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Ternary Complex of Ni(II) Derived from Substituted Benzothiazole and Benzoimidazole : Synthesis and Biological Evaluation

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ABSTRACT

Mixed ligand derived metal complexes have wide range of applications in medicinal and biological fields.[1-2] Our present work report synthesis of novel ligands using 4-methylacetophenone with 2-aminobenzothiazole (L_1) and 2-aminobenzimidazole (L_2) respectively. Above synthesized ligands (L_1, L_2) were characterized by elemental analysis, molecular weight determination, magnetic moment measurements and various spectroscopic techniques (UV-VIS, FTIR, NMR etc.). Further metal salt of Ni(II) was allowed for complexation with synthesized ligands and characterized. On the basis of above studies a six coordinated octahedral geometry has been proposed for above complex (Ni L_1 L_2 Cl_2. nH_2O). Further, synthesized compounds were evaluated for biological activity against various bacterial and fungal strains and results were concluded. In continuation of our research work, attention is made to synthesize new biologically active compounds by greener methods also.

Keywords: Mixed ligand complex, spectroscopic techniques, 4-methylacetophenone, 2-aminobenzothiazole, 2-aminobenzimidazole.

INTRODUCTION

In recent decades, heterocyclic compounds with nitrogen and sulphur as donor atoms like benzothiazole, benzoimidazole etc. received a broad area of research having wide range of applications in different fields of pharmaceutical, medicinal and agrochemical. Further, metal coordination of these compounds and their derivatives show a significant role in

biological screening. Benzothiazole and benzoimidazole rings are important skeleton of drugs like Ethoxozolomide and Albendazole respectively. As reported earlier, Schiff base complexes and mixed ligand complexes have vast range of application in various fields as confirmed by biological studies.[3-6] An attempt was made to synthesize new ligands derived from 4-methylacetophenone with 2-aminobenzothiazole (L_1) and 2-aminobenzimidazole (L_2) respectively. The ligands act as bidentate with potent nitrogen and sulphur as donor atoms. Further work continued to prepare Ni(II) mixed ligand complex using above synthesized ligands. Stoichiometry revealed 1:1:1 metal ligands ratio in metal ligand complex.[7] Further microwave assisted technique was also employed for above synthetic processes and compared with conventional method.

EXPERIMENTAL

(I) MATERIALS AND METHODS

All chemicals used were of AR grade (Sigma Aldrich) and used without further purification. For preparation of solutions, double distilled water redistilled over alkaline $KMnO_4$ was used. Melting point determinations were done in open capillaries and were uncorrected. Purity of synthesized compounds were checked by TLC using Silica Gel-G plates. All glass apparatus used were thoroughly cleaned, rinsed properly with alcohol and dried in electric oven. Further kept in desiccator to protect from atmospheric moisture.

Methods of analysis

Liebig's method was used for elemental analysis of carbon and hydrogen, nitrogen and sulphur were estimated by **Kjeldahl's** method and **Messenger's** method respectively. Nickel(II) was estimated by **EDTA** (Vogel, 1962) method. Molecular weight determinations were done by **Rast** method. For molar conductance measurement of complex (in DMSO), Systronics Direct Reading Conductivity Meter-304 using glass cell (cell constant = 1.0 cm^{-1}) at room temperature was employed. For measurement of magnetic moment, Gouy's Balance Model no: HO-ED-EM-08 was used. Electronic absorption spectra (UV-Vis) measurements (Lever, 1984) were made on spectro scan UV-2600 double beam spectrophotometer at room temperature. For measurement of FTIR spectra (Kemp, 1991) of synthesized compounds were recorded on model SHIMADZU-JAPAN 8400S FTIR spectrophotometer in region 4000-400 cm^{-1} (Silversein,1981). ^{1}HNMR spectra (Duddeck and Dietrich, 1992) were recorded on Hitachi Perkin Elmer Spectrometer using TMS as internal standard in DMSO-d_6.

(II) SYNTHESIS

(A) SYNTHESIS OF LIGANDS:

(a) Synthesis of MPEIBT [L_1] : 2-N-(4-methylphenylethanimine) benzothiozole.

Equimolar aqueous ethanolic solution of 4-methylacetophenone (10mmol) and 2-aminobenzothaizole (10mmol) were prepared. 10 ml of each of above solutions poured in round bottom flask fitted with water condenser in presence of condensing agent with few drops of glacial acetic acid. The reaction mixture was refluxed for 4 hours on heating mental. Progress of reaction was monitored by TLC using Silica Gel-G plates. After completion of reaction, reaction mixture was cooled at room temperature, kept overnight. Product obtained was filtered washed with alcohol, recrystallized and dried in vacuum. Pale Yellow crystals obtained with yield 55.6% (m.p. 248.3^{o} C) Scheme-I.

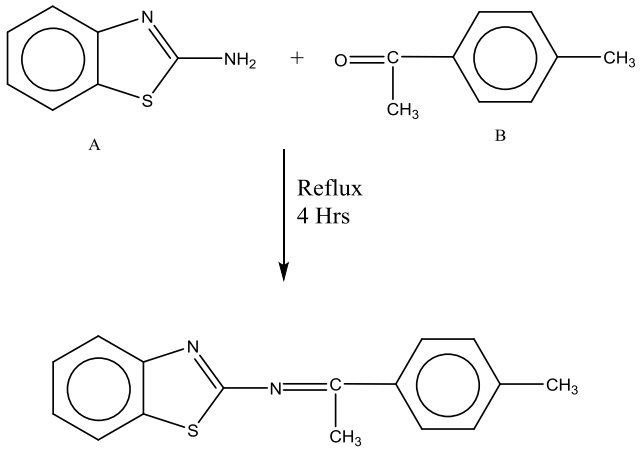
(b) SYNTHESIS OF MPEