Synthesis and Complexation Study Of Copper (II) and Oxovanadium (IV) Ions with Some Pharmaceuticals Preparation.

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ABSTRACT

Copper (II) and oxovanadium(IV)chelating complexes of a tetra dentate ligands using acetazolamide ((N– [5 – (amino sulfonyl) – 1,3,4 – thiadiazol – 2 –yl] acetamide)) and amoxicillin ((6 – [[amino (4 – hydroxy phenyl) acetyl] – amino] – 3,3 – dimethyl –7 – oxo– 4 – thia –1 – aza bicyclo [3,2,0] heptane – 2– carboxylic acid)) drugs as a chelating agents have been prepared .Infrared , UV– visible techniques and molar conductivity measurements and solubility test were used to characterize and investigate the geometrical structure and nature of complexation in the new complexes .we obtained that Cu (II) complexes had ionic properties and dissolve in polar solvent but VO (IV) complexes had no ionic properties and dissolve in polar and non polar solvents . Dissociation constant (K_d) , molar conductivity in zero concentration (Λ_0) for all prepared complexes were obtained from molar conductivity measurements and from these we obtained that VO (IV) complexes had low value in molar conductivity and act as a weak electrolyte in DMSO but Cu (II) complexes had higher value than VO (IV) complexes .

INTRODUCTION

Most of drugs consist natural products which means that these structures containing organic compounds ,but recently some drugs were prepared by inserting free metal in these structures through bonding with organic ligands. As reviewed elsewhere[1,2] ,there have been considerable studies that showed the nature of complexation between copper (II) and platinum (II) ions with drugs such as the complexation between captopril and α-methyl dopa drugs with Cu(II) , VO (IV) was obtained and explained the kind of symmetry between them, molar conductivity for these complexes explained that they are considered as weak electrolytes .Amoxicillin is a semi –synthetic penicillin combining bactericidal activity with proven safety[3] . It is active against a wide range of gram-negative and gram-positive bacteria and the indications for this drug that genitourinary tracts infections,gonorrhea ,acute otitis media ,sinusitis and soft tissue infections[4]. There are some adverse reactions from the use of this drug , the more frequent reactions are abdominal or stomach cramps pain ,bloating fever ,skin rash and itching .Acetazolamide has indications that it is carbonic anhydrase inhibitor, diuretic, treatment of glucoma [5] .It has some adverse reactions from using such as :Drowsiness ,fever ,paraesthesia and blood disorders .Acetazolamide promotes HCO_3 diuresis and metabolic acidosis which may be a useful stimulus to respiration during exacerbation of chronic obstructive pulmenary disease .In this paper we described first the extraction of amoxicillin and acetazolamide and synthesis complexes between them and copper (II) , oxovanadium(IV) and then have investigated the stability and complexation of new prepared complexes.

EXPERIMENTAL

Extraction of the active material :

1-Extraction of **amoxicillin trihydrate** :

Dissolve two capsules containing (1gm) of amoxicillin trihydrate in (25 ml) of water with gently heating at 45 C° and stirring , filtered and the filtrate minimize by evaporation then leave it in a vacuums oven , white crystals forms , yield 90 ٪ , (M.p 216-218 Cº) , {literature (M.p217-218 C°) [6] }.

.3H2O
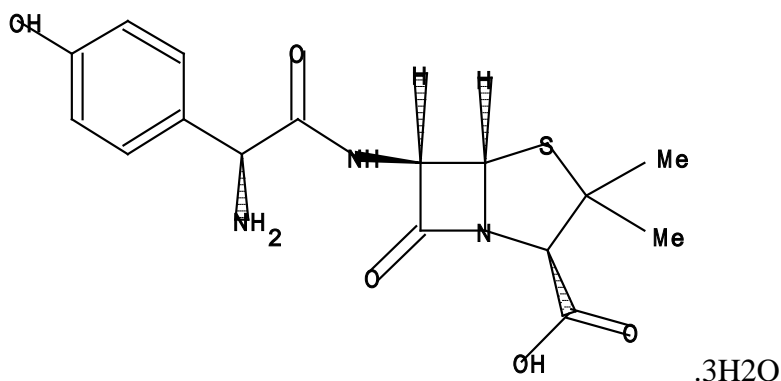
2- Extraction of **acetazolamide** :

