STUDY OF THE INTERACTIONS BETWEEN COPPER(II) ACETATE MONOHYDRATE AND OROTIC ACID AND OROTATE LIGANDS

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ABSTRACT

Different complexes by reacting copper(II) acetate monohydrate with orotic acid and orotate as ligands were prepared. These compounds were characterized by elemental analysis, spectroscopy, and thermal analysis. It is suggested that in both compounds, the $\text{Cu}_2(\text{acetate})_4$ suffers the break of both acetate groups by a substitution of orotic or orotate ligands, increasing the Cu-Cu distance. It was corroborated by the magnetic moment values of 1.65 and 1.82 B.M for these compounds.

The anion orotato(-1) coordinates through the carboxylic acid and the orotic acid by the oxygen from exocyclic C=O.

Semiempirical PM3 calculations for both compounds were also carried out.

Keywords : Copper(II) acetate, metal acetate, orotic acid, semi-empirical calculations.

INTRODUCTION

Metal orotates and acetates are widely used in medicine field to incorporate metals to the organism to decrease the absence of these in some sickness. The incorporation of transition metal ions to form coordination compounds with orotates, the redox, optic, and magnetic properties surely will change^{1,2}.

Besides, it is biologically important as orotic acid (see figure 1) and it has also an interesting coordination chemistry. It may coordinate through the carboxyl group, the two oxygens from carbonyl, and the two nitrogen atoms of the pyrimidine ring.

Fig.1. Structure of orotic acid.

Between pH 3 and 9, orotic acid is present in aqueous solutions mainly as orotate anion, the carboxylic acid group has $\text{pK} = 2.07$ ³. At acid pH it coordinates through carboxylic acid group. The most potential coordination sites in the range 5-9 are the carboxylic oxygen and the adjacent pyrimidine nitrogen atom (N1). In order to evaluate the pharmaceutical properties, many metal complexes of orotic acid have been studied⁴⁻⁷.

Transition metal complexes where the orotate(1-) ligand shows a mono coordination through the carboxylic acid group⁴ and for orotate(2-), where the main coordination site corresponds to adjacent nitrogen have been reported. When they coordinate a metal ion, the complexing ability of the exocyclic carbonyl oxygen is strongly enhanced⁵. Corroborating this theory, polynuclear compounds have been reported, where one of the oxygen coming from exocyclic carbonyl group coordinates with a neighbor metal ion as polymer complex- $\text{Cu}[(\text{C}_5\text{H}_2\text{N}_2\text{O}_4)_2\text{Cu}(\text{H}_2\text{O})_2]_n$ ^{6,7}.

In a non-aqueous neutral medium has been reported that the coordination is produced through exocyclic oxygen coming from carbonyl group C(4)=O (1).

Copper acetate monohydrate can react with monomeric ligands forming an adduct by replacing the water molecules. In these compounds the Cu-Cu distances and the magnetic moments change slightly⁷⁻¹¹. It is also possible to lose an acetate group to allow the coordination of other ligands or even change de coordination of the acetate group to monodentate coordination with the break of the $\text{Cu}_2(\text{acetate})_4$ unit, as it occurs with the imidazole ligand¹²⁻¹⁵. With polymeric ligands interact loosing one or two water molecules but also an acetate group to coordinate with the polymer as occur with poly(DL-aspartic acid)¹⁶⁻¹⁷.

The goal of the current manuscript is the study of the interactions of orotic acid and orotate anion with copper(II) acetate monohydrate.

EXPERIMENTAL

Materials: $\text{Cu}_2(\text{CH}_3\text{COO})_4 \cdot 2\text{H}_2\text{O}$ p.a (Merck), sodium orotate (Aldrich), orotic acid (Aldrich) were used without further purification.

Preparation of complex

$\text{Cu}_2(\text{acetate})_4(\text{H}_2\text{OR})_2$, ($\text{H}_2\text{OR}=\text{orotate}(1-)$)

This compound was synthesized by reacting under stirring aqueous solutions of sodium orotate and $\text{Cu}_2(\text{acetate})_4 \cdot 2\text{H}_2\text{O}$, at pH=3, controlling the pH by CH_3COOH . It was obtained a green precipitate, which was filtered and washed with distilled water, and dried at 60°C up to constant weight.

