The Crystal Structure of Tetrahydrothiamine and its Co(II) Complex

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Abstract

The structures of tetrahydrothiamine and its Co(II) complex have been determined by X-ray crystallography. The parent ligand crystallizes in the monoclinic space group $P2_1/c$ with two independent molecules in the unit cell. The most notable feature of the structure of the title compound is the fact that the tetrahydrothiazolidine ring is, as expected, distinctly non-planar in contrast to its unsaturated analog thiazolidine, which has a planar (N–C–S–C–C) ring. The two substituents of the tetrahydrothiazolidine ring, $-CH_3$ and $-CH_2CH_2OH$, adopt a *syn* conformation in both independent molecules of the unit cell. The final *R* factor obtained was 6.3% for 2124 reflections. The Co(II) complex was prepared by reacting equivalent amounts of the ligand and $CoCl_2$ in $CHCl_3$. The complex crystallizes from hot methanol as its tetrahydrothiaminium salt. [Tetrahydrothiaminium]$^+$-[$CoCl_3$(tetrahydrothiamine)]$^-$ forms triclinic crystals (space group $P\bar{1}$), and its structure was refined to a final *R* factor of 4.8% for 2568 reflections. The cobalt atom is tetrahedrally coordinated by three chloride ions and the parent ligand. The most significant feature of the structure of this complex is the fact that cobalt binds to the N_1' site of the pyrimidine ring, which is consistent with earlier suggestions that this atom acts as the metal-binding site in enzymatic reactions involving thiamine as a cofactor.

Introduction

Tetrahydrothiamine, or 3-[(4′-amino)-2′-methyl-5′-pyrimidinyl)methyl]-5-(β-hydroxyethyl)-4-methylthiazolidine, was first prepared by Hirano [1], by the action of $NaBH_4$ on thiamine chloride hydrochloride. Clark and Sykes [2] obtained this ligand in two diastereoisomeric forms, *syn* and *anti* (Fig. 1) showing two C^4–CH_3 doublets in the ^{1}H NMR spectra at 1.05 and 1.29 ppm. After many recrystallizations they isolated the isomer with the C^4–CH_3 at 1.05 ppm which was in excess in the original mixture [2], without identifying it as either the *syn* or the *anti* isomer.

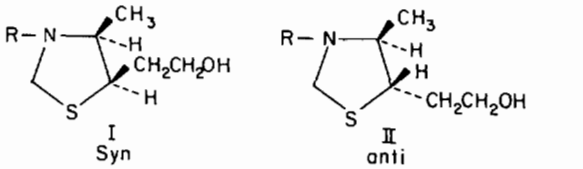

Fig. 1. Schematic sketches of the *syn* and *anti* conformations of the tetrahydrothiazolidine ring.

Tetrahydrothiamine, although not playing any role in the enzymatic action of thiamine [3], as originally proposed by Lipmann [4, 5], is an interesting ligand containing a pyrimidine and a thiazolidine ring. A comparison of the donor properties of the two rings towards various metal ions can thus be made, besides the fact that the thiazolidine moiety is a part of the antibiotic penicillin.

In the Pd(II) and Pt(II) complexes of this ligand [6, 7], the metals were found to bind the thiazolidine moiety, although the bonding site was not unambiguously identified, being either the N or the S atom. On the other hand, Hg(II) attacks the S atom of thiazolidine, which then decomposes and results in a rearrangement of the ligand [8].

The present paper deals with (i) the crystal structure of the ligand tetrahydrothiamine (isolated, as described earlier [2], after many recrystallizations and showing the C^4–CH_3 signals in the ^{1}H NMR spectra at 1.10 ppm in $CDCl_3$ solution) [7] and (ii) the crystal structure of its Co(II) complex as obtained from methanolic solutions.

