oil: bp 168 °C (0.050 mm); ^{1}H NMR (90 MHz, acetone-d_6) δ 2.95–3.75 (m, 4 H, –CH$_2$N–, NH, methine CH), 3.85 (d, 2 H, –CH$_2$O–), 4.70 (broad s, 1 H, OH), 6.55–730 (m, 10 H aromatic); IR (thin film) 3600–3200 (s, b O–H, N–H), 3055, 3027, 2925, 2875, 1603, 1505, 1454, 1433, 1320, 1260, 1182, 1072, 1056, 1030, 756, 706, 700 cm^{-1}. Anal. Calcd for C$_{15}$N$_{17}$NO: C, 79.26; H, 7.54; N, 6.16. Found: C, 79.41; H, 7.75; N, 6.09.

***cis*- and *trans*-2-(Dimethylamino)-2-oxo-3,5-diphenyl-1,3,2-oxazaphosphorinane (5 and 6).** A solution of Me$_2$NP(O)Cl$_2$ (1.62 g, 10.0 mmol) in ethyl acetate (15 mL) was added to a solution of *N*-phenyl-2-phenyl-3-aminopropan-1-ol (2.27 g, 10.0 mmol) and triethylamine (2.02 g, 20.0 mmol) in ethyl acetate (10 mL). The reaction mixture was refluxed for 2 days and then filtered. The filtrate was treated with activated charcoal and the solvent removed under reduced pressure, leaving 5.50 g of residue. The residual product was dissolved in benzene, treated with pentane, cooled in ice, and then filtered. The solvents were removed from the filtrate, leaving 2.67 g (85% crude yield) of yellow crystalline residue. A 1.00-g sample of the residue was purified by MPLC on a silica gel column eluting with tetrahydrofuran/hexane (1:1) to give 496 mg of pure *trans*-2-(dimethylamino)-2-oxo-3,5-diphenyl-1,3,2-oxazaphosphorinane (**6**) [mp 129–131 °C; ^{31}P NMR (C$_6$D$_6$) δ 9.78 ppm; IR (KBr) 3040, 2985, 2950, 2930, 2875, 2845, 2815, 1600, 1496, 1250, 1224, (s, P=O), 1132, 1023, 1010, 1002, 966, 899, 869, 810, 780, 765, 752, 711, 705 cm^{-1}; mass spectrum, *m/e* 316 (M$^+$, 16%), 106 (16%), 105 (100%), 104 (41%), 77 (14%), 43 (12%)], 110 mg of pure *cis*-2-(dimethylamino)-2-oxo-3,5-diphenyl-1,3,2-oxazaphosphorinane (**5**) [mp 173–175 °C; ^{31}P NMR (C$_6$D$_6$) δ 6.69 ppm; IR (KBr) 2910, 1600, 1496, 1478, 1456, 1312, 1300, 1264, 1226 (s, P=O), 1138, 1099, 1077, 1042, 1036, 1008, 1000, 965, 888, 800, 774, 760, 745, 708, 700 cm^{-1}; mass spectrum, *m/e* 316 (M$^+$, 16%), 106 (14%), 105 (100%), 104 (36%), 77 (12%), 43 (10%)], and a 100-mg mixture of the two diastereomers (706 mg total, 59.4% yield). Anal. Calcd for C$_{17}$H$_{21}$N$_2$O$_2$P: C, 64.54; H, 6.71; N, 8.85; P, 9.79. Found: C, 64.45; H, 6.63; N, 8.76; P, 9.76.

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Supplementary Material Available: Thermal parameters (Table A), fixed hydrogen atom parameters (Table B), least-squares mean planes (Table C), and a listing of observed and calculated structure factors amplitudes for **5** (9 pages). Ordering information is given on any current masthead page.

Synthesis and Crystal and Molecular Structure of a Cu(I) Complex of Vitamin B$_1$, Cu(thiamin)Cl$_2$

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Abstract: The structure of the complex Cu(thiamin)Cl$_2$ has been determined by single-crystal X-ray diffraction methods. Yellow, bladelike crystals were obtained by vapor diffusion of acetone into an aqueous reaction mixture of Cu$_2$(CH$_3$CO$_2$)$_4$·2H$_2$O and thiamin chloride hydrochloride (1:4 mole ratio). The triclinic cell, space group $P\bar{1}$, containing two complex molecules, has cell parameters (25 °C) a = 9.203 (4) Å, b = 14.866 (6) Å, c = 5.985 (2) Å, α = 99.56 (3)°, β = 94.59 (3)°, γ = 104.23 (3)°, V = 776.36 Å^3, ρ_{calcd} = 1.711 g/cm^3, and ρ_{obsd} = 1.699 (2) g/cm^3. The structure has been refined by the full-matrix least-squares technique to a final error index of R_1 = 0.035 for the 264 variables and 3227 unique, absorption-corrected data for which $I > 3\sigma(I)$. The Cu(I) ion is coordinated to two chloride ions and the N(1′) atom of the pyrimidine ring of the thiamin molecule in a distorted trigonal-planar arrangement. The effect of metal-ion complexation on the organic ligand is similar to that observed in the only other metal–thiamin complex, Cd(thiamin)Cl$_3$·0.6H$_2$O. The torsion angles ϕ_{T} = −10.1° and ϕ_{P} = −83.8° correspond to the frequently observed *F* conformation. A hydrogen-bonding network and base-stacking interactions between parallel pyrimidine planes are the predominant intermolecular forces in the crystal.

