Synthesis and Characterization of a New Complex of Cobalt (III) Sulfasalazine

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Abstract

In this work Cobalt(III) Sulfasalazine complex was synthesized and characterized by micro elemental analysis (C.H.N), spectral methods (UV-visible) and (FT.IR) , and other physical measurements (molar conductance in 10^{-3}M solution of ethanol, magnetic susceptibility for solid complex and studied in solution using Job's method to obtain metal to ligand (M:L) ratio for complex in ethanol , Furthermore , Microbial sensitivity test on five microorganisms were tested .

Key words : Sulfasalazine, Cobalt(III) , spectrophotometry , microbial sensitivity .

Introduction

Sulfasalazine (Fig.1,SSZ) is a sulfa drug, a derivative of mesalazine (5-aminosalicylic acid abbreviated as 5-ASA), used primarily as an anti-flammatory agent in the treatment of inflammatory bowel disease as well as for rheumatoid arthritis.[1-4] When dealing with the interaction between drugs and metal ions in living systems, a particular interest has been given to the interaction of metal ions with antibiotics. Antibiotics that interact with metal ions constitute a class of drugs which has been widely used in medicine both towards human beings and animals.[5,6] In particular, the interaction between transition metals and ß-lactamic antibiotics such as cephalexin has been recently investigated by several physicochemical and spectroscopic methods, and with detailed biological data .[7-10] Many drugs possess modified pharmacological and toxicological properties when administered in the form of metallic complexes. Probably the most widely studied cation in this respect is Cu(II), since a host of low-molecular- weight copper complexes have been proven beneficial against several diseases such as tuberculosis, rheumatoid, gastric ulcers, and cancers [11-14]. In the literature survey, there is little attention concerning the mode of coordination of SSZ with metal ions. Previous studies[15-22] of the complexation of sulfa drugs did not focus on the coordination behavior, but only dealt with the solution state and crystal structures of its metal complexes. In this study we synthesized new complex containing Cobalt -Sulfasalazine .We have employed in this current article the coordination mode of (SSZ) complex *via* Co (III). The

solid product was isolated and characterized by some physico-chemical properties , molar conductance and spectroscopic methods .

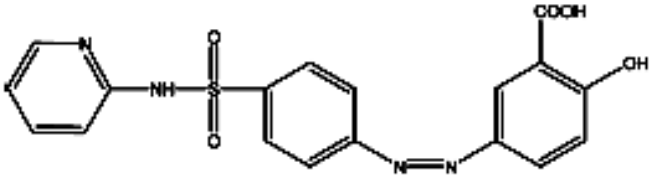

Fig.(1) .Chemical structure of Sulfasalazine

Experimental :-

Apparatus :-

1- Shimadzu – 160A Double beam UV-Visible spectrophotometer.
00 Infrared spectrophotometer .
2- SP3-3
3- Perkin – Elmer 240 Elemental Analyzer.
4- Corning conductivity meter 220.
5- Kent pH meter.

Chemical Materials :-

All chemicals used were of the analytical reagent grade. They include : , ethanol 99 %, $CoCl_2.6H_20$,HCl , and Azulfidine drug (Sulfasalazine) from Pharmacia AB Stockholm
(Sweden) .

Procedure :-

A- Synthesis of complex :-

Co – SSZ complex was prepared as follows : $CoCl_2.6H_2O$ (1mmol) was added with stirring to SSZ (2 mmol) in EtOH (50 ml) , then 1 ml of 1N HCl was added . The mixture was refluxed for six hrs at 80 C^0. To this solution 2 ml of 30% H_2O_2 was added with stirring to complete the oxidation of cobalt, the reaction mixture was refluxed for two hrs and left to stand overnight . The rose precipitate was removed by filtration , washed with EtOH and dried at room temperature.

B- Magnetic Moment

Magnetic moment was performed according to the Gauy method.[23]

C- Conductivaty

The conductivity value was measured in EtOH at room temperature .

