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Structure of Thiamine Bromide Sesquihydrate

BY NING-HAI HU*

Changchun Institute of Applied Chemistry, Chinese Academy of Sciences, Changchun 130022, People's Republic of China

AND SUI-LI ZHANG

Jilin Institute of Biology, Changchun 130012, People's Republic of China

Abstract. 3-[(4-Amino-2-methyl-5-pyrimidinyl)-methyl]-5-hydroxyethyl-4-methylthiazolium bromide sesquihydrate, $C_{12}H_{17}N_4OS^+.Br^-.1.5H_2O$, $M_r = 372.28$, monoclinic, $P2_1/a$, $a = 11.676$ (2), $b = 24.819$ (7), $c = 12.344$ (3) Å, $\beta = 113.74$ (2)°, $V = 3274$ (1) Å^3, $Z = 8$, $D_x = 1.51$ g cm^{-3}, λ(Mo $K\alpha$) = 0.71069 Å, $\mu = 26.2$ cm^{-1}, $F(000) = 1528$, $T = 293$ K, $R = 0.062$ for 2720 observed reflections. Both the independent thiamine molecules A and B in the asymmetric unit adopt the common F conformation. A bromide anion is held by four neighbouring thiamine molecules through C(2)—H···Br hydrogen bonds and Br···thiazolium-ring electrostatic interactions. Another bromide anion (or a water molecule) bridges the pyrimidine and thiazolium moieties of molecule A (or B) through a hydrogen bond with the amino group and an electrostatic interaction with the thiazolium ring.

Introduction. The pyrophosphate of thiamine is a coenzyme in a number of important enzymes which include the α-keto acid decarboxylases and the transketolases. Thiamine C(2) adducts are intermediates in a proposed mechanism for thiamine action (Breslow, 1958). X-ray studies on the thiamine–anion compounds show that a thiamine molecule captures an anion in the vicinity of the C(2) catalytic site *via* both hydrogen-bond and electrostatic interactions, serving as a model of coenzyme–substrate interactions in the enzyme systems (Aoki & Yamazaki, 1985; Aoki, Yamazaki, Waragai & Itokawa, 1988). The crystal structure of thiamine bromide sesquihy- drate reported here is an additional example of such a thiamine–anion complexation.

Experimental. Thiamine.Br.1.5H$_2$O was prepared by mixing aqueous solutions of thiamine.Cl.HCl and NaBr in a 1:2 molar ratio and adjusting the pH to 7 with dilute NaOH solution. Colourless tabular crys- tals formed after a few weeks. A crystal of dimen- sions $0.15 \times 0.51 \times 0.52$ mm was used for data collection on a Nicolet $R3m$ diffractometer, with graphite-monochromated Mo $K\alpha$ radiation. Cell parameters were determined from a least-squares fitting of diffractometer setting angles for 21 centred reflections ($10 < 2\theta < 28°$). Data were collected using ω scans, scan speed 5.88° min^{-1}, scan width 1.25°, 2θ range 3–42°, and h $-11 \rightarrow 10$, k $0 \rightarrow 29$, l $0 \rightarrow 14$. A total of 3811 unique reflections were measured, of which 2720 with $I > 2\sigma(I)$ were used in the refinement. One standard reflection showed no sig- nificant intensity variation. Lp and empirical absorp- tion corrections (maximum and minimum trans- mission coefficients 0.99 and 0.47) were applied. The structure was solved by the heavy-atom method and refined by block-diagonal least squares on F. The hydroxyethyl side chain of a thiamine molecule and a water molecule were disordered, with each atom in two positions. The occupancy factors were estimated on the basis of their electron densities. The non-H atoms were refined anisotropically, except the minor disordered ones which refined isotropically. The positions of 29 of the 40 H atoms were determined from a difference map and their stereo- chemistry, and fixed in the final cycles of the refinement ($U = 0.06$ Å^2). $R = 0.062$, $wR = 0.080$, S

Table 1. *Atomic coordinates and isotropic/equivalent isotropic thermal parameters* ($\AA^2$) *with e.s.d.'s in parentheses*