Elemental analysis: (Found: Cu: 20.2 % N: 10.1 %, C: 28.1 %, H: 2.2 %, Calcd.: Cu: 22.8 %, N: 10.1 %, C: 30.3 %, H: 2.2 %).

$\text{Cu}_2(\text{acetate})_4(\text{H}_3\text{OR})_4$, ($\text{H}_3\text{OR}=\text{orotic acid}$)

It was obtained by reacting orotic acid with $\text{Cu}_2(\text{acetate})_4 \cdot 2\text{H}_2\text{O}$ under refluxing in neutral medium using ethyl acetate as solvent. The precipitate was washed with the same solvent, filtered and dried at 60°C up to constant weight.

(Found: Cu: 13.8 %, N: 11.6 %, C: 33.0 %, H: 2.0 %, Calcd.: Cu: 12.9 %, N: 11.4 %, C: 34.2 %, H: 2.5 %).

The coordination compounds are insoluble in water and in common organic solvents as acetone, acetonitrile and ethanol.

Measurements: Elemental analysis were obtained using a Series II CHNS 10 analyzer 2400 Perkin Elmer. Cu(II) was analyzed by atomic absorption spectrometry (AAS) with a Perkin Elmer model 3100. The FT IR spectra of the samples were recorded on a Nicolet Nexus spectrophotometer. The diffuse reflectance spectra were measured on a Perkin Elmer Lambda 20 spectrophotometer coupled to Labsphere reflectance diffuse attachment and Spectralon as reference. Thermogravimetric analyses of the polychelates were performed with a TA Instrument Q50 analyzer.

Quantum Chemical Calculations: PM3 semi-empirical calculations were carried out using a MOPAC program that is included in HyperChem 7. The compounds were created graphically with support of the HyperChem Program. It was optimized by molecular mechanical and subsequently by PM3 calculation method.

RESULTS AND DISCUSSION

The λ_{max} values of the absorption bands and the effective magnetic moments of the complexes are summarized in Table 1.

Both compounds show a similar spectrum to the copper(II) acetate monohydrate, absorption bands near to 700 nm and 400 nm. The last one has been reported as a characteristic band to the acetates with bridge coordination type ¹⁶⁻¹⁹.

The magnetic moments for the compounds I and II 1.82 and 1.65 M.B respectively are higher than that 1.4 M.B reported for copper(II) acetate monohydrate ²⁰.

Table 1. Properties of the complexes

Complex	$\lambda(\text{nm})$	$\mu_{\text{eff}}(\text{B.M.})$	Tmax (°C)	Group
$\text{Cu}_2(\text{acetate})_2(\text{H}_2\text{OR})_2$ (I)	385 705	1.82	275.88	acetate
			286.60	acetate
			355.52	orotate
			412.25	orotate
			264.81	acetate
$\text{Cu}_2(\text{acetate})_4(\text{H}_3\text{OR})_4$ (II)	441 700	1.65	327.62	orotic acid

Fig. 2. TGA and DTG curves of $\text{Cu}_2(\text{acetate})_2(\text{H}_2\text{OR})_2$. Heating rate: $20^\circ\text{C min}^{-1}$ under N_2 atmosphere.

Fig. 3 TGA and DTG curves of $\text{Cu}_2(\text{acetate})_4(\text{H}_3\text{OR})_4$. Heating rate: $20^\circ\text{C min}^{-1}$ under N_2 atmosphere.

TGA-DTG of $\text{Cu}_2(\text{acetate})_2(\text{H}_2\text{OR})_2$ show two maxima between 250-300°C which can be attributed to loss of acetate ligands and other two maxima peaks between 350-450°C are due to orotate weight loss ²¹ (see Figure 2).