Dissolve two tablet containing (1 gm) of acetazolamide in (40 ml) of absolute ethanol with stirring while maintaining temperature about 70 C° on water bath . Filtered then the filtrate minimize by evaporation then leave it in a vacuums oven , white crystals forms, yield 91 ٪ .(M.p 258-259 C°) ,{ literature (M.p 258-259 C°)[(6)] }.
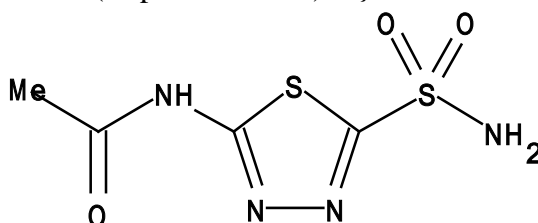
Preparation of complexes:

1- Complex I   [Bis amoxicillin trihydrate copper (II)]

A solution of Amoxicillin trihydrate (5.5 mmole) in water (50 ml) was added to a solution of $CuCl_2$.$2H_2O$ (2.75 mmole) in water (20 ml).The mixture was heated with stirring. A brown precipitate formed which was filtered off ,washed with methanol and dried . Decomposition point (85-88 C°) , yield 82 ٪ .

2-Complex I I   [Bis amoxicillin trihydrate VO(IV)]

The preparation method is similar to the above , using $VOSO_4.5H_2O$ instead of $CuCl_2.2H_2O$, A green precipitate formed . Decomposition point (176-179 C°) , yield 81 ٪ .

3- Complex I I I   [Bis acetazolamide copper (II)]

A solution of Acetazolamide (9 mmole) in absolute ethanol(40 ml)was added to a solution of $CuCl_2.2H_2O$ (4.5 mmole) in absolute ethanol (25 ml).The mixture was heated at 60 C° with continuous stirring for 20 min . A green precipitate formed which was filtered off ,washed with acetone and dried . Decomposition point (95-98 C°) , yield 88 ٪

4- Complex I V   [Bis acetazolamide VO (IV)]

The preparation method is similar to the above , using $VOSO_4.5H_2O$ instead of $CuCl_2 .2H_2O$, a blue precipitate formed . Decomposition point (199-203 C°) , yield 79 ٪ .

MEASUREMENTS

Infrared spectrum was recorded on a pye –Unicam model SP3-300-I R spectrometer using KBr disc .

UV ─Visible absorption spectrum was recorded on Beckman model SP3-100 spectrophotometer, using 1 cm quartz cell. (Using solvent is H_2O) .

Molar conductivity was recorded on W.T.W conductivity Mester LBR meter .

The melting point was recorded on "Gallen Kamp Melting Point Apparatus" .

RESULTS AND DISCUSSION
Analysis of the IR spectra

The binding sites in the complexes between amoxicillin and acetazolamide with Cu (II) and VO(IV) are deduced from their infrared spectra .Table (1) summarizes the IR data for amoxicillin , acetazolamide and their complexes with Cu (I I) and VO (I I) .According to I R spectra of Amoxicillin and their complexes , O—H stretch(3526 cm^{-1} S)phenol remain practically unchanged ,indicating that O—H group is not taking part in coordination .

However ,changing the shape and the position of N— H antisym and sym. stretch and NH$_2$ bending in amine and changing the position of C=O stretch as compared to spectra of free ligand indicate that nitrogen atom in amine and oxygen atom in the carbonyl group are involved in coordination to preparing amoxicillin complexes. In addition we obtained new bands , the two weak bands centered at 533 cm^{-1} and 573 cm^{-1} are assigned to Cu— O and Cu-N[7] stretching frequency in complex I .But in complex II a strong and sharp band centered at 975 cm^{-1} is assigned to V=O stretching frequency and a medium band centered at 390 cm^{-1} is assigned to V— N stretch[8] , V- O stretch centered at 360 cm^{-1} , see Figures (1) and (2) .

