Inorganica Chimica Acta 372 (2011) 389–393

Contents lists available at ScienceDirect

Inorganica Chimica Acta

journal homepage: www.elsevier.com/locate/ica

Note

Dipicolinato complexes of cobalt(II), copper(II) and zinc(II) with thiamine dications

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ARTICLE INFO

Article history:
Available online 13 January 2011

This article is dedicated to Prof. S.S. Krishnamurthy on his 70th Birthday.

Keywords:
Dipicolinato complexes
Vitamin B_1
Dual medicine
Hydrogen bond
X-ray structures

ABSTRACT

Cobalt(II), copper(II) and zinc(II) dipicolinato complexes having thiamine dication with compositions $[HT][CoL_2]\cdot 5H_2O$ (**1**), $[HT][CuL_2]\cdot 5H_2O$ (**2**) and $[HT][ZnL_2]\cdot 5H_2O$ (**3**) (L = dipicolinato anion, T = thiamine cation) are synthesized, characterized by X-ray diffraction and other spectroscopic techniques. The thiamine part in these complexes exists as divalent cations. The second protonation of thiamine takes place at the less crowded nitrogen atom of the pyrimidine ring. These complexes are stabilized by electrostatic and hydrogen-bonding interactions of $-N^+-H$ and $-COO^-$ groups along with crystallized water molecules. The complexes are stable in solution as determined by ^1H NMR and visible study. The complex **1** has two medicinal components which can be easily separated by controlling pH in aqueous medium. It gets decomposed on treatment with sodium hydroxide at pH > 8 to form neutral complex $\{[Na_2(\mu\text{-}H_2O)_3(H_2O)_3][CoL_2]\cdot H_2O\}_2$.

1. Introduction

Vitamin B_1 alternately known as thiamine, plays important role in human life [1,2]. It undergoes decomposition easily by light, heat and change of pH [3]. When Vitamin B_1 is used as a medicine, its delivery in a protective form with formation of harmless materials to animal bodies is desirable [4]. One way to deliver vitamin B_1 to animals could be *via* preformed metal complexes which would dissociate and release it *in vivo* at ambient condition. Thus, synthesis of metal complexes having vitamin B_1 as ligand could release thiamine without degrading to multiple products or to toxic substances, will help in storage and delivery of vitamin B_1. Vitamin B_1 is obtained in the form of monoprotonated salt and it also easily forms dication (Fig. 1). Thus, it should be possible to use such dication with complex metal anion and intercalate them *via* weak interactions. It would be possible to control the release of vitamin B_1 from such metal complexes by adjusting hydrogen ion concentrations. For such study, prior knowledge of the structures of different types of metal complexes of vitamin B_1 is essential. Several metal complexes of vitamin B_1, such as that of tin [5], cadmium [6], platinum [6–10], are reported in literature. It has also been observed that the poisoning effects that can be caused by metal ions such as manganese and cadmium on biological systems are controlled by vitamin B_1 [11–13]. Thus, metal complexes [14,15] of vitamin B_1 are important in biology. Further to this, such metal complexes act as mimic of enzymes having potential utility in biocatalysis [16–18,22]. Recently, we have shown that various nitrogen containing cations can be easily intercalated in dipicolinato complexes [19–21]. Here we show synthesis and characterization of complexes having dual medicinal values that are comprised of thiamine dication and metal dipicolinato anion. The cobalt(II) dipicolinato complex anion is known to have insulin like activity [23].

