

tween potential energy minima cannot be ruled out by the use of X-ray diffraction.

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## The Crystal and Molecular Structure of Thiamine Chloride Monohydrate

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The crystal structure of thiamine chloride monohydrate ( $C_{12}H_{17}ClN_4OS \cdot H_2O$ ) has been determined from three-dimensional diffractometer data. The crystals are monoclinic, space group  $P2_1/c$ , with four molecules in the unit cell;  $a = 8.914$  (3),  $b = 16.775$  (3),  $c = 10.405$  (1) Å,  $\beta = 94.28$  (2)°. The structure was refined by the full-matrix least-squares technique to a final  $R$  value of 0.033 for the 2368 observed reflections. The conformation found for the free base of thiamine is very similar to that which is observed for the protonated form. The absence of the proton on the pyrimidine ring reduces the latter's 'quinoidal' character, but the bond to the amino group, although longer in the unprotonated compound, still exhibits considerable double-bond character.

### Introduction

The pyrophosphate ester of thiamine is a coenzyme for a number of different enzyme systems. Since thiamine alone catalyzes many of the same reactions as the enzyme systems, we have been studying thiamine and its derivatives in an effort to correlate its structural features with its chemical properties. The present structure, which contains the free base of thiamine, is the only one studied in which the pyrimidine ring is not protonated.

### Experimental

The free base of thiamine was prepared by titrating a 2M solution of thiamine chloride hydrochloride (Eastman Organic Chemicals) with sodium hydroxide to pH 8. The compound was crystallized by adding an equal volume of acetone to the resulting 1M solution and then maintaining it at approximately  $-15^\circ\text{C}$ . Colorless, tabular crystals grew slowly over several days' time. The space group was determined from Weissenberg photographs. The unit-cell parameters were determined from the axial reflections using a Picker four-circle diffractometer with Cu  $K\alpha$  radiation. The  $\alpha_1$  peak was used whenever the  $\alpha_1\alpha_2$  doublet was resolved. The e.s.d.'s are the r.m.s. deviations for the various determinations of the cell parameters. The crystal data are summarized in Table 1.

Table 1. *Crystal data*

Thiamine chloride monohydrate	$C_{12}H_{17}ClN_4OS \cdot H_2O$
M.W. 318.83	Data measured at ambient temperature, $22^\circ\text{C}$
$a = 8.914$ (3) Å	$\lambda(\text{Cu } K\alpha_1\alpha_2) = 1.54178$ Å
$b = 16.775$ (3)	$\lambda(\text{Cu } K\alpha_1) = 1.54051$
$c = 10.405$ (1)	$Z = 4$
$\beta = 94.28$ (2)°	Systematic absences $h0l \quad l = 2n + 1$
$V = 1551.55$ Å <sup>3</sup>	$0k0 \quad k = 2n + 1$
Space group $P2_1/c$	
$F(000) = 672$	
$\mu(\text{Cu } K\alpha) = 34.47$ cm <sup>-1</sup>	
$\rho_o = 1.361$ g.cm <sup>-3</sup> (by flotation in benzene- $\text{CCl}_4$ )	
$\rho_c = 1.365$	
M.p. $194\text{--}196^\circ\text{C}$ unc. (Thermolyne melting point apparatus)	
begins losing water of hydration at $\sim 110^\circ\text{C}$	

Coordinates of crystal corners ( $\times 10^5$ ) in cm in reference coordinate system:

$X$  along  $-c^*$ ,  $Y$  along  $a$ ,  $Z$  along  $-b^*$ .

$X$	$Y$	$Z$	$X$	$Y$	$Z$
1453	108	2540	2830	734	318
-922	-68	2540	2102	679	1497
-1572	404	1497	-1572	-640	1497
-2830	312	-527	-2830	-734	-527
-2217	357	-1497	-2217	-688	-1497
-1568	-117	-2540	1696	-396	-1497
1045	78	-2540	2830	-312	318
1696	648	-1497	2102	-366	1497

The intensity data were collected (Shiono, 1968a) from a crystal that was mounted about the  $b$  axis

having the approximate dimensions  $0.1 \times 0.5 \times 0.5$  mm along the  $a$ ,  $b$  and  $c$  axes. The data were obtained on a Picker four-circle diffractometer equipped with a thallium activated sodium iodide scintillation detector using Ni-filtered Cu radiation. Within the range of  $\sin \theta < 0.909$ , 2660 unique reflections in one quadrant were measured using the  $2\theta$  scan technique at a scan rate of  $1^\circ$  per min over a  $2^\circ$  range. The background was measured for 30 sec at each end of the scan range. For 285 reflections the integrated intensity was less than  $3\sigma(I)$ , where  $\sigma(I) = [I' + 4(b_1 + b_2)]^{1/2}$ ;  $I'$  is the total number of counts accumulated during the scan;  $b_1$  and  $b_2$  are the background counts. These reflections were considered unobserved. Later in the analysis, four of the unobserved reflections were continually being calculated significantly above their observed values. Remeasurement of these reflections revealed that the original ones were in error. The redetermined values were used for the remainder of the analysis. During the data collection seven standard reflections were monitored regularly; at least two were measured at two hour intervals and all seven were measured at least once every 24 hours. Over the course of the data collection, which lasted 10 days, the standard reflections showed systematic fluctuations of  $\pm 2\%$ . The variation in the standard reflections was used to place the intensity data on a uniform scale. The integrated intensities were reduced to their structure amplitudes using the proper Lorentz and polarization factors (Shiono, 1968*b*). The dimensions of the crystal faces were measured using a binocular microscope with a calibrated grid for which one division equals  $0.00095$  cm. An absorption correction was calculated (Craven, 1963) and applied to the data in the final stages of the refinement. An experimental estimation of the relative absorption was obtained from measurements of the  $0k0$  reflections ( $k=4, 8, 14$ ) at  $10^\circ$  intervals in  $\varphi$  over a range of  $180^\circ$ . The relative intensities of these three reflections decreased maximally by a factor of 0.65, 0.61 and 0.51 respectively. The relative intensities as a function of  $\varphi$ , which were obtained from the calculated absorption corrections, agree on average within 0.03 (largest difference is 0.06). The absorption corrections that were applied to the structure amplitudes had an average value of 1.32, with the maximum and minimum values of 1.831 and 1.182 respectively.

