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A Metal Ion Complex of Vitamin B_1: The Preparation and Structure of Cd(thiamine)$Cl_3 \cdot 0.6H_2O$

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Abstract: The reaction of cadmium acetate with thiamine chloride hydrochloride in water affords the complex Cd(thiamine)$Cl_3 \cdot 0.6H_2O$, and its structure has been determined by single-crystal X-ray methods. The compound crystallizes with eight molecules in space group C_{2h}^6—$C2/c$ of the monoclinic system in a cell with dimensions at −166 °C of a = 25.86 (1) Å, b = 8.528 (4) Å, c = 17.779 (8) Å, β = 107.20 (2)°, V = 3745 Å^3, ρ_{calcd} = 1.756 g/cm^3, and ρ_{obsd} (25 °C) = 1.72 (1) g/cm^3. The structure has been refined by least-squares methods to a final R index on F of 0.025 for the 219 variables and the 4931 data. Three chloro ligands and atom N(1′) of the pyrimidine ring of the thiamine molecule complete an uncommon tetrahedral coordination about the Cd(II) ion. This is the first structural report of a thiamine ion bonded to a metal ion. In general the structural effect on thiamine of Cd(II) coordination is similar to that of protonation but smaller. The thiamine ligand is in the uncommon S conformation with torsional angles ϕ_T = +112.6° and ϕ_p = +129.8°.

Introduction

Thiamine (Vitamin B_1), as its pyrophosphate ester, is a cofactor for the enzyme pyruvate decarboxylase which also requires a divalent metal ion for its function.[2] In order to understand the mechanism of the enzyme, we must consider the possibility of metal ion binding to thiamine. If such coordination occurs, its structural and electronic effects must be determined to illuminate its role in the enzymatic action. Although Schellenberger[2] has presented evidence that the pyrimidine ring of thiamine binds to Mg^{2+} ion in the holoenzyme, probably at atom N(1′), and there is NMR evidence for metal ion binding to thiamine in solution,[3,4] all crystals of thiamine containing metal ions have proven to be salts, with no bonds between the metal ions and thiamine.[5-8] Since Cd^{2+} is among those ions which can activate pyruvate decarboxylase[9] and since thiamine complex formation is a possible mechanism for the prevention of cadmium poisoning, we attempted to produce crystals of a Cd^{2+} complex of thiamine. The reaction of $Cd(CH_3CO_2)_2$ with (thiamine)Cl·HCl produced the complex, Cd(thiamine)Cl_3, whose structure, the first of a metal ion complex of thiamine, is reported here.

Experimental Section

The complex Cd(thiamine)$Cl_3 \cdot 0.6H_2O$ was prepared by mixing $Cd(CH_3CO_2)_2$ with (thiamine)Cl·HCl in a one-to-two molar ratio in water. Vapor diffusion of acetone into the resulting solution produced large crystalline plates of Cd(thiamine)$Cl_3 \cdot 0.6H_2O$. Anal. Calcd for $C_{12}H_{18.2}CdCl_3N_4O_{1.6}S$: C, 29.23; H, 3.71; N, 11.36. Found: C, 29.77; H, 3.81; N, 11.11. The degree of hydration was established from the X-ray analysis (vide infra).

X-ray film data obtained at room temperature by the precession method revealed the crystal system as monoclinic with systematic absences consistent with the space groups C_{2h}^6—$C2/c$ or C_s^4—Cc. The correct space group at −166 °C was determined to be $C2/c$ by the observed equality of Friedel pairs and was confirmed by the successful refinement of the structure in this space group. Cell dimensions at −166 (2) °C, obtained by manual centering[10] of 15 reflections between 28° ≤ 2θ(Mo Kα_1) ≤ 34° on a Picker FACS-I diffractometer, are a = 25.86 (1) Å, b = 8.528 (4) Å, c = 17.779 (8) Å, and β = 107.20 (2)°. For a cell volume of 3745 Å^3 the density of 1.756 g/cm^3 calculated for eight formula units in the low-temperature cell agrees with that of 1.72 (1) g/cm^3 measured by flotation at room temperature.

Table I. Summary of Crystal Parameters and Data Collection

compd	Cd(thiamine)$Cl_3 \cdot 0.6H_2O$
formula	$C_{12}H_{18.2}CdCl_3N_4O_{1.6}S$
fw	494.93
a, Å	25.86 (1)
b, Å	8.528 (4)
c, Å	17.779 (8)
β, deg	107.20 (2)
V, Å^3	3745
Z	8
density, g/cm^3	1.756 (calcd) (−166 °C)[a] 1.72(1) (exptl) (25 °C)
space group	C_{2h}^6–$C2/c$
cryst dimens, mm	0.57 × 0.55 × 0.12
cryst vol, mm^3	0.034
cryst shape	centric octagonal plate with short dimen along [100] and with {010}, {001}, {111}
radiatn	Mo Kα (λ(Mo Kα_1) = 0.709 30 Å) from graphite monochromator
temp, °C	−166 (2)[a]
μ, cm^{-1}	17.2
transmissn factors	0.43–0.80
receiving aperature	4 × 4 mm, 32 cm from crystal
takeoff angle, deg	2.8
scan speed	2.0° in 2θ/min
scan range	0.95° below Kα_1 to 0.95° above Kα_2
bkgd counting	10 s with rescan option[b]
2θ limits, deg	3.0–60.0
p	0.04
final no. of variables	219
unique data measd	6505
unique data used ($F_o^2 > 3\sigma(F_o^2)$)	4931
error in observation of unit weight	1.36 electrons
R	0.025
R_w	0.037

[a] The low-temperature system is based on a design by: Huffman, J. C. Ph.D. Thesis, Indiana University, 1974. [b] The diffractometer was run under the Vanderbilt disk oriented system (Lenhert, P. G. *J. Appl. Crystallogr.* **1975**, *8*, 568–570).

