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Synthesis Characterization and Antibacterial Evaluation of Cephradine and Ceftriaxone Schiff Base Copper Complexes

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Abstract

In the present study, new Schiff bases were synthesized from condensation of cephradine and ceftriaxone with Terephthalaldehyde and their corresponding metal complexes with copper (II) have been synthesized. Assignment of Schiff bases and their copper complexes was performed by FT-IR, elemental analysis and [1] H NMR analysis. Their antibacterial activity were assessed against several bacterial strains namely *S. aureus*, *E. coli* and *P. aeruginosa*. The antibacterial screening tests reveal that both Schiff bases and their copper complexes counterparts exhibited promising antibacterial activity against the tested bacterial species so that they are of improved antibacterial activity than the parent drugs.

Keywords: Schiff base; Cephradine; Ceftriaxone; Metal complexes; Terephthalaldehyde

Introduction

Imines are products of the condensation reaction of primary amines with aldehydes or ketones which is represented by a characteristic C=N double bond [1]. Schiff bases are interesting compounds due to their variety of applications in the biological field as well as industrial applications. They have been found to own wide range of pharmacological activities such as antibacterial, antifungal, antineoplastic, anti- inflammatory, antimalarial, ant tubercular, and antiviral etc. They also can be utilized in the synthesis of various heterocyclic compounds [2-4]. It is well known that the presence of metal ions linked to pharmacologically active Schiff base compounds may improve their activities [5,6]. Cephalosporins are bactericidal antibiotics and amongst the safer antibiotics in clinical use, however their extensive use has resulted in a significant problem of drug resistance. Many strains of bacteria have developed resistance to the many members of Cephalosporin [7,8]. Schiff base and their corresponding metal complexes preparations are among the strategies that have been experienced and attempted to overcome the problem of bacterial resistance and promote the activity, or to extend the spectrum of drugs [9,10]. Schiff bases derivatives of certain cephalosporin antibiotics have been synthesized together with their metal complexes and both Schiff base and their metal complexes are assessed for their antimicrobial activity against selected strains of bacteria from both Gram positive and Gram negative bacteria.it is generally found that These derivatives showed enhanced antibacterial activity in the following order: metal complexes > Schiff base ligands > parent drugs [8,10-13].

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These findings may be interpreted depending on the overtone concept and chelation theory, which indicates that metal complexes' lipophicity is raised on chelation. This raised lipophilicity promotes the partitioning of complexes into the biological membranes in addition to hindering of the binding sites in enzymes of microorganisms [10,14-18].

Some antibiotics like penicillin, Streptomycin, aspergillic acid, and tetracycline possess chelating properties. There is evidence that that resistance to antibiotics has emerged by certain bacterial strains through an alteration of their own enzyme systems that can compete successfully with the antibiotics. The chelating potential of antibiotics may be utilized in the diffusion of metals across biological membranes or to bind the antibiotic to a specific site from which it can disrupt the bacterial growth. Schiff base derivatives have chelating abilities can benefit from this property to overcome resistance problem [12,17,18].

Experimental

Materials

All chemicals and solvents used were of analytical grade (Merk, Fluka and Sigma- Aldrich) and were used without further purification.

Measurement

Melting points were measured by open capillary method and are uncorrected (TABLE 1). IR spectra were obtained on Perkin Elmer IR spectrophotometer (KBr disc) in faculty of pharmacy/ university of kufa. Elemental microanalysis was accomplished at the Jordanian University using CHN Elemental Analyzer (Euro-vector EA3000A, Italy). Nuclear magnetic resonance spectrum [1] H NMR for schiff base and copper complexes was recorded in DMSO-d6 using a Bruker 500 MHz instrument using a tetra methyl silane (TMS) as an internal standard in Tarbiat Modares University (TABLE 2).

TABLE 1: **Physical properties and micro analytical data of ligand and its metal complexes.**

Complexes	Color	Melting point	Percent of yield	Elemental analysis Found (calculated)%			
				C	H	N	M
Terephthalaldehydeneceftriaxone L1	yellow	228	73	43.16 (-43.77)	2.97 (-3.17)	18.77 (-18.56)	-
Terephthalaldehydenecephradine L2	yellow	245	67	6.53 (-60.29)	4.76 (-5.06)	9.95 (-10.55)	-
Terephthalaldehydeneceftriaxone-(II)	Light green	312	61	38.95 (-39.39)	3.07 (-2.85)	16.28 (-16.7)	4.32 (-4.74)
Terephthalaldehydenecephradine-(II)	Light green	287	62	51.06 (51.58)	3.81 (4.33)	9.29 (9.02)	6.48 (6.82)

TABLE 2: **IR spectral data of the synthesized compounds.**

Compound	C=O	C=N	M-N	M-O
Terephthalaldehydeneceftriaxone	1653	1615	-	-
Terephthalaldehydenecephradine	1647	1623	-	-
Terephthalaldehydeneceftriaxone-Cu	1635	1605	467	435
Terephthalaldehydenecephradine-Cu	1627	1582	497	416

