

TRANSITION AND GROUP IIB METAL COMPLEXES WITH "ACTIVE ALDEHYDE" DERIVATIVES OF THIAMINE

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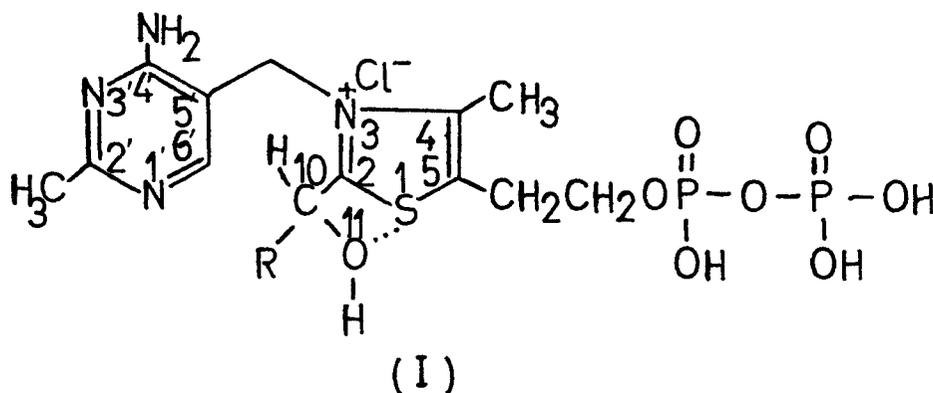
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Abstract: The Zn^{2+} , Cd^{2+} , Hg^{2+} , Co^{2+} and Ni^{2+} ions produce zwitterionic type complexes with the ligands (L), 2-(α -hydroxy-benzyl)thiamine=HBT and 2-(α -hydroxy-cyclohexyl-methyl)thiamine = HCMT, of the type $MLCl_3$. The ligands are in the S conformation, the metals are bound to N_1 of the pyrimidine moiety of thiamine and the complexes have a trigonally distorted tetrahedral structure, as the crystal structure of the complex $Zn(HCMT)Cl_3$ (orthorhombic, $a=14.4$ $b=14.1$ $c=17.4$ $\beta=105.6^\circ$ $V=3392 \text{ \AA}^3$ $R=13.8\%$), the one and two dimensional 1H nmr spectra of the Zn^{2+} , Cd^{2+} and Hg^{2+} complexes and the electronic spectra of the Co^{2+} and Ni^{2+} complexes show. A brief review of the previous techniques (structure of the $Hg(HBT)Cl_3$ complex, IR-Raman spectra, ^{13}C nmr in solution and solid state etc) used to characterize these complexes, is also given here and the proper conclusions drawn.

Introduction: The pyrophosphate ester of thiamine (vitamin B₁) is the coenzyme of many enzymes like carboxylase, transketolase etc, catalyzing the decarboxylation of α -ketoacids or the formation of α -ketols [1]. Mg²⁺ ions are required *in vivo* for its action, but *in vitro* other bivalent metal ions like Co²⁺, Zn²⁺, Ni²⁺ etc are also active as well. The enzymatic mechanism of action of thiamine enzymes requires the formation of the so called "active aldehyde" intermediates (I) which were isolated [1,2]. However the role played by the bivalent metal ions is not as yet quite clear. Attempts to prepare metal complexes of thiamine with



bivalent metals were resulted for many years to the formation of ionic salts of the type $[L]^{2+}[MX_4]^{2-}$, $[L]^{2+}([MX_3]^-)_2$, $([L]^+)_2[MX_4]^{2-}$, without a direct metal-ligand bonding, due to the net positive charge on thiamine and to the easy protonation of the N₁' site of pyrimidine (pK_a-5) [3]. Despite this difficulty, a few metal complexes of thiamine with Cd²⁺, Zn²⁺, Pt²⁺, Mn²⁺ etc containing mainly a M-N₁' direct bonding were prepared in recent years and their structures were solved with X-rays [4].

The use however of the "active aldehyde" intermediates of thiamine as ligands for the formation of complexes with bivalent metal ions, presented the advantage of the delocalization of the net positive charge on N₃ of the thiazolium moiety to the sulfur atom and resulted to the easier formation of compounds with M-N₁' bonds [3-7].

