Chemistry of Natural Compounds, Vol. 37, No. 4, 2001

SECONDARY WEAK INTERACTIONS IN THE CRYSTAL STRUCTURE OF THIAMINE BROMIDE

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UDC 548.737

The x-ray crystal structure of thiamine bromide hydrate was studied. The crystals are monoclinic, a = 12.348, b = 24.852, c = 11.682 Å, β = 113.67 °, Z = 4, space group $P2_1/c$. The crystal structure is constructed of two crystallographically independent thiamine cations, bromide anions, and water molecules. The thiamine cations have the F-conformation. The structure contains intermolecular short contacts involving S and N atoms of the thiazole ring.

Key words: thiamine, crystal structure, conformation, secondary weak interactions.

Thiamine, or vitamin B_1 (4-methyl-5-β-hydroxyethyl-N-(2-methyl-4-amino-5-methylpyrimidyl)-thiazolium), as the diphosphate (cocarboxylase) fulfills the role of a cofactor for dehydrogenase of pyrotartaric and α-ketoglutaric acids and for transketolase. It participates in the regulation of carbohydrate exchange and facilitates the utilization of glucose and the metabolism of pyrotartaric and lactic acids [1].

We report results for the x-ray crystal structure of a previously unstudied thiamine compound, $T \cdot Br \cdot H_2O$ (**1**, T is the thiamine cation). Although crystals of **1** and the previously studied chloride analog ($TCl \cdot H_2O$) (**2**) [2] belong to space group $P2_1/c$, nevertheless the unit-cell constants of the crystals are different. Therefore, these structures are not isomorphous. The x-ray crystal structure of **1** was studied to determine differences in the crystal structures of these compounds and to investigate secondary weak interactions, which we observed previously in the crystal structure of $[HT][CoCl_4]$ [3]. The atomic coordinates and thermal parameters are listed in Table 1; bond lengths and angles, Table 2.

The crystal structure of **1** is constructed of two crystallographically independent cations T^+ (A and B) (Fig. 1), two Br^- anions, and two water molecules, one of which is disordered over two equally occupied positions. The crystal structure of **2**, in contrast with that of **1**, is constructed of one crystallographically independent structural unit. The water molecule is located in a position with unit occupancy.

Bond lengths C(2)—N(3) [1.30(1) (A and B) Å] and C(4)—C(5) [1.34(1) (A) and 1.35(1) (B) Å] in the thiazole rings are consistent with double bonds (Table 2). Bond lengths C(14)—N(18) (1.30 Å in both cations) are typical of analogous compounds [4]. The planar configuration of the NH_2 group is consistent with n,π-conjugation of the unshared electron pair on N with the π-system of the pyrimidine ring.

The heteroatom N(11) in the pyrimidine rings is unprotonated. Bond angle C(12)N(11)C(16), which is sensitive to protonation of N(11), is 113(1)° (A) and 115(1)° (B). This angle is 120.7(4)° and 119(1)° in the structures of $TCl \cdot HCl \cdot H_2O$ [5] and $TI \cdot HI \cdot H_2O$ [6], where N(11) is protonated.

The conformation of the thiamine cation is determined by torsion angles C(2)N(3)C(10)C(15) (τ_1) and N(3)C(10)C(15)C(14) (τ_2) [7]. Torsion angles τ_1 and τ_2 in **1** are -8(1)° and -75(1)° in cation A and 6(1)° and -81(1)° in cation B, respectively. This corresponds to the F-conformation of thiamine. Such a conformation for the cation is most common and is also observed in the structure of **2**.

The structure of **1** contains 10 independent H atoms capable of forming H-bonds. A maximum of 12 short contacts corresponding to H-bonds can form in the structure because of the disordering of the water over two positions (Table 3). These all are observed in the structure. Donor protons or assumed donors (for H atoms that were not found) are listed first in the H-bonds.

