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Research Article

Synthesis, characterization and antimicrobial studies of schiff base transition metal complexes of Cr (II), Mn (II), Co (II), Ni (II), Zn (II) and Cd (II) derived from cefadroxil

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Abstract

In this study, the complexes of transition metals such as Cr (II), Mn (II), Co (II), Ni (II), Cu (II), Zn (II) and Cd (II) are synthesized from Schiff base(derived from cefadroxil). The techniques such as elemental analysis, TGA and DTA, UV-Spectral study, molar conductivity, atomic absorption spectroscopy and FTIR have been used for the characterization of Schiff base and the metal complexes. The compositions of the complexes are found to be ML_2 ratio. The IR study shows that ligand is bi-dentate and have coordinate bonds to metal atom by N-azomethine and phenolic-O. The conductivity test of Schiff base and metal complexes show non-electrolytic nature. The thermal analysis data shows that water molecules have coordinate bonds with transition metal atom or ion. The antibacterial study of both Schiff base and metal complexes are made and they were found to be better than the parent antibiotic.

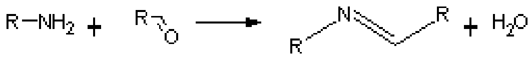
Key words: Synthesis, Characterization, Antibacterial, Schiff base, Complexes, Cefadroxil

1. Introduction

Schiff bases are very important compounds and are being used in various fields, especially the Schiff bases derived from the aromatic amines and aromatic aldehydes have various applications in different fields including biological, inorganic and analytical chemistry[1,2]. They are used in many enzymatic reactions having interaction of amino group of an enzyme, that is generally a lysine residue and its respective substrate have a carbonyl group[3]. Schiff bases have the great important as ligands when they are derived form pyridoxal (a active form of vitamin B_6) and amino acids in the biological point of view[4]. In the processes of non-enzymatic glycosylations they act as intermediates[5].

There are many biological applications of the Schiff bases. A further significant role of Schiff base structure is in transamination[6]. Transamination reactions are catalyzed by a group of enzymes called transaminases. Transaminases are found in mitochondria and cytosal of eukaryotic cells.

Schiff bases are normally produced by the condensation of a primary amine and an aldehyde or ketone. The consequential compound is called a Schiff base, named after the scientist who synthesized it first.



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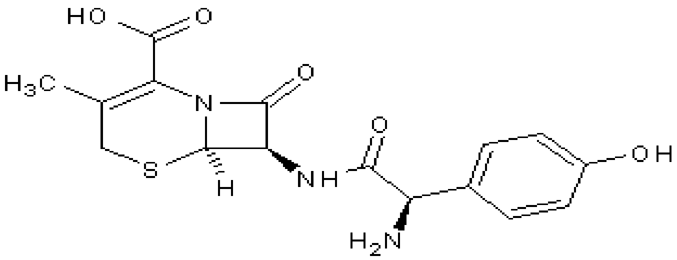
Here "R" may be an aliphatic or an aromatic group. Normally they are bidentate, tridentate, tetradentate, or polydentate ligands and they can form very stable complexes with transition metals.

Cefadroxil monohydrate is a semi-synthetic cephalosporin, it is effect via oral route in the case of sensitive gram-positive and gram-negative organisms[7]. IUPAC name of cefadroxil is (6S,7S)-7 {[amino(4hydroxyphenyl)acetyl]amino}-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0] oct-2-ene-2-carboxylic acid. The structure and the formula is given below.(Fig 1-3)

Fig 1 Structural formula of Cefadroxil



Cefadroxil is the para hydroxyl derivative of the cefalexin. Cefadroxil shows the antibacterial activity against the clinically isolated of different kinds of bacteria as similar to cefalexin and cefradine[7]. There are a number of antibiotics which can bind with the metal ions through the electron donor groups or atoms such as cephalosporins and their decomposition products are included in the afor-said. Such combination form chelates and the metals ions can cause reduction of these antibiotics in the intestinal absorption by forming their chelates. Cefadroxil (antibiotic) also forms complexes with various metal ions or atoms[8] and their characterization can be carried out by the electrophoresis[9]. Cefadroxil shows little solubility in water but it is soluble in alcohol and ether. It gives an orange color with the H_2SO_4.