#### Structure determination and refinement

The structure was solved and refined using the X-ray 67 and X-ray 70 system of computer programs (Stewart, 1967; Stewart, Kundell & Baldwin, 1970). The amplitudes of the normalized structure factors were derived and approximately placed on an absolute scale using the *DATFIX* program. Utilization of the program *PHASE* resulted in the determination of signs for 306 reflections. The  $E$  map (Karle, Hauptman, Karle & Wing, 1958) calculated with these coefficients contained recognizable peaks for all 20 nonhydrogen atoms. The

initial  $R$  index,  $R = \sum(|F_o| - |F_c|) / \sum|F_o|$ , based on these positions was 0.49. Three cycles of isotropic, full-matrix least-squares refinement (*ORFLS*) reduced the  $R$  value to 0.168 and two cycles of anisotropic refinement lowered it to 0.102. The function minimized in the refinement was  $\sum w(|F_o| - k|F_c|)^2$  where  $k$  is a single scale factor. The positions of the 17 hydrogen atoms were located in a difference Fourier map and were included and refined at this time. Since the effects of absorption were apparent, the absorption corrected data were used in the subsequent refinement. Refinement (*CRYLSQ*) of the nonhydrogen atoms lowered  $R$  to 0.058. When the hydrogen parameters (positional and isotropic thermal) were also refined, the refinement converged to an  $R$  of 0.033 for the 2368 observed reflections and an  $R$  of 0.038 over all 2660 reflections. In the final cycle of refinement the average shift/error for all the nonhydrogen atoms was 0.19. Five of the parameters (four of which were thermal parameters) had shifted by more than one e.s.d. with the largest being 1.30 e.s.d. The  $z$  coordinate for the water molecule, O(19), had also shifted by 1.17 e.s.d. The anomalous dispersion corrections for Cl and S were included in the later stages of the refinement. The final weighting scheme used in the refinement was defined by  $w = 1/\sigma^2$  where  $\sigma^2 = A + B\sigma^2(|F_o|) + D|F_o| + E|F_o|^2$ ;  $A = 0.1$ ,  $B = 10.0$ ,  $D = 0.005$ ,  $E = 0.0003$ ,  $\sigma(|F_o|)$  is the standard deviation in  $|F_o|$  based on counting statistics and is given by  $(k/2LpF_o)\sigma(I)$ . The unobserved reflections plus an additional eleven which were affected by extinction were given zero weight in the refinement. The atomic scattering factors for Cl<sup>-</sup>, S, O, N and C are from Cromer & Waber (1965); the scattering factor for H is from Stewart, Davidson & Simpson (1965). The  $\Delta f'$  and  $\Delta f''$  values for Cl and S are from Cromer (1965). The final atomic parameters are listed in Table 2 and the structure factors are presented in Table 3. The atomic numbering scheme is given in Fig. 1. The final difference Fourier map is relatively clean. There is a residual positive density ranging between 0.05 and 0.1 e.Å<sup>-3</sup> along the bonds between most of the atoms in the structure. The highest peak in the map is 0.20 e.Å<sup>-3</sup> at a distance of approximately 1 Å from the water molecule O(19). This could be disordered hydrogen but it does not seem very likely since a hydrogen bond acceptor is not available. The difference map does give some indication of 'rotational' disorder in the C(14) methyl group. There are three peaks, all approximately 1 Å from C(14), which have electron densities between 0.10 and 0.18 e.Å<sup>-3</sup>. Each of these peaks is related to one of the hydrogen atoms H(141), H(142), H(143) by a twofold axis along the C(10)–C(14) bond. The locations of the three hydrogen atoms are at zero electron density on the difference map. However, since their isotropic thermal parameters were refined, the lower electron density could be accommodated by higher thermal factors which are actually observed. Similarly, the C(15) methyl group shows some tendency for disorder although the evidence is much weaker.

Table 2. *Positional and thermal parameters*

Positions are designated in fractional coordinates of unit-cell axes and the thermal vibration coefficients are for the expression  
 $\exp \{-2\pi^2 (h^2 a^2 U_{11} + k^2 b^2 U_{22} + l^2 c^2 U_{33} + 2hka^* b^* U_{12} + 2hla^* c^* U_{13} + 2klb^* c^* U_{23}) \sin^2 \theta / \lambda^2\}$ .

(a) Nonhydrogen atoms. All values  $\times 10^4$ ; estimated standard deviations in parentheses.