D - Determination of stoichiometry of complex :-

Job's method of continuous varations was used to determine the nature of the complex . In this
method a series of mixtures are prepared, which two constituents are present at varying concentrations , but their sum is held constant . 0.01M solutions of

SSZ and Co(II) ions were prepared in EtOH and 0.1N HCI respectively . To five 50ml volumetric flasks 1, 3 , 5 , 7 , and 9 ml of SSZ and then 9 , 7 , 5 , 3 , and 1ml of Co(II) ions were transferand , 5 ml of 30 % H_2O_2 was added with shaking then diluted with EtOH. The sum of the concentrations of the SSZ and Co(III) ions in each flask was a constant as required by the method . the reaction was allowed to proceed to equilibrium at least 30 min .The absorbances of the mixtures were measured at 654 nm .Normally , amaximum appears in the curve at amole fraction corresponding to the complex that forms .

F-Evaluation of the antimicrobial activity:-

The antimicrobial activity of the test compound was assayed against five bacteria. *Escherichia coli (Gram -ve) , Streptococcus, Staphylococcus aureus, Streptococcus and Pseudomonias*, all these organisms, were *(Gram+ve)*. All are regarded as pathogenic to humans and animals. All media and bacteria suspensions were prepared using a method adapted from that of Cruickshank (1965)[24] . About 15 – 20 cm^3 of agar was poured into sterile Petri plates about 10cm in diameter. After solidification of the agar, three cups (10 mm in diameter and 5 mm deep) were removed from each agar dish and fresh bacteria suspension was then uniformly spread on each cup. At this point, each of the cups was spotted three times with test solution at concentration of 50, 100 and 200 $\mu g/cm^3$ in dimethylsulphoxide (DMSO). After incubating the plates at $37C^o$ overnight, the diameter of the zone of inhibition of the bacteria growth was then recorded. A 5% phenol solution was used as a positive control and DMSO as solvent control each time the experiments were performed.

Results and Discussion

Infrared spectrum analysis's

The infrared spectrum of SSZ fig.(2) shows that acid exist as hydrogen – bonded acid characteristically broad hydrogen - bonded stretching bands around 2820 cm^{-1}. This broad band (superimposed on C-H stretching) plus a strong carbonyl band at 1676 cm^{-1} suggests –COOH[25]. In contrast to the assignment data of SSZ-Co(III) Complex fig.(3)
shows no absorption band at 1677 cm^{-1}, characteristic of the ν (C =O)[25] vibration of the carboxylic group (in case of free SSZ ligand), that is indicative of the involvement of the carboxylic group in the coordination with metal ion. A broad diffuse band of strong intensity in the 3410cm^{-1} region may be assigned to the OH stretching vibration for the coordinated and uncoordinated water molecules in the SSZ complex. To ascertain the involvement of OH of phenolic group of SSZ in the coordination process to be followed the stretching vibration bands of ν (C–O) in SSZ complex. Examination of the SSZ complex found that the ν (C–O) is shifted to lower wave number from 1280 cm^{-1} in case

of free ligand to 1193 cm^{-1} in case of complex. This result indicates that the phenolic
group is participated in the complexation and the SSZ ligand acts as bidentate. The lower shift of $\delta(OH)$[25] from 1398 cm^{-1} in the free SSZ ligand to 1375 cm^{-1} in the complex is the another factor confirmation wihch proves the involvement of OH phenolic group in the coordination process. The ν(C=O) vibration located at 1676 cm^{-1} and 1622 cm^{-1} in the SSZ and complex respectively , which renders it difficult to attribute to the involvement of C=O group in coordination . The spectra of complex shows a broad diffuse band of strong intensity in the 3400 cm^{-1} may be assigned to the OH stretching for coordinated and uncoordinated water molecules . Conclusive evidence regarding the bonding of oxygen to the metal ion is provided by occurrence of bands at 493 and 461 cm^{-1} as the result of ν (M-O)[26-27] band , supports coordination by SSZ ligand as a bidentate chelating agent *via* OH of carboxylic and phenolic groups.[28]The infrared spectra of SSZ complex was exhibited with the main of coordination bands which reveals to the mode of bonding are summarized in Table 1.

