



Microwave assisted synthesis of indole derivatives and their complexation behaviour possessing good biological activities

Mohd. Asif Khan and Shamim Ahmad

Department of Chemistry, Bareilly College, Bareilly U.P., India

ABSTRACT

A series of Ti (III), V (III), Cr (III), Mn (III), Fe (III), Co (III) and Ru (III) complexes have been synthesized from the Schiff base ligand. The Schiff base ligand is N' - Tosyl - 1H -Indole-2- Carbohydrazide has been synthesized by the condensation of Indole-2-carboxylic acid with p-toluene sulfonyl hydrazide. The resulting complexes were characterized by elemental analyses, magnetic moment measurement, conductivity measurement, I.R. ¹HNMR and E.P.R. spectral studies. All the complexes were tested for their anti-Inflammatory and analgesic activities. From the data, an octahedral geometry around the central metal ion has been suggested for all the metal complexes. The biological activity data show that the ligand and its complexes possess good analgesic activity.

Key Words : Schiff base, N'- tosyl-1H-Indole-2- carbohydrazide, metal complexes, analgesic activity and anti-inflammatory activity.

INTRODUCTION

The chemistry of the carbon-nitrogen double bond plays a vital role in the progress of chemical science (1). Schiff base compounds have been used as fine chemicals and medical substrates in the field of coordination chemistry, Schiff base metal complex have a curious history (2,3) Metal ion play vital roles in the vast number of biological processes. Metal complexes with Schiff base ligand have been studied for their application in biological, clinical, analytical and pharmacological areas(4).

The derivatives of indole possessing antimicrobial (5), anti-fungal (6), antibacterial (7) and antidepressant (8) activity have been reported in literature. Above mentioned few references indicate versatile nature of indole derivatives from biological point of view. Use of microwave irradiation for the synthesis of various organic compounds is also reported in literature (9-10). Manganese, Vanadium and Ruthenium possess a number of oxidation states and have excellent complexing property. The last two metals and their complexes exhibits biological properties(11-12). Keeping in view these facts we have synthesized ligand having oxygen, nitrogen, sulphur donor atoms and complexation behaviour and biological activity.

EXPERIMENTAL SECTION

Material

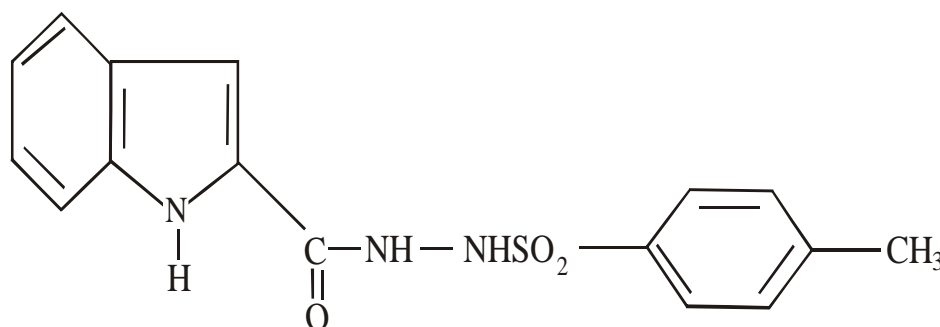
All material used in this investigation were purchased from Sigma/Aldrich and used as received. They include Indole-2- carboxylic acid (Sigma-Aldrich, CAS No. 1477-50-5) and p-toluene sulfonyl hydrazide (LOBO INDIA). The ligand N'-tosyl-1H-Indole-2-carbohydrazide was prepared by reported method(13). Titanium (III) chloride was prepared in the lab from 12% solution of Ti (III) chloride (B.D.H) by the reported method. All other metal salts were purchased from market and used as such.

Instrumentation:

Domestic microwave oven model IN- 197DL (Samsung) was used for microwave irradiation. Melting points were determined on a JSGW apparatus and are uncorrected. I.R. spectra were recorded using a perkin Elmer 1600 FT spectrometer. ¹HNMR spectra were measured on a Bruker WH-500 MHz spectrometer at a Ca 5-15% solution in DMSO - d⁶ (T.M.S. as internal standard). Elemental analyses was carried out on vitro EL III Elementor. Thin layer chromatography (TLC) was performed on Silica gel G for TLC (Merck) and spots were Visualized by Iodine Vapours.