We summarize here all the techniques used thus far for the characterization of these complexes, adding a few more, as well as the conclusions drawn concerning the enzymatic action of thiamine.

Materials and Methods: The preparation of the ligands (L) 2-(α -hydroxybenzyl)thiamine = HBT and 2-(α -hydroxycyclohexyl-methyl) thiamine = HCMT and the complexes $MLCl_3$ ($M=Zn^{2+}$, Cd^{2+} , Hg^{2+} , Co^{2+} , Ni^{2+}) was described previously [3,6]. The structure of the complex $Zn(2-(\alpha$ -hydroxycyclohexylmethyl) thiamine) Cl_3 was solved with the same method and instrument used for the $Hg(HBT)Cl_3$ complex [3]. Crystals of the complex were grown by slowly diffusing acetone and ether in a solution of the complex in methanol. They were unstable in the absence of the solvents and were mounted in a sealed capillary and the data collection followed.

The 1D- 1H nmr spectra were recorded on a Bruker AC 200 Spectrometer with TMS as an internal standard.

The 2D- 1H nmr spectra were also obtained on a Bruker AC 200 spectrometer at 200 MHz. The pulse sequence $90^\circ-t_1-90^\circ-r_m-90^\circ$ was followed with mixing time of 500 ms.

The DRS and the solution UV-Vis spectra were recorded as described [6].

Results and Discussion: Metal complexes of the II $_B$ group metal ions as well as Co^{2+} , Ni^{2+} and Cu^{2+} were used for the preparation of the 1:1 complexes with the "active aldehyde" derivatives of the thiamin HBT and HCMT that corresponded to the general formulae $MLCl_3$, with L the above thiamine derivatives and M all the metal ions except Cu^{2+} [3-7]. The latter was oxidizing both ligands to thiochrome [6,8], producing the complexes $[Cu^{II}L'Cl_2].H_2O$ and $[Cu^I(HL)Cl]^+[Cu^{II}Cl_3(MeOH)]^-$ [6]. The various techniques used were :

(i) X-ray crystal structures

The first crystal structure reported was the one of Hg^{2+} with 2-(α -hydroxybenzyl)thiamine, $Hg(HBT)Cl_3$ [3]. Here the ligand had the less common S conformation with $\Phi_P = [N(3)-C(3,5')-C(5')-C(4')] = 172.7^\circ$ and $\Phi_T = [C(5')-C(3,5')-N(3)-C(2)] = -100.0^\circ$ (Pletcher and Sax [9] defined the S conformation of thiamine with $\Phi_T = \pm 100^\circ$, $\Phi_P = \pm 150^\circ$, the V conformation with $\Phi_T = \pm 90^\circ$, $\Phi_P = \pm 90^\circ$ and the F conformation with $\Phi_T = 0^\circ$, $\Phi_P = \pm 90^\circ$). These was a direct Hg- $N_{1'}$ bonding of 2.23Å [3].

A second crystal structure of the compound $Zn(2-(\alpha$ -hydroxycyclohexylmethyl)thiamine) Cl_3 , $Zn(HCMT)Cl_3$ was subsequently solved but only to an R value of about 13.8%. Despite the low accuracy in the details of the structure, it is clear that the bonding of the metal takes place again with the $N_{1'}$ of the pyrimidine moiety (The bond distance Zn- $N_{1'}$ is about 2.1 Å).

The HCMT ligand is also in the S conformation with $\Phi_P-172.8^\circ$ and $\Phi_T-92.7^\circ$ and the configuration around Zn is pseudotetrahedral [3].

