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Microwave Assisted Synthesis of Indole Derivatives, an their Complexation Behaviour and Biological Studies

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ABSTRACT

Indole 2-Carboxyllic acid on condensation with benzene sulfonyl hydrazide gives the condensation product – Schiff base. This has been characterized by analytical data I.R. N.M.R. spectra. The complexes of Schiff base have been prepared with metals Mn (III), V (III), Co (III), Ti (III) and Fe (III). The complexes has been characterized by elemental analyses, I,R., ^{1}H N.M.R., electronic spectra, molar conductance and Magnetic susceptibilities. These studies suggested Octahedral geometry around the respective metal ions. The ligand and its metal complexes have been screened for their biological activity.

Key words: Microwave assisted synthesis, Indole Derivatives, Biological studies.

INTRODUCTION

The importance of Indole derivatives is quite evident from the number of papers, patents etc. published every year. Indole derivatives possessing antimicrobial[1], antifungal[2], antibacterial[3] and antideprescent[4] activity have been reported in literature. Above mentioned few references indicate versatile nature of Indole derivatives from biological activity point of view. Use of Microwave Irradiation for synthesis of various organic compounds is also reported in literature[5,6]. Maganese, Vanadium and molybdenum possess a number of oxidation states and have excellent complexing property. The last two metals and their complexes exhibit biological properties[7,8]. Keeping in view these facts we have synthesized ligand having oxygen, nitrogen and sulphur donor and studied its structures, complexation behaviour & biological activity.

EXPERIMENTAL

All the chemicals used were of AR grade or equivalent purity. The chemicals used for the preparation of the ligand were Indole 2- Carboxylic acid (Sigma-Aldrich, CAS No. 1477-50-5) and benzene Sulfonyl hydrazide (LOBO India). The ligand N-(phenyl sulfonyl) - 1H-Indole -2-Carbohydrazide was prepared by reported method[9]. 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.

Domestic microwave oven model M 197 DL (Samsung) was used for microwave irradiation. Melting points (m.p.) were determined on a JSGW apparatus and are uncorrected. I.R. spectra were recorded using a Perkin Elmer 1600 FT

spectrometer. ^{1}HNMR spectra were measured on a Brucker WH-500 MHz spectrometer at a Ca 5-15% solution in DMSO - d^6 (TMS 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 benzene sulfonyl hydrazide (344 mg, 2mmol) were mixed throughly. This mixture was subjected to microwave irradiation (keeping inside a microwave oven) for 2.0 Min. at 600 W power Level and reaction progress was monitored by TLC. This process was repeated three times when one of the starting materials disappeared. Crude product was washed with ethyl acetate: diethylether (5:1) (10 ml.) and the product so obtained was further purified by recrystallization from methanol to give pure product.

Preparation Of Metal Complexes

The complexes were prepared by adding the solution of metal in ethanol drop by drop to the solution of ligand till complete precipitation.

The precipitate was filtered, washed with ethanol to remove any unreacted part of either of the reactants. The precipitate was filtered and dried in vacuum dessicator.

Anti-inflammatory activity evaluation

Anti-inflammatory activity evaluation[10] was carried out using carrageenin induced paw Oedema in albino rats. Oedema in 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 was measured by writhing assay[11] using mice (15-20g). Female mice were screened for writhing on day-1 by injecting intraperitonially 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 minutes. 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 Minutes. prior to phenylquinone challenge. Writhing was again recorded for each mouse in a group and a percentage protection was calculated using following formula:

Protection = 100-[{No. of writhings for treated mice)/(No. of writhings for untreated mice)} x 100]. This was taken as a percent of analgesic responce 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. (s) of the ligand and its metal complexes were determined and compared in order to find out the possibilities of formation of complexes. The m.p. (s) 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 1.

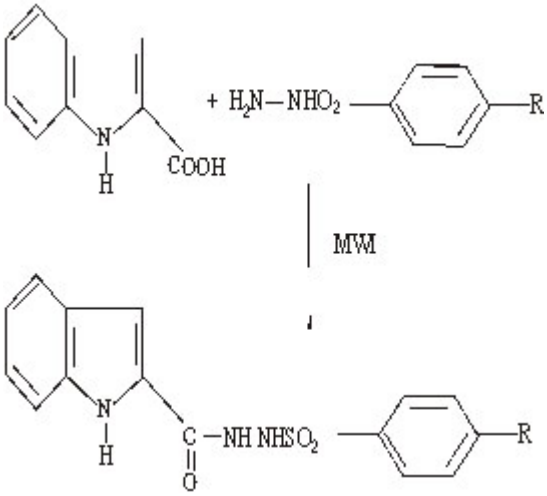
Electronic Spectra

The electronic spectrum of the complex of Ti (III) exhibits a single broad band at 19230 cm^{-1}

