Original Research Paper

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Chemistry

MICROWAVE ASSISTED SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL STUDIES OF INDOLE DERIVATIVE AND THEIR COMPLEXES.

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ABSTRACT Insole-2–carboxylic acid on condensation with p-chloro phenyl hydrazine gives the condensation product Schiff base. This has been characterized by analytical data, I.R., and 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 have been characterized by elemental analysis, I.R., 1H NMR, electronic spectra, molar conductance, and magnetic susceptibilities. These studies suggested octahedral geometry around the respective metal ions. The ligands and their metal complexes have been screened for their biological activity.

KEYWORDS : 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 antidepressant[4] activity have been reported in the literature. Above-mentioned references indicate the versatile nature of indole derivatives from a biological activity point of view. Use of microwave irradiation for synthesizing various organic compounds is also reported in literature[5-6]. Manganese, 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 ligands having oxygen, and nitrogen, donor atoms, and studied their structure, complexation behavior, and biological activity.

Experimental

All the chemicals used were of A.R. grade or equivalent purity. The chemicals used for the preparation of ligand were indole-2-carboxylic acid (Sigma-Aldrich, CAS No. 1477-50-5) and *p*-chloro phenyl hydrazine hydrochloride (Sigma-Aldrich, CAS No. 1073-70-7). The ligand N-(4-chloro Benzene)-1H-indole-2-carbohydrazide was prepared in the lab from 12% solution of Ti(III) chloride (B.D.H.) by the reported method[9]. All other metal salts were purchased from the market and used as such-

Microwave Oven Model FBIO 80L5F BK (FABER) was used for microwave irradiation. Melting points (m.p.) were determined on JSGW apparatus and are uncorrected. I.R. spectra were recorded using Perkin Elmer 1600 FT spectrometer. ^{1}H NMR spectra were measured on a Bruker WH-500 MHz spectrometer at a ca. 5–15% solution in DMSO-d^6 (TMS as internal standard). Elemental analysis 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 vapors.

Preparation of Ligands

Indole-2-carboxyllic acid (322 mg, 2 mmol) and *4*-chloro-phenyl hydrazine hydrochloride (358.1 mg, 2 mmol) were mixed thoroughly. This mixture was subjected to microwave irradiation (keeping inside a microwave oven) for 2 minutes at 600W power level, and the reaction progress was monitored by TLC. This process was repeated three times until one of the starting materials disappeared.

The crude product was washed with ethyl acetate:diethyl ether (5:1, v/v), 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 until complete precipitation.

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

Anti-inflammatory Activity Evaluation

Anti-inflammatory activity evaluation[10] was carried out using carrageenan-induced paw edema in albino rats. Edema in one of the Kind paws was induced by injection of carrageenan solution (0.1 ml of 1%) into the plantar aponeurosis. The volume of the paw was measured plethysmographically, immediately after and 3.0 hours after the injection of the irritant. The difference in volume gave the amount of edema developed. Percent inhibition of the edema between the control group and compound-treated groups was compared with a standard drug.

Analgesic Activity Evaluation

Analgesic activity was measured by the writhing assay method[11] using mice (15–20 gm). 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 a 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 the 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 groups, and a percentage protection was calculated by using the following formula-

Protection = 100 – [(No. of writhings for treated mouse) / (No. of writhings for untreated mice)] × 100.

This was taken as the percentage 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 ligands and its transition metal complexes with Ti(III), V(III), Mn(III), Co(III), Fe(III) were subjected to elemental analysis where metal and chloride were estimated gravimetrically in the lab. All this analytical data suggested 1:2 M:L stoichiometries for all the complexes.

The m.p. of ligand and its metal complexes were determined and compared in order to find out the possibilities of formation of complexes. The m.p. are given in Table (1). 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 magnetic moments 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) complex is diamagnetic in nature as expected for low spin d^6 ion. The values 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} assignable to $^2T_2g \rightarrow {}^2Eg$ transition for O_h geometry.[12]

The electronic spectrum of complex of V(III) exhibits band at 16000 cm^{-1} with a shoulder at 20500 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

→ $^3T_2g(P)$ transition. These bands are characteristic of octahedral geometry.[13]

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 band occurring at lower frequency with increased intensity indicates the lowering of symmetry from octahedral configuration.[14]

The electronic spectrum of the complex of Fe(III) exhibited three bands at 11230, 21460 and 27790 cm^{-1} assignable to $^6A_1g \rightarrow {}^4T_1g$, $^6A_1g \rightarrow {}^4T_2g$ and $^6A_1g \rightarrow {}^4Eg$ transitions respectively. These transitions are characteristic of octahedral Fe(III) complexes.[15]

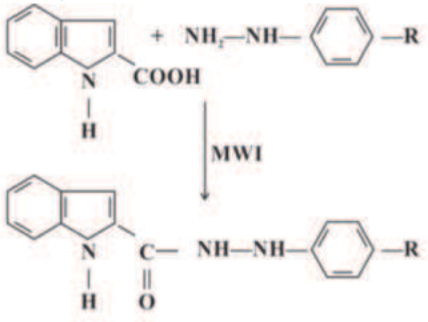
The electronic spectrum of Co(III) complex displays bands at 15110, 21090 and 23370 cm^{-1} assignable to $^3A_1g \rightarrow {}^3T_2g$, $^1A_1g \rightarrow {}^1T_1g$ and $^1A_1g \rightarrow {}^1T_2g$ transitions respectively. These are similar to those reported for other six coordinated Co(III) complexes.[16]