Crystal Structure of Tetrahydrothiamine

The parent ligand tetrahydrothiamine crystallizes in the space group $P2_1/c$ with two independent

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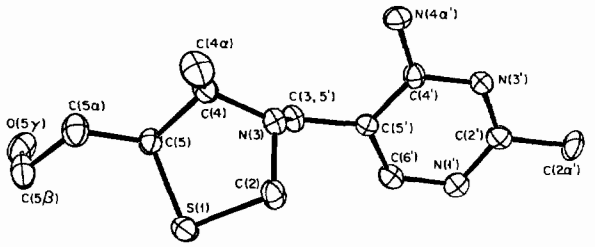

Fig. 2. The free ligand tetrahydrothiamine crystallizes with two independent molecules in the unit cell. This particular diagram is a plot of the one labelled 'molecule 1' in the text. The other one (molecule 2) is virtually superimposable to this one.

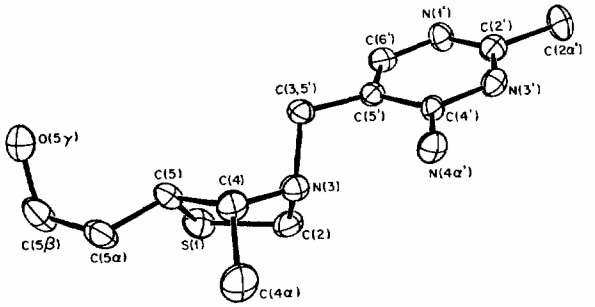

Fig. 3. 'Molecule 2' of tetrahydrothiamine, plotted from a different viewpoint to emphasize the non-planarity of the tetrahydrothiazolidine [S(1)–C(2)–N(3)–C(4)–C(5)] ring. Also note the *syn* conformation of the two substituents [C(4α) and C(5α)–C(5β)–O(5γ)] on this ring.

molecules in the unit cell.* Both have essentially identical configurations, and both adopt the *syn* conformation (Figs. 2 and 3). Atomic positions are given in Table I. The distances and angles have normal values (see Tables II and III), with the most notable feature being that the tetrahydrothiazolidine ring (in contrast to the planar thiazolidine ring in thiamine) is, as expected, distinctly non-planar (Fig. 3).

The torsion angles ϕ_P and ϕ_T for the two crystallographically independent molecules are virtually identical: for molecule 1, ϕ_P[N(3)–C(3,5')–C(5')–C(4')] = −57.6°, ϕ_T[(C(2)–N(3)–C(3,5')–C(5')] = −80.0°; for molecule 2; ϕ_P = −63.8° and ϕ_T = −79.1°. These values do not correspond to any of the F, S or V configurations commonly found in the corresponding unsaturated thiamine derivatives [10]. Since the space group is centrosymmetric, the crystal is racemic: in other words, four of the molecules in the unit cell have the absolute configurations shown in Figs. 2 and 3, while the other four are their mirror images; however, all eight molecules in the unit cell have the *syn* configuration (Fig. 1).

*Tetrahydrothiamine crystallizes in the monoclinic space group $P2_1/c$, with unit cell dimensions a = 9.524(6), b = 23.560(9), c = 13.634(5) Å, β = 103.3(4)°, V = 2977(1) Å^3, Z = 8. The structure was solved by direct methods (MULTAN [9]) and refined to a final R factor of 6.3% for 2124 reflections having $I > 3\sigma(I)$. There are two independent molecules in the unit cell, as discussed in the text and shown in Figs. 2 and 3.