Disordered atoms are indicated with an asterisk and have occupancy factors 0.70 for C(51B), C(52B), O(53B) and O($W3$), and 0.30 for C(51′B), O(53′B) and O($W3$′), which were refined with isotropic thermal parameters. U_{eq} is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U_{iso}/U_{eq}
Br(1)	0.44501 (8)	0.27574 (4)	1.19675 (7)	0.0544 (4)
Br(2)	0.0584 (1)	0.05601 (4)	0.7809 (1)	0.0831 (6)
O($W1$)	0.2983 (6)	0.3998 (3)	0.5770 (6)	0.086 (4)
O($W2$)	0.5521 (9)	0.0673 (4)	0.4770 (8)	0.147 (6)
O($W3$)*	−0.193 (1)	0.4313 (6)	0.0175 (9)	0.134 (7)
O($W3$′)*	−0.112 (2)	0.4157 (9)	−0.054 (2)	0.091 (7)
N(1′A)	0.0389 (7)	0.3285 (3)	0.8917 (5)	0.057 (3)
C(2′A)	0.1069 (7)	0.3251 (3)	0.8288 (6)	0.052 (3)
N(3′A)	0.1424 (6)	0.2799 (2)	0.7930 (5)	0.048 (3)
C(4′A)	0.1086 (7)	0.2335 (3)	0.8247 (6)	0.041 (3)
C(5′A)	0.0360 (7)	0.2319 (3)	0.8932 (6)	0.039 (3)
C(6′A)	0.0043 (8)	0.2812 (3)	0.9221 (6)	0.053 (4)
C(21′A)	0.1496 (9)	0.3774 (4)	0.7941 (7)	0.068 (4)
N(41′A)	0.1451 (7)	0.1892 (3)	0.7871 (6)	0.059 (3)
C(35′A)	−0.0035 (7)	0.1811 (3)	0.9330 (6)	0.044 (3)
S(1A)	0.2950 (2)	0.1505 (1)	1.2217 (2)	0.065 (1)
C(2A)	0.2047 (7)	0.1833 (3)	1.0993 (6)	0.045 (4)
N(3A)	0.0983 (6)	0.1586 (2)	1.0427 (5)	0.037 (3)
C(4A)	0.0814 (7)	0.1118 (3)	1.0950 (6)	0.041 (3)
C(5A)	0.1830 (8)	0.1020 (3)	1.1945 (7)	0.058 (4)
C(41A)	−0.0368 (8)	0.0815 (3)	1.0446 (7)	0.061 (4)
C(51A)	0.2080 (9)	0.0549 (4)	1.2813 (8)	0.070 (5)
C(52A)	0.2707 (9)	0.0116 (4)	1.2473 (9)	0.080 (5)
O(53A)	0.3873 (7)	0.0262 (4)	1.2521 (8)	0.133 (5)
N(1′B)	0.4023 (6)	0.1532 (3)	0.5281 (5)	0.060 (3)
C(2′B)	0.3325 (8)	0.1544 (4)	0.5904 (6)	0.060 (4)
N(3′B)	0.2869 (6)	0.1978 (3)	0.6225 (5)	0.053 (3)
C(4′B)	0.3146 (7)	0.2465 (3)	0.5887 (6)	0.049 (4)
C(5′B)	0.3854 (7)	0.2497 (4)	0.5200 (6)	0.049 (4)
C(6′B)	0.4276 (7)	0.2015 (4)	0.4938 (6)	0.053 (4)
C(21′B)	0.3009 (9)	0.1018 (4)	0.6304 (8)	0.078 (5)
N(41′B)	0.2691 (6)	0.2897 (3)	0.6212 (6)	0.059 (3)
C(35′B)	0.4213 (7)	0.3015 (3)	0.4814 (6)	0.053 (4)
S(1B)	0.1099 (2)	0.3431 (1)	0.2175 (2)	0.063 (1)
C(2B)	0.2077 (5)	0.3042 (3)	0.3246 (6)	0.047 (3)
N(3B)	0.3160 (4)	0.3272 (3)	0.3809 (4)	0.044 (3)
C(4B)	0.3247 (8)	0.3784 (4)	0.3388 (7)	0.055 (4)
C(5B)	0.2180 (8)	0.3942 (4)	0.2496 (7)	0.065 (4)
C(41B)	0.4482 (9)	0.4077 (4)	0.3921 (8)	0.077 (5)
C(51B)*	0.177 (2)	0.4524 (4)	0.193 (1)	0.073 (9)
C(51′B)*	0.205 (3)	0.439 (1)	0.164 (3)	0.04 (1)
C(52B)*	0.142 (1)	0.4445 (5)	0.058 (1)	0.066 (6)
C(52′B)*	0.120 (3)	0.476 (1)	0.205 (3)	0.07 (1)
O(53B)*	0.0242 (8)	0.4169 (3)	0.0037 (8)	0.075 (4)
O(53′B)*	0.010 (2)	0.450 (1)	0.164 (2)	0.097 (8)