Tashkent Regional State Pedagogical Institute, Republic of Uzbekistan. Translated from Khimiya Prirodnykh Soedinenii, No. 4, pp. 324-329, July-August, 2001. Original article submitted July 18, 2001.

Table 1. Atomic Coordinates ($\times 10^4$; for H atoms, $\times 10^3$) and Thermal Parameters U_{eq} (10^3 Å^2) for **1**

Atom	x	y	z	U_{eq}	Atom	x	y	z	U_{eq}
Br (1)	3025 (1)	2245 (1)	5546 (1)	54 (1)	C (16A)	38 (10)	2983 (6)	-4280 (11)	54 (2)
Br (2)	7191 (2)	4438 (1)	9423 (2)	77 (1)	C (16B)	5771 (9)	2814 (6)	4957 (12)	59 (2)
S (1A)	2828 (3)	1567 (2)	-1100 (3)	63 (1)	C (17A)	-1303 (11)	3987 (5)	-3042 (11)	78 (3)
S (1B)	2789 (3)	1506 (2)	2051 (3)	66 (1)	C (17B)	7074 (11)	3781 (6)	3548 (13)	65 (2)
O (1)$_w$	4821 (17)	4290 (9)	6912 (18)	92 (3)	H (2A)	165	234	-201	
O (2)$_w$	197 (14)	672 (7)	-472 (15)	63 (3)	H (2B)	428	217	273	
O (3)$_w$	-757 (9)	997 (4)	-2938 (11)	93 (2)	H (6A)	126	109	-499	
O (9A)	4974 (12)	844 (6)	-207 (13)	138 (2)	H′ (6A)	23	87	-472	
O (9B)	2445 (12)	256 (6)	1138 (12)	135 (2)	H′′ (6A)	140	55	-438	
N (3A)	1168 (7)	1716 (4)	-3166 (9)	46 (2)	H (6B)	455	105	605	
N (3B)	4581 (7)	1599 (4)	4028 (8)	39 (2)	H′ (6B)	530	69	545	
N (11A)	-292 (8)	3468 (5)	-4036 (10)	63 (2)	H′′ (6B)	408	51	529	
N (11B)	6060 (9)	3288 (4)	4619 (11)	62 (2)	H (7A)	318	20	-113	
N (13A)	-1227 (8)	3010 (5)	-2868 (9)	56 (2)	H (7A)	286	30	-256	
N (13B)	7059 (8)	2808 (4)	3567 (9)	49 (2)	H (7B)	155	71	250	
N (18A)	-1218 (9)	2110 (4)	-2704 (10)	58 (2)	H′ (7B)	220	44	373	
N (18B)	7112 (9)	1901 (4)	3552 (10)	59 (2)	H (8A)	477	21	-137	
C (2A)	1754 (9)	1954 (5)	-2102 (11)	48 (2)	H′ (8A)	454	76	-206	
C (2B)	4021 (9)	1845 (5)	2965 (11)	44 (2)	H (8B)	331	-1	283	
C (4A)	1600 (10)	1202 (6)	-3252 (11)	56 (2)	H′ (8B)	199	-18	224	
C (4B)	4053 (9)	1119 (5)	4193 (10)	43 (2)	H (10A)	40	212	-480	
C (5A)	2506 (11)	1063 (6)	-2194 (12)	62 (2)	H′ (10A)	-48	174	-459	
C (5B)	3057 (11)	1013 (5)	3166 (12)	58 (2)	H (10B)	620	154	516	
C (6A)	1068 (12)	902 (7)	-4450 (13)	80 (2)	H′ (10B)	549	185	567	
C (6B)	4559 (11)	820 (6)	5349 (11)	64 (2)	H (16A)	37	294	-496	
C (7A)	3130 (13)	499 (7)	-1799 (15)	102 (2)	H (16B)	527	286	549	
C (7B)	2210 (12)	550 (6)	2947 (13)	69 (2)	H (17A)	-173	394	-252	
C (8A)	4403 (16)	553 (9)	-1428 (17)	131 (3)	H′ (17A)	-62	421	-262	
C (8B)	2525 (14)	111 (7)	2331 (14)	88 (2)	H′′ (17A)	-180	415	-382	
C (10A)	177 (10)	1981 (5)	-4208 (11)	51 (2)	H (17B)	682	404	385	
C (10B)	5654 (10)	1825 (5)	5029 (11)	46 (2)	H′ (17B)	678	373	266	
C (12A)	-921 (10)	3444 (6)	-3309 (11)	57 (2)	H′′ (17B)	792	379	388	
C (12B)	6708 (10)	3257 (6)	3915 (12)	54 (2)	H (18A)	-157	218	-206	
C (14A)	-889 (9)	2535 (5)	-3126 (10)	45 (2)	H′ (18A)	-123	173	-275	
C (14B)	6755 (9)	2335 (5)	3918 (10)	40 (2)	H (18B)	684	157	345	
C (15A)	-202 (9)	2499 (5)	-3874 (11)	48 (2)	H′ (18B)	756	186	310	
C (15B)	6071 (9)	2320 (4)	4641 (10)	39 (2)					