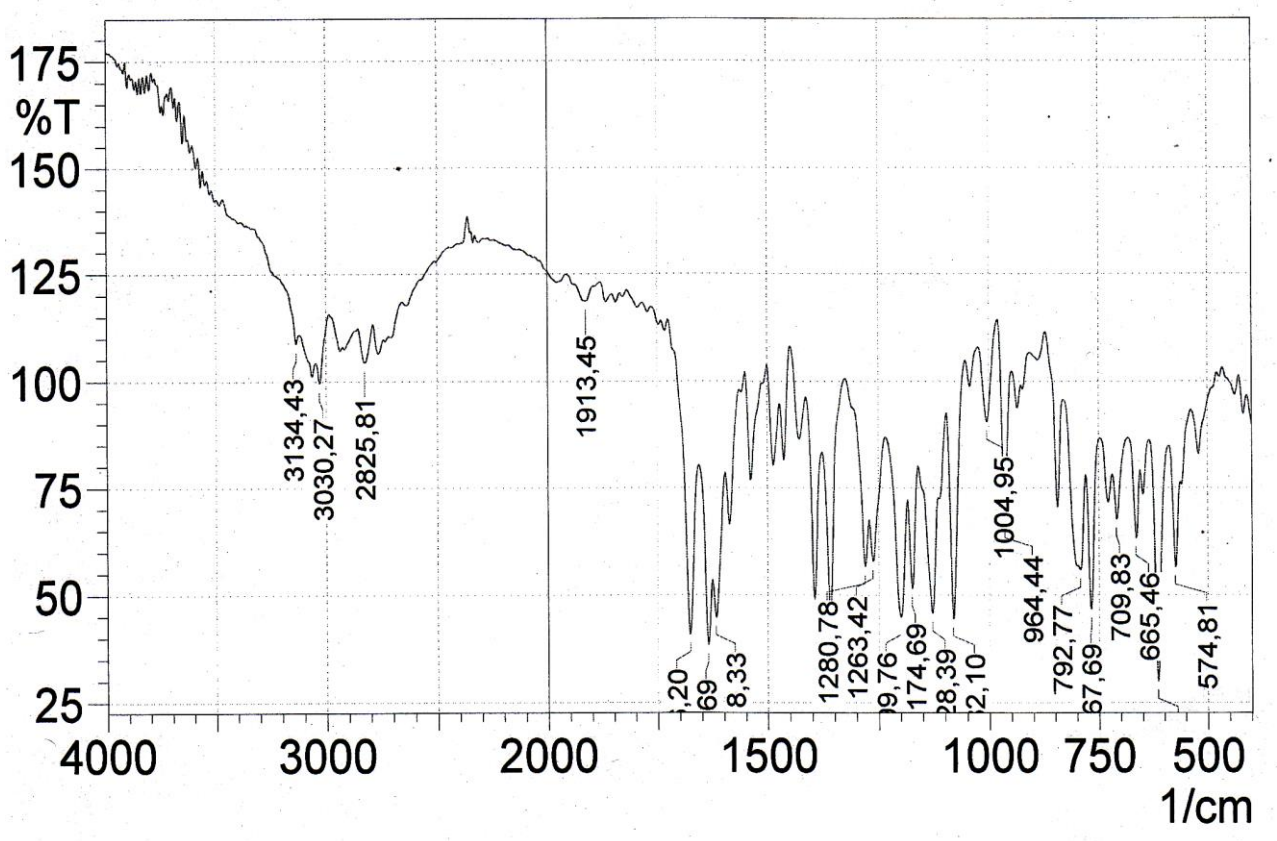

Fig . (2) IR Spectrum of Sulfasalazine (SSZ).