Table (1): selected IR bands (cm^{-1}) for amoxicillin and acetazolamide and their prepared compounds . (vs. = very strong , s= strong ,m= medium , w= weak , Sym.=Symmetrical , antisym.= antisymmetrical) .

| Compound I R bands	Amoxicillin	Complex I	Complex I I	Acetazo-lamide	Complex I I I	Complex I V
NH$_2$ antisym., Sym stretch (m)	3448,3290	3407,3240	3430,3250	-----------	----------	---------
C=O stretch (vs.	1760	1627	1640	-----------	----------	----------
NH$_2$ bending (s)	1680	1607	1613	----------	-----------	---------
N-H stretch (m)	-------------	-----------	-----------	3340	3300	3325
C=O stretch (vs.	-------------	-------------	------------	1669	1650	1658
C=N stretch (vs.	-------------	------------	------------	1560	1525	1530
V=O stretch (s)	--------------	-------------	975	----------	-----------	910
Cu-N stretch (w	--------------	573	------------	-----------	560	----------
Cu-O stretch (w	-------------	533	------------- -----------		520	-----------
V-N stretch (m)	--------------	-------------	390	----------	-----------	385
V-O stretch (m)	--------------	-------------	360	-----------	-----------	350
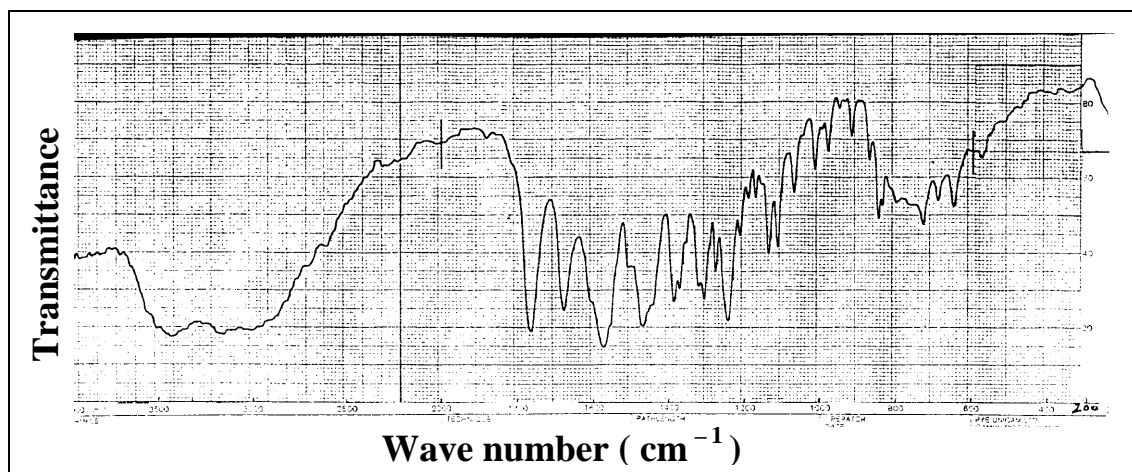
Figure(1): I R spectrum for amoxicillin .
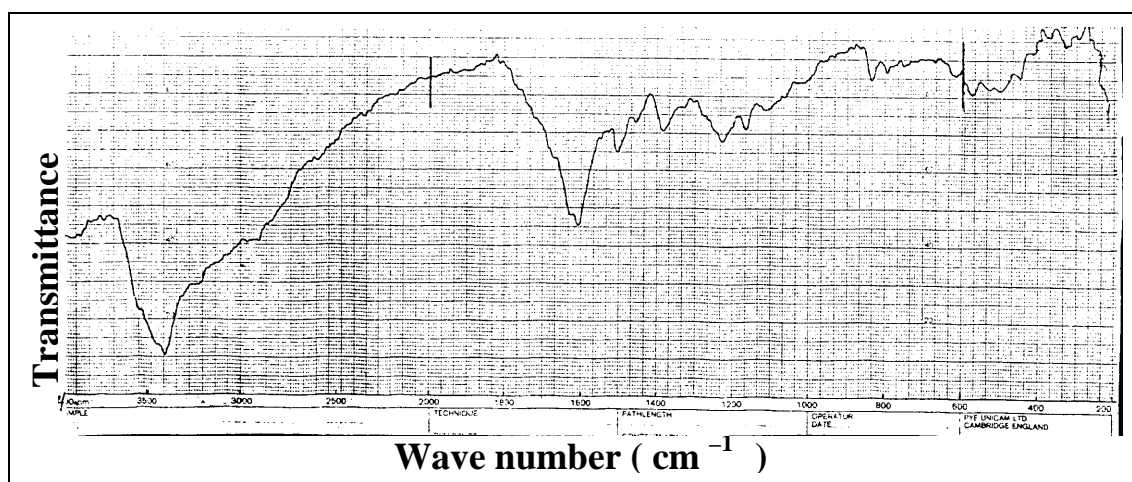
Figure (2): I R spectrum for complex I.