Data collection and processing were carried out by procedures standard in this laboratory[11] (Table I). The intensities of seven standard reflections, measured every 100 reflections, did not vary beyond counting statistics. The final parameters reported here are based on the 4931 unique, absorption corrected[12] data for which $F_o^2 > 3\sigma(F_o^2)$.

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Table II. Positional and Thermal Parameters for the Atoms of Co(thiamine)Cl_3

ATOM	X[A]	Y	Z	B11[B]	B22	B33	B12	B13	B23
CO	0.168147(6)	0.17553(2)	0.162866(8)	0.69(1)	3.13(2)	0.83(1)	-0.19(1)	0.34(1)	-0.02(1)
CL(1)	0.22703(2)	0.30895(5)	0.09810(3)	0.62(1)	3.50(6)	1.13(1)	-0.11(2)	0.35(1)	0.29(2)
CL(2)	0.17723(2)	-0.11142(6)	0.16753(3)	1.28(1)	3.20(6)	1.12(1)	-0.22(2)	0.53(1)	-0.02(2)
CL(3)	0.07524(2)	0.24616(8)	0.08838(4)	0.61(1)	9.69(9)	2.59(2)	-0.02(2)	0.18(1)	0.04(4)
S	0.07989(2)	-0.34274(6)	0.37142(3)	0.78(1)	3.92(7)	1.81(2)	-0.43(2)	0.40(1)	-0.77(3)
N(1≠)	0.17863(7)	0.2343(2)	0.28922(9)	0.54(3)	2.9(2)	0.86(5)	-0.08(6)	0.25(3)	0.03(8)
C(6≠)	0.17684(8)	0.1171(2)	0.3397(1)	0.53(3)	2.4(2)	1.03(6)	0.00(7)	0.23(3)	0.02(9)
C(2≠)	0.18132(8)	0.3821(2)	0.3179(1)	0.55(3)	2.8(2)	1.02(6)	0.00(6)	0.28(3)	0.08(9)
C(21≠)	0.18000(9)	0.5148(2)	0.2619(1)	0.94(3)	3.3(2)	1.20(6)	-0.17(7)	0.43(4)	0.26(10)
N(3≠)	0.18324(7)	0.4183(2)	0.39137(10)	0.67(3)	2.5(2)	1.02(5)	-0.03(6)	0.34(3)	-0.03(8)
C(4≠)	0.18138(8)	0.3002(2)	0.4415(1)	0.46(3)	3.0(2)	0.95(6)	0.04(6)	0.22(3)	-0.21(9)
N(41≠)	0.18367(8)	0.3431(2)	0.5152(1)	1.03(3)	3.3(2)	0.85(5)	-0.27(6)	0.38(3)	-0.43(8)
C(5≠)	0.17758(8)	0.1420(2)	0.4161(1)	0.45(3)	2.4(2)	0.91(6)	0.06(6)	0.22(3)	0.08(9)
C(35≠)	0.17538(8)	0.0059(2)	0.4692(1)	0.58(3)	3.0(2)	0.83(5)	-0.04(6)	0.23(3)	-0.01(9)
N(3)	0.12991(7)	-0.1011(2)	0.43222(10)	0.55(3)	2.9(2)	1.08(5)	-0.04(6)	0.32(3)	0.03(8)
C(2)	0.13811(9)	-0.2462(2)	0.4108(1)	0.72(3)	3.0(2)	1.21(6)	-0.03(7)	0.38(4)	-0.18(10)
C(4)	0.07583(8)	-0.0616(3)	0.4175(1)	0.56(3)	4.1(2)	1.87(7)	0.23(7)	0.35(4)	-0.2(1)
C(41)	0.0611(1)	0.0958(3)	0.4423(2)	0.66(4)	5.6(3)	3.7(1)	0.25(8)	0.64(5)	-1.5(1)
C(5)	0.04259(10)	-0.1809(3)	0.3837(1)	0.68(4)	5.5(3)	2.04(8)	-0.07(8)	0.37(4)	-0.4(1)
C(51)	-0.0185(1)	-0.1849(3)	0.3605(2)	0.61(4)	9.0(4)	3.3(1)	-0.23(9)	0.31(5)	-1.0(2)
C(52)	-0.0404(1)	-0.3302(4)	0.3888(2)	0.79(4)	11.3(4)	3.6(1)	-0.9(1)	0.60(5)	-1.6(2)
O(53)	-0.02860(9)	-0.4591(3)	0.3445(2)	1.15(4)	9.1(3)	5.2(1)	-1.35(9)	0.92(5)	-2.1(1)
O(W1)	0.0434(5)	0.295(1)	0.2709(6)	3.1(3)	27.(3)	5.6(5)	1.4(7)	0.9(3)	4.6(8)
O(W2)	-0.0497(6)	0.116(2)	0.2448(8)	2.3(3)	34.(4)	4.3(5)	-0.5(8)	0.9(3)	-1.(1)

[A] ESTIMATED STANDARD DEVIATIONS IN THE LEAST SIGNIFICANT FIGURE(S) ARE GIVEN IN PARENTHESES IN THIS AND ALL SUBSEQUENT TABLES. [B] THE FORM OF THE ANISOTROPIC THERMAL ELLIPSOID IS: $EXP[-(B11H^2+B22K^2+B33L^2+2B12HK+2B13HL+2B23KL)]$. THE QUANTITIES GIVEN IN THE TABLE ARE THE THERMAL COEFFICIENTS X 10^3.

