(9) R. W. Fessenden, *J. Chem. Phys.*, **37**, 747 (1962).
(10) H. Fischer, *Z. Naturforsch., Teil A*, **19**, 866 (1964).
(11) H. Zeldes and R. Livingston, *J. Am. Chem. Soc.*, **93**, 1082 (1971).
(12) H. Zeldes and R. Livingston, unpublished results.

(13) (a) C. Heller and H. M. McConnell, *J. Chem. Phys.*, **32**, 1535 (1960); (b) E. W. Stone and A. H. Maki, *ibid.*, **37**, 1326 (1962).
(14) R. W. Fessenden and R. H. Schuler, *J. Chem. Phys.*, **39**, 2147 (1963).
(15) H. Fischer, *Z. Naturforsch., Teil A*, **20**, 428 (1964).

Reactions of Metals with Vitamins. I. Crystal and Molecular Structure of Thiaminium Tetrachlorocadmate Monohydrate

Mary Frances Richardson,*[1a] Kenneth Franklin,[1a] and Doris M. Thompson[1b]

Contribution from the Department of Chemistry, Brock University, St. Catharines, Ontario L2S 3A1, Canada, and Department of Chemistry, Wofford College, Spartanburg, South Carolina 29301. Received December 23, 1974

Abstract: The X-ray crystal structure of (protonated thiamine) tetrachlorocadmate monohydrate, $CdCl_4C_{12}H_{20}N_4O_2S$, has been determined. The unit cell parameters are $a = 16.874$ (2), $b = 15.553$ (2), $c = 7.906$ (2) Å; $\beta = 97.61$ (6)°; space group $P2_1/n$; $Z = 4$. A total of 2498 reflections having $F^2 > 2\sigma(F^2)$, $2\theta < 50°$ were collected on a four-circle diffractometer with Mo $K\alpha$ radiation by the θ–2θ scan technique. The structure was solved by conventional heavy atom methods. All atoms heavier than hydrogen were refined anisotropically; positional parameters only were refined for the hydrogen atoms. Successive block-diagonal least-squares cycles yielded a conventional R factor of 0.027. The structure consists of protonated thiamine cations, tetrachlorocadmate anions, and a water molecule of hydration. The protonation site is on the pyrimidine nitrogen opposite the amino group. The observed thiamine conformation differs grossly from that usually found for thiamine derivatives but is one of the conformations theoretically predicted to be stable. The large number of hydrogen bonds, together with the short dipolar contacts involving the thiazolium sulfur and nitrogen atoms, may help to stabilize the present conformation. The tetrachlorocadmate anion is an almost regular tetrahedron with an average Cd–Cl distance of 2.453 Å. The coordination of thiamine to a metal appears to be an unlikely event since the electron pairs which would be used to bond a metal are generally involved in the π systems of the thiazolium and pyrimidine rings.

Various studies have indicated that metal complexes might be formed with thiamine and its derivatives.[2-7] There are several areas where complexing might be an important facet of the chemistry of thiamine. For example, complex formation is a possible mechanism for the prevention of cadmium[8,9] or manganese[10,11] poisoning by thiamine and would be involved if the oxidation of thiamine by metal ions[12,13] proceeded by an inner-sphere mechanism. However, definitive proof of metal–thiamine bonding is lacking, although some recent research[14-19] has been directed toward just this point.

We have been examining the reactions of thiamine with metal ions and report herein the structure of (protonated thiamine) tetrachlorocadmate monohydrate, $HThiCdCl_4 \cdot H_2O$.

Experimental Section

Crystals of $HThiCdCl_4 \cdot H_2O$, $CdCl_4C_{12}H_{20}SO_2N_4$, were prepared by mixing aqueous solutions of thiamine hydrochloride and cadmium nitrate (2:1 mole ratio) and allowing the solution to evaporate. Well-formed, colorless monoclinic crystals were obtained. A plate-like crystal, $0.20 \times 0.31 \times 1.1$ mm, was mounted on a glass fiber with epoxy cement and aligned about the c^* axis on a Picker four-circle diffractometer. The long dimension of the crystal was approximately parallel to the ϕ axis of the diffractometer. Cell dimensions were determined from scans of the axial and $h0l$ reflections out to $2\theta = 60°$ with Mo $K\alpha$ radiation at a take-off angle of 1.5° ($\lambda = 0.70926$ Å for Mo $K\alpha_1$): $a = 16.874$ (2), $b = 15.553$ (2), $c = 7.906$ (2) Å; $\beta = 97.61$ (6)°; space group $P2_1/n$; $Z = 4$; $d_{obsd} = 1.78$ g/cc, $d_{calcd} = 1.74$ g/cc.

Previously described procedures were used for the data collection and reduction to the structure factors.[20] Of the 3816 reflections with $2\theta < 50°$ in the independent quadrant, 2948 had $F_o^2 > 2\sigma(F_o^2)$ and were classified as observed. Although the crystal turned brown during the data collection, it remained transparent

and there was no significant decrease in the intensities of the standard reflections, which were measured approximately every 2 hr. No absorption correction was made in view of the low absorbance of the crystal (μ for Mo $K\alpha$ radiation = 1.72 mm^{-1}).

Scattering factors for neutral Cl, S, O, N, C, and H atoms were taken from the International Tables for X-Ray Crystallography,[21] as were the real and imaginary parts of the anomalous scattering of cadmium. The neutral cadmium scattering factors were obtained from Cromer et al.[22] Major computer programs employed included Zalkin's FORDAP, Busing and Levy's ORFLS, and Busing, Martin, and Levy's ORFFE. In the least-squares refinements, the function minimized was $\Sigma w \Delta^2$, where $w = 1/\sigma^2(F)$ and $\Delta = ||F_o| - |F_c||$. Unweighted and weighted residuals, R_1 and R_2, respectively, were calculated after each refinement.

$$R_1 = \Sigma\Delta / \Sigma|F_o|$$

$$R_2 = \Sigma w\Delta^2 / \Sigma w F_o^2$$

The structure was solved by the usual heavy atom methods. All atoms heavier than hydrogen were located and their positions and anisotropic thermal parameters were refined in the block diagonal approximation (position and thermal parameters for the Cd, 4(Cl), and thiazolium atoms were refined in one cycle, whereas the corresponding variables for the pyrimidine atoms and the water molecule were refined in the next). At this stage, $R_1 = 0.055$, $R_2 = 0.074$. A difference map yielded the positions of the hydrogen atoms. Their positional parameters were refined but the isotropic temperature factors were kept fixed at 4.0 Å^2. Subsequent refinements of the nonhydrogen atoms yielded final values of 0.027 and 0.037 for R_1 and R_2, respectively. The average parameter shift on the last cycle was 0.4 σ. The error in an observation of unit weight was 1.0.