TGA-DTG of $\text{Cu}_2(\text{acetate})_4(\text{H}_3\text{OR})_4$ show two maxima at 265°C and at 328°C attributed to weight loss of acetate and orotic acid ligands respectively (see Figure 3).

TGA-DTG (see table 1, Figures 2 and 3) did show not for both compounds the weight loss of water molecules, therefore, it is suggested that the coordination of orotate and orotic acid groups displace the water molecules

coordinated to Cu(II) ²².

According to elemental analysis and TGA, the following reactions can be suggested:

Cu(II) acetate monohydrate react with orotate ion losing two water molecules and two acetate groups. Cu(II) ions keep bound by two bridge acetate groups and the orotate ions coordinate through carboxylic acid group with each Cu(II) ion.

In neutral medium the orotic acid coordinates through an oxygen coming from C=O group losing two water-molecules. To replace two orotic acid, each water-molecule, the bridge coordination of two acetate groups which keep coordinated to Cu(II) ions through a monodentate coordination.

Semiempirical calculations PM3, AM1, and CNDO of reported orotic acid charge data of orotic acid indicate that the oxygen from C(2)=O has the highest net charge (see Table 2) ^{23,24}. Therefore, it is possible suggest that the orotic acid coordinates with Cu(II) ion through this oxygen as it was reported for the complex obtained from Zn(II) acetate and orotic acid ²³.

Table 2. PM3 calculations of net charge of orotic acid.

Atom	net charge
N (1)	0.081
O (11)	-0.374
N (3)	-0.004
O (12)	-0.328
O (9)	-0.298
O (8)	-0.252

Table 3. Some FT-IR characteristic absorption bands of H_3OR , H_2OR^- , $\text{Cu}_2(\text{acetate})_2(\text{H}_2\text{OR})_2$, and $\text{Cu}_2(\text{acetate})_4(\text{H}_3\text{OR})_4$.

	H_3OR	H_2OR^-	$\text{Cu}_2(\text{acetate})_2(\text{H}_2\text{OR})_2$	$\text{Cu}_2(\text{acetate})_4(\text{H}_3\text{OR})_4$
$\nu(\text{O-H}_{\text{acid}})$	3515 s			3407 w
$\nu(\text{N-H})$	3168 s	3211s	3209s	3159 s
	3111 s			
$\nu(\text{O-H}_{\text{acid}})$	2500 w			2500w
$\nu(\text{C=O}_{\text{acid}})^+$	1700vs	1744 vs	1726 s	1694vs
$\nu(\text{C}_2=\text{O})$				
$\nu(\text{C}_4=\text{O})^+$	1666 vs	1694 vs	1659vs	1648vs
$\nu(\text{C}=\text{C})$				
$\nu(\text{COO}^-)_a$	1513 ms	1492ms	1481 ms	1515ms
$\nu(\text{N-H})$	1430 ms	1426 s	1421 ms	1436s
$\nu(\text{COO}^-)_s$	1337	1380 vs	1381s	1326ms

$\nu(\text{COO}^-)_a$, anti-symmetrical vibration, $\nu(\text{COO}^-)_s$, symmetrical vibration

Table 3 shows some characteristic absorption bands of functional groups of orotic acid, orotate, and the Cu(II) complexes according to the assignment made by Maitralis et al. ³.

$\text{Cu}_2(\text{acetate})_2(\text{H}_2\text{OR})_2$ did not show the absorption band at 2500 cm^{-1} corresponding to the stretching vibration $\nu(\text{O-H})$ of carboxylic acid, due to intermolecular interactions occur between the carboxylic acids indicating the coordination through this group. The presence of the absorption band at 3209 cm^{-1} assigned to stretching vibration $\nu(\text{N-H})$ implies no shift in the stretching vibration (expected at 3211 cm^{-1}) and corroborates that this group is not involved in the coordination. The asymmetric stretching vibration of H_2OR^- is observed at 1492 cm^{-1} and it is shifted at 1481 cm^{-1} in the complex due to the effect of coordination, but the symmetric stretching vibration $\nu(\text{COO}^-)_s$ does not suffer change. At 1585 cm^{-1} is observed a shoulder which can be assigned to stretching vibration $\nu(\text{COO}^-)_a$ from bridge acetate groups.