$= 1.61$, where $w = 1/[\sigma^2(F_o) + 0.0014(F_o)^2]$; $(\Delta/\sigma)_{max} = 0.08$; maximum and minimum heights in final difference map 0.69 and -0.52 e $\AA^{-3}$, respectively. Final atomic coordinates with their e.s.d.'s are listed in Table 1.* Atomic scattering factors were taken from *International Tables for X-ray Crystallography* (1974, Vol. IV). All calculations were performed using the *SHELXTL* program system (Sheldrick, 1983).

Discussion. Bond distances and angles are listed in Table 2. The molecular structure is shown in Fig. 1

* Lists of structure factors, anisotropic thermal parameters, H-atom coordinates and hydrogen bonds have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 55209 (29 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England. [CIF reference: AS0586]

Table 2. *Bond distances* ($\AA$), *bond angles* (°), *and selected hydrogen-bond lengths* ($\AA$), *with e.s.d.'s in parentheses*

Thiamine molecules	A	B
N(1′)—C(2′)	1.32 (1)	1.33 (1)
C(2′)—N(3′)	1.33 (1)	1.33 (1)
N(3′)—C(4′)	1.33 (1)	1.36 (1)
C(4′)—C(5′)	1.42 (1)	1.41 (1)
C(5′)—C(6′)	1.37 (1)	1.38 (1)
C(6′)—N(1′)	1.34 (1)	1.34 (1)
C(2′)—C(21′)	1.51 (1)	1.49 (1)
C(4′)—N(41′)	1.33 (1)	1.33 (1)
C(5′)—C(35′)	1.49 (1)	1.49 (1)
C(35′)—N(3)	1.504 (8)	1.494 (8)
S(1)—C(2)	1.666 (7)	1.663 (6)
C(2)—N(3)	1.307 (9)	1.304 (7)
N(3)—C(4)	1.38 (1)	1.39 (1)
C(4)—C(5)	1.342 (9)	1.35 (1)
C(5)—S(1)	1.710 (9)	1.719 (9)
C(4)—C(41)	1.47 (1)	1.51 (1)
C(5)—C(51)	1.53 (1)	1.59 (1)
C(51)—C(52)	1.45 (2)	1.56 (2)
C(52)—O(53)	1.39 (1)	1.44 (2)
C(5)—C(51′)		1.50 (3)
C(51′)—C(52′)		1.58 (5)
C(52′)—O(53′)		1.35 (4)
N(1′)—C(2′)—N(3′)	126.2 (8)	127.1 (8)
C(2′)—N(3′)—C(4′)	117.7 (8)	117.1 (8)
N(3′)—C(4′)—C(5′)	121.4 (7)	120.4 (8)
C(4′)—C(5′)—C(6′)	114.8 (7)	116.4 (8)
C(5′)—C(6′)—N(1′)	124.5 (9)	123.8 (9)
C(6′)—N(1′)—C(2′)	115.5 (7)	115.2 (8)
N(1′)—C(2′)—C(21′)	117.3 (8)	117.6 (8)
N(3′)—C(2′)—C(21′)	116.5 (8)	115.3 (9)
N(3′)—C(4′)—N(41′)	116.1 (8)	116.9 (8)
C(5′)—C(4′)—N(41′)	122.5 (7)	122.7 (8)
C(4′)—C(5′)—C(35′)	124.0 (7)	123.5 (8)
C(6′)—C(5′)—C(35′)	121.2 (8)	120.0 (9)
C(5′)—C(35′)—N(3)	111.9 (6)	113.0 (6)
C(35′)—N(3)—C(2)	122.9 (6)	123.6 (6)
C(35′)—N(3)—C(4)	121.5 (6)	122.7 (6)
S(1)—C(2)—N(3)	112.0 (6)	112.2 (6)
C(2)—N(3)—C(4)	115.4 (5)	113.7 (5)
N(3)—C(4)—C(5)	109.9 (7)	112.8 (7)
C(4)—C(5)—S(1)	112.1 (7)	109.1 (7)
C(5)—S(1)—C(2)	90.7 (4)	92.3 (4)
N(3)—C(4)—C(41)	121.2 (6)	118.5 (6)
C(5)—C(4)—C(41)	128.8 (8)	128.7 (9)
S(1)—C(5)—C(51)	119.1 (6)	120.5 (7)
C(4)—C(5)—C(51)	128.9 (8)	129.5 (9)
C(5)—C(51)—C(52)	109.7 (9)	105.0 (9)
C(51)—C(52)—O(53)	113.3 (9)	111 (1)
S(1)—C(5)—C(51′)		122 (1)
C(4)—C(5)—C(51′)		126 (1)
C(5)—C(51′)—C(52′)		96 (3)
C(51′)—C(52′)—O(53′)		104 (3)