Preparation of Schiff base ligands

Two series of Schiff base ligands were synthesized by reacting each drug substances with Terephthalaldehyde separately. They were prepared as follows. Terephthalaldehyde (1 mmol) dissolved in 25 ml of absolute methanol then added dropwise to the solution of either Cephradine or Ceftriaxone (2 mmol). To this mixture, 0.1% KOH (in methanol) was added to set the solution between pH 7 and 8 and the mixture was refluxed for about half an hour in case of Cephradine and 4 hours in case of Ceftriaxone. A clear, yellow colored solution was obtained. Then the volume was reduced by vacuum evaporation and the formed crystals of ligand was isolated and dried under vacuum and kept away from moisture till further use.

Preparation of Schiff base copper complexes

The Schiff base ligands (2 mmol) dissolved in 25 ml of absolute methanol to which methanolic solution of the copper chloride Cu (II), (2 mmol) was added. The reaction mixture was refluxed for 4 h. a dark colored products was isolated after reducing the solvent volume by evaporation, then the products were filtered, washed several times with methanol and then dried under vacuum.

Antimicrobial activity

The synthesized Schiff bases and their copper complexes were assessed for their in vitro antibacterial activity against some selected microorganisms, especially against one gram positive bacteria staphylococcus aureus and two gram negative bacteria Escherichia coli and Pseudomonas aeruginosa by measuring the zone of inhibition in mm. The antibacterial activity was accomplished by filter paper disc plate method at concentration 100 µg/mL and reported in TABLE 3. Muller Hinton agar & Sabouroud Dextrose agar were used as culture medium and DMSO was the solvent control for antimicrobial activity.

TABLE 3: **The antibacterial activity of ligands and complexes**

Compound	***S.aureus***	***E. coli***	***P. aeroginosa***
Ceftriaxone	22	28	20
Cephradine	14	13	16
Terephthalaldehydeneceftriaxone	28	33	22
Terephthalaldehydenecephradine	16	14	19
Terephthalaldehydeneceftriaxone-Cu	29	35	25
Terephthalaldehydenecephradine-Cu	21	19	24

Results and Discussion

The Schiff base metal complexes were obtained by refluxing the copper chloride anhydrous with Schiff base ligands in methanol. The solubility of schiff bases and complexes was checked in water and number of organic solvents. The ligands were soluble in water, methanol, DMF (Dimethylformamide) and DMSO (Dimethyl sulfoxide), while metal complexes were soluble in DMF and DMSO but not in other organic solvents. The ligands and complexes were found to possess certain degree of hygroscopicity.

It is possible to investigate the bonding of ligands to the metal elements from the comparison of FT-IR spectra of the ligands to those of metal complexes counterparts. The absorption bands indicate the formation of free ligands through the –C=N- bond and the coordination of those ligands with cupric ions through nitrogen and oxygen (FIG. 1).

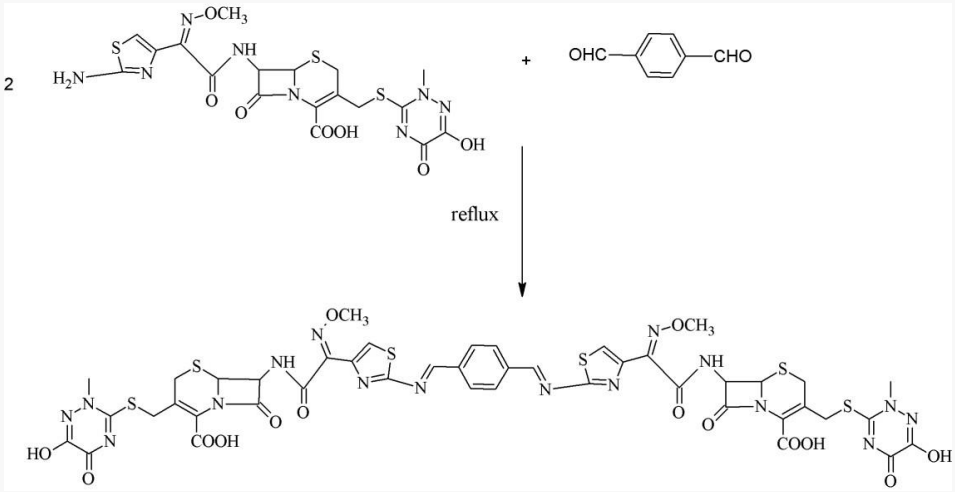

FIG. 1. **Bonding of Ligands to Metal Complexes.**

The free ligands have absorption bands in the range of 1610-1650 for azomethine group which are shifted to slightly higher values in metal complexes to propose the coordination of schiff bases with cupric ion through –N=C-. This contrasts with bands due to the carboxylic acid group which is not shifted to indicate the in participation of this group with the metal ion. The appearance of new absorption bands in the range of 460-510 for (M–N) and 410-440 for (M-O) elicit the coordination of the ligands with the metal ion through N and O atoms (FIG. 2).