The positions of the Cd^{2+} ion, all three chloro ligands, the sulfur atom, and atoms N(1′), C(2′), and C(21′) were determined from a sharpened, origin-removed, Patterson function. The remaining nonhydrogen atoms of the complex were located in the ensuing Fourier map. Full-matrix least-squares refinement with anisotropic thermal parameters for all atoms led to the agreement indices on F of $R = 0.090$ and $R_w = 0.124$. An ensuing difference Fourier map revealed the positions of all hydrogen atoms. The positions of those attached to C or N were idealized (C-H = N-H = 0.95 Å) and fixed in subsequent calculations. Those attached to oxygen were not idealized but were also fixed. Each H atom was assigned a fixed isotropic thermal parameter 1 Å^2 greater than the effective isotropic thermal parameter of the atom to which it is attached. Refinement of this model converged to values of R and R_w of 0.032 and 0.057, respectively, and to an error in an observation of unit weight of 2.04 electrons, on the basis of 199 variables and 4931 observations. An ensuing difference Fouier map revealed significant electron density near the twofold axis which we interpret as partially occupied water molecules. In a final round of calculations the model was expanded to include the occupancies, positions, and anisotropic thermal parameters of the oxygen atoms of these water molecules. No attempt was made to define the hydrogen atoms of the water molecules. Presumably as a consequence of the low-temperature data set, there were no correlations of occupancies with positional or thermal parameters of the water molecules above 0.5. This refinement of 219 variables smoothly converged to values of R and R_w of 0.025 and 0.037, respectively, and to an error in an observation of unit weight of 1.36 electrons. Inclusion of the water molecules in the model has led to a significant improvement in the agreement indices. The water positions are separated by less than 1.6 Å so that the contact between them is prohibitively short. Thus each of the water positions may be half-occupied at most. The refined occupancies of the two independent water molecules are 0.37 (2) and 0.23 (2) for O(W1) and O(W2), respectively, and this establishes the crystal examined as containing 0.60 (3) water molecules/Cd ion.

An analysis of $\sum w(|F_o| - |F_c|)^2$ as a function of $|F_o|$, setting angles, and Miller indices revealed only one unexpected trend. If we define $q = F_o^2/\sigma(F_o^2)$, then of the 369 reflections of the class $h0l$, l odd, 25 have $q > 3$. Of these 14 have q between 3 and 4, 5 have q between 4 and 5, and the remaining have indices and q values of $\bar{2}07$ and 5.3, $\bar{8}01$ and 5.7, 205 and 7.4, 203 and 7.7, $\bar{4}01$ and 11.6, and $\bar{6}01$, 14.8. This class of reflections is extinguished in space groups $C2/c$ or Cc. With a final agreement index R of 0.025 there is no doubt that the Cd(thiamine)Cl_3 portion of the structure is correct and properly refined. It is unlikely that so many significant $h0l$, l odd, intensities arise from multiple diffraction effects. It is more likely that our model for the water scattering is inadequate and that the actual arrangement of these water molecules is such as to violate the symmetry conditions for space groups $C2/c$ or Cc.

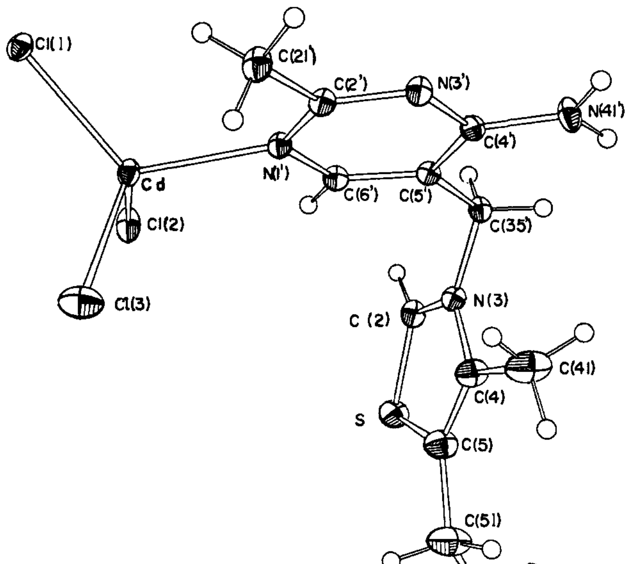

Figure 1. View of Cd(thiamine)Cl_3. The 50% probability thermal ellipsoids are shown except for hydrogen atoms which are artificially set at $B = 0.6$ Å^2.

The positional and thermal parameters from the last cycle of least-squares refinement are listed in Table II, along with the standard deviations estimated from the inverse matrix. The fixed positions of the hydrogen atoms are listed in Table III.[13] The final values of $10|F_o|$ and $10|F_c|$ in electrons are given in Table IV.[13] Table V[13] presents the root-mean-square amplitudes of vibration. Figure 1 displays a drawing of the complex and the labeling scheme, while Figure 2 presents a stereoview of the Cd(thiamine)Cl_3 molecule.

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(12) Computer programs used are as listed in: Kaduk, J. A.; Ibers, J. A. *Inorg. Chem.* **1977**, *16*, 3278-3282.

(13) Supplementary material.

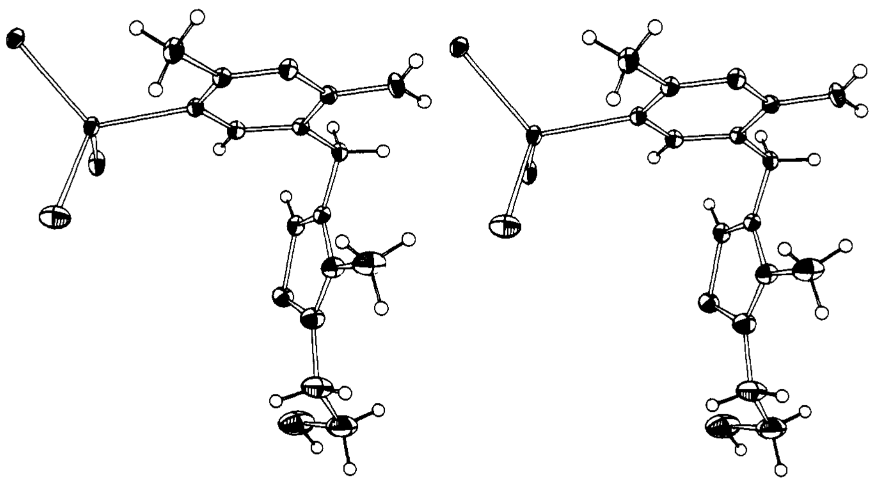

Figure 2. Stereoview of Cd(thiamine)Cl_3. Thermal ellipsoids are those described for Figure 1.

