Asian Journal of Chemistry;   Vol. 25, No. 1 (2013), 297-300

ASIAN JOURNAL OF CHEMISTRY

http://dx.doi.org/10.14233/ajchem.2013.13005

Synthesis, Spectral and Biological Studies of Novel Schiff Base Metal Complexes Derived from Cephalexin and Sugars

NARJIS NAZ*, ZUBI SADIQ and MUHAMMAD ZAFAR IQBAL

Department of Chemistry, Lahore College for Women University, Lahore-54000, Pakistan

*Corresponding author: E-mail: narjis107@gmail.com

(*Received*: 3 November 2011;   *Accepted*: 23 July 2012)   AJC-11866

Fe(II), Co(II) and Ni(II) metal complexes of novel Schiff bases derived from cephalexin and sugars (D-glucose, D-xylose) were synthesized and characterized by physio-chemical (elemental analysis, magnetic susceptibility and electrolytic conductance) and spectral techniques. It has been found that Schiff bases behave as bidentate ligands forming complexes with 1:2 (metal:ligand) stoichiometry. Thermal behaviour of complexes has been investigated using thermogravimetric techniques. The biological activities of complexes have been evaluated against two gram negative (*Escherichia coli* and *Pseudomonas aeruginosa*) and two gram positive (*Bacillus subtilis* and *Staphylococcus aureus*) bacteria by Agar diffusion disc method. It has been found that the complexes have higher activity as compared to the pure cephalexin against the bacteria.

Key Words: Schiff base complexes, Cephalexin, Sugars.

INTRODUCTION

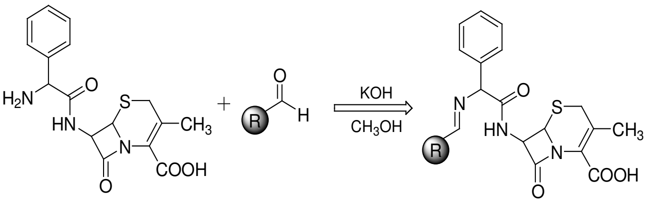
The widely use of the antibiotics leads to the serious medical problem of drugs resistance and public health concern[1-4]. Studies of new synthetic derivatives of antibiotics with novel mechanism of action has become an important chore to deal with drugs resistance dilemma[5-7].

Literature suggests that some antibiotics showed improved activity when administered as metal complex rather than as simple organic molecule[8-11] and that the coordinating possibility of antibiotics has been improved by condensing with a variety of carbonyl compounds to make chemotherapeutic Schiff base metal complexes[12,13]. Schiff bases are distinctive class of chelating ligands in coordination chemistry[14-16] and have diversity of applications in different fields[17,18] owing to its greater pick, sensitivity and synthetic flexibility to coordinate with different transition metal ions[19,20].

In continuance[21,22] of our research work, we reported the synthesis, spectroscopic and biological studies of new schiff base derivatives of cephalexin with sugars and their Fe(II), Co(II) and Ni(II) metal complexes (**Scheme-I**).

EXPERIMENTAL

All the solvents and regents used for this study were of analytical grade and obtained from E. Merck. The Cephalexin was obtained from Remington Pharmaceutical Industries Pvt. Ltd.



where, R = $C_5H_{11}O_5$ or $C_4H_9O_4$

Scheme-I: Systematic approach of Schiff base ligand

The electronic spectra of the Schiff base and their metals complexes were obtained in DMSO on a Hitachi 220 S spectrophotometer in the range 900-200 nm. Elemental analysis (C, H, N, S) was performed using a Carlo Erba 1106 elemental analyzer. The FTIR spectra in the range 4000-200 cm^{-1} were obtained using KBr discs on a Michaelson Bomen series spectrophotometer. Magnetic measurements were carried out by the Gouy's method using Hg[Co(SCN)$_4$] as a calibrant. Molar conductance of the Schiff base metal complexes was determined in DMSO at room temperature using Wescan-212 conductometer. Metal contents in complexes were determined by Hitachi Z-8000 atomic absorption spectrophotometer after undertaking proper acid digestion. Thermal Analysis was performed on Netzsch simultaneous thermal analyzer.