TABLE 2. Bond Lengths (d, Å) and Angles (φ) in **1**

Bond	d, Å		Bond	d, Å	
	cation A	cation B		cation A	cation B
S(1)-C(2)	1.68 (1)	1.69 (1)	C(10)-C(15)	1.47 (2)	1.47 (2)
S(1)-C(5)	1.72 (1)	1.72 (1)	N(11)-C(12)	1.36 (2)	1.36 (2)
C(2)-N(3)	1.30 (1)	1.30 (1)	N(11)-C(16)	1.34 (2)	1.34 (2)
N(3)-C(10)	1.49 (1)	1.48 (1)	C(12)-N(13)	1.31 (2)	1.32 (2)
C(4)-N(3)	1.40 (2)	1.41 (2)	C(14)-N(18)	1.30 (2)	1.30 (2)
C(4)-C(5)	1.34 (1)	1.35 (1)	C(12)-C(17)	1.50 (2)	1.50 (2)
C(4)-C(6)	1.49 (2)	1.45 (2)	C(14)-N(13)	1.33 (2)	1.35 (2)
C(5)-C(7)	1.58 (2)	1.51 (2)	C(14)-C(15)	1.44 (2)	1.41 (2)
C(7)-C(8)	1.46 (2)	1.44 (2)	C(15)-O(16)	1.37 (2)	1.37 (2)
C(8)-O(9)	1.50 (2)	1.40 (2)			

TABLE 2. (Continued)

Angle	φ, deg		Angle	φ, deg	
	cation A	cation B		cation A	cation B
C(2)S(1)C(5)	91.0 (6)	91 (1)	N(3)C(10)C(15)	114 (1)	113 (1)
C(10)C(15)C(14)	123 (1)	125 (1)	S(1)C(2)N(3)	113 (1)	111 (1)
C(10)C(15)C(16)	123 (1)	120 (1)	C(2)N(3)C(4)	114 (1)	115 (1)
C(14)C(15)C(16)	115 (1)	115 (1)	C(2)N(3)C(10)	123 (1)	122 (1)
C(4)N(3)C(10)	124 (1)	122 (1)	C(12)N(11)C(16)	113 (1)	115 (1)
N(11)C(16)C(15)	126 (1)	125 (1)	N(3)C(4)C(5)	112 (1)	110 (1)
N(11)C(12)N(13)	127 (1)	125 (1)	N(3)C(4)C(6)	119 (1)	121 (1)
C(12)N(13)C(14)	118 (1)	118 (1)	S(1)C(5)C(4)	111 (1)	111 (1)
N(13)C(14)C(15)	120 (1)	121 (1)	C(4)C(5)C(7)	129 (1)	128 (1)
N(11)C(12)C(17)	113 (1)	116 (1)	S(1)C(5)C(7)	119 (1)	120 (1)
N(13)C(14)N(18)	118 (1)	117 (1)	C(5)C(4)C(6)	129 (1)	129 (1)
N(13)C(12)C(17)	119 (1)	118 (1)	C(5)C(7)C(8)	110 (1)	111 (1)
N(18)C(14)C(15)	122 (1)	122 (1)	O(9)C(8)C(7)	111 (1)	112 (1)