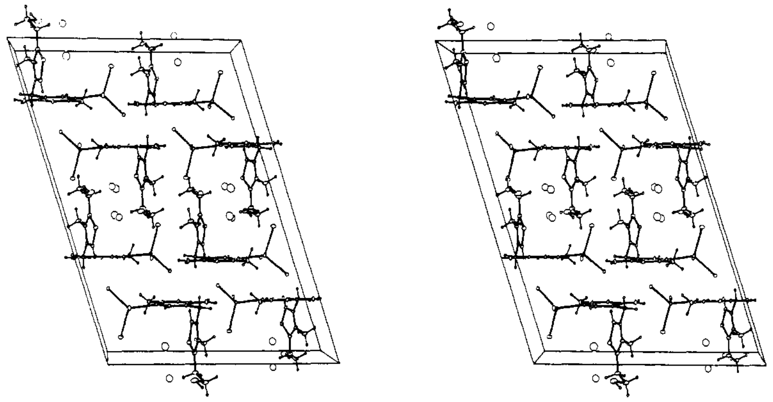

Figure 3. Stereoview of the contents of a unit cell of Cd(thiamine)Cl_3·$0.6H_2O$. The view is down *b*. The 20% thermal ellipsoids are shown, except for hydrogen atoms which have been artificially set at $B = 0.6$ Å^2.

Description of the Structure

The crystal structure of Cd(thiamine)Cl_3·$0.6H_2O$ consists of the packing of 8 formula units in the cell, as shown in the stereoview (Figure 3). Forces between molecules in the unit cell include dipolar interactions between each of the atoms of the postively charged thiazolium ring and the coordinated chloro ligands, hydrogen bonds, and a base-stacking interaction between pyrimidine rings. Short intermolecular distances are summarized in Table VI. All other contacts are van der Waals', and none is shorter than 3.70 Å.

The strongest interactions between molecules in the crystal are hydrogen bonds (Table VI). The N(41′)–Cl and O(53)–Cl hydrogen bonds in this structure are similar to those found in many thiamine structures. The range of N(41′)–Cl distances observed in other structures is 3.12[14] to 3.44 Å[7,15] and the range for O(53)–Cl distances is 3.04[16]–3.26 Å,[6] with the longer hydrogen bonds involving the present structure and those with $CuCl_4^{2-}$ [7] and $CdCl_4^{2-}$ [6] counterions. Presumably a bound chloro ligand is not as good a hydrogen bond acceptor as a free chloride ion. Hydrogen bonding between the acidic C(2)–H group and various acceptors has often been noted in thiamine structures. A Cl^- ion is the most common acceptor,[7,8,14,16,17] but the list of those observed also includes O(53),[6] a pyrophosphate oxygen atom of thiamine pyrophosphate,[18] and an oxygen atom of a picrolonate counterion.[15] In the present structure atom C(2) may be weakly hydrogen bonded to atom N(3′) of the pyrimidine ring of a neighboring molecule. The distance, 3.146 (3) Å, is in very good agreement with that predicted by Pletcher and Sax[14] (3.12 Å) for such an interaction from their analysis of the hydrogen bonding radius of a C–H group.

Table VI. Possible Hydrogen Bonding Interactions, A–H···B, and Other Short Contacts

A	B	equiv postn for B	A–B, Å	A–H–B, Deg
		Hydrogen Bonds		
N(41′)	Cl(1)	$x, 1-y, 1/2+z$	3.355 (2)	158
N(41′)	Cl(2)	$x, -y, 1/2+z$	3.395 (2)	168
O(53)	Cl(3)	$-x, y-1, 1/2-z$	3.170 (3)	167
C(2)	N(3′)	$x, y-1, z$	3.146 (3)	120
		Other Interactions[a]		
S	O(53)	x, y, z	2.879 (3)	
C(2)	Cl(1)	$x, -y, 1/2+z$	3.484 (3)	
C(2)	Cl(1)	$1/2-x, y-1/2, 1/2-z$	3.568 (3)	
N(3)	Cl(3)	$x, -y, 1/2+z$	3.682 (2)	
N(3)	Cl(1)	$x, -y, 1/2+z$	3.710 (2)	
C(4)	Cl(3)	$x, -y, 1/2+z$	3.425 (3)	
C(41)	Cl(3)	$-x, y, 1/2-z$	3.638 (3)	
C(5)	Cl(3)	$x, -y, 1/2+z$	3.528 (3)	
C(35′)	Cl(1)	$1/2-x, y-1/2, 1/2-z$	3.522 (2)	
C(35′)	Cl(1)	$x, -y, 1/2+z$	3.526 (2)	
C(35′)	Cl(2)	$x, -y, 1/2+z$	3.626 (2)	
O(W1)	O(53)	$-x, 1+y, 1/2-z$	2.88 (1)	
O(W1)	O(W2)	x, y, z	2.77 (2)	
O(W2)	O(W2)	$-x, y, 1/2-z$	2.52 (2)	
O(W2)	Cl(3)	$-x, y, 1/2-z$	3.41 (1)	

[a] Since the hydrogen atom positions on the partially occupied water molecules were not located, interactions involving O(W1) or O(W2) are listed here rather than as hydrogen bonds.