C(2A)	Br(1)	3.444 (8)	C(2B)	Br(1^i)	3.455 (6)
N(41′A)	N(3′B)	3.10 (1)	N(41′B)	N(3′A)	3.05 (1)
N(41′A)	Br(2)	3.449 (7)	N(41′B)	O($W1$)	2.834 (9)

Symmetry code: (i) $x - \frac{1}{2}, \frac{1}{2} - y, z - 1$.

and crystal packing in Fig. 2. The asymmetric unit contains two independent chemical units. The dimensions of the thiamine molecules resemble those of other unprotonated forms of thiamine (Pletcher, Sax, Sengupta, Chu & Yoo, 1972; Aoki, Hu, Yamazaki & Adeyemo, 1990). Both thiamine molecules A and B assume the usually observed F conformation as defined by Pletcher, Sax, Blank & Wood (1977); the torsion angles are $\varphi_T[C(5')—C(35')—N(3)—C(2)] = 4.4$ (11) (A) and -6.8 (11)° (B), and $\varphi_P[N(3)—C(35')—C(5')—C(4')] = 82.0$ (8) (A) and -76.6 (9)° (B). The hydroxyethyl side chain folds back toward the thiazolium moiety with a short contact: O(53A)···S(1A) = 3.241 (9),   O(53B)···S(1B) =

3.034 (9) and O(53'B)···S(1B) = 2.87 (3) Å [sum of van der Waals radii for O···S = 3.32 Å (Bondi, 1964)].

The interactions between a thiamine molecule and an anion which forms a hydrogen bond with the C(2)H and electrostatic contacts with the electropositive S(1) and the pyrimidine ring have been suggested to have mechanistic importance for substrate fixation near the C(2) site (Aoki & Yamazaki, 1985). In the present structure, the Br(1) interacts simultaneously with A and B ($\frac{1}{2}$ + x, $\frac{1}{2}$ − y, 1 + z) via C(2)—H···Br(1) hydrogen bonds and S(1)···Br(1) close contacts [3.640 (3) (A) and 3.474 (3) Å (B); sum of van der Waals radii for S···Br = 3.65 Å (Bondi, 1964)]. There are no anion–pyrimidine stacking contacts, however, as illustrated by the long perpendicular distances from Br(1) to pyrimidine rings
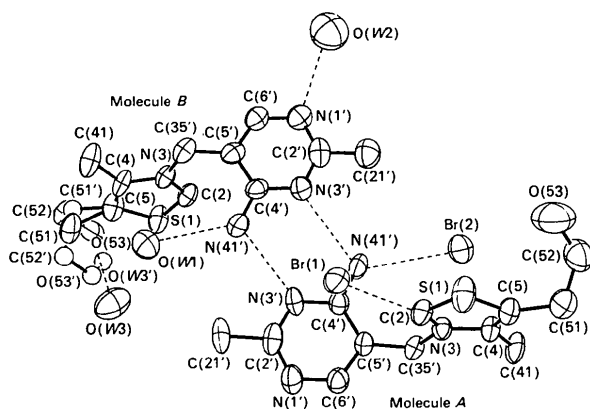