The spectrum of $\text{Cu}_2(\text{acetate})_4(\text{H}_3\text{OR})_4$ shows the absorption band at 2500 cm^{-1} corresponding to the stretching vibration $\nu(\text{O-H})$ of carboxylic acid, due to intermolecular interactions of carboxylic acids and there is not change on the $\nu(\text{N-H})$. In this compound it is also observed a shoulder at 1585 cm^{-1} attributed

to $\nu(\text{COO}^-)$ of bridge acetate groups.

The FT IR spectrum of orotic acid shows at region of stretching vibration $\nu(\text{C}=\text{O})$ two bands at 1700 and 1666 cm^{-1} which are assigned for other authors to $\nu(\text{C}=\text{O}_{\text{acid}}) + \nu(\text{C}(2)=\text{O})$ and $\nu(\text{C}(4)=\text{O}) + \nu(\text{C}=\text{C})$, respectively ³.

Based on PM3 calculations of vibration spectrum from the compound $\text{Cu}_2(\text{CH}_3\text{COO})_4(\text{H}_3\text{Or})_4$ the absorption band at 1694 cm^{-1} attributed to $\nu(\text{C}(4)=\text{O})$ and that at 1648 cm^{-1} to $\nu(\text{C}(2)=\text{O})$ (see Table 4).

Table 4. Calculations of some stretching vibrations of H_3Or and $\text{Cu}_2(\text{CH}_3\text{COO})_4(\text{H}_3\text{Or})_4^*$

ν (cm^{-1})	H_3Or		$\text{Cu}_2(\text{CH}_3\text{COO})_4(\text{H}_3\text{Or})_4$	
	Exp.	Calc.	Exp.	Calc.
$\nu(\text{C}(3)=\text{O})$.	1739	1978		1982
$\nu(\text{C}(4)=\text{O})$.	1699	1938	1694	1947
$\nu(\text{C}(2)=\text{O})$.	1660	1897	1648	1840

*PM3 calculations have been not corrected.

According to the experimental data, the structures of both compounds and the orotate anion(-1) were calculated by semi-empirical PM3 method and these were compared with the reported date of the Cu(II) acetate monohydrate (see Fig. 4) and the orotic acid.

Fig. 4 Structure of $\text{Cu}_2(\text{acetate})_4 \cdot 2\text{H}_2\text{O}$

Fig. 5. PM3 structure of $\text{Cu}_2(\text{CH}_3\text{COO})_2(\text{H}_2\text{OR})_2$

For $\text{Cu}_2(\text{acetate})_4(\text{H}_3\text{OR})_4$ is suggested a structure where the Cu(II) ions are bound to two bridge acetate groups and the orotate anion coordinates through the carboxylic groups with a bidentate coordination (see Figure 5).

Table 5. Selected PM3 structural parameters of $\text{Cu}_2(\text{CH}_3\text{COO})_4 \cdot 2\text{H}_2\text{O}$, H_2OR^- , $\text{Cu}_2(\text{acetate})_2(\text{H}_2\text{OR})_2$

Parameter	$\text{Cu}_2(\text{acetate})_2(\text{H}_2\text{OR})_2$	$\text{Cu}_2(\text{CH}_3\text{COO})_4 \cdot 2\text{H}_2\text{O}$	H_2OR^-
<i>Bond length ($\text{\AA}^\circ$)</i>			
Cu(1)-Cu(8)	3.957	3.38	
Cu(1)-O(2)	1.930	2.013	
Cu(1)-O(9)	1.927	2.018	
Cu(1)-O(31)	1.919		
Cu(1)-O(32)	1.955		
C(3)-O(2)	1.250	1.25	
C(3)-O(7)	1.368	1.34	
C(33)-C(34)	1.489		1.562
C(33)-O(32)	1.286		1.243
C(33)-O(31)	1.300		1.253
C(37)-C(38)	1.224		1.228
C(40)-C(41)	1.220		1.235
<i>Bond angle ($^\circ$)</i>			
O(31)-C(33)-O(32)	122	130	
<i>Net charge atom (N°)</i>			
Cu(1)	-0.307	-0.212	
O(2)	-0.098	-0.241	
O(9)	-0.135	-0.251	
C(10)	0.363	0.343	
O(11)	-0.183		
O(32)	-0.282		-0.609
C(33)	0.399		0.467