Research efforts by several workers[1–4] directed toward preparing metal-ion complexes of thiamin have led only to the isolation of thiamin salts with a metal-containing anion. These repeated failures led Richardson[3] to conclude that it was not possible to prepare such complexes. However, the successful preparation and structure determination of the first metal-ion comlex of thiamin, Cd(thiamin)Cl$_3$·0.6H$_2$O, proved that metal–thiamin complexes exist.[5]

Continuing our research on the interaction of metal ions with this biomolecule, we have investigated its reaction with copper. Our interest in this metal ion is due to the possible role that Cu(II) may have in the oxidation of thiamin to thiochrome.[6] Previous attempts to prepare a copper–thiamin complex have failed. The crystal structure of a tetrachlorocuprate(II) salt of thiamin showed no bonding between the Cu(II) ion and the ligand.[2] Another structural report on the complex [(thiamin pyrophosphate)(1,10 phenanthroline)aquacopper(II)] demonstrated that the metal ion coordinated to the thiamin moiety only via the pyrophosphate chain.[7] We have now prepared a Cu(I)–thiamin complex, Cu(thiamin)Cl$_2$, and report its crystal and molecular structure.

Experimental Section

Preparation of Cu(thiamin)Cl$_2$. The complex Cu(thiamin)Cl$_2$ was prepared by reacting 2.5 mmol (0.9982 g) of Cu$_2$(CH$_3$CO$_2$)$_4$·2H$_2$O with 10 mmol of thiamin hydrochloride (3.373 g) in 20 mL of distilled water at room temperature. Yellow, bladelike crystals were obtained after 4 days by vapor diffusion of acetone into the cooled solution. The crystals were allowed to grow for another week, after which they were collected by suction filtration and washed with small amounts of water and ace-

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Table I. Summary of Crystal Parameters

compd	Cu(thiamin)Cl_2
formula	$C_{12}H_{17}CuCl_2N_4OS$
M_r	399.83
a, Å	9.203 (4)
b, Å	14.866 (6)
c, Å	5.985 (2)
α, deg	99.56 (3)
β, deg	94.59 (3)
γ, deg	104.23 (3)
V, Å^3	776.36
Z	2
ρ_{calcd}, g/cm^3	1.711 (25 °C)
ρ_{exptl}, g/cm^3	1.699 (2) (25 °C)
space group	$P\bar{1}$
radiation	Mo Kα (λ(Mo Kα_1) = 0.709 30 Å), λ(Mo Kα_2) = 0.713 59 Å)
μ, cm^{-1}	19.3
transmission coeff	0.64–0.74
grid size	4 × 4 × 4

tone. The crystals were dried at room temperature in the presence of $CaCl_2$ under vacuum for 3 h. Microanalysis[8] showed that the crystals (mp 193–194 °C) had the composition $C_{12}H_{17}CuCl_2N_4OS$. Calcd: Cu, 15.89; Cl, 17.73; C, 36.04; H, 4.29; N, 14.02; S, 8.02; O, 4.01. Found: Cu, 16.18; Cl, 17.27; C, 36.30; H, 3.52; N, 13.78; S, 8.29; O, 4.21 (by difference).

Isolation and Quantitative Analysis of Thiochrome. The aqueous filtrate from the above reaction was lyophilized, and the resulting solid was washed repeatedly (20 mL, 10 times) with isobutyl alcohol. The fluorescence spectrum of the isobutyl alcohol extract, with a maximum emission at 430 nm, was identical with that of a thiochrome standard, confirming that the oxidized product was thiochrome. Quantitative fluorometric measurements of thiochrome, together with the mass of the recovered Cu(thiamin)Cl_2 product, established the stiochiomery of the reaction as

$$Cu_2(CH_3CO_2)_4{\cdot}2H_2O + 3C_{12}N_4OSH_{18}Cl_2 \rightarrow 2Cu(C_{12}N_4OSH_{17})Cl_2 + C_{12}N_4OSH_{14} + 4CH_3CO_2^- + 2Cl^- + 6H^+ + 2H_2O$$

Thiochrome was recovered in 90% yield based on the amount of Cu(I) complex obtained.

Fluorescence Measurements. Fluorescence measurements were carried out with a Hitachi Perkin-Elmer fluorescence spectrophotometer, Model MPF-2A. A 4-nm slit width was used. The excitation wavelength in all measurements was 370 nm. All determinations were done at room temperature (25 ± 2 °C). All solutions were degassed prior to measurement of fluorescence intensities.

A standard calibration curve was obtained by using commercially available thiochrome (Sigma Chemical Co.) in the concentration range 3.0×10^{-6} to 3.0×10^{-5} M. Thiochrome from the Cu(II)–thiamin reaction was determined by direct comparison of fluorescence intensities with those of standard solutions.

X-ray Data Collection and Reduction. A crystal with maximum dimensions 0.54 mm × 0.25 mm × 0.20 mm was mounted on a glass fiber parallel to its longest edge with epoxy cement. Intensity data were collected on a Syntex $P\bar{1}$ four-circle diffractometer with a pulse height analyzer using graphite-monochromatized Mo Kα radiation. The unit cell parameters at 25 °C as determined by a least-squares analysis of the angular coordinates of 15 independent reflections with 2θ values from 12° to 28° are shown in Table I along with other pertinent crystal data.