Both the thiazolium and pyrimidine rings of the thiamine ligand are planar, as shown in Table VII. There is a weak base-stacking

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Table VII. Best Weighted Least-Squares Planes

Deviations from Planes (Å)

plane 1		plane 2[a]	
N(1′)	0.003 (2)	N(3)	0.000 (2)
C(6′)	0.004 (2)	C(2)	−0.002 (2)
C(2′)	−0.009 (2)	S	0.0002 (6)
N(3′)	0.003 (2)	C(4)	0.002 (2)
C(4′)	0.004 (2)	C(5)	−0.004 (3)
C(5′)	−0.007 (2)	C(41)	0.070[b]
Cd	−0.199[b]	C(35′)	0.014
C(21′)	−0.094	C(51)	0.024
N(41′)	0.022	C(52)	1.057
C(35′)	−0.007	O(53)	0.602

Parameters Defining Planes

	plane 1	plane 2
σ^c	0.005	0.002
A^d	24.755	−6.665
B	−0.489	−2.838
C	−0.231	16.761
D	4.237	6.665

[a] The angle between planes 1 and 2 is 88.4°. [b] If no error is given, the atom was not used in the calculation of the plane. [c] Mean deviation from the plane. [d] The equation of the plane is $Ax + By + Cz = D$ in monoclinic coordinates as defined by: Hamilton, W. C. *Acta Crystallogr.* **1961**, *14*, 185-189.

Table VIII. Bond Distances (Å) and Angles (Deg) about the Cadmium Ion in $Cd(thiamine)Cl_3 \cdot 0.6H_2O$

Bond Distances			
Cd-N(1′)	2.239 (2)	Cd-Cl(2)	2.451 (1)
Cd-Cl(1)	2.444 (1)	Cd-Cl(3)	2.457 (1)
Bond Angles			
Cl(1)-Cd-N(1′)	117.45 (5)	Cl(1)-Cd-Cl(3)	106.17 (4)
Cl(2)-Cd-N(1′)	101.96 (4)	Cl(2)-Cd-Cl(3)	109.37 (2)
Cl(3)-Cd-N(1′)	107.20 (5)	Cd-N(1′)-C(6′)	118.9 (1)
Cl(1)-Cd-Cl(2)	114.38 (2)	Cd-N(1′)-C(2′)	124.3 (1)

interaction along the *a* direction between pyrimidine planes of pairs of molecules related by the centering and inversion operations. The average separation between these two parallel planes is 3.52 Å, a distance perhaps shorter than the van der Waals' thickness. The ring of one pyrimidine is overlapped by the N(41′) amino group of the second, as can be seen in Figure 4. Although this arrangement is the most commonly observed stacking pattern for pyrimidine,[19] it has been observed previously in only one other thiamine structure, where the distance between rings is 3.42 Å.[18]

Not only is this structure unique in being the first metal ion complex of thiamine but also the coordination about the Cd(II) ion is unusual. The most commonly encountered coordination geometry for Cd(II) is octahedral. Here the geometry of the cadmium coordination sphere, composed of three chloro ligands and a nitrogen atom N(1′) of the pyrimidine ring of the thiamine moiety, is tetrahedral as shown by the bond angles in Table VIII. While tetrahedral complexes of Cd(II) are known, they are not common and this appears to be the first example of a Cd(II) complex with a Cl_3N coordination sphere. The Cd–Cl bond lengths, which in this structure average 2.451 (6) Å, fall within the range observed for both $CdCl_4^{2-}$ [2,20,21] and CdL_2Cl_2 [22,23] complexes. The Cd–N distance in this structure, 2.239 (2) Å, is shorter than the Cd–N distances in $Cd(bpy)[Mn(CO)_5]_2$, 2.353 (6) Å,[24] $Cd(o\text{-phen})[Mn(CO)_5]_2$, 2.36 (3) Å,[24] and $[(bpy)CdFe(CO)_4]_3$, 2.37 (2) Å,[29] but is comparable with the Cd–N distance of 2.22 (1) Å in $Cd(dicyandiamide)_2I_2$.[25]

