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Synthesis ,Characterization and antibacterial activity study of Cu(II) and Co(II) complexes with Nystatin

Iman A.J.AL-Timimi
Department. of Chemistry,College of Science,University of Basrah
E-mail: imanjaffer@yahoo.com
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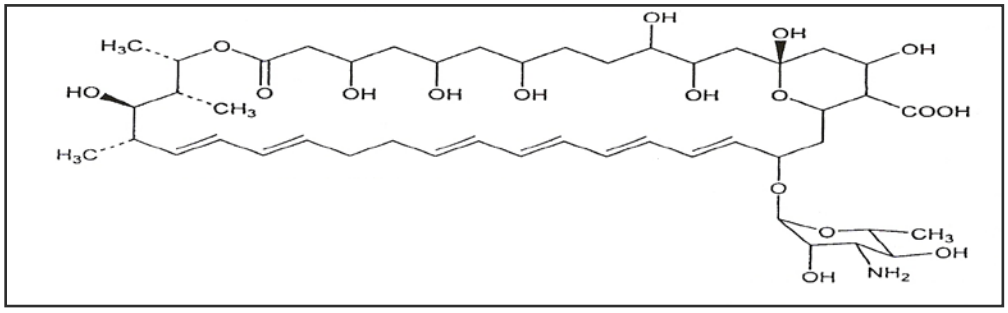
Abstract

Cu(II) and Co(II) complexes were prepared by the reaction of metal ions with Nystatin in (1:1) and (1:2) metal ratio, respectively. These complexes were characterized by IR ,UV-Vis spectroscopy and conductivity measurements.All complexes shows relatively high antibacterial activity against***S.aureus*** and***E.coli*** whereas Nystatin has no antibacterial activity against the same bacteria. All complexes are weak electrolytes in DMSO solution .
Keywords. Nystatin, Copper (II) complexs ,Cobalt (II) complexs , antibacterial.

1.Introduction

Nystatin is a polyene antibiotic of broad antifungal spectrum and it inhibits many fungi, including ***candida .sp***, dermatophytes, and organisms producing deep mycoses in humans.Nystatin has no effect on allbacteria.The important chemical properties,the mode of action and development of resistance of Nystatin were studied extensively[1,2]. Nystatin derivatives containing an amino suger moiety and carboxylic group are useful in the treatment of fungal infections[3-5]. Metal ions (Mg(II),Ca(II),Zn(II) and Ni (II) complexes have been studied and discussed in the light of polyene mode of action theories [6].The aim of this work is to prepare four complexes of Nystatin and study their antibacterial activity .



Scheme 1 Nystatin

2 . Experimental

The sodium salt of Nystatin was prepared by gradually adding (15)drops of (0.1)N NaOH to the equeous solution of(0.5g,0.539mmol) Nystatin until pH=9 with stirring for (10)min.

Cu(II) complex(1:1) was prepared by the reaction of sodium salt of Nystatin solution with (o.2 g,1.174 mmol) of cupper chloride in (10) ml H_2O at room temperature in basic solution.The reaction mixture was stirred for about (15) min,green precipitate formed was filtered ,washed with methanol and dried [7]. All other complexes were prepared in the same method and Table (1) outlines the mole ratio for complexes. The Molar conductivity and pH values for all complexes were measured in dimethyl sulfoxide (DMSO) [8] and the cell constant was ($1cm^{-1}$) at 40C . Infrared spectra were recorded by a FTIR shimadzu8000 model,usingKBrdisk.UV-Vis spectra were recordered by spectrophotometer SC, using (1)cm quartz cell.

Table 1 . Mole ratio for Cu(II) and Co(II) complexes with Nystatin.

Complexes	$CuCl_2$		$CoCl_2$	
	gm	mmol	gm	mmol
Cu 1:1	0.2	1.174		
Cu 1:2	0.045	0.2642		
Co 1:1			0.1284	0.539
Co 1:2			0.06422	0.2699

2.1 .Determination of the biological activity for Cu(II)and Co(II) complexes with Nystatin

A filter disk assay was used to determine the biological activity of the Nystatincomplexes against strains of gram positive and gram negative bacteria which are (***Staphylococcus aureus*** and ***Escherichia coli***) which were tested using plates of Muller- Hinton agar .Thebiological activity was defined as the clear zone of growth inhibition [9] .