Diffraction intensities were measured by using the θ–2θ scan technique with a scan range of 0.8° below Kα_1 to 1.0° above Kα_2 and variable scan rates ranging from 2 to 24°/min. The intensities of 3 check reflections, measured every 100 reflections, were monitored throughout data collection as a check on the stability of the crystal. Variation in these intensities was less than 2%. Of the 3591 unique reflections measured, 3227 had intensities greater than three times their standard deviations, and only these were included in subsequent calculations. An absorption correction was performed. It and the major computer programs for this structure determination were previously described.[9] Atomic scattering factors for Cu^+, Cl^-, S^0, O^0, N^0, C (val), and H (bonded), as well as the real and imaginary parts of the anomalous dispersion corrections for Cu^+, Cl^-, and S^0, were taken from ref 10.

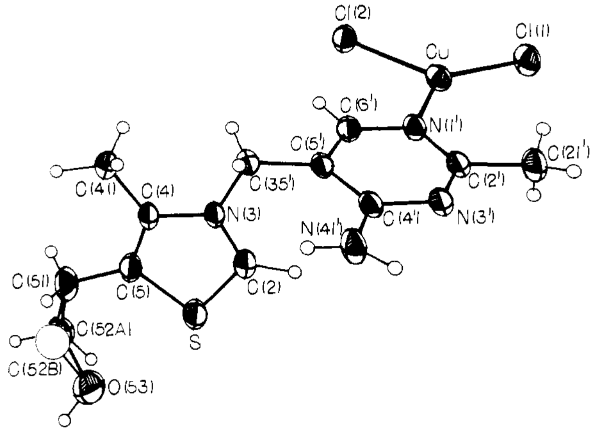

Figure 1. Perspective view and labeling scheme of Cu(thiamin)Cl_2. The 50% probability ellipsoids are shown, except for hydrogen atoms, which are artifically set at $B = 0.6$ Å^2.

Solution and Refinement of the Structure. The space group $P\bar{1}$ was assumed and confirmed by the solution and satisfactory refinement of the structure. The structure was solved with some difficulty, employing the usual heavy-atom methods. The position of the copper ion was determined from a three-dimensional Patterson function. An R_1 value of 0.537 ($R_1 = \sum(|F_o - |F_c|)/\sum F_o$) was obtained from a Fourier synthesis phased on this copper ion. On this electron density map, four large peaks were located and initially assumed to be chloro ligands in the coordination sphere of the metal ion. A series of least-squares refinements and Fourier calculations eventually demonstrated that two of these peaks did represent chloro ligands bound to the Cu(I) ion. Another proved to be the N(1′) of the pyrimidine ring, while the last was completely false. The positions of the pyrimidine ring and the methylene bridge were eventually deduced from difference Fourier maps. Three cycles of isotropic refinement of these 12 atoms gave $R_1 = 0.471$ and $R_2 = 0.537$, where $R_2 = (\sum w(F_o - |F_c|)^2/\sum wF_o^2)^{1/2}$. Subsequent use of these as phasing atoms for the ensuing electron density map led to the location of the thiazolium ring. After both the pyrimidine and thiazolium rings were included, the hydroxyethyl side chain was easily located. Three cycles of isotropic refinement of these 21 non-hydrogen atoms further decreased the R values ($R_1 = 0.137$, $R_2 = 0.222$). Application of the absorption correction to the data and the addition of anisotropic thermal parameters to the refinement resulted in considerably better R values ($R_1 = 0.058$, $R_2 = 0.106$).

An ensuing difference Fourier synthesis revealed the positions of 10 of the 17 hydrogen atoms. After two cycles of isotropic refinement of these hydrogen positions, R had decreased slightly ($R_1 = 0.054$, $R_2 = 0.094$). An examination of a Fourier map revealed substantial electron density (~1.5 electrons) near C(52), which remained unchanged in ensuing refinements. Since calculations showed reasonable bond distances to the adjacant C(51) and O(53) atoms, it was concluded that the C(52) atom was disordered. Refinement of occupancies of the two positions C(52A) and C(52B) converged at 0.694 (6) and 0.269 (7). Disorder within the hydroxyethyl side chain is not unique to this structure. Sax and his co-workers[11] have observed a similar disorder for the hydroxyl oxygen position in 2-(α-hydroxyethyl)thiamin chloride hydrochloride.

The seven remaining hydrogen atoms were located in the next Fourier map. A series of three full-matrix least-squares refinements of the hydrogen coordinates using isotropic thermal parameters and assigned partial occupancies for the C(52A) hydrogens converged at $R_1 = 0.035$ and $R_2 = 0.054$. Final error indices of $R_1 = 0.035$ and $R_2 = 0.053$ were obtained after three cycles of anisotropic refinement for the 22 non-hydrogen positions. In the last cycles of refinement, the esd for each of the positional and thermal parameters was greater than the shift of that parameter. The "goodness-of-fit", $\{[\sum w(F_o - |F_c|)^2]/(m - s)\}^{1/2}$, where m is the number of reflections and s is the total number of variables in the least-squares calculations, is 1.75. A final difference Fourier map with an esd of 0.087 e$^-$/Å^3 showed no peak greater than 0.6 e$^-$/Å^3, which was located about 0.9 Å from the copper position.

The final positional and thermal parameters are given in Table II. A listing of the observed and calculated structure factors, given as $10|F_o|$ and $10|F_c|$ after the final cycle of least-squares refinement is given in Table III.[12] A perspective view of the Cu(thiamin)Cl_2 molecule and the

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[8] Microanalysis was performed by Schwarzkopf Laboratories.