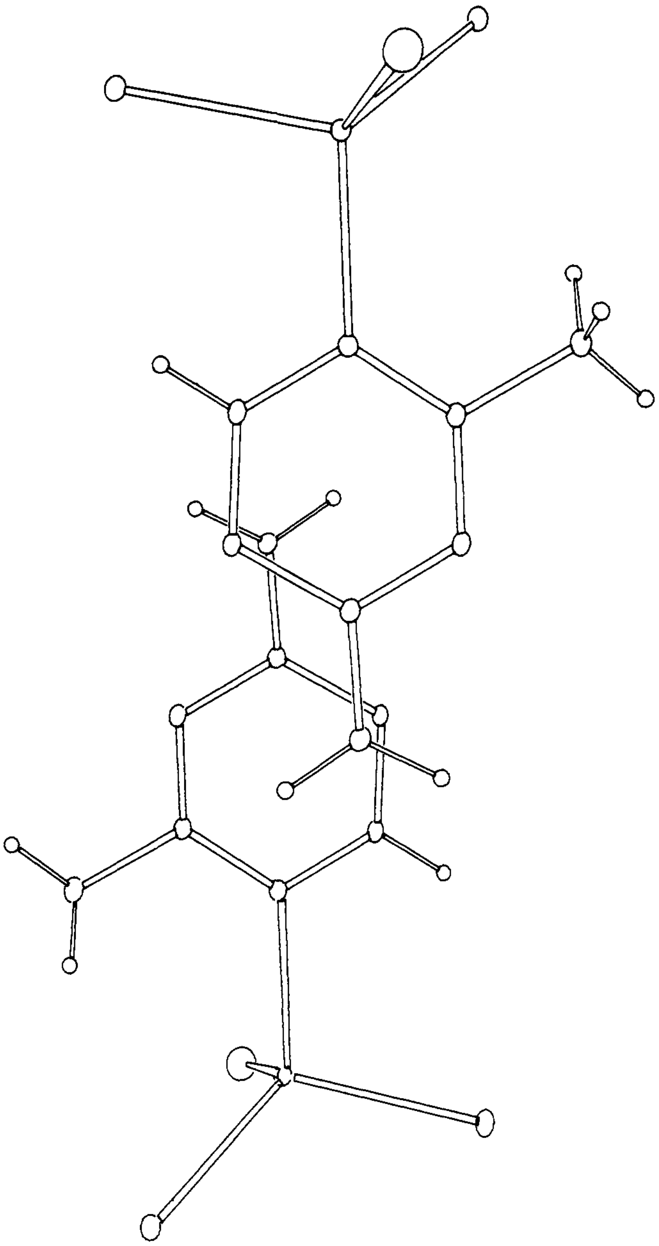

Figure 4. View of the $CdCl_3$(pyrimidine) portion of the $Cd(thiamine)Cl_3$ molecule showing overlap of the pyrimidine rings. The view, drawn with 20% thermal ellipsoids, is perpendicular to the pyrimidine planes and shows portions of the molecules at x, y, z and $^1/_2 - x, ^1/_2 - y, z$.

One feature of thiamine structures which has received considerable attention is the conformation about the methylene group joining the pyrimidine and thiazolium rings. The torsion angles ϕ_T and ϕ_P, as defined by Pletcher and Sax,[14] have been collected for all thiamine structures in a recent publication.[15] For $Cd(thiamine)Cl_3 \cdot 0.6H_2O$ these torsion angles are $\phi_T = +112.6°$ and $\phi_P = +129.8°$, corresponding to the S form of thiamine which has been observed in only 3 of the 18 reported thiamine structures.[15] In two of these structures the thiazolium ring bears a bulky substituent on the C(2) carbon atom[26,27] while the other is $(H\text{-}thiamine)(CdCl_4) \cdot 2H_2O$.[6] The torsion angles ϕ_T and ϕ_P in the

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Table IX. Comparison of Bond Distances (Å) and Angles (Deg) for Various Thiamine Derivatives

