

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Synthesis and characterization of Mixed-Ligand Complexes of Oxalic Acid and Trimethoprim with Mn(II), Co(II), Ni(II), Cu(II), Zn(II), and Cr (III) Ions: and antimicrobial Activities

Taghreed Hashim Al-Noor*, and Ghassan Thabit Shinan.

Department of Chemistry, Education for Pure Science College, University of Baghdad Ibn- Al Haitham_Baghdad, Iraq

ABSTRACT

A series of new mixed metal ligand complexes is reported with Oxalic Acid ($H_2C_2O_4$) as a primary ligand and Trimethoprim (TM) as secondary ligand. The structures of these complexes are confirmed by using FT-IR and UV- electronic spectroscopies, magnetic moments, melting points, molar conductivity measurements. and the metal % analysis revealed that the complexes analyze indicates a six coordinated as $K_2[M(Oxalate)_2(TM)(H_2O)]$. $M=Mn(II), Co(II), Ni(II), Cu(II), Zn(II)$ and $K[Cr(Oxalate)_2(TM)(H_2O)]$. Interestingly, the in-vitro antimicrobial studies on (Trimethoprim and Oxalic Acid) ligands and mixed metal ligand complexes against {(Staphylococcus aureus (G+), Bacillus subtilis (G+), Enterobacter Cloaca e (G-)} by measuring the zone of inhibition in mm.

Keywords: Trimethoprim, Oxalic acid, oxalate, antimicrobial activity and complexes.

*Corresponding author :drtaghreed2@gmail.com

INTRODUCTION

Mixed ligands complexes is a subject of increasing interest in coordination bioinorganic chemistry. Mixed-ligand complexes containing (2 or more) different ligand molecules generally found to be more active biologically than the free ligand and its binary complexes. [1,2]

Many research papers have been published on preparing of metal complexes with mixed ligands and characterization [3-5].

The organic bidentate ligands as Oxalic Acid or amino acids are the important class of ligands in coordination chemistry and find extensive application in different fields such in the field of medicines and bioinorganic chemistry. [5]

Oxalic acid (Ethanedioic Acid) or called Wood bleach ,acts as a bidentate ligand in the form of the dianion, functions as a involving the two-carboxylate groups (and forms a 5 membered ring with the metal ion). The oxalate complexes of metal ions have been extensively studied, the sustained interest in their study in solution is a consequence of their use as model systems in the investigation of physic- chemical property. [6-8]

The literature survey [9] reported the synthesis and crystal structure of trimethoprim (TMP) 2,4-diamino-5-(39,49,59-trimethoxybenzyl) pyrimidine with Co atom. Naldini *et al.* [10] reported the synthesis, magnetic susceptibilities and X-ray structure of Cu(II) with (TMP) while Canton,, *et al.* [11] studied the interaction of Cu(II), Zn(II) and Cd(II) with trimethoprim and reported the crystal structures of $[Zn(TMP)_2Cl_2]$. Taghreed and Ieqa reported the synthesis and characterization of mixed ligand complexes of (TMP)and amino acids (L-proline,L-Alanin and Anthranilic acid) respectively with some transition metals ions .[12 -14]

Metal ions such as {Fe(III),Cu(II), and Zn(II)} penetrate a large range of biological tasks in the brain due to their uses in redox reactions which are the origin pathogenesis of Alzheimer' disease. [15]

The literature survey shows that no work has been done on transition mixed ligand complexes of Trimethoprim and with M (II) = Mn(II), Co(II), Ni(II), Cu(II) ,Zn(II) and Cr(III). In the present work,describes the investigation of mixed ligand complexes and their characterization. The structure is determined using; (UV-Visible ,FTIR) Spectroscopy, and magnetic susceptibility by Gouy balance method .

EXPERIMENTAL

All the chemicals and solvents were purchased of A.R. Grade quality obtained from Aldrich .Merck and BDH and were used without further purification.