A weighting analysis showed that the strong reflections and those with low sin θ/λ were somewhat overweighted, but as the number of affected reflections was small, no correction was made to the weighting scheme. A final difference Fourier map revealed no peaks higher than about 0.5 e/Å^3 and no holes deeper than

Table I. Positional and Anisotropic Thermal Parameters for the Nonhydrogen Atoms in HThiCdCl$_4\cdot$H$_2$O[a]

Atom	10^4x	10^4y	10^4z	$10^4\beta_{11}$	$10^4\beta_{22}$	$10^4\beta_{33}$	$10^4\beta_{12}$	$10^4\beta_{13}$	$10^4\beta_{23}$
Cd	1847.4 (1)	1717.2 (2)	−1204.5 (3)	22.0 (1)	30.1 (1)	107.2 (5)	4.87 (8)	5.3 (2)	6.8 (2)
Cl(1)	2958.0 (6)	737.2 (7)	−198 (1)	29.4 (4)	44.1 (5)	214 (2)	15.6 (4)	8.2 (7)	24.4 (8)
Cl(2)	693.3 (6)	862.7 (6)	−2445 (1)	29.1 (4)	33.0 (4)	177 (2)	1.7 (3)	−8.1 (7)	−7.8 (7)
Cl(3)	1477.0 (7)	2484.1 (7)	1255 (1)	40.2 (4)	46.4 (5)	145 (2)	3.4 (4)	28.3 (7)	−13.0 (7)
Cl(4)	2204.7 (6)	2700.3 (7)	−3423 (1)	28.8 (4)	52.8 (5)	169 (2)	6.9 (4)	15.4 (7)	44.7 (8)
O(1)	4381 (2)	3719 (2)	5122 (3)	38 (1)	65 (2)	120 (5)	4 (1)	17 (2)	−6 (2)
C(1)	3680 (3)	4167 (3)	4400 (5)	39 (2)	57 (2)	122 (7)	5 (2)	19 (3)	−22 (3)
C(2)	3195 (2)	3652 (3)	2995 (5)	30 (2)	67 (2)	129 (7)	−4 (2)	24 (3)	−15 (3)
C(3)	3623 (2)	3556 (2)	1449 (4)	24 (1)	39 (2)	101 (6)	−4 (1)	9 (2)	−8 (3)
C(4)	4143 (2)	2944 (2)	1094 (4)	25 (1)	28 (1)	98 (6)	−5 (1)	5 (2)	−3 (2)
C(5)	4432 (3)	2170 (3)	2118 (5)	52 (2)	32 (2)	153 (7)	−6 (1)	11 (3)	11 (3)
C(6)	4230 (2)	3881 (2)	−1091 (4)	34 (2)	31 (2)	95 (6)	7 (1)	11 (2)	0 (2)
S	3565.9 (6)	4370.2 (7)	−33 (1)	37.9 (4)	42.5 (4)	120 (2)	16.7 (4)	11.8 (7)	2.0 (7)
N(1)	4476 (2)	3149 (2)	−374 (3)	24 (1)	25 (1)	91 (5)	0.8 (9)	8 (2)	−8 (2)
C(7)	5121 (2)	2652 (2)	−1012 (5)	21 (1)	29 (1)	169 (7)	−1 (1)	13 (2)	−21 (2)
C(8)	4812 (2)	1828 (2)	−1877 (4)	18 (1)	24 (1)	109 (5)	−1 (1)	8 (2)	7 (2)
C(9)	5235 (2)	1039 (2)	−1598 (4)	20 (1)	26 (1)	114 (5)	1 (1)	8 (2)	1 (2)
N(2)	5938 (2)	972 (2)	−647 (4)	26 (1)	28 (1)	192 (6)	4 (1)	−15 (2)	1 (2)
N(3)	4930 (2)	295 (2)	−2333 (4)	28 (1)	26 (1)	165 (6)	1 (1)	−2 (2)	−9 (2)
C(10)	4257 (2)	334 (2)	−3374 (4)	30 (1)	29 (2)	120 (6)	−3 (1)	12 (2)	−5 (2)
C(11)	3891 (3)	−473 (3)	−4160 (6)	43 (2)	36 (2)	217 (9)	−9 (1)	−4 (3)	−16 (3)
N(4)	3871 (2)	1073 (2)	−3768 (3)	23 (1)	33 (1)	115 (5)	1 (1)	−3 (2)	−2 (2)
C(12)	4142 (2)	1815 (2)	−3002 (5)	25 (1)	28 (2)	130 (6)	1 (1)	5 (2)	−2 (2)
O(2)	2573 (2)	1040 (2)	3719 (4)	45 (1)	64 (2)	196 (6)	5 (1)	−20 (2)	16 (3)

[a] The expression for the anisotropic temperature factor is $T_i = \exp(-\beta_{11}h^2 - \beta_{22}k^2 - \beta_{33}l^2 - \beta_{12}hk - \beta_{13}hl - \beta_{23}kl)$. The estimated standard deviation in parentheses refers to the least significant figure.

