (2)	4	$P2_1/n$	Te <i>et al.</i> (2003)
THIAMC12 reoriented to $P2_1/c$		6.9928	20.6631 114.369	12.775	1681.0	4	$P2_1/c$	
Group II results								
THIAMC13 173 K	III	9.1437 (2)	7.3438 (2) 92.112 (1)	24.7447 (6)	1660.47 (7)	4	$P2_1/c$	Balasubramanian <i>et al.</i> (2006)

[†] Also given as THIAMC11 (Suh & Kim, 1982)

Table 2

Some torsion angles ($^{\circ}$) calculated from the published atomic coordinates.

The nomenclature follows that of Balsubramanian *et al.* (2006). Standard uncertainties are about 0.1° . As the molecules are chiral (although the crystals are racemic) it is necessary to specify the enantiomer when making comparisons; all our values refer to the enantiomer with $\phi D \approx 79^{\circ}$. There are some differences of sign between our values and those of Balsubramanian *et al.* (2006), presumably due to different choices of enantiomer.

Refcode	ϕT $\tau(C2-N1-C7-C8)$	ϕD $\tau(N1-C7-C8-C9)$	$\phi S\alpha$ $\tau(S1-C1-C4-C5)$	$\phi S\beta$ $\tau(C1-C4-C5-O1)$	$\tau(C7-C8-C9-N2)$
THIAMC	170.8	76.1	103.4	53.8	176.8
THIAMC01	170.6	74.8	100.8	50.6	177.2
THIAMC12	170.9	75.7	103.1	53.6	3.5
THIAMC13	179.2	79.3	24.2	63.4	176.4

reported standard uncertainties, suggesting unspecified systematic differences; dehydration (Te *et al.*, 2003) does not appear to provide an explanation. Comparison of torsion angles (Table 2) provides some more information; it is not clear whether the differences in torsion angles for the three examples of group I are due to real structural differences. Te *et al.* (2003) describe the $P2_1/n$ polymorph as ‘a nonstoichiometric solvate, a class of solvates where the water molecules occupy voids in a stable network that does not collapse after dehydration.’

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Key indicators

Single-crystal X-ray study
T = 173 K
Mean $\sigma(C-C)$ = 0.002 Å
R factor = 0.033
wR factor = 0.081
Data-to-parameter ratio = 17.5

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

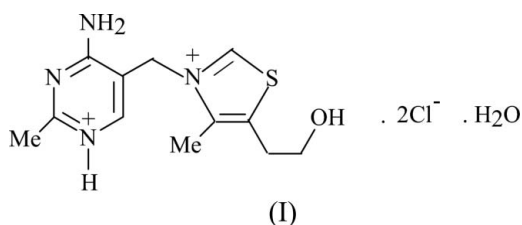
Thiamine dichloride monohydrate: vitamin B1 (form III)

Two different forms of the title compound, $C_{12}H_{18}N_4OS^{2+} \cdot 2Cl^- \cdot H_2O$, have already been reported [Kraut & Reed (1962). *Acta Cryst.* **15**, 747–757; Suh *et al.* (1982). *J. Korean Phys. Soc.* **15**, 114–121]. In this third form, in which the H atoms were located, a different conformation is observed. The planes of the pyrimidine and thiazolium rings are at a dihedral angle of 79 (15)°. The structure contains two weak O–H...Cl hydrogen bonds.

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Comment

Thiamine, as its pyrophosphate ester, is a coenzyme in a number of important metabolic processes, such as the decarboxylation of α -keto acids and the transfer of aldehyde or acyl groups (Krampitz, 1969). In the present work, the H atoms were located in a difference map, leading to a better understanding of the hydrogen-bonding pattern in vitamin B1. A molecular diagram of the title compound, (I), is given in Fig. 1. Bond angles within the pyrimidine ring are all close to 120°. The small difference between the angle of 120.93 (12)° at N4 and 118.76 (12)° at N3 is somewhat surprising in view of the fact that N4 is protonated whereas N3 is not. It has already been pointed out that one would expect the angle at the ring N atom in pyrimidines to approach 125° for the protonated or otherwise substituted case or 106° for the unsubstituted case (Pauling & Corey, 1956).