From IR spectra for acetazolamide and their complexes with Cu (II) and VO (IV) , we obtained that SO_2 antisym. and sym. Stretching (1360 cm^{-1}vs) and (1167 cm^{-1} vs) , and C- S stretching (613 cm^{-1} m) remains practically unchanged , indicating that sulfur atom is not taking part in coordination .The change in the position of C=O stretch (amide) and C=N stretch as compared to spectra of free ligand indicates that oxygen atom in carbonyl group and nitrogen atom in C=N groups are involved in coordination between acetazolamide and Cu (II),VO(IV) .In complex III we obtained new bands, the weak bands centered at 520 cm^{-1} and 560 cm^{-1} are assigned to Cu-O stretch and Cu-N stretch frequency respectively[9].But in complex IV , weak band centered at 385 cm^{-1} is assigned to V-N stretch and medium band centered at 360 cm^{-1} is assigned to V-O stretch . Strong and sharp band centered at 910 cm^{-1} is assigned to V= O stretching frequency , see Figures (3) and (4) .

UV –Visible absorption spectra

The electronic spectra of the complexes between amoxicillin and acetazolamide with Cu (II) and VO (IV) were obtained in H_2O solvent . In preparing Cu (II)complexes , one wide band was observed due to flocculation between two transitions ($b_2g \rightarrow b_1g$) and (eg $\rightarrow$ b_1g) and this state is similar to that of some Cu (II) complexes[10] .The values of molar absorbance Є are 442 and 370 for complex I and complex III .Є values were led us to attriblete the bands to that kind d –d transitions .According to D_{4h} symmetry[11] , these absorptions are assigned as shown in Table (2) , see Figure (5) .

Table (2): The assignment of the electronic transitions (cm^{-1}) for Cu (I I) complexes .

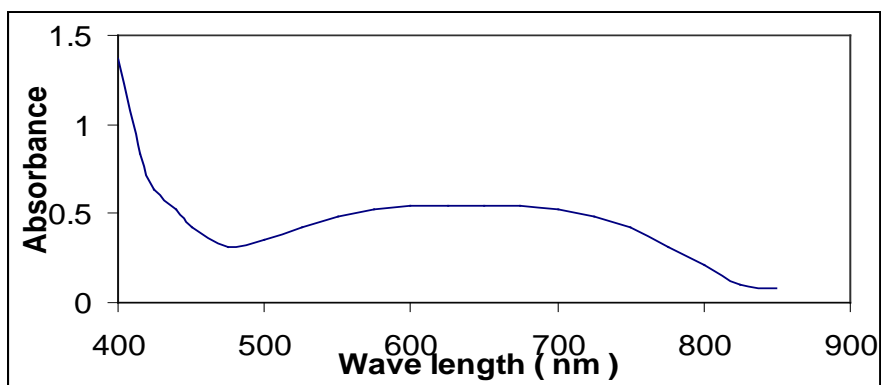| Complexes	ΔE ($b_2g \rightarrow b_1g$) ΔE ($b_2g \rightarrow eg$)
I	13605
I I I	15748