2. Experimental

Synthesis of the complexes $[HT][CoL_2]\cdot 5H_2O$ **(1)**, $[HT][CuL_2]\cdot 5H_2O$ **(2)** and $[HT][ZnL_2]\cdot 5H_2O$ **(3)**: To a solution of cobalt(II) acetate tetrahydrate (249 mg, 1 mmol) or copper(II) acetate monohydrate (199 mg, 1 mmol) or zinc(II) acetate dehydrate (219 mg, 1 mmol) in water (2 ml) was added to a 20 ml methanolic solution of dipicolinic acid (334 mg, 2 mmol), followed by drop wise addition of a solution of thiamine chloride hydrochloride (337 mg, 1 mmol in 2 ml water). The resulting reaction mixture was left at ambient temperature. Upon slow evaporation of water {dark red (cobalt), blue (copper) and colorless (zinc) respectively} crystals were obtained after a period of 3–4 days. Spectroscopic data for complex **1**: Isolated yield, 64%. Elemental *Anal.* Calc. for $C_{26}H_{44}CoN_6O_{14}S$: C, 41.29; H, 5.82. Found: C, 40.94; H, 5.67%. IR (KBr, cm^{-1}): 3442 (bs), 3239 (m), 3103 (m), 2969 (w), 1659 (m), 1615 (s), 1590 (s), 1421 (m), 1376 (s), 1357 (m), 1278 (m). Molar conductance: 333.0 S cm^2 mol^{-1} in water, μ_{eff}. at 298 K: 4.36 BM. Vis (H_2O) λ_{max}: 580.0 nm; ε = 52.1 M^{-1} cm^{-1} and 502.0 nm; ε = 79.3 M^{-1} cm^{-1}. Thermal analysis: decomposition range: ~45–90 °C (evaporation of five water molecules of crystallization); further decomposition occurs at ~188 °C. Complex **2**: Isolated yield: 66%. Elemental *Anal.* Calc. for $C_{26}H_{44}CuN_6O_{14}S$: C, 41.04; H, 5.79. Found: C, 40.88; H,

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doi:10.1016/j.ica.2011.01.022

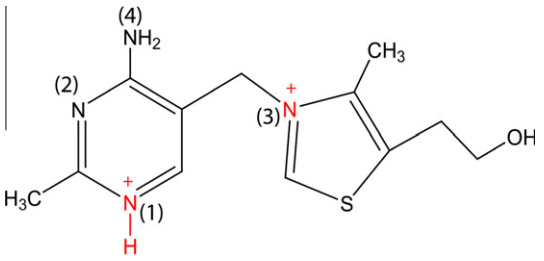

Fig. 1. Structure of thiamine dication derived from vitamin B_1.

5.64%. IR (KBr, cm^{-1}): 3441 (bs), 2925 (w), 1622 (bs), 1591 (m), 1380 (s), 1274 (m). Molar conductance: 328.0 S cm^2 mol^{-1} in water, $\mu_{eff.}$ at 298 K: 1.67 BM. Vis (H_2O) λ_{max}: 773.0 nm; ε = 73.6 M^{-1} cm^{-1}. Thermal analysis: decomposition range: ~45–113 °C (loss of crystallization water molecules). Complex **3**: Isolated yield: 65%. Elemental *Anal.* Calc. for $C_{26}H_{44}ZnN_6O_{14}S$: C, 40.94; H, 5.77. Found: C, 40.75; H, 5.60%. IR (KBr, cm^{-1}): 3442 (bs), 3108 (w), 2926 (w), 1659 (m), 1622 (s), 1591 (m), 1379 (s), 1279 (m). Molar conductance: 327.0 S cm^2 mol^{-1} in water. Thermal analysis: decomposition range: ~48–96 °C (loss of five water molecules of crystallization).

The X-ray crystallographic data were collected at 296 K with Mo Kα radiation (λ = 0.71073 Å) using a Bruker Nonius SMART CCD diffractometer equipped with graphite monochromator. The SMART software was used for data collection and also for indexing the reflections and determining the unit cell parameters; the collected data were integrated using SAINT software. The structures were solved by direct methods and refined by full-matrix least-squares calculations using SHELXTL software [24]. All the non-H atoms were refined in the anisotropic approximation against F^2 of all reflections. The H-atoms, except those attached to N and O were placed at their calculated positions and refined in the isotropic approximation; those attached to hetero-atoms (N, O) were located in the difference Fourier maps, and refined with isotropic displacement coefficients. However some of the hydrogen atoms attached to oxygen of water molecules in the structures could not be located. The crystallographic parameters are given in Table 1.