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Table II. Positional and Thermal Parameters for Cu(thiamin)Cl$_2$

A. Anisotropically Refined Atoms

atom	x^a	y	z	$\beta_{11}{}^b$	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
Cu	0.36246 (2)	0.18589 (2)	0.43232 (4)	7.20 (4)	4.15 (2)	18.9 (1)	4.73 (4)	−2.11 (9)	3.56 (6)
Cl(1)	0.58400 (6)	0.15944 (5)	0.51124 (1)	8.94 (7)	6.28 (4)	23.4 (2)	8.91 (8)	−4.5 (2)	2.2 (1)
Cl(2)	0.29071 (6)	0.29364 (4)	0.70323 (9)	9.71 (7)	4.24 (3)	20.0 (2)	6.20 (7)	3.1 (2)	0.5 (1)
S	0.91466 (6)	0.41441 (4)	0.6918 (1)	10.13 (8)	4.27 (3)	32.0 (2)	6.84 (8)	16.3 (2)	10.3 (1)
N(1′)	0.2013 (2)	0.1467 (1)	0.1659 (3)	6.7 (2)	3.26 (8)	14.8 (4)	4.6 (2)	−2.1 (4)	8.29 (3)
C(6′)	0.0800 (2)	0.1831 (1)	0.1766 (3)	8.2 (2)	3.34 (9)	14.9 (5)	5.0 (2)	0.9 (5)	1.1 (3)
C(2′)	0.2025 (2)	0.0878 (1)	−0.0320 (3)	7.0 (2)	2.48 (8)	16.3 (5)	3.8 (2)	−0.3 (5)	2.0 (3)
C(21′)	0.3355 (2)	0.0478 (1)	−0.0559 (4)	7.6 (2)	4.04 (1)	22.7 (6)	6.0 (3)	−1.6 (6)	0.1 (4)
N(3′)	0.0948 (2)	0.0630 (1)	−0.2080 (3)	7.5 (2)	2.70 (9)	15.8 (4)	4.3 (2)	−1.3 (4)	0.5 (3)
C(4′)	−0.0244 (2)	0.1013 (1)	−0.1978 (3)	7.1 (2)	2.93 (8)	15.1 (5)	4.2 (2)	−1.5 (5)	1.8 (3)
N(41′)	−0.1278 (2)	0.0762 (1)	−0.3830 (3)	10.2 (2)	5.1 (1)	18.0 (5)	9.0 (3)	−8.3 (5)	−3.8 (4)
C(5′)	−0.0351 (2)	0.1646 (1)	0.0022 (3)	6.9 (2)	2.89 (8)	15.1 (5)	4.5 (2)	1.0 (5)	1.9 (3)
C(35′)	−0.1665 (2)	0.2064 (1)	0.0337 (3)	7.7 (2)	3.40 (7)	16.5 (5)	5.2 (2)	2.5 (5)	3.2 (3)
N(3)	−0.1567 (2)	0.2922 (1)	−0.0687 (3)	5.6 (2)	2.94 (7)	15.7 (4)	4.0 (2)	1.2 (4)	0.9 (3)
C(2)	−0.0568 (2)	0.3213 (1)	−0.2041 (4)	7.6 (2)	3.9 (1)	23.0 (6)	5.6 (2)	6.8 (6)	4.4 (4)
C(4)	−0.2623 (2)	0.3448 (1)	−0.0389 (3)	6.3 (2)	3.04 (8)	18.7 (5)	4.4 (2)	2.6 (5)	1.2 (3)
C(41)	−0.3848 (3)	0.3208 (2)	0.1059 (4)	9.4 (3)	4.7 (1)	26.2 (7)	7.2 (3)	12.8 (7)	7.9 (5)
C(5)	−0.2386 (2)	0.4154 (1)	−0.1579 (4)	8.3 (2)	3.50 (9)	24.0 (6)	5.3 (2)	8.3 (6)	3.5 (4)
C(51)	−0.3288 (3)	0.4866 (2)	−0.1671 (5)	14.8 (4)	4.4 (1)	42 (1)	11.0 (4)	22 (1)	11.7 (6)
C(52A)^c	−0.2602 (4)	0.5702 (2)	−0.2653 (6)	14.9 (6)	3.3 (2)	30 (1)	7.2 (5)	10 (1)	59 (7)
O(53)	−0.2360 (3)	0.5418 (2)	−0.4928 (4)	29.4 (5)	8.8 (2)	46.8 (9)	22.2 (5)	40 (1)	22.5 (7)

B. Isotropically Refined Atoms

atom	x	y	z	B, Å^2	atom	x	y	z	B, Å^2
C(52B)^c	−0.357 (1)	0.5094 (8)	−0.366 (2)	4.7 (3)	H(2)	0.029 (3)	0.291 (2)	−0.249 (5)	3.7 (6)
H(6′)	0.077 (2)	0.224 (1)	0.320 (4)	2.2 (4)	H(41A)	−0.458 (4)	0.369 (3)	0.121 (7)	7 (1)
H(21′A)	0.398 (4)	0.095 (3)	−0.103 (7)	8 (1)	H(41B)	−0.361 (4)	0.296 (3)	0.227 (8)	7 (1)
H(21′B)	0.387 (3)	0.052 (2)	0.087 (5)	3.6 (6)	H(41C)	−0.455 (5)	0.243 (4)	0.014 (9)	4 (1)
H(21′C)	0.319 (3)	−0.017 (2)	−0.149 (5)	3.0 (5)	H(51A)	−0.430 (4)	0.448 (2)	−0.279 (6)	7.1 (9)
H(41′A)	−0.213 (3)	0.095 (2)	−0.384 (4)	2.7 (5)	H(51B)	−0.367 (4)	0.480 (3)	−0.058 (7)	6.3 (8)
H(41′B)	−0.107 (3)	0.031 (2)	−0.491 (5)	4.1 (6)	H(52A)^d	−0.329 (4)	0.623 (3)	−0.267 (7)	3.7 (9)
H(35′A)	−0.172 (3)	0.222 (2)	0.178 (5)	3.8 (6)	H(52B)^d	−0.178 (3)	0.578 (2)	−0.352 (4)	0.5 (4)
H(35′B)	−0.252 (3)	0.163 (2)	−0.038 (4)	3.2 (5)	H(53)	−0.270 (6)	0.577 (4)	−0.59 (1)	13 (2)