TABLE I. Final Atomic Positions for Tetrahydrothiamine

Atom	x	y	z
Molecule 1			
S(1)	0.893(2)	−0.103(1)	−0.752(2)
C(2)	0.907(7)	−0.072(3)	−0.625(5)
N(3)	0.768(6)	−0.082(2)	−0.599(4)
C(4)	0.716(8)	−0.138(3)	−0.638(5)
C(4α)	0.804(12)	−0.184(4)	−0.572(6)
C(5)	0.727(7)	−0.142(3)	−0.748(5)
C(5α)	0.725(9)	−0.202(3)	−0.789(6)
C(5β)	0.708(11)	−0.205(4)	−0.899(6)
O(5γ)	0.573(6)	0.080(1)	0.226(1)
C(3, 5')	0.623(7)	−0.036(3)	−0.639(5)
N(1')	0.709(6)	0.117(2)	−0.559(4)
C(2')	0.703(7)	0.112(3)	−0.464(5)
C(2α')	0.711(9)	0.166(3)	−0.401(6)
N(3')	0.694(6)	0.061(2)	−0.417(4)
C(4')	0.689(7)	0.013(3)	−0.470(4)
N(4α')	0.681(6)	−0.036(2)	−0.422(4)
C(5')	0.689(7)	0.015(3)	−0.573(5)
C(6')	0.701(7)	0.068(3)	−0.612(5)
Molecule 2			
S(1)	0.970(2)	0.080(1)	0.226(7)
C(2)	0.960(7)	0.050(3)	0.099(4)
N(3)	0.848(5)	0.081(2)	0.030(3)
C(4)	0.859(7)	0.140(3)	0.061(4)
C(4α)	0.989(8)	0.168(3)	0.031(5)
C(5)	0.865(7)	0.142(3)	0.175(4)
C(5α)	0.926(8)	0.197(3)	0.227(5)
C(5β)	0.907(8)	0.203(3)	0.333(5)
O(5γ)	0.759(6)	0.208(2)	0.335(4)
C(3, 5')	0.703(6)	0.057(3)	0.023(5)
N(1')	0.636(5)	−0.095(2)	−0.064(4)
C(2')	0.635(6)	−0.087(3)	−0.162(4)
C(2α')	0.612(8)	−0.141(3)	−0.228(5)
N(3')	0.655(5)	−0.037(2)	−0.205(3)
C(4')	0.679(6)	0.010(3)	−0.147(4)
N(4α')	0.698(6)	0.058(2)	−0.194(4)
C(5')	0.681(6)	0.006(3)	−0.043(4)
C(6')	0.659(6)	−0.046(3)	−0.008(5)
H_2O	0.644(5)	0.318(2)	−0.660(2)

Crystal Structure of [Tetrahydrothiaminium]$^+$-[$CoCl_3$(tetrahydrothiamine)]$^-$

The structure of the Co(II) complex of tetrahydrothiamine is given in Figs. 4 and 5.

This complex was prepared by mixing equivalent amounts of the ligand dissolved in $CHCl_3$ and $CoCl_2 \cdot 6H_2O$ in ethanol in a 1:1 ratio. After stirring the mixture for 24 h at room temperature, the resulting clear solution was evaporated to dryness and the precipitate washed with small amounts of cold

TABLE II. Bond Distances in Tetrahydrothiamine

Molecule 1		Molecule 2	
S–C Distances			
S(1)–C(2)	1.854(8)	S(1)–C(2)	1.860(7)
S(1)–C(5)	1.841(7)	S(1)–C(5)	1.834(7)
C–N Distances			
C(2)–N(3)	1.457(9)	C(2)–N(3)	1.449(8)
C(4)–N(3)	1.475(9)	C(4)–N(3)	1.460(8)
C(3,5')–N(3)	1.481(8)	C(3,5')–N(3)	1.478(8)
C(2')–N(1')	1.317(9)	C(2')–N(1')	1.341(8)
C(6')–N(1')	1.365(9)	C(6')–N(1')	1.365(8)
C(2')–N(3')	1.347(9)	C(2')–N(3')	1.343(8)
C(4')–N(3')	1.347(8)	C(4')–N(3')	1.354(8)
C(4')–N(4α')	1.332(8)	C(4')–N(4α')	1.332(8)
C–O Distances			
C(5β)–O(5γ)	1.417(10)	C(5β)–O(5γ)	1.419(9)
C–C Distances			
C(4)–C(4α)	1.516(12)	C(4)–C(4α)	1.526(10)
C(5)–C(5α)	1.521(10)	C(5)–C(5α)	1.524(10)
C(3,5')–C(5')	1.488(9)	C(3,5')–C(5')	1.488(8)
C(4')–C(5')	1.409(9)	C(4')–C(5')	1.409(8)
C(4)–C(5)	1.528(10)	C(4)–C(5)	1.546(9)
C(5α)–C(5β)	1.477(12)	C(5α)–C(5β)	1.507(10)
C(2')–C(2α')	1.533(11)	C(2')–C(2α')	1.527(10)
C(5')–C(6')	1.370(9)	C(5')–C(6')	1.370(9)