Preparation of Schiff base metal complexes: A methanolic solution (50 mL) of cephalexin (1 mmol) was mixed with sugar (1 mmol) dissolved in methanol (50 mL) under constant stirring. Solution of KOH (0.1 % in methanol)

TABLE-1
PHYSICAL PROPERTIES OF SCHIFF BASE METAL COMPLEXES (I-VI)

S. No.	Compounds	Colour	Empirical formula	Yield (%)	Elemental analysis (%): Calcd. (found)					Conductivity Ω^{-1} cm^2 mol^{-1}	μ_{eff} (BM)	λ_{max} nm (ε cm^{-1} mol^{-1})
					M	C	H	N	S			
1	(gluceph)$_2$ Fe	Reddish brown	$(C_{22}H_{26}N_3O_9S)_2Fe$	59	4.96 (5.20)	49.16 (49.24)	4.72 (4.88)	7.65 (7.83)	5.74 (5.96)	5.96	5.15	284 (41015), 338 (8011)
2	(gluceph)$_2$ Co	Dark brown	$(C_{22}H_{26}N_3O_9S)_2Co$	64	5.33 (5.48)	49.05 (49.10)	4.73 (4.87)	7.69 (7.81)	5.71 (5.95)	3.06	2.21	286 (41025), 335 (8024)
3	(gluceph)$_2$ Ni	Light green	$(C_{22}H_{26}N_3O_9S)_2Ni$	55	5.42 (5.45)	48.98 (49.11)	4.76 (4.87)	7.73 (7.81)	5.76 (5.95)	5.24	-	280 (41011), 330 (8095) 480 (66)
4	(xylceph)$_2$ Fe	Reddish brown	$(C_{21}H_{24}N_3O_8S)_2Fe$	64	5.35 (5.51)	49.70 (49.79)	4.74 (4.77)	8.22 (8.29)	6.09 (6.32)	4.96	5.12	285 (41006), 335 (7899)
5	(xylceph)$_2$ Co	Dark brown	$(C_{21}H_{24}N_3O_8S)_2Co$	58	5.76 (5.80)	49.52 (49.63)	4.72 (4.76)	8.18 (8.27)	6.13 (6.30)	3.15	2.24	288 (41024), 330 (8094)
6	(xylceph)$_2$ Ni	Light breen	$(C_{21}H_{24}N_3O_8S)_2Ni$	60	5.72 (5.78)	49.59 (49.65)	4.71 (4.76)	8.22 (8.27)	6.11 (6.30)	5.13	-	282 (41012), 330 (8000), 482 (69)

*Theoretical values are given in brackets

was gradually added to the above reaction mixture and refluxed for *ca.* 0.5 h. A yellow solution of Schiff base was formed. The coloured solution, thus obtained was mixed with the solution of metal salt (4 mmol) in methanol and refluxed. The refluxing was continued for *ca.* 2 h. The coloured solid (depends upon the metal salt used) formed was isolated by filtration and washed with distilled water, ethanol and methanol and dried in vacuum over $CaCl_2$.

Biological activity: *In vitro* biological screening effect of the investigated compounds have been screened against bacteria by Agar diffusion disc method[23,24]. Two gram negative (*Escherichia coli* and *Pseudomonas aeruginosa*) and two gram positive (*Staphylococcus aureus* and *Bacillus subtilis*) bacteria were grown in nutrient agar medium at 37 ºC for 24 h[25,26]. The sterile (5 mm) diameter sensitivity discs were prepared by soaking the blank discs in the solution of appropriate concentration (10 µg/10 µL in DMSO) of the complex to be tested. Test discs and standard cephalexin (10 µg/10 µL) disc were placed on the nutrient agar slightly pressing them on to the medium. The plates were then incubated for 24 h at 37 ºC for bacteria. The results were recorded by measuring the zone of growth inhibition (mm) surrounding the discs.

