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Vitamin B_1: Chemical Interaction with $CdCl_2$ and *in Vivo* Effects on Cadmium Toxicity in Rats. Crystal Structure of $[Cd(thiamine)Cl_3]_2 \cdot 2H_2O$, a Complex Containing Pyrimidine and Cadmium−Hydroxyethyl Bonds

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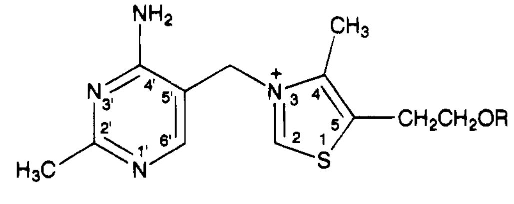
The title compound was prepared by mixing thiamine chloride hydrochloride, KOH and $CdCl_2 \cdot H_2O$ in water in various mole ratios. Its crystal structure was solved by X-ray diffraction (crystal data: monoclinic, space group $P2_1/c$, $a = 6.999(2)$ Å, $b = 12.811(3)$ Å, $c = 20.587(4)$ Å, $\beta = 91.88(2)°$, $V = 1844(1)$ Å^3, and $Z = 4$). The compound is a centrosymmetric dimer with two N(1′), O(5γ)-bond thiamines bridging between the two cadmium atoms. The metal coordination numbers are made up to five by three chloro ligands each. The thiamine ligand is in the F conformation, with $\Phi_T = 11.0(9)$ and $\Phi_P = 98.3(8)°$. These structural characteristics and the spectral behavior of the compound (IR, ^{13}C, ^{15}N, and ^{113}Cd NMR, and CP MAS ^{13}C NMR) are compared with those of previously studied cadmium(II)/vitamin B_1 compounds. The effect of thiamine on the survival rate among male Sprague rats injected intraperitoneally with 5 mg of $CdCl_2 \cdot H_2O$/kg and on the Cd burden in some of their organs is also reported.

Introduction

Oral administration of a vitamin B complex (a mixture of vitamins B_1, B_2, B_3, B_5, B_6, B_{12}, and B_c) reduces the hepato- and nephrotoxic effects of $CdCl_2 \cdot H_2O$ in rats.[2] If this action is generalizable to human beings, prophylactic treatment of the population exposed to high cadmium levels might be possible. Although the mechanism of the prophylaxis in rats was not established, the formation of a readily excreted Cd/vitamin B coordination compound or compounds was suggested as a possible explanation.[2] We have previously explored the coordination chemistry of $CdCl_2$ with vitamins B_{12} and B_6, and also the antidotal activity of both vitamins in rats after injection of $CdCl_2 \cdot H_2O$.[3] We have now extended our studies to the system composed of $CdCl_2$ and vitamin B_1 (thiamine, structure I).



I

R	
H	Thiamine
$P_2O_5^{2-}$	Thiamine pyrophosphate

For its catalytic action, vitamin B_1 pyrophosphate (structure I), a cofactor of several metabolic enzymes, requires the presence of a bivalent metal ion.[4] Therefore, in recent years, much attention has been focused on the interaction of thiamine chloride (TCl) with metal ions. From early complexation studies, it was evident that thiamine and its derivatives do not readily form "true" complexes with direct metal−T^+ bonds; instead, they give ionic salts, mainly (but not exclusively) of the type $(HT)^{2+}[MX_4]^{2-}$ due to the net positive charge on the thiazolium ring and the easy protonation of the pyrimidine N(1′) atom. In fact, the first attempt to prepare a Cd/thiamine complex afforded $(HT)[CdCl_4] \cdot H_2O$.[5] Later the reaction of TCl·HCl with $Cd(OOCCH_3)_2$ was carried out (2:1 mole ratio in water, with subsequent diffusion of acetone through the solution) and produced $[CdTCl_3] \cdot 0.6H_2O$, the first "true" thiamine complex studied by X-ray diffraction[6] (although the direct M−T bond had previously been postulated on spectroscopic grounds in complexes of Pt(II) and Pd(II) with thiamine and its phosphate esters,[7a] and the crystal structure of the ternary complex [aquo(1,10-phenanthroline)(thiaminepyrophosphate)copper(II)] dinitrate monohydrate, in which the metal is bound to the pyrophosphate group, had been published[7b] a year earlier). In $[CdTCl_3] \cdot 0.6H_2O$ each T^+ cation is coordinated via its N(1′) pyrimidine atom to one cadmium atom, whose coordination number is made up to four by three chloro ligands. More recently, cadmium(II)−thiamine coordination chemistry has been advanced by Aoki et al.,[8] who isolated the complex [CdT-

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$(SCN)_3]$, in which the metal is bound to the vitamin through the oxygen atom of the hydroxyethyl side chain of the thiazolium ring.

The Cd−thiamine complex reported here combines the coordination characteristics of the "true" cadmium−thiamine complexes previously prepared,[6,8] showing that thiamine, despite its reluctance to form direct bonds with metal ions, is a versatile ligand. The utility of spectroscopic probes to distinguish between salts and "true" complexes of cadmium and thiamine and the antidotal effects of the vitamin on cadmium poisoning in rats were also investigated in this work.

Experimental Section

Materials and Methods. Thiamine chloride hydrochloride (Merck or Ega Chemie) and cadmium chloride monohydrate (Sigma) were used as supplied. Thiamine chloride was prepared from TCl·HCl using the method of Pletcher et al.[9] Elemental analyses (C, H, and N) were performed in a Perkin-Elmer 240B analyser or by Galbraith Lab. Inc., Knoxville, TN. IR spectra were recorded in KBr pellets and Nujol mulls on a Mattson Cygnus 100 spectrometer. The deuterated compounds were prepared by dissolving them in D_2O and reprecipitating with acetone. Solution phase NMR spectra were run in a Bruker WM-250, AMX-300, or AMX-500 spectrometer with external TMS (^{13}C), pure nitromethane (^{15}N), and 0.1 M $Cd(ClO_4)_2$ (^{113}Cd) as references. Solid state NMR spectra were recorded in 7 mm ZrO_2 rotors at 4.0 kHz in a Bruker MSL-400 apparatus using a TOSS pulse sequence with glycine (176.03 ppm) as external reference, with contact time 2.0 ms, recycle time 10.0 s, and relaxation delay 50 μs. Conductivity measurements were made with a WTW conductivity meter in H_2O (conductivity 1×10^{-6} S. cm^{-1}).