Table II. Hydrogen Positional Parameters in HThiCdCl$_4\cdot$H$_2$O

Atom	10^3x	10^3y	10^3z
H(O1)	475 (5)	377 (6)	456 (11)
H(C1A)	382 (3)	484 (4)	402 (7)
H(C1B)	337 (4)	430 (5)	533 (9)
H(C2A)	262 (4)	393 (4)	262 (7)
H(C2B)	307 (4)	312 (4)	341 (9)
H(C6)	443 (4)	402 (4)	−210 (8)
H(C5A)	442 (4)	158 (4)	147 (8)
H(C5B)	502 (4)	220 (5)	269 (9)
H(C5C)	401 (4)	214 (4)	264 (8)
H(C7A)	538 (3)	299 (4)	−176 (7)
H(C7B)	553 (3)	260 (3)	−2 (8)
H(N2A)	614 (3)	45 (4)	−42 (7)
H(N2B)	623 (3)	145 (4)	−15 (8)
H(C11A)	369 (3)	−32 (3)	−522 (7)
H(C11B)	421 (4)	−90 (4)	−410 (8)
H(C11C)	359 (4)	−70 (4)	−357 (7)
H(N4)	342 (4)	104 (5)	−455 (10)
H(C12)	386 (3)	230 (3)	−328 (7)
H(O2A)	270 (4)	91 (5)	246 (10)
H(O2B)	230 (4)	149 (5)	359 (10)

Table III. Interatomic Distances in HThiCdCl$_4\cdot$H$_2$O

Bond	Distance, Å	Bond	Distance, Å
Cd–Cl(1)	2.465 (1)	O(1)–H(O1)	0.81 (9)
Cd–Cl(2)	2.453 (1)	C(1)–H(C1A)	1.12 (6)
Cd–Cl(3)	2.432 (1)	C(1)–H(C1B)	0.98 (8)
Cd–Cl(4)	2.461 (1)	C(2)–H(C2A)	1.07 (6)
O(1)–C(1)	1.426 (5)	C(2)–H(C2B)	0.93 (7)
C(1)–C(2)	1.518 (6)	C(5)–H(C5A)	1.05 (6)
C(2)–C(3)	1.507 (6)	C(5)–H(C5B)	1.04 (7)
C(3)–C(4)	1.349 (6)	C(5)–H(C5C)	0.87 (7)
C(4)–C(5)	1.496 (5)	C(6)–H(C6)	0.93 (7)
C(4)–N(1)	1.392 (5)	C(7)–H(C7A)	0.94 (7)
N(1)–C(6)	1.314 (4)	C(7)–H(C7B)	0.98 (6)
C(6)–S	1.668 (4)	N(2)–H(N2A)	0.89 (6)
S–C(3)	1.719 (4)	N(2)–H(N2B)	0.95 (6)
N(1)–C(7)	1.478 (5)	C(11)–H(C11A)	0.89 (5)
C(7)–C(8)	1.512 (5)	C(11)–H(C11B)	0.85 (6)
C(8)–C(9)	1.422 (5)	C(11)–H(C11C)	0.81 (6)
C(9)–N(2)	1.323 (4)	N(4)–H(N4)	0.92 (7)
C(9)–N(3)	1.364 (4)	C(12)–H(C12)	0.90 (5)
N(3)–C(10)	1.312 (5)	O(2)–H(O2A)	1.07 (8)
C(10)–C(11)	1.496 (5)	O(2)–H(O2B)	0.84 (7)
C(10)–N(4)	1.337 (4)		
N(4)–C(12)	1.356 (4)		
C(12)–C(8)	1.343 (5)		

about 0.4 e/Å^3. Most of these features were located in the vicinity of the CdCl$_4{}^{2-}$ ion.

The final coordinates and thermal parameters are given in Tables 1 and 11. Observed and calculated structure factors are given in the supplementary material.[23]

Results and Discussion

The structure consists of protonated thiamine cations, tetrachlorocadmate anions, and water molecules of hydration (Figures 1 and 2). The bond distances and angles are listed in Tables III and IV, respectively. Table V presents the magnitudes and orientations of the thermal ellipsoids.[23] The equations for the unweighted least-squares planes of some important structural moieties are given in Table VI. Data for hydrogen bonds and other close contacts[23] appear in Table VII.

Structure of the Thiaminium Cation. The N(4) atom in the pyrimidine ring is the protonation site in the thiamine cation, as has been observed in other structures containing protonated thiaminium cations.[15,24-27] The bond lengths

and angles are generally quite close to the corresponding quantities for other thiamine structures.[15,16,24-29]

The atoms defining the pyrimidine and thiazolium rings are coplanar or nearly so (Table VI). The thiazolium ring with its substituents is bowl-shaped; C(2), C(5), and C(7) lie above the ring plane by more than 0.1 Å. The deviation of a given atom from the plane of the pyrimidine ring appears to be related to the deviation of the substituent on that atom, which in turn is probably due to packing effects.

The atoms C(9), N(2), H(N2A), and H(N2B) lie in a common plane (Table VI), which is slightly tilted with respect to the pyrimidine plane (angle $\simeq 7°$). The planarity of N(2) is evidence of significant overlap of a filled p$_z$ orbital on N(2) with the π system of the pyrimidine ring. The C(9)–N(2) distance of 1.323 Å is comparable with the C–N distances in the pyrimidine and thiazolium rings, thus
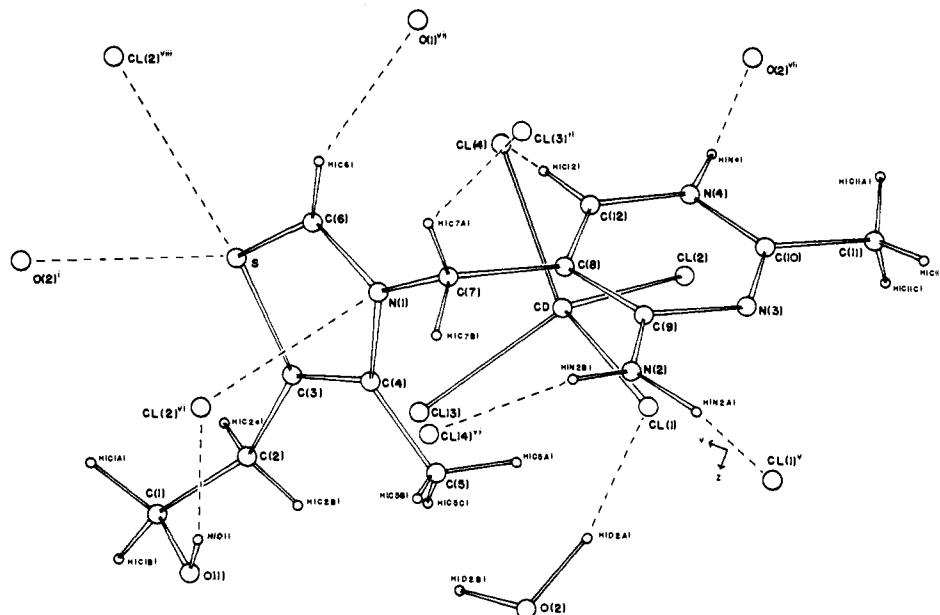
Figure 1. The structure of $HThiCdCl_4 \cdot H_2O$ projected onto the (001) plane. Hydrogen bonds and short contacts involving the thiaminium cation are also shown (the dashed line showing the hydrogen bond from H(O2B) to Cl(3) has been omitted for clarity). A listing of the symmetry superscripts may be found in Table VII.