Figure (5):Electronic spectrum for complex II

In prepared VO(IV) complexes , we noticed complex II has two intese absorption bands. But in complex IV one weak absorption band and intense band were obtained and this state is similar to that in some VO (IV) complexes [12]. Є values are 500 , 450 for complex II and complex IV respectively, which one attributed to d-d transition too .According to C_{2V} symmetry[11] , these absorptions are assigned as shown in Table (3) .see Figure (6) .

Table (3): The assignment of the electronic transitions(cm^{-1})for VO (I V) complexes.

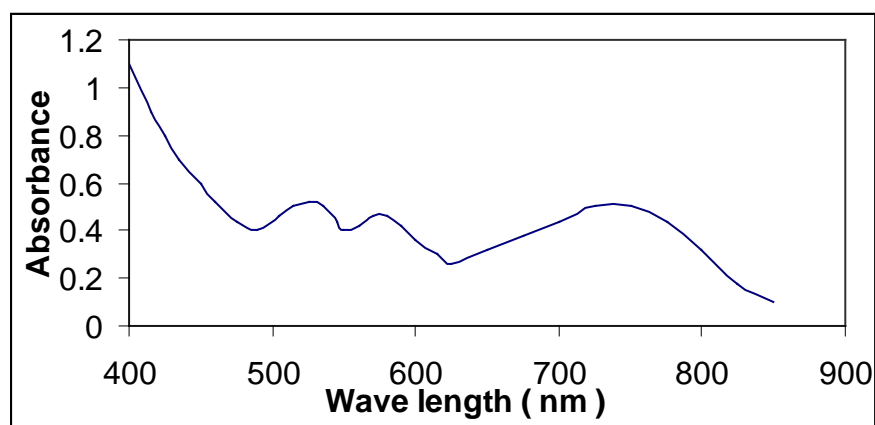| Complexes	$\Delta E\ (\ b_2 \rightarrow e^*_\pi)$	$\Delta E\ (\ b_2 \rightarrow b_1^*)$	$\Delta E\ (\ b_2 \rightarrow 1a_1^*)$
I I	13333	17391	19047
I V	13986	18181	--------

Figure (6): Electronic spectrum for complex II

Solubility Test

We obtained from solubility test that complexes (I , III) dissolve in polar solvents such as (H_2 O , Ethanol , DMSO) but not dissolve in nonpolar solvents such as (CCl$_4$, Cyclohexane) and that is due to the ionic properties of these complexes. In complexes (II, IV) we founded that these complexes dissolved in (H_2 O , Ethanol , DMSO , CCl$_4$) and partialy soluble in cyclohexane ,they are dissolved in nonpolar solvents due to that these complexes do not have any charge ,but the complexation between complexes (II , IV) with polar solvents such as H_2O, Ethanol , DMSO explain the reason solubility of these complexes in polar solvents . Table (4) shows solubility test for complexes (I , II , III , IV) in polar and nonpolar solvents.

Table (4) shows solubility test for prepared complexes in polar and nonpolar   solvent .

Complex	H2O	Ethanol	DMSO	CCl 4	Cyclohexane
I	soluble	soluble	soluble	non soluble	nonsoluble
I I I	soluble	soluble	soluble	non soluble	nonsoluble
I I	soluble	soluble	soluble	soluble	partial soluble
I V	soluble	soluble	soluble	soluble	partial soluble

Molar conductivity

The specific conductivity increased when the concentration of the solution was increased , this property is due to the increase of the number of ions that are found in the solution, this increase of conductivity perhaps is due to the change in the concentration of electrolyte or the change in the degree of dissociation [13] , for these reasons molar conductivity should be used to explain the variation of the chemical conductivity with concentration.

