

Synthesis, Structures and Antibacterial Activity of Some 2-Amino-5-(2-acetyloxyphenyl)-1,3,4-Thiadiazole complexes

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الخلاصة:

تم تحضير معقدات لليكاند ٢-أمينو-٥-(٢-اسيتوكسيفينيل)-١,٣,٤-ثايودايازول مع الايونات الفلزية التالية: الكروم(III) والحديد(III) والذهب(III) الكوبلت(II) والنحاس(II) في وسط كحولي مائي. شخصت المعقدات المحضرة بتقنية الأطياف تحت الحمراء بتحويلات فورير(FTIR) والامتصاصات الأليكترونية وتحليل العناصر والتوصيلية الكهربائية والحساسية المغناطيسية. تم قياس النسب المولية والمتغيرة في المحلول فأعطت نتائج مطابقة مع تلك التي تم الحصول عليها في الحالة الصلبة. حيث تم اقتراح هندسة الوحدة الأساسية للمعقدات. تم تقييم الفعالية البيولوجية للمعقدات الجديدة المحضرة ضد انواع منتجة من البكتيريا (خارج الجسم) وقد دلت النتائج المستحصلة بان لهذه المعقدات فعالية جيدة ضد البكتيريا.

ABSTRACT

New metal complexes of the ligand 2- Amino-5-(2-acetyloxyphenyl)-1,3,4-thiadiazole with the metal ion Cr(III), Fe(III), Au(III), Co(II) and Cu(II) were prepared in alcoholic water medium.

The prepared complexes were characterized by FTIR Spectroscopy, electronic spectroscopy, elemental analysis, conductivity and magnetic susceptibility measurement. Molar ratio and continuous variation studies in solution gave comparable result with those obtained from solid state study. From the spectral measurement, monomer structures for the complexes were proposed. The newly metal complexes were subjected to *in vitro* testing against pathogenic microorganisms. The results obtained revealed that these complexes showed measurable activity against bacteria.

INTRODUCTION

An important and versatile class of well established biologically active compound are those containing the $-N-C=S$ moiety(1-3). This group is included in many basic structures of drugs either to be a part of an open chain, e.g. thiocarbamates, isothiocyanates and thiosemicarbazides, or involved in heterocyclic ring, e. g. mercapto derivatives of thiodiazoles, triazoles and oxadiazole.

In particular, the 1,3,4-thiadiazole derivatives showed these activities(4-9). Metal complexes of 1,3,4-thiadiazole also have been used as antifungal(10), and other applications.

These complexes are suggested as a possible measure of drugs, since the action of many drugs is based on the ability of complex compound of metal ions to traverse biomembranes, whereas individual aqua-ions and ligands almost or completely lack this ability.

A case in point is antibiotics whose activity increase drastically in the presence of metal ions(11). Metal chelates differ in their mode of action and activity in biological system in accord with their structural

considerations, e.g., inert, highly stable metal chelates have a considerable activity against microorganisms, fungi and viruses and are used in controlling the speed of neoplastic tissue.

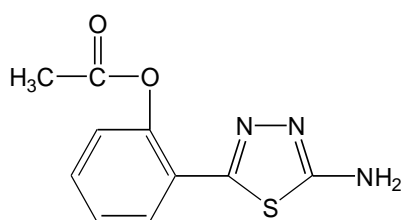
Later, it was found that certain copper and gold complexes appear to have antitumor activity(12).

MATERIALS AND METHODS

All chemical used were of reagent grade (supplied by either Merk or Fluka) and used as supplied. The FTIR spectra in the range (4000-200) cm^{-1} were recorded as CsI disc on *FTIR 8300 Shimadzu* Spectrophotometer. The electronic spectra of the complexes were obtained using *Shimadzu Uv-Vis-160A* Ultra-violet spectrophotometer at room temperature in the range (200-1000) nm. Magnetic susceptibility measurements for complexes were obtained at room temperature using (Magnetic Susceptibility Balance) *Jhonson Matthey catalytic system division. Gallencamp M.F.B600.01F* melting point apparatus were used to measure the melting point of all the prepared compounds. Conductivity measurement by using *Coring Conductivity Meter 220*. Elemental microanalysis was carried out using elemental C, H, N and S analysis were carried out on *afison EA 1108* analyzer instruments (Malaysia).