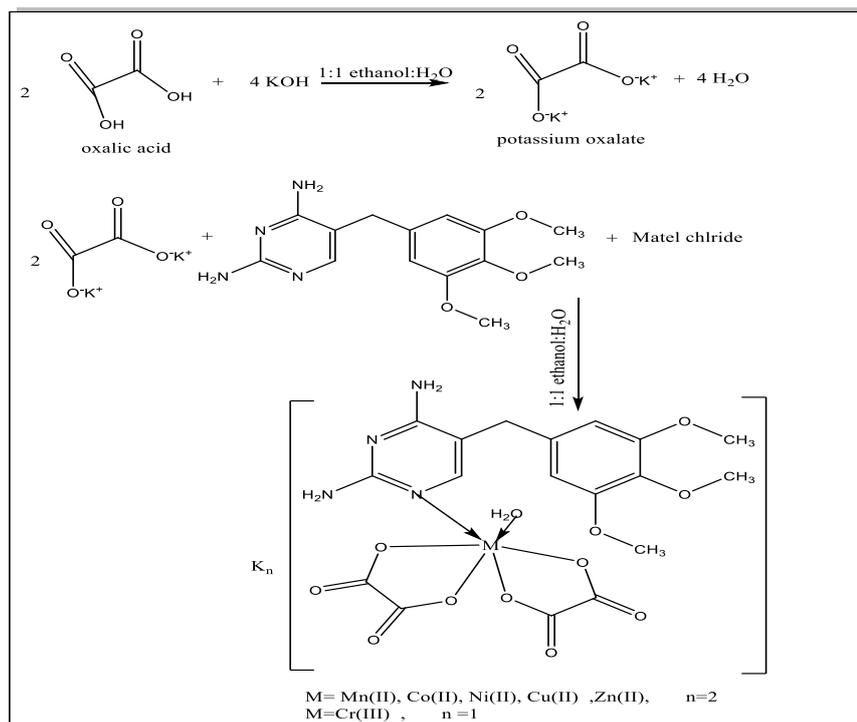
Synthesis of $K_2[M(C_2O_4)_2(TM)(H_2O)]$ Complexes

The 1:1:2 [M:MA:OX] complexes were prepared from $MCl_2 \cdot nH_2O$ or $M'Cl_3 \cdot nH_2O$.n=0-6. M = Mn(II), Co(II), Ni(II), Cu(II),and Zn(II), M'=Cr(III).

Oxalic acid H_2OX as a primary ligand and Trimethoprim (TM) as secondary ligand.

All complexes were prepared by the following general procedure (scheme -1)

The formed product was separated by filtration and washed with1:1 water: ethanol .This solid complex was recrystallized by using ethanol and measure physical constant of complex. The complexes were analyzed for their (metal% and chloride%) contents were determined by standard methods [16] .



Scheme -1: The synthesis route of Metal Mixed Ligand Complexes

RESULTS AND DISCUSSION

The complexes are air-stable, hygroscopic and the metal analysis (M %) of the complexes is approximate with the calculated results from the empirical formula of each complex and exhibit various shades of color:

(Table 1). The solubility of the complexes in the six solvents (H₂O, aceton, methanol, ethanol, DMF and DMSO) used, varied according to Cr(III) and M (II) used: All complexes were very soluble in water, and insoluble in all the solvents except in DMSO. The high (M.P./De.)°C are shown in Table °C >250

The molar conductivity (ohm-1.cm².mol⁻¹) of all complexes solutions measurements (1 x 10⁻³ M) at room temperature in DMSO as solvents. The Mn(II), Co(II), Ni(II), Cu(II), and Zn(II) complexes are an electrolytes types 1:2 while Cr (III) complex types 1:1 [17]. see table (1).