Table IV. Bond Angles in $HThiCdCl_4 \cdot H_2O$ (in deg)[a]

Angle	Deg	Angle	Deg
Cl(1)–Cd–Cl(2)	108.87 (4)	N(1)–C(6)–H(C6)	116 (4)
Cl(1)–Cd–Cl(3)	108.07 (5)	S–C(6)–H(C6)	132 (4)
Cl(1)–Cd–Cl(4)	111.51 (5)	C(3)–S–C(6)	91.5 (2)
Cl(2)–Cd–Cl(3)	108.11 (5)	N(1)–C(7)–H(C7A)	110 (4)
Cl(2)–Cd–Cl(4)	107.95 (5)	N(1)–C(7)–H(C7B)	104 (4)
Cl(3)–Cd–Cl(4)	112.23 (4)	N(1)–C(7)–C(8)	111.9 (3)
H(O1)–O(1)–C(1)	113 (6)	H(C7A)–C(7)–H(C7B)	102 (5)
O(1)–C(1)–H(C1A)	112 (3)	H(C7A)–C(7)–C(8)	111 (4)
O(1)–C(1)–H(C1B)	107 (4)	H(C7B)–C(7)–C(8)	117 (3)
O(1)–C(1)–C(2)	111.9 (4)	C(7)–C(8)–C(9)	121.7 (3)
C(2)–C(1)–H(C1A)	114 (3)	C(7)–C(8)–C(12)	121.4 (3)
C(2)–C(1)–H(C1B)	112 (4)	C(9)–C(8)–C(12)	116.8 (3)
H(C1A)–C(1)–H(C1B)	99 (5)	C(8)–C(9)–N(2)	123.4 (3)
C(1)–C(2)–H(C2A)	112 (3)	C(8)–C(9)–N(3)	120.9 (3)
C(1)–C(2)–H(C2B)	110 (4)	N(2)–C(9)–N(3)	115.8 (3)
C(1)–C(2)–C(3)	112.1 (3)	C(9)–N(2)–H(N2A)	119 (3)
H(C2A)–C(2)–H(C2B)	103 (5)	C(9)–N(2)–H(N2B)	123 (3)
H(C2A)–C(2)–C(3)	109 (3)	H(N2A)–N(2)–H(N2B)	118 (5)
H(C2B)–C(2)–C(3)	111 (4)	C(9)–N(3)–C(10)	118.3 (3)
C(2)–C(3)–C(4)	129.3 (3)	N(3)–C(10)–C(11)	119.8 (3)
C(2)–C(3)–S	119.4 (3)	N(3)–C(10)–N(4)	122.7 (3)
C(4)–C(3)–S	110.9 (3)	C(11)–C(10)–N(4)	117.5 (3)
C(3)–C(4)–N(1)	110.9 (3)	C(10)–C(11)–H(C11A)	105 (3)
C(3)–C(4)–C(5)	129.1 (3)	C(10)–C(11)–H(C11B)	114 (4)
C(5)–C(4)–N(1)	119.8 (3)	C(10)–C(11)–H(C11C)	112 (4)
C(4)–C(5)–H(C5A)	117 (3)	H(C11A)–C(11)–H(C11B)	118 (5)
C(4)–C(5)–H(C5C)	94 (4)	H(C11B)–C(11)–H(C11C)	94 (6)
H(C5A)–C(5)–H(C5B)	102 (5)	C(10)–N(4)–H(N4)	116 (5)
H(C5A)–C(5)–H(C5C)	103 (5)	C(10)–N(4)–C(12)	120.2 (3)
H(C5B)–C(5)–H(C5C)	126 (6)	C(12)–N(4)–H(N4)	123 (5)
C(4)–N(1)–C(7)	124.1 (3)	N(4)–C(12)–H(C12)	118 (3)
C(4)–N(1)–C(6)	114.8 (3)	N(4)–C(12)–C(8)	120.9 (3)
C(6)–N(1)–C(7)	120.8 (3)	C(8)–C(12)–H(C12)	121 (3)
N(1)–C(6)–S	111.9 (3)	H(O2A)–O(2)–H(O2B)	103 (7)

[a] The estimated standard deviation in parentheses refers to the least significant figure.

providing additional evidence for a C(9)–N(2) bond order greater than unity.

The thiazolium sulfur and nitrogen atoms make some significant short contacts with chloride and oxygen atoms (Table VIId,[23] vide infra), which are relevant for discussing the bonding in the thiazolium ring. The fact that Cl(2)[vi] sits almost directly above the thiazolium N(1) atom, so that one of its electron pairs is pointing toward the p_z orbital on N(1), is evidence of positive charge (empty p_z orbital) on N(1). There may also be positive charge on the thiazolium sulfur atom, to judge by the fact that lone pairs of electrons from O(2)[i] and Cl(2)[viii] are directed toward the sulfur atom.

