

Preparation, Investigation and Enzymatic Activity of Mixed Ligand Complexes of Mefenamic Acid and Phenyl Alanine with some Transition Metal

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Abstract: This research contain preparation of transitions metal complexes for metals (Mn^{+2} , Co^{+2} , Ni^{+2} , Cu^{+2}) with the mixed ligands of mefenamic acid and L-phenylalanine. The prepared complexes were investigated by using spectra methods of FTIR, UV-visible spectroscopy, molar conductivity, susceptibility magnetic measurements as well as melting points. Stereo chemistry of complexes were accomplished which showed that geometry of mixed ligand Mef:M:Phenyl alanine with (Mn^{+2} , Ni^{+2} , Cu^{+2}) metal which have the molecular formula (513, 516.7, 521.5), respectively. Cobalt complex only has the distorted octahedral with molecular formula (588). Enzymatic activity study for prepared Ni^{+2} , Cu^{+2} complexes were calculated the possibility of activation and reactivation (for previously inhibited enzymes) deactivation of enzymes AChE, MAO at human serum. These complexes showed ability for activation or reactivation of enzymes activity at human serum. Metal complexes of (Ni^{+2} , Cu^{+2}) were deactivated the enzymatic reaction. The order reaction of enzymatic reaction were achieved and it were first order reaction for (Ni^{+2} , Cu^{+2}) complexes as inhibitors for enzymatic reaction. K_m and V_{max} were calculated for the tow reactions.

Key words: Mefenamic acid, phenyl alanine, enzymatic study of metal complexes, MAO, AChE, human serum

INTRODUCTION

Mefenamic acid chemistry: Mefenamic acid is non-steroidal anti-inflammatory drug. It's mechanism of activity is unknown completely like all (NSAIDS) drug. The mechanism may be attributed to prostaglandine synthesize inhibition (Anonymous, 2008). Mefenamic acid drugs are used for treatment of minor pain and for the many of edema and tissue damage resulting from inflammatory joint disease arthritis (DeRuiter, 2002). At the other side transition metal ions have the ability of interaction to molecules of additional of different biomolecule such that have organic, inorganic water parts residue at human body. It's commonly that ions metal associate to human bio molecule, construct of N, O, S or different donor atom (Krstic *et al.*, 2015). Many pain killer was synthesized from transition metal complexes with drugs. A new pain killer was produced from ferric form of iron with aspirin (iron interaction to aspirin). The prepared complex was absorbed at pH lower than if aspirin was used alone. This new pain killer exploit the feature of Fe^{+2} transport and storage of oxygen and electrons because it was found in its reduced form which was consist hemoglobin at human body (Ashiq *et al.*, 2003). Many transition metal complexes with mefenamic acid were prepared. These complexes have an important place within

medical chemistry. This can be explained by the interaction between the negative charged molecule with metal of different oxidation state (Chatterjee, 2012). Spectrophotometry study of Fe (III) ion-Mefenamic acid complex was achieved and characterized by 1H , $^{13}CNMR$, IR, Uv-visible and elemental analysis (Selvaganapathy and Raman 2016). At biological chemical processes, transition metal ions play an important role in the diagnosis and treatment of different diseases (Bojarowicz *et al.*, 1996). Rh ions were used as coordination centre of potential anticancer (Ang and Dyson, 2006). The mechanism which illustrated this coordination centre was such as "Activity by reduction and transferrin-targeted delivery". Hence, the interest is concentrated in the first class research care about with a few pharmacological activities of first row transition metal complexes such as V(II), Co (II), Ni (II), Cu (II) and Zn (II) which are available and cheap (Sigel *et al.*, 2007; Silva, 1997).

Metal ions have enzymatic activity. These ions have the ability of modify electron from enzyme to substrate or the opposite. Thus was controlling the enzyme-catalyzed reactions (Glusker *et al.*, 1999). Copper was found at many enzyme or protein as active site. This open new gate way of development of coordination complexes which gave new structural, functional aspect similar to nature of protein or enzymes (Mukheljee, 2003).

Table 1: Physical properties of prepared complexes

Comp.	Color (%)	MP	Yield (%)	Suggested structure
[Mn(Mef)(Phynel-Ala)(H ₂ O) ₃]2Cl	Pagde	213d*	80	Octahedral
[Co(Mef)(Phynel-Ala)(H ₂ O) ₃]2Cl	Dark green	220	65	Octahedral distorted
[Ni(Mef)(Phynel-Ala)(H ₂ O) ₃]2Cl	Light green	290	90	Octahedral
[Cu(Mef)(Phynel-Ala)]Cl ₂	Green	197	90	Octahedrald

*Decomposed

MATERIALS AND METHODS

Physical measurement and analysis: Melting points of prepared complexes were calculated by using gallien K_m melting point apparatus. FTIR spectra were recorded at Al-Mustansiryah University by using fourier transform Infrared spectrophotometer-Shimadzu in rang of (400-4000) cm⁻¹.