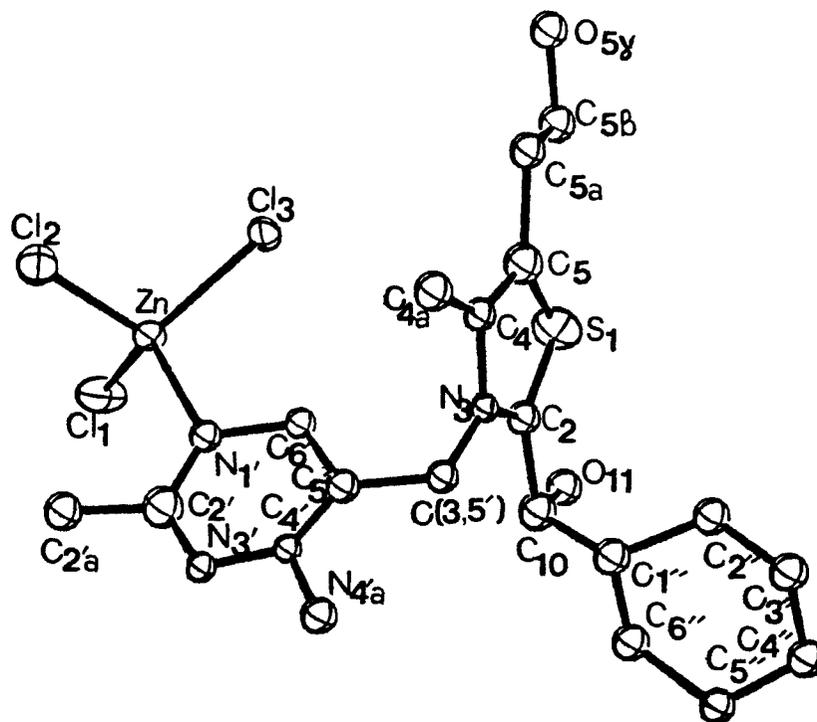


Fig.1. The structure of the complex $Zn(HCMT)Cl_3$

(ii) Vibrational IR-Raman Spectra

The comparison of the IR and Raman spectra of the various complexes with the ones of known structure, showed that they were all similar band by band, except the metal-ligand (M-N, M-Cl) stretching vibrations [5]. Another difference of the various complexes was the difference at the position of the first $\nu_{C=N}$ vibration of the pyrimidine moiety, varying with the bulkiness of the $N_{1'}$ coordinated metal ion and the protonation. This frequency was increasing in the order $H^+ > Co^{2+} \sim Ni^{2+} \sim Zn^{2+} > Cd^{2+} > Hg^{2+}$ [3,5].

(iii) NMR Spectra

Comparison of the ^{13}C nmr of the various metal complexes in solution and the solid state showed that they were all isostructural in both phases, to the ones with

known structures and that both the M-N_{1'} bonding and the S conformation of the ligands were retained in D₂O and DMSO-d₆ solutions [7]. This was also confirmed with the ¹⁹⁹Hg nmr spectra [7] of the mercury complexes.

(a) ¹H nmr spectra (1D): The ¹H nmr chemical shifts of the various ligands and their II_B metal complexes in DMSO-d₆ solutions, are included in Table I.

Protonation of both ligands at N_{1'} of pyrimidine causes downfield shifts to its adjacent protons, C₆-H and C₂-CH₃. This however, does not cause significant changes to the neighboring coupling constants (Table I), indicating the absence of conformational changes of the molecule upon protonation.

The broad bands of HBT.HCl and HCMT.HCl located at -8.9 and 9.254 ppm respectively, are assigned to the N(4'a)H₂ protons in exchange with their N(1')-H protons. This is evidenced from the fact that in the non protonated ligands, they are located at 7.3-7.5 ppm as sharp bands as expected for aminopyrimidines [10].

Unexpectedly, the neighboring protons to the N_{1'} site of pyrimidine are not shifted significantly upon metal coordination.

In a first approach this can be explained as the result of two opposite effects : (a) The localization of the net negative charge of the [MCl₃]⁻ ion at the N_{1'} position of the pyrimidine, causing an upfield shift of the adjacent protons and (b) the metal complexation at N_{1'} causing an opposite downfield shift of the same protons [11,12]. Similar were the results of the ¹³C nmr in D₂O and DMSO-d₆ solutions for the carbon atoms adjacent to N_{1'} that can not be due to the breaking of the M-N_{1'} bonding in solution, since the behavior was also similar in the solid state ¹³C nmr spectra [7].