Reaction of Thiamine and Cadmium(II) Chloride. TCl·HCl (1.69 g, 5×10^{-3} mol) was dissolved in 5 mL of water and reacted with 5 mL of 1 M aqueous KOH solution (5×10^{-3} mol). Addition of $CdCl_2 \cdot H_2O$ (1.00 g, 5×10^{-3} mol) dissolved in 2 mL of water caused almost immediate precipitation of a white solid, which was filtered out and was discarded when found to be unsuitable for X-ray diffraction. The mother liquor was refrigerated, and after 2 days, a white crystalline solid formed which was isolated and analyzed. Anal. Calcd for monomer $[CdTCl_3] \cdot H_2O$ ($C_{12}H_{19}N_4O_2SCdCl_3$): C, 28.7; H, 3.8; N, 11.2. Found: C, 28.4; H, 3.7; N, 11.0.

The reaction between TCl·HCl and $CdCl_2$ was further explored with different mole ratios between the reagents and also at acidic pH. Under the acidic conditions (ca. pH 2) obtaining on mixing TCl·HCl and $CdCl_2$ in 1:1 mole ratio, a white crystalline solid formed with analytical data corresponding to the salt $(HT)[CdCl_4] \cdot H_2O$.[5] With a TCl·HCl:KOH:$CdCl_2$ mole ratio of 2:2:1, the reaction proceeded as with mole ratio 1:1:1 (*vide supra*), but when the crystals obtained following filtration and refrigeration as before were left in contact with the mother liquor for about 1 month, the $[CdTCl_3]_2 \cdot 2H_2O$ complex was slowly converted to a white crystalline solid with a stoichiometry of the complex $[CdT_2Cl_4]$ or the salt $(T)_2[CdCl_4]$, neither of which has previously been reported. Anal. Calcd for $C_{24}H_{36}N_8O_3S_2CdCl_4$: C, 35.9; H, 4.5; N, 13.9. Found: C, 36.5; H, 4.5; N, 14.0. (One of the several experiments performed using 2:2:1 mole ratio did not give the white precipitate usually observed upon mixing the reagents, and in this experiment, no solid with the stoichiometry of $[CdTCl_3] \cdot H_2O$ was detected; instead $[CdT_2Cl_4]$ (or $(T)_2[CdCl_4]$) was formed directly after only a few hours in the refrigerator.) The same process occurred when a TCl·HCl:KOH:$CdCl_2$ mole ratio of 3:3:1 was used. Attempts to solve the structure of these crystals have so far been unsuccessful.

X-ray Crystallography. Crystals were obtained by 2 days of refrigeration of the filtered reaction mixture obtained with a TCl·HCl:KOH:$CdCl_2$ mole ratio of 2:2:1.

Crystal Data. An irregular crystal of maximum and minimum dimensions 0.65 and 0.15 mm was used for data collection. The unit cell was determined by least-squares refinement of diffraction angles obtained from 25 automatically centered reflections ($17 < \theta < 37°$). Crystal data are given in Table 1.

Table 1. Crystallographic Data and Data Collection Parameters for $[CdTCl_3]_2 \cdot 2H_2O$

chem formula	$C_{12}H_{19}CdCl_3N_4O_2S$	V, Å^3	1844(1)
fw	502.13	T, °C	20 ± 1
space group	$P2_1/c$	λ, Å	1.54053
a, Å	6.999(2)	d_{calcd}, g cm^{-3}	1.808
b, Å	12.811(3)	μ(Cu Kα), cm^{-1}	15.03
c, Å	20.587(4)	data collcn	CAD4
β, deg	91.88(2)	transm coeff	1.45−0.79
Z	4	R, R_w	0.036, 0.038

Table 2. Fractional Atomic Coordinates and Equivalent Isotropic Temperature Factors (Å^2)

atom	x/a	y/b	z/c	B_{iso}[a]
Cd	0.1267(1)	0.1812(0)	0.8548(0)	2.25(2)
Cl(1)	0.1182(3)	0.1856(2)	0.7365(1)	3.35(7)
Cl(2)	0.4326(3)	0.2841(2)	0.8838(1)	3.09(7)
Cl(3)	0.1755(3)	0.0189(1)	0.9133(1)	3.48(7)
S	−0.7081(3)	0.0936(2)	1.0662(1)	3.22(7)
N(1′)	−0.0440(8)	0.2825(4)	0.9219(3)	1.9(2)
C(6′)	−0.099(1)	0.2416(5)	0.9789(3)	2.0(2)
C(2′)	−0.087(1)	0.3826(6)	0.9114(3)	2.0(3)
C(2′α)	−0.028(1)	0.4287(6)	0.8481(3)	2.9(3)
N(3′)	−0.1748(8)	0.4450(4)	0.9520(3)	2.2(2)
C(4′)	−0.230(1)	0.4040(5)	1.0089(3)	1.8(2)
N(4′α)	−0.3189(9)	0.4673(5)	1.0493(3)	3.0(2)
C(5′)	−0.192(1)	0.2982(5)	1.0246(3)	1.7(2)
C(3,5′)	−0.229(1)	0.2522(5)	1.0898(3)	2.1(2)
N(3)	−0.4113(8)	0.1939(4)	1.0937(2)	1.8(2)
C(2)	−0.525(1)	0.1662(6)	1.0440(3)	2.5(3)
C(4)	−0.475(1)	0.1559(5)	1.1520(3)	1.7(3)
C(4α)	−0.350(1)	0.1741(7)	1.2150(3)	4.7(4)
C(5)	−0.637(1)	0.1019(5)	1.1463(3)	2.1(3)
C(5α)	−0.743(1)	0.0504(5)	1.1993(3)	2.6(3)
C(5β)	−0.681(1)	−0.0631(6)	1.2106(3)	2.7(3)
O(5γ)	−0.7562(7)	−0.1243(4)	1.1578(2)	3.2(2)
O(w)	−0.375(1)	0.6102(6)	0.8788(4)	8.9(4)

[a] $B_{iso} = {}^4/_3 \sum_{ij} B_{ij} \mathbf{a}_i \mathbf{a}_j$.

Data Collection and Processing. A CAD 4 diffractometer was used in $\omega/2\theta$ scan mode with scan width $w = 1.5 + 0.35 \tan \theta$. Cu K$\alpha$ radiation was graphite-monochromated, and 2018 reflections were measured ($0 < \theta < 50°$, $-6 \le h \le 6$, $0 \le k \le 12$, $0 \le l \le 20$), of which 1824 were unique (merging $R = 0.025$) and 1616 had $I > 3\sigma(I)$. Lorentz and polarization corrections were applied, and at a later stage in the refinement, absorption corrections[10] (maximum and minimum transmission factors were 1.45 and 0.79 respectively). The intensity of three standard reflections was essentially constant throughout the experiment.