Preparation of the Ligand:

Indole-2-carboxylic acid (322 mg, 2 mmol) and p-toluene sulfonyl hydrazide (372 mg, 2 mmol) work mixed thoroughly and mixture was subjected to microwave irradiation for 3.0 min. at 850 W power level and reaction progress was monitored by TLC, This process was repeated three times when one of the starting material disappeared. Crude product was recrystallized from methanol to give pure product.

Structure of Schiff base**Preparation of Metal complexes :**

The complexes were prepared by adding the solution of metal salt in ethanol drop by drop to the solution of ligand till complete precipitation. The precipitate was filtered washed with ethanol to remove any un-reacted part of either of the reactants. The precipitate was filtered and dried in vacuum dessicator.

Anti-inflammatory activity evaluation:

Anti-inflammatory activity evaluation (14) was carried out using carrageenin induced paw Oedema in albino rats. Oedema is one of the kind paws was induced by injection of carrageenin solution (0.1 ml. of 1%) into planter apponeurosis. The volume of the paw was measured plethysmographically immediately after and 3.0 hour after the injection of the irritant. The difference in volume gave the amount of Oedema developed. Percent inhibition of the Oedema between the control group and compound treated groups was calculated and compared with group receiving a standard drug.

Analgesic Activity Evaluation:

Analgesic activity was measured by writhing assay(15) using mice (15-20g). Female mice were screened for writhing on day-1 by injecting intraperitoneally 0.2 ml of 0.02% aqueous solution of phenylquinone. They were kept on flat surface and the number of writhes of each mouse was recorded for 20 min. The mice showing significant writhes (>10) were sorted out and used for analgesic assay on following day. The mice consisting of 5 in each group and showing significant writhing were given orally a 50 or 100 mg/kg p.o. dose of the test compounds 15 Min. prior to phenylquinone challenge. Writhing was again recorded for each mouse in a group and a percentage protection was calculated using following formula:

$$\text{Protection} = 100 - \left[\frac{\text{No. of writhings for treated mice}}{\text{No. of writhings for untreated mice}} \right] \times 100$$

This was taken as a percent of analgesic response and was averaged in each group of mice. Percent of animals exhibiting analgesia was determined with each dose.

RESULTS AND DISCUSSION

The ligand and its transition metal complexes with Ti (III), V (III), Mn (III), Co (III), Fe (III) were subjected to elemental analyses where as metal and chloride were estimated gravimetrically in the lab. All this analytical data suggested 1:2, M:L stoichiometric for all the complexes.