All the protons of pyrimidine in HBT, HBT.HCl and their complexes are more deshielded compared to the ones of HCMT, HCMT.HCl and their complexes and therefore more upfield shifted than the latter (Table I). This is due to the stacking effect of the benzyl ring, being almost parallel to the pyrimidine in the HBT derivatives (dihedral angle 90° and shorter distance 3.4Å) [3,13,14]. The same was observed in the solution and solid state ¹³C nmr spectra of all the HBT and HCMT complexes for the adjacent to N_{1'} carbon atoms [7].

The O(5γ)H, C(3,5')H₂, C(10)-H and O(11)-H protons on the other hand, were more influenced upon complexation than protonation. They were all upfield shifted with the same magnitude for the complexes of both ligands with the three metals.

These results may be explained by the facts : (a) that the methylenic C(3,5')H₂ protons and the C(10)H proton are in close contact (electrostatic interaction) with

Table 1. ¹H nmr spectral data of the compounds

Compound	0(11)-H	N(4e')-H	C(6')-H	C(10)-H	C(3,5')-H ₂	O(5y)-H	C(5B)-H ₂	C(5a)-H ₂	2'-CH ₃	4-CH ₃
HBT	8.012 3J _{11,10} =4.86	7.280	6.851	6.590 3J _{10,11} =4.87	5.782, 5.526 2J _{AB} =17.00	5.514 3J _{y,β} =5.09	3.787	3.152 3J _{α,β} =5.33	2.361	2.351
HBT.HCl	7.973 3J _{11,10} =4.77 (-0.039)	~8.9 ^a	7.232 (0.381)	6.542 3J _{10,11} =4.71 (-0.048)	5.765, 5.542 2J _{AB} =18.03 (-0.017), (0.016)	~5.5 ^a	3.816 (0.029)	3.165 3J _{α,β} =5.51 (0.013)	2.559 (0.198)	2.415 (0.064)
Zn(HBT)Cl ₃	7.775 3J _{11,10} =4.60 (-0.237)	7.219 (-0.061)	6.909 (0.058)	6.481 3J _{10,11} =4.60 (-0.109)	5.441 -0.341), (-0.083)	5.416 3J _{y,β} =4.96 (-0.098)	3.814 (0.027)	3.160 3J _{α,β} =5.44 (0.008)	2.403 (0.042)	2.358 (0.007)
Cd(HBT)Cl ₃	7.754 3J _{11,10} =4.62 (-0.258)	7.186 (-0.094)	6.850 (-0)	6.483 3J _{10,11} =4.62 (-0.107)	5.443 (-0.339), (-0.083)	5.406 3J _{y,β} =5.00 (-0.108)	3.813 (0.026)	3.160 3J _{α,β} =5.40 (0.008)	2.370 (0.009)	2.354 (0.003)
Hg(HBT)Cl ₃	7.752 3J _{11,10} =4.57 (-0.260)	7.211 (-0.069)	6.862 (0.011)	6.476 3J _{10,11} =4.55 (-0.114)	5.435 (-0.347), (-0.091)	5.409 3J _{y,β} =4.91 (-0.105)	3.813 (0.026)	3.158 3J _{α,β} =5.38 (0.006)	2.382 (0.021)	2.353 (0.002)
HcMT	7.385 3J _{11,10} =5.12	7.501	7.348	5.264 3J _{10,11} =5.10	5.837, 5.609 2J _{AB} =17.10	5.490 ^a	3.763	3.147 ^a	2.399	2.433
HcMT.HCl	7.398 ^a (0.013)	9.254 (1.753)	7.791 (0.443)	5.254 ^a (-0.010)	5.897, 5.687 2J _{AB} =17.90 (0.060), (0.078)	~5.5 ^a	3.788 (0.025)	3.144 3J _{α,β} =5.41 (-0)	2.645 (0.246)	2.427 (-0.006)
Zn(HcMT)Cl ₃	7.141 3J _{11,10} =5.12 (-0.244)	7.316 (-0.185)	7.316 (-0.032)	5.182 3J _{10,11} =5.10 (-0.082)	5.570 (-0.280), (-0.052)	5.382 3J _{y,β} =4.95 (-0.108)	3.796 (0.033)	3.138 3J _{α,β} =5.39 (-0.009)	2.468 (0.069)	2.399 (-0.034)
Cd(HcMT)Cl ₃	7.122 3J _{11,10} =5.10 (-0.263)	7.288 (-0.213)	7.288 (-0.060)	5.179 3J _{10,11} =5.10 (-0.085)	5.550 (-0.287), (-0.059)	5.372 3J _{y,β} =4.90 (-0.118)	3.797 (0.034)	3.138 3J _{α,β} =5.38 (-0.009)	2.456 (0.057)	2.397 (-0.036)
Hg(HcMT)Cl ₃	7.120 3J _{11,10} =5.15 (-0.265)	7.327 (-0.174)	7.301 (-0.047)	5.173 3J _{10,11} =5.12 (-0.091)	5.546 (-0.291), (-0.063)	5.380 3J _{y,β} =4.94 (-0.110)	3.801 (0.038)	3.139 3J _{α,β} =5.42 (-0.008)	2.466 (0.067)	2.401 (-0.032)

