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Acetate Catalyzed Interactions of Divalent Metal Ions With Vitamin B_1

ADEGBOYE ADEYEMO* and ABDULLAH SHAMIM

Department of Chemistry, Howard University, Wash., D.C. 20059, U.S.A.

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Introduction

The need to investigate the chemistry of Vitamin B_1 and its complexes is due to the fact that it is an important dietary constituent for many animals. Its deficiency causes the disease beri-beri [1] and its pyrophosphate ester is the coenzyme cocarboxylase which catalyzes the decarboxylation of α-keto acids. Such catalysis is enhanced by the presence of divalent metal ions such as Mg(II), Mn(II), CO(II), *etc.* [2, 3]. This important observation led to the proposal of mechanisms for the thiamine pyrophosphate action [4]. The need to know [5] just what role metal ions play in enzymatic processes led to the brilliant proposal of Schellenberger that N-1′ position of the pyrimidine ring might be involved in metal–nitrogen bonding [6].

As a follow-up on this famous idea, some investigators [2, 3] studied the interaction in solution between thiamine pyrophosphate and divalent metal ions such as Ni(II) and Co(II), employing both ^1H and ^{31}P NMR techniques. These authors concluded that N-1′ nitrogen of the pyrimidine moiety was bound to the metal through the water molecule. To better understand these systems, efforts were made to isolate solid metal complexes of thiamine for X-ray studies. The solid complexes isolated were, however, found to be ionic [5, 7–9]. About five years ago, Theophanides *et al.* [10] isolated solid and stable Pd(II) and Pt(II) complexes of thiamine which were the first examples having a direct metal–nitrogen bond by utilizing NMR techniques. Later, we reported the preparation and NMR studies of Hg(II), Cd(II) and Zn(II) complexes of thiamine [11, 12] where we suggested an alternative binding site. However, X-ray studies proved these complexes to be ionic complex salts with a bunch of hydrogen bonds [13]. Recently, we found that these complex salts, $Hg(Th)Cl_4 \cdot H_2O$, $Cd(Th)Cl_4 \cdot H_2O$ and $Zn(Th)Cl_4 \cdot H_2O$ are very labile [14]. Even more recently, Cramer *et al.* [15] reported the preparation and structure of $Cd(thiamine)Cl_3 \cdot 0 \cdot 6H_2O$ which is the first structural report of a thiamine ion bonded to a metal ion.

Perhaps the most obvious, quite logical and natural question one would ask is why are the thiamine metal complexes in which there is a direct ligand–metal bonding such a rarity in spite of the wide variety of coordination sites that thiamine has to offer [5]? In an attempt to answer this question, we have carried out an extensive investigation of reactions of thiamine with metal acetate, $M(Ac)_2$, where M = Zn, Cd, Hg, Cu, Cr, Co, Mg, Mn, Ni, and Fe. The solid complexes in form of chloride, iodide, perchlorate and phosphorus hexafluoride have been isolated in this laboratory. The ^1H, ^{13}C, IR, magnetic susceptibility measurements and elemental analyses of these complexes will be reported later. Meanwhile, this paper reports the possible mechanism for the acetate catalyzed metal ion interaction with thiamine chloride hydrochloride (Vitamin B_1).

Discussion

The first method employed in the preparation of thiamine metal complexes involves mixing aqueous solutions of thiamine and metal salt in chloride form (2:1 mole ratio). Thiamine metal complexes isolated by this method were found to be ionic complex salts [5, 7–9, 13]. Although many investigators reached the same conclusion, there has been no satisfactory explanation for such observation especially when one considers thiamine as having a wide variety of coordination sites [5]. When thiamine chloride hydrochloride disolves in water, its resulting solution has a pH of between 2.8 and 3. Earlier [11–18], it was established beyond all reasonable doubt that thiamine has only one coordination site, N-1′ position of the pyrimidine moiety (pK = 5). Between pH of 2.8 and 3, there is an equilibrium between the protonated and unprotonated thiamine according to the following equation:

$$LH^+ \longrightarrow L + H^+ \qquad (1)$$

where LH^+ is the protonated thiamine and L is the unprotonated form. Addition of solution of metal salts especially the chloride and the nitrate salt to the thiamine solution will tend to shift the equilibrium to the left according to eqn. 1. It should be borne in mind that the chloride and the nitrate salts are capable of generating chloride and nitrate ions which are anions of strong acids. It is therefore not surprising to observe unfavorable interaction between thiamine and metal salts under this condition.

The second metal employed involves mixing aqueous solutions of thiamine and metal salts after the pH of the individual solutions have been adjusted

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*Author to whom all correspondence should be addressed.

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to between 3.5 and 5. This method resulted in the isolation of the first solid and stable Pd(II) and Pt(II) complexes of thiamine [10] which was a major break through in the chemistry of thiamine metal complexes. Attempts to isolate other thiamine metal complexes employing the same method however, proved abortive, a result which implies that other factors aside from pH may be very important in this study.

The indication that pH is a very important factor in this study led us to think of using acetate metal salts which could bring the pH of the resulting solution to between 4 and 5 since thiamine should be mostly in the unprotonated form. The encouraging results we have achieved using this method has led us to propose the following mechanism:

$$\mathrm{M(Ac)_2} \longrightarrow \mathrm{M^{2+}} + 2\mathrm{Ac^-} \qquad (2)$$

$$\mathrm{LH^+} + \mathrm{Ac^-} \rightleftharpoons \mathrm{L} + \mathrm{HAc} \qquad (3)$$

$$\mathrm{L} + \mathrm{M^{2+}} \longrightarrow \mathrm{LM^{2+}} \qquad (4)$$

Summarily, while the coordination of metal ions to a ligand depends on a number of factors—coordination ability of the metal ion, solvent, pH, nature of the ligand *etc.*, the pH and the type of metal salt used are definitely important in this investigation.

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