	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> <sub>11</sub>	<i>U</i> <sub>22</sub>	<i>U</i> <sub>33</sub>	<i>U</i> <sub>12</sub>	<i>U</i> <sub>13</sub>	<i>U</i> <sub>23</sub>
S(1)	6695 (0.6)	888 (0.4)	5897 (0.5)	488 (3)	716 (4)	579 (3)	25 (3)	161 (2)	-142 (3)
C(2)	4934 (2)	1226 (1)	5859 (2)	492 (11)	505 (11)	408 (10)	-15 (9)	89 (8)	-21 (8)
N(3)	4582 (2)	1498 (1)	6979 (1)	448 (8)	349 (7)	398 (7)	0 (6)	81 (6)	-1 (6)
C(4)	5741 (2)	1444 (1)	7949 (2)	505 (10)	349 (9)	433 (9)	9 (8)	39 (8)	3 (8)
C(5)	6998 (2)	1118 (1)	7517 (2)	463 (10)	409 (10)	574 (12)	-37 (8)	44 (9)	-40 (8)
C(6)	3073 (2)	1838 (1)	7208 (2)	487 (10)	396 (10)	487 (10)	64 (8)	95 (8)	-45 (8)
C(7)	1992 (2)	1801 (1)	6045 (2)	429 (10)	365 (9)	487 (10)	35 (8)	89 (8)	7 (8)
C(8)	1252 (2)	1093 (1)	5626 (2)	406 (9)	375 (9)	480 (10)	22 (8)	117 (8)	40 (8)
N(9)	256 (2)	1098 (1)	4584 (2)	431 (8)	377 (8)	579 (9)	-3 (7)	45 (7)	60 (7)
C(10)	16 (2)	1791 (1)	3966 (2)	419 (10)	427 (10)	627 (12)	24 (8)	53 (9)	87 (9)
N(11)	650 (2)	2487 (1)	4286 (2)	562 (10)	376 (9)	726 (11)	-6 (8)	-57 (9)	107 (8)
C(12)	1626 (2)	2470 (1)	5334 (2)	518 (11)	348 (10)	686 (13)	-14 (9)	27 (10)	24 (9)
N(13)	1496 (2)	393 (1)	6221 (2)	641 (11)	374 (8)	560 (10)	-30 (8)	-26 (8)	72 (7)
C(14)	-1078 (4)	1773 (2)	2803 (3)	632 (16)	568 (15)	809 (18)	-42 (13)	-166 (14)	157 (13)
C(15)	5523 (3)	1745 (2)	9269 (2)	740 (17)	662 (16)	460 (12)	122 (14)	-2 (12)	-97 (11)
C(16)	8469 (2)	932 (1)	8235 (2)	459 (11)	639 (14)	802 (16)	-12 (10)	-15 (11)	-125 (11)
C(17)	8768 (2)	51 (1)	8375 (2)	548 (12)	713 (15)	624 (13)	117 (11)	-19 (11)	-59 (11)
O(18)	7720 (2)	-323 (1)	9136 (2)	871 (13)	804 (12)	547 (9)	-31 (10)	-26 (9)	12 (8)
O(19)	3333 (3)	63 (1)	8489 (2)	1110 (17)	786 (14)	607 (12)	306 (12)	91 (12)	138 (10)
Cl(20)	4555 (0.7)	1203 (0.3)	2675 (0.5)	898 (4)	632 (3)	489 (3)	31 (3)	48 (3)	-64 (2)

Table 2 (cont.)

(b) Hydrogen atoms. All values  $\times 10^3$ .

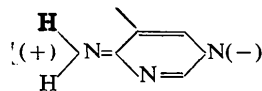
Thermal-vibration coefficients are for the expression  
 $\exp [-(8\pi^2 U) \sin^2 \theta / \lambda^2]$ .

	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i>
H(21)	422 (3)	119 (1)	515 (2)	53 (8)
H(61)	324 (2)	237 (1)	747 (2)	44 (6)
H(62)	272 (2)	155 (1)	794 (2)	49 (6)
H(121)	208 (2)	297 (1)	559 (2)	53 (7)
H(131)	205 (3)	36 (1)	692 (2)	52 (9)
H(132)	94 (3)	-4 (1)	593 (2)	64 (8)
H(141)	-111 (3)	225 (2)	235 (3)	104 (9)
H(142)	-200 (5)	166 (2)	300 (4)	155 (17)
H(143)	-64 (5)	139 (3)	219 (4)	159 (17)
H(151)	653 (3)	170 (2)	985 (2)	82 (8)
H(152)	469 (2)	150 (1)	956 (2)	77 (5)
H(153)	520 (3)	230 (2)	927 (2)	96 (8)
H(161)	934 (3)	118 (2)	780 (2)	73 (10)
H(162)	848 (3)	117 (2)	908 (3)	52 (10)
H(171)	989 (3)	-5 (1)	878 (2)	88 (9)
H(172)	872 (3)	-20 (1)	746 (2)	68 (8)
H(181)	711 (3)	-52 (2)	870 (3)	86 (10)
H(191)	378 (4)	-32 (2)	832 (3)	99 (13)
H(192)	300 (4)	2 (2)	908 (3)	116 (15)