all three chloride ions of Hg^{2+} ($\sim 3.5\text{\AA}$) as found in the crystal structure of $\text{Hg}(\text{HBT})\text{Cl}_3$ [3]. The same is true in the structure of $\text{Zn}(\text{HCMT})\text{Cl}_3$ that does not change in solution as well [7]. It should be noted here that the $\text{C}(3,5)\text{H}_2$ methylenic protons behave as an AB system in the protonated and non protonated ligands due to the chiral center at $\text{C}(10)$ [15]. In their metal complexes however, they are seen as isochronous. To account for the observed upfield shift of the $\text{O}(5\gamma)\text{H}$ proton, we compare the torsional angles $\Phi_{5\alpha}$ and $\Phi_{5\beta}$ of the complexes $\text{Hg}(\text{HBT})\text{Cl}_3$ and the ligand $\text{HBT}\cdot\text{HCl}$.

Thus in the complex $\text{Hg}(\text{HBT})\text{Cl}_3$ with $\Phi_{5\alpha}=78.6^\circ$ and $\Phi_{5\beta}=65.5^\circ$, the thiazolium side chain is brought under the influence of the aromatic thiazolium ring itself. This causes the upfield shift of the $\text{O}(5\gamma)\text{H}$ proton, being under the influence of the ring. In the ligand $\text{HBT}\cdot\text{HCl}$ on the other hand, the thiazolium side chain ($\Phi_{5\alpha}=3.3^\circ$, $\Phi_{5\beta}=63.4^\circ$) is directed far away and not influenced at all by the aromatic thiazolium ring.