Electronic spectra were determined by using Uv-1650R Shimadzu spectrophotometer with (10⁻³) concentration. The magnetic suscepti-bility measurements were achieved on Gouy balance at (25°C) using Hg[Co(SCN)₄] as calibrant on Sherewood magnetic balance. All chemicals were prepared by Fluka and BHD.

Preparation of metal complexes: Preparation of metal mixed ligand complexes were prepared by getting 10 mL of ethanolic solutions of equal weights with equal (1 mmol) of the first ligand Mefenamic acid, second ligand L-phenyl alanine and metal chloride. All the three different solution were mixed and refluxed for 2 h. Then the mixture were cooled and filtered. The precipitation was gathered and dried (Abid and Abbas, 2013).

The enzymatic activity study: Enzyme activity was measured in healthy human serum as: MAO activity was measured by using Mewen method (McEwen and Cohen, 1963). AChE activity was detected by using Ellman methods (Ellman *et al.*, 1961). Different concentration of complexes was prepared (0.1, 0.01, 0) to show % inhibition. Different concentration of substrate was prepared to show Inhibition type, K_m, V_{max}. Physical properties were illustrated in Table 1.

RESULTS AND DISCUSSION

FTIR-infra red spectra of mefenamic acid: Figure 1 showed the important peaks of the first ligand mefenamic acid. This spectrum showed band at (1772 cm⁻¹) refers to carbonyl group of the acid. Another peak appeared at (1645 cm⁻¹) refer to (NH) group and band at (3308 cm⁻¹)

Table 2: Thermogravimetric analysis data for the ligands and Cobalt (II) complexes

Comp.	No. of steps	Losing atoms	TG weight loss % calc.(Mwt.)	TG weight loss % found
[Co(Mef) (Ph-alanine) (H ₂ O) ₃]2Cl	1	2Cl, 20H, 1N,15C,1O	46 (271)	46.43
	2	5 H, 6C	22.94 (72.85)	24.25
	3	3 H,1C,1N	11.02 (26.5)	12.90

refer to overlap between the two groups NH and OH of mefenamic acid. The bands at (3111, 3061, 2914) cm⁻¹ refer to CH₃ group (Derebe *et al.*, 2002).

FT-infra red spectra of prepared mixed ligand complexes:

The stretching band derivatization of NH residue for amino acid were not indicated for this groups which should be assigned at 3200-3000 cm⁻¹. The probability of absent of NH beak caused by nitrogen converted in to tertiary nitrogen. Tertiary nitrogen does not show any peak in the region.

The prepared mixed ligand complexes were investigated by using FT-IR measurements. These spectra were illustrated at Table 2. It had been clear to researcher that Mn(II) complex was attached to OC-O⁻ carboxylic acid of mefenamic acid ligand. This explained the shifting of C-O carboxylic peak to lower vibration from 1157-1155-1024 cm⁻¹. The band of carbonyl of carboxylic acid group was disappeared which gave an evidence for OCO⁻-metal ion conjugated as showed at Fig. 2 (Shahanaz and Punitha, 2015; Zapala *et al.*, 2016; Al-Dulimia *et al.*, 2016).

At the other side, the metal ion (MnII) was conjugated to oxygen of carboxylic acid group of amino acid (L-phenylalanine) which can explained the shifting of amino acid carbonyl group to lower vibration by 30 cm⁻¹ from 1645-1610 cm⁻¹. Alanine associated to Mn (II) from amine group which showed by the shifting of this group to lower frequency by 30 cm⁻¹. The molar ratio was 1 Mefenamic acid:1 Metal ion:1 Amino acid.

Spectra of CoII metal ion showed that molar ratio of prepared complex 1 Mefenamic:1 M:1 Phenyl-alanine. The conjugation between the metal ion (CoII) and mefenamic acid was from the oxygen of carboxylic group for mefenamic acid by losing the frequency at (1772) cm⁻¹ which mean that it can explained by resonance state between the two oxygen of carboxylic acid (Silverstein *et al.*, 2005). The frequency of ionic carboxylic group of phenyl alanine was clarified by showing the shifting of spectrum of carbonyl group from the vibration 1683 cm⁻¹ to lower frequency (1635 cm⁻¹) and the weak vibration of C-O at 1446 cm⁻¹ was shifted to 1456 cm⁻¹. These proof that the linkage between the metal and amino acid is from the ionic carboxylic group. The amine group of the L-phenylalanine was attached to the metal ion and