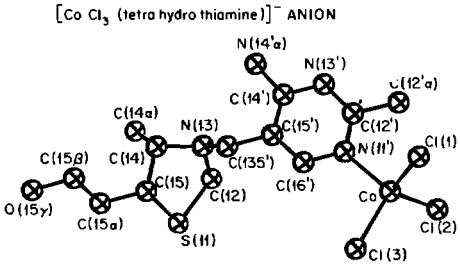

Fig. 4. A plot of the $[CoCl_3(tetrahydrothiamine)]^-$ anion. The tetrahedral coordination of the cobalt atom to N(1') of the pyrimidine ring is clearly seen.

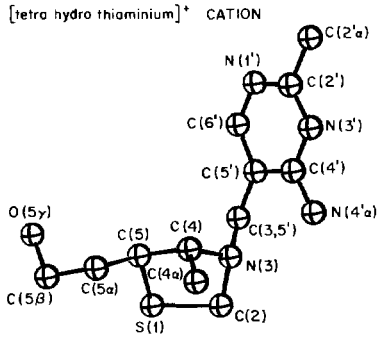

Fig. 5. A plot of the tetrahydrothiaminium ($[LH]^+$) cation, again showing the non-planarity of the tetrahydrothiazolidine ring and the *syn* conformation of the C(4α) and C(5α)–C(5β)–O(5γ) groups. This is the only structure which contains a *trans* ϕ_T torsion angle [C(5')–C(3,5')–N(3)–C(2)]. All other ϕ_T and ϕ_P angles reported in this paper have a *gauche* configuration.

TABLE III. Bond Angles (°) in Tetrahydrothiamine

Molecule 1		Molecule 2	
C–S–C Angle			
C(2)–S(1)–C(5)	92.3(3)	C(2)–S(1)–C(5)	92.5(3)
S–C–N Angle			
S(1)–C(2)–N(3)	107.1(5)	S(1)–C(2)–N(3)	106.6(4)
C–C–S Angles			
S(1)–C(5)–C(4)	105.0(5)	S(1)–C(5)–C(4)	104.7(4)
S(1)–C(5)–C(5α)	113.0(5)	S(1)–C(5)–C(5α)	112.9(5)
C–N–C Angles			
C(2)–N(3)–C(4)	107.8(5)	C(2)–N(3)–C(4)	107.8(5)
C(4)–N(3)–C(3,5')	111.8(5)	C(4)–N(3)–C(3,5')	113.2(5)
C(2')–N(3')–C(4')	119.1(6)	C(2')–N(3')–C(4')	118.9(5)
C(2)–N(3)–C(3,5')	112.0(5)	C(2)–N(3)–C(3,5')	112.5(5)
C(2')–N(1')–C(6')	114.6(6)	C(2')–N(1')–C(6')	114.8(5)
N–C–N Angles			
N(1')–C(2')–N(3')	125.7(6)	N(1')–C(2')–N(3')	125.1(6)
N(3')–C(4')–N(4α')	118.4(6)	N(3')–C(4')–N(4α')	119.8(5)

(continued)