The metal content of the complexes was measured using atomic absorption technique by *Pye Unicam of Philips scientific* instrument which employed the Hallow cathode lamp of Pye Unicam Ltd. Cambridge.

Synthesis of the ligand: 2-Amino-5-(2-acetyloxyphenyl)-1, 3, 4-thiadiazole (L):



A mixture of 2-acetyl salicylic acid (0.01 mol), thiosemicarbazide (0.01mol), and phosphorus oxy chloride (5 ml). The mixture was refluxed for five hours. After cooling, water was added (25 ml).The mixture was refluxed for four hours and filtered. The solution was neutralized with potassium hydroxide. The precipitate was filtered and washed with distilled water and recrystallized from ethanol to give the ligand.

Preparation of complexes:

Ethanol solution of (1 mmol) of the metal salts $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$, $\text{FeCl}_3 \cdot 9\text{H}_2\text{O}$, $\text{HAuCl}_4 \cdot \text{H}_2\text{O}$, $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$ and $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ were added to (2 mmol) of (L) dissolve in ethanol. The mixture was stirred at room temperature for one hour. Fine precipitate was formed in all cases which was filtered on sintered glass crucible and recrystallized using ethanol/water mixture, then dried under vacuum at about 50°C .

RESULTS AND DISCUSSION**(A)Elemental analysis**

The physical analytical data of (L) and its complexes are given in Table (1), in a satisfactory agreement with the calculated values. The suggested molecular which are formulas also supported by subsequence spectral and molar ratio, as well as magnetic susceptibility.

Table -1: Physical data for L and its complexes

Symbol	Melting point, $^\circ\text{C}$	Color	M% Found	M% Calc.	Elemental analysis				Suggested Formula
					Found (Calc.)%				
					C	H	N	S	
L	208	White	-	-	50.90 (51.04)	3.35 (3.85)	17.00 (17.87)	13.81 (13.61)	$\text{C}_{10}\text{H}_9\text{N}_3\text{SO}_2$
CuL	(123)d	Blue	9.98	10.21	38.77 (38.56)	2.90 (2.89)	13.55 (13.49)	10.55 (10.28)	$[\text{Cu}(\text{L})_2]\text{Cl}_2 \cdot \text{H}_2\text{O}$
AuL	155	White	24.01	24.33	29.33 (29.65)	2.09 (2.22)	10.22 (10.38)	8.04 (7.91)	$[\text{Au}(\text{L})_2]\text{Cl}_3 \cdot 2\text{H}_2\text{O}$
CoL	(98-100)	Blue	11.22	10.59	39.00 (38.84)	2.88 (2.91)	13.70 (13.59)	10.22 (10.36)	$[\text{Co}(\text{L})_2]\text{Cl}_2 \cdot \text{H}_2\text{O}$
CrL	(230)d	Deep Green	7.88	8.04	37.05 (37.13)	2.66 (2.78)	12.88 (12.99)	10.09 (9.90)	$[\text{Cr}(\text{L})_2\text{Cl}_2]\text{Cl} \cdot \text{H}_2\text{O}$
FeL	(>250)d	Brown	8.00	8.59	36.55 (36.91)	2.80 (2.77)	13.00 (12.91)	9.88 (9.84)	$[\text{Fe}(\text{L})_2\text{Cl}_2]\text{Cl} \cdot \text{H}_2\text{O}$

(B)-Electronic and Infrared Spectra

The bands are classified into the intermolecular transitions appear in the uv region, and d-d transitions appear in the visible region. These transitions are assigned in relevant to the structures of complexes. Table (2), show the position of electronic absorption band and its transitions, and also include the calculated value of Racah parameter (B), $10Dq$ and nephelauxetic factor (β) for CoL, CrL and FeL.

The complex of CuL shows a broad band(13) at $15,780\text{ cm}^{-1}$ which can be assigned to ${}^2B_{1g} \rightarrow {}^2B_{2g}$ and ${}^2B_{1g} \rightarrow {}^2E_g$ transitions.