Structure Analysis and Refinement. Standard direct methods followed by normal difference Fourier techniques were used. Full matrix least-squares refinement was carried out with all non-H atoms anisotropic, and hydrogens included as fixed contributors, at positions found with one overall fixed isotropic temperature factor ($U_{iso} = 0.05$ Å) in difference syntheses. The function minimized was $\sum w(|F_o| - |F_c|)^2$ with the weighting scheme $w = 1/[\sigma^2|F_o| + 0.0002|F_o|^2]$, which gave final R $[=\sum(|F_o| - |F_c|)/\sum|F_o|]$ and R' $\{=[\sum w(|F_o| - |F_c|)^2/\sum w|F_o|^2]^{1/2}\}$ values of 0.036 and 0.038, respectively. Computer programs used were SHELX76[11] and ORTEP.[12] Scattering factors: for non-H atoms from Cromer & Mann,[13] with corrections for anomalous dispersion taken from Cromer & Liberman;[14] for H atoms from Stewart, Davidson, and Simpson.[15] Table 2 lists the positional and thermal parameters.

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Experimental Animals and Protocols. The weights of 30 individually labelled adult male Sprague rats (ranging from 200 to 300 g) were accurately recorded, following which the rats were given food and water *ad lib.* TCl·HCl and CdCl$_2$·H$_2$O, as solutions in physiological saline (the former brought to pH ca. 6.5 with NaOH), were administered in accordance with the general procedure and protocols outlined in ref 3. The LD$_{50}$ for intraperitoneal TCl·HCl in rats has not been reported,[16] so the value for mice[16] (200 mg/kg) was taken as indicative of the lethality of the vitamin. To suppress any thiamine-induced reduction in survival rates after the cadmium administration, only 20 mg/kg of vitamin were used throughout protocols A, B and C (see ref 3). The determination of cadmium levels in organs of rats surviving more than 15 days, and the statistical analysis of these data, were performed as before.[3]

Results and Discussion

On the Reaction between CdCl$_2$ and TCl·HCl. We are aware of 14 crystal structures of "true" complexes of thiamine and its derivatives.[6,7b,8,17] Most of these contain N(1′)−M bonds, some have phosphate−M[7b] or O(5γ)-M[8,17f] bonds, and in one both M−N(1′) and M−O(5γ) bonds are present.[17i] These complexes have usually been prepared in aqueous solution by mixing TCl·HCl (or other TX·HX derivatives, where X = halide or pseudohalide) with an aqueous metal salt. The drawbacks of this method are that, under the resulting acidic conditions, protons often successfully compete with metal cations for the thiamine N(1′) donor atom[17g] (except when, as in the case of Pd(II) and Pt(II), the metal has a very high affinity for nitrogen); and that the high concentration of chloride ion favours the formation of polychlorometal anions and thus of thiamine salts, rather than "true" thiamine complexes.

Two approaches have been developed to obtain direct thiamine−metal bonds under aqueous conditions. The first,[6] followed in most of the preparative work described in previous X-ray studies,[8,17] uses the metal acetate as M^{n+} source (the CH$_3$COO$^-$ counterion probably acting as a proton sink) and an excess of thiamine (normally 2:1 mole ratio). In the second procedure,[17b,g,f] before or during the reaction, the pH of the aqueous TX·HX (X = halide or pseudohalide) is adjusted with aqueous alkali to a final value close to pH 7, above which thiamine tends to decompose.[18]

Our results on the aqueous reaction between thiamine and cadmium(II) chloride are in keeping with the above considerations. Thus, when CdCl$_2$ and TCl·HCl are directly mixed in aqueous solution, the resulting low pH (ca. 2) means that the N(1′) coordination position is blocked by a proton (so forming the thiaminium cation HT^{2+}), which prevents direct bonding to the Cd(II) at this position. The other basic positions on HT^{2+} are probably very weak electron donors, so Richardson et al.'s salt[5] forms in preference to a "true" complex, in accordance with eq 1.

$$\text{CdCl}_2\text{(aq)} + \text{TCl·HCl(aq)} \rightarrow \text{(HT)[CdCl}_4\text{]} \qquad (1)$$

Table 3. Interatomic Distances (Å) and Angles (deg) with Esd's in Parentheses[a]

(a) Cd Atoms			
Cd−Cl(1)	2.435(2)	Cd−N(1′)	2.264(5)
Cd−Cl(2)	2.567(2)	Cd−O(5γ)^{i}	2.697(5)
Cd−Cl(3)	2.421(2)		
Cl(1)−Cd−Cl(2)	102.33(6)	Cl(2)−Cd−N(1′)	90.9(1)
Cl(1)−Cd−Cl(3)	121.05(7)	Cl(2)−Cd−O(5γ)^{i}	162.3(1)
Cl(1)−Cd−N(1′)	126.9(1)	Cl(3)−Cd−N(1′)	104.9(1)
Cl(1)−Cd−O(5γ)^{i}	85.3(1)	Cl(3)−Cd−O(5γ)^{i}	86.3(1)
Cl(2)−Cd−Cl(3)	102.84(6)	N(1′)−Cd−O(5γ)^{i}	71.9(2)
(b) Ligand			
S−C(2)	1.659(8)	S−C(5)	1.710(6)
N(1′)−C(6′)	1.352(8)	N(1′)−C(2′)	1.333(9)
C(6′)−C(5′)	1.369(9)	C(2′)−C(2′α)	1.501(9)
C(2′)−N(3′)	1.322(9)	N(3′)−C(4′)	1.352(8)
C(4′)−N(4′α)	1.330(9)	C(4′)−C(5′)	1.416(9)
C(5′)−C(3,5′)	1.496(9)	C(3,5′)−N(3)	1.483(9)
N(3)−C(2)	1.324(9)	N(3)−C(4)	1.382(8)
C(4)−C(4α)	1.56(1)	C(4)−C(5)	1.33(1)
C(5)−C(5α)	1.493(9)	C(5α)−C(5β)	1.53(1)
C(5β)−O(5γ)	1.427(8)		
C(2)−S−C(5)	91.6(3)	C(5′)−C(3,5′)−N(3)	114.9(5)
C(6′)−N(1′)−C(2′)	116.4(6)	C(3,5′)−N(3)−C(2)	126.1(6)
N(1′)−C(6′)−C(5′)	123.1(6)	C(3,5′)−N(3)−C(4)	121.8(5)
N(1′)−C(2′)−C(2′α)	116.9(6)	C(2)−N(3)−C(4)	112.0(6)
N(1′)−C(2′)−N(3′)	125.9(6)	S−C(2)−N(3)	112.8(5)
C(2′α)−C(2′)−N(3′)	117.2(6)	N(3)−C(4)−C(4α)	118.8(6)
C(2′)−N(3′)−C(4′)	117.7(6)	N(3)−C(4)−C(5)	113.9(6)
N(3′)−C(4′)−N(4′α)	117.2(6)	C(4α)−C(4)−C(5)	127.2(6)
N(3′)−C(4′)−C(5′)	120.8(6)	S−C(5)−C(4)	109.7(5)
N(4′α)−C(4′)−C(5′)	121.9(6)	S−C(5)−C(5α)	122.8(5)
C(6′)−C(5′)−C(4′)	116.1(6)	C(4)−C(5)−C(5α)	127.4(6)
C(6′)−C(5′)−C(3,5′)	120.5(6)	C(5)−C(5α)−C(5β)	112.6(6)
C(4′)−C(5′)−C(3,5′)	123.0(6)	C(5α)−C(5β)−O(5γ)	108.1(6)

[a] Symmetry operation: (i) −1 − *x*, −*y*, 2 − *z*.