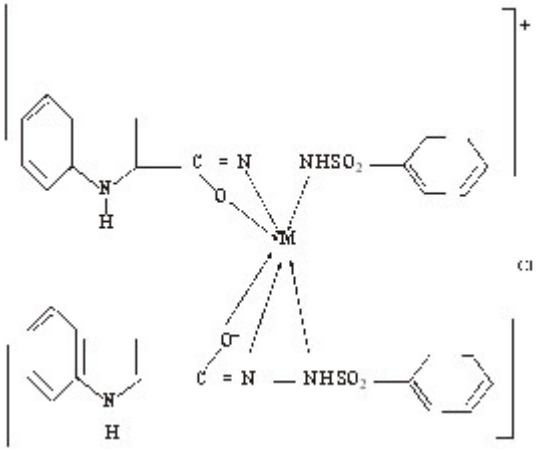
Table. 1: Characterization of synthesised Complexes

S. No.	Formula of the Ligand and Complex and Molecular Weight	Colour	m.p./ D.T. ^{0}C	Elemental analyses						Molar Conductance ohm^{-1} cm^2 mole^{-1}	Magnetic Moments in (B.M.)
				% of C	% of H	%of N	% of S	% of M	% of C		
1a	$C_{15}H_{13}N_3SO_3$ Mol. Wt. = 315	Yellow	180	57.14 (56.97)	4.12 (4.10)	13.33 (13.22)	10.15 (10.0)	-	-	-	-
1b	$[C_{30}H_{24}N_6S_2O_6$ Ti]Cl Mol. Wt. = 711.5	Yellow	235	50.59 (50.50)	3.37 (3.35)	11.80 (11.76)	8.99 (8.90)	6.74 (6.71)	4.98 (4.97)	61	1.71
1c	$[C_{30}H_{24}N_6S_2O_6$ V]Cl Mol. Wt. = 714.5	Yellow	253	50.38 (50.36)	3.35 (3.34)	11.75 (11.72)	8.95 (8.90)	7.12 (7.0)	4.96 (4.93)	64	2.94
1d	$[C_{30}H_{24}N_6S_2O_6$ Mn]Cl Mol. Wt. = 718.5	Brown	261	50.10 (50.0)	3.34 (3.33)	11.69 (11.67)	8.90 (8.88)	7.65 (7.63)	4.94 (4.91)	68	5.40
1e	$[C_{30}H_{24}N_6S_2O_6$ Fe]Cl Mol. Wt. = 719.5	Dark Brown	268	50.03 (50.0)	3.33 (3.32)	11.65 (11.62)	8.89 (8.85)	7.78 (7.75)	4.93 (4.90)	73	5.24
1f	$[C_{30}H_{24}N_6S_2O_6$ Co]Cl Mol. Wt. = 722.5	Yellowish Brown	271	49.82 (49.75)	3.32 (3.31)	11.62 (11.60)	8.85 (8.82)	8.16 (8.06)	4.91 (4.89)	79	Diamagnetic

Figures in parenthesis are observed values.



1a (R=H)



(1b, 1c, 1d, 1e and 1f)
Where M = Ti(III), V(III), Mn (III), Fe (III) and Co (III

assignable to $^2t_2g \rightarrow ^2Eg$ transition for O_h symmetry[12]. The electronic spectrum of complex V (III) exhibits band at 1600 cm^{-1} with a shoulder at 20,500 cm^{-1}. The low energy band has been assigned to ^2A_1g ^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[12].

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 $^5Eg \rightarrow ^5T_2g$ at 18500 cm^{-1}. This broad band occuring at lower frequency with increased intensity indicates the lowering of symmetry from Octahedral Configuration[13].

The electronic spectrum of the complex of Fe (III) exhibited there bands at 11235, 21470 and 27780 cm^{-1} assignable to $^6A_1g \rightarrow ^4T_1g$, $^6A_1g \rightarrow ^4T_2g$ and $^6A_1g \rightarrow ^4Eg$ transitions respectively. These transitions are characteristics of Octahedral Fe (III) complexes[14]. 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[16].

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 n (C=0), amide I [b (NH) + ν (CN)] amide-II [ν (CN) + β (NH)], ν (C=S)

Table 2 : Anti-Inflammatory and Analgesic activity evaluation

Compound	Dose P.O. mg/kg	Anti-Inflammatory activity %	Dose P.O. mg/kg	Activity
1a	100	0.0	100	50
			50	25
1b	100	0.0	100	60
1c	100	0.00	100	20
1d	100	0.0	100	50
1e	100	0.0	100	20
1f	100	0.0	100	25

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

and ν (N-N) modes respectively[17]. In the I.R. spectra of complexes bands due to nν N-H, and ν (C=0) 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 30-40 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.

The ^{1}H-NMR spectrum of the ligand shows signals at 89.66 ppm due to NHCO which disappear on D_2O exchange suggesting removal of NHC(o) proton via enolization. Benzene ring proton appears at 87.63, 7.33 and 7.16 ppm[18].

Biological Studies

Compounds 1a and 1b, 1c, 1d, 1e and 1f at 100 mg./kg. P.O. were tested for anti-inflammatory activity in the Carrageenin induced paw edema model[10] and the results are summarized in Table 2. Compounds 1a, 1b, 1c, 1d, 1e and 1f at 100 mg/kg P.O. were screened for analgesic activity using phenylquinone writhing assay[11] and the results are reported in Table 2.

CONCLUSION

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

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