In free ligand (oxalic acid has two dissociable carboxylate protons and Identification of peak strong and sharp bands at 3132 cm⁻¹ which is affected by the presence of hydrogen bonds [18]. The bands observed around 1440-1450 cm⁻¹ and 2854-3100 cm⁻¹ were assigned to $\nu(\text{C}=\text{C})$ and $\nu(\text{C}-\text{H})$ aromatic stretching, respectively. The peaks ligand around (1635-1593)cm⁻¹(C=N)shifted to the region 1635-1697 cm⁻¹ for all the complexes are due to $\nu(\text{C}=\text{N})$ Pyrimidine nitrogen group present in complexes. Identification of peaks for $\nu(\text{M}-\text{N})$ & $\nu(\text{M}-\text{O})$ is very difficult as these can be observed at any value between (400-800)cm⁻¹. Many authors have defined peaks at different values for these signals (15-18). In the present case, the peaks of weak intensity observed in the regions (424-650) cm⁻¹ and (435-501) cm⁻¹ can be assigned to $\nu(\text{M}-\text{N})$ and $\nu(\text{M}-\text{O})$ respectively. [5,19] In their paper, they have reported a peak at 1535-1560 cm⁻¹ for -NH₂ group in complexes. The carbonyl (C=O) stretching in oxalic acid group (-COOH) peak at 1519-1404 cm⁻¹. and very strong band at 1230cm⁻¹ has been assigned to C-O str. of Carboxylic acid. In the complexes, the carbonyl vibration is shifted to higher frequencies. In the complexes broad peaks appear at range (3417-3456) cm⁻¹, followed by sharp at (725-775). cm⁻¹ assignable to-OH stretching, and rocking vibrations respectively indicating the presence of coordinated water molecules in the complexes [12-15]. The Trimethoprim ligand coordinates as neutral ligand monodentate ligand while the oxalato ligand (OX²⁻) coordinates as a dianionic bidentate towards Cr(III) and M(II) [8,18-20]. All of the complexes in this paper are paramagnetic except Zn(II) complex and their magnetic moments (μ_{ef}) are given in Table 2.

The electronic spectra of all the complexes solutions under study were recorded in 10^{-3} M in DMSO at room temperature summarized in Table (3).

Table(1): Some Physical properties of the compounds.

Compounds	Color	M.WT g/mol	M.P. /De. °C	M% Calculate (found)	Λ_m (ohm ⁻¹ .cm ² .mol ⁻¹) in DMSO 10 ⁻³ M. in (H ₂ O)
TM =C ₁₄ H ₁₈ N ₄ O ₃	white	290.32	-	-	-
H ₂ C ₂ O ₄ .2H ₂ O	white	90.3	-	-	-
K [Cr(C ₂ O ₄) ₂ (TM) (H ₂ O)]	Dark green	575.47	285 De.	9.04 (10.12)	49 (127)
K ₂ [Mn(C ₂ O ₄) ₂ (TM) (H ₂ O)]	rose	616.97	215 De.	10.19 (10.45)	89 (240)
K ₂ [Co (C ₂ O ₄) ₂ (TM)(H ₂ O)]	pink	620.97	223-255 De.	10.85 (11.29)	81 (240)
K ₂ [Ni(C ₂ O ₄) ₂ (TM) (H ₂ O)]	Light-green	621.26	216	9.45 (11.01)	78 (240)
K ₂ [Cu(OX) ₂ (TM) (H ₂ O)]	Light green	626.12	253-255	10.15 (10.11)	78 (240)
K ₂ [Zn(OX) ₂ (TM) (H ₂ O)]	Off white	627.95	216-220	10.41 (11.19)	76 (239)