### Discussion

The free base of thiamine is the predominant form existing at physiological pH. It is of interest to compare the structure of this form with that of the protonated compound as seen in several different crystal structures (Kraut & Reed, 1962; Karle & Britts, 1966; Pletcher & Sax, 1966, 1972; Carlisle & Cook, 1969). The interatomic distances and angles are presented in Fig. 1. As expected, the removal of the proton at N(11) does influence the bond lengths in the pyrimidine ring. Kraut & Reed (1962) predicted that on deprotonation of the pyrimidine ring, the relative contributions of the

analogous resonance forms would remain unchanged except for the form which would become a minor con-



tributor to the structure. In accordance with the prediction, the bond lengths in the free base for C(7)-C(12), C(8)-N(13) and N(9)-C(10) are significantly longer, while C(7)-C(8), C(8)-N(9), C(10)-N(11) and N(11)-C(12) are all shorter than has been observed in the protonated structures. Nevertheless, considerable double-bond character is still evident in the bond to the pyrimidine amino group. The remaining bonds with a few exceptions are in good agreement with the other structures. The slight shortening of the C(6)-C(7) bond from the average value of 1.505 Å for an  $sp^3-sp^2$  carbon-carbon bond (Bartell & Bonham, 1960) may be significant. Although this shortening may be simply the effect of the thermal motions of the atoms, as is undoubtedly the case for the short C(16)-C(17) and C(17)-O(18) bonds, it is not very likely. In the thiazolium ring the C(2)-N(3) and the S(1)-C(5) bonds exhibit greater variability between structures. The significance of these differences is still uncertain, especially in the absence of thermally corrected bond distances.

Both the pyrimidine and thiazolium rings exhibit a high degree of planarity. The equations of the least-squares planes calculated for the atoms in the rings, and their deviations from the planes are listed in Table 4. The r.m.s. deviations for the planar rings in this structure are smaller by a factor of 0.5 to 0.25 than those observed in the other thiamine structures. How-

Table 3. Observed and calculated structure factors

Columns are  $I$ ,  $10F_0$  and  $10F_c$ . Unobserved reflections are marked by \*. Reflections effected by extinction which were excluded in the refinement are marked with an  $E$ .