For AuL complex the charge transfer bands appear at longer wavelength, in the same time ligand field transition are expected to appear at shorter wave length. This result in an over lap between the two absorption bands, which make the interpretation of the spectra more difficult (14,15). Only one band has been observed at $27,030\text{ cm}^{-1}$, which can be assigned to the transition ${}^1A_{1g} \rightarrow {}^1B_{1g}$ in the square planar geometry.

The CoL complex spectrum in DMF shows three bands.

The first two bands at $16,611$ and $14,880\text{ cm}^{-1}$ were assigned to the transition ${}^4A_2 \rightarrow {}^4T_1^{(P)}(v_3)$, since this transition is known to be a triplet in the range $(14,000-17,500)\text{ cm}^{-1}$ in divalent cobalt of tetrahedral geometry. This splitting is due to spin orbital coupling(16). Therefore v_3 have been calculated as the average of these two bands.

The third band which appear as a weak band at $9,346\text{ cm}^{-1}$ was assigned to the transition of ${}^4A_2 \rightarrow {}^4T_1^{(F)}(v_2)$, while v_1 could not be observed since it is expected to appear in the range out of the instrument scale so it was calculated using Tanabe-sugano diagram for d^7 system(17) and found to be $6,265\text{ cm}^{-1}$ which belong to the transition ${}^4A_2 \rightarrow {}^4T_2^{(F)}$. The different ligand field parameters have been calculated using the same diagram, the results are found in Table (2). Comparison of the results obtained in this work with the literature data suggests high spin tetrahedral geometry around Cobalt (II) ion(18-20).

The relatively high value of $10Dq$ and the low value of nephelauxetic factor (β) indicate the covalent character between the Co (II) ion and the ligand.

The CrL complex spectrum in DMF shows three bands, the first two bands at $16,420$ and $22,883\text{ cm}^{-1}$ were assigned as belonging to transitions ${}^4A_{2g} \rightarrow {}^4T_{2g}^{(F)}(v_1)$ which is equal to $10Dq$, and ${}^4A_{2g} \rightarrow {}^4T_{1g}^{(F)}(v_2)$ (17).

The third band could not be observed since it was expected to appear in the ligand or charge transfer absorption region, so it was calculated using the Tanabe-Sugano diagram(18) and was found to be at $35,568\text{ cm}^{-1}$ and assigned to the transition ${}^4A_{2g} \rightarrow {}^4T_{1g}^{(P)}(v_3)$ (18).

The uv-vis spectrum of the FeL complex showed two transitions, the first transition at $28,517\text{ cm}^{-1}$ which assigned to ${}^6A_{1g} \rightarrow {}^4T_{2g}$ and the second at $20,000\text{ cm}^{-1}$ belong to ${}^6A_{1g} \rightarrow {}^4T_{1g}$ both as a shoulders. This complex and came in accordance to other available data so an octahedral geometry was suggested to the FeL complex (21). The value of the measured magnetic moment in accordance with the presumption of high-spin d^5 ferric ion in octahedral geometry(17).

From Tanabe-Sugano diagram for d^5 octahedral field(17) , the value of $10Dq$ equal to $25,800\text{cm}^{-1}$ and the high value of nephelauxetic factor (β) (0.99) indicated the ionic character between iron (III) ion and the ligand. The infrared data are shown in table (3).The Table lists the stretching frequency (ν) for some of the characteristic groups exhibited by the ligand and complexes.

The formations of these complexes were confirmed by monitoring the changes both in location and intensity of the certain bands.

In the free ligand, the band at 1614cm^{-1} is assigned to the stretching of C=N (22). On complexation, this band is shifted to a lower frequency region. This shift is probably due to the lowering of bond order of the carbon-nitrogen bond resulted from complexation of the metal to the ligand through nitrogen. The frequencies for the ν (N-H) asm. and ν (N-H) sym. in the complex was not seen because it was covered by a broad band appear in the range $(3400-3550)\text{cm}^{-1}$ assigned to -OH stretching of outer sphere water molecules.

Stretching of metal-nitrogen and metal-chloride bonds of the complexes appeared in low frequency regions (23), Table (3).