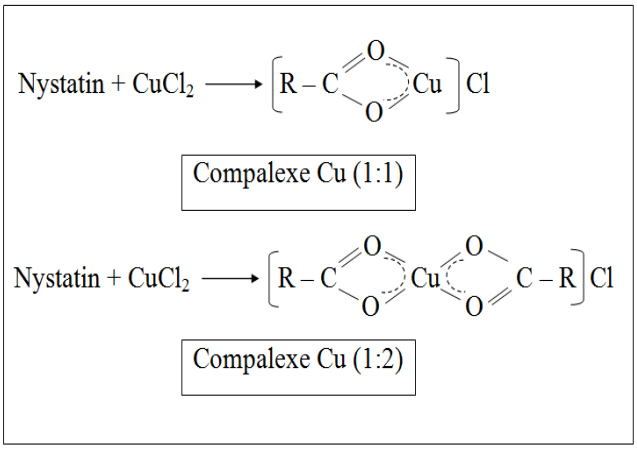
2.2 .The minimum inhibitory concentration forthe Cu(II) and Co(II) complexes withNystatin

The minimum inhibition concentration (MIC) for complexes with Nystatin was estimated according to the method ofCollee**[9] ,** against types of clinical strains of bacteria, with defferent concentrations of

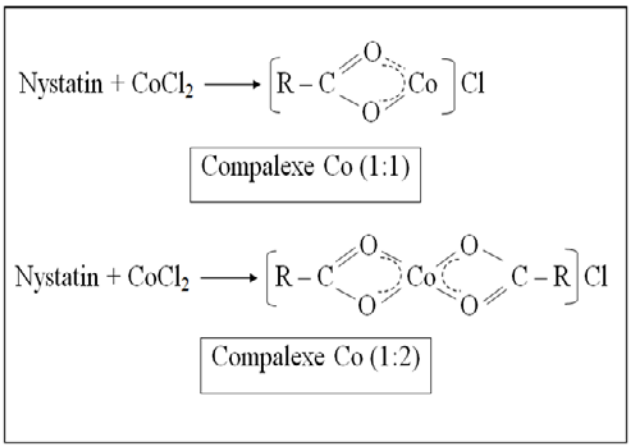
the complexes ranging from (1.08 – 20.1) mg/ml.

3.Results and discussion

The scheme (2,3) shows the preparation of Cu(II) and Co(II) complexes with Nystatin (----RCOOH) using NaOH.



Scheme 2



Scheme 3

Two regions in the FTIR spectra of the prepared complexes have proven the structural characteristics of these complexese .These bands which can coordinate to copper ion and cobalte ion via the carbocxylic group in Nystatin because Cu(II)is hard acid.Therefore coordinate with hard base and (O) atom is harder than (N) Atom.The carbonyl group was shifting between (1655-1648)$cm^{-1}$for Cu(II) complexes and between(1655-1646) $cm^{-1}$for Co(II) complexese. The bands absorb between (1164-1176)$cm^{-1}$for (C-O) group8 (Table 2). .The FTIR spectra of the prepared complexes were explained in Fig.(1-5) .

Table2. FTIR bands(cm^{-1}) for Cu(II) and Co(II) complexes with Nystatin

complexes	$\upsilon_{C=O}$	υ_{C-O}
Ligand	1655	1164
Cu(1:1)	1646	1172
Cu (1:2)	1648	1170
Co(1:1)	1647	1172
Co(1:2)	1646	1176