TABLE III. *(continued)*

Molecule 1		Molecule 2	
N–C–C Angles			
N(3)–C(4)–C(4α)	109.4(6)	N(3)–C(4)–C(4α)	109.8(5)
N(3)–C(4)–C(5)	107.8(5)	N(3)–C(4)–C(5)	103.5(4)
N(1')–C(6')–C(5')	124.9(6)	N(1')–C(6')–C(5')	124.7(6)
N(3')–C(4')–C(5')	119.6(6)	N(3')–C(4')–C(5')	119.8(5)
N(3)–C(3,5')–C(5')	110.9(5)	N(3)–C(3,5')–C(5')	110.7(5)
N(1')–C(2')–C(2α')	116.7(5)	N(1')–C(2')–C(2α')	116.4(6)
N(3')–C(2')–C(2α')	117.5(6)	N(3')–C(2')–C(2α')	118.6(5)
N(4α')–C(4')–C(5')	122.0(6)	N(4α')–C(4')–C(5')	124.0(5)
O–C–C Angles			
O(5γ)–C(5β)–C(5α)	111.9(7)	O(5γ)–C(5β)–C(5α)	111.4(6)
C–C–C Angles			
C(4α)–C(4)–C(5)	112.9(6)	C(4α)–C(4)–C(5)	113.9(5)
C(4)–C(5)–C(5α)	114.5(6)	C(4)–C(5)–C(5α)	114.7(5)
C(3,5')–C(5')–C(6')	121.5(6)	C(3,5')–C(5')–C(6')	121.4(5)
C(5)–C(5α)–C(5β)	114.6(7)	C(5)–C(5α)–C(5β)	114.2(6)
C(3,5')–C(5')–C(4')	122.2(6)	C(3,5')–C(5')–C(4')	121.8(5)
C(4')–C(5')–C(6')	116.0(6)	C(4')–C(5')–C(6')	116.8(5)

chloroform, ethanol and ether and dried to yield the intermediate compound $CoL(H_2O)_3Cl_2$ (L = tetrahydrothiamine). *Anal.* Calc. for $CoL(H_2O)_3Cl_2$: C, 31.85; H, 5.57; N, 12.37. Found: C, 31.83; H, 5.72; N, 12.21%. The complex used in the actual structure determination was prepared by recrystallizing $CoL(H_2O)_3Cl_2$ in hot methanol. The title compound corresponds to the empirical formula $[LH]^+[CoLCl_3]^-$, where L = tetrahydrothiamine, with the Co(II) bound to N_1' of the pyrimidine moiety of tetrahydrothiamine in a tetrahedral environment (Fig. 4). *Anal.* Calc. for $[LH]^+[CoLCl_3]^-$: C, 40.98; H, 5.95; N, 11.90. Found: C, 40.15; H, 5.55; N, 15.72%. The cation of $[LH]^+[CoLCl_3]^-$, as its formula indicates, is a protonated tetrahydrothiamine moiety (Fig. 5). The site of the protonation has not been ascertained in this structural analysis – it is probably N(1'), but the possibility of N(3') or N(3) as alternative protonation sites cannot be ruled out.

Final atomic coordinates in $[LH]^+[CoLCl_3]^-$ are tabulated in Table IV, and relevant distances and angles in Tables V and VI. A summary of the structural analysis is given*. As in the case of the parent ligand, the non-planarity of the tetrahydrothiazolidine ring is clearly seen (Fig. 5). For the $[CoLCl_3]^-$ anion, the torsion angle ϕ_P [N(3)–C(3,5')–C(5')–C(4')] = +61.9° and ϕ_T [C(2)–N(3)–C(3,5')–C(5')] = +70.9; those of the $[LH]^+$ cation are ϕ_P = +47.7° and ϕ_T = –171.8°. Again, none of these correspond to the standard F, S or V configurations found in thiamine derivatives [10], thereby implying that saturation (and puckering) of the five-membered S(1)–C(2)–N(3)–C(4)–C(5) ring essentially restricts the ϕ_P and ϕ_T angles to more-or-less *gauche* (±60°) or *trans* (~180°) configurations. As in the free ligand (Figs. 2, 3), the tetrathiazolidine ring is in the *syn* conformation (Figs. 4, 5).