If, following the second approach to the synthesis of complexes, TCl·HCl is reacted with an equimolar aqueous alkali solution and then with CdCl$_2$(aq), the pyrimidine N(1′) atom loses its proton and becomes available for coordination, giving N(1′)-bound complexes. In the case of the reaction with 1:1:1 mole ratio

$$\text{TCl·HCl(aq)} + \text{MOH(aq)} + \text{CdCl}_2\text{(aq)} \rightarrow {}^{1}/_{2}[\text{CdTCl}_3]_2\cdot 2\text{H}_2\text{O} + \text{M}^+\text{(aq)} + \text{Cl}^-\text{(aq)} \qquad (2)$$

If this approach is followed using a mole ratio of 2:2:1 or higher and the [CdTCl$_3$]$_2$·2H$_2$O first formed is left in contact with the mother liquor, the excess of chloride and thiamine ions brings about slow conversion to either the complex [CdT$_2$Cl$_4$] or the salt (T)$_2$[CdCl$_4$]. Although the whole process has not yet been fully explored, it seems evident from the experiments performed that high thiamine:cadmium(II) chloride mole ratios encourage this transformation; each additional mole of TCl·HCl increases the excess of T$^+$ and Cl$^-$.

Crystal Structure. The crystalline complex is composed of discrete [CdTCl$_3$]$_2$ units and molecules of water of crystallization. The former each contain two N(1′), O(5γ)-bound T$^+$ cations bridging head-to-tail between two Cd(II) ions to give cyclic, centrosymmetric dimers (Figure 1) similar to those observed in the cation [MnTCl$_2$(H$_2$O)]$_2$$^{2+}$.[17i] However, whereas the coordination geometry of Mn(II) in the latter complex is described as distorted square pyramidal, the coordination polyhedron of cadmium(II) in [CdTCl$_3$]$_2$·2H$_2$O is better described as a distorted trigonal bipyramid, with Cl(2) and O(5γ) occupying the apical positions. The Cd−Cl(1) and Cd−Cl(3)

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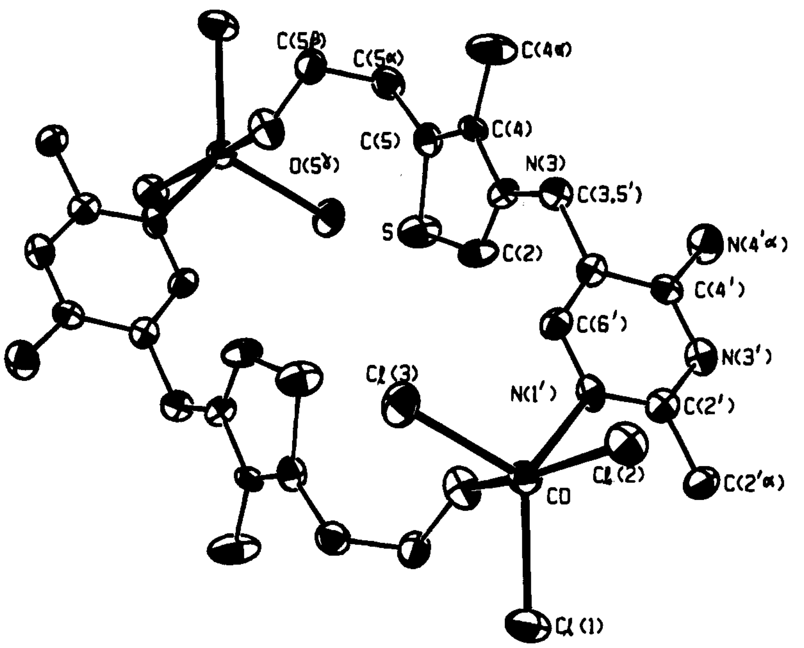

Figure 1. Molecular structure of $[CdTCl_3]_2{\cdot}2H_2O$, with atomic numbering scheme (H atoms and water molecules omitted).

Table 4. Main Structural Parameters[a,b] of Thiamine/Thiaminium Ligands and Complexes

compound	ϕ_T	ϕ_P	$\phi_{5\alpha}$	$\phi_{5\beta}$	C(2')−N(1')−C(6')	C(4')−N(4'α)	C(5β)−O(5γ)	C(5α)−C(5β)−O(5γ)	ref
$(HT)[CdCl_4]{\cdot}H_2O$	110.4	137.3	83.0	67.8	120.2	1.323	1.426	111.9	5
$[CdTCl_3]{\cdot}0.6H_2O$	112.6	129.8	46.5	−68.8	116.5	1.346	1.437	106.5	6
$[CdT(SCN)_3]$	−10.2	−82.8	64.7	−66.6	116.3	1.34	1.44	106.4	8
$[CdTCl_3]_2{\cdot}2H_2O$	11.0	98.3	86.4	−73.2	116.4	1.330	1.427	108.1	*c*
$TCl{\cdot}H_2O$	−2.6	−76.8	66.8	64.6	115.3	1.334	1.416	111.7	9
$TCl{\cdot}HCl{\cdot}H_2O$	−9.0	−76.1	103.4	−68.2	121.0(8)	1.316	1.417	113.0	22

[a] For identification of parameters, see text or Figure 1. [b] Angles in degrees and bond distances in Å. [c] This work.

bond lengths (Table 3) are unexceptional and close to those observed in previous $CdCl_2$/thiamine or $CdCl_2$/thiaminium compounds[5,6] but the Cd−Cl(2) bond is longer, like those found in the pentacoordinated anion $[CdCl_5]^{2-}$ [19] (but clearly shorter than the sum of the van der Waals radii, 3.30−3.50 Å[20]). The Cd−O(5γ) distance is also long, longer than in $[CdT(SCN)_3]$[8] and above the upper limit quoted for Cd−O bonds in pentacoordinated cadmium compounds (2.03−2.30 Å[21]). These weak apical bonds, which produce an axially elongated coordination polyhedron, suggest that our complex might be described as a step toward that of Cramer et al.,[6] in which the Cd−Cl(2) (and Cd−N(1)) bonds are shorter and probably stronger while the Cd−O(5γ) bond and the dimeric structure have been lost. Deviations from the regular trigonal bipyramidal structure are also observed (Table 3) in the angles Cl(2)−Cd−O(5γ), Cl(3)−Cd−N(1'), and N(1')−Cd−O(5γ) (162.3(1), 104.9(1), and 71.9(2)° instead of the ideal values 180, 120, and 90°, respectively). The Cd(II) ion lies 0.3642(5) Å to the Cl(2) side of the plane through Cl(1), Cl(3), and N(1').