2. Experimental

The chemicals used in this research were analytical grade they were obtaind from E.Merck/BDH. Ofloxacin was obtained from Pharmagen Beximco, Pakistan and was used without further purification. The IR spectras of the ligand and the complexes are recorded from the IR Prestge-21, SHIMADZU. UV spectras are obtained from UV-1700, SHIMADZU. Elemental Analysis is done from CHNS-(England). Atomic absorption data obtained from AA-6300, SHIMADZU and TGA and DTA spectras are obtainde from SDT Q 600, SHIMADZU. The antibacterial activity was determined by the Disc Diffusion Method[10].

2.1 Synthesis Schiff base

Cefadroxil 0.386g was dissolved in the methanol (about 25 cm^3), then mixed with the salicylaldehyde which was 2 m mol or 0.2092 cm^3, also dissolved in methanol(25 cm^3). Then one percent solution of potassium hydroxide(prepared in methanol) was added to adjust the $_pH$ of solution in the range of 7-8 and after that the refluxation process was carried for about 30 min. The resultant had brown color and isolation of ligand was carried out by reducing the volume of the resultant via evaporation process. To dry, the product was dried out under vacuum and reserved in a desicator untill further use[11].

2.2 Synthesis of Metal Complexes

Cefadroxil 0.386g was dissolved in the methanol (about 25 cm^3), then mixed with the salicylaldehyde which was 2 m mol or 0.2092 cm^3, also dissolved in methanol(25 cm^3). Then one percent solution of potassium hydroxide(prepared in methanol) was inserted to adjust the $_pH$ in the range of 7-8 and refluxation of resultant was done about 30 min. After that the solution of metal salt, made in methanol added to refluxed solution and it was further refluxed for two to two half hours. The product was dried out under vacuum and reserved in a desiccator [7].

2.3 Antibacterial Study

For antibacterial study of both ligand and complexes, the disc diffusion method [2] is adopted using peptone, beef extract, sodium chloride and agar-agar as the agar medium. The discs which are used in this method have 5 mm diameters. 0.01 ml of DMF (as a solvent) is used for equally amount of ligand and complexes each(about 30 µg). After that the filter paper discs were dipped in the in the above mentioned solutions, then these discs were dried and placed in the the petri dishes cultured with the investigation organisms. The plates were incubated for 24 hrs at 37°C. After 24 hrs the inhibition zone was evaluated in the each case.

3. Result and Discussion

The physical, microanalytical data, IR, electronic absorption thermal data and antimicrobial studies of ligand and complexes is given in the tables 1-5. It summarizes the elemental percentage of the carbon, hydrogen and nitrogen of ligand and complexes. The results obtained from the elemental analysis show that the ligand is formed in the reaction of the antibiotic with Salicylaldehyde. The results gained from elemental analysis and atomic absorption also show that there is 1:2 molar ratio in all the complexes formed from the reaction of the metal salts with the ligand having ML_2 stoichiometry. The solubility of ligand and complexes is checked in water and many organic solvents. The ligand is found to be soluble in the water, methanol, DMF (Dimethylformamide) and DMSO (Dimethyl sulfoxide), while the solubility of the complexes is found diversity. Some are soluble in methanol and water, some are slightly soluble in methanol and water. And some are not soluble in both but soluble in DMSO.

Figure-2 Salicylaldehyden cefadroxil

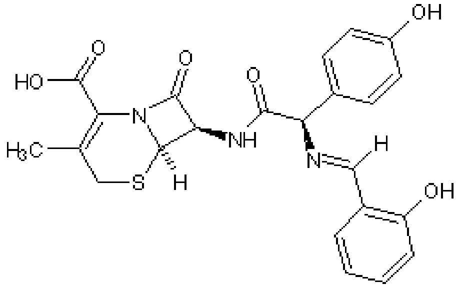


Table-1-Physical properties and microanalytical data of ligand and its metal complexes.

Complexes	Color	D. P °C (Decomposition Point)	Elemental analysis % found (calculated/experimental)				Conductance µS/cm
			C	H	N	M	
L	Brown	222 -225	59.03 58.12	4.49 3.76	8.99 8.01	=	10.50
$[Cr(L)_2.(H_2O)_2]$	Dark brown	274 -276	54.11 50.15	4.36 3.37	8.23 7.21	5.09 4.11	7.40
$[Mn(L)_2.(H_2O)_2]$	Brown	231 - 237	53.90 52.11	4.33 3.56	8.21 7.70	5.37 4.77	9.05
$[Co(L)_2.(H_2O)_2]$	Reddish	270 - 277	53.69 52.50	4.31 3.36	8.17 7.23	5.73 4.79	8.12
$[Ni(L)_2.(H_2O)_2]$	Dull green	257 - 263	53.71 51.79	4.32 3.79	8.18 7.51	5.71 4.73	12.40
$[Cu(L)_2.(H_2O)_2]$	Dark brown	285 - 287	58.22 57.03	5.43 4.66	10.86 9.71	6.18 5.71	15.55
$[Zn(L)_2.(H_2O)_2]$	Dark yellow	232 - 241	53.36 52.47	4.29 3.27	8.12 7.14	6.32 5.34	10.30
$[Cd(L)_2.(H_2O)_2]$	Yellow	250-258	51.04 50.09	4.10 3.09	7.77 6.79	10.39 9.58	13.02