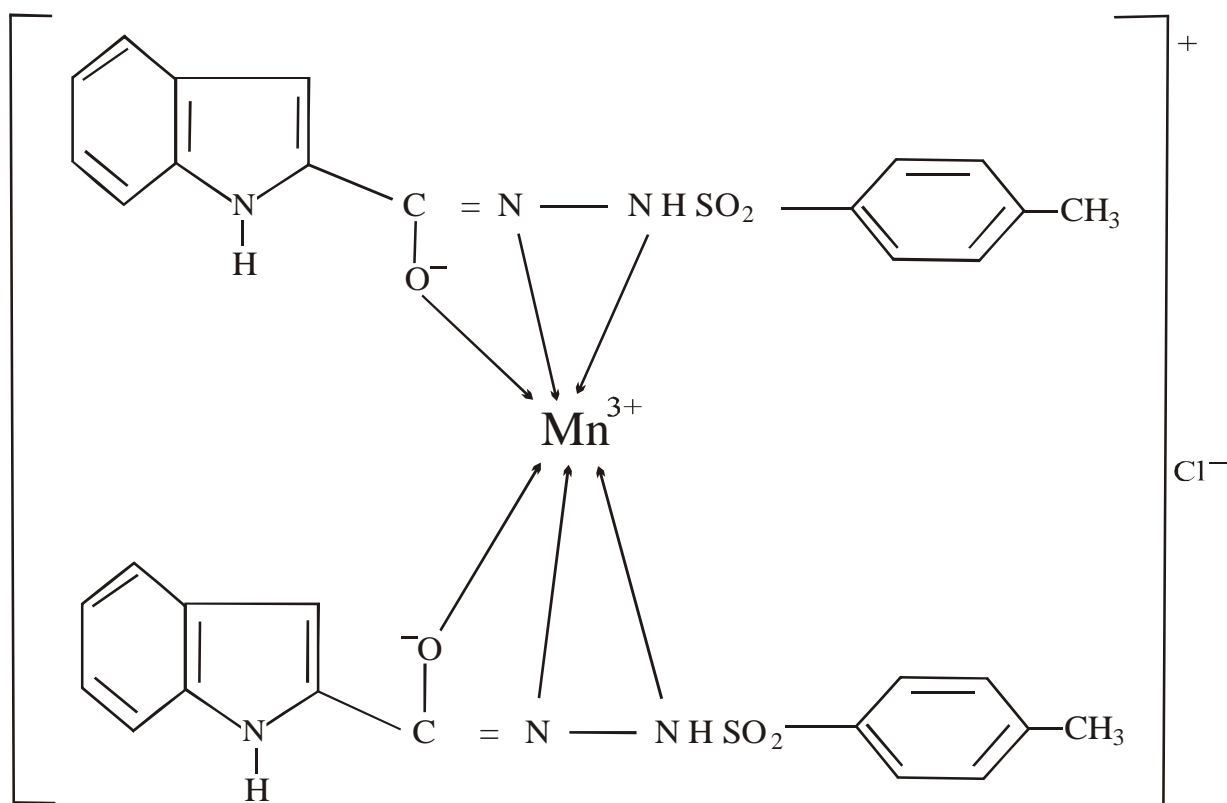
The M.P. of the ligand and its metal complexes were determined and compared in order to find out the possibilities of formation of complexes. The M.Pts are given in Table I. The determination of molar conductance in DMSO at 10^{-3} M dilution suggested 1:1 electrolytic nature for all the synthesized complexes.

The observed value of magnetic susceptibility was used to calculate to magnetic moment of the complexes. These values suggested paramagnetic nature for Ti (III), V(III), Mn (III), Fe (III) complexes as expected for Octahedral d^1 d^2 d^4 and d^5 complexes. The Co (III) complexes is diamagnetic in nature as expected for low spin d^6 Ion. The value of magnetic moments of complexes are given in Table-I.

Table-1: Characterization of Ligand & Metal Complexes Prepared

Sl No	Formula of the Ligand and Complex and Molecular Weight	Colour	M.P. °C	Elemental analyses						Molar Conductance $\text{ohm}^{-1} \text{cm}^2 \text{mole}^{-1}$	Magnetic Moments in (B.M.)
				% of C	% of H	% of N	% of S	% of M	% of Cl		
1	$\text{C}_{16}\text{H}_{15}\text{N}_3\text{SO}_3$ Mol. Wt. = 329	Yellow	120	58.35 (58.21)	4.55 (4.47)	12.76 (12.70)	9.72 (9.69)	-	-	-	-
2	$[(\text{C}_{16}\text{H}_{15}\text{N}_3\text{SO}_3)_2(\text{H}_2\text{O})_2 \text{Ti}] \text{Cl}$ Mol. Wt. = 775.5	Yellow	195	49.51 (49.38)	4.38 (4.32)	10.83 (10.75)	8.25 (8.15)	6.18 (6.10)	4.57 (4.51)	65	1.77
3	$[(\text{C}_{16}\text{H}_{15}\text{N}_3\text{SO}_3)_2(\text{H}_2\text{O})_2 \text{Mn}] \text{Cl}$ Mol. Wt. = 782.5	Dark Brown	197	49.07 (49.0)	4.34 (4.30)	10.73 (10.65)	8.17 (8.05)	7.02 (7.98)	4.53 (4.45)	55	4.86
4	$[(\text{C}_{16}\text{H}_{15}\text{N}_3\text{SO}_3)_2(\text{H}_2\text{O})_2 \text{V}] \text{Cl}$ Mol. Wt. = 778.5	Light Yellow	201	49.32 (49.25)	4.36 (4.31)	10.78 (10.70)	8.22 (8.10)	6.55 (6.50)	4.56 (4.50)	60	2.90
5	$[(\text{C}_{16}\text{H}_{15}\text{N}_3\text{SO}_3)_2(\text{H}_2\text{O})_2 \text{Fe}] \text{Cl}$ Mol. Wt. = 783.5	Brown	206	49.01 (49.00)	4.33 (4.30)	10.72 (10.65)	8.16 (8.10)	7.14 (7.10)	4.53 (4.50)	58	5.96
6	$[(\text{C}_{16}\text{H}_{15}\text{N}_3\text{SO}_3)_2(\text{H}_2\text{O})_2 \text{Co}] \text{Cl}$ Mol. Wt. = 786.5	Dark Brown	209	48.82 (48.75)	4.32 (4.30)	10.68 (10.60)	8.13 (8.10)	7.50 (7.42)	4.51 (4.48)	55	Dia magnetic
7	$[(\text{C}_{16}\text{H}_{15}\text{N}_3\text{SO}_3)_2(\text{H}_2\text{O})_2 \text{Ru}] \text{Cl}$ Mol. Wt. = 828.5	Green	241	46.34 (46.32)	4.10 (4.08)	10.13 (10.09)	7.72 (7.69)	12.19 (12.15)	4.28 (4.25)	61	1.84