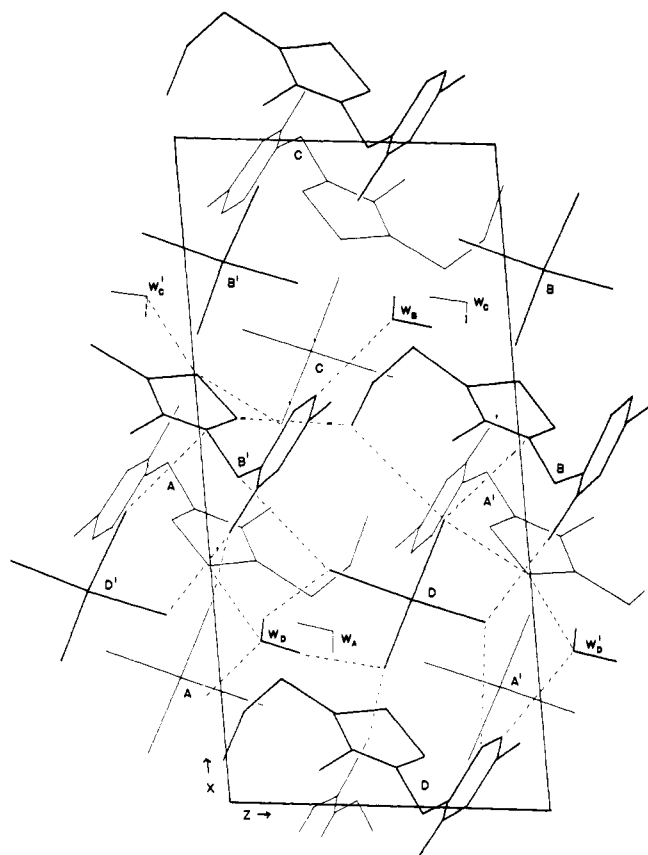In terms of the orbitals being used in the thiazolium ring,

Figure 2. Molecular packing in $HThiCdCl_4 \cdot H_2O$. The letters A, B, C, and D designate molecules at (x, y, z), $(1 - x, 1 - y, 1 - z)$, $(\frac{1}{2} + x, \frac{1}{2} - y, \frac{1}{2} + z)$, and $(\frac{1}{2} - x, \frac{1}{2} + y, \frac{1}{2} - z)$, respectively. Primes denote translation by ± 1 along z. W_A, W_B, W_C, and W_D are the water molecules. In order to avoid unnecessary clutter, hydrogen atoms have been omitted (except on the water molecules) and complete sets of contacts are shown for only one formula unit (water molecule D, tetrachlorocadmate D, and thiaminium cation B).

the N(1) atom may be assumed to use sp^2 orbitals to bond to C(4), C(6), and C(7), leaving a p_z orbital to participate in the π system or to accept electron density from $Cl(2)^{vi}$. The sulfur atom, which lies in a square plane (Table VIId) defined by C(3), C(6), $Cl(2)^{viii}$, and $O(2)^i$, can use two dsp^2 hybrid orbitals to bond to C(3) and C(6), the other two empty dsp^2 orbitals then being available to accept electron density from $Cl(2)^{viii}$ and $O(2)^i$. The remaining four electrons would be accommodated in a filled p_z orbital, which is of the proper symmetry to contribute to the π molecular orbitals, and in a filled d_{z^2} orbital, which does not have the correct symmetry for π bonding.

The Tetrachlorocadmate Anion. The cadmium ion is bonded to four chloride ions, with the resulting formation of a slightly distorted tetrahedron. The Cd–Cl distances range from 2.432 (1) to 2.465 (1) Å, with an average of 2.453 Å. The average is comparable to the distances observed in other chlorocadmates[30–32] when consideration is given to the variation in bond length with coordination number. The deviations from the mean in the $CdCl_4{}^{2-}$ ion are probably due to the fact that the chloride ion environments vary significantly (Table VIIc). The Cl–Cd–Cl angles lie within the limits 107.95–112.23°.

Hydrogen Bonding and Other Short Contacts. There are a large number of hydrogen bonds and short contacts in $HThiCdCl_4 \cdot H_2O$ (Figures 1 and 2, Table VII). All six hydrogen atoms in O–H or N–H bonds are hydrogen bonded to oxygen or chloride acceptors. Hydrogen atoms from C(7) and C(12) are also hydrogen bonded to chloride ions, and

Table VI. Deviations from Least-Squares Planes[a]

Atoms used in calculating plane	Deviation, Å	Atoms not used in calculating plane	Deviation, Å
		Pyrimidine Ring	
	$0.62901X + 0.16945Y - 0.75871Z = 6.85626$		
C(8)	0.027	C(7)	0.054
C(9)	−0.029	N(2)	−0.130
N(3)	0.005	H(N2A)	−0.057
C(10)	0.022	H(N2B)	−0.237
N(4)	−0.023	C(11)	0.104
C(12)	−0.001	H(N4)	−0.053
		H(C12)	−0.013
		Thiazolium Ring	
	$-0.67554X - 0.48169Y - 0.55823Z = -7.32688$		
C(3)	−0.001	C(2)	0.149
C(4)	0.002	C(5)	0.127
C(6)	0.002	C(7)	0.126
S	0.000	H(C6)	−0.036
N(1)	−0.003	$O(2)^I$	−0.439
		$Cl(2)^{viii}$	−1.035
	C(9)–N(2)–H(N2A)–H(N2B) Plane		
	$0.57696X + 0.06494Y - 0.81419Z = 6.32041$		
H(N2A)	0.004		
N(2)	−0.011		
H(N2B)	0.004		
C(9)	0.003		

[a] The equations of these unweighted least-squares planes have the form $aX + bY + cZ = d$, where X, Y, and Z are orthogonal coordinates (in Å) of the atoms in a system where the x, y, and z axes are parallel to the a^*, b, and c axes of the unit cell, respectively.