The molar conductivity of Cu (II) and VO(IV) complexes was studied in dimethyl sulf oxide (DMSO) as a solvent and concentrations of these complexes were (10^{-4} -10^{-5}M) at

room temperature .kolorash equation was applied to these complexes, plot of Λ_m against $(C)^{1/2}$ were shown , for example complex I in Figure(7) and complex I V in Figure(8) .
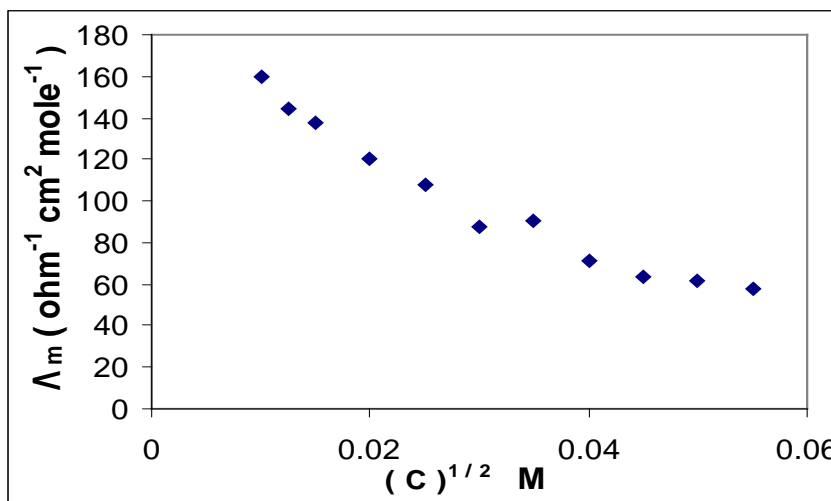

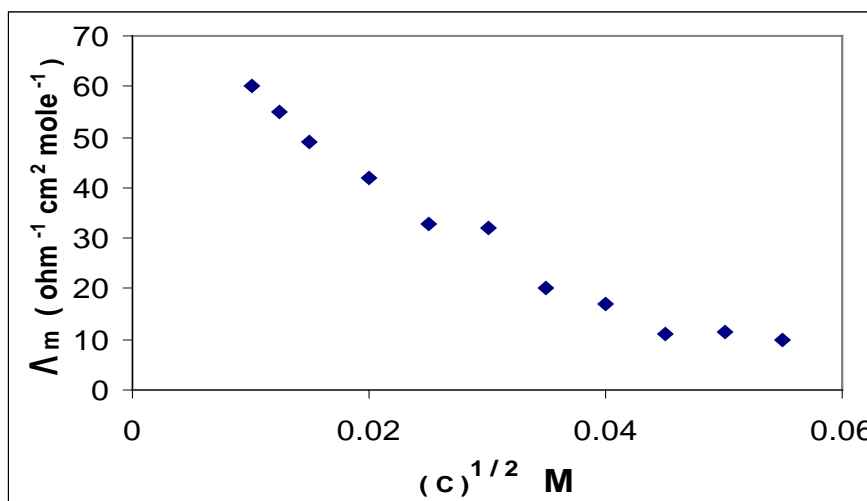**Figure (7):Molar conductivity Λ_m against $(C)^{1/2}$ M for complex I .**

Figure (8):Molar conductivity Λ_m against $(C)^{1/2}$ M for complex I V .

$$\Lambda_m = \Lambda_0 - S\sqrt{C} \qquad .... (1)$$

It was shown that molar conductivity for these complexes increased in dilute concentration and explained that these complexes are weak electrolytes in DMSO solvent . Dissociation constant K_d and molar conductivity in zero concentration Λ_0 for all prepared complexes were obtained when kraos equation was drawn for all prepared complexes had gave linear function , for example Figures (9) and (10) . Table(5) shows K_d and Λ_0 values for all prepared complexes .

$$C . \Lambda_m = K_d . \Lambda^2_0 (1 /\Lambda_m) - K_d . \Lambda_0 \qquad .... (2)$$

Λ_m = Molar conductivity . $\qquad\qquad$ C =The molar concentration.

Λ_0 = Molar conductivity at infinite dilution . $\qquad$ K_d = Dissociation constant .