The bond lengths and angles in this structure are similar to those of the two different forms reported previously [forms I (Kraut & Reed, 1962) and II (Suh *et al.*, 1982)]. Both of the aromatic rings in the cation are essentially planar. The conformation of the cation is described by two torsion angles, φ_T (C2–N1–C7–C8) and φ_P (N1–C7–C8–C9), centring the methylene atom C7 to the respective rings (Pletcher & Sax, 1972). Three conformations have been observed for thiamine, namely F, S and V conformations. The values of φ_T and φ_P determine whether the conformation is F, S or V. The torsion angle of φ_T is 0° for F, $\pm 100^\circ$ for S and $\pm 90^\circ$ for V (Shin *et al.*, 1977). The value of φ_P is $\pm 90^\circ$ for F, $\pm 150^\circ$ for S and $\pm 90^\circ$ for V (Shin *et al.*, 1977). The F conformation has been the most frequently found in thiamine derivatives. The

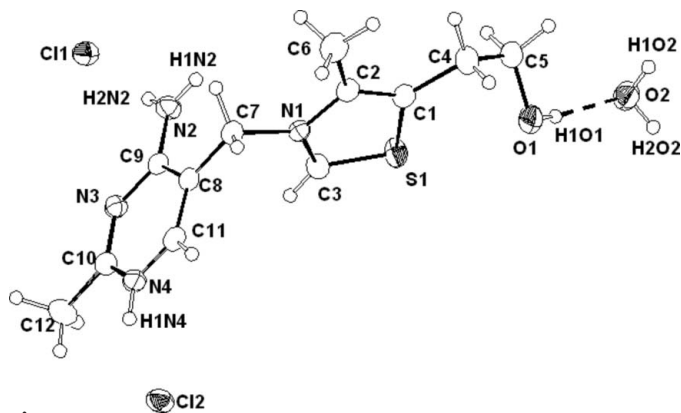


Figure 1
View of (I), with 50% probability displacement ellipsoids.

present structure, in which the torsion angles $\varphi_T = 179.18$ (11) $^\circ$ and $\varphi_P = -79.27$ (15) $^\circ$, also belongs to the F conformation.

The C5-hydroxyethyl side chain is folded back towards the thiazolium ring from the opposite side to the pyrimidine ring. The thiazolium ring is described by the two torsion angles $\varphi_{5\alpha}$ (S1–C1–C4–C5) and $\varphi_{5\beta}$ (C1–C4–C5–O1). In the present work, the values of $\varphi_{5\alpha}$ and $\varphi_{5\beta}$ are 24.2 (20) and -63.35 (18) $^\circ$, respectively. However, these angles differ widely from those of the two forms reported earlier. We have calculated these angles $\varphi_{5\alpha}$ and $\varphi_{5\beta}$ as 103.4 (6) and 53.76 (7) $^\circ$, respectively, for form I, and -100.8 (3) and 50.6 (8) $^\circ$, respectively, for form II. The values of $\varphi_{5\alpha}$ and $\varphi_{5\beta}$ for most thiamine derivatives have been observed to lie in the range ± 60 to $\pm 90^\circ$ (Shin *et al.*, 1977) and within 10° from $\pm 60^\circ$ (Shin *et al.*, 1977). The essential difference occurs in the angle $\varphi_{5\alpha}$ of the present structure. This difference appears due to the packing requirements for the hydroxy group participating in hydrogen bonding. The geometries of the hydrogen bonds are given in Table 2. This structure contains two weak O–H...Cl and N–H...Cl hydrogen bonds.

Experimental

Thiamine hydrochloride (660 mg, Sigma) was dissolved in 75 ml of water. The mixture was heated for about 4 h and allowed to cool. After a week, colourless block-shaped crystals appeared.

Crystal data

$C_{12}H_{18}N_4OS^{2+} \cdot 2Cl^- \cdot H_2O$
 $M_r = 355.28$
 Monoclinic, $P2_1/c$
 $a = 9.1437$ (2) Å
 $b = 7.3438$ (2) Å
 $c = 24.7447$ (6) Å
 $\beta = 92.112$ (1) $^\circ$
 $V = 1660.47$ (7) Å³
 $Z = 4$

$D_x = 1.421$ Mg m⁻³
 Mo $K\alpha$ radiation
 Cell parameters from 25 reflections
 $\theta = 2-30.8^\circ$
 $\mu = 0.53$ mm⁻¹
 $T = 173$ (2) K
 Block, colourless
 $0.5 \times 0.32 \times 0.24$ mm