(b) ^1H nmr spectra (2D, NOESY): In order to detect whether or not a stacking

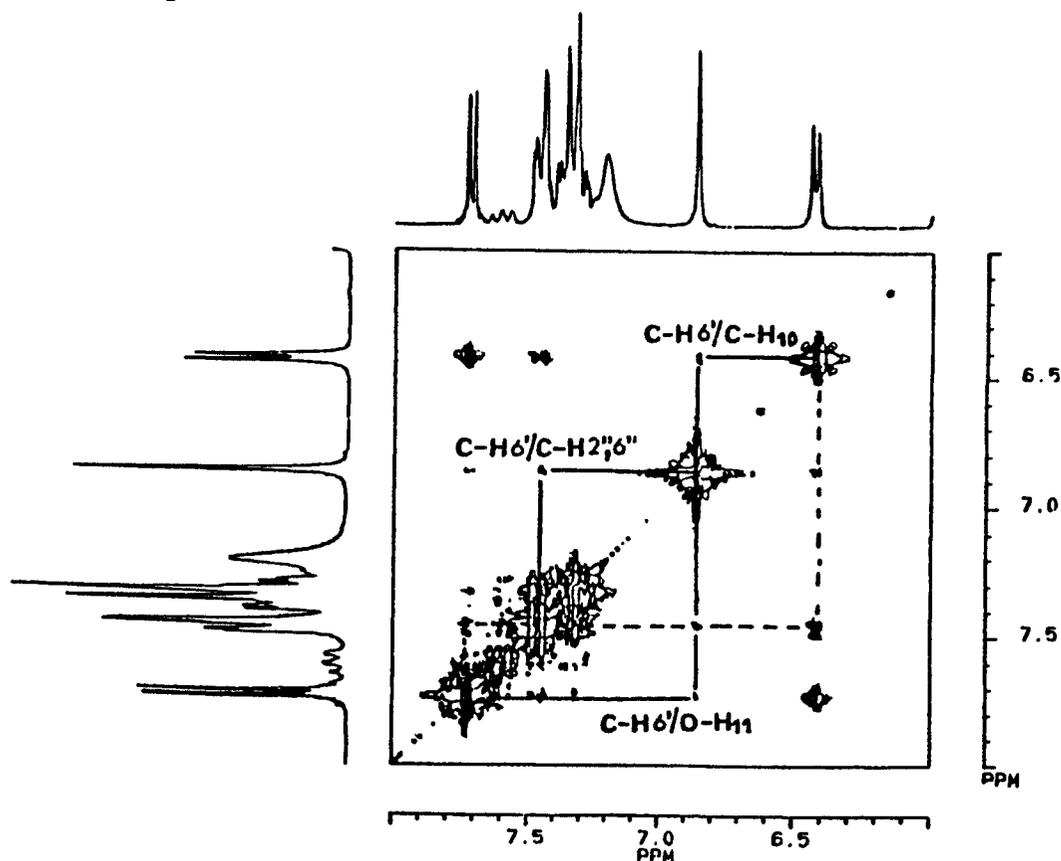


Fig.2. ^1H nmr NOESY spectrum (contour plot) of the complex $\text{Zn}(\text{HBT})\text{Cl}_3$, in DMSO-d_6 .

interaction between the benzyl and the pyrimidine rings found in the solid state [3] persists also in solution, we have recorded the 2D-NOE spectrum of the complex $\text{Zn}(\text{HBT})\text{Cl}_3$ in DMSO-d_6 (Fig.2). For comparison the 2D-NOE spectrum of the complex $\text{Zn}(\text{HCMT})\text{Cl}_3$ was recorded as well. From Fig.2, it is easily seen that enhanced connectivities exist between the protons $\text{C}(6')\text{-H}/\text{C}(10)\text{-H}$, $\text{C}(6')\text{-H}/\text{C}(2'',6'')\text{-H}$ and a weak cross peak between $\text{C}(6')\text{-H}$ and $\text{O}(11)\text{-H}$. Therefore the pyrimidine $\text{C}(6')\text{-H}$ proton approaches the $\text{C}(10)\text{-H}$ and $\text{O}(11)\text{-H}$ and the $\text{C}(2'',6'')$ protons of the benzene ring. This indicates that the benzene and pyrimidine rings are almost parallel, like in the solid phase.

Comparison of the 2D-NOE spectra of the complexes $\text{Zn}(\text{HBT})\text{Cl}_3$ and $\text{Zn}(\text{HCMT})\text{Cl}_3$ show that in the second case there were not observed any cross peak connectivities between pyrimidine and cyclohexane, thus excluding any interaction (stacking, hydrophobic) between these two rings, as this is also true in the solid phase.