$h$	$k$	$l$	$I$	$10F_0$	$10F_c$
0 0 1	0 0 1	0 0 1	2 5286	188	188
0 1 21	0 1 21	0 1 21	1 27	37	37
0 8 88	0 8 88	0 8 88	1 87	83	83
10 77 76	10 77 76	10 77 76	1 77	76	76
0 0 19 L	0 0 19 L	0 0 19 L	6 231	233	233
1 26 23	1 26 23	1 26 23	7 41	50	50
3 63 58	3 63 58	3 63 58	11 18	15	15
0 0 18 L	0 0 18 L	0 0 18 L	0 55	55	55
0 0 6	0 0 6	0 0 6	1 872	891	891
1 114 111	1 114 111	1 114 111	2 384	391	391
2 58 55	2 58 55	2 58 55	3 102	95	95
3 70 66	3 70 66	3 70 66	4 100	105	105
4 61 62	4 61 62	4 61 62	5 251	241	241
5 28 23	5 28 23	5 28 23	7 41	50	50
0 0 17 L	0 0 17 L	0 0 17 L	7 22	217	217
1 53 56	1 53 56	1 53 56	10 11	112	112
2 53 53	2 53 53	2 53 53	11 6	6	6
3 0 5	3 0 5	3 0 5	1 109	114	114
5 56 57	5 56 57	5 56 57	2 666	660	660
6 26 25	6 26 25	6 26 25	3 180	179	179
0 0 16 L	0 0 16 L	0 0 16 L	0 145	145	145
1 87 85	1 87 85	1 87 85	2 88	84	84
2 53 53	2 53 53	2 53 53	3 45	52	52
3 45 52	3 45 52	3 45 52	4 100	102	102
5 10 20	5 10 20	5 10 20	7 18	18	18
7 18 18	7 18 18	7 18 18	10 126	126	126
0 0 15 L	0 0 15 L	0 0 15 L	1 222	124	124
2 45 49	2 45 49	2 45 49	3 33	34	34
4 34 35	4 34 35	4 34 35	5 20	23	23
7 50 57	7 50 57	7 50 57	8 21	20	20
9 28 27	9 28 27	9 28 27	10 441	449	449
1 208 201	1 208 201	1 208 201	12 160	155	155
2 140 145	2 140 145	2 140 145	3 31	33	33
4 46 46	4 46 46	4 46 46	5 99	96	96
7 50 57	7 50 57	7 50 57	8 66	67	67
9 28 27	9 28 27	9 28 27	10 13	13	13
0 0 14 L	0 0 14 L	0 0 14 L	0 441	449	449
1 171 167	1 171 167	1 171 167	2 27	26	26
3 31 31	3 31 31	3 31 31	4 96	94	94
5 99 96	5 99 96	5 99 96	7 48	48	48
8 66 67	8 66 67	8 66 67	9 28	27	27
10 13 13	10 13 13	10 13 13	11 171	167	167
0 0 13 L	0 0 13 L	0 0 13 L	0 145	147	147
1 87 88	1 87 88	1 87 88	2 183	180	180
3 146 146	3 146 146	3 146 146	4 218	216	216
5 18 21	5 18 21	5 18 21	7 79	83	83
8 105 106	8 105 106	8 105 106	10 18	18	18
0 0 12 L	0 0 12 L	0 0 12 L	0 145	147	147
1 87 88	1 87 88	1 87 88	2 183	180	180
3 146 146	3 146 146	3 146 146	4 218	216	216
5 18 21	5 18 21	5 18 21	7 79	83	83
8 105 106	8 105 106	8 105 106	10 18	18	18
0 0 11 L	0 0 11 L	0 0 11 L	1 220	220	220
2 45 49	2 45 49	2 45 49	3 33	34	34
4 34 35	4 34 35	4 34 35	5 20	23	23
7 50 57	7 50 57	7 50 57	8 21	20	20
9 28 27	9 28 27	9 28 27	10 441	449	449
11 6 6	11 6 6	11 6 6	12 126	126	126
0 0 10 L	0 0 10 L	0 0 10 L	1 171	167	167
2 45 49	2 45 49	2 45 49	3 33	34	34
4 34 35	4 34 35	4 34 35	5 20	23	23
7 50 57	7 50 57	7 50 57	8 21	20	20
9 28 27	9 28 27	9 28 27	10 441	449	449
11 6 6	11 6 6	11 6 6	12 126	126	126
0 0 9 L	0 0 9 L	0 0 9 L	1 220	220	220
2 45 49	2 45 49	2 45 49	3 33	34	34
4 34 35	4 34 35	4 34 35	5 20	23	23
7 50 57	7 50 57	7 50 57	8 21	20	20
9 28 27	9 28 27	9 28 27	10 441	449	449
11 6 6	11 6 6	11 6 6	12 126	126	126
0 0 8 L	0 0 8 L	0 0 8 L	1 220	220	220
2 45 49	2 45 49	2 45 49	3 33	34	34
4 34 35	4 34 35	4 34 35	5 20	23	23
7 50 57	7 50 57	7 50 57	8 21	20	20
9 28 27	9 28 27	9 28 27	10 441	449	449
11 6 6	11 6 6	11 6 6	12 126	126	126
0 0 7 L	0 0 7 L	0 0 7 L	1 220	220	220
2 45 49	2 45 49	2 45 49	3 33	34	34
4 34 35	4 34 35	4 34 35	5 20	23	23
7 50 57	7 50 57	7 50 57	8 21	20	20
9 28 27	9 28 27	9 28 27	10 441	449	449
11 6 6	11 6 6	11 6 6	12 126	126	126
0 0 6 L	0 0 6 L	0 0 6 L	1 220	220	220
2 45 49	2 45 49	2 45 49	3 33	34	34
4 34 35	4 34 35	4 34 35	5 20	23	23
7 50 57	7 50 57	7 50 57	8 21	20	20
9 28 27	9 28 27	9 28 27	10 441	449	449
11 6 6	11 6 6	11 6 6	12 126	126	126
0 0 5 L	0 0 5 L	0 0 5 L	1 220	220	220
2 45 49	2 45 49	2 45 49	3 33	34	34
4 34 35	4 34 35	4 34 35	5 20	23	23
7 50 57	7 50 57	7 50 57	8 21	20	20
9 28 27	9 28 27	9 28 27	10 441	449	449
11 6 6	11 6 6	11 6 6	12 126	126	126
0 0 4 L	0 0 4 L	0 0 4 L	1 220	220	220
2 45 49	2 45 49	2 45 49	3 33	34	34
4 34 35	4 34 35	4 34 35	5 20	23	23
7 50 57	7 50 57	7 50 57	8 21	20	20
9 28 27	9 28 27	9 28 27	10 441	449	449
11 6 6	11 6 6	11 6 6	12 126	126	126
0 0 3 L	0 0 3 L	0 0 3 L	1 220	220	220
2 45 49	2 45 49	2 45 49	3 33	34	34
4 34 35	4 34 35	4 34 35	5 20	23	23
7 50 57	7 50 57	7 50 57	8 21	20	20
9 28 27	9 28 27	9 28 27	10 441	449	449
11 6 6	11 6 6	11 6 6	12 126	126	126
0 0 2 L	0 0 2 L	0 0 2 L	1 220	220	220
2 45 49	2 45 49	2 45 49	3 33	34	34
4 34 35	4 34 35	4 34 35	5 20	23	23
7 50 57	7 50 57	7 50 57	8 21	20	20
9 28 27	9 28 27	9 28 27	10 441	449	449
11 6 6	11 6 6	11 6 6	12 126	126	126
0 0 1 L	0 0 1 L	0 0 1 L	1 220	220	220
2 45 49	2 45 49	2 45 49	3 33	34	34
4 34 35	4 34 35	4 34 35	5 20	23	23
7 50 57	7 50 57	7 50 57	8 21	20	20
9 28 27	9 28 27	9 28 27	10 441	449	449
11 6 6	11 6 6	11 6 6	12 126	126	126

Table 3 (cont.)

Table with multiple columns and rows containing numerical data, likely representing bond lengths and angles for different parts of the thiamine molecule structure.

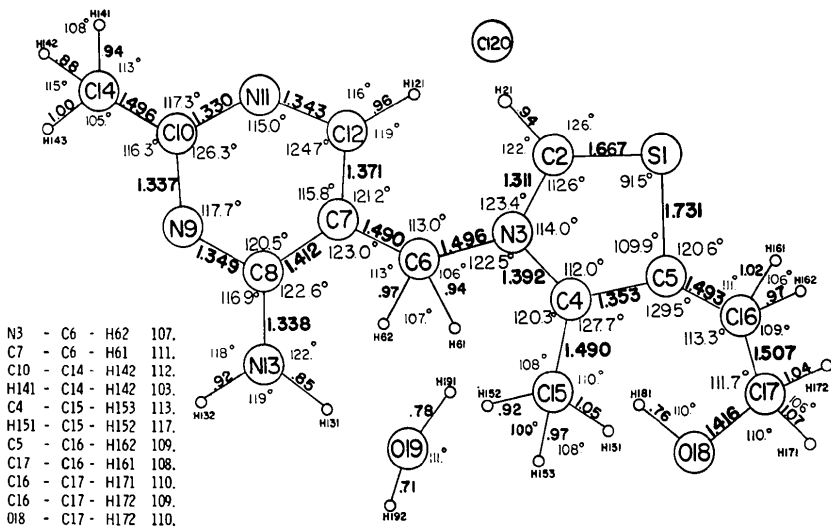


Fig. 1. Schematic representation of the molecule showing the numbering system, the bond distances (Å) and the bond angles (°). The estimated standard deviations in bond lengths range from 0.002 to 0.004 Å for bonds between nonhydrogen atoms, and from 0.02 to 0.04 Å for bonds involving hydrogen atoms. The estimated standard deviations in bond angles vary from 0.1 to 0.2° for angles between nonhydrogen atoms, and from 1.0 to 2.0° for angles including hydrogen atoms, except those of the C(14) methyl group and the water molecule, which vary from 2.0 to 4.0°.