Data collection

Bruker SMART CCD diffractometer
 ω scans
 Absorption correction: multi-scan (SADABS; Bruker, 1998)
 $T_{min} = 0.817$, $T_{max} = 0.881$
 11933 measured reflections

4716 independent reflections
 3913 reflections with $I > 2\sigma(I)$
 $R_{int} = 0.026$
 $\theta_{max} = 30.8^\circ$
 $h = -12 \rightarrow 11$
 $k = -10 \rightarrow 10$
 $l = -35 \rightarrow 29$

Refinement

Refinement on F^2
 $R[F^2 > 2\sigma(F^2)] = 0.033$
 $wR(F^2) = 0.081$
 $S = 1.05$
 4716 reflections
 270 parameters
 All H-atom parameters refined

$$w = 1/[\sigma^2(F_o^2) + (0.0341P)^2 + 0.5004P]$$

where $P = (F_o^2 + 2F_c^2)/3$
 $(\Delta/\sigma)_{max} < 0.001$
 $\Delta\rho_{max} = 0.27$ e Å⁻³
 $\Delta\rho_{min} = -0.27$ e Å⁻³

Table 1

Selected geometric parameters (Å, $^\circ$).

S1–C3	1.6753 (15)	N2–C9	1.3161 (17)
S1–C1	1.7229 (14)	N3–C10	1.3087 (17)
O1–C5	1.419 (2)	N3–C9	1.3570 (17)
N1–C3	1.3146 (17)	N4–C11	1.3477 (19)
N1–C2	1.3897 (17)	N4–C10	1.3497 (19)
N1–C7	1.4883 (17)		
C3–S1–C1	91.68 (7)	N1–C3–S1	112.17 (11)
C3–N1–C2	113.93 (11)	O1–C5–C4	108.20 (13)
C3–N1–C7	123.82 (12)	N1–C7–C8	112.35 (11)
C2–N1–C7	122.25 (11)	N2–C9–N3	116.55 (12)
C10–N3–C9	118.76 (12)	N2–C9–C8	122.23 (13)
C11–N4–C10	120.93 (12)	N3–C9–C8	121.21 (12)
C2–C1–S1	109.86 (10)	N3–C10–N4	122.08 (13)
C4–C1–S1	122.80 (11)	N3–C10–C12	119.72 (14)
C1–C2–N1	112.36 (11)	N4–C10–C12	118.21 (13)
N1–C2–C6	120.17 (13)	N4–C11–C8	120.59 (13)
C1–C4–C5–O1	-63.35 (18)	N1–C7–C8–C9	-79.27 (15)
N1–C7–C8–C11	103.29 (14)	C7–C8–C9–N2	3.1 (2)

Table 2

Hydrogen-bond geometry (Å, $^\circ$).

D–H...A	D–H	H...A	D...A	D–H...A
O2–H1O2...Cl2 ⁱ	0.82 (2)	2.40 (3)	3.2120 (14)	171 (2)
O2–H2O2...Cl1 ⁱⁱ	0.84 (3)	2.32 (3)	3.1636 (13)	175 (2)
N2–H1N2...Cl2 ⁱⁱⁱ	0.85 (2)	2.36 (2)	3.1934 (14)	166 (2)
O1–H1O1...O2	0.83 (2)	1.95 (2)	2.7555 (17)	166 (2)
N2–H2N2...Cl1	0.83 (2)	2.36 (2)	3.1744 (13)	168 (2)
N4–H1N4...Cl2	0.85 (2)	2.28 (2)	3.0659 (12)	153 (2)

Symmetry codes: (i) $-x + 1, y - \frac{1}{2}, -z + \frac{1}{2}$; (ii) $x, -y + \frac{1}{2}, z + \frac{1}{2}$; (iii) $x + 1, y, z$.

All H atoms were found in a difference Fourier map and refined isotropically [C–H = 0.89 (3)–1.003 (19) Å].

Data collection: SMART (Bruker, 1998); cell refinement: SAINT (Bruker, 1998); data reduction: SAINT; program(s) used to solve structure: SIR97 (Altomare *et al.*, 1999); program(s) used to refine structure: SHELXL97 (Sheldrick, 1997); molecular graphics: ZORTEP (Zsolnai & Pritzkow, 1995); software used to prepare material for publication: SHELXL97.

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