There are now six known structures of metal complexes [involving Cu(II), Zn(II), Cd(II) and Rh(II) and Pt(II)] of the unsaturated thiamine ligand [12], showing the N_1' atom of the pyrimidine ring as the preferred coordination site. In only one somewhat related case, the complex [Cu(thiaminepyrophosphate)(1,10-phenanthroline)(H_2O)] [13], does the coordinated metal atom interact solely with the oxygen atoms of the pyrophosphate group of thiamine.

Discussion

These structures, together with the various ^1H NMR and ^{13}C NMR studies [14, 15] of metal complexations with thiamine and its derivatives in solution, seem to provide further support for the

*[Tetrahydrothiaminium]$^+$[$CoCl_3$(tetrahydrothiamine)]$^-$ crystallizes in the triclinic space group $P\bar{1}$ with unit cell parameters a = 10.501(3), b = 16.679(7), c = 10.334(5) Å, α = 103.8(4)°, β = 108.0(3)°, γ = 75.5(3)°, V = 1641(1) Å^3, Z = 2. The structure was solved using standard heavy-atom methods, and refined to a final R factor of 4.8% for 2568 reflections having $I > 3\sigma(I)$. Calculations were performed using the UCLA crystallographic computing package [11]. The anion and cation are shown in Figs. 4 and 5, respectively.

TABLE IV. Final Atomic Coordinates of [Tetrahydrothiaminium]$^+$[Co(Tetrahydrothiamine)Cl_3)]$^-$

Atom	*x*	*y*	*z*
[Co(tetrahydrothiamine)Cl_3]$^-$anion			
Co	0.8663(1)	0.2754(1)	0.5531(1)
C(11)	0.7001(2)	0.3752(1)	0.4456(2)
C(12)	1.0740(2)	0.3127(1)	0.6101(2)
C(13)	0.8261(2)	0.2539(1)	0.7429(2)
S(11)	1.3369(3)	0.0516(2)	0.1532(4)
C(12)	1.1630(8)	0.0315(5)	0.1203(10)
N(13)	1.1725(6)	−0.0342(4)	0.1892(7)
C(14)	1.3031(8)	−0.0965(4)	0.1710(8)
C(14α)	1.2679(11)	−0.1386(7)	0.0267(9)
C(15)	1.4125(8)	−0.0454(5)	0.2150(8)
C(15α)	1.5407(9)	−0.0908(6)	0.1660(10)
C(15β)	1.6195(8)	−0.1652(5)	0.2371(9)
O(15γ)	1.7311(5)	−0.2047(3)	0.1802(5)
C(135′)	1.1712(7)	−0.0069(4)	0.3339(7)
N(11′)	0.8831(6)	0.1602(3)	0.4298(5)
C(12′)	0.7826(7)	0.1168(5)	0.3793(7)
C(12′α)	0.6426(7)	0.1603(4)	0.3942(8)
N(13′)	0.7946(6)	0.0367(4)	0.3145(6)
N(14′α)	0.9286(6)	−0.0841(3)	0.2362(6)
C(14′)	0.9189(7)	−0.0036(4)	0.2982(7)
C(15′)	1.0311(7)	0.0370(4)	0.3469(6)
C(16′)	1.0066(7)	0.1182(4)	0.4114(6)
[Tetrahydrothiaminium]$^+$cation			
S(1)	1.1252(2)	0.4358(1)	1.3069(2)
C(2)	0.9493(7)	0.4541(4)	1.3257(7)
N(3)	0.8649(5)	0.4200(3)	1.1935(5)
C(4)	0.9454(6)	0.3408(4)	1.1385(6)
C(4α)	0.9538(7)	0.2727(4)	1.2168(7)
C(5)	1.0884(7)	0.3575(4)	1.1501(7)
C(5α)	1.2000(7)	0.2796(5)	1.1479(8)
C(5β)	1.3400(7)	0.2953(5)	1.1612(9)
O(5γ)	1.3413(5)	0.3319(3)	1.0525(5)
C(35′)	0.8115(6)	0.4805(4)	1.0986(6)
N(1′)	0.6148(6)	0.4351(3)	0.7292(6)
C(2′)	0.5140(7)	0.4007(4)	0.7390(7)
C(2′α)	0.4111(8)	0.3778(6)	0.6079(7)
N(3′)	0.5055(5)	0.3888(3)	0.8554(6)
C(4′)	0.6026(6)	0.4098(4)	0.9728(7)
N(4′α)	0.5915(5)	0.3946(3)	1.0880(5)
C(5′)	0.7095(6)	0.4484(4)	0.9712(7)
C(6′)	0.7113(7)	0.4582(4)	0.8448(8)