Fig. 1. Molecular structure of thiamine.Br.1.5H$_2$O. Circles denote the minor disordered positions. Hydrogen bonds are indicated by dashed lines.
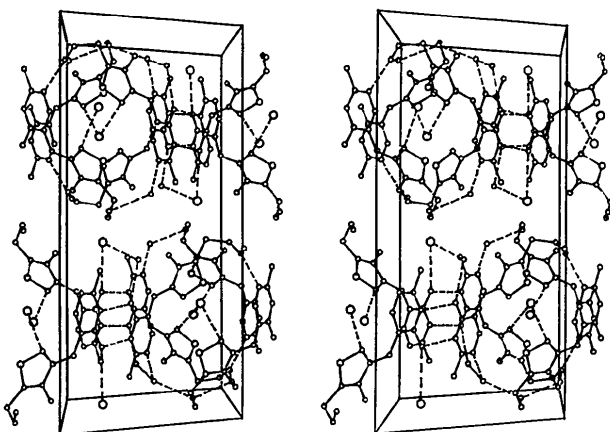

Fig. 2. Stereoscopic view of the crystal packing viewed down the a axis. Dashed lines indicate the hydrogen bonds. The minor disordered positions are ignored for clarity.

[4.654 (1) (A) and 5.020 (1) Å (B)], although such a contact has been observed in many thiamine structures, e.g. thiaminium.Br$_2$.$\frac{1}{2}$H$_2$O (Thompson & Richardson, 1977), thiamine.SCN, thiamine.BF$_4$.H$_2$O (Aoki, Hu, Yamazaki & Adeyemo, 1990) and thiaminium.(NO$_3$)$_2$ (Yang, Pletcher, Rose, Yoo, Furey, Wang & Sax, 1987). It is interesting to note that the Br(1) also participates in electrostatic interactions with the other two thiazolium moieties of the neighbouring molecules A ($\frac{1}{2}$ + x, $\frac{1}{2}$ − y, z) and B (x, y, 1 + z), the closest contact being with the cationic quarternary nitrogen N(3) [3.495 (7) (A) and 3.440 (6) Å (B)]. In other words, the four thiamine molecules hold the anion Br(1) in a cage formed by them. Another noteworthy structural feature is the formation of an anion bridge between the pyrimidine and thiazolium rings. The Br(2) bridges the pyrimidine and thiazolium rings of A by forming a hydrogen bond with the amino group N(41'A) and an electrostatic interaction with the thiazolium ring [perpendicular distance Br(2)···thiazolium A = 3.445 (1) Å]. In a similar manner, the O(W1) bridges the two aromatic rings of B [perpendicular distance O(W1)···thiazolium B = 2.919 (8) Å]. This type of thiamine–anion (or electronegative atom) interaction, which widely exists in the thiamine compounds, has been considered to be an important factor affecting the conformation of thiamine (Cramer, Kirkup & Carrie, 1988; Archibong, Adeyemo, Aoki & Yamazaki, 1989). The F conformation is favoured by smaller anionic groups because of the reduced steric effect (Hu, 1991).

There are two types of interbase interactions: a base pair formed between A and B via a pair of N(41')—H···N(3') hydrogen bonds (Fig. 1) and a base–base stacking between A and B (x − $\frac{1}{2}$, $\frac{1}{2}$ − y, z) with an average spacing of 3.43 (2) Å. Although the H atoms were not located, it is likely that O(W3) is hydrogen bonded to O(53B) while O(W3') is hydrogen bonded to O(53'B). Thus the disorder reflects crystal-packing requirements.