Figures in parenthesis are observed values.



Where M = Ti(III), V(III), Mn (III), Fe (III), Co (III), Ru (III) and Cr (III).
(Structure of metal complex)

Electronic Spectra :

The electronic spectrum of the complex of Ti (III) exhibits a single broad band at 19230 Cm^{-1} assignable to ${}^2t_{2g} \rightarrow {}^2E_g$ transition for O_h symmetry (16). The electronic spectrum of complex V (III) exhibits band at 16000 Cm^{-1} with a shoulder at $20,500 \text{ Cm}^{-1}$. The low energy band has been assigned to ${}^2A_{1g} \rightarrow {}^3A_{2g}$ while the high energy band may be due to ${}^2A_{1g} \rightarrow {}^3T_{2g}(P)$ transition. These bands are characteristic of Octahedral geometry (17).

The electronic spectrum of Mn (III) complex showed an intense and sharp charge transfer band at 22000 Cm^{-1} and a spin allowed d-d transition band ${}^5E_g \rightarrow {}^5T_{2g}$ at 18500 Cm^{-1} . This broad band occurring at lower frequency with increased intensity indicates the lowering of symmetry from Octahedral Configuration(18).

The electronic spectrum of the complex of Fe (III) exhibited these bands at 11235 , 21470 and 27780 Cm^{-1} assignable to ${}^6A_{1g} \rightarrow {}^4T_{1g}$, ${}^6A_{1g} \rightarrow {}^4T_{2g}$ and ${}^6A_{1g} \rightarrow {}^4E_g$ transitions respectively. These transitions are characteristics of Octahedral Fe (III) complexes (19).

The electronic spectrum of Co (III) complex displays bands at 15110 , 21095 and 23370 Cm^{-1} assignable to ${}^3A_{1g} \rightarrow {}^3T_{2g}$, ${}^1A_{1g} \rightarrow {}^1T_{1g}$ and ${}^1A_{1g} \rightarrow {}^1T_{2g}$ transitions respectively. These are similar to those reported for other six coordinated Co (III) complexes (20).

The chromium (III) complex spectrum displays three bands at 25000 , 32840 and 34542 cm^{-1} due to ${}^4A_{2g}(F) \rightarrow {}^4T_{2g}(F)$, ${}^4A_{2g}(F) \rightarrow {}^4T_{1g}(F)$ and charge transfer transitions. The intensity of the bands indicate the presence of an octahedral geometry(21). The oxygen atom from the furan ring in coordination to the metallic ion.

I.R. SPECTRA :

The I.R. spectrum of the ligand shows bands at 3370 and 3310 Cm^{-1} due to the presence of two N-H groups. The bands at 1640 , 1450 , 1380 , 890 and 1000 cm^{-1} are assign to ν (C=O), amide I [β (NH) + ν (CN)] amide-II [ν (CN) + β (NH)], ν (C=S) and ν (N-N) modes respectively(22).

In the I.R. spectra of complexes bands due to ν N-H, and ν (C=O) are absent. But new band appears at 1600 Cm^{-1} due ν (N=C) of NCO suggesting removal of N-H proton via enolization and bonding of resulting enolic oxygen with the metal ion. Furthermore, the amide I and II band and ν (N-N) band in the free hydrazide undergo positive shifts of $30\text{-}40 \text{ Cm}^{-1}$ suggesting involvement of both hydrazinic group in bonding in addition to the enolic oxygen. Thus the ligand is behaving in univegative tridentate manner.