D.T = decompose temperature , (OX)₂(TM) (H₂O) = C₁₈H₂₀N₄O₁₂

Table(3): Electronic spectral Data of compounds

Comp.	nm	ϵ max mol ⁻¹ . L.cm ⁻¹	ν cm ⁻¹	Assignments	μ_{eff} B.M
H ₂ C ₂ O ₄ = OX	262 310	166 1141	38167 28490	$\pi \rightarrow \pi^*$ $n \rightarrow \pi^*$	-
TM	274 313	1614 1131	36496 31948	$\pi \rightarrow \pi^*$ $n \rightarrow \pi^*$	-
K [Cr (C ₂ O ₄) ₂ (TM) (H ₂ O)]	277 386 574 842	81 62 43 76	36101 25906 17421 11876	Charge transfer ${}^4A_{2g} \rightarrow {}^4T_{1g}(P) \nu_3$ ${}^4A_{2g} \rightarrow {}^4T_{1g} \nu_2$ ${}^4A_{2g} \rightarrow {}^4T_{2g} \nu_1$	5.71
K ₂ [Mn(C ₂ O ₄) ₂ (TM) (H ₂ O)]	255 550 785	127 5 6	39215 18181 12738	Charge transfer $6A_{1g} \rightarrow 4T_{1g}(G)$ $6A_{1g} \rightarrow 4T_{2g}(G)$	5.60
K ₂ [Co (C ₂ O ₄) ₂ (TM) (H ₂ O)]	252 532 834	69 18 15	39682 18796 11990	Charge transfer $4T_{1g}(F) \rightarrow 4T_{2g}(F)$, $4T_{1g}(F) \rightarrow 4T_{1g}(P)$	5.08
K ₂ [Ni(C ₂ O ₄) ₂ (TM) (H ₂ O)]	252 292 403 655	757 41 87 55	39682 43246 24813 1526	Charge transfer ${}^3A_{2g}^{(F)} \rightarrow {}^3T_{1g}^{(F)} (\nu_3) {}^3A_{2g}^{(F)}$ $\rightarrow {}^3T_{1g}^{(p)} (\nu_2) {}^3A_{2g}^{(F)} \rightarrow {}^3T_{2g}^{(f)}$ ν_1	2.85
K ₂ [Cu(C ₂ O ₄) ₂ (TM) (H ₂ O)]	275 613	1915 118	36363 15847	Charge transfer ${}^2E_g \rightarrow {}^2T_{2g}$	1.7
K ₂ [Zn(C ₂ O ₄) ₂ (TM) (H ₂ O)]	201 294	142 7		C.T	Diamag.

Table(2) :Assignment of infrared in Cm^{-1} of $[\text{M}(\text{OX})_2(\text{TM})(\text{H}_2\text{O})]$ complexes

Compounds	$\nu_{\text{OH}}(\text{H}_2\text{O})$	$\nu(\text{N-H})_{\text{sym}}$ $\nu(\text{N-H})_{\text{asym}}$	$\nu(\text{C=N})$ Pyrimidine nitrogen	$\nu(-\text{OCH}_3)$	$\nu(-\text{CO})_{\text{asym}}$ of Oxalic acid	$\nu(-\text{CO})_{\text{sym}}$ of Oxalic acid	(C-O) str Oxalic acid	$\nu \text{ M-OH}_2$	$\nu \text{ M-N}$	$\nu \text{ M-O}$
Oxalic acid	3132vs	-	-	-	1519vs-br	1404vs	1230vs	-	-	-
TM	3468vs	3317vs 3116vs	1635vs 1593	11226vs	-	-	1234v	-	-	-
$\text{K}[\text{Cr}(\text{OX})_2(\text{TM})(\text{H}_2\text{O})]$	3425vs	3232vs 3186	1635s	1149m	1635vs	1400w	1249	725	543	501 435
$\text{K}_2[\text{Mn}(\text{OX})_2(\text{TM})(\text{H}_2\text{O})]$	3425vs	3251vs 3116	1697s	1134	1635vs	1435 vs	1273	748	482w	466 451
$\text{K}_2[\text{Co}(\text{OX})_2(\text{TM})(\text{H}_2\text{O})]$	3456vs	3294br	1651vs	1131	1635vs	1435 vs	1276	752	528	470 443
$\text{K}_2[\text{Ni}(\text{OX})_2(\text{TM})(\text{H}_2\text{O})]$	3417vs-br	3228v 3187	1654	1130	1597	1330	1242w	775	621	489 451
$\text{K}_2[\text{Cu}(\text{OX})_2(\text{TM})(\text{H}_2\text{O})]$	3421vs	3259vs 3182	1651s	1126	1635s	1400	1234	744	424	513 474
$\text{K}_2[\text{Zn}(\text{OX})_2(\text{TM})(\text{H}_2\text{O})]$	3441vs-br	3286vs	1647s	1130	1639s	1330	1338	748	542	493 459

ν = stretching , , br = broad arom. = aromatic , aliph = aliphatic

The antibacterial studies

The control (DMSO) , two free ligands and synthesized complexes were screened for their *in vitro* antimicrobial activity against (*Staphylococcus aureus* , *Bacillus subtilis* , *Enterobacter Cloaca* by measuring the zone of inhibition in mm. are presented in Tables 5 and scheme (2). [12-15]