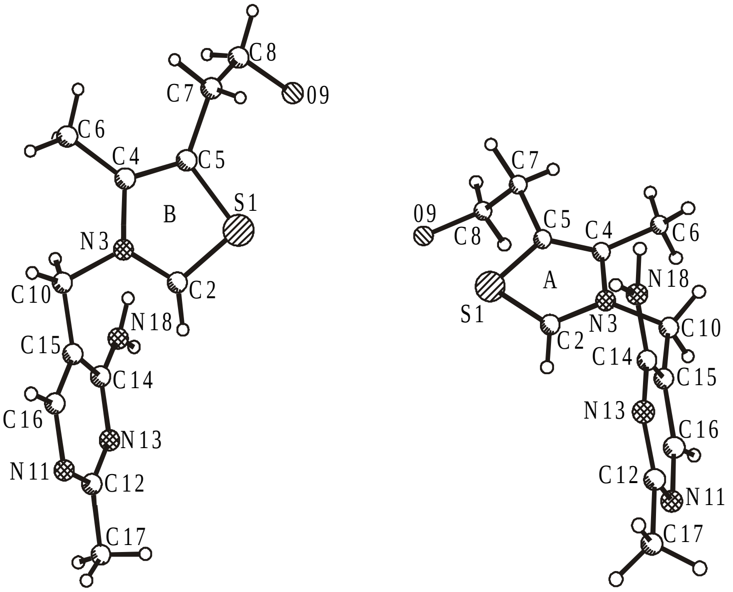

Fig. 1. Structure of thiamine A and B cations in **1**.

Cationic dimers with parallel pyrimidine rings are formed through two N(18)–H...N(13) intermolecular H-bonds between neighboring thiamine cations (A and B). These are bonded into a three-dimensional framework through H-bonds formed with Br^- ions and H_2O molecules (Fig. 2). These cationic dimers are found in all crystal structures of thiamine compounds and possibly are also retained in its solutions.

Besides the H-bonds, the structure also contains a series of short intermolecular and intramolecular contacts that correspond to secondary weak interactions (Figs. 2 and 3 and Table 4). These are formed by atoms of the thiazole and can be assigned to three types. The first type is formed by S(1); the second, by N(3); the third, by H(2) as a weak H-bond. Analogous weak interactions were noted previously in [HT][$CoCl_4$] and were described by us [3].

TABLE 3. Geometry of H-Bonds

Contact* D–H...A	Distance, Å			Angle D–H...A, deg
	D-H, Å	A...H, Å	D...A, Å	
N(18A)-H(18A)...N(13B)^{a}	1.0	2.09	3.05	154
N(18A)-H′(18A)...O(3)$_{w}$	0.9	1.98	2.76	161
N(18B)-H(18B)...Br(2)^{b}	0.9	2.71	3.47	145
N(18B)-H′(18B)...N(13A)^{c}	0.9	2.23	3.12	165
C(2A)-H(2A)...Br(1)^{b}	0.9	2.97	3.48	114
C(2B)-H(2B)...Br(1)^{b}	0.9	2.79	3.44	125
O(2)$_{w}$...N(11A)^{f}			2.92	
O(9A)...N(11B)^{b}			2.59	
O(1)$_{w}$...Br(2)			3.23	
O(1)$_{w}$...O(9A)^{b}			2.58	
O(9B)...O(1)$_{w}$			2.93	
O(3)$_{w}$...Br(2)^{e}			3.29	
O(3)$_{w}$...O(2)$_{w}$			2.76	
O(2)$_{w}$...O(9B)			2.85	

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*Upper indices denote atoms related to initial ones by transformations: x-1, 1/2-y, 1/2+z (a); x, 1/2-y, -1/2+z (b); 1+x, 1/2-y, 1/2+z (c); x, 1/2-y, 1/2+z (d); x-1, 1/2-y, z-3/2 (e); x, y, z-1 (f).