[a] Esd's in the least significant figure are given in parentheses in these and all subsequent tables. [b] The form of the anisotropic temperature factor is $\exp(-[\beta_{11}h^2 + \beta_{22}k^2 + \beta_{33}l^2 + \beta_{12}hk + \beta_{13}hl + \beta_{23}kl])$. The quantities given in (A) are the thermal coefficients × 10^3. [c] C(52A) and C(52B) represent the two positions of the disordered C(52) atom. [d] These hydrogens have been assigned occupancies equal to that of the C(52A) atom.

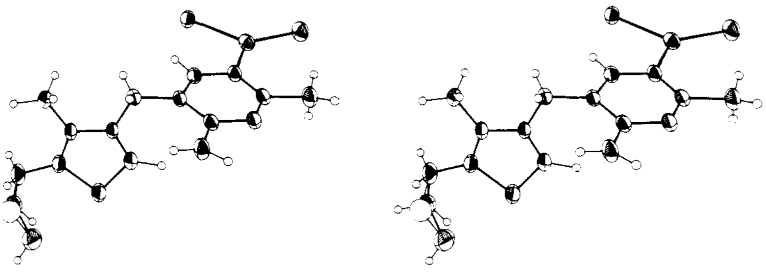

Figure 2. Stereoview of Cu(thiamin)Cl$_2$. Thermal ellipsoids are those described for Figure 1.

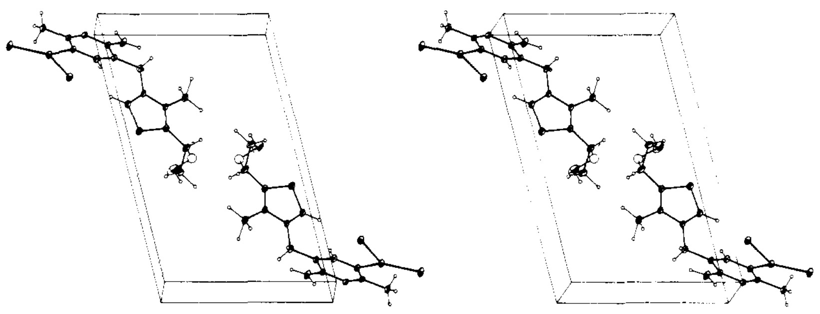

Figure 3. Stereoview of the contents of a unit cell of Cu(thiamin)Cl$_2$. The view is down c. The 20% thermal ellipsoids are shown, except for hydrogen atoms, which have been artificially set at B = 0.6 Å^2.

labeling scheme are shown in Figure 1. Figure 2 shows a stereoview of the molecule, and Figure 3 shows the contents of the unit cell. Bond distances and bond angles are listed in Tables IV and V, respectively.

Description of the Structure

The structure consists solely of Cu(thiamin)Cl$_2$ complexes, as can be seen in Figure 3. Interactions between complexes include base stacking of pyrimidine rings, electrostatic interactions, and hydrogen bonds.

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(12) Supplementary material.

Table IV. Bond Distances (Å) in Cu(thiamin)Cl_2

Cu-N(1′)	1.993 (2)
Cu-Cl(1)	2.2002 (6)
Cu-Cl(2)	2.3366 (6)
N(1′)-C(6′)	1.356 (2)
N(1′)-C(2′)	1.354 (2)
C(2′)-N(3′)	1.324 (2)
C(2′)-C(21′)	1.494 (3)
N(3′)-C(4′)	1.355 (2)
C(4′)-N(41′)	1.339 (3)
C(4′)-C(5′)	1.421 (3)
C(5′)-C(6′)	1.368 (3)
C(5′)-C(35′)	1.500 (3)
C(35′)-N(3)	1.491 (2)
N(3)-C(2)	1.315 (2)
N(3)-C(4)	1.395 (2)
C(2)-S	1.676 (2)
C(5)-S	1.734 (2)
C(4)-C(41)	1.487 (3)
C(4)-C(5)	1.348 (3)
C(5)-C(51)	1.502 (3)
C(51)-C(52A)	1.484 (4)
C(51)-C(52B)	1.31 (1)
C(52A)-O(53)	1.408 (4)
C(52B)-O(53)	1.43 (1)