Table VII. Packing in $HThiCdCl_4 \cdot H_2O$[a]

a	b	c	$\angle abc$, deg	$d(a-c)$, Å	$d(b-c)$, Å
		(a) Hydrogen Bonds			
$O(1)-H(O1)$	$\cdots Cl(2)^{vi}$		169 (8)	3.261 (4)	2.46 (9)
$C(6)-H(C6)$	$\cdots O(1)^{vii}$		145 (5)	3.049 (5)	2.24 (6)
$C(7)-H(C7A)$	$\cdots Cl(3)^{iv}$		129 (5)	3.355 (4)	2.68 (7)
$N(2)-H(N2A)$	$\cdots Cl(1)^{v}$		163 (5)	3.263 (3)	2.40 (6)
$N(2)-H(N2B)$	$\cdots Cl(4)^{vi}$		162 (5)	3.306 (3)	2.39 (6)
$N(4)-H(N4)$	$\cdots O(2)^{vii}$		174 (7)	2.757 (4)	1.84 (7)
$C(12)-H(C12)$	$\cdots Cl(4)$		132 (4)	3.522 (4)	2.85 (6)
$O(2)-H(O2A)$	$\cdots Cl(1)$		176 (6)	3.282 (3)	2.22 (8)
$O(2)-H(O2B)$	$\cdots Cl(3)$		143 (7)	3.362 (3)	2.65 (7)

[a] Key to the symmetry transformations: no superscript (x, y, z); i $(\frac{1}{2} - x, \frac{1}{2} + y, \frac{1}{2} - z)$; ii $(\frac{1}{2} - x, -\frac{1}{2} + y, \frac{1}{2} - z)$; iii $(x, y, 1 + z)$; iv $(\frac{1}{2} + x, \frac{1}{2} - y, -\frac{1}{2} + z)$; v $(1 - x, -y, -z)$; vi $(\frac{1}{2} + x, \frac{1}{2} - y, \frac{1}{2} + z)$; vii $(x, y, -1 + z)$; viii $(\frac{1}{2} - x, \frac{1}{2} + y, -\frac{1}{2} - z)$; ix $(-\frac{1}{2} + x, \frac{1}{2} - y, -\frac{1}{2} + z)$; x $(\frac{1}{2} - x, -\frac{1}{2} + y, -\frac{1}{2} - z)$; xi $(-\frac{1}{2} + x, \frac{1}{2} - y, \frac{1}{2} + z)$.

$H(C6)$ is bonded to $O(1)^{vii}$. Hydrogen bonding involving the corresponding C–H bonds has been observed in many other thiamine structures.[15,24–26,28] The H$\cdots$O distances range from 1.84 to 2.24 Å, and the H$\cdots$Cl distances from 2.22 to 2.85 Å. These values correspond to interactions of moderate to weak strength. The X–H$\cdots$Y angles vary from 129 to 176°. The larger angles are associated with shorter H$\cdots$Y distances, as has been observed for a variety of hydrogen bonds.[33,34]

The $HThiCdCl_4 \cdot H_2O$ structure is one of the few in which there are short contacts to both thiazolium nitrogen and sulfur atoms; contacts between the sulfur atom and electronegative groups are commonly found but not contacts involving the nitrogen atom. In the present case, $Cl(2)^{vi}$ is 3.269 Å distant from N(1), and $O(2)^i$ and $Cl(2)^{viii}$ are respectively 3.471 and 3.404 Å away from S. These distances are on the order of the sum of the van der Waals radii (N$\cdots$Cl 3.3 Å, S$\cdots$O 3.25 Å, S$\cdots$Cl 3.65 Å).[35] What makes these plausible dipolar interactions is not so much the distances as the orientations. For example, the C–N(1)$\cdots$

Table VIII. Conformations of Thiamine Derivatives[a]

Compound	ϕ_P	ϕ_T	Ref
HThiCdCl$_4$·H$_2$O	137.3	110.4	This work
2-(α-Hydroxyethyl)thiamine chloride hydrochloride	145.6	100.3	24
(HThi)$_2$UO$_2$Cl$_4$	83.7	−5.4	16
HThiCuCl$_4$	82.6	14.1	15
Thiamine chloride hydrochloride	76.1	9.0	26
Thiamine chloride hydrate	76.2	2.6	28
Hydrolyzed cocarboxylase	85.4	6.6	27
Thiamine pyrophosphate hydrochloride	93.1	2.7	25

[a] ϕ_P and ϕ_T are the N(1)−C(7)−C(8)−C(9) and C(8)−C(7)−N(1)−C(6) torsion angles, respectively. The sign is positive if, when looking from the second atom toward the third, a clockwise motion of the first atom would superimpose it on the fourth. The mirror image of a particular conformation will have opposite signs for ϕ_P and ϕ_T. The above structures, which belong to centrosymmetric space groups, thus also contain the conformer having negative ϕ_P and ϕ_T values.

Cl(2)^{vi} angles are close to 90° (Table VIId), showing that the Cl(2)^{vi} ion is positioned right on the p$_z$ orbital of the sp^2 nitrogen atom. Furthermore, the groups surrounding Cl(2) define a distorted tetrahedron (Table VIIc), suggesting that the Cl(2) is sp^3 hybridized and that its electron pairs are directed toward the moieties surrounding it. Similar arguments apply to the contacts between sulfur and O(2)^i or Cl(2)^{viii}. The angles about O(2) are even closer to the tetrahedral value than they were for Cl(2). Lone pairs of electrons from Cl(2)^{viii} and O(2)^i are thus directed toward the sulfur atom.

Conformation of the Thiamine Cation. Recent theoretical calculations[36] have shown that there is an almost continuous range of stable conformations for thiamine, provided that the rings do not approach coplanarity. There are several ways to define the thiamine conformation, perhaps one of the simplest being to calculate the torsion angles C(8)−C(7)−N(1)−C(6) and N(1)−C(7)−C(8)−C(9), ϕ_T and ϕ_P, respectively.[24] These angles are listed in Table VIII for eight accurately determined structures. Surprisingly, in view of the large number of conformations whose energies are predicted to be similar,[36] only two basic conformations have been found for crystalline compounds: one in which ϕ_P = 85 ± 10°, ϕ_T = 5 ± 10°, the other in which ϕ_P = 140 ± 5°, ϕ_T = 105 ± 5°. The former is more common and corresponds to the origin (ϕ_{CC} = 0°, ϕ_{CN} = 0°) on Jordan's maps of stable conformations for the free thiamine cation.[36] The second conformation also occurs in a low-energy region (ϕ_{CC} = 320°, ϕ_{CN} = 60°). However, until the present structure was completed, the only example of the second conformation was 2-(α-hydroxyethyl)thiamine, and its unique (at that time) conformation was believed to be due to the presence of the 2-(α-hydroxyethyl) side chain.[24]