ever, it is likely that the comparable improvement in the degree of planarity is simply reflecting a somewhat more accurate analysis for the thiamine base. In spite

of the small magnitude of the deviations in the thiazolium ring, their systematic nature (Pulsinelli, 1970) is still apparent. Another systematic feature of interest

concerns the pyrimidine amino group. Although the amino hydrogen atoms are virtually planar with respect to the pyrimidine ring, the amino group displays a

slight pyramidal character with both hydrogen atoms displaced to the same side of the plane but opposite to that of N(13). This tendency does not appear to be

Table 4. *Least-squares planes and atomic deviations*

The planes are expressed by the equation  $Px + Qy + Rz = S$  where  $x$ ,  $y$  and  $z$  are in fractional unit-cell coordinates. The deviations of the atoms from the plane are in (Å); column  $a$  lists atoms defining the plane and column  $b$  the remaining atoms

Plane		$P$	$Q$	$R$	$S$
1		3.007	15.273	-2.745	1.749
2		7.020	-3.368	-6.657	-3.236
1a	1b	2a	2b		
S(1)	C(6)	C(7)	C(6)	-0.024	
C(2)	C(15)	C(8)	N(13)	0.012	
N(3)	C(16)	N(9)	C(14)	0.016	
C(4)	H(21)	C(10)	H(121)	-0.025	
C(5)		N(11)	H(131)	-0.055	
r.m.s.	0.001	C(12)	H(132)	-0.038	
		r.m.s.	0.004		

Table 5. *Comparison of torsion angles about the C(6)-N(3) bond,  $\varphi_T$ , and the C(6)-C(7) bond,  $\varphi_P$ , and dihedral angle between the ring planes*

	Thiamine base	Thiamine HCl (Kraut & Reed)	Thiamine phosphate (Karl & Britts)	Thiamine pyrophosphate (Pletcher & Sax)
$\varphi_T$	-2.6°	-9.4°	-19.9°	3.6°
$\varphi_P$	-76.0	-73.5	-85.7	93.2
Dihedral angle	77.2	76	90	83.3