We obtained from molar conductivity measurements that complexes (I , III) are ionic shape and the molar ratio is 1 : 2 , this similar with the results of solubility test that shown these complexes have ionic properties . We prepared the complex between Amoxicillin with $CuSO_4$ instead of $CuCl_2 .2H_2O$ to explain the high value that We obtained from molar conductivity measurements and we founded the value in molar conductivity is similar in the

two complexes because the masses of the complexes are large and have slowly movements , see Figure (11) .

1: 2   [(Amoxicillin) 2   Cu (I I)] Cl_2

1: 1   [(Amoxicillin) 2   Cu (I I)] SO_4

   From complexes (II , IV) ,we obtained that these complexes dissolve in polar and non polar solvents , these complexes dissolve in non polar solvents because they have non ionic shapes .The solubility of these complexes in polar solvents is due to the similarity between polar DMSO with the complex tregonalbipyramidal to produce distorted octahedral .

     According to IR spectra ,UV-Visible spectra, solubility test and molar conductivity measurements for amoxicillin and acetazolamide complexes with Cu (II) and VO (IV) , it is possible to suggest the geometrical structure for them, as shown below:

Complex III

     Complexes (II , IV) have a reasonable molar conductivity in spite of they have no ionic property , the reason is the similarity between polar DMSO with the complex tregonal bi pyramidal to produce distorted octahedral :

Complex IV + 1 DMSO →

Complex I I

Table (3): The assignment of the electronic transitions(cm^{-1})for VO (I V) complexes.

Complexes	$\Delta E\ (\ b_2 \rightarrow e^*_\pi)$	$\Delta E\ (\ b_2 \rightarrow b_1^*)$	$\Delta E\ (\ b_2 \rightarrow 1a_1^*)$
I I	13333	17391	19047
I V	13986	18181	--------

Table (4) shows solubility test for prepared complexes in polar and nonpolar   solvent .

Complex	H2O	Ethanol	DMSO	CCl 4	Cyclohexane
I	soluble	soluble	soluble	non soluble	nonsoluble
I I I	soluble	soluble	soluble	non soluble	nonsoluble
I I	soluble	soluble	soluble	soluble	partial soluble
I V	soluble	soluble	soluble	soluble	partial soluble

Table(5):Dissociation constant K_d and molar conductivity at infinite Λ_0 for Cu (I I) and VO(I V) complexes .

Complexes	$K_d \times 10^{-4}$ (mole . cm^{-3})	Λ_0 (ohm^{-1} .cm^2 .mole^{-1})
I	39.26	17.829
I I	5.14	11.667
I I I	46.58	3.220
IV	2.90	10.645

I.

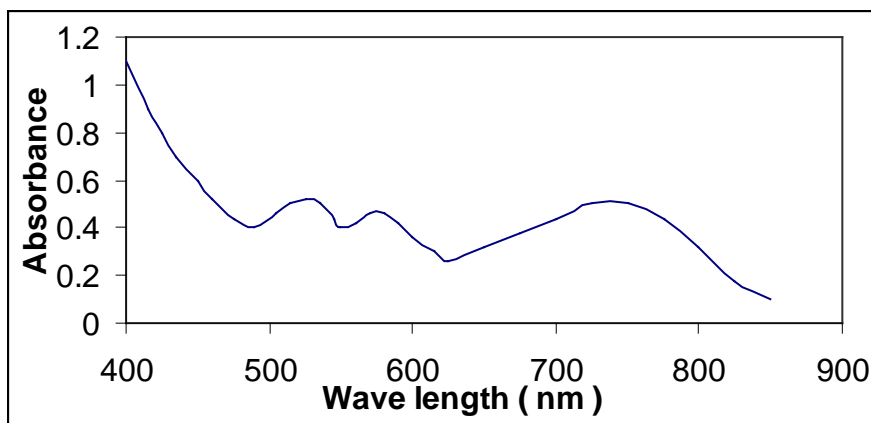**Figure (5): Electronic spectrum for complex III**

Figure (6): Electronic spectrum for complex II

Figure (7):Molar conductivity Λ_m against $(C)^{1/2}$ M for complex I .