The occurrence of only a limited number of conformations in the solid state is probably due to the favorable packing which may be obtained for certain values of ϕ_T and ϕ_P. Molecular models suggest that for some ring orientations, at least, the extensive hydrogen bonding usually observed would be disrupted. This happens when the hydrogen bond donors are pointed in the direction of the other ring and the electronegative acceptor atoms cannot occupy their normal hydrogen bonding positions. If this reasoning is correct, the number of conformations in the solution state would also be expected to be limited, since hydrogen bonding in polar solvents should be important. It has been proposed[24] that 2-(α-hydroxyethyl)thiamine maintains its solid-state confor-

mation even in solution, since its NMR spectrum is different from the spectra of other thiamine derivatives.

Implications for the Potential Formation of Metal–Thiamine Complexes. The extensive delocalization of electrons which occurs in both the thiazolium and pyrimidine rings, particularly of the electron pairs on the sulfur and nitrogen atoms, makes bonding to a metal atom a difficult task. Considerable resonance energy would be lost, for example, if the pyrimidine nitrogen atoms or the thiazolium sulfur atom were to coordinate to a metal. The metal–ligand bond energy must then be greater than the loss of resonance energy plus the loss of solvation energy for the metal ion. This condition is likely to be met only rarely. Metal–thiamine coordination, if it does occur, will considerably change the bonding in thiamine and should have significant effects on its redox reactions.

In conclusion, the present structure shows that it is unlikely that thiamine alleviates cadmium poisoning[8,9] by forming a complex, unless some other form of thiamine, such as the pyrophosphate, is the active ligand. Other studies in which thiamine–metal complexes are proposed should similarly be regarded with caution.

Supplementary Material Available. The structure factor table, Table V, and parts b–d of Table VII will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Remit check or money order for $4.50 for photocopy or $2.50 for microfiche, refering to code number JACS-75-3204.

References and Notes

(1) (a) Brock University; (b) Wofford College.
(2) (a) W. D. White and R. S. Drago, *Inorg. Chem.*, **10**, 2727 (1971); (b) A. A. Gallo, I. L. Hansen, H. Z. Sable, and T. J. Swift, *J. Biol. Chem.*, **247**, 5913 (1972).
(3) P. M. Bernard and M. L. Jacquet-Francillon, *Ann. Phys. Biol. Med.*, **2**, 67 (1968).
(4) A. Tanaka, *Vitamins*, **33**, 497 (1966).
(5) A. Tanaka, *Vitamins*, **34**, 399 (1966).
(6) A. Tanaka, *Vitamins*, **39**, 330 (1969).
(7) A. Tanaka, *Shiga-Kenritsu Tanki Daigaku Gakujutsu Zasshi*, **6**, 5 (1965).
(8) M. Yasuda, T. Fugita, and S. Morimoto, *Yakugaku Zasshi*, **94**, 153 (1974).
(9) T. Abe, Y. Itokawa, and K. Inoue, *Nippon Eiseigaku Zasshi*, **26**, 498 (1972).
(10) V. A. Mikhailov, *Vopr. Gig. Fiziol. Tr., Profpatol. Prom. Toksikol., Sverdl. Nauchn.-Issled. Inst. Gig. Tr. Profpatol., Sb.*, **6**, 268 (1963).
(11) A. P. Dorinovskaya, *Klin., Patog. Profil Profzabol. Khim. Etiol. Predpr. Tsvetn. Chern. Metall.*, **2**, 57 (1969).
(12) K. Kobayashi, *Vitamins*, **45**, 239 (1972).
(13) J. Holzbecher and D. E. Ryan, *Anal. Chim. Acta*, **64**, 333 (1973).
(14) G. Blank, M. Rodrigues, J. Pletcher, and M. Sax, American Crystallography Association Summer Meeting, Abstracts, University Park, Pa., 1974, paper B13.
(15) M. Caira, V. Fazakerley, P. W. Linder, and L. R. Nassimbeni, *Acta Crystallogr., Sect. B*, **30**, 1660 (1974).
(16) D. A. Clemente, G. Bandoli, F. Benetollo, and A. Marzotto, *J. Cryst. Mol. Structure*, **4**, 1 (1974).
(17) P. T. Talbert and J. A. Weaver, *J. Inorg. Nucl. Chem.*, **32**, 2147 (1970).
(18) M. R. Caira and L. R. Nassembeni, *Acta Crystallogr., Sect. B*, **30**, 2332 (1974).
(19) M. M. Thackeray and L. R. Nassembeni, *Acta Crystallogr., Sect. B*, **30**, 2469 (1974).
(20) M. F. Richardson, *Can. J. Chem.*, **52**, 3716 (1974).
(21) "International Tables for X-Ray Crystallography", Vol. III, Kynoch Press, Birmingham, 1968, p 201, Table 3.3.1.A, and p 215, Table 3.3.2.C.
(22) D. T. Cromer, A. C. Larson, and J. T. Waber, *Acta Crystallogr.*, **17**, 1044 (1964).
(23) See paragraph at the end of the paper regarding supplementary material.
(24) M. Sax, P. Pulsinelli, and J. Pletcher, *J. Am. Chem. Soc.*, **96**, 155 (1974).
(25) J. Pletcher and M. Sax, *J. Am. Chem. Soc.*, **94**, 3998 (1972).