RESULTS AND DISCUSSION

New Schiff base derivatives of cephalexin were prepared by refluxing it with sugars *i.e.*, D-glucose and D-xylose. Amino group available in Cephalexin was allowed to react with the aldehydic group of sugars (aldoses) to obtain Schiff bases. Formation of Schiff base ligands was indicated by yellowing of solution and development of an absorption band with a maximum at 400 nm[27] in the visible region. It is known that Schiff bases obtained from aliphatic carbonyl compounds are readily hydrolyzed[28]. However these Schiff bases are isolated as metal chelates. The newly synthesized Schiff base metal complexes are coloured, non-hygroscopic and stable at room temperature. They are soluble in DMF and DMSO. The analytical data of the complexes with some physical properties are presented in Table-1. The analytical data reveals that these have metal:ligand stoichiometry of 1:2 corresponding to the general formula of $M(L)_2$ where M is metal and L is ligand. The lower conductance values of the complexes support their non electrolytes nature[29,30].

The electronic absorption data of the complexes dissolved in DMSO is given in Table-1. In the spectra of complexes the band in the 288-280 nm range is assigned to phenyl ring π-π^* transition[31]. The bands appear in the range 338-330 nm are attributed to π-π^* transition originating in the C=N chromophore group[32]. The band for chromophore group is usually present in range 348-390 nm. During the formation of the complexes this band is shifted to the lower wavelength suggesting that nitrogen atom of the azomethine is coordinated to metal ion[33]. The lower energy bands in range of 482-480 nm are due to *d-d* transition. The magnetic susceptibilities of the iron (II) complexes under investigation are in the range of 5.15-5.12 BM, tetrahedral geometry is proposed for these complexes[34]. Schiff base complexes of cobalt(II) are usually low spin with magnetic moments in the range of 2.24-2.21 BM[35] and possess square planar geometry.

Diamagnetic complexes of nickel are square planner[36] where as paramagnetic complexes are tetrahedral, the nickel(II) complexes under observation are diamagnetic so square planar structure is proposed.

The most pertinent FTIR spectral bands of complexes and their assignments are presented in Table-2. The assignments are made in comparison with the spectrum of pure cephalexin. The bands present in the 3278-3276 cm^{-1} region in spectra of the complexes exclude the involvement of NH group in coordinating with metal ions[37]. The new band at 1602-1598 cm^{-1} region in the spectra of complexes is assigned to the azomethine group coordinated to the metal ion. The spectrum of pure cephalexin shows stretching vibration at 2610 cm^{-1} due to NH_2 group[38,39]. The stretching vibrations at 2610 cm^{-1} due to NH_2 group of cephalexin and at 2840 cm^{-1} due to free CO group of aldehyde were absent in the FTIR spectra of these complexes. This indicates that NH_2 group of Cephalexin and aldehyde group of sugar condensed to produce the -CH=N- group. The absorption band for the azomethine group is generally observed at 1650-1630 cm^{-1} [40]. The observed low value of this band confirms the coordination through the azomethine nitrogen[41,42]. The spectra of these complexes exhibited a strong bands around 1775-1773 cm^{-1} and 1695-1690 cm^{-1}, which are assigned to β-lactam ν(C=O) and amide ν(C=O) respectively[38,39]. The invariance of the frequencies of β-lactam ν(C=O) and amide ν(C=O) groups relative to the spectra of

TABLE-2
ASSIGNMENT OF MORE SIGNIFICANT ABSORPTION BANDS (cm^{-1}) of SCHIFF BASE TRANSITION METAL COMPLEXES (**1-6**)