Table V. Bond Angles (Deg) in Cu(thiamin)Cl_2

Cl(1)-Cu-N(1′)	135.96 (5)
Cl(2)-Cu-N(1′)	106.98 (5)
Cl(1)-Cu-Cl(2)	116.91 (2)
Cu-N(1′)-C(6′)	118.5 (1)
Cu-N(1′)-C(2′)	125.8 (1)
C(2′)-N(1′)-C(6′)	115.6 (2)
N(3′)-C(2′)-N(1′)	125.0 (2)
N(3′)-C(2′)-C(21′)	117.0 (2)
N(1′)-C(2′)-C(21′)	117.9 (2)
C(2′)-N(3′)-C(4′)	118.9 (2)
N(41′)-C(4′)-N(3′)	116.6 (2)
N(41′)-C(4′)-C(5′)	123.2 (2)
N(3′)-C(4′)-C(5′)	120.2 (2)
C(6′)-C(5′)-C(4′)	116.0 (2)
C(6′)-C(5′)-C(35′)	120.0 (2)
C(4′)-C(5′)-C(35′)	123.9 (2)
N(1′)-C(6′)-C(5′)	124.1 (2)
N(3)-C(35′)-C(5′)	113.5 (2)
C(2)-N(3)-C(4)	114.3 (2)
C(2)-N(3)-C(35′)	124.2 (2)
C(4)-N(3)-C(35′)	121.3 (2)
N(3)-C(2)-S	112.3 (2)
C(2)-S-C(5)	91.1 (1)
C(4)-C(5)-C(51)	126.9 (2)
C(4)-C(5)-S	110.5 (2)
C(51)-C(5)-S	122.6 (2)
C(5)-C(4)-N(3)	111.7 (2)
C(5)-C(4)-C(41)	126.8 (2)
N(3)-C(4)-C(41)	121.5 (2)
C(5)-C(51)-C(52A)	116.4 (2)
C(5)-C(51)-C(52B)	117.3 (5)
C(51)-C(52A)-O(53)	110.6 (3)
C(51)-C(52B)-O(53)	120.5 (8)

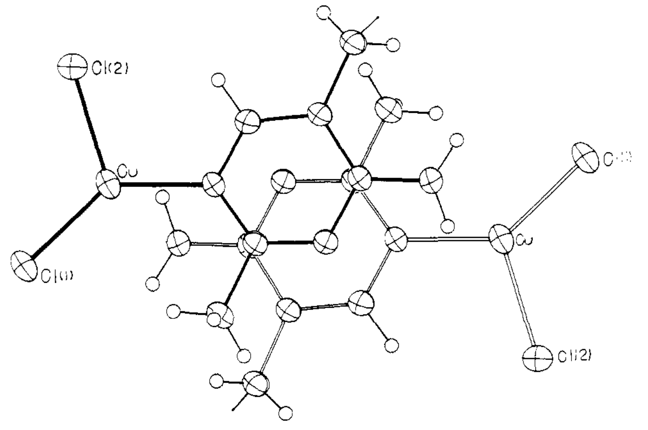

Figure 4. View of the Cu(pyrimidine)Cl_2 portion of the Cu(thiamin)Cl_2 molecule showing the overlap of the pyrimidine rings. The view is perpendicular to the pyrimidine planes and shows portions of the molecules at *x*, *y*, *z* and -*x*, -*y*, -*z*.

Table VII. Possible Hydrogen-Bonding Interactions, A–H- - -B, and Other Short Contacts

Hydrogen Bonding

A	B	equiv postn for B	A–B, Å	H- - -B, Å	A–H–B, deg
N(41′)	Cl(1)	$x-1, y, z-1$	3.251 (2)	2.38 (2)	163 (2)
N(41′)	N(3′)	$-x, -y, -z-1$	3.019 (3)	2.11 (3)	166 (2)
O(53)	Cl(2)	$-x, 1-y, -z$	3.056 (3)	2.18 (6)	155 (6)
C(2)	Cl(2)	$x, y, z-1$	3.400 (2)	2.44 (3)	154 (2)

Other Interactions

A	B	equiv postn for B	A–B, Å
S	O(53)	x, y, z	2.913 (3)
C(2)	Cl(1)	$x-1, y, z-1$	3.665 (2)
N(3)	Cl(1)	$x-1, y, z-1$	3.311 (2)
C(4)	Cl(1)	$x-1, y, z-1$	3.439 (2)
C(41)	Cl(1)	$x-1, y, z$	3.670 (3)
C(41)	Cl(2)	$x-1, y, z-1$	3.581 (2)
C(52A)	Cl(2)	$-x, 1-y, -z$	3.602 (4)
C(52A)	Cl(2)	$-x, 1-y, 1-z$	3.697 (4)
C(35′)	Cl(1)	$x-1, y, z-1$	3.583 (2)

The pyrimidine rings stack in a head-to-tail fashion across the inversion center at (0, 0, 0), separated by a mean distance of 3.42 (1) Å. As can be seen in Figure 4, this causes the amino group of one pyrimidine to approach the copper ion of the other at a nonbonding distance of 3.913 (2) Å. The separation between pyrimidine planes is 0.10 Å shorter than that observed in the similarly stacked Cd–thiamin complex[5] and is almost identical with that reported for thiamin pyrophosphate tetrahydrate.[13] The observation that base stacking occurs in both Cu(thiamin)Cl_2 and Cd(thiamin)Cl_3 suggests that metal-ion coordination may facilitate such interactions. This is interesting in light of studies on the coenzyme thiamin pyrophosphate which indicate that the pyrimidine ring of the thiamin portion of the molecule stacks with the indole group of a tryptophan residue in the active center of the apoenzyme.[14]

In addition to the base-stacking interactions of the pyrimidine rings, other intermolecular forces within the crystal consist of hydrogen-bonding and dipolar interactions between the positively charged thiazolium ring and the chloro ligands. Relevant intermolecular distances are listed in Table VII. The O(53)–Cl(2) distance, 3.056 (3) Å, is the shortest yet observed in thiamin structures where the chloro ligand is bound to a metal ion. While the high thermal parameter of O(53) and the disorder in the hydroxyethyl group render this length somewhat uncertain, it is 0.09 Å (30σ) shorter than found in Cd(thiamin)$Cl_3 \cdot 0.6H_2O$[5] and 0.18 Å (60σ) shorter than that observed in the $[CuCl_4]^{2-}$[2] and $[CdCl_4]^{2-}$ salts.[3] This stronger hydrogen bond may be related to the lengthening of the Cu–Cl(2) bond, which makes the chloro ligand a more effective hydrogen-bond acceptor. As in other thiamin structures[2,4,15-18] the acidic H(2) of the thiazolium ring interacts with a donor—in this case, for the first time, a chloro ligand. The C(2)–Cl(1) distance of 3.400 (2) Å is identical with that predicted by Pletcher and Sax from their calculations of the

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C–H hydrogen-bonding radius.[15] There is also intermolecular hydrogen bonding between the N(41′) amino hydrogens and two different acceptors, the N(3′) atom and a chloro ligand.