(iv) Electronic Spectra

The Co^{2+} and Ni^{2+} complexes of the general formulae MLCl_3 should have similar structures (M-N_1 bonding and S conformation of the ligands, pseudotetrahedral structures around the metals) with the ones of known structures $\text{Hg}(\text{HBT})\text{Cl}_3$ and $\text{Zn}(\text{HCMT})\text{Cl}_3$ as exposed above (similar IR-Raman spectra band by band). Their pseudotetrahedral structures are further substantiated by their electronic DRS (diffuse reflectance spectra) and DMF solution spectra (Table II). In the DRS of the CoLCl_3 complexes the multiple bands near 6600 cm^{-1} and 15700 cm^{-1} correspond to the ${}^4\text{A}_2(\text{F})\text{---}{}^4\text{T}_1(\text{F})$ and ${}^4\text{A}_2(\text{F})\text{---}{}^4\text{T}_1(\text{P})$ transitions respectively, in a tetrahedral environment [16]. The multiplicity of the bands however show reduction of T_d to C_{3v} symmetry (trigonal distortion). The various components of the multiple bands are assigned as follows : the one near 5200 cm^{-1} to ${}^4\text{A}_2(\text{F})\text{---}{}^4\text{A}_2(\text{T}_1, \text{F})$, the ones near 6600 and 7400 cm^{-1} to the ${}^4\text{A}_2(\text{F})\text{---}{}^4\text{E}(\text{T}_1, \text{F})$, the 14800 cm^{-1} to the ${}^4\text{A}_2(\text{F})\text{---}{}^4\text{A}_2(\text{T}_1, \text{P})$ and the 15700 and 16500 cm^{-1} to the ${}^4\text{A}_2(\text{F})\text{---}{}^4\text{E}(\text{T}_1, \text{P})$ transition [17-19]. Since two bands correspond to each of the ${}^4\text{A}_2(\text{F})\text{---}{}^4\text{E}(\text{T}_1, \text{F})$ and ${}^4\text{A}_2(\text{F})\text{---}{}^4\text{E}(\text{T}_1, \text{P})$ transitions, the ${}^4\text{E}$ term might further split to B_1 and B_2 levels.

The same geometries are retained in DMF solutions, while in D_2O they are transformed to octahedral ones (Table II) and the band observed near 20000 cm^{-1} is assigned to the ${}^4\text{T}_{1g}\text{---}{}^4\text{T}_{1g}(\text{P})$ transition [16].

Table II. Vis and near IR spectral data of the compounds				
Compound	Maxima (kK)	Assignments in T_d symmetry	Assignments in C_{3v} symmetry	Solvent
Co(HBT)Cl_3 $10Dq=3722\text{cm}^{-1}$ $B=734\text{cm}^{-1}$	5.21 6.69 7.44 14.99 15.72 16.47	$4A_2(F) \rightarrow 4T_1(F)$ $4A_2(F) \rightarrow 4T_1(P)$	$4A_2(F) \rightarrow 4A_2(T_1,F)$ $4A_2(F) \rightarrow 4E(T_1,F)$ $4A_2(F) \rightarrow 4A_2(T_1,P)$ $4A_2(F) \rightarrow 4E(T_1,P)$	DRS
Co(HBT)Cl_3 $10Dq=4026\text{cm}^{-1}$ $B=719\text{cm}^{-1}$	6.49 6.94 7.40 14.88 16.44	$4A_2(F) \rightarrow 4T_1(F)$ $4A_2(F) \rightarrow 4T_1(P)$	$4A_2(F) \rightarrow 4A_2(T_1,F)$ $4A_2(F) \rightarrow 4E(T_1,F)$ $4A_2(F) \rightarrow 4A_2(T_1,P)$ $4A_2(F) \rightarrow 4E(T_1,P)$	DMF
Co(HBT)Cl_3	19.68 21.27	$4T_{1g} \rightarrow 4T_{1g}(P)$	in octahedral environment	H_2O
Co(HCMT)Cl_3 $10Dq=3665\text{cm}^{-1}$ $B=734\text{cm}^{-1}$	5.14 6.55 7.40 14.71 15.69 16.53	$4A_2(F) \rightarrow 4T_1(F)$ $4A_2(F) \rightarrow 4T_1(P)$	$4A_2(F) \rightarrow 4A_2(T_1,F)$ $4A_2(F) \rightarrow 4E(T_1,F)$ $4A_2(F) \rightarrow 4A_2(T_1,P)$ $4A_2(F) \rightarrow 4E(T_1,P)$	DRS
Co(HCMT)Cl_3 $10Dq=4028\text{cm}^{-1}$ $B=716\text{cm}^{-1}$	6.48 6.98 7.39 14.78 16.42	$4A_2(F) \rightarrow 4T_1(F)$ $4A_2(F) \rightarrow 4T_1(P)$	$4A_2(F) \rightarrow 4A_2(T_1,F)$ $4A_2(F) \rightarrow 4E(T_1,F)$ $4A_2(F) \rightarrow 4A_2(T_1,P)$ $4A_2(F) \rightarrow 4E(T_1,P)$	DMF
Co(HCMT)Cl_3	19.82 21.13	$4T_{1g} \rightarrow 4T_{1g}(P)$	in octahedral environment	H_2O
Ni(HBT)Cl_3 $10Dq=4704\text{cm}^{-1}$ $B=852\text{cm}^{-1}$	4.39 5.12 8.69 15.04 15.87 17.24	$3T_2(F) \rightarrow 3A_2(F)$ $3T_1(F) \rightarrow 3A_2(F)$ $3T_1(F) \rightarrow 3T_1(P)$	$3E(T_1,F) \rightarrow 3E(T_2,F)$ $3E(T_1,F) \rightarrow 3A_2(F)$ $3E(T_1,F) \rightarrow 3E(T_1,P)$ $3E(T_1,F) \rightarrow 3A_2(T_1,P)$	DRS
Ni(HBT)Cl_3 $10Dq=4390\text{cm}^{-1}$ $B=860\text{cm}^{-1}$	8.29 14.55 16.13 17.35	$3T_1(F) \rightarrow 3A_2(F)$ $3T_1(F) \rightarrow 3T_1(P)$	$3E(T_1,F) \rightarrow 3A_2(F)$ $3E(T_1,F) \rightarrow 3E(T_1,P)$ $3E(T_1,F) \rightarrow 3A_2(T_1,P)$	DMF
Ni(HBT)Cl_3	13.96 25.72	$3A_{2g} \rightarrow 3T_{1g}$ $3A_{2g} \rightarrow 3T_{1g}(P)$	in octahedral environment	H_2O