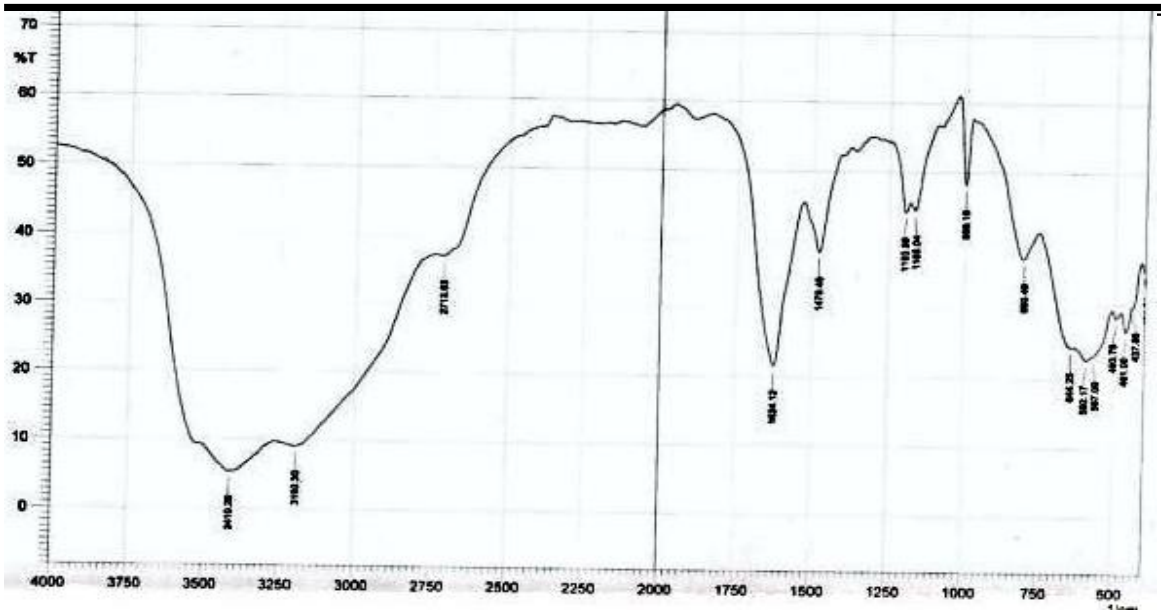

Fig . (3) IR Spectrum of Cobalt – Sulfasalazine (SSZ) Complex.

Table (1). Diagnostic IR data for the SSZ and complex (cm^{-1}).

Compound	C–O cm^{-1}	C–O Δcm^{-1}	δ(OH) cm^{-1}	δ(OH) Δcm^{-1}	νC=O cm^{-1}	νC=O Δcm^{-1}
SSZ Co-SSZ complex	1280 1193	87	1398 1375	23	1676 1622	54

UV–VIS Spectra

The UV/VIS spectra of SSZ and its complex in EtOH are exhibited and the detected peaks are tabulated in Table 3. There are two absorption maxima peaks at ranged from 235 nm and 348— 362 nm, assigned to π –π* and n–π* transitions within the organic moiety of SSZ ligand. The electronic absorption spectra of SSZ complex show a bathochromic shift rather than free ligand within n–π * transition region.[29–33] This shift attributed to the place of complexation and the change in the electronic configuration for the SSZ complex formed. The electronic spectrum with respect to the Co(III)/SSZ complex shows a band of strong intensity at 554 ,654 ,and 659 nm wich is assigned to the transition $^4T_1gF \rightarrow {}^4T_1gP$ (ν_3) , the transition $^4T_1gF \rightarrow {}^4A_2gF$ (ν_2) and $^4T_1gF \rightarrow {}^4T_2gF$ (ν_1) of an octahedral cobalt (III) complex. The spectra of the complex shows different compared to the reagent . Moreover , electronic absorption spectra of the complex , show a band at 652 nm which can be seen clearly , improve that formation anew complex of Co(III) Sulfasalazine complex .