The neutral complex Cu(thiamin)Cl$_2$ consists of a Cu(I) ion bound in a trigonal planar fashion to the thiamin molecule and to two chloro ligands. The metal ion is bonded to the N(1′) atom of the pyrimidine ring of thiamin, as has been previously observed in Cd(thiamin)Cl$_3$.[5] Trigonal-planar geometry about the metal ion is indicated by bond angles (Table V) and least-squares calculations for the coordination plane (Table VI).[12] The CuCl$_2$N plane is nearly coplanar with the pyrimidine plane of thiamin, with the dihedral angle between them being 3.5°.

Least-squares calculations of the pyrimidine and thiazolium planes (Table VI)[12] show small deviations from strict planarity. Kraut and Reed[18] have suggested that the torsion angle between these planes may be significant in the oxidation of thiamin to thiochrome and to its biological function. In this structure this dihedral angle is 75.3°, almost identical with those found in other related structures.[1,18] A more specific description of the relative orientation of the pyrimidine and thiazolium rings is provided by the torsion angles ϕ_T and ϕ_P as defined by Pletcher and Sax.[20] In this structure, the torsion angles $\phi_T = -10.1°$ and $\phi_P = -83.8°$ correspond to the more common *F* conformation. With the inclusion of this work, 17 of 21 thiamin-related structures so far determined assume the *F* conformation. This result is in agreement with predictions that in thiamin structures where C(2) is unsubstituted, the *F* conformation would be favored. However, the recent structure determination of Cd(thiamin)Cl$_3$·0.6H$_2$O by Cramer[5] and an earlier report of a $[CdCl_4]^{2-}$ thiamin salt by Richardson[3] have shown that this is not always the case.

It has recently been pointed out[5] that the angles ∠C(2)–N(3)–C(35′) and ∠C(4)–N(3)–C(35′) are sensitive to molecular conformation. A comparison of previously determined thiamin structures in the *S* and *F* conformations shows that in all cases, the ∠C(2)–N(3)–C(35′) angle is 1–3° smaller than the ∠C(4)–N(3)–C(35′) angle for the *S* conformation while the opposite trend is observed in the *F* form. This pattern holds in the present structure where the ∠C(2)–N(3)–C(35′) = 123.8 (2)° and ∠C(4)–N(3)–C(35′) = 121.3 (2)°.

The torsion angles that describe the conformation of the 5-(β-hydroxyethyl) side chain[16] are $\phi_{5\alpha} = 14.2°$ and $\phi_{5\beta} = -60.2°$. A comparison of these angles for various thiamin structure by Pletcher and Sax[16] has shown that althouh there is a great variation in the values for $\phi_{5\alpha}$, in a majority of the reported structures, they fall between 60° and 90°. The values for $\phi_{5\beta}$ are less random and lie within10° of ±60°. In this structure, although $\phi_{5\alpha}$ is unusually small, $\phi_{5\beta}$ is characteristic of thiamin structures where the side chain is folded back towards the positively charged thiazolium ring, resulting in a close S–O(53) contact. The flexibility of the C(5) side chain demonstrated in this structural feature indicates that its conformation is determined largely by crystal packing or intermolecular hydrogen-bonding forces. The S–O(53) intramolecular distance of 2.913 (3) Å is slightly longer than that observed in the Cd–thiamin complex (2.879 (3) Å)[5] but shorter than observed for any other thiamin structure.[13,16,19,20] This type of interaction between the thiazolium sulfur and electronegative atoms such as oxygen[13,15,19,20] or negative ions such as chloride[3] and bromide[20] has been explained in terms of contributions from resonance forms that place a positive charge on the sulfur.[18] The fractional contribution of these resonance forms may become more significant upon complexation to a metal ion, resulting in a tighter S–O(53) interaction as reflected in the shorter contacts noted in Cu(thiamin)Cl$_2$ and Cd(thiamin)Cl$_3$.

Discussion

While the copper reagent used to synthesize Cu(thiamin)Cl$_2$ consisted of copper in the +2 oxidation state, the trigonal-planar geometry of the product suggests Cu(I). This is confirmed by a count of the charges in the crystal and the requirement for overall electrical neutrality. Thus there are only two negative charges in the molecule, the two chloro ligands, which must be countered by two positive charges, one being that of the thiazolium ring. The copper ion must therefore carry the single positive charge of Cu(I). This oxidation state assignment is confirmed by the observed diamagnetism of the complex.[21]

The coordination about the Cu(I) ion in Cu(thiamin)Cl$_2$ is unusual in several respects. The most common geometry observed for Cu(I) is that of a four-coordinate tetrahedron.[22] Trigonal Cu(I) structures are not numerous and have consisted mostly of polymeric[22-25] or dinuclear[26-28] complexes. The Cu(I)–thiamin complex reported here is the first among the few tricoordinate Cu(I) mononuclear complexes[29-35] to have a Cl$_2$N coordination sphere.