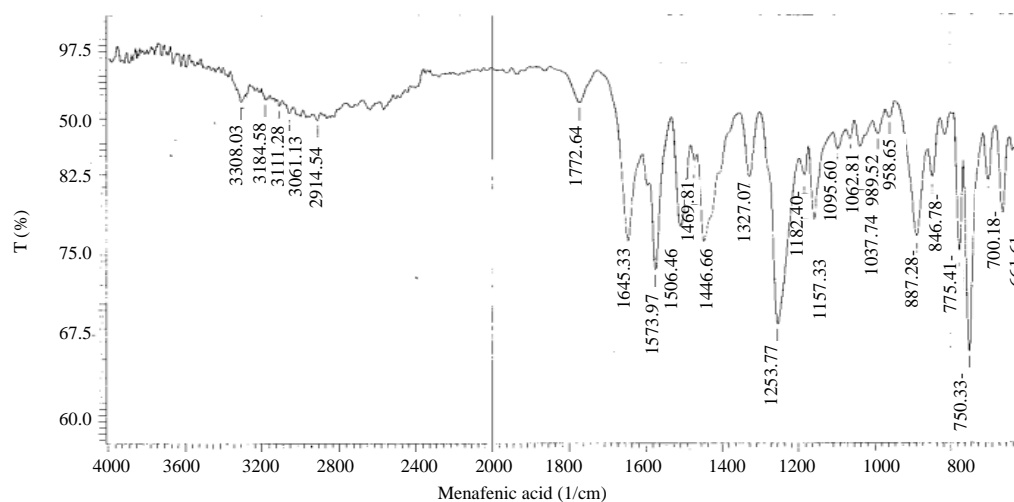


Fig. 1: FTIR spectrum of Mefenamic acid

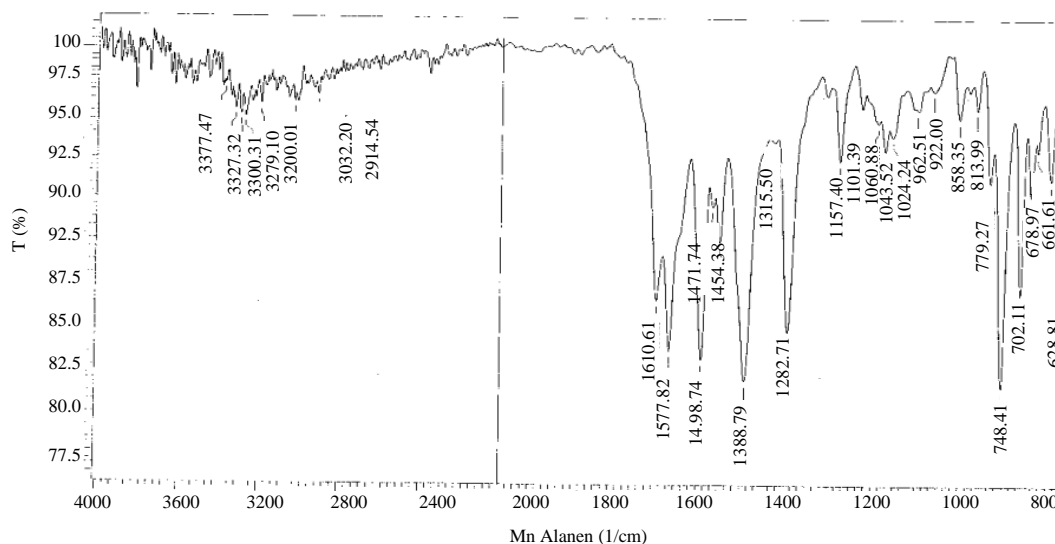


Fig. 2: FTIR spectrum of mixed ligand complex of manganese

this clarify by the shifting of this group by 30 cm^{-1} for all prepared complexes, Fig. 3 illustrate this explanation. (Rabindra and Mohan, 2000; Derebe *et al.*, 2000; Joseyphus *et al.*, 2006; Patil *et al.*, 2012; Kabbani *et al.*, 2005).

IR spectra of Ni complex showed shifting for COO^- of L-phenylalanine to lower frequency ($1635\text{--}1608\text{ cm}^{-1}$) which prove the linkage between the ionic carboxylic group with the nickel ion. The band at (1150 cm^{-1}) of C-O of carboxylic acid of mefenamic acid was shifted to lower 1095 cm^{-1} which confirm the coordination of OC-O of mefenamic acid with metal iron. Copper complexes gave the same bands and illustrations for linkage with the tow ligands in the drug and amino acid as showed at Fig. 4. The same illustration of Ni is similarity to CuII complex.

All complexes assigned M-N and M-O peaks vibrations at $750\text{--}200\text{ cm}^{-1}$. The M-Cl stretching band is supporting bands include a MO-C stretching vibration that appears between ($1245\text{--}1200\text{ cm}^{-1}$). The (M- OH_2O) bands also were indicated at the positions ($400\text{--}450\text{ cm}^{-1}$) and conductivity measurement showed that all complexes were conductance. This gives evidence for the octahedral structure of the four prepared complexes (Fig. 5).

Uv-visible spectra of prepared complexes: Uv-visible spectra of prepared were achieved. All complexes showed bands at Uv region referred to „* and n,* for C = O, NH and NH_2 .