Here L= ligand and M= transition metal

Fig.3 General Formula of Complex

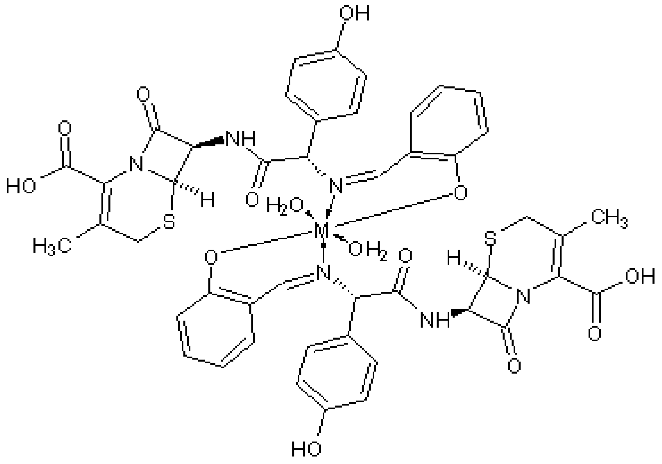


Table-2-IR (Infra Red) Data of Ligand and Metal Complexes

Complexes	υ (OH)	υ (C=N)	ρr (H_2O)	ρx (H_2O)	∞ (CO)	Π (CO)	υ (MN)	υ (MO)
L	3521	1576	814	543	1747	1386	=	=
$[Cr(L)_2.(H_2O)_2]$	3515	1604	819	528	1661	1433	615	464
$[Mn(L)_2.(H_2O)_2]$	3512	1612	819	-	-	1355	569	497
$[Co(L)_2.(H_2O)_2]$	3516	1572	827	-	1672	1417	551	447
$[Ni(L)_2.(H_2O)_2]$	3518	1590	817	536	1741	1381	557	451
$[Cu(L)_2.(H_2O)_2]$	3568	1564	831	538	1676	1394	550	417
$[Zn(L)_2.(H_2O)_2]$	3564	1678	835	526	1730	1394	551	458

The investigation of the peaks or bonding of ligand and complexes is carried out through the comparison of the FT-IR (Fourier Transform Infra-Red) spectras of complexes with that of ligand. There is indication of the absorption bands or the peaks of the free ligand formation through -C=N- bond and coordination of the ligand to transition metal ion or atom via nitrogen and oxygen of the ligand. The band spectra of around about 3380-3500 cm^{-1} is due to water molecule, υ(OH) linked with Schiff based transition metal complexes. Moreover $pr(H_2O)$ and $\rho(H_2O)$ have showed the rocking in region of 880-820 cm^{-1} and wagging in region of 530-550 cm^{-1} respectively[12]. Since free ligand have the band range from1590 to1630 cm^{-1} and shifting to a higher range in all the Schiff base transition metal complexes is the indication of co-ordinated bond of the ligand with the metal ion via –C=N- [13]. While carboxylic acid's band is not absent showing that it is not involved in the coordination. Whereas appearance of bands for υ(M-N) and υ(M-O) in the range of 530-560 cm^{-1} and 435-455 cm^{-1} respectively[11] showed the coordination of the ligand with the metal via "N" and " O" atoms.

Table-3-Electronic absorption spectral data nm (є, cm^2 mol^{-1})

Complex	Π – π	d-d	n- π*	μeff
L	275	=	308	=
$[Cr(L)_2.(H_2O)_2]$	272	653	325	5.34
$[Mn(L)_2.(H_2O)_2]$	262	631	332	6.12
$[Co(L)_2.(H_2O)_2]$	266	612	340.5	4.03
$[Ni(L)_2.(H_2O)_2]$	299	756	340	2.09
$[Cu(L)_2.(H_2O)_2]$	263	619	345	diamagnetic
$[Zn(L)_2.(H_2O)_2]$	243	643	355	diamagnetic

Electronic spectra of the ligand shows two bands in the region 275 nm and 308 nm for the transition from Π – π* and n- π* correspondingly.