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Structure of (17α)-Androstano[3,4-c][1,2,5]oxadiazole-17-ol (HS963)

BY DOMINIQUE MAES, PETER FIDDELAERS, LODE WYNS AND JOHN LISGARTEN

Department of Ultrastructure, Instituut voor Molekulaire Biologie, Vrije Universiteit Brussel, Paardenstraat 65, B-1640 Sint-Genesius Rode, Belgium

AND DAVID LISGARTEN AND REX PALMER

Department of Crystallography, Birkbeck College, University of London, Malet Street, London WC1E 7HX, England

Abstract. $C_{19}H_{28}N_2O_2$, $M_r = 316$, orthorhombic, $P2_12_12_1$, $a = 10.231$ (7), $b = 11.171$ (7), $c = 14.759$ (5) Å, $V = 1687$ Å^3, $Z = 4$, $D_x = 1.24$ g cm^{-3}, $\lambda(\text{Cu } K\alpha) = 1.5418$ Å, $\mu = 5.57$ cm^{-1}, $F(000) = 688$, room temperature, $R = 0.055$ for 3179 observed reflections. Ring A is strained and rings B and C are in chair conformations. Ring D has an intermediate envelope–half-chair conformation. The oxadiazole ring is planar.

Introduction. Medicinal chemists have modified the structure of testosterone in various ways (Drill & Riegel, 1958) with the object of increasing the anabolic (nitrogen retention) propensity and decreasing its effect as a male hormone. This assumes that the target receptors associated with these two effects are sufficiently different to be sensitive to small changes in the structure of the drug molecule and to react accordingly. One successful approach has been to introduce different *A*-ring fused heterocycles [see, for example, Clinton *et al.* (1961), Ohta, Takegoshi, Veno & Shimizu (1965) and Kasahara, Ondera, Mogi, Oshima & Shimizu (1965)]. The title compound (HS963), depicted in Fig. 1, was prepared during the course of work on the synthesis of steroid oxadiazoles (Singh, Yadav & Jindal, 1987). We have determined the structure of HS963 in order to study the effect of the 5-en-oxadiazole system on the steroid skeleton and to clarify some conformational aspects for future structure–function studies.

Experimental. Crystallization from ethanol gave colourless needles; a specimen $0.8 \times 0.2 \times 0.1$ mm was used for data collection. Preliminary Weissen-

berg photographs yielded approximate cell dimensions and showed orthorhombic (*mmm*) symmetry. Space group $P2_12_12_1$ was determined unambiguously from systematic absences ($h00$, $h = 2n + 1$; $0k0$, $k = 2n + 1$; $00l$, $l = 2n + 1$). Data were collected on an Enraf–Nonius CAD-4 automated diffractometer, with graphite monochromator, Cu $K\alpha$ radiation, ω–2θ scans [scan width $(0.85 + 0.15\tan\theta)°$], and vertical aperture 4 mm. 25 high-angle reflections ($25 < 2\theta < 28°$) were used to obtain accurate cell dimensions by least-squares fit. 3179 unique reflections ($3 < \theta < 69°$) were measured ($-12 < h < 12$, $1 < k < 8$, $0 < l < 17$). Three intensity standards (220, 200, 008) monitored at intervals of 100 measurements showed no significant variations during data collection. Intensity data were corrected for Lorentz–polarization factors. An empirical absorption correction was applied, based on φ scans for each of three reflections (North, Phillips & Mathews, 1968) for $\chi = 90°$ measured at 10° intervals from $\varphi = 0$–360°; normalized transmission factors were 0.82 to 0.91. $R_{int} = 0.027$. Structure solution was by direct methods using *SHELX*76 (Sheldrick, 1976). Refinement was by full-matrix least squares with
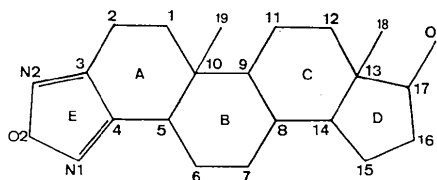

Fig. 1. Structural formula and numbering scheme. The numbers refer to C atoms unless otherwise indicated.