The I.R. spectrum of the ligand shows ring vibration of indole moiety at 1625 , 1565 and 1520 Cm^{-1} which remain unaltered in the I.R. spectra of complexes excluding the possibility of involvement of the N atom of indole in bonding.

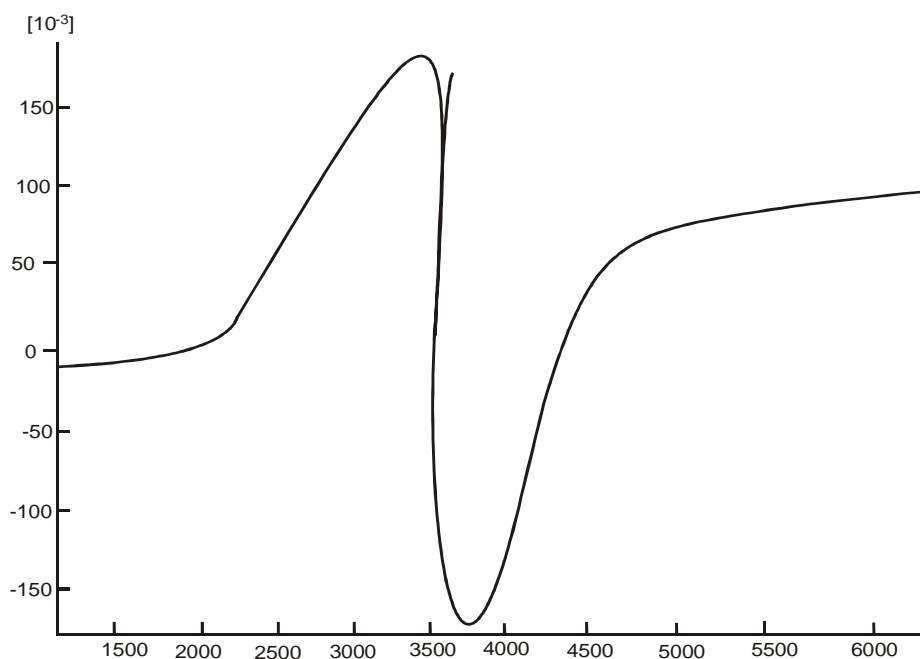


Fig. (3) : Electron paramagnetic resonance spectrum of Cr (III) complex

¹H-NMR Spectra :

The ¹H-NMR spectrum of the ligand shows signals at 89.66 ppm due to NHC(o) which disappear on D₂O exchange suggesting removal of NHC(o) proton via enolization. Benzene ring proton appears at 87.63, 7.33 and 7.16 ppm(23).

Electron Paramagnetic Resonance Spectrum :

The EPR spectrum of Cr (III) was recorded in DMSO at Liquid Nitrogen temperature. Electron paramagnetic resonance spectrum of Cr (III) complex shows a g-eff value of 1.990. The large deviation of g-eff value than the ideal value (2.0023) results from the partial ionic character of the covalent bond between the Cr (III) ion and the Schiff base under investigation. This value supports the existence of an octahedral geometry(24) and confirms the obtained data from the electronic spectra.

CONCLUSION

On the basis of above mentioned studies an octahedral geometry may be proposed for all the synthesized complexes.

Biological Studies:

Ligand and its complexes of Ti(III), V (III), Mn (III), Fe (III) and Co (III) at 100 mg./kg. P.O. were tested for anti-inflammatory activity in the Carrageenin induced paw oedema model and the results are summarized in Table-II. Ligand and its complexes of Ti(III), V (III), Mn (III), Fe (III) and Co (III) at 100 mg/kg P.O. were screened for analgesic activity using phenylquinone writhing assay and the results are reported in Table-II.