The chief structural characteristics of T^+ in $[CdTCl_3]_2{\cdot}2H_2O$ are listed in Table 4 together with those reported for the other Cd(II)/thiamine (or thiaminium) compounds studied by X-ray diffraction and for $TCl{\cdot}H_2O$[9] and $TCl{\cdot}HCl{\cdot}H_2O$.[22] As in all these other compounds, the pyrimidine and the thiazolium rings in $[CdTCl_3]_2{\cdot}2H_2O$ are planar (X^2 = 2.0 and 37.3, respectively). However, unlike the monomeric complex,[6] the dimer has thiamine in F conformation:[23] Φ_T [=C(5')−C(3,5')−N(3)−C(2)] = 11.0°; Φ_P [=N(3)−C(3,5')−C(5')−C(4')] = 98.3°. The angle between the two rings is 101.9(2)°. It has been suggested[17d,24] that this conformation is adopted in thiamine/thiaminium compounds with small polychlorometal moieties indicated by short nonbonding Cl••Cl distances [average 3.4(3) Å], whereas longer Cl••Cl distances [average 3.9(2) Å] favor the S form; but our cadmium complex, with an average Cl••Cl value of 4.009(3) Å, is a clear counterexample (as also are $[CuTCl_2]$ and $[CuTBr_2]$,[17a,e] which have X••X distances of 3.867[17d] and 3.995(2),[17e] respectively, but F conformation). More recently,[17e] the F conformation of thiamine in metal halide compounds has been associated with the presence of "one point" halide bridges P••X•••Th (in which a single metal-bound halide forms a hydrogen bond with the $-N(4'\alpha)H_2$ group of the pyrimidine and a weak electrostatic link with the thiazolium ring), and the S conformation with the existence of "two point" bridges P••X−M−X••Th (in which one metal-bound halide forms a hydrogen bond with N(4'α) and another, bound to the same metal cation, stacks on the thiazolium ring). No "one point" or "two point" bridges exist in our complex (*vide infra*), but a C(2)−H••X••P anion bridge does contribute to the weak lattice forces (*vide infra*), as is usual in thiamine with F conformation. As Cramer et al.[17d] have pointed out, "the factors which determine thiamine conformation can be very subtle forces" since the F and S conformers are likely to have similar energies even though the F form seems to be the global minimum in the free derivative.[25] In $[CdTCl_3]_2{\cdot}2H_2O$ the bidentate nature of the T^+ ligand might be one of the factors determining the

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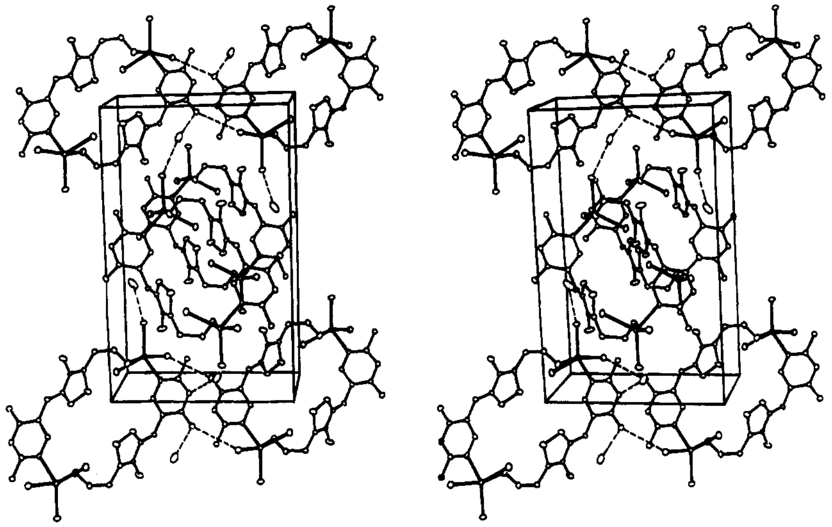

Figure 2. Stereoscopic view of the crystal packing. Hydrogen bonds are indicated by dotted lines.

Table 5. Hydrogen Bonds and Miscellaneous Interatomic Close Contacts

Hydrogen Bonds

A−H···B[c]	H···B, Å	A−H−B, deg	A−B, Å
O_w−H···N(3′)	1.692(5)	168.1(4)	2.928(9)
O_w^{i}−H′···Cl(1)	2.119(8)	179.8(8)	3.174(8)
N(4′α)^{ii}−H′···O_w	1.793(8)	166.7(4)	2.82(1)
N(4′α)^{iii}−H···Cl(2)	2.903(7)	126.4(4)	3.569(6)
C(2)^{iv}−H···Cl(2)	2.723(7)	147.2(4)	3.631(7)

Close Contacts

contact	A−B, Å	contact	A−B, Å
S···Cl(3)^{v}	3.364(3)	Cl(3)···Th^{vi}	3.362(7)[b]
Cl(2)···P^{iv}	3.485(7)[a]		

[a] Distance to the centroid of the pyrimidine ring. [b] Distance to the centroid of the thiazole ring. [c] Symmetry operations: (i) $-x$, $y - 1/2$, $3/2 - z$; (ii) $-1 - x$, $1 - y$, $2 - z$; (iii) $-x$, $1 - y$, $2 - z$; (iv) $1 + x$, y, z; (v) $x - 1$, y, z; (vi) $-x$, $-y$, $2 - z$.

Table 6. Major IR Bands (cm^{-1}) of Thiamine, Thiaminium, and the Cadmium Complex[a]

TCl·HCl	TCl	$[CdTCl_3]_2·2H_2O$	assignment
3509 s	3441 s,b	3512 b	ν(OH)
3443 s		3437 s	
3234 s, b	3304 s, b	3329 s,b	ν(NH)
3101 s	3132 s	3209 s	
1657 vs, b	1662 s	1655 m	δ(NH_2) + pyrimidine ring (8a)
1607 s	1603 vs	1632 vs	
(1654)	(1610)	(1632)	pyrimidine ring (8a)
1553 m	1560 s	1549 m	pyrimidine ring (8b)
1042 s	1067 s	1053 m	δ(C−OH)

[a] The numbers in parentheses belong to the deuterated compounds.

stability of the F conformation. In the only other known complex with bidentate T^+ $[MnTCl_2(H_2O)]_2T_2Cl_4·2H_2O$,[17i] the ligand is also in the F conformation.

The remaining structural parameters in Table 4 are typical of thiamine compounds. Note that the C(2′)−N(1′)−C(6′) angle is closer to that observed in $T^+Cl^-·H_2O$ than to the angle reported for the hydrochloride; although metalation at N(1′) must, like protonation, cause contraction of the electron cloud of the nitrogen lone pair, so allowing this angle to widen, the inductive effect of the negatively charged polychlorometallo group must be far less than the influence of a proton. For the same reason, metalation does not significantly alter the thiamine C(4′)−N(4′α) bond distance.