The molar ratio method and continues variation were followed to detect the ratio of metal ion to ligand of complex (24). Ethanol was used as a solvent. The M: L ratio was found 1:2 to all complexes. The values of magnetic moment and conductivity measurements in table (4) supported the suggested structures.

Table-2:Electronic spectra for L and its complexes in DMF solvent(cm^{-1})

Symbol	Absorption band (cm^{-1})	Transition	B	Dq/\bar{B}	\bar{B}	β	$10Dq$	$15\bar{B}$
L	35,715 37,735	$\pi \rightarrow \pi^*$ $n \rightarrow \pi^*$						
CuL	15,780	${}^2B_{1g} \rightarrow {}^2B_{2g}$ ${}^2B_{1g} \rightarrow {}^2E_g$						
AuL	27,030	${}^1A_{1g} \rightarrow {}^1B_{1g}$						
CoL	6,265 9,346 15,664	$(\nu_1) {}^4A_2 \rightarrow {}^4T_2^{(F)}$ $(\nu_2) {}^4A_2 \rightarrow {}^4T_1^{(F)}$ $(\nu_3) {}^4A_2 \rightarrow {}^4T_1^{(P)}$	1,135	1.2	522	0.46	6,265	16,920
CrL	16,420 22,883 35,568	$(\nu_1) {}^4A_2g \rightarrow {}^4T_2g^{(F)}$ $(\nu_2) {}^4A_2g \rightarrow {}^4T_1g^{(F)}$ (ν_3) ${}^4A_2g \rightarrow {}^4T_1g^{(P)}$	1,030	2.4	684	0.66	16,420	15,450
FeL	20,000 28,517	${}^6A_{1g} \rightarrow {}^4T_{1g}$ ${}^6A_{1g} \rightarrow {}^4T_{2g}$	1300	2.0	1,290	0.99	25,800	19,350

Table -3: The absorption band in infrared spectrum for L and its complexes

Symbol	$\nu(\text{C}=\text{N})$	$\nu(\text{N-H})_{\text{asm}}$	$\nu(\text{N-H})_{\text{sym}}$	$\nu(\text{O-H})$	$\nu(\text{M-N})$	$\nu(\text{M-Cl})$
L	1614	3402	3288	-	-	-
CuL	1608	-	-	3300	483	-
AuL	1605	-	-	3313	480	-
CoL	1607	-	-	3374	480	-
CrL	1606	-	-	3390	480	395
FeL	1606	-	-	3380	483	399

Table -4: Magnetic moment, Conductivity and suggested structures for complexes

Complex	Magnetic moment $\mu_{\text{eff}}(\text{B.M.})$	Conductivity $\mu\text{s.cm}^{-1}$	Suggested structure
CuL	1.11	140	Square planar
AuL	0.99	155	Square planar
CoL	4.35	134	Tetrahedral
CrL	3.80	145	Octahedral
FeL	5.90	156	Octahedral

Antibacterial activity

With a view to explore the possibility of obtaining biologically useful compounds that contain 1,3,4-thiadiazole ring system (25-27), such biological activity prompt us to prepare some new series containing the above mentioned unite. The antimicrobial activity of these compounds was determined by the agar diffusion method ⁽²⁸⁾ used were *Staphylococcus aureus* , *Escherishia coli* , *Pseudomonas aeruginosa* and *Candida albicans* .

In this method a slandered (5mm) diameter sterilized filter paper disc impregnated with the compound (1mg per 1 ml of acetone) was placed on an agar plate seeded with the test organism. The plate were incubated for 24 hours at 37 °C .

The zone of inhibition formed was measured in mm and are represented by (+), (++) , (+++) depending upon the diameter and clarity, Table (5).