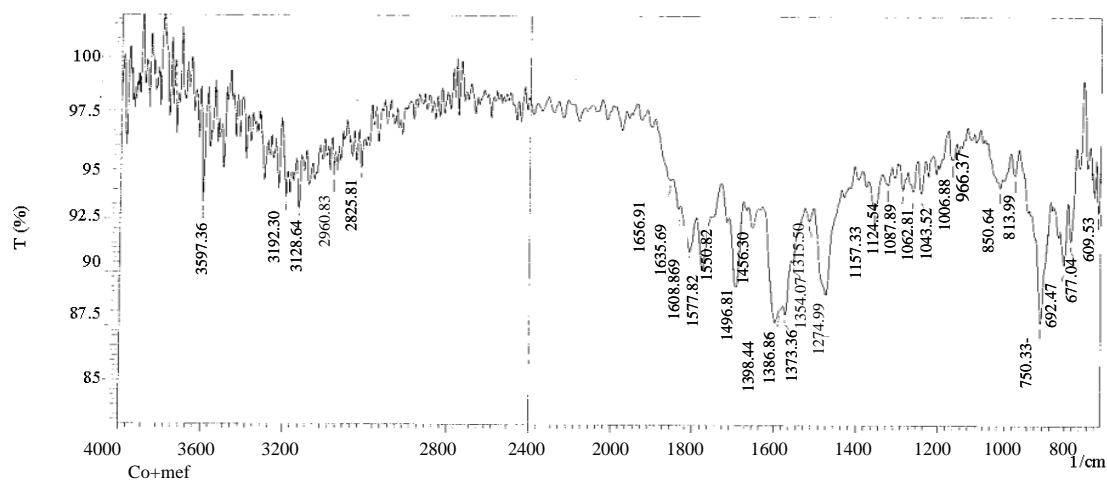


Fig. 3: FTIR spectrum of mixed complex of cobalt

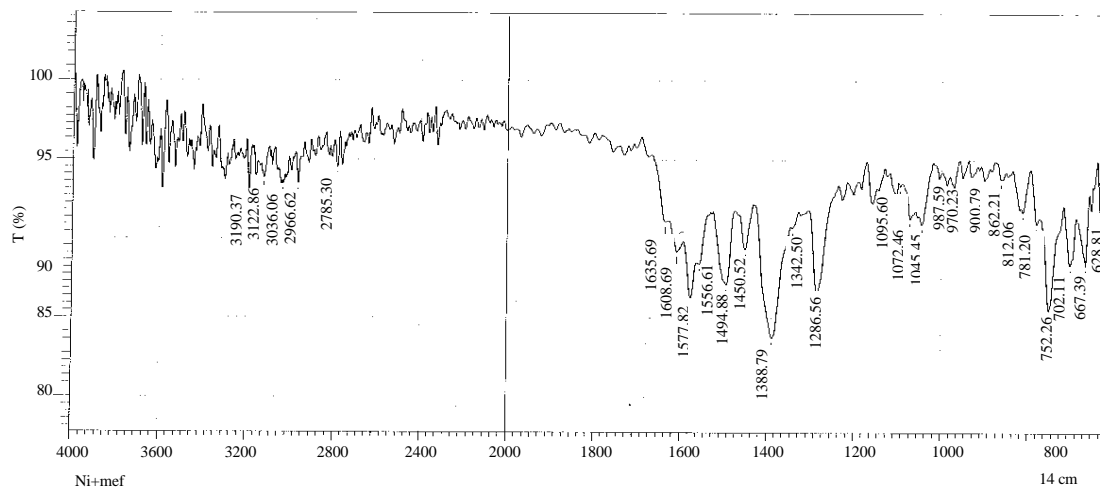


Fig. 4: FTIR spectrum of mixed complex of nickel

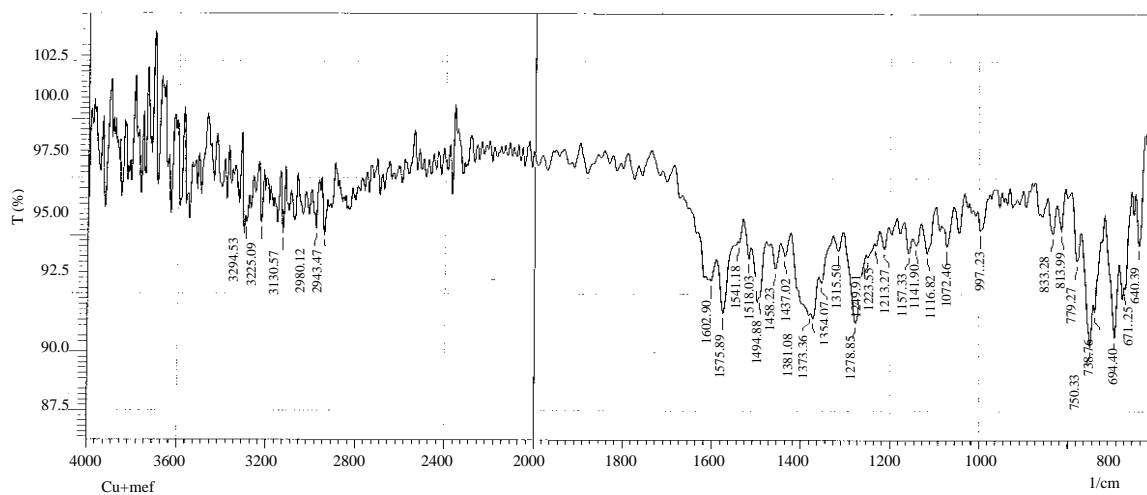


Fig. 5: FTIR spectrum of mixed complex of copper

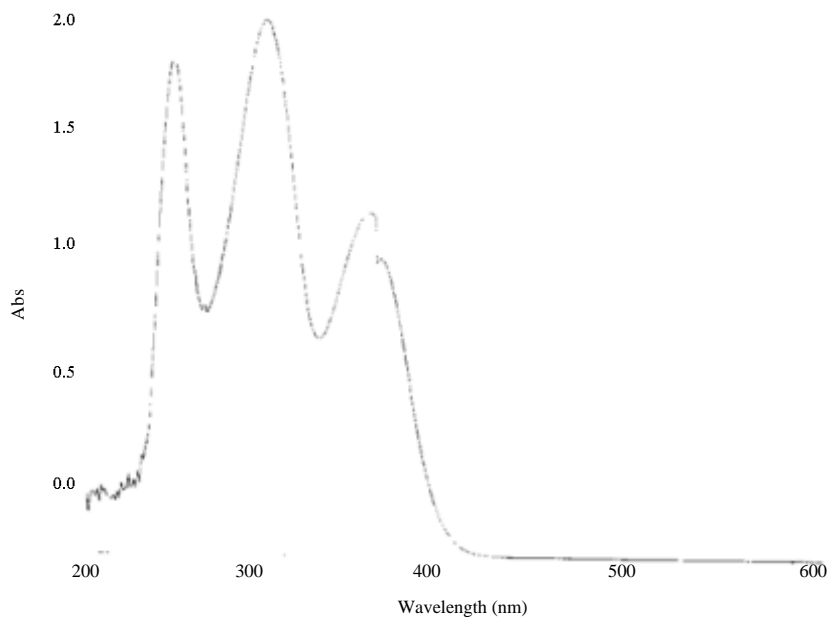


Fig. 6: UV-visible spectrum of mefenic acid

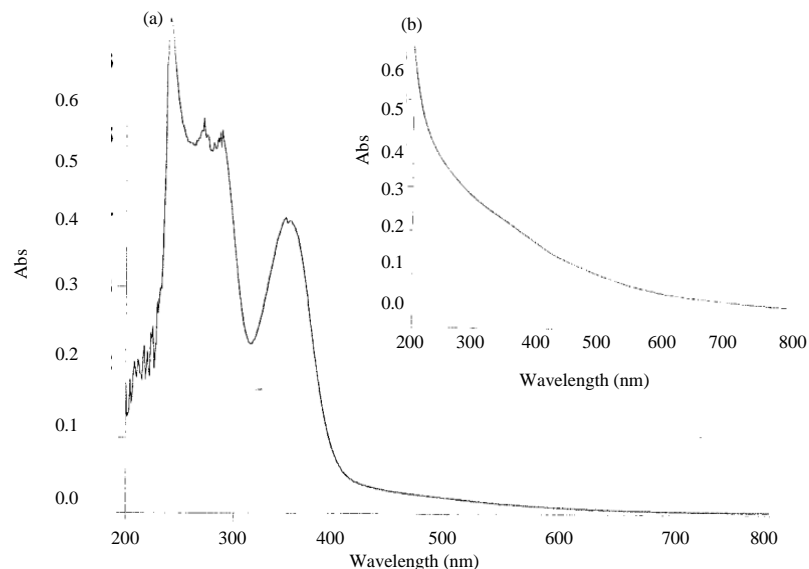
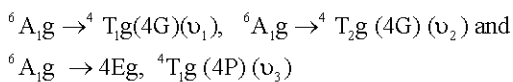


Fig. 7: UV-visible spectrum of mixed ligand complex of manganese

The electronic spectra of Mn^{II} complex: The Mn^{II} complex showed more than weak one bands around 335-560 nm bands:



This band was overlap together and can be imputed to forbidden d-d transitions. These bands enhanced the chemical structure octahedral geometry. Magnetic

moment of the Mn (II) complex is (5.12) BM. Due to single five electrons marking high spin octahedral environment (Negoiu *et al.*, 2005; Fayad *et al.*, 2013; Liwang *et al.*, 2004; Lever, 1984). Figure 6 showed the Uv-visible spectrum of manganese.

Co^{II} complex showed band at (550) nm as a broad shoulder assigned to ${}^2T_{2g} \rightarrow {}^2E_g$ transition which give us evidence for octahedral distorted geometry. Magnetic moment was (4.3) BH which deal with the other characterization measurements (Singh and Singh, 2009). Figure 7 showed the UV-vissible spectrum of cobalt.