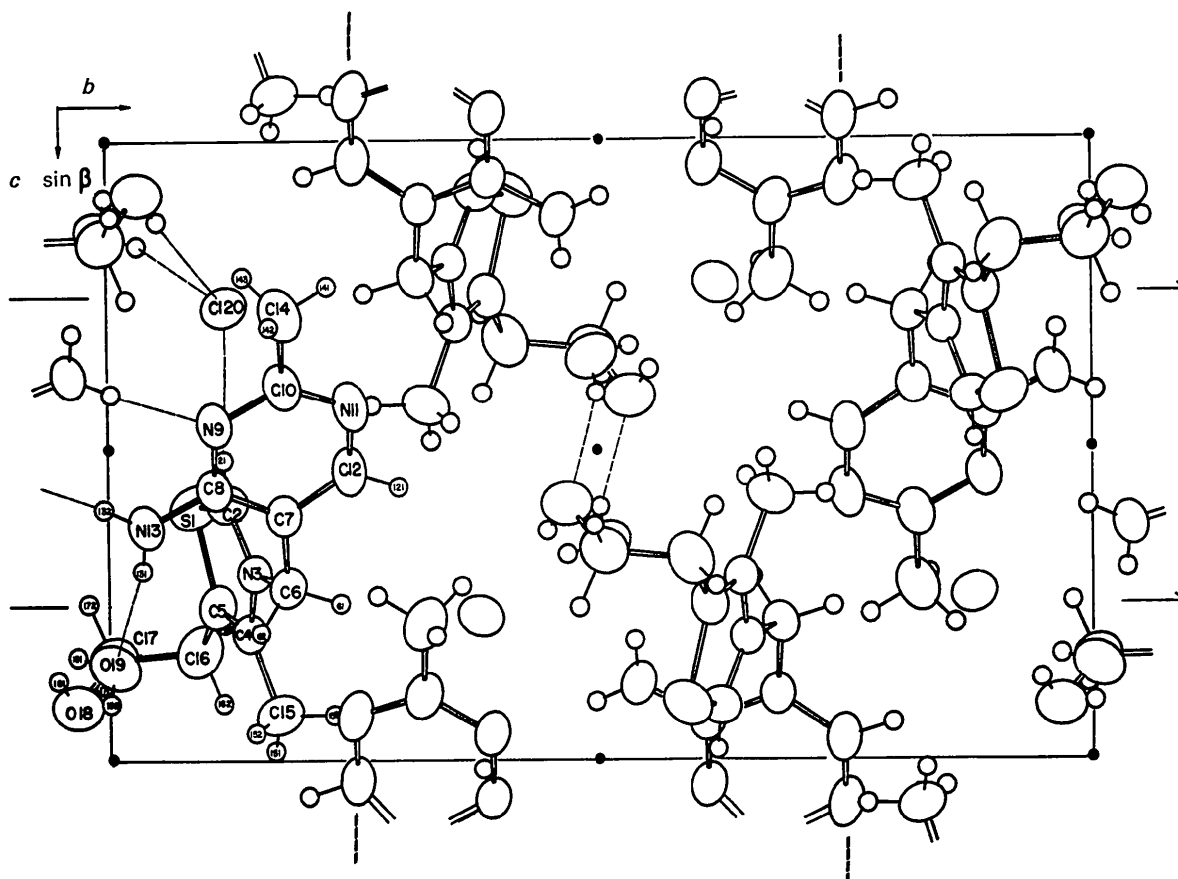


Fig. 2. The unit-cell contents projected down the  $a$  axis as drawn by the ORTEP program (Johnson, 1965). Hydrogen bonds are indicated by dashed lines. Thermal-ellipsoid boundaries are at the 50% probability level.

enhanced in the thiamine base, even though the amino group exhibits less double-bond character.

The relative orientation of the pyrimidine and thiazolium rings is a characteristic feature in the protonated thiamine structures. This feature is maintained in the free base of thiamine. Table 5 contains a comparison of the torsion angles (as previously defined, Pletcher & Sax, 1972) about the bonds from the methylene bridge carbon to the two aromatic rings. These data show that the relative ring orientations are all similar, even though the sense of the rotation may be different. It is also clear that the positive charge on the pyrimidine ring does not significantly influence the relative disposition of the rings.

The packing of the molecule in the unit cell, and intermolecular contacts are shown in Figs. 2, 3 & 4 and Table 6. There are several features in the hydrogen

bonding scheme that are worthy of comment. The hydrogen bond from the C(2) position of the thiazolium ring is an observed feature in the six different structures containing a thiazolium ring which is unsubstituted at C(2). This characteristic is in accord with the acidic nature of the C(2) hydrogen atom, an important property in the proposed mechanism for thiamine catalysis (Breslow, 1958; Breslow & McNelis, 1959). Another noteworthy feature in this structure is the absence of hydrogen bonding to the N(11) position of the pyrimidine ring. This nitrogen atom, the most basic in the pyrimidine ring, is the one that is protonated under acidic conditions. The lack of hydrogen bonding to this position may result simply because other, more favorable packing forces place this atom in a non-polar environment in the unit cell. This explanation is plausible in light of the fact that N(9)

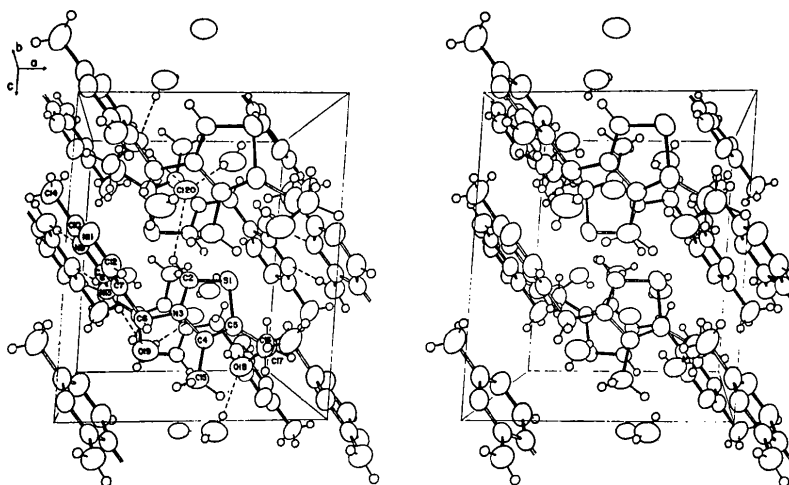


Fig. 3. A stereoscopic view of the molecular packing as drawn by the *ORTEP* program (Johnson, 1965). The *a* axis runs from 0 to 1, the *b* axis runs from  $-\frac{1}{2}$  to  $+\frac{1}{2}$  and the *c* axis runs from 0 to 1. Hydrogen bonds are indicated by dashed lines. The thermal-ellipsoid boundaries are at the 50% probability level.

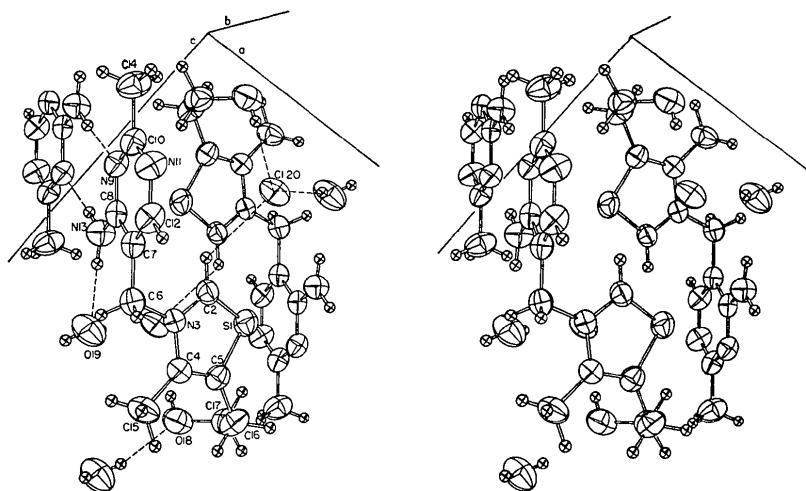


Fig. 4. A stereoscopic view showing the hydrogen bonding between neighboring molecules as drawn by the *ORTEP* program (Johnson, 1965). Thermal-ellipsoid boundaries are at the 50% probability level.

is an acceptor in this structure as well as in three others. Table 6 shows that the nearest neighbors to N(11) are non-polar. Nevertheless, it is interesting that in the structure of the free base, the form that exists under physiological conditions, neither the ring nitrogen, N(11), nor the amino group, N(13), participate as hydrogen-bond acceptors even though it has been suggested that they may serve as internal proton acceptors in the mechanism of catalysis.