3. Results and discussion

The metal dipicolinato complexes 1–3 of cobalt(II), copper(II) and zinc(II) having thiamine dications were prepared by simple reactions of corresponding metal(II) acetates with thiamine chloride hydrochloride and dipicolinic acid in one pot, at ambient condition (Scheme 1). The reactions were carried out at neutral conditions in water or methanol. The complexes 1–3 are soluble in water. The complexes show broad and sharp IR absorptions around 3440 cm^{-1} due to O–H and N–H bonds stretching. Cobalt(II) and copper(II) complexes are paramagnetic and their room temperature effective magnetic moment values tally to calculated value corresponding +2 oxidation state. The molar conductance for each complex is ~320 S cm^2 mol^{-1}. These values are high for 2:2 electrolytes, this suggests that each complex possess some amount of proton conductivities in addition to the contributions from the simple dissociation in aqueous solution.

All of these complexes have similar compositions, and have five molecules of water of crystallization. Water molecules are removed around 45–115 °C on heating (*vide* thermogravimetry) and thereby the complexes become amorphous. The complexes **1–3** are isostructural. One representative structure namely the structure of the cobalt(II) complex is shown in Fig. 2. The structure consists of thiamine dications, metal dipicolinato anion and water molecules. The hydrated water molecules are held together by hydrogen bond interactions. The second protonation on thiamine takes place at less sterically crowded nitrogen atom of the pyrimidine ring. Such cation was observed earlier from vitamine B_1 [5]. Thiamine monophosphate cations with different anions were studied [10]; in those cases also similar protonations were observed. All these complexes **1–3** have distorted octahedral geometry around the metal ions. The metal–ligand bond distances and bond angles are shown in Table 2.

In the crystal lattice the thiamine dications are held in between two metal dipicolinato complex anions. The cations are held *via* hydrogen bonds to the anionic part (Fig. 3a). The hydroxyl group of the thiamine is involved in hydrogen bond with an oxygen atom of the coordinated carboxylate group (O9–H···O7 interaction). There are also strong (+) N4–H···O8 interactions of the cationic part to hold another dipicolinato complex anion (Fig. 3a). The N5

Table 1
Crystallographic refinement parameters of the complexes **1–4**.

	1	**2**	**3**	**4**
Formula	$C_{26}H_{44}CoN_6O_{14}S$	$C_{26}H_{44}CuN_6O_{14}S$	$C_{26}H_{44}N_6O_{14}SZn$	$C_{28}H_{52}Co_2N_4Na_4O_{36}$
Formula weight	755.58	760.27	762.02	1230.56
Crystal size (mm^3)	0.32 × 0.24 × 0.15	0.36 × 0.22 × 0.14	0.32 × 0.18 × 0.10	0.35 × 0.20 × 0.12
Crystal system	monoclinic	monoclinic	monoclinic	monoclinic
Space group	$P2_1/c$	$P2_1/c$	$P2_1/c$	$P2_1/c$
a (Å)	9.924(3)	9.855(2)	9.941(7)	8.418(7)
b (Å)	20.342(7)	20.395(4)	20.320(13)	22.258(2)
c (Å)	16.074(5)	16.064(3)	16.093(11)	15.378(12)
α (°)	90.00	90.00	90.00	90.00
β (°)	92.040(2)	92.050(10)	91.980(4)	118.707(4)
γ (°)	90.00	90.00	90.00	90.00
V ($Å^3$)	3242.86(18)	3226.69(11)	3248.9(4)	2527.3(4)
Z	4	4	4	2
ρ_{calc} (g cm^{-3})	1.527	1.565	1.537	1.617
μ (mm^{-1})	0.670	0.820	0.897	0.798
F(0 0 0)	1548	1596	1560	1268
Reflections collected	47065	39073	37936	16363
Reflections unique	7127	7986	7837	4354
Goodness-of-fit on F^2	1.020	1.047	0.989	1.142
R_{int}	0.0659	0.0398	0.0581	0.1017
R_1 [$I \geqslant 2\sigma(I)$]	0.0561	0.0404	0.0475	0.0738
wR_2 [$I \geqslant 2\sigma(I)$]	0.1498	0.1228	0.1403	0.2124
R_1 (all data)	0.0877	0.0603	0.0791	0.1025
wR_2 (all data)	0.1827	0.1297	0.1513	0.2486