interaction of the N_1' atom of the pyrimidine moiety of thiamine with metal ions during its enzymatic action, either directly or indirectly [15b, c]. The same conclusion was also reached by Schellenberger [16] in studies with model compounds. He suggested that the metal ions might form a bridge between the pyrimidine base and the enzyme, thus fixing the coenzyme in the catalytic site of the enzyme.

The most significant feature of the present crystal structure determination is the existence of the N_1'–Co(II) bonding. The dominating N_1'–metal inter-

TABLE V. Bond Distances and Angles in the [$CoCl_3$(tetrahydrothiamine)]$^-$ Anion

Bond distances (Å)	
Co–N(11′)	2.050(5)
Co–Cl(3)	2.260(2)
Co–Cl(2)	2.273(2)
Co–Cl(1)	2.287(2)
S(11)–C(15)	1.787(8)
S(11)–C(12)	1.852(9)
C(12)–N(13)	1.411(9)
N(13)–C(135′)	1.459(8)
N(13)–C(14)	1.533(9)
C(14)–C(14α)	1.464(11)
C(14)–C(15)	1.495(10)
C(15)–C(15α)	1.540(11)
C(15α)–C(15β)	1.520(11)
C(15β)–O(15γ)	1.417(9)
C(135′)–C(15′)	1.502(9)
N(11′)–C(12′)	1.331(8)
N(11′)–C(16′)	1.358(8)
C(12′)–N(13′)	1.338(8)
C(12′)–N(12′α)	1.505(10)
N(13′)–C(14′)	1.352(8)
N(14′α)–C(14′)	1.336(8)
C(14′)–C(15′)	1.403(9)
C(15′)–C(15′)	1.359(9)
Bond angles (°)	
N(11′)–Co–Cl(3)	104.2(2)
N(11′)–Co–Cl(2)	106.0(2)
N(11′)–Co–Cl(1)	112.7(2)
C(13)–Co–Cl(2)	109.8(1)
C(3)–Co–Cl(1)	113.1(1)
C(12)–Co–Cl(1)	110.6(1)
C(15)–S(11)–C(12)	91.5(4)
N(13)–C(12)–S(11)	108.2(6)
C(12)–N(13)–C(135′)	114.4(6)
C(12)–N(13)–C(14)	105.3(6)
C(135′)–N(13)–C(14)	112.6(6)
C(14α)–C(14)–C(15)	117.8(7)
C(14α)–C(14)–N(13)	104.7(7)
C(15)–C(14)–N(13)	105.8(6)
C(14)–C(15)–C(15α)	113.4(7)
C(14)–C(15)–S(11)	106.6(5)
C(15α)–C(15)–S(11)	112.5(6)
C(15β)–C(15α)–C(15)	113.0(7)
O(15γ)–C(15β)–C(15α)	108.4(6)
N(13)–C(135′)–C(15′)	111.1(5)
C(12′)–N(11′)–C(16′)	116.7(5)
C(12′)–N(11′)–Co	123.7(5)
N(12′)–C(12′)–N(13′)	125.5(6)
N(11′)–C(12′)–C(12′α)	118.3(6)
N(13′)–C(12′)–C(12′α)	116.2(6)
C(12′)–N(13′)–C(14′)	117.5(6)
N(14′α)–C(14′)–N(13′)	116.1(6)
N(14′α)–C(14′)–C(15′)	122.5(6)
N(13′)–C(14′)–C(15′)	121.3(6)
C(16′)–C(15′)–C(14′)	115.9(6)
C(16′)–C(15′)–C(135′)	121.6(6)
N(11′)–C(16′)–C(15′)	124.1(6)