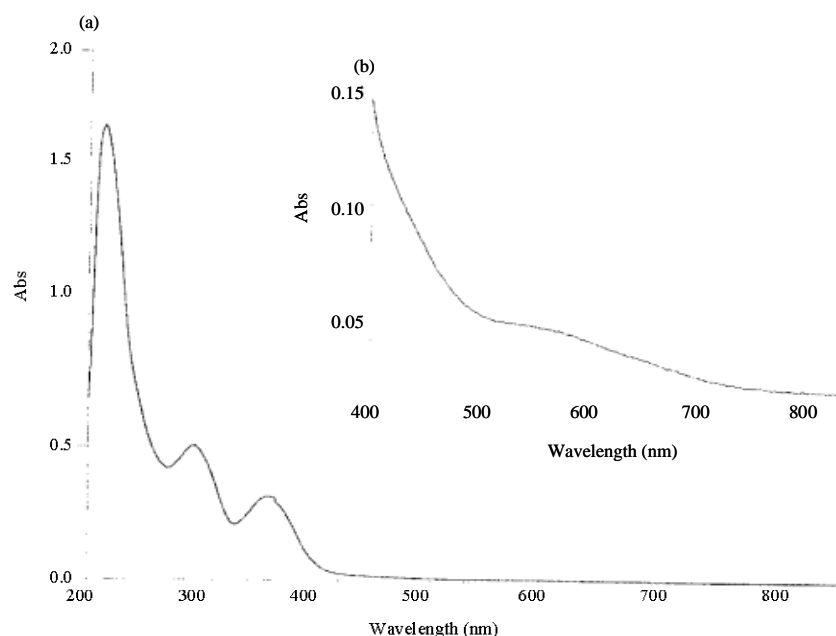


Fig. 8: UV-visible spectrum of mixed ligand complex of cobalt

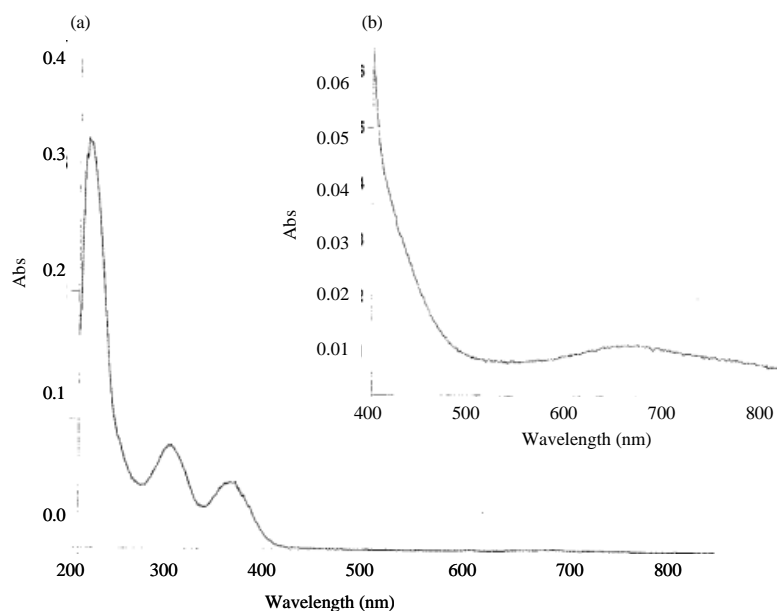


Fig. 9: UV-visible spectrum of mixed ligand complex of nickel

NiII complex electronic spectrum showed weak band at 650 nm which can be attributed to d-d forbidden transition from 540-790 nm which referred to ${}^3A_2g(F) \rightarrow {}^3T_2g(F)$, ${}^3A_2g(F) \rightarrow {}^3T_1g(F)$ and ${}^3A_2g(F) \rightarrow {}^3T_1g(P)$ transitions for an octahedral Ni (II) complex. This data agreed with magnetic susceptibility measurement where (3.22) BM represented the magnetic moment of nickel mixed ligand complex (Hubner *et al.*, 2011). Figure 8 and 9 showed the UV-visible spectrum of nickel.

UV-visible spectra of copper complex showed one broad electronic spectrum at 680 nm referred to the electronic transition ${}^2B_1g \rightarrow {}^2A_1g$. This given data of electronic transition supposed that copper complex made dimer complex with octahedral geometry. Copper magnetic moment was (2.1) BM which fostered the chemical geometry suggestion (Aiyelabola *et al.*, 2017). Figure 10 showed the UV-visible spectrum of copper.