atoms	thiamine^{+} [a] F conformatn	$Cd(thiamine)Cl_3$ S conformatn	(H-thiamine)$^{2+}$ [d] S conformatn	(H-thiamine)$^{2+}$ [f] C-2 substd S conformatn	H(thiamine)$^{2+}$ [g] O(53)–S interactn F conformatn	(H-thiamine)$^{2+}$ [h] no O(53)–S interactn F conformatn
			Distances (Å)			
N(1')–C(6')	1.342 (4)[b]	1.353 (3)[c]	1.356 (4)[e]	1.353 (8)[b]	1.352 (4)[b]	1.350 (9)[b]
N(1')–C(2')	1.335 (7)	1.353 (3)	1.337 (4)*	1.338 (8)	1.348 (6)	1.346 (9)
C(2')–N(3')	1.332 (7)	1.329 (3)	1.312 (5)	1.313 (8)	1.314 (4)*	1.310 (2)
C(2')–C(21')	1.49 (1)	1.500 (3)	1.496 (5)	1.479 (8)	1.490 (4)	1.481 (7)
N(3')–C(4')	1.350 (4)	1.355 (3)	1.364 (4)	1.355 (8)	1.365 (4)	1.361 (7)
C(4')–N(41')	1.334 (5)	1.346 (3)	1.323 (4)*	1.313 (8)*	1.316 (4)*	1.316 (7)*
C(4')–C(5')	1.416 (6)	1.417 (3)	1.422 (5)	1.433 (8)	1.433 (4)*	1.432 (7)
C(5')–C(6')	1.369 (4)	1.369 (3)	1.343 (5)*	1.354 (8)	1.355 (8)	1.357 (9)
C(5')–C(35')	1.490 (4)	1.508 (3)	1.512 (5)	1.505 (8)	1.497 (4)	1.49 (1)
C(35')–N(3)	1.499 (5)	1.480 (3)	1.478 (5)	1.479 (8)	1.494 (4)	1.485 (9)
N(3)–C(2)	1.315 (6)	1.331 (3)	1.314 (4)*	1.337 (8)	1.316 (4)	1.32 (2)
N(3)–C(4)	1.390 (4)	1.387 (3)	1.392 (5)	1.395 (8)	1.399 (6)	1.393 (7)
C(2)–S	1.673 (8)	1.676 (2)	1.668 (4)	1.676 (9)	1.675 (4)	1.669 (6)
C(5)–S	1.72 (1)	1.735 (2)	1.719 (4)*	1.729 (8)	1.727 (5)	1.723 (8)
C(4)–C(5)	1.357 (6)	1.352 (3)	1.349 (5)	1.360 (8)	1.360 (4)	1.349 (8)
C(5)–C(51)	1.497 (5)	1.510 (4)	1.507 (6)	1.50 (1)	1.499 (7)	1.499 (8)
C(4)–C(41)	1.487 (5)	1.496 (3)	1.496 (5)	1.494 (8)	1.483 (4)	1.49 (1)
C(51)–C(52)	1.509 (4)	1.510 (4)	1.518 (6)	1.513 (8)	1.510 (4)	1.523 (8)
C(52)–O(53)	1.413 (5)*	1.437 (4)	1.426 (5)	1.415 (8)	1.435 (4)	1.420 (9)[i]
			Angles (Deg)			
C(2')–N(1')–C(6')	115.3 (5)	116.5 (2)	120.2 (3)*	120.7 (6)*	119.8 (7)*	121.0 (8)*
N(3')–C(2')–N(1')	126.1 (2)*	124.7 (2)	122.7 (3)*	122.6 (5)*	122.9 (5)*	122.0 (9)
N(3')–C(2')–C(21')	116.4 (2)*	117.6 (2)	119.8 (3)*	120.1 (5)*	119.9 (2)*	120.4 (5)
N(1')–C(2')–C(21')	117.4 (2)	117.6 (2)	117.5 (3)	117.2 (5)	117.3 (3)	117.6 (6)
C(2')–N(3')–C(4')	117.8 (2)	118.4 (2)	118.3 (3)	118.5 (5)	118.6 (2)	118.9 (4)
N(41')–C(4')–N(3')	116.6 (4)	116.1 (2)	115.8 (3)	116.8 (5)	115.8 (5)	116.4 (4)
N(41')–C(4')–C(5')	123.0 (6)	123.2 (2)	123.4 (3)	122.7 (5)	123.4 (3)	122.6 (4)
N(3')–C(4')–C(5')	120.4 (2)	120.7 (2)	120.9 (3)	120.5 (5)	120.8 (2)	120.9 (5)
C(6')–C(5')–C(4')	116.0 (3)	116.3 (2)	116.8 (3)	116.8 (5)	116.3 (6)	116.3 (6)
C(6')–C(5')–C(35')	120.8 (6)	120.6 (2)	121.4 (3)	122.6 (5)*	119.9 (4)	120.5 (7)
C(4')–C(5')–C(35')	123.1 (2)	123.0 (2)	121.7 (3)*	120.5 (5)*	123.7 (2)	123.2 (4)
N(1')–C(6')–C(5')	124.3 (5)	123.4 (2)	120.9 (3)*	120.5 (5)*	121.6 (6)	120.7 (5)*
N(3)–C(35')–C(5')	113.4 (6)	111.6 (2)	111.9 (3)	111 (2)	113 (2)	113 (2)
C(2)–N(3)–C(4)	114.1 (2)	114.2 (2)	114.8 (3)	114.0 (6)	114.0 (2)	113.6 (4)
C(2)–N(3)–C(35')	123.5 (2)*	121.9 (2)	120.8 (3)*	123.6 (6)	124.3 (2)*	124.1 (9)
C(4)–N(3)–C(35')	122.1 (2)*	124.0 (2)	124.1 (3)	122.3 (5)*	121.7 (2)*	122 (1)
N(3)–C(2)–S	112.4 (2)	112.1 (2)	111.9 (3)	111.7 (6)	112.7 (2)	112.7 (4)
C(2)–S–C(5)	91.5 (2)	91.2 (2)	91.5 (2)	92.1 (5)	91.3 (2)	91.3 (4)
C(4)–C(5)–C(51)	129 (1)	127.9 (2)	129.3 (3)*	129 (1)	127.5 (3)	129 (1)
C(4)–C(5)–S	110.2 (4)	110.6 (2)	110.9 (3)	110.0 (5)	110.5 (2)	110.5 (5)
C(51)–C(5)–S	121.0 (6)	121.5 (2)	119.4 (3)*	121 (1)	122.0 (2)	120 (1)
C(5)–C(4)–N(3)	111.9 (2)	112.0 (2)	110.9 (3)*	112.3 (5)	111.6 (5)	112.0 (4)
C(5)–C(4)–C(41)	127.5 (3)	128.5 (2)	129.1 (3)	126 (1)	127.7 (4)	127.4 (8)
N(3)–C(4)–C(41)	120.6 (4)	119.5 (2)	119.8 (3)	121.3 (9)	120.7 (8)	120.6 (4)
C(5)–C(51)–C(52)	112.9 (6)	113.1 (2)	112.1 (3)	115 (1)	113.9 (6)	111.5 (6)
C(51)–C(52)–O(53)	111 (1)*	106.5 (2)	111.9 (4)*	108.5 (5)*	107.7 (2)*	112.2 (9)[i]

[a] Average of (thiamine)$Cl\cdot H_2O$[15] and thiamine picrolonate dihydrate.[14] [b] The number in parentheses is the larger of the standard deviations estimated for an individual value from the inverse matrix or calculated on the assumption that the values are from the same population. [c] The estimated standard deviations in parentheses are from the structural work reported here. [d] From the structure of (H-thiamine)$CdCl_4\cdot H_2O$.[5] [e] Estimated standard deviations reported in ref 5. [f] Average of DL-2-(α-hydroxybenzyl)thiamine chloride hydrochloride trihydrate[26] and DL-2-(α-hydroxyethyl)thiamine)chloride hydrochloride.[25] [g] Average of the two independent molecules of thiamine pyrophosphate tetrahydrate reported in ref 17. [h] Average of (thiamine)$Cl\cdot HCl\cdot {}^1/_2[Mg(H_2O)_6]Cl\cdot 2H_2O$ reported in ref 7, [H-thiamine]$CuCl_4$, reported in ref 6, thiamine pyrophosphate hydrochloride, reported in ref 13, and (thiamine)$Cl\cdot HCl$, reported in ref 16. [i] This average does not include the thiamine pyrophosphate hydrochloride structure.

present structure are very close to those reported for the $CdCl_4^{2-}$ salt (ϕ_T = 110.4° and ϕ_p = 137.3°)[6] but are, as might be expected, less like those found for the two C(2)-substituted derivatives.[26,27] Richardson et al.[6] have suggested that the conformation of thiamine found in a particular structure is largely the result of packing forces. On the other hand, since the F form has been found in 13 of the 18 known structures, occurring with a variety of counterions and space groups, Shin et al. argue that the "evidence strongly indicates that the conformation of thiamine with respect to the C(35′) methylene bridge is largely influenced by its intramolecular properties".[15] The present work, which doubles the number of known structures in which an unsubstituted thiamine is in the S conformation, further complicates the situation and so does not resolve this disagreement.