Table(2). Electronic Spectral Data of the Free SSZ Ligand and Its Complex

Compound	λ_{max}(nm)	Assignment
SSZ	235 348 362	π –π* π –π* n–π*
Co-SSZ complex	226 355 554 654 659	π –π* n–π* n–π* n–π* n–π*

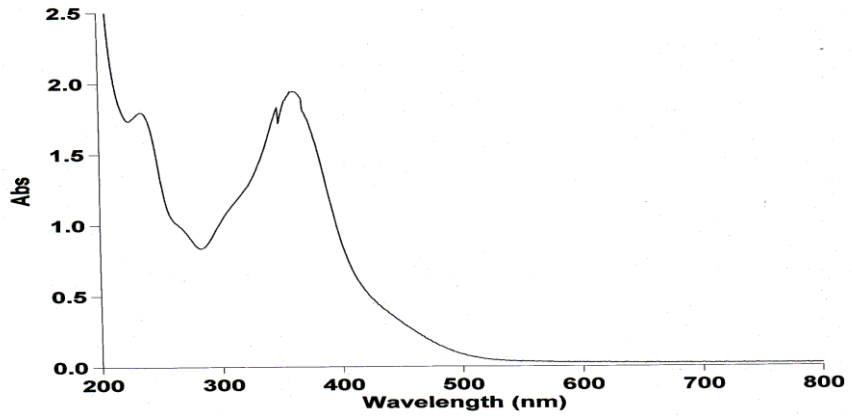

Fig.(4) UV-VIS. Spectrum of Sulfasalazine (SSZ).

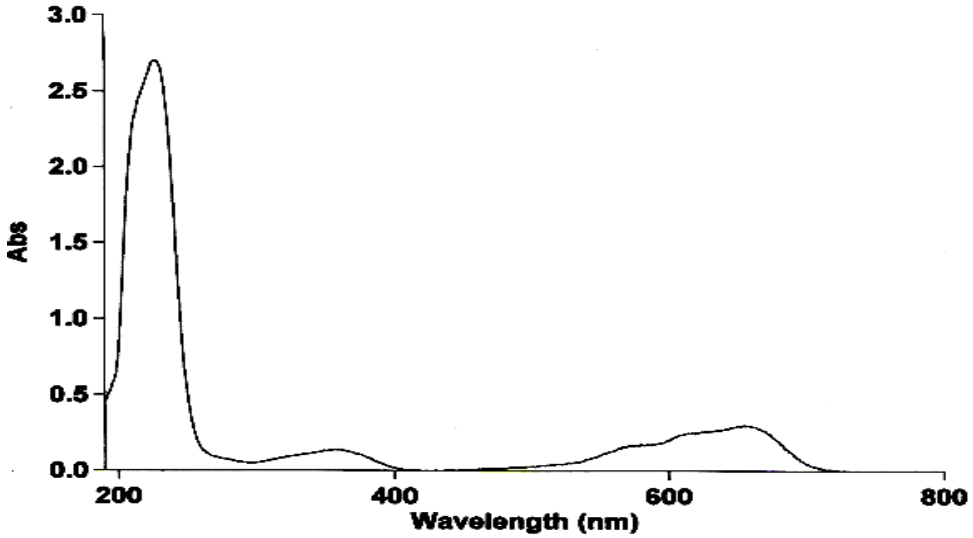

Fig . (5) UV-VIS. Spectrum of Cobalt – Sulfasalazine (SSZ) Complex.

Equation of Reaction :-

General scheme of the reaction is shown in figure (6) . The carboxylic OH group and phenolic OH group of the SSZ are reacted with cobalt ion solution to form complex compound for the metal ion by form six membered ring . The SSZ behaves as a bidentate ligand coordinated to the metal Co(III) through the phenolic OH group and carboxylic OH group .