The conformation of the hydroxyethyl side chain is usually described[23] in terms of the torsion angles $\Phi_{5\alpha}$ [S(1)−C(5)−C(5α)−C(5β)] and $\Phi_{5\beta}$ [C(5)−C(5α)−C(5β)−O(5γ)]. In many thiamine compounds this chain folds back toward the thiazolium ring and forms an electrostatic link between the electronegative O(5γ) and the electron-deficient S atom. This intramolecular contact can only occur when $\Phi_{5\alpha}$ is less than ≈+70° and $\Phi_{5\beta}$ is negative.[26] In the complex $[CdTCl_3]_2·2H_2O$, $\Phi_{5\alpha}$ is clearly larger than 70° (Table 4), leading to an O(5γ)···S distance (3.391(5) Å) that exceeds the sum of the van der Waals radii (3.32 Å[20]). This also occurs in the $[MnTCl_2(H_2O)]_2^{2+}$ cation, in which T^+ is also N(1′), O(5γ)-bound[17i], but not in the O(5γ)-bound $[CdT(SCN)_3]$ complex.[8] From the data in Table 4 it appears that the metal-oxygen bonds in this latter compound and in $[CdTCl_3]_2·2H_2O$ do not markedly alter the C(5β)−O(5γ) bond length or C(5α)−C(5β)−O(5γ) bond angle.

Figure 2 shows that the dimers are packed along a glide plane that bisects the angle formed by the *a* and *b* axes of the unit cell. As is usual in thiamine/thiaminium derivatives, hydrogen bonds and electrostatic interactions contribute to the packing forces. Thus each H_2O forms dative hydrogen bonds with the N(3′) atom of the base molecule (for which positional parameters are given in Table 2) and with the Cl(1) of a second molecule (see Table 5). In addition, the oxygen atom of the same water molecule is involved in another hydrogen bond with the N(4′α)-H_2 group of a third molecule, and the remaining hydrogen atom (H′) of this N(4′α)H_2 group forms a further hydrogen bond with the Cl(2) atom of the base molecule. All these interactions are shown as dashed lines in Figure 2. The hydrogen bond network is completed by a C(2)−H···Cl(2) interaction (see Table 5) that has been excluded, for the sake of clarity, from the figure.

Some other weak forces are also present in the lattice (Table 5). Thus S interacts with the Cl(3) of a fourth molecule (S···Cl(3)^{v} distance 3.364(3) Å; sum of the van der Waals radii = 3.55 Å;[20] (v) $x - 1$, y, z); the Cl(2) atom that is hydrogen-bonded to the thiazolium C(2)-H group (*vide supra*) stacks on the pyrimidine ring of the same thiamine (Cl(2)···P^{iv} distance 3.485(7) Å; sum of the van der Waals radii for Cl···aromatic ring = 3.52 Å[20]; (iv) $1 + x$, y, z), giving rise to the C(2)···X···P interaction that often occurs in thiamine−metal halide compounds with F conformation;[17e] Cl(3) of the base molecule forms a weak electrostatic link with the thiazolium ring of a fifth molecule. Note that this last interaction is not part of a "two

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Table 7. ^{13}C NMR Chemical Shifts[a] of TCl, TCl·HCl, and Cadmium Compounds in D_2O Solution (δ in ppm from TMS, J in Hz)

	pD	C(2′)	C(4′)	C(2)	C(6′)	C(4)	C(5)	C(5′)	C(5β)	C(3,5′)	C(5α)	C(2′α)	C(4α)	[M][b]	^{113}Cd ($W_{1/2}$)
TCl	6.3	169.3	163.4	155.3 155.0 (t, J_{CD} = 31.8)	156.3	144.2	137.4	106.0	61.8	52.2	30.6	24.9	12.6	0.4	
$[CdTCl_3]_2 \cdot 2H_2O$	6.3	170.3	163.2	155.2 (t, J_{CD} = 33.7)	158.0	144.3	137.6	106.2	61.8	52.2	30.6	25.5	12.5	0.1	74.7 (241)
TCl·HCl	2.1	164.5	164.5	155.8	146.6	144.3	137.8	107.2	61.8	51.6	30.9	22.8	13.1	0.1	
$(HT)[CdCl_4] \cdot H_2O$	3.2	164.3	164.6	156.1	146.0	144.2	137.9	107.5	61.6	51.6	30.5	22.3	12.4	0.2	104.3 (70)

[a] All signals are singlets except those marked with "t", which are triplets. [b] Molar concentration.

Table 8. CP MAS ^{13}C NMR Chemical Shifts of TCl, TCl·HCl, and Cadmium Compounds

	C(2′)	C(4′)	C(2)	C(6′)	C(4)	C(5)	C(5′)	C(5β)	C(3,5′)	C(5α)	C(2′α)	C(4α)
TCl	169.0	163.4	*a*	*a*	144.1	137.2	104.9	*a*	*a*	*a*	25.5	12.3
TCl·HCl	163.8	163.0	152.7	147.4	145.0	134.0	107.3	59.8	52.4	28.4	22.2	14.2
$[CdTCl_3]_2 \cdot 2H_2O$	167.7	159.3	151.7	159.3	141.8	136.6	107.4	60.3	49.3	30.1	27.3	12.7
$(HT)[CdCl_4] \cdot H_2O$	163.2	161.5		145.7	143.5	139.8	109.3	66.1	49.8	34.3	23.5	13.5

[a] Bands not observed due to the poor quality of the spectrum.

point bridge": the thiazolium interacting with Cl(3) and the pyrimidine ring that is hydrogen-bonded via N(4′α)−H to Cl(2) (*vide supra*) belong to *different* thiamines (whereas the definition of the "two point bridge" requires[17e,h] that they belong to the same molecule).

IR Spectra. Table 6 lists the major IR bands of TCl, TCl·HCl, and $[CdTCl_3]_2 \cdot 2H_2O$, together with assignments based on previous work on the thiaminium ligand and its derivatives.[7a,27,28]

The three compounds show two bands in the 1600−1700 cm^{-1} range that are attributed to coupling of the pyrimidine ring (8a) and $\delta(NH_2)$ vibrations. Deuteration experiments indentifying the pyridine ring (8a) band (Table 6) showed that upon protonation or metalation this band shifts in the same directions as previously reported for thiamine and thiamine derivatives.[7a,28] Neither protonation nor metalation has much effect on the pyrimidine ring vibration located at 1560 cm^{-1} in TCl.