The torsion angles which describe the conformation of the β-hydroxyethyl side chain[15] are $\phi_{5\alpha}$ = +46.5° and $\phi_{5\beta}$ = −68.8° in the present structure. These angles are typical for those structures, including the present one, in which the side chain folds back so that a short O(53)–S contact results.[15,18,27,28] However the O(53)–S distance, 2.879 (3) Å, is shorter than that found in other thiamine derivatives with this structural feature, namely, 3.064 (2) Å in thiamine picrolonate dihydrate[15] and 3.003 (5) Å in DL-2-(α-hydroxybenzyl)thiamine chloride.[27] It is slightly shorter than that observed for thiochrome[28] (2.937 (2) Å) and for thiamine pyrophosphate[18] (2.952 (5) and 2.917 (2) Å) where the pyro-

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phosphate group bears a negative charge. This tight intramolecular O–S interaction may be the result of a small amount of additional positive charge on the S atom owing to the coordination of the Cd^{2+} ion. Whatever the reason, it results in a long C(52)–O(53) bond, 1.437 (4) Å, nearly as long as that seen in the pyrophosphate esters, 1.435 (1)[18] and 1.454 (4)[14] Å, and a small C(51)–C(52)–O(53) angle. As the O(53)–S interaction becomes stronger, one would expect the C(2)–S and C(5)–S bonds to lengthen. Indeed these bonds in this structure are the longest ever found for thiamine (Table IX).

Effects of Cadmium Ion Coordination on the Thiamine Geometry

In order to examine the impact of Cd^{2+} coordination on the structure of thiamine we turn to Table IX. There the structural parameters for the title complex (column 2) are compared with those of other forms of the vitamin. All structures for which the standard deviations are small enough to allow meaningful comparisons are included. When the structure of a particular form of thiamine has been determined more than once, averages of equivalent distances and angles are listed. Those metrical parameters in the other forms of thiamine which differ in a possibly significant manner from the parameters in the present structure are starred in Table IX. It should be borne in mind that while the present structure determination was carried out at −166 °C, the other structure determinations summarized in Table IX were carried out at room temperature. In none of these structures were corrections made for the foreshortening effects of thermal motion. Accordingly, the fact that most of the starred quantities in Table IX are shorter than found in the present structure may simply be a consequence of the temperature at which the experiment was performed.

Differences in bond lengths between the various structural forms are in general very small. In fact there are no differences of significance in the bond lengths of the thiazolium ring. There are some small differences in the bond lengths in the pyrimidine ring, with the bond lengths for the Cd^{2+} complex being between those of the protonated and free-base forms but closer to those of the free base. The effect of Cd^{2+} coordination is greater near the coordination site so that the bonds about atom N(1′), i.e., N(1′)–C(6′) and N(1′)–C(2′), are closer to those of protonated rather than deprotonated thiamine.

The most important structural effect of Cd^{2+} coordination is probably the increase of the C(4′)–N(41′) bond length by about 0.03 Å compared with the protonated base. Thus while protonation of atom N(1′) shortens the C(4′)–N(41′) distance significantly, Cd^{2+} coordination to N(1′) has much less effect. In fact in this structure the C(4′)–N(41′) distance is longer by about 0.01 Å than in the free base. However this small increase is not statistically significant.

While most changes in bond lengths are in general small and barely significant, larger changes in some bond angles occur upon Cd^{2+} coordination. Within the pyrimidine ring significant changes about atom N(1′) are seen for angles C(2′)–N(1′)–C(6′), N(3′)–C(2′)–N(1′), C(5′)–C(6′)–N(1′), and N(3′)–C(2′)–C(21′). In all cases the values for the Cd^{2+} complex lie between those for the protonated and free-base forms of thiamine but lie closer to those of the free base.

Large differences are also observed for angles around atom N(3). The angles C(2)–N(3)–C(35′) and C(4)–N(3)–C(35′) in the present structure are most like those found for (H-thiamine)($CdCl_4$)·$2H_2O$,[6] the only other structure in which an unsubstituted thiamine exists in an S conformation. For unsubstituted thiamine, we suggest that these two angles are sensitive to the molecular conformation. The angles around atom C(5′) appear to be less sensitive to conformation and are similar for all forms of the molecule except those with C(2) substituents.

Significance

The most important feature of this structure is the coordination of the thiamine molecule to the cadmium ion. We thus prove that at least one such complex exists and therefore add support to those mechanisms of protein activity which require metal ion coordination to thiamine. The complex is easily produced from the reaction of Cd(acetate)$_2$ and (thiamine)Cl·HCl, analogues of which may be found in biological systems. Once formed, the complex as a solid or in solution is stable.

Schellenberger[2] has shown that the N(41′) amino group plays a role in the mechanism of enzyme action of thiamine. Mechanisms have been proposed[30] in which this $-NH_2$ group acts either as a base or as a hydrogen-bond donor in the reaction of thiamine with substrate. If protonation or metal ion coordination at atom N(1′) has an effect on the base strength of the N(41′) amino group, it could be an important step in the enzymatic mechanism. Protonation of atom N(1′) causes the C(4′)–N(41′) bond length to decrease by about 0.02 Å, decreasing the base strength of the N(41′) amino group and enhancing its ability to act as a hydrogen bond donor. One might expect a metal ion acting as a Lewis acid to have a similar influence upon coordination at atom N(1′). This expectation is clearly not met in Cd(thiamine)Cl_3. We therefore conclude that Cd^{2+} coordination at atom N(1′) has much less effect on the amino group at atom C(4′) than does protonation. In fact if Cd^{2+} coordination produces any effect on the base strength of atom N(41′), it is not detectable within the accuracy of our structural measurements.

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Supplementary Material Available: A listing of hydrogen atom parameters (Table III), observed and calculated structure amplitudes (Table IV), and root-mean-square amplitudes of vibration (Table V) (19 pages). Ordering information is given on any current masthead page.

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