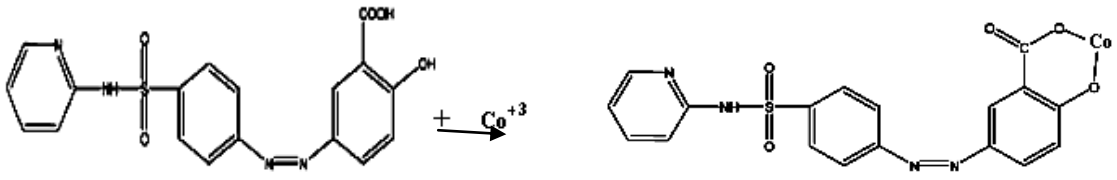

Fig.(6) Equation of reaction

Magnetic moment

The room temperature magnetic moment value for cobalt complex lies within the range for their observed octahedral geometries[34] . The magnetic moment (μ_{eff}) for cobalt complex (0.3 B.M) is expected to contain an even number of electrons .

Molar conductance:-

The conductivity values measured in EtOH at room temperature located of non-electrolyte for Co(III)–SSZ complex. The interpretation concerning the decreasing of conductivity values back to the deprotonation of both OH of carboxylic and OH of phenolic groups for the SSZ ligand. This assumption proves that free ligand acts as a bidentate fashion *via* carboxylic and phenolic groups and also attributed to the participation of carboxylic group as a monodentate chelate.

Element analysis :-

The physical analytical data of complex is given in Table (3) , in a satisfactory agreement with the calculated values . The suggested molecular which is formula also supported by subsequent spectral and magnetic moment , as well as molar conductance.

Table 3 .Magnetic Moment and Anlysis data of the Complex

Complex	Suggested Formula	M.Wt	Microanalysis found (calc) %			μeff B.M	Molar Cond. μscm^{-1}
			C	H	N		
Co(III)–SSZ	$[Co(C_{18}H_{12}N_4O_5S)_2](H_2O)_2$	809	53.39 54.02	3.44 3.32	13.82 13.75	0.3	11

Job's contunious variation method

A Job's contunious variation method plot of spectrophotometric data from varying the Ligand and Co(III) concentrations , showed the existence of a 1:2 complex M:L .

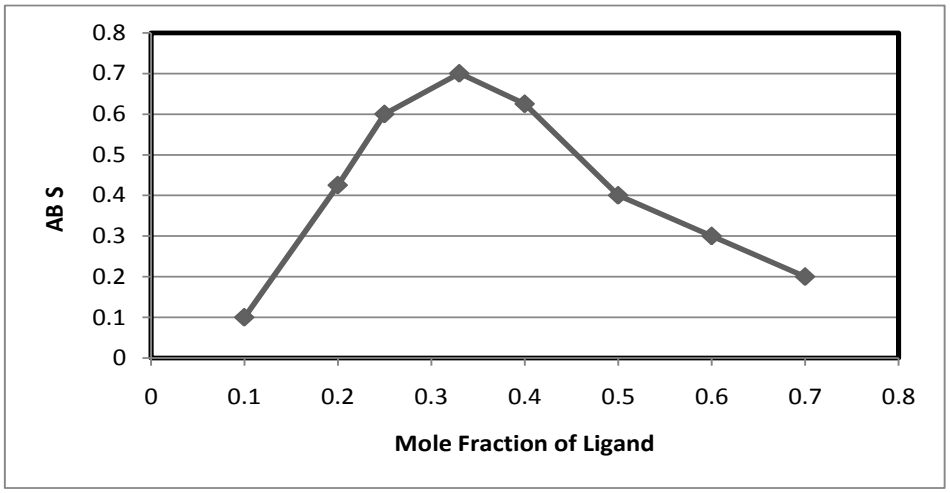

Fig .(7) Determination of Stoichiometry of complex.