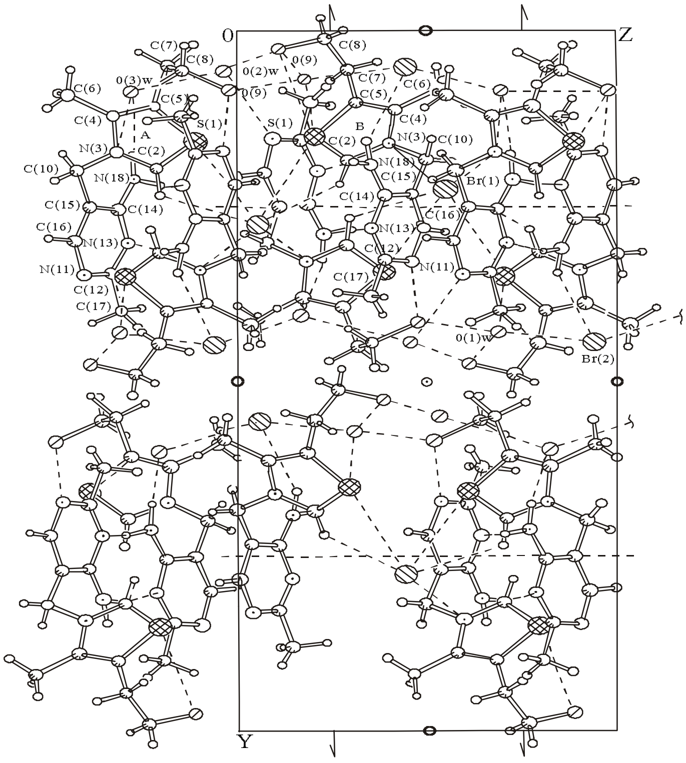

Fig. 2. Projection of the crystal structure of **1** on the yz plane.

TABLE 4. Geometry of Secondary Interactions

Contact* D...A	Distance, D...A, Å	Angle, deg C(2)DA	C(5)DA
S(1A)...Br(1)^{e}	3.48	76	167
S(1B)...Br(1)^{e}	3.64	69	161
S(1A)...O(9A)	3.02	157	74
S(1B)...O(9B)	3.26	130	62
S(1B)...O(1)$_{w}$	3.25	79	72
N(3A)...Br(1)^{f}	3.46	92	89
N(3A)...O(3)$_{w}$	3.07	109	79
N(3B)...Br(1)	3.48	94	74

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*Upper indices denote atoms related to the initial ones by transformations: x-1, 1/2-y, -1/2+z (a); x, 1/2-y, -1/2+z (b); 1+x, 1/2-y, 1/2+z (c); x, 1/2-y, 1/2+z (d); x-1, 1/2-y, z-3/2 (e); x, y, z-1 (f).

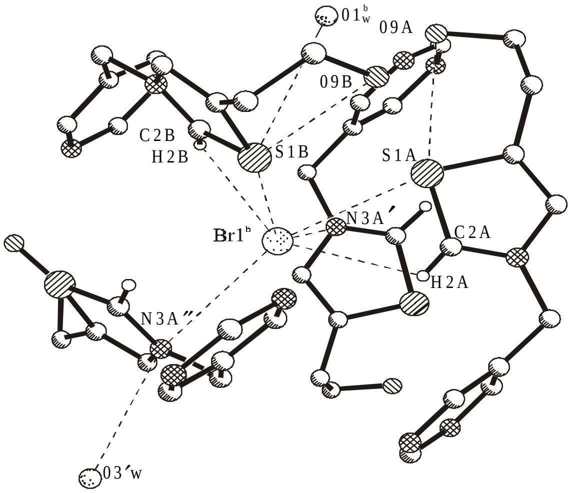


Fig. 3. Secondary weak interactions in the structure of **1**. Dotted lines and upper indices denote atoms related to the asymmetric unit by space-group symmetry transformations.