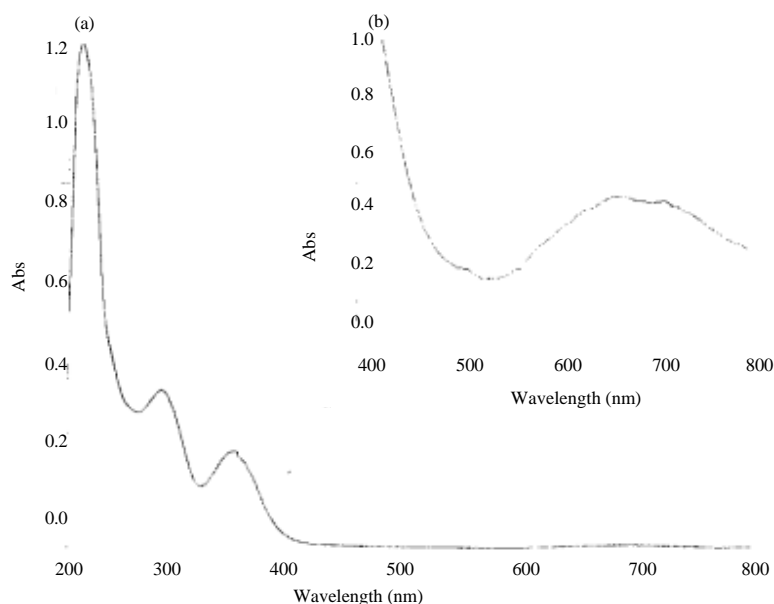


Fig. 10: Uv-visible spectrum of mixed ligand complex of copper

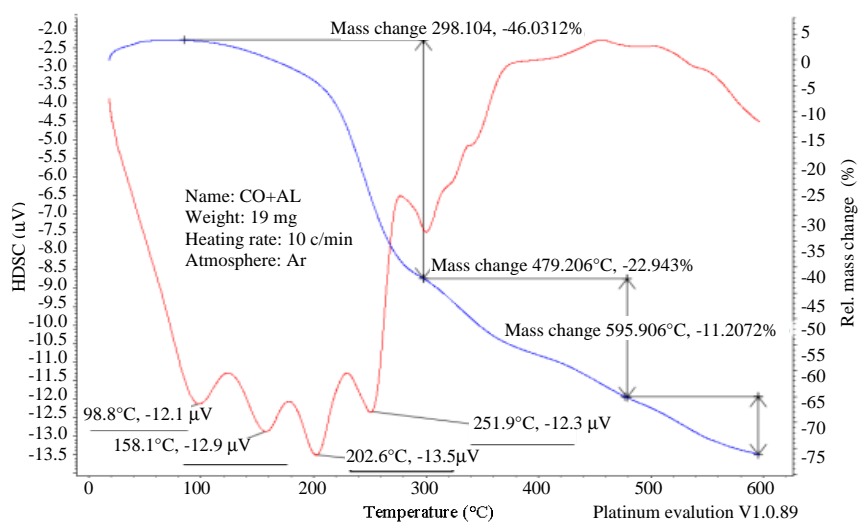


Fig. 11: TGA analysis of mixed ligand complex of cobalt a) Blu line refer to TGA curve (Thermogravimetric analysis), b) Red line refer to DSC curve (Differential Scanning Calorimetry); University of Baghdad/College of education for pure sciences Ibn Al-Haitham Central Service Laboratory

TGA analysis of CoII complex: Thermal analysis was carried out for CoII complex. The heating was appropriately at 50°C under nitrogen atmosphere. At 595°C temperature, weight losing of complex was calculated. The data which were gained, showed that the thermal decomposition of CoII complex was at three steps under three different temperatures. TGA of cobalt gave idea about thermal stability of its complexes. At the end of thermal decomposition was finished by conformation of cobalt oxide. Table 2 gave a brief statement of TGA/DTG

data and Fig. 11 demonstrated thermogram. This data agreed with the suggestion structure of the prepared complex (Kavitha and Lakshmi, 2017; Ahmadi and Amani, 2012).

Enzymatic activity of mixed ligand complexes (Ni, Cu):

The results obtained showed that this complex has inhibitory effect on both MAO and AChE as in Table 3. Type of inhibition and kinetic parameters for MAO and AChE with complex has been studies and the results