Suggested Structural formula of Complex

The structural formula of the complex is given in Fig (8) , it is concluded that from spectroscopic methods analysis, the SSZ behaves as a bidentate ligand coordinated to the metal ions through the phenolic OH group and COOH group of the SSZ . It is known that cobalt metal values in solution commonly exists as either Co(II) or Co(III) and that these two oxidation states have widely different chemistries when complexed by a ligand . Under oxidizing conditions , presence of air , normally Co(II)converts to Co(III) when complexed with a bidentate ligand or chelting agent[35] . One that bonds to metal ion through at least two atoms thereby , forming a chelate ring complex and that Co(III) chelate formed is usually irreversible and not readily strippable . Finally, it is concluded that from magnetic properties , IR and UV-Vis. spectra, the SSZ behaves as a bidentate ligand coordinated to the metal ions of Co (III) through the phenolic OH group and carboxylic OH group (Fig. 6).

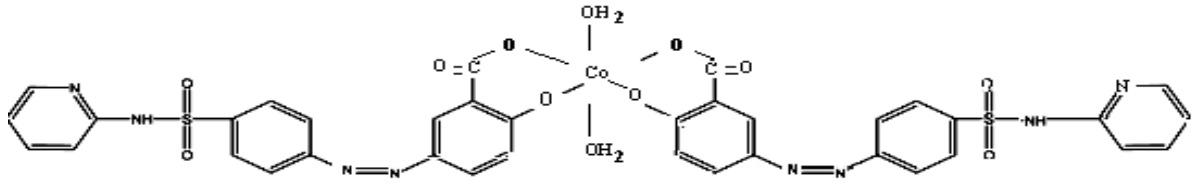

Fig.(8)Structure of Co (III) SSZ Complex

Antimicrobial activity test :-

The microbial sensitivity test carried out on Cobalt (III) complex showed activity on the microorganism under investigation. Table (4), Shows the

microbial sensitivity test against five microorganisms as indicated in the table. The antimicrobial activity was estimated on the basis of size of inhibition zone around dishes . Cultured microorganisms with halos equal to or greater than 5mm were considered susceptible to the test .The minimum inhibitory concentration (MIC) of complex against the tested fungal 50µg/ml ,with further increasing in the concentration of the tested complex a detectable suppression in fungal growth was observed .

Table (4). Microbial sensitivity test for Co – SSZ

Microorganisms	MIC (50µg/ml) Co- SSZ Complex
Escherichia coli	5
Streptococcus	5
Staphylococcus aureus	1.25
Streptococcus	5
Pseudomonias	5

Conclusion

In this study , a new complex of Co(III) – Sulfasalazine was synthesized . Sulfasalazine was reacted with Co(II) ions which converted to Co(III) ions in the presence of air (oxygen source) and H_2O_2 .From magnetic properties and IR and UV-Visible spectra , the SSZ behaves as a bidentate ligand coordinated to the metal ions through the phenolic OH group and carboxylic OH group .

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الخلاصة :

تم في هذا البحث تحضير معقد Co(III) –SSZ ، شخص المعقد بالتحليل الدقيق للعناصر (كاربون،هيدروجين، نتروجين) و الطرق الطيفية (طيف الأشعة تحت الحمراء وطيف الاشعة فوق البنفسجية – المرئية) فضلا عن قياس الحساسية المغناطيسية للمعقد في الحالة الصلبة ، دراسة التو صيل المولاري لمحلول (10^{-3}) مولاري لمذيب الايثانول ، و قيا س طبيعة المعقد المتكون في محلول الايثانول لتعيين نسبة الليكاند : فلز باتباع طريقة جوب . علاوة على ذلك تم اجراء اختبار الحساسية البيولوجية على خمسة أنواع من الأحياء المجهرية .