Figure (8):Molar conductivity Λ_m **against (C)$^{1/2}$ M for complex I V .**

Figure(9) : $\Lambda_m . C \times 10^{-3}$ against $10^{-4}/ \Lambda_m$ for complex I .

Figure(10) : $\Lambda_m . C \times 10^{-3}$ against $10^{-4}/ \Lambda_m$ for complex IV .
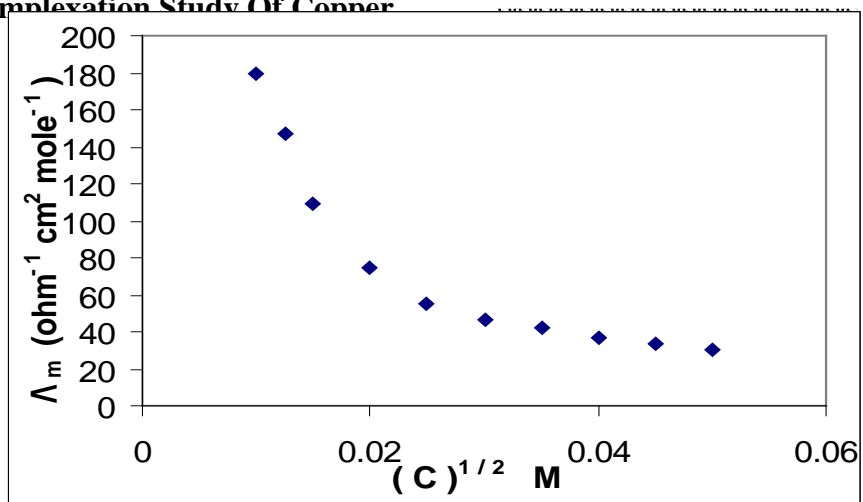
Figure (11):Molar conductivity Λ_m against $(C)^{1/2}$ M for complex between amoxicillin with $CuSO_4$.

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الملخص

تم تحضير معقدات جليتيه (مخلبية ،رباعية التناسق) بين عقار كل م ن الاسيتازولاماید والاسم العلمي له هو
((**N– [5-(amino sulfonyl)-1,3,4- thiadiazol – 2 –yl] acetamide**)) والاموكسيلين [[–6
amino(4-hydroxy phenyl)acetyl]– amino] – 3,3 – dimethyl –7– oxo– 4 – thia –1 – aza
bicyclo [3,2,0] heptane – 2– carboxylic acid)) , **مع كل من النحاس الثنائي والفناديو** م الرباعي
حيث تسلك هذه العقارات كليكاندات رباعية التناسق. لقد استخدمت تقنيات الأشعة تحت الحمراء والأشعة المرئية وفوق
البنفسجية وقياسات التوصيلية المولارية واختبار الذائبية لتشخيص الليكاندات المستخدمة والمعقدات المحضرة ، كما درست
طبيعة تكوين المعقدات الجديدة المحضرة والتركيب الهندسي لها بوساطة التقنيات المذكورة   . لقد حصلنا على ان معقدات
النحاس الثنائي المحضرة تمتلك خو اص ايونية حيث تذوب في المذيبات القطبية في حين ان معقدات الفناديوم الرباعي
المحضرة تذوب في المذيبات القطبية وغير القطبية الا انها لا تمتلك صفات ايونية ، كما تم حساب k_d (ثابت التفكك
للمعقدات) ، Λ_0 (التوصيلية المولارية عند التركيز الصفر) من قياسات التوصيلية المولارية حيث اعطت معقدات
الفناديوم الرباعي قيم   واطئة للتوصيلية المولارية مما يدل كونها الكتروليتات ضعيفة في مذيب   DMSO الا ان قيم
التوصيلية المولارية التي اعطتها معقدات النحاس الثنائي كانت اكبر مما في معقدات الفناديوم الرباعي .