Compound No	ν(NH) (amide)	ν(C=O) β-lactam	ν(C=O) (amide)	ν_{as}(COO)	ν(C=N-)	ν_s(COO)	$\Delta\nu$	ν(CN)	ν(CS)	ν(M-N)	ν(M-O)
1	3276	1760	1695	1626	1598	1385	241	1017	580	406	369
2	3278	1758	1692	1622	1600	1382	240	1021	580	408	360
3	3273	1758	1690	1626	1600	1385	241	1020	580	400	358
4	3276	1760	1692	1626	1600	1385	241	1017	584	406	369
5	3276	1760	1692	1624	1602	1385	238	1022	584	402	362
6	3278	1758	1692	1626	1600	1382	244	1022	584	398	362

pure cephalexin (at 1758 and 1688) ruled out the involvement of β-lactam ν(C=O) and amide ν(C=O) in coordination. Coordination of the Sulphur atom can be excluded on the basis of the absorption band at 582-580 cm^{-1}, which is at almost at same region as in the spectrum of free Cephalexin[38,39].

Free carboxylate (COO) in pure cephalexin shows absorption band at 1582 cm^{-1} and 1400 cm^{-1} region for asymmetric and symmetric vibrations[38,39]. In all the complexes the carboxylate $\nu(COO)_{asy}$ were shifted towards higher wave numbers at 1626-1622 cm^{-1} while $\nu(COO)_{sy}$ were shifted towards lower wave numbers at 1385-1382 cm^{-1}. This experimental finding evidently indicates that carboxylate is involved in coordination in all complexes[43]. The $\Delta\nu$ value [$\Delta\nu = \nu(COO)_{sy} - \nu(COO)_{asy}$] is equal to 182 for pure cephalexin. The $\Delta\nu$ values in all the complexes increased, which are characteristic of monodentate carboxylate ion in coordination with metal[44]. New absorption bands for ν(MN) and ν(MO) appeared at 408-398 cm^{-1} and 369-358 cm^{-1} respectively[45]. The FTIR spectral data indicate that coordinating groups are C=N- and -COO present in the Schiff base ligands.

The thermal behaviour of the complexes has been investigated using thermogravimetric technique. The decomposition temperature and weight loss of the complexes were calculated from TGA data listed in Table-3. These complexes do not possess sharp melting points but decompose when heated above 200 ºC. Thermal analysis indicates that these complexes are anhydrous as there was no weight loss for coordination or lattice water when heated between 100-180 ºC[46]. The thermal behaviour of all the complexes is same and they undergo complete decomposition in single step to the corresponding metal oxides[47].

TABLE-3
THERMAL DECOMPOSITION OF THE METAL COMPLEXES

Compounds number	Decomposition temperature range	Weight loss (%) calculated (found)	Residue (%) calculated (found)
I	215-725	93.52 (93.48)	6.70 (6.66)
II	220-723	93.26 (93.20)	6.96 (6.90)
III	218-722	93.28 (93.23)	6.94 (6.91)
IV	220-725	93.52 (93.75)	7.09 (6.98)
V	222-722	93.26 (93.18)	7.38 (7.22)
VI	218-723	93.28 (93.25)	7.35 (7.28)

Antimicrobial activities: The antimicrobial activities of all the Schiff base transition metal complexes derived from cephalexin, sugars and metals such as Fe(II), Co(II), Ni(II) against four bacteria: *Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa* and *Bacillus subtilis* in comparison of pure cephalexin were recorded in Fig. 1.

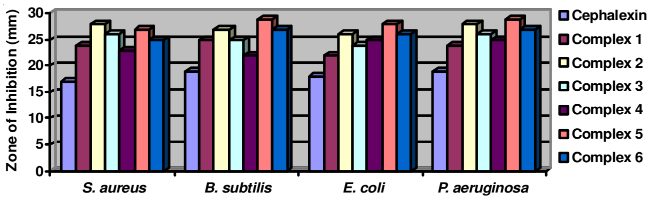
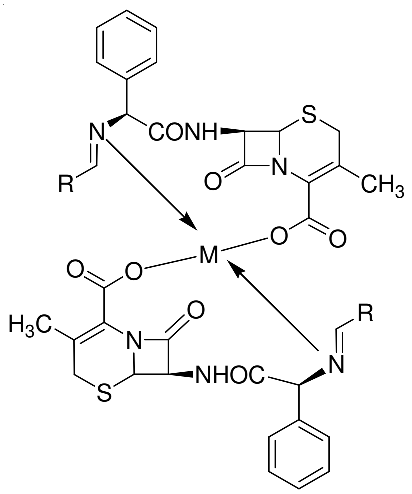