Table 6. *Intermolecular interactions*

## (a) Hydrogen bonds

<i>i</i>	<i>j</i>	<i>k</i>	$d_{ik}$	$d_{jk}$	$\angle ijk$
C(2)—H(21)····Cl(20)			3·305 Å	2·62 Å	130°
N(13)—H(131)····O(19)			2·824	1·98	170
N(13)—H(132)····N(9 <sup>i</sup> )			3·034	2·12	174
O(18)—H(181)····Cl(20 <sup>ii</sup> )			3·044	2·29	174
O(19)—H(191)····Cl(20 <sup>iii</sup> )			3·141	2·39	162
O(19)—H(192)····O(18 <sup>iiii</sup> )			2·743	2·07	158

## (b) Nearest neighbors, N(11)

<i>i</i>	<i>j</i>	$d_{ij}$	<i>i</i>	<i>j</i>	$d_{ij}$
N(11)	C(16 <sup>iv</sup> )	3·419 Å	N(11)	H(161 <sup>iv</sup> )	2·91 Å
N(11)	C(6 <sup>v</sup> )	3·365	N(11)	H(162 <sup>v</sup> )	2·97
			N(11)	H(62 <sup>v</sup> )	2·89

## (c) Nearest neighbors, S(1)

<i>i</i>	<i>j</i>	$d_{ij}$	<i>i</i>	<i>j</i>	$d_{ij}$
S(1)	N(13 <sup>ii</sup> )	3·551 Å	S(1)	H(132 <sup>ii</sup> )	3·27 Å
S(1)	N(9 <sup>vi</sup> )	3·567			
S(1)	Cl(20)	3·769	S(1)	Cl(20 <sup>ii</sup> )	3·999

## (d) Nearest neighbors, C(6)

<i>i</i>	<i>j</i>	$d_{ij}$	<i>i</i>	<i>j</i>	$d_{ij}$
C(6)	N(13)	2·947 Å	C(6)	H(131)	2·66 Å
C(6)	C(15)	2·949	C(6)	H(152)	2·81
C(6)	O(19)	3·263	C(6)	H(153)	2·86
C(6)	N(11 <sup>vii</sup> )	3·365	H(62)	N(11 <sup>vii</sup> )	2·89
C(6)	Cl(20 <sup>vii</sup> )	3·563	H(62)	H(131)	2·33
H(61)	Cl(20 <sup>vii</sup> )	2·67	H(62)	H(152)	2·34
			H(61)	H(153)	2·47

## (e) Miscellaneous contacts

<i>i</i>	<i>j</i>	$d_{ij}$	<i>i</i>	<i>j</i>	$d_{ij}$
C(17)	N(13 <sup>vi</sup> )	3·475 Å	H(172)	H(132 <sup>vi</sup> )	2·64 Å
C(15)	O(19)	3·491	H(152)	O(19)	2·88
C(17)	H(171 <sup>viii</sup> )	3·11	H(171)	H(171 <sup>viii</sup> )	2·53
H(192)	H(181 <sup>iii</sup> )	2·46	H(172)	H(143 <sup>ii</sup> )	2·64
C(17)	H(143 <sup>ii</sup> )	3·03	H(171)	H(143 <sup>ii</sup> )	2·58
C(14)	H(132 <sup>i</sup> )	3·20	H(132)	H(132 <sup>i</sup> )	2·46
C(16)	H(141 <sup>ix</sup> )	3·21	H(161)	H(141 <sup>ix</sup> )	2·69
Cl(20)	H(153 <sup>v</sup> )	3·05			

## Symmetry code

None	<i>x</i>	<i>y</i>	<i>z</i>	<i>i</i>	$-x$	$-y$	$1-z$
ii	$1-x$	$-y$	$1-z$	iii	$1-x$	$-y$	$2-z$
iv	$-1+x$	$\frac{1}{2}-y$	$-\frac{1}{2}+z$	v	<i>x</i>	$\frac{1}{2}-y$	$-\frac{1}{2}+z$
vi	$1+x$	<i>y</i>	<i>z</i>	vii	<i>x</i>	$\frac{1}{2}-y$	$\frac{1}{2}+z$
viii	$2-x$	$-y$	$2-z$	ix	$1+x$	$\frac{1}{2}-y$	$\frac{1}{2}+z$

It has been observed by Sax, Pulsinelli & Pletcher (1972) that in the various thiamine structures the thiazolium sulfur atom is invariably surrounded by electronegative atoms, often at short contact distances. From the S(1) nearest neighbor distances listed in

Table 6, it is apparent that this characteristic is maintained in the present structure, although none of the distances is less than the sum of the van der Waals radii. Another feature in this structure, which was noted by Pulsinelli (1970) as a characteristic in thiamine compounds, is the close contacts to the methylene bridge carbon, C(6). From the list of C(6) nearest neighbors in Table 6, it is evident that the chloride ion is closer to C(6) and H(61) than is expected from their van der Waals radii.

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