Atoms S(1A) and S(1B) form two and three short contacts, respectively, in which the nonbonded interatomic distances are short compared with the sum of the Van-der-Waals radii of the adjoining atoms (Fig. 3).

The distance S(1A)...S(1B) is 3.70(1)Å, which is 0.1 Å greater than twice the Van-der-Waals radius of S (1.80 Å) [8].

Distances in the S(1A)...Br(1) (3.48 Å) and S(1B)...Br(1) (3.64 Å) contacts are short compared with the sum of the Van-der-Waals radii of the S and Br atoms (3.80 Å) by 0.32 Å in the first and 0.16 Å in the second. The Br^{-} ion in both contacts is actually situated in the plane of the thiazole rings of cations A and B. The deviation of the Br^{-} ion from the plane of the thiazole ring is 0.09 Å for A and 0.20 Å for B. The S(1)...Br(1) contacts are oriented almost along the C(5)—S(1) bonds. Angle C(5)S(1)Br(1) is 167° in the first and 161° in the second contact.

Contacts S(1A)...O(9A) and S(1B)...O(9B) (3.25 Å) are intramolecular. The S...O distance (3.02 Å) in the first is short compared with the sum of the Van-der-Waals radii of the S and O atoms (3.32 Å) by 0.30 Å. The angle C(2A)S(1A)O(9A) is 157° and indicates that O(9A) is located almost along the continuation of the C(2A)—S(1A) bond. The second contact is insignificantly shortened (0.07 Å). Atom O(9B) is located off the continuation of the C(5B)—S(1B) bond [angle C(5B)S(1B)O(9B) is 130°].

The interatomic distance in the S(1B)...O(1)$_{w}$ contact (3.25 Å) is also short by 0.07 Å. Atom O(1)$_{w}$ is located over the plane of the thiazole ring. Angles C(2B)S(1B)O(1)$_{w}$ and C(5A)S(1A)O(1)$_{w}$ are 79.5° and 71.7°, respectively.

Thus, secondary interactions of S(1) can be arbitrarily divided into linear, weak C—S...X interactions where atom X is located almost along the continuation of the C(2)—S(1) or C(5)—S(1) bonds, and nonlinear, where C(2)S(1)X or C(5)S(1)X angles are significantly different from 180° and atom X is located off the plane of the thiazole ring. The S...X distance is much shortened when atom X is located along the C(2)—S(1) or C(5)—S(1) bonds. A general feature of all weak S...X bonds is the electron-donor nature of the atoms interacting with S.

Secondary weak interactions N(3A)...Br(1) (3.64 Å) and N(3B)...Br(1) (3.48 Å) that are formed by the Br^- anion simultaneously with two thiamine cations are also considered nontraditional. Such short contacts are also observed in other structures of thiamine halogenides [5-7, 9, 10]. As a rule, the halogenide ion in all structures is located almost over N(3) of the thiazolium ring.

Angle C(2)N(3)Br(1) in the present structure is 92° (A) and 94° (B); angle N(3A)Br(1)N(3B), 130°. Such mutual placement of the Br^- and N(3) atoms of the thiazolium rings facilitates the formation of a charge-transfer interaction between N(3) and Br^- through an electron-deficient p_z orbital of the N atom.