Fig. 1. Antibacterial activity data of metal complexes

It is known that chelation tends to make simple organic molecule a more powerful and potent bactericidal agent[48]. All the complexes show more antibacterial activities as compared to the pure cephalexin. The antibacterial activities of Schiff base metal complexes were found in the order:

Co(II) > Ni(II) > Fe(II)



where, M = Fe, Co and Ni
Proposed structure of Schiff base metal complex

ACKNOWLEDGEMENTS

The authors are thankful to the Remington Pharmaceutical Company Pvt. and Kundian Chemical Plant I Pakistan for providing assistance in this work.

REFERENCES

1. K. Singh, M.S. Barwa and P. Tyagi, *Eur. J. Med. Chem.*, **42**, 394 (2007).
2. J.G. Lara, M. Masalha and S.J. Foster, *Drug Discovery Today*, **10**, 643 (2005).
3. S. Tehranchian, T. Akbarzadeh, M.R. Fazeli, H. Jamalifar and A. Shafiee, *Bioorg. Med. Lett.*, **5**, 1023 (2005).
4. N. Gumrukcouglu, M. Serdar, E. Celik, A. Sevim and N. Demirbas, *Turk. J. Chem.*, **31**, 335 (2007).
5. M.S. Iqbal, I.H. Bukhari and M. Arif, *Appl. Organomet. Chem.*, **19**, 864 (2005).
6. G.B. Bagihalli, P.G. Avaji, S.A. Patil and P.S. Badami, *Eur. J. Med. Chem.*, **43**, 2639 (2008).