TABLE VI. Bond Distances and Angles in the [Tetrahydrothiaminium]$^+$Cation

Bond distances (Å)	
S(1)–C(5)	1.827(7)
S(1)–C(2)	1.859(7)
C(2)–N(3)	1.452(8)
N(3)–C(35′)	1.464(7)
N(3)–C(4)	1.471(7)
C(4)–C(4α)	1.515(9)
C(4)–C(5)	1.558(9)
C(5)–C(5α)	1.518(9)
C(5α)–C(5β)	1.516(10)
C(5β)–O(5γ)	1.405(9)
C(35′)–C(5′)	1.498(9)
N(1′)–C(6′)	1.352(8)
N(1′)–C(2′)	1.363(8)
C(2′)–N(3′)	1.297(8)
C(2′)–C(2′α)	1.484(10)
N(3′)–C(4′)	1.358(8)
C(4′)–N(4′α)	1.319(7)
C(4′)–C(5′)	1.433(8)
C(5′)–C(6′)	1.361(8)
Bond angles (°)	
C(5)–S(1)–C(2)	92.5(2)
N(3)–C(2)–S(1)	107.1(4)
C(2)–N(3)–C(35′)	112.4(5)
C(2)–N(3)–C(4)	107.6(5)
C(35′)–N(3)–C(4)	113.7(5)
N(3)–C(4)–C(4α)	109.7(5)
N(3)–C(4)–C(5)	107.9(5)
C(4α)–C(4)–C(5)	112.6(5)
C(5α)–C(5)–C(4)	114.9(5)
C(5α)–C(5)–S(1)	113.4(5)
C(4)–C(5)–S(1)	105.1(4)
C(5β)–C(5α)–C(5)	115.3(6)
O(5γ)–C(5β)–C(5α)	112.4(6)
N(3)–C(35′)–C(5′)	111.2(5)
N(3′)–C(2′)–N(1′)	122.9(6)
N(3′)–C(2′)–C(2′α)	120.8(7)
N(1′)–C(2′)–C(2′α)	116.3(7)
C(2′)–N(3′)–C(4′)	118.9(6)
N(3′)–C(4′)–C(5′)	121.3(6)
C(6′)–C(5′)–C(4′)	115.9(6)
C(6′)–C(5′)–C(35′)	120.2(6)
C(4′)–C(5′)–C(35′)	123.9(6)

action in metal–thiamine complexes was suggested by Aoki and Yamazaki [12e] to be due mainly to the high basicity of this site and not to steric effects. This site is more basic than the N_3' site and the exocyclic N(4α′) amino group, whose lone pair is part of the π-system of the pyrimidine ring. The N_1' site is also more basic than the thiazole binding sites, since the thiazole ring bears a net positive charge [17].

In the present structure determination, in which the planar thiazole ring is transformed to the nonplanar thiazolidine ring, the positive charge on the N_3 atom is no longer present and furthermore electrons are expected to be localized on the sulfur atom. Nevertheless, metal binding is still taking place through N_1'. The same site was also found to be preferentially protonated in the tetrahydrothiamine ligand [6, 7]. It does not coordinate only with heavy metals [such as Pd(II), Pt(II) or Hg(II), which normally show a marked preference towards sulfur donors] [6–8]. First row transition metals on the other hand, like Co(II) (which show some catalytic activity) as well as the naturally-occurring (and catalytically most active) Mg(II) ions prefer this site. All these observations seem to substantiate earlier suggestions [14–17] that the N_1' site is intimately involved in the enzymatic action of thiamine.

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