Cu-Cu distance in the compound $\text{Cu}_2(\text{acetate})_2(\text{H}_2\text{OR})_2$ is 3.957 $\text{\AA}^\circ$, which is higher than that reported value 3.38 $\text{\AA}^\circ$ for $\text{Cu}_2(\text{CH}_3\text{COO})_4 \cdot 2\text{H}_2\text{O}$, calculated with the same method ¹⁶, but the Cu-O distances did not suffer important change (see Table 5). In the complex, the distance C(33)-C(34) 1.489 $\text{\AA}^\circ$ is lower than that free orotate anion 1.562 $\text{\AA}^\circ$. Respect to the net charge, important changes are produced in the distribution due to the effect of the coordination of the orotate ligand.

For the compound $\text{Cu}_2(\text{acetate})_4(\text{H}_3\text{OR})_4$ it is suggested a structure where the Cu(II) ions keep linked by two bridge acetate groups and each Cu(II) ion maintains coordinated to an acetate group with a monocoordination, moreover, two coordinated orotic acid through oxygen from C(2)=O group (see Fig. 6).

Fig. 6 PM3 structure of $\text{Cu}_2(\text{CH}_3\text{COO})_4(\text{H}_3\text{OR})_4$

Table 6. Selected PM3 structural parameters of $\text{Cu}_2(\text{CH}_3\text{COO})_4 \cdot 2\text{H}_2\text{O}$, H_3OR , $\text{Cu}_2(\text{acetate})_4(\text{H}_3\text{OR})_4$

Parameter	$\text{Cu}_2(\text{acetate})_4(\text{H}_3\text{OR})_4$	$\text{Cu}_2(\text{CH}_3\text{COO})_4 \cdot 2\text{H}_2\text{O}$	H_3OR
<i>Bond length (Å)</i>			
Cu(1)-Cu(3)	4.230	3.38	
Cu(1)-O(4)	1.936	2.013	
Cu(1)-O(2)	2.039	2.018	
Cu(1)-O(9)	1.850		
Cu(1)-O(70)	1.932		
Cu(1)-O(41)	2.086	1.25	
C(5)-O(4)	1.297	1.34	
C(65)-O(70)	1.269		1.223
C(67)-O(72)	1.229		1.218
Cu(1)-OH ₂		1.98	
<i>Bond angle (°)</i>			
O(4)-C(5)-O(87)	105	130	
<i>Net charge atom (N^o)</i>			
Cu(1)	-0.315	-0.212	
O(2)	-0.206	-0.241	
O(4)	-0.236	-0.251	
O(9)	-0.371		
O(70)	-0.172		-0.374
O(72)	-0.334		-0.328

In this compound, the distance Cu-Cu, 4.23 Å, is higher than that the reported for Cu(II) acetate monohydrate 3.38 Å. C=O distances of orotic acid in the complex are higher than that for free acid. For Cu(II) acetate monohydrate the distance is 1.98 Å and those Cu-ORH₃, Cu(1)-O(70) are de 1.932 Å. Important changes of the net charge distribution are observed (see Table 6).

CONCLUSIONS

In these compounds, both Cu(II) ions are bound through the acetate group bridge but at an enough distance to present a higher magnetic moments than that the reported for copper(II) acetate monohydrate.

PM3 calculations suggested that the anion orotate coordinated with Cu(II) through the carboxylic groups with a bidentate coordination and that in neutral medium the orotic acid coordinated through the exocyclic group at a distance Cu-ORH₃ lower than that Cu-OH₂.

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