7. N. Raman, J.D. Raja and A. Sakthivel, *J. Chem. Sci.,* **119**, 303 (2007).
8. M.S. Iqbal, A.R. Ahmad, M. Sabir and S.M. Asad, *J. Pharm. Pharmacol.*, **51**, 371 (1999).
9. Z.H. Chohan and M.F. Jaffery, *Metal Based Drugs*, **7**, 265 (2000).
10. R. Di Stefano, M. Scopelliti, C. Pellerito, T. Fiore, R. Vitturi, M.S. Colomba, P. Gianguzza, G.C. Stoccoa, M. Consiglioa and L. Pelleritoa, *J. Inorg. Biochem.*, **89**, 279 (2002).
11. R. Ramesh and M. Sivagamasundari, *Synth. React. Inorg. Met.-Org. Chem.*, **33**, 809 (2003).
12. P. Singh, R.L. Goel and B.P. Singh, *J. Indian Chem. Soc.*, **52**, 958 (1975).
13. A.M. Mahindra, J.M. Fisher and Rabinovitz, *Nature (London)*, **64**, 303 (1983).
14. M. Sonmez, *Turk. J. Chem.*, **25**, 181 (2001).
15. K.S. Abou-Melha and H. Faruk, *J. Iran. Chem. Soc.*, **5**, 122 (2008).
16. W. Radecka-Paryzek, V. Patroniak and J. Lisowski, *Coord. Chem. Rev.*, **249**, 2156 (2005).
17. N. Raman, A. Kulandaisamy and K. Jeyasubramanian, *Transition Met. Chem.*, **26**, 131 (2001).
18. M. Sonmez, *Polish J. Chem.*, **77**, 397 (2003).
19. C. Spinu and A. Kriza, *Acta Chim. Slov.*, **47**, 179 (2000).
20. S. Baluja, A. Aolanki and N. Kachhadia, *J. Iran. Chem. Soc.*, **3**, 312 (2006).
21. N. Naz and M.Z. Iqbal, *J. Chem. Soc. Pak.*, **31**, 440 (2009).
22. N. Naz and M.Z. Iqbal, *Sci. Int.*, **23**, 27 (2011).
23. Z.H. Chohan and S.K.A. Sheazi, *Synth. React. Inorg. Met.-Org. Chem.*, **29**, 105 (1999).
24. A.K. Halve, D. Bhadauria, B. Bhaskar, R. Dubey and S. Vasudha, *Indian J. Pharm. Sci.*, **69**, 680 (2007).
25. V.K. Tandon, D.B. Yadav, R.V. Singh, M. Vaish, A.K. Chaturvedi and P.K. Shukla, *Bioorg. Med. Chem.*, **15**, 3463 (2007).
26. A.K. Sadana, Y. Miraza, K.R. Aneja and O. Prakash, *Eur. J. Med. Chem.*, **38**, 533 (2003).
27. D.E. Metzler, *J. Am. Chem. Soc.*, **91**, 627 (1968).
28. M.S. Iqbal, S.J. Khurshid and M.Z. Iqbal, *Can. J. Chem.*, **71**, 629 (1993).
29. S.M.E. Khalil, S.L. Stefan and K.A. Bashir, *Synth. React. Inorg. Met.-Org. Chem.*, **29**, 1685 (1999).
30. M. Sekerci and E. Tas, *Heteroatom Chem.*, **11**, 254 (2000).
31. B. Bosnich, *J. Am. Chem. Soc.*, **90**, 627 (1968).
32. R.S. Downing and F.L. Urbach, *J. Am. Chem. Soc.*, **91**, 5977 (1969).
33. M. Sonmez and M. Sekerci, *Polish J. Chem.*, **76**, 907 (2002).
34. F.A. Cotton and G. Wilkinson, Advance Inorganic Chemistry, Academic Press, New York, edn. 4, p. 790 (1980).
35. N.N. Green and A. Earnshaw, Chemistry of the Elements, Pergamon Press, Oxford, U.K., p. 1315 (1984).
36. R.L. Duta and A. Syamal, Elements of Magnetochemistry, edn. 2 (1992).
37. R. Di Stefano, M. Scopelliti, C. Pellerito, G. Casella, T. Fiore, G.C. Stocco, R. Vitturi, M. Colomba, L. Ronconi, I.D. Sciacca and L. Pellerito, *J. Inorg. Biochem.* **98**, 534 (2004).
38. P.K. Bhattacharrya and W.M. Cort, Analytical Profiles of Drug Substances, p. 28 (1978).
39. E. Ivashikiv, Analytical Profiles of Drug Substances, p. 5 (1973).
40. K. Nakamoto, Infrared and Raman Spectra of Inorganic and Coordination Compounds, New York, NY: John Wiley Interscience, p. 59 (1997).
41. N. Raman, S. Ravichandran and A. Kulandaisamy, *Asian J. Chem.*, **14**, 1261 (2002).
42. R.K. Agarwal, D. Sharma, L. Singh and H. Agarwal, *Bioinorg. Chem. Appl.*, article 29234 (2006).
43. Z.H. Chohan, M. Arif, M.A. Akhtar and C.T. Supuran, *Bioinorg. Chem. Appl.*, article 83131 (2006).
44. G.B. Deacon, F. Huber and R.J. Phillips, *Inorg. Chim. Acta*, **41**, 104 (1985).
45. X. Tai, X. Yin, Q. Chen and M. Tan, *Molecules*, **8**, 439 (2003).
46. N. Raman and S. Ravichandran, *Polish J. Chem.*, 78 (2004).
47. E. Canpolat and M. Kaya, *Russian J. Chem.*, **31**, 415 (2005).
48. Z.H. Chohan, C.T. Supuran and A. Scozzafava, *J. Enzyme Inhib. Med. Chem.*, **19**, 79 (2004).