(26) J. Kraut and J. J. Reed, *Acta Crystallogr.*, **15**, 747 (1962).
(27) I. L. Karle and K. Britts, *Acta Crystallogr.*, **20**, 118 (1966).
(28) J. Pletcher, M. Sax, S. Sengupta, J. Chu, and C. S. Yoo, *Acta Crystallogr., Sect. B*, **28**, 2928 (1972).
(29) C. H. Carlisle and D. S. Cook, *Acta Crystallogr., Sect. B*, **25**, 1359 (1969).
(30) A. F. Cameron, K. P. Forrest, and G. Ferguson, *J. Chem. Soc. A*, 1286 (1971).
(31) T. V. Long, II, A. W. Herlinger, E. F. Epstein, and I. Bernal, *Inorg. Chem.*,

9, 459 (1970).
(32) J. T. Veal and D. J. Hodgson, *Inorg. Chem.*, **11**, 597 (1972).
(33) W. C. Hamilton and J. A. Ibers, "Hydrogen Bonding in Solids", W. A. Benjamin, New York, N.Y., 1968.
(34) I. D. Brown, Department of Physics, McMaster University, Hamilton, Ontario, private communication, 1974.
(35) L. Pauling, "The Nature of the Chemical Bond", 3rd ed, Cornell University Press, Ithaca, N.Y., 1960, p 260.
(36) F. Jordan, *J. Am. Chem. Soc.*, **96**, 3623 (1974).

Nucleic Base–Metal Ion Interactions. Acidity of the N(1) or N(3) Proton in Binary and Ternary Complexes of Mn²⁺, Ni²⁺, and Zn²⁺ with the 5′-Triphosphates of Inosine, Guanosine, Uridine, and Thymidine

Helmut Sigel

*Contribution from the Institute of Inorganic Chemistry,
University of Basel, CH-4056 Basel, Switzerland.
Received August 20, 1974*

Abstract: By uv difference spectra and potentiometric titrations the acidity constants, K^H_{NTP}, of the nucleic base residues, i.e., the proton at N(1) in ITP⁴⁻ and GTP⁴⁻, or at N(3) in UTP⁴⁻ and TTP⁴⁻, and of their complexes with Mn²⁺, Ni²⁺, and Zn²⁺ ($K^H_{M(NTP)}$) have been determined; the data for the Cu²⁺ and Mg²⁺ complexes were taken from earlier work. The influence of the metal ions was characterized by $\Delta p K_A = p K^H_{NTP} - p K^H_{M(NTP)}$, which is in the order of 0.2 for Mg²⁺, 0.3 for Mn²⁺, 0.9 for Ni²⁺, 1.9 for Cu²⁺, and 1.2 for Zn²⁺. As the difference in pK_A for the proton of N(1) or N(3) for the nucleotides and the corresponding nucleosides is about 0.4 log units, the following is concluded. (i) There is a considerable interaction between the metal ion and the nucleic base residue in the nucleotide complexes of Ni²⁺, Cu²⁺, and Zn²⁺. (ii) On the structure of the complexes with Mg²⁺ and Mn²⁺ nothing can be said, as the small shift in acidity may simply be due to the partial neutralization of the negatively charged phosphate chain by the metal ion. In the mixed-ligand 2,2′-bipyridyl nucleotide complexes with Ni²⁺, Cu²⁺, and Zn²⁺ $\Delta p K_{A(Bipy)}$ is always about 0.6, thus indicating similar structures. Based on known structures, a folded form is suggested which allows an intramolecular charge-transfer interaction between the purine or pyrimidine and pyridyl moieties. The tendency of the binary complexes to form hydroxo species, $M(L)(OH)^{n-}$, increases for a given nucleotide, with Mn²⁺ < Ni²⁺ < Zn²⁺ < Cu²⁺, while it decreases for a given metal ion, with L = CTP⁴⁻ ∼ ATP⁴⁻ > (UTP-1H)⁵⁻ ∼ (TTP-1H)⁵⁻ > (ITP-1H)⁵⁻ ∼ (GTP-1H)⁵⁻, hence, indicating in the latter series an increasing degree of saturation of the coordination sphere of the metal ion.

Virtually all enzymes requiring nucleoside phosphates as substrates need in addition a divalent metal ion.[1] To understand the role of these metal ions, it is necessary to learn more about the structures of their binary[2-5] and ternary (mixed-ligand)[6-8] nucleotide complexes. So far the 3d metal ion–adenine nucleotide complexes are best studied; several of the corresponding ATP complexes exist in the ring bound form,[9-11] i.e., the metal ion coordinates both to the phosphate chain *and* to N(7) of the adenine moiety. Considerably less is known on the interaction between metal ions and the base moieties of other nucleotides.

Even though the stability of divalent earth alkali and 3d metal ion nucleotide complexes is governed by the coordination tendency of the phosphate chains,[2,3,12-14] the nucleic bases determine at least in part the specificity because in most enzyme reactions the nucleotides are not freely interchangeable. Hence, there is a clear relationship between structure and reactivity. This is also evident from the Cu²⁺ promoted dephosphorylation of nucleoside 5′-di- and -triphosphates, where the rate depends on the extent of the metal ion–nucleic base interaction,[15,16] which in turn is dependent on the nucleic base.

Before the understanding of such structure-reactivity relationships will improve, it is necessary to study metal ion–nucleic base interactions more in detail. It is the aim of this study to shed some light on the structures of the complexes

formed by Mn²⁺, Ni²⁺, and Zn²⁺ with ITP, GTP, UTP, and TTP. The IUPAC numbering system is indicated on Chart I; for convenience N(1) of the purine and N(3) of the pyrimidine nucleotides are both labeled N(A).

In contrast to ATP and CTP, the nucleotides of Chart I

Chart I
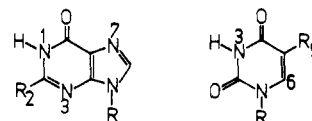
R = ribosyl 5′-triphosphate

ITP: R₂ = –H   UTP: R₅ = –H

GTP: R₂ = –NH₂   TTP: R₅ = –CH₃

Abbr: N(A) = N(1) of ITP or GTP, and

N(3) of UTP or TTP

have a proton at N(A). In case the base moieties of the nucleotides participate in complex formation one expects that this proton ionizes at a lower pH than in the free ligands.[17] Due to the recent work of Clarke and Taube[18] on guanosine–ruthenium complexes, it is now possible to reach conclusive results also for "labile" metal ions, like Ni²⁺ and Zn²⁺. Certainly, if the base moieties are prevented from a