Table -5: Antibacterial activity for ligand and complexes at (conc. 1mg/ml)

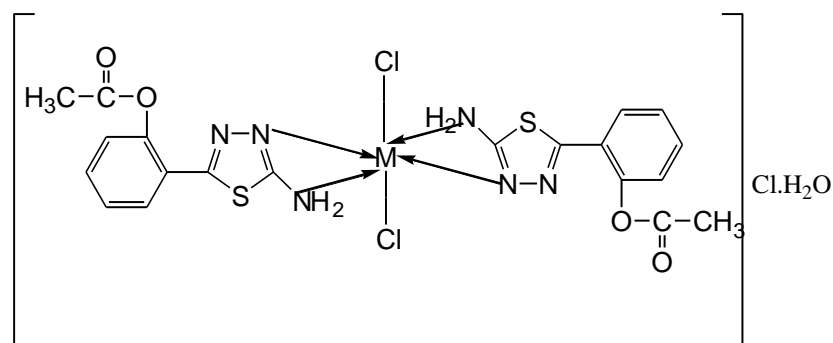
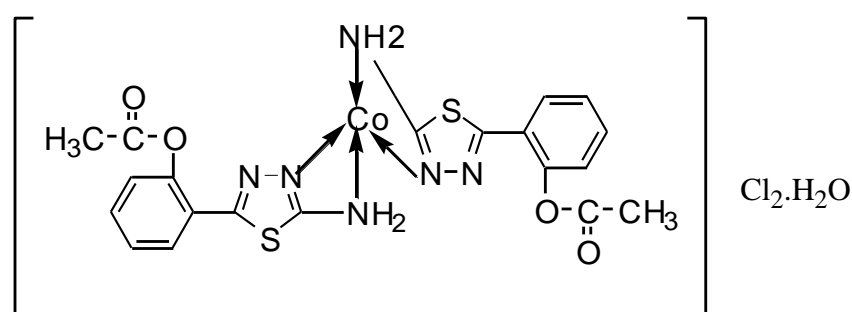
Symbol	<i>Staphylococcus aureus</i>	<i>Escherishia coli</i>	<i>Pseudomonas aeruginosa</i>	<i>Candida albicans</i>
L	+	+++	-	-
CuL	+	+++	+	++
AuL	+	+++	++	+
CoL	++	++	++	++
CrL	+	+++	+++	+
FeL	++	+++	++	+

Note:

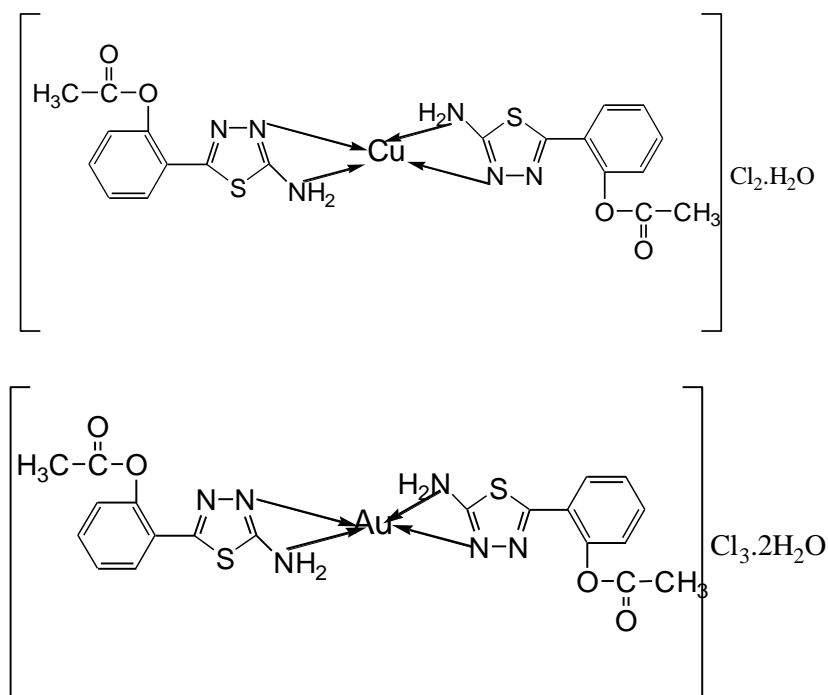
(-) = No Inhibition, (+) = Inhibition zone (6-8) mm, (++) = Inhibition zone (8-10) mm and

(+++)= Inhibition zone >10mm

On the basis of the preceding discussion, the structure of the complexes may be suggested as follow:



Where, M= Cr(III) and Fe(III)



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