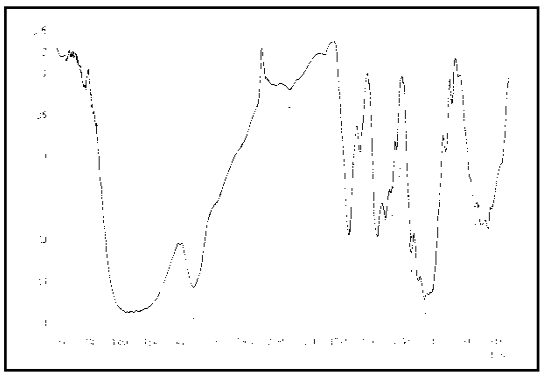


Figure 1. IR spectrum of free ligand

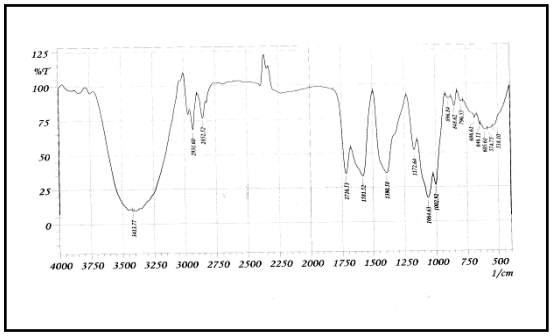


Figure 2. IR spectrum of Cu(1:1) complex

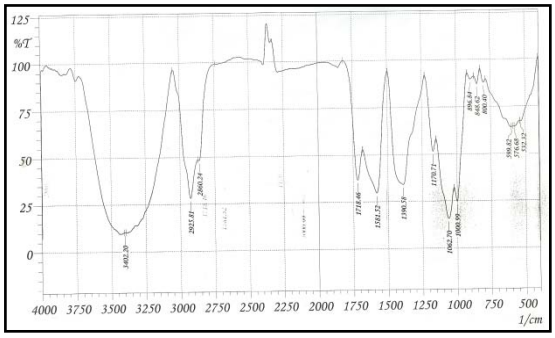


Figure 3. IR spectrum of Cu(1:2) complex

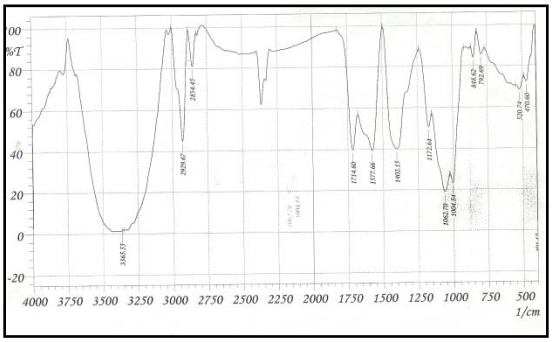


Figure 4. IR spectrum of Co(1:1) complex

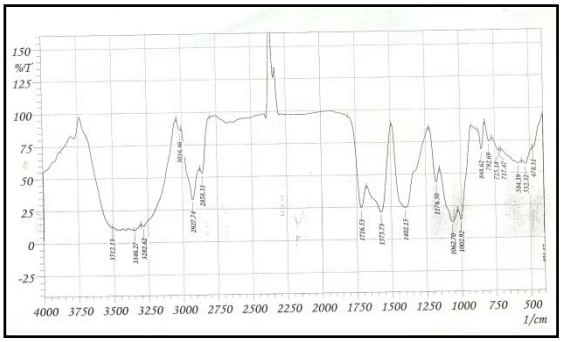


Figure 5 . IR spectrum of Co(1:2) complex

The electronic spectra of these complexes led to bands for(π-π^*) ,(n-π^*) and (d-d) transitions. The (€ and ΔE) were calculated in Table(3).

Table 3. UV-Vis data for Cu(II) and Co(II) complexes with Nystatin

Complexes	€ ($mol^{-1}.cm^2$)	ΔE (cm^{-1})	λ_{max} (nm)	C (M)
Cu(1:1)	66.66	16393.44	570,590,610	0.00210
Cu(1:2)	127.10	15384.61	590,630,650	0.00107
Co(1:1)	145.70	19801.98	505	0.00221
Co(1:2)	425.84	500000	500	0.000681
Ligand			291,305,319	0.0010

All the complexes are weak electrolyts,usingKolorashequation[8] . The values of molar conductivities (1.6-4.7).10^{-6} Ω^{-1} in (DMSO) solution correspond to these results. Co (II) complexes are relatively better electrolytes because the values of molar conductivities are slightly higher than that of Cu(II) complexes .The lower ionic mobility of bulky Nystatin ion gives lower values of molar conductivity in all complexes.

On applying Ostwald equation for these complexes,the dissociation constant for Cu(II)complexes are higher than Co(II) complexes which coincide with the values of dissociation constants [10,11] ,as shown in Table(4) .

Table 4. Molar conductivity and Dissociation Constant for complexes.

Complexes	Conc.	$G(\Omega^{-1}).10^{-6}$	pH	$Kd.10^{-3}$ $(mol.cm^{-3})$
Cu(1:1)	0.00229	1.6	9.3	2.65
Cu(1:2)	0.00115	1.1	9.6	0.0425
Co(1:1)	0.00221	5.2	9.4	0.206
Co(1:2)	0.00119	4.7	9.3	0.08

3.1 .The biological activity of the Cu(II) and Co(II) complexes with Nystatin

The results of antibacterial activity of the complexes were shown in Table (5) and Figure(6). Nystatin is not active against bacteria ,because it acts by binding to specifc sterol present only in plasma of fungi 12 ,but the bacteria membrane is not injured by Nystati[13]. Generally, all bacteria tested were more sensitive to Cu(II)complexese than Co(II) complexese.The Cu(1:2) complex was very effective against gram positive strain(***Staphylococcus aureus***) but less active against gram negative strain (***Escherichia coli***).It has been postulated that cell membrane of (***Escherichia coli***)contains many condensed fat layers compared with(***Staphylococcus aureus*** [14] . The Co(II) complexes are very active against selected bacteria .Accordingly, this model predicts that the change in their structure of complexes with Nystatin containing an non polar part(hydrophorbic) in a large ring (haydrocarbonic chain) and polar part (hydrophilic) (a conjugated –double bond- system , the ionic species such as($-NH_2$,-OH ,Cu (II) or Co (II)) in the molecule is responsible for the absorption by the cell membrane of the bacteria [13] .Chemicals and antibiotics or antiseptics face difficulty in penetrating these membranes and, therefore, their effectiveness is diminished.