Table-II Anti-Inflammatory and Analgesic activity evaluation

Compound	Dose mg/kg P.O.	Anti-Inflammatory activity %	Dose mg/kg P.O.	Analgesic Activity %
Ligand C ₁₆ H ₁₅ N ₃ SO ₃	100	0.0	100	50
[(C ₁₆ H ₁₅ N ₃ SO ₃) ₂ (H ₂ O) ₂ Ti]Cl	100	0.0	100	55
[(C ₁₆ H ₁₅ N ₃ SO ₃) ₂ (H ₂ O) ₂ V]Cl	100	0.00	100	25
[(C ₁₆ H ₁₅ N ₃ SO ₃) ₂ (H ₂ O) ₂ Mn]Cl	100	0.0	100	50
[(C ₁₆ H ₁₅ N ₃ SO ₃) ₂ (H ₂ O) ₂ Fe]Cl	100	0.0	100	20
[(C ₁₆ H ₁₅ N ₃ SO ₃) ₂ (H ₂ O) ₂ Co]Cl	100	0.0	100	30

P.O. = from Latin word per OS (means by mouth)

REFERENCES

- [1] S. Patai, The chemistry of Carbon-nitrogen double bond, John Wiley & Sons Ltd., London, (1970).
- [2] Yamada S, *Coord Chem. Rev.* (1999), 537, 190-192.
- [3] Singh S, Das S and Dhakarey R, *E-J Chem*, (2009), 6(1), 99-105.
- [4] Raman N, Syed Ali Fathima S and Dhaveethu Raja J. *Serbian Chem. Soc.* (2008), 73 (II), 1063 - 1071.
- [5] Saundane A.R., Sharma P.M.V. and Badiger J., *Indian J. Heterocyclic chem.*, (2005), 14, 307.
- [6] Agarwal A., Agarwal S.K., Shukla P.K. and Khan Z.K., Indian IN 183635; *Chem. Abstr.* (2004), 141, 260731.
- [7] Palluotto F., Campagna F., Carrotti A., Ferappi M., Rosato A. and Vitalic, *Farmaco*, (2002), 57, 63.
- [8] Stack G.P., Tran M and Bravo B.A., *Pct Int. appl WO*; 2002088146; *Chem Abstr.* (2002), 137, 353044
- [9] Varughese D.J. Manhas MS and Bose A.K., *Tetrahedron Lett.* (2006), 47, 6795.
- [10] Bose A.K., Ganguly S.N., Manhas M.S. Guha A and Pombo-Villass E., *Tetrahedron Lett.*, (2006), 47, 4605.
- [11] Sondhi S.M, Dinodia M. and Kumar A. *Bioorg. Med. Chem.* (2006), 14, 4657.
- [12] Sondhi S.M. Dinodia M. Singh J. and Rani R, *Current bioactive compounds* (2007), 3, 91.
- [13] Sham M. Sondhi, Shubhi Jain, Reshma Rani and Ashok Kumar, I.J.C. (2007), 46-B, 1848-1854.
- [14] Winter C.A., Risley E.A. and Nuss GW, *Proc. Soc. Exp. Biol. Med.* (1962), 111, 544.
- [15] Singh P.P., Junnarkar AV, Seshagiri Rao C, Verma R.K. and Shridhar D.R., *Meth and find exptl. Clini Pharmacol*, (1983), 5, 601.
- [16] Mohammad Azim and Shamim Ahmad, *oriental J.C.* (2011), Vol. 27, No. (2), 673-677.
- [17] Rahul Kumar Rastogi, Poonam Garg and Shamim Ahmad, *Asian Journal of Chem.* (2009), Vol. 21, No.8 , 6144-6148.
- [18] G.S. Bhadange, R.B. Mohod and A.S. Aswar, *Indian Journal of Chem.* (2001), Vol. 40A, PP 1110-1113.
- [19] Patel M.M., Patel M.R., Patel M.N. and Patel R.P., *Indian J. Chem. Soc.* (1981) 20A, 6623.
- [20] Chaudhary C.K., Chaudhary Ratan K and Mishra L.K. J. *Indian Chem. Soc.* (2003), 80, 693-695.
- [21] D.L.Lee "New Concise in Inorganic Chemistry" ELBS, Van No strand, New York-1991.
- [22] Singh M.K. and Kushawaha S.K., I.J.C., (2004), Vol. 43-A, 333-336.
- [23] Sham M. Sondhi, Shubhi Jain, Reshma Rani and Ashok Kumar, I.J.C. (2007), 46-B, 1848-1854.
- [24] M.M. El-ajaily, A.A. Maihub, M. Aboukrisha, A.I.Salem, *Jerash for Researches and studies, Part I*, (2002) 6(2), 7-20.