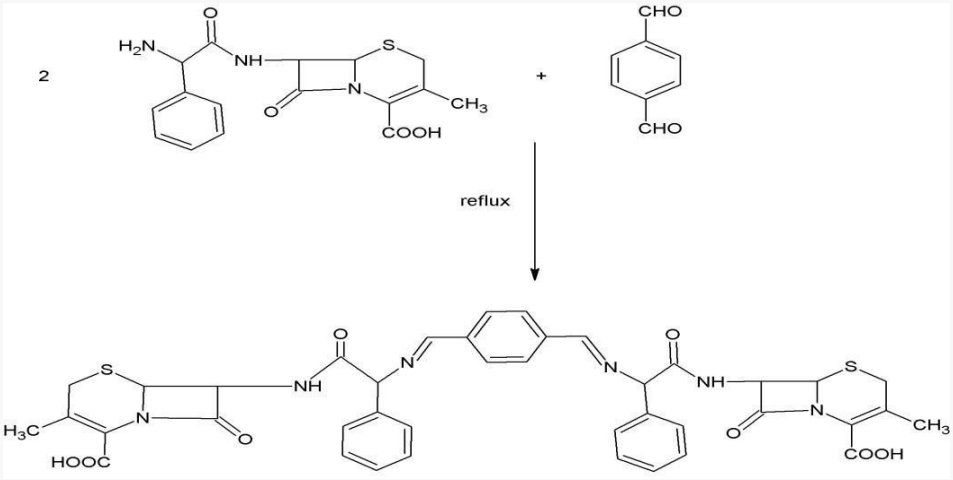

FIG. 2. **Coordination of Ligands with Metal Ions.**

The 1H NMR spectrum of L1 displayed a signal existed at δ (2.73) ppm which was assigned to the chemical shift of protons S-CH2 on the dihydrothiazine ring. The signals found at δ 4.55, 4.32 and 9.14 ppm were related to chemical shifts of the protons of N-CH and CO-CH on the beta-lactam ring and NH proton of amide respectively. The signals belong to protons of methyl group were observed at the range (3.38-3.75) ppm. The signal attributed to the proton of thiazole ring observed at δ 8.23 ppm. Signals related to the azomethine proton and aromatic protons found at δ 8.76 ppm and 6.72-7.85 (m) respectively. No signal occurred in the spectrum due to the free amino group of ceftriaxone which advocate the utilization of this group in the schiff base formation. The 1H NMR spectrum of the Cu (II) complex of L1 in DMSO demonstrated signals observed at δ (6.67-7.82), 4.91, 5.16 and (3.21-3.74) ppm and were assigned to chemical shifts of the protons of aromatic moiety, protons of CO-CH and N-CH on the beta-lactam ring and protons of methyl group respectively, while the NH proton of the amide and azomethine proton appear at δ 9.65 and 8.56 respectively [19-22].

The 1HNMR spectrum of L2 demonstrated signals that belong to the NH proton of amide, proton of azomethine and aromatic protons at δ 9.18, 8.95 and (6.75-7.81) respectively. The signals related to the chemical shift of protons of S-CH2 on the dihydrothiazine ring, protons of CO-CH and N-CH on the beta-lactam ring were observed at δ2.67, 4.83 and 5.15 respectively. Chemical shifts of CO-CH of the acyl side chain and protons of methyl group were observed at δ4.98 and 2.15 respectively. The signal belong to the free amino group of cephradine did not appear which support the utilization of this group in the schiff base formation. The 1H NMR spectrum of the Cu (II) complex of L 2 in DMSO elicited signals appeared at δ 2.27, 3.15, 5.38 and 5.11 and were assigned to chemical shifts of methyl protons, S-CH_2 protons on the dihydrothiazine ring, protons of N-CH and CO-CH on the beta-lactam ring respectively. The signals related to the chemical shift of the proton of amide group NH, proton azomethine, CO-CH of the acyl side chain and aromatic protons appeared at δ9.45, 8.86, 5.45 and (6,67-7.79) respectively [19-22].

Conclusion

Schiff bases of Terephthalaldehyde with either ceftriaxone (LI) or cephradine (LII) were successfully synthesized and their structures were confirmed by elemental analysis, NMR and FTIR spectra. The elemental analysis suggest that the 1:2 (ML2) coposition of the Schiff base metal complexes where “M” represents transition metal ion and “L” represents the uncomplexed Schiff base ligand, proving that two Schiff base ligands are coordinated with the central metal ion ligand via "N" and "O" atoms, which is supported by the FT-IR spectral analysis.

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