While the Cu(I) coordination sphere is nicely planar, it is severely distorted from regular trigonal geometry, with bond angles ranging from 107.58 (6)° for ∠Cl(2)–Cu–N(1′) to 135.26 (6)° for ∠Cl(1)–Cu–N(1′). The Cu–N(1′) bond of 1.993 (2) Å is shorter than that found in Cu(en)COBPh$_4$ (2.040 (4) Å)[30] but is comparable to that in Cu(2-Mepy)$_3^+$ where the Cu–N bond lengths average to 1.99 (3) Å.[29] Copper(I)–Cl bond lengths in trigonal complexes have been observed as short as 2.209 Å for [Cu(SPMe$_2$)Cl]$_3$[25a] and as long as 2.28 (3) Å found for bridging chloro ligands in dinuclear Cu(I) complexes.[26-28] In this structure the two Cu–Cl bonds are of very different lengths, with the Cu–Cl(1) bond at 2.2002 (6) Å falling on the short end of the above range and the Cu–Cl(2) bond at 2.3366 (6) Å being longer than this range.

The distortion in the coordination sphere of Cu(thiamin)Cl$_2$ can be rationalized in terms of steric crowding and hydrogen-bonding interactions. The coordination plane and the pyrimidine plane are essentially coplanar, a very sterically unfavorable situation. Rotation about the Cu–N(1′) bond until the coordination and pyrimidine planes were perpendicular would minimize the steric congestion. However, such a rotation is prevented in the crystal by the close proximity of a stacked pyrimidine ring of a neighboring complex. In the coplanar arrangement, Cl(1) and the C(21′) methyl group are 3.894 (2) Å apart, and to relieve this contact, the ∠Cl(1)–Cu–N(1′) angle opens to 135.26 (6)°. This in turn crowds Cl(2), decreasing the ∠Cl(2)–Cu–N(1′) angle to 107.58 (6)° and lengthening the Cu–Cl(2) bond. The short

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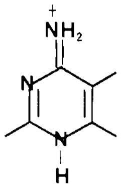
electrostatic contacts between Cl(2) and the atoms of the thiazolium ring and hydrogen bonds with H(2) and H(53) (Table VII) also enhance this lengthening.

The parameters of protonated, deprotonated, and metal-complexed forms of thiamin were recently compared.[5] In general, only a few small differences are observed in the bond lengths and bond angles of the thiamin molecule in this structure and those in the Cd–thiamin complex. The effect on bond distances and bond angles (Tables IV and V) of metal coordination to the ligand is similar to that of protonation, only to a smaller degree. A small but significant difference in the ∠C(2′)–N(1′)–C(6′) between the two metal–thiamin complexes may be due to the different acid strengths and softness of the two metal ions toward the N(1′) pyrimidine atom.

One structural feature that varies significantly in the protonated and metal-complexed forms of thiamin is the C(4′)–N(41′) bond length. It is 1.339 (3) Å in this structure, practically identical with that observed in the free base, and is slightly shorter than that measured for the cadmium–thiamin complex,[5] 1.346 (3) Å, but is 0.03 Å longer than that of the protonated form. Thus, the effect of metal-ion coordination markedly contrasts with that of protonation. This unexpected result can be explained by examining resonance structure III of Kraut and Reed:[18]



Removal of the proton from the N(1′) atom produces the free base and results in an unfavorable separation of positive and negative charges and hence in a longer C(4′)–N(41′) bond. In the case of metal-ion coordination, the coordinating unit is not a bare metal cation, but the negatively charged $[CdCl_3]^-$ or $[CuCl_2]^-$ anion. Replacement of the proton by such an electron-rich group would destabilize resonance form III, decreasing its fractional contribution to the overall structure of the pyrimidine ring and thus increasing the C(4′)–N(41′) bond length.

Significance

This structure, only the second example of a metal–ion complex of thiamin, is consistent with Schellenberger's hypothesis[36] that the most likely metal coordination site in the biomolecule is the N(1′) atom of the pyrimidine ring. Further, the lengthening of the C(4′)–N(41′) bond, in contrast to protonated thiamin and now observed in both metal-complexed forms of thiamin, lends support to postulated enzymatic mechanisms that attribute more base character to the exocyclic amino group.[36]

The formation of a Cu(I)–thiamin complex indicates that a redox reaction has occurred. Divalent copper has been reduced, and some of the thiamin has been oxidized to thiochrome. Since reductive chelation of copper has been suggested as a mechanism for the bioregulation of tissue copper levels,[37] the observation that thiamin will complex Cu(I) and reduce Cu(II to Cu(I) in aqueous solution raises the possibility that thiamin is involved in such a bioregulation.[37–39]

It is known that blood-serum copper levels are abnormal in those afflicted with rheumatoid arthritis,[40,41] and that penicillamine, which is known to affect the bioregulation of copper,[37–39] is effective in treating both rheumatoid arthritis[39,42] and Wilson's disease.[43] If the biologically ubiquitous thiamin molecule has a role in the bioregulation of copper, it may then be involved in either the prevention or aggravation of conditions such as Wilson's disease or rheumatoid arthritis. Although the nature of this role is at present speculative, studies of the solution chemistry of the metal-ion complexes of thiamin should be illuminating. We are presently engaged in such studies.

Registry No. Cu(thiamin)Cl_2, 87803-91-6; $Cu_2(CH_3CO_2)_4$, 23686-23-9.

Supplementary Material Available: Table III, a listing of observed and calculated structure amplitudes, and Table VI, the best weighted least-squares planes (17 pages). Ordering information is given on any current masthead page.

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