The band at 1067 cm^{-1} in thiamine chloride (corresponding to the δ(C−OH) vibration) shifts upon N(1′) protonation to 1042 cm^{-1} in TCl·HCl, which is attributable to changes in the hydrogen bonding of the CH_2OH group; and is similarly altered by formation of the Cd-O bond in $[CdTCl_3]_2 \cdot 2H_2O$ (1053 cm^{-1}). This suggests that this band is not useful for predicting the presence of weak M−O interactions in complexes, in spite its having in the past been appealed in claiming their absence in related systems.[7a,27,28] The ν(OH) vibration of the lattice water occurs at 3512 cm^{-1}, and the δ(OH) vibration reinforces the band at 1655 cm^{-1}.

^{13}C NMR spectroscopy in D_2O. The spectra of the cadmium complexes were recorded at the pD of their solutions. The pD of the TCl·HCl solution was adjusted with NaOD in order to match approximately that of the $[CdTCl_3]_2$ complex. The chemical shift data and assignments are given in Table 7 (for HT^{2+}/T^+ these are based on the work of Gallo and Sable[29]). The observed chemical shifts for TCl·HCl and $[CdTCl_3]_2$ are in good agreement with the values reported by Adeyemo et al.,[30] who prepared the cadmium complex $[CdTCl_3]$ by Cramer's method.[6]

Due to the rapid base-catalysed exchange of the C(2) proton with the solvent,[31] and since the samples were proton- and not deuteron-decoupled, the C(2) signal should be observed in the spectra as a triplet. Usually, the loss of NOE and the presence of a nuclear quadrupole moment "wash out" the splitting due to deuterium, even at very low pH values.[29] However, in our experiments, the spectra of both the complexed and free T^+ ligand (both recorded at pD = 6.3) showed triplets attributable to C(2)−D, at 155.0 (J_{CD} = 31.8 Hz) and 155.2 (J_{CD} = 33.7 Hz) ppm respectively. An additional singlet at 155.3 ppm, possibly due to some residual (nonexchanged) protons at C(2), was present in the ligand spectrum, suggesting that the exchange reaction is slow at pD 6.3 under our experimental conditions but is increased by coordination of the metal. At pD 3.2, no coupling was observed for C(2) in $(HT)[CdCl_4] \cdot H_2O$.

Protonation of T^+ mainly affects the carbons close to N(1′) [C(2′), C(6′), and C(2′α)], which are shielded. This is typical of N-heterocycles, and is due to charge polarization and electric field effects.[32] The remaining carbons are affected less or not at all.

While the spectrum of $(HT)[CdCl_4]$ (Table 7) closely resembles that of the protonated ligand, that of $[CdTCl_3]_2$ is similar to the thiamine chloride spectrum, the chief differences being [as in other N(1′)-bound metal complexes of thiamine or thiamine derivatives (ref 33 and references therein)] the shift to higher frequencies of the C(2′), C(6′), and (C2′α) signals in the complex (by 1.0, 1.7, and 0.6 ppm respectively; see Table 7). The fact that the $[CdTCl_3]_2$ and TCl spectra are more similar in D_2O than in the solid state (vide infra) implies that substantial dissociation of the complex occurs in solution. Nevertheless, the differences between the $[CdTCl_3]_2$ and TCl spectra suggest that the Cd−N(1′) bond does persists to some extent in D_2O solution.

The situation appears to be different for the Cd−O(5γ) interaction. None of the signals associated with the hydroxyethyl side chain show any shift when the spectra of TCl and $[CdTCl_3]_2$ are compared (Table 7), suggesting that this weak metal-ligand bond is labile in aqueous solution. The correspondence between the carbon signals in the spectrum of $[CdTCl_3]_2$ and that of Cramer's complex[30] (in the latter there is no Cd−O(5γ) interaction) supports this conclusion.

^{13}C CP MAS Spectra. Table 8 lists the ^{13}C CP MAS chemical shifts of TCl, TCl·HCl, and the cadmium compounds. The assignments are based on those published for similar compounds,[33] and on the corresponding solution-phase spectra. Chemical shifts for thiamine chloride hydrochloride in the solid

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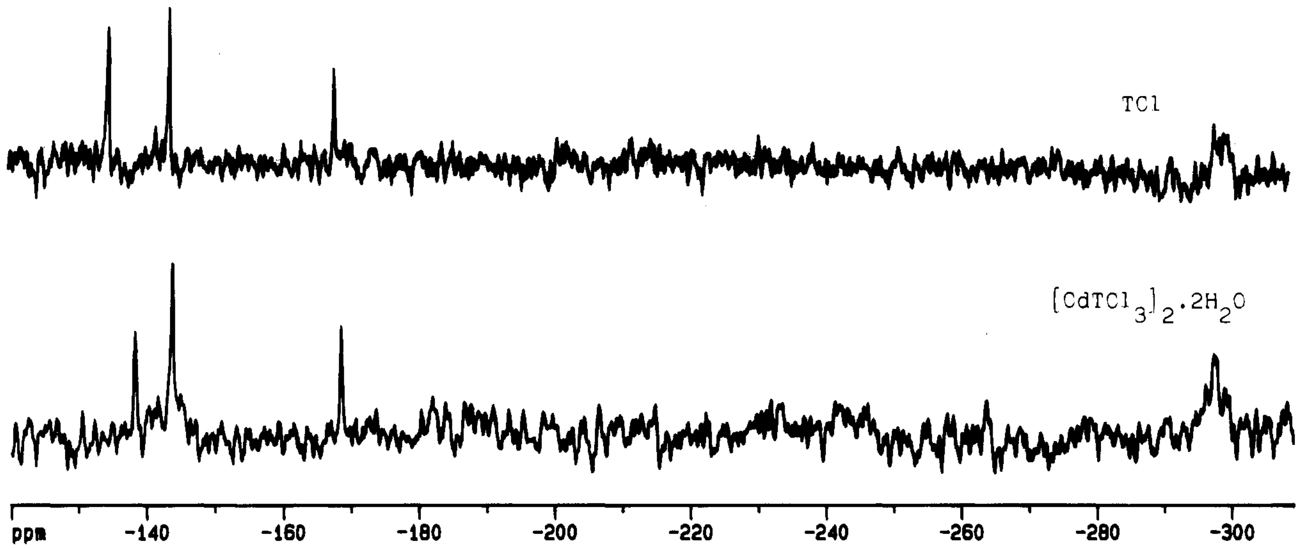

Figure 3. ^{15}N NMR spectrum of TCl and $[CdTCl_3]_2{\cdot}2H_2O$ in 2:1 H_2O/D_2O solution (concentration ca. 0.2 M).