I.R. Spectra

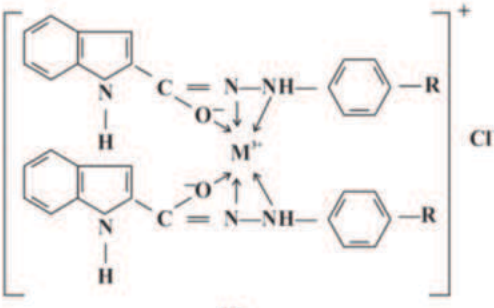
The I.R. spectrum of ligand shows bands at 3370 and 3310 cm^{-1} due to presence of two N–H groups. The bands at 1630, 1450 and 1360, and 1000 cm^{-1} are assigned to ν(C=O), amide-I [ν(NH)+ν(CN)] amide-II [ν(CN) + β(NH)] and ν(N–N) modes respectively.[17]

In the I.R. spectra of complexes, bands due to ν N–H and ν(C=O) are absent. But new bands appear at 1600 cm^{-1} due to ν(N=C) of NCO, suggesting removal of N–H proton via enolization and bonding of enolic oxygen with the metal ion. Furthermore, the amide-I and amide-II bands 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 enolic oxygen. Thus the ligand is behaving in Uninegative tridentate manner.

The I.R. spectrum of the ligand shows ring vibration of indole moiety at 1620, 1560 and 1530 cm^{-1} which remain unaltered in I.R. spectra of complexes excluding the possibility of involvement of N atom of indole in bonding.



1a (R=Cl)



1b

(1a, 1b, 1c, 1d, 1e and 1f)

Where : M= Ti (III), V (III), Mn (III), Fe (III) and and Co (III)

Table 1. Characterization Of Synthesized Complexes

S. No.	Formula of the Ligand and Complexes and Molecular Weight	Colour	M.P. / D.T. ºC	Elemental Analysis					Molar Conductance Ohm^{-1} Cm^2 Mole^{-1}	Magnetic Moments in (B.M.)
				% of C	% of H	% of N	% of Cl	% of M		
1a	$C_{15}H_{12}N_3$ OCl Mol. Wt. = 285.5	Yellow	172	63.05 (63.50)	4.20 (4.16)	14.71 (14.65)	(12.40)	—	–	–
1b	[$C_{30}H_{22}N_3OCl_2$ Ti] Cl Mol wt = 594.37	Yellow	220	60.57 (60.50)	3.70 (3.65)	7.07 (7.05)	17.92 (17.90)	8.05 (8.05)	61	1.71
1c	[$C_{30}H_{22}N_3OCl_2$ V] Cl Mol Wt. = 597.44	Yellow	243	60.26 (60.20)	3.68 (3.60)	7.03 (7.10)	17.83 (17.85)	8.53 (8.50)	64	2.94
1d	[$C_{30}H_{22}N_3Ocl_2$ Mn]Cl Mol Wt. = 601.44	Brown	257	59.86 (59.75)	3.66 (3.60)	6.98 (6.90)	17.70 (17.65)	9.13 (9.10)	68	5.40
1e	[$C_{30}H_{22}N_3Ocl_2$ fe]Cl Mol Mol. Wt. = 602.35	Dark Brown	265	59.76 (59.60	3.65 (3.60)	6.97 (6.95)	17.68 (17.60)	9.27 (9.15)	73	5.24
1f	[$C_{30}H_{22}N_3OCl_2$ Co] Cl Mol. Wt. = 604.44	Yellowish Brown	274	59.55 (59.40)	3.63 (3.60)	6.94 (6.85)	17.62 (17.55)	9.25 (9.20)	79	Diamgnetic

(Figures are in Parenthesis are observed value)

Table 2- Anti-inflammatory And Analgesic Activity Evaluation

Compounds	Dose F.O. mg/kg	Anti-inflammatory Activity %	Dose P.O. Mg/kg	Analgesic Activity %
1a	100	0.0	100 50	60 30
1b	100	3	100	45
1c	100	5	100	20
1d	100	7	100	50
1e	100	0.0	100	30
1f	100	2	100	35

P.O. = From Latin Word per 0. S (means by mouth)

N.M.R. Spectra

The ^{1}H NMR spectrum of the ligand shows signals at 89.66 ppm due to NHCO which disappears 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

Compound 1a, 1b, 1c, 1d, 1e and 1f at 100 mg/Kg p.o. were tested for anti-inflammatory activity in the Carrageenan induced paw edema model and the results are summarized in Table 1.

Compounds 1a, 1b, 1c, 1d, 1e and 1f at 100 mg/Kg p.o. were screened for analgesic activity using phenylquinone writhing assay 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 and these complexes having good anti-inflammatory and analgesic activity.

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