The crystal field strength $10Dq$ was about 3700 cm^{-1} in the solid state and about 4000 cm^{-1} in DMF solutions. The approximately equal value of the Racah parameter B for both Co^{2+} complexes on the other hand, indicate a comparable covalent character in their Co-N_F bonds.

In the case of the Ni(HBT)Cl_3 the multiple bands near 8700 cm^{-1} and 15900

cm^{-1} in the DRS are due to the ${}^3\text{T}_1(\text{F}) \rightarrow {}^3\text{A}_2(\text{F})$ and ${}^3\text{T}_1(\text{F}) \rightarrow {}^3\text{T}_1(\text{P})$ transitions in a tetrahedral environment [16]. Their multiplicity is again due to a trigonal distortion (C_{3v} symmetry) (See Table II) [18]. In DMF solutions the geometry is retained but it becomes again octahedral in aqueous solutions (See Table II). The band at 4390 cm^{-1} is assigned to the $(\nu_1) {}^3\text{T}_2(\text{F}) \rightarrow {}^3\text{A}_2(\text{F})$ transition. Therefore $10Dq = \nu_1 = 4390 \text{ cm}^{-1}$.

Finally, the ligand HBT shows a maximum at 274 nm, the HBT.HCl at 276 nm and the complexes $\text{Co}(\text{HBT})\text{Cl}_3$ and $\text{Ni}(\text{HBT})\text{Cl}_3$ at 275.5 and 275 nm respectively, in DMF solutions. The HCMT, HCMT.HCl and $\text{Co}(\text{HCMT})\text{Cl}_3$ show the same band at 272, 273 and 272.5 nm correspondingly. This band is assigned to a $\pi \rightarrow \pi^*$ transition of the pyrimidine ring of thiamine. Its bathochromic shift in the protonated and metallated ligands indicate the involvement of the pyrimidine (N_1) moiety to protonation and metallation [20].

Concluding Remarks: The easy formation of metal complexes with the "active aldehyde" derivatives of thiamine with a $\text{M}-\text{N}_1$ bonding, may indicate that the intervention of the metal ions follows the formation of these intermediates during the enzymatic process. The S conformation of the ligand seems to be important during the enzymatic action, since it persists in all the C(2a) substituted thiamine derivatives. (The V conformation of thiamine and the pyrophosphate metal binding are also important, after liberation of the C(2a) substituent, since it was recently found in the structure of transketolase, containing Ca^{2+} ions [21].

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Received: June 1, 1993