Table 9. ^{15}N NMR Chemical Shifts of TCl, TCl·HCl, and Cadmium Compounds in 2:1 H_2O/D_2O Mixtures (δ in ppm Upfield from Nitromethane)

	N(3)	N(1′)	N(3′)	N(4′α)H_2
TCl	−143.9	−134.9	−168.2	−298.9
TCl·HCl	−140.3	−215.0	−172.4	−276.8
$[CdTCl_3]_2{\cdot}2H_2O$	−143.7	−138.2	−168.5	−297.3
$(HT)[CdCl_4]{\cdot}H_2O$	−140.5	−215.0	−172.5	−274.4

state and in D_2O solution differ by less than 2.0 ppm, except for C(2), C(5) and the carbons of the hydroxyethyl side chain. Exchange of the C(2) proton in solution may be responsible for the first of these exceptions, while the changes in the chemical shifts of C(5), C(5α), and C(5β) may be due to differences in the side-chain conformation and/or interactions upon dissolution: in the solid compound there is a hydrogen bond between the −O(5γ)H group and one chloride ion,[21] which is rather improbable in solution. TCl gives a very poor quality solid state spectrum, but the chemical shifts of the signals identified are again in good agreement with those observed in D_2O solution.

The main differences between the CP MAS spectra of (HT)-$[CdCl_4]{\cdot}H_2O$ and TCl·HCl are observed for C(5) and the hydroxyethyl side chain signals, even though the −O(5γ)H···Cl hydrogen bond found in solid TCl·HCl is also present in the tetrachlorocadmate compound;[5] in this case the differences may be attributable to a (C(2)−H···O(5γ)) hydrogen bond found only in solid $(HT)[CdCl_4]{\cdot}H_2O$, and to the two compounds having clearly different C(5) side chain conformations (cf. angles $\phi_{5\alpha}$ and $\phi_{5\beta}$ in ref 34).

Comparison of the spectra for $(HT)[CdCl_4]{\cdot}H_2O$ and $[CdTCl_3]_2{\cdot}2H_2O$ reveals that, as in D_2O solution, the signals for C(2′), C(6′), and C(2′α) all lie further downfield in the complex than in the salt, confirming the value of this spectral feature for distinguishing between "true" complexes and salts.

There is, however, one respect in which the spectral differences between the complex and the salt are not the same in the solid state as in solution. In D_2O the C(5), C(5α), and C(5β) signals of the complex are almost at the same position as those of the salt; in the CP MAS spectra, they lie further upfield in $[CdTCl_3]_2{\cdot}2H_2O$, and this relative shielding increases with proximity to the −O(5γ)H group (C(5β) > C(5α) > C(5)), possibly because of the weak cadmium−oxygen interaction in the complex.

^{15}N NMR Spectroscopy in D_2O. The ^{15}N NMR chemical shifts of TCl, TCl·HCl, and the cadmium compounds are listed in Table 9, and Figure 3 shows the spectrum of TCl and $[CdTCl_3]_2{\cdot}2H_2O$. The TCl·HCl spectrum is in good agreement with a previous study by Roberts et al.[35] As observed in the latter work,[35] deprotonation of TCl·HCl to TCl led to deshielding of the N(1′) nucleus. In fact, the N(1′) signal at −134.9 ppm in the TCl spectrum (assigned on the basis of the broadening induced by coupling with the C(6′) proton) is at higher frequency than the signals of N(3) and N(3′). As expected, the spectrum of $(HT)[CdCl_4]{\cdot}H_2O$ closely resembles that of TCl·HCl; the only major difference is seen in the N(4′α)H_2 signal, which is shifted ca. 2.5 ppm toward higher frequencies in the cadmium salt. Similar concordance is seen between the spectra of $[CdTCl_3]_2{\cdot}2H_2O$ and TCl, though the relative shift of the N(4′α) signal is smaller and additionally the N(1′) signal shifts 3.3 ppm to lower frequency in the cadmium complex. These observations suggest that the Cd-N(1′) bond persists at least partially in aqueous solution.

^{113}Cd NMR Spectroscopy in D_2O. The ^{113}Cd NMR chemical shifts of $[CdTCl_3]_2{\cdot}2H_2O$ and $(HT)[CdCl_4]{\cdot}H_2O$ are included in Table 7. The Cd resonance is at lower frequency in the complex than in the salt, as would be expected if the solid state kernel of each compound persits in D_2O/H_2O solution; in this case, one of the four chloride ligands in the salt is replaced by a pyrimidine nitrogen atom in the complex, and the probably greater shielding effect of the nitrogen atom relative to the chloride ion[36] causes the Cd signal to shift to lower frequencies. However, since the chemical shift for the salt in solution is considerably smaller than the isotropic shift reported for the solid (451 ppm[37]), it seems likely that its kernel was not in fact conserved. This suggests that chemical exchange between solvent and chloride ions occurs in the salt solution and possibly also in the solution of the complex. In fact, the molar conductivity of a millimolar aqueous solution of the monomer (assumed to result from the breaking of Cd-O(5γ)

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Table 10. Survival Rates and Cadmium Levels[a] ± MSE in the Organs of Rats after Intraperitoneal Administration of $CdCl_2 \cdot H_2O$ and Vitamin B_1 (Thiamine), in Accordance with Protocols A, B, and C

treatment	survival ratio	liver	kidney	brain	heart	testicle
control	4/6	53.67 ± 3.80	57.22 ± 5.09	6.87 ± 0.23	8.87 ± 1.00	7.70 ± 0.72
protocol A	4/8	46.00 ± 1.47	55.57 ± 3.12	9.50 ± 1.20	9.75 ± 0.75	8.50 ± 0.28
protocol B	2/8	20.75 ± 0.75	21.50 ± 1.50	5.00 ± 0.00	6.00 ± 0.50	5.50 ± 0.70
protocol C	3/8	36.30 ± 3.38	48.00 ± 6.24	5.16 ± 0.16	7.00 ± 1.52	6.50 ± 1.32

[a] In μg of Cd/g of dry tissue.

bond in D_2O; see ^{13}C NMR results) is 175 S cm^2 mol^{-1} which is higher than values for 1:1 electrolytes.[38] Which bonds are being disrupted (Cd−N or Cd−Cl) cannot be distinguished from these data, which therefore throw no light on the extent to which the pyrimidine remains bound to the Cd ion in solution.

In Vivo Studies. From the survival rates (Table 10) it is evident that vitamin B_1 does not reduce the lethality of cadmium(II) chloride, at least at the concentration levels used in this study. Protocol B (20 mg/kg of vitamin B_1 administered in five hourly doses starting 1 h after the injection of cadmium(II) chloride) gives the lowest survival rate, but also shows a statistically significant ($p < 0.05$) reduction in the cadmium content of the target organs liver and kidney, suggesting that some renal damage possibly occurs upon excretion of the cadmium. Protocol C appears to afford a slightly better survival rate than protocol B, but is less effective for mobilization of cadmium from these organs.

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Supplementary Material Available: Tables of hydrogen atom parameters, anisotropic thermal parameters, and least-squares planes (Tables S1−S3) (3 pages). Ordering information is given on any current masthead page.

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