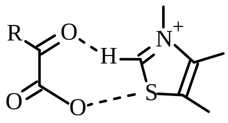
The Br(1)...H(2) distance in weak H-bond interactions C(2A)—H(2A)...Br(1) and C(2B)—H(2B)...Br(1) (2.97 and 2.79 Å, respectively) is markedly shortened compared with the sum of Van-der-Waals radii of the Br and H atoms (3.25 Å). The Br(1)...C(2) distance [3.48 Å (A) and 3.44 Å (B)] is short compared with the sum of Van-der-Waals radii of the Br and C atoms (3.55 Å) by 0.07 Å (A) and 0.11 Å (B). Angles C(2)—H(2)...Br(1) are 114° and 125° for cations A and B, respectively.

The acidic center of thiamine is known to be the C(2)—H(2) group. A weak interaction forms because of the increased acidity of H(2). This group can form weak C(2)—H(2) interactions with all proton-acceptors.

An analysis of more than 30 thiamine structures shows that analogous secondary weak interactions occur in many crystals. As a rule, they form after saturation of H-bonds, i.e., when active atoms or ions are completely incorporated into H-bonds, secondary weak interactions by S(1) do not form. An example is the structure of **2**, where all active atoms are incorporated into H-bonds and S(1) participates in no weak interaction.

A pair of intermolecular weak S(1)...O(9) interactions between two thiamine cations related by a crystallographic center forms in anhydrous TCl crystal [11].

The observed weak interactions of S(1) can play a key role in thiamine catalysis of α-ketoacids. An x-ray crystal structure study of the thiamine-dependent enzyme pyruvate dehydrogenase (2.3 Å resolution) [12] indicates that the hydrophobic portion of cocarboxylase (coenzyme), which includes S(1) and C(2)—H(2), is situated outside the enzyme and is available for substrate approach. If weak interactions are included in the mechanism of enzymatic conversion of α-ketoacids, then it can be assumed that the initial catalytic step includes formation of a complex of α-ketoacids with thiamine according to one of the models:



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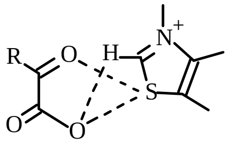
or



2

The compatibility of the S(1)—C(2)—H(2) configuration of the thiazole ring and the configuration of α-ketoacids indicates that two weak interactions may form simultaneously between the thiazole substituent and the α-ketoacid in enzymatic conversions of α-ketoacids. This condition agrees with the key—lock model of enzymatic substrate conversions.

EXPERIMENTAL

Crystals of **1** are monoclinic, at room temperature $a = 12.348(2)$, $b = 24.852(3)$, $c = 11.682(2)$ Å, $\beta = 113.67(2)°$, $V = 3283(2)$ Å^3, ρ(calc.) = 1.42 g/cm^3, $Z = 4$, space group $P2_1/c$. Intensities of 3283 reflections with $I > 2\sigma(I)$ were measured on a Siemens P3/PC automated diffractometer [Mo Kα-radiation, graphite monochromator, $\Theta/2\Theta$-scanning, μ(Mo Kα) = 26.4 cm^{-1}, $2\Theta_{max} = 64°$]. The structure was solved by direct methods. All calculations were performed using SHELXTL-PLUS/PC programs without absorption corrections. Nonhydrogen atoms were refined by full-matrix least-squares methods. Of the two crystallographically independent waters of crystallization, one is disordered over two equally occupied positions. The positions of this water [$O(1)_w$ and $O(2)_w$] were refined isotropically. Atoms O(9A), O(9B), C(7A), and C(8A) of the hydroxyethyl group have comparatively large thermal parameters. Positional disordering of these atoms was not found.

Interatomic distances obtained for the hydroxyethyl groups differ from the statistical average for the corresponding bond lengths. The H atoms of the thiamine OH and the water molecules could not be located. The positions of the remaining H atoms were found in an electron-density difference synthesis. The final discrepancy factors were $R = 0.072$ and $R_w = 0.076$ (unit-weighting scheme).

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