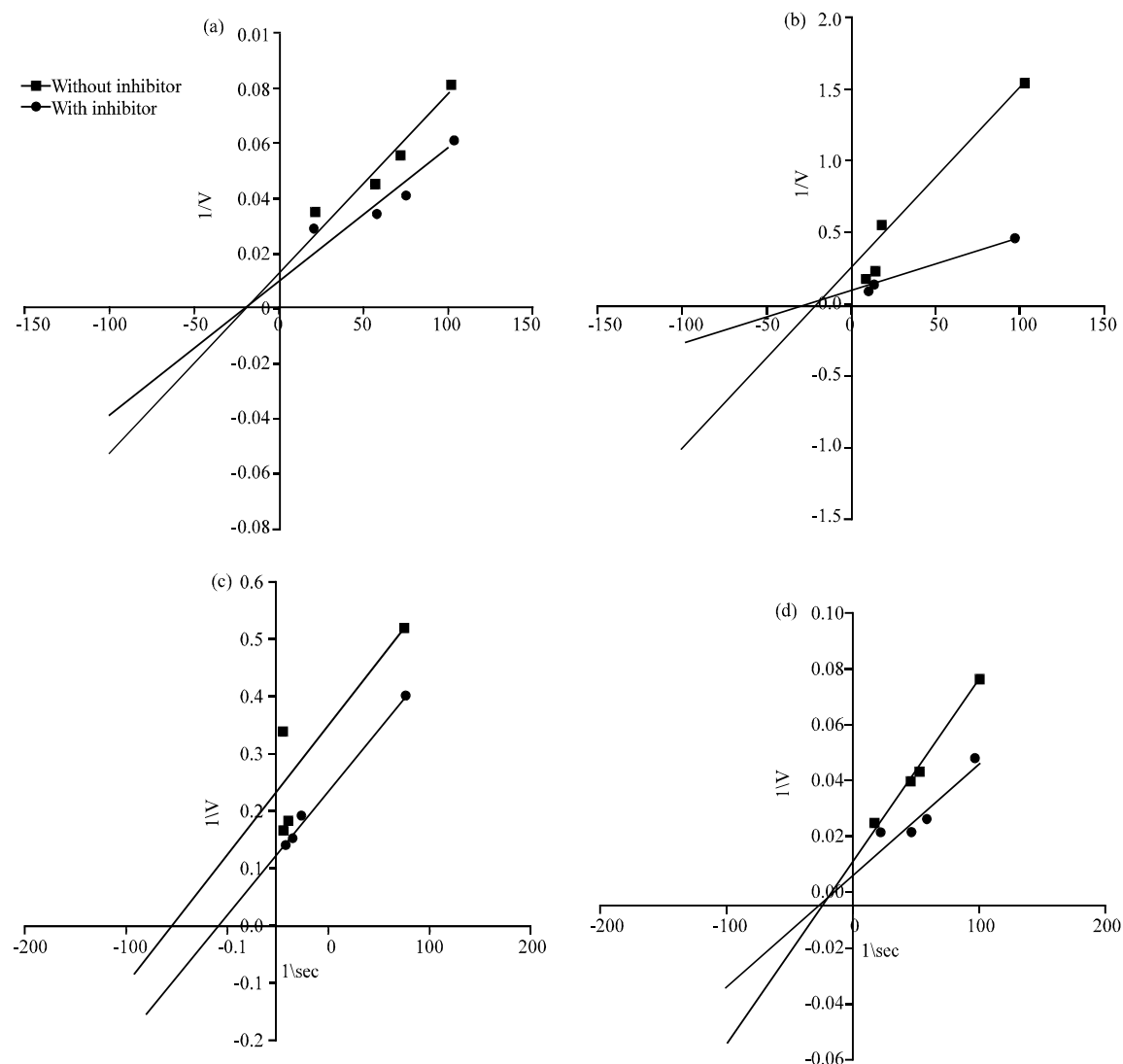


Fig. 12: Lineweaver burk plot for NiII and CuII complex with MAO and AChE enzyme: a) Ni complex with MAO; b) Ni complex with AChE; c) Cu complex with AChE and d) Cu complex with MAO

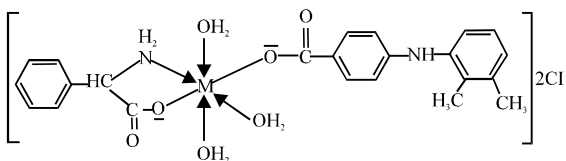


Fig. 13: Prepared complexer (M = MnII, CoII, NiII, CuII)

showed that competitive inhibition for complex with MAO and inhibition for complex with AChE as in Table 4 and Fig. 12.

This complex decrease MAO enzyme activity refer to amine group of complex which attached to

active site or to pocket site of enzyme instead of (NH₂) group of substrate and this complex prohibit (AChE) activity on account of complex attaching to amine acid residue in active site of enzyme and gives rise to inhibition.

The effect of Cu and Ni complex on Mono Amino Oxidase (MAO) and Acetylcholinesterase (AChE) (Abid and Abbas, 2013; McEwen and Cohen, 1963).

Suggestion structure: All measurements proved that geometry of all prepared complexes with octahedral structure (Fig. 13).

Table 3: The effect of different concentrations of Cu²⁺ and Ni²⁺ complex on MAO and AChE activity

Ni complex	MAO activity	Inhibition (%)
Nil	38.14	-
0.00001	32.01	16.07
0.0001	21.68	43.16
0.001	17.23	54.82
0.01	9.18	75.93
Ni complex	AChE activity	Inhibition (%)
Nil	6.74	-
0.00001	6.10	9.5
0.0001	5.14	23.74
0.001	3.09	54.15
0.01	2.16	67.90
Cu complex	MAO activity	Inhibition (%)
Nil	38.14	-
0.00001	30.62	19.72
0.0001	23.47	38.46
0.001	14.11	63.00
0.01	7.03	81.57
Cu complex	AChE activity	Inhibition (%)
Nil	6.74	-
0.00001	5.91	12.3
0.0001	4.54	32.64
0.001	2.80	58.46
0.01	1.77	73.74

Table 4: Kinetic properties of MAO and AChE with Cu complex and Ni complex

Parameters	V _{max}	K _m	Inhibition types
A	66.70	0.0500	Competitive
B	3.33	0.0450	Competitive
C	4.34	0.0125	Un competitive
D	55.50	0.0380	Competitive

CONCLUSION

The IR data clearly showed that at preparing complexes, the mefenamic acid behaves as monodentate donor ligand involving a carbonyl and the L-phenylalanine as ligand is as bidentate ligand (Kafarska *et al.*, 2017; Smolkova *et al.*, 2016; Zampakou *et al.*, 2014). Study remakes the main data of CuII prepared complex.

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