The antibacterial activity results revealed that the ligand and there complexes shown weak to good and excellent activity when compared to the Control (DMSO). In general free ligand (TM) shows the highest (IZ) against four bacteria. This confirms earlier reports (12-13.). The complexes examined showed different patterns. The complexes exhibit a higher activity than the corresponding (Oxalic Acid) ligand. All the complexes that showed activity of less than 6 mm against *Enterobacter cloacae* and *Bacillus subtilis* but highest (IZ)against *Staphylococcus ureus* except for $K[Cr(OX)_2(TM)(H_2O)]$ complex. Whereas $K_2[Cu(OX)_2(TM)(H_2O)]$,and showed activity against *Esherichia Coli* only. In metal complexes, on complications the polarity of the metal ion will be reduced to a greater extent due to the overlap of the two ligands orbital and partial sharing of the positive charge of the metal ion with (Nitrogen and oxygen as donor atoms . Further, it increases the delocalization of π - electrons over the whole chelate ring. The ring of (Trimethoprim) moiety makes the complexes more lipophillic . [24]

Table(4): Antibacterial activity of the ligands and the complexes

Componds (ligands & M-comp.)	<i>Enterobacter cloacae</i>	<i>Bacillus subtilis</i>	<i>Staphylococcus aureus</i>	<i>Esherichia Coli</i>
Control (DMSO)	5	4	4	5
H ₂ C ₂ O ₄ = OX	5	5	4	4
TM	37	5	58	29
$K [Cr (C_2O_4)_2(TM) (H_2O)]$	5	5	4	4
$K_2[Mn(C_2O_4)_2(TM) (H_2O)]$	5	5	22	4
$K_2[Co (C_2O_4)_2(TM) (H_2O)]$	5	5	33	4
$K_2[Ni(C_2O_4)_2(TM) (H_2O)]$	5	5	44	4
$K_2[Cu(C_2O_4)_2(TM) (H_2O)]$	5	5	33	15
$K_2[Zn(C_2O_4)_2(TM) (H_2O)]$	5	5	23	4

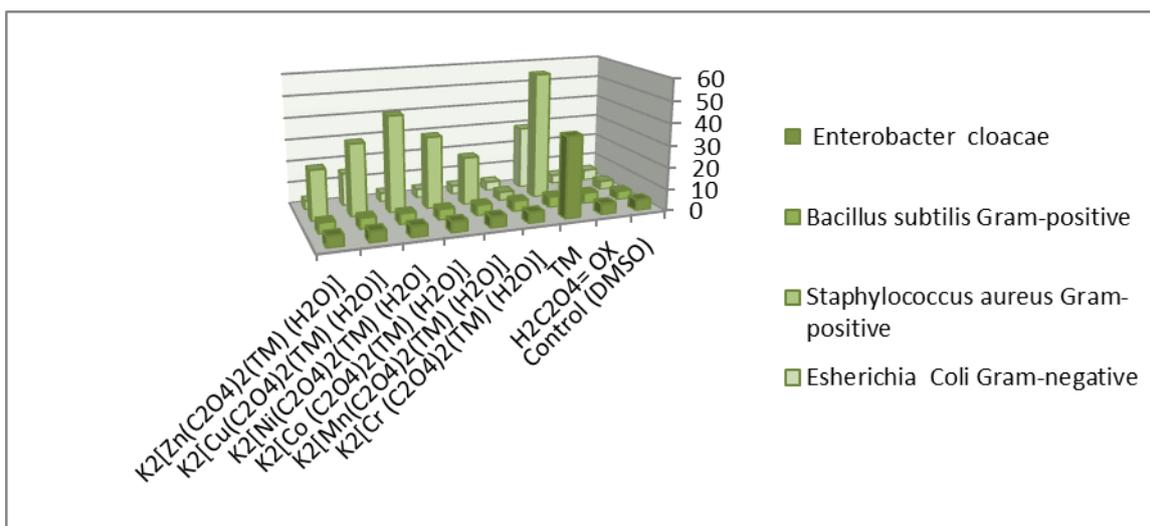


Chart (1) Biological effect of the compounds

CONCLUSIONS

The new mixed ligand complexes were synthesized and characterized. The data collected from electronic spectra and magnetic measurements, indicated an octahedral stereochemistry for the metal complexes. FT-IR spectra showed that the Trimethoprim ligand coordinates as neutral mono dentate ligand while the oxalate ligand (OX^{2-}) coordinates as a dianionic bidentate towards and showing that the molecules of coordinated water bacteriological studies were carried out against four species. The results showed increase in antimicrobial activity of metal complexes as compared with oxalic acid. The complexes exhibited varying degrees of inhibitory effects on the growth of the tested bacterial species.