Table 5. The biological activity of the complexes.

Bacterial strains	Inhibition zone (mm)			
	Co 1:2	Co 1:1	Cu 1:2	Cu 1:1
S. aureus	15	15	30	7
E. coli	17	15	20	15

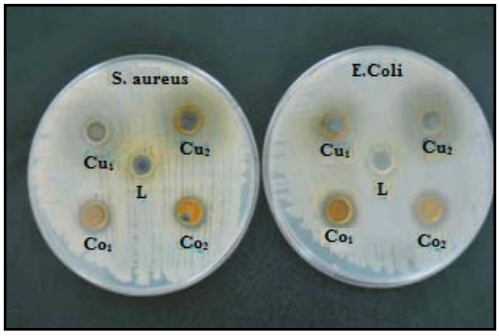


Figure 6:- The in hibition zone frmed Cu(II) and Co(II) activity against some selected bacteria.

3.2 .The minimum inhibitory concentration for Cu (II) and Co(II) Complexes with Nystatin

Table (6)obtainedfromtheanalysis of Figures (7-9), shows that the results of the MICvalues for complexes against selected bacteria were varied (10) mg/ml.The complexes appeared to have high antibacterial activity, this may be justified due to the ionic

combination between each complex and the phospholipids of the bacterial cell wall, which led to destroy the cell membrane and then led to inhibit the microbial growth and may change the cell protein nature (Denaturation) and increase the permeability of the cell membranes [15] ,as many types of antibacterial compounds [16] .

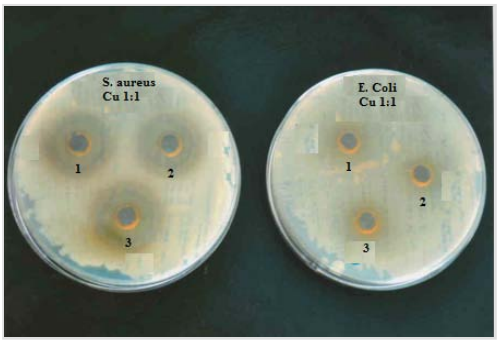


Figure 7. The (MIC) fromed from Cu (1:1) complex against some selected bacteria.

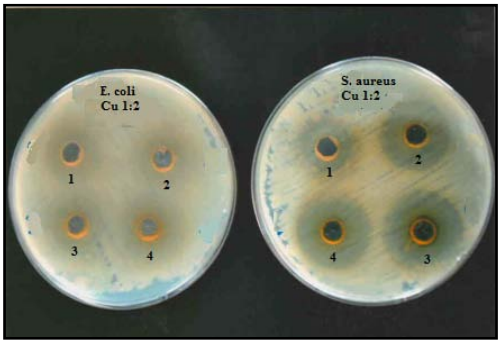


Figure 8. The (MIC) fromed from Cu (1:1) complex against some selected bacteria.

Figure 9. The (MIC) fromed from Co (1:1) and Co (1:2) complex against some selected bacteria.

Table 6. The minimal inhibitory concentration of complexes.

Bacterial strains	MIC (mg/ml)			
	Cu 1:1	Cu 1:2	Co 1:1	Co 1:2
S. aureus	10	10	10	10
E. coli	10	10	10	10

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تحضير وتشخيص ودراسة الفعالية البايلوجية
لمعقدات النحاس الثنائي والكوبلت الثنائي مع النستاتين

أيمان عبدالله جعفر التميمي

قسم الكيمياء – كلية العلوم – جامعة البصرة

المستخلص

تم في هذة الدراسة تحضير بعض معقدات النحاس الثنائي والكوبلت الثنائي مع النستاتين بنسب مولية (1:1) و(2:1) . شخصت المعقدات المحضرة من خلال مطيافية تحت الحمراء والمطيافية المرئية وقياسات التوصيلية , ومن ثم تم دراسة فاعليتها تجاه البكتيريا *E.coli* و *S. aureus* . تبين من هذة الدراسة ان جميع المعقدات المحضرة ذات فعالية عالية نسبيا ضد البكتريا المدروسة بينما لم يظهر النستاتين أي فعالية ضد نفس البكتريا. كما تبين أن جميع المعقدات المحضرة هي ألكتروليتات ضعيفة في محلول DMSO.

الكلمات المفتاحية : النستاتين, معقدات النحاس الثنائي ,معقدات الكوبلت الثنائي, الفعالية البايلوجية.