

The Synthesis and Characterization of Thiaminium Tribromocadmium (II) and Thiaminium Triiodocadmium (II) Complexes

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Summary: Thiaminium tribromocadmium (II) and thiaminium triiodocadmium (II) have been synthesized and characterized by elemental analysis, proton and ^{13}C nmr techniques. The chemical shifts and splitting pattern of amino protons are found independent of the nature of halide ions. Some chemical shifts, however, do show dependence on the electronegativities/polarizabilities of the halide ions.

Introduction

The potential hazard of mercury on humans and animals has been known and widely investigated. Recent studies (1-5) have shown that other metal ions such as manganese and cadmium could also be hazardous due to their high toxicity and longer biological half-lives in the mammalian organisms (6-8).

Numerous studies have been made on the metal complexes of thiamine and its derivatives (5, 9-13, 17,19) to investigate the nature of complex formation, suggest possible mechanisms and to evolve a method preventing cadmium (1,2) and manganese (3, 4, 14, 15) poisoning. This study was undertaken for the same purpose.

Experimental

Cadmium bromide was purchased from General Chemical Co., N.Y. while cadmium iodide, thiamine hydrochloride and deuterated dimethyl sulfoxide were procured from Aldrich Co. All chemicals were used without further purification.

The elemental analysis was performed by Galbraith Labs., Tenn. ^1H nmr spectrum for the bromo complex was recorded on EM-360 sixty mHz spectrometer fully equipped with optional alpha numeric printer. ^1H nmr and ^{13}C for the iodo complex were recorded on Nicolet two hundred mHz spectrometer. All chemical shifts are reported in ppm.

Preparation of Complexes

Detailed procedure of synthesis has been described elsewhere (12, 13). Typically, the bromo and iodo complexes were prepared by mixing the aqueous solution of thiamine hydrochloride and metal salts (1:2 mole ratio) and allowing the resulting solution to evaporate. The complexes were recrystallized with hot water.

Results

Elemental analysis. a) Thiaminium tribromocadmium (II): $\text{Cd}(\text{Th})\text{Br}_3 \cdot (\text{C}_{12}\text{H}_{18}\text{N}_4\text{OS Cd Br}_3)$. Calc. C, 23.29; H, 2.91; N, 9.06; S, 5.19; Cd, 18.18; Br, 38.78; Found. C, 22.80; H, 2.94; N, 8.82; S, 4.98; Cd, 17.98; Br, 37.97. b) Thiaminium triiodocadmium (II): $\text{Cd}(\text{Th})\text{I}_3 \cdot (\text{C}_{12}\text{H}_{18}\text{N}_4\text{OS CdI}_3)$. Calc. C, 18.97; H, 2.37; N, 7.38; Cd, 14.81; I, 50.15; Found. C, 18.80; H, 2.31; N, 7.29; Cd, 14.78; I, 51.72.

Tables 1 and 2 summarize the nmr data for thiamine as a free ligand and when complexes with Cd^{2+} used as bromo and iodo salts. ^1H and ^{13}C chemical shifts for thiamine have been previously assigned (10) and are included here for comparison.

Table 1 shows the trend in the chemical shifts for $5'\text{-CH}_2$ protons in the free ligand and in the bromo and iodo complexes. Similarly Table 2 shows the trend in the ^{13}C nmr for 4-CH_3 , $2'\text{-CH}_3$ as well as $4'\text{-C}$ signal

Table 1. Proton Chemical Shifts of Thiamine Hydrochloride and Its Cadmium(II) Complexes.

PROTON	THC ¹	Cd(TH)Br ₃	Cd(TH)I ₃
C-2-H ₅	9.99	9.87	9.82
O-CH ₂	3.68(t) ²	3.67(t)	3.69(t)
5-CH ₂	3.10(t)	3.12(t)	3.11(t)
C-4-CH ₃	2.56	2.60	2.55
C-4'-NH ₂	9.25(s) ³	9.26-8.84(d) ⁴	9.26-8.83(d)
C-2'-CH ₃	2.54	2.59	2.55
C-5'-CH ₂	5.65	5.53	5.45
C-6'-H	8.39	8.47	8.35

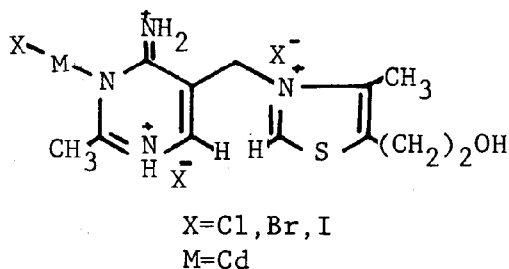
Abbreviations:

- 1) THC: Thiamine Hydrochloride
- 2) t: triplet; 3) s: singlet
- 4) d: doublet; 5) adjacent to hydroxyl group.

Table 2(a)
¹³C Chemical Shifts of Thiamine Hydrochloride and Its Cadmium(II) Complexes

CARBON	THC ¹	Cd(TH)Br ₃	Cd(TH)I ₃
C-2	155.23	154.84	155.51
C-4	142.21	141.99	142.01
C-5	135.31	135.38	135.54
O-CH ₂ ²	59.56	59.50	59.60
Bridged CH ₂	49.88	48.88	49.94
4-CH ₃	11.63	11.85	11.81
5-CH ₃	29.33	29.37	29.41
C-2'	163.13	163.09	163.22
C-4'	161.83	161.84	162.12
C-5'	105.28	104.85	105.01
C-6'	146.65	146.52	146.27
2'-CH ₃	21.13	21.46	21.65

a) For abbreviations see Table 1.



changes in the free ligand and the complexes. Figure 1 shows the amino protons (4'-NH₂) appearing as a doublet in the cadmium complexes.

Discussion

This work is a part of the studies made by us (11, 12) and others (13, 14, 16) on the metal-ion interaction with thiamine. It has been shown elsewhere that only the pyrimidinium part of thiamine is the reactive site for the metal ions to interact. While Theophanides et al. (13) have shown that Pt²⁺ and Pd²⁺ bond on the N-1' site (see structure 1), we believe that in our study bonding occurs between N-3' site and the metal ion as the complexation was carried out below pH 3 whereas the pK of thiamine is about 5, thus making the availability of N-1' position difficult for bonding due to protonation.

The amino protons which appear as a singlet in the free ligand are observed as a doublet in the cadmium complexes. This splitting can be ascribed to the hindered rotation of the amino protons about C-4' carbon, making the two protons non-equivalent (Figure 1, structure 1). A similar observation was made by earlier investigators (20). We also found that the splitting and chemical shifts of these amino protons were independent of the nature of the halide ions. Y. Kokono et al. (21) found that the chemical shifts of cytidine-metal ion complexes (group II-B) depended on the nature of the halide ions. A slight upfield trend is observed for C-5'-CH₂ protons in the bromo and iodo complexes compared to the free ligand. This is presumably due to the displacement of chloride by bromide and iodide ions and the ensuing electronegative difference between these halide ions. Similarly, increase in the polarizability (I > Br > Cl) also gives rise to the same effect. Thus the observed trend is internally consistent.

Group IIB metals have a tendency for C.N.4 albeit progressively so with Hg²⁺ which has a definite C.N.2 preference in the complexation reactions. However, complexes of zinc and cadmium ions are known to show C.N.2 chemistry in particular with organic ligand (22). Cd²⁺ ion has a lesser tendency toward covalency together with the fact that thiamine is a bulky ligand a C.N. 2 complex formation is assumed in the present work. X-ray crystal studies are being made on these complexes.

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