ACKNOWLEDGEMENTS

We are grateful for the technical assistance provided by the Departments of Chemistry, in Baghdad and al-Mustansiriya university in the preparation of the samples for antimicrobial activities are also acknowledged.

REFERENCES

- [1] A. A.Osunlaja, N. P. Ndahi and J. A. Ameh. African J. Biotechnology 8 (1), 004-011, 5 January, (2009).
- [2] Jadhav SS, Kolhe NH and Athare AE., Int J pham Bio Sci (2013) July; 4(3); 45-54.
- [3] Yam V. W. W. and Lo. K. K. W.. J. Coord. Chem. Rev., 184, (1999). 158-240.
- [4] Venkataraman D., Gardner G. B., Lee S. and Moore. J. S.. J. Am. Chem. Soc., 117, (1995) 11600-11601.
- [5] Samanta, B., Chakraborty, J., Dey, D. K., Gramlich, V. and Mitra, S. . J.Struct Chem.,18, (2007).287–293.
- [6] Vasca, E., Ferri, D., Manfredi, C., Torello, L., Fontanella, C.,Caruso, T. and Orru, S. J.Dalton Trans.4, (2003). 2698– 2703.
- [7] Tesfahun Kebede, B.B.V. Sailaja, G. Nageswara Rao and M.S. Prasada, J.Chemical Speciation and Bioavailability, 22(4) (2010)241-246.
- [8] Dennatin, F, Manassero, M., Naldini, 1., Zoroddu, M. A. J. Inorg, Chim.Acta. 77(6), (1983). 1213-L214.
- [9] Naldini, L Cabras, M. A., Zoroddu, M A., Dermaitn, F., Manassero, M, Sansoni, M. J.Inorg. Chim.Acta, 88(1), (1984). 45-50.
- [10] Simo, B., Perello, Ortiz, R., Castineiras, A., Latorre, J., Canton, E. J. Inorg. Biochem. 81(4), (2000); 275-283
- [11] Taghreed.H.AL-Noor, Lekaa K. Abdul Karim, j. Chemistry and Materials Research, 7 (3), (2015), 32-39.
- [12] Taghreed.H.AL-Noor Lekaa K. Abdul Karim, j. Chemistry and Materials Research, 7 (.5), 2015, 82, 90.
- [13] Taghreed.H.AL-Noor and Lekaa K. Abdul Karim, j. TOFIQ of Medical Sciences, Vol. 3, Issue 2, (2016), 64-75
- [14] Budimir A., Humbert N., Elhabiri M., J. Inorg. Biochem. 105 (2011) 490–496.
- [15] Vogel AJ. A Textbook of Quantitative Chemical Analysis. ELBS London. 5th edition 1989;440-474.
- [16] Geary W. J., *Coordination Chemistry Reviews*,7, (1), 81–122, 1971.
- [17] Bellamy L J 1975 The infrared spectra of complex molecules 3rd edn (London: Chapman and Hall)
- [18] Cotton, F.A., G. Wilkinson and P.L. Gaus, 2004. Basic Inorganic Chemistry. Student Edn., John Wiley and Sons Pt.Ltd, Singapore, pp: 503-541, 569-582.
- [19] Amudat L. and Joshua A. Obaleye, J.Biochemistry 19(1):9-15 (June 2007)
- [20] Nakamoto K (1986). Infrared and Raman spectra of Inorganic and Coordination Compounds. 3rd .Wiley Interscience, New York, 194-197.
- [21] Lever A B P (1968).Inorganic electronic spectroscopy (Amsterdam: Elsevier)
- [22] Yeamin R, Belayet H, Saidul I, Shahidil A.. Pak. J. Biol. Sci. 6(15): (2003). 1314-1316.
- [23] Williams DH and Fleming I. Spectroscopic Methods in Organic Chemistry. 4th Edition., Mcgraw-Hill Book Company (UK) Limited, 1989; 1 – 33.