The bands in the region 612-756 nm are found in all the metal complexes expect zinc metal complex. The band in the 308 nm corresponding to the n-π* transition in the ligand shows a bath chromic shift in the metal complexes. The shifting of this band in metal complexes together with color change also supports complex formation. The magnetic moment data of all the synthesized metal complexes is obtained using Gouy's method[14].

Table-4-Thermal data

Complex	Temp. range ^{0}C	Stage	TG Wt. Lose in %	DTA Temp. Peak. ^{0}C	Evolved moiety	
					Formula	Mass calculated. %
$[Cr(L)_2.(H_2O)_2]$	100-220 220-600	8.5 20.73	1 2	324.55 (exo) 394.46 (endo)	Water Ligand	8.6 20.90
$[Mn(L)_2.(H_2O)_2]$	100-220 220-600	1 2	12.5 59.83	498.73 (exo) 507.02 (endo)	Water Ligand	11.22 60.02
$[Co(L)_2.(H_2O)_2]$	100-220 220-400	1 2	12.67 58.37	363.56 (exo) 373.13 (endo)	Water Ligand	12.80 58.32
$[Ni(L)_2.(H_2O)_2]$	100-220 220-600	1 2	13.21 60.00	264.38(exo) 396.14(endo)	Water Ligand	12.89 60.5
$[Cu(L)_2.(H_2O)_2]$	100-220 220-600	1 2	11.58 60.08	542.57 (exo) 581.67(endo)	Water Ligand	11.60 60.80
$[Zn(L)_2.(H_2O)_2]$	100-220 220-836	1 2	3.76 60.6	338.27 (exo) 365.29(endo)	Water Ligand	3.89 60.9

TGA=Thermogravimetric Analysis and DTA=Differential thermal analysis

The thermal decomposition of the complexes have been studied in the nitrogen atmosphere by using the TGA and DTA techniques.

There is a weight loss corresponding to two water molecules in the case of $[Mn(L)_2.(H_2O)_2]$, $[Ni(L)_2.(H_2O)_2]$ and other metal complexes around about 120 °C indicating the coordination of water. The sharp decrease from 200 to 500 °C showed the loss of ligand from Schiff based transition metal complexes. The complexes begins to lose of weight around 80 °C showing the presence of the moisture and around 120 °C suggesting the presence of the coordinated water, it is the dehydration stage at which the water molecules are eliminated. This indicates that the complexes are hygroscopic as well as hydrated. A sharp decrease from 200 to 500 °C in the weight indicate lose of the Schiff base ligand from the complexes[12].

Table-5 Antimicrobial studies by Zone of inhabitation (mm)

Complexes	***E. coli***	***S. aureus***	***P. aeruginos***
Cefadroxil	35	8.96	30
L	29	13.53	32
$[Cr(L)_2.(H_2O)_2]$	22	15.21	34
$[Mn(L)_2.(H_2O)_2]$	19	18.90	33
$[Co(L)_2.(H_2O)_2]$	25	14	28
$[Ni(L)_2.(H_2O)_2]$	17	23	31
$[Cu(L)_2.(H_2O)_2]$	23	27	29
$[Zn(L)_2.(H_2O)_2]$	16	20	.5

The ligand and the complexes are subjected in a vitro for biological study against the *Eschesrichia coli, P. aeruginos and Staphylococcus aureus*. The MIC (minimum inhibition concentration) values of both ligand and Schiff based transition metal complexes are given in the above table. The results showed that metal complexes have more antibacterial activity then the free ligand and ligand has more antibacterial activity then the parental antibiotic. In the case of metal complexes, this may be due to various factors such as solubility, formation constants, chelation effect, cell permeability or may be some other factor[15]. However the exact mechanism is unrevealed..

4. Conclusion

The physioanalytical data showed that all the complexes are formed from the reaction of the ligand and the metal salts. The 1:2(ML_2) of the Schiff base metal complexes is suggested by the elemental analysis, here “M” represents tranistion metal and “L” represents the ligand, showing that with the central metal ion two ligand are coordinated via "N" and "O" atoms, this is confirmed by the FT-IR spectral analysis. The thermal analysis shows that there are also coordination of water molecules with the metal ions. The minimum inhibition zone data suggested that the Schiff base transition metal complexes have more antibacterial activity then the ligand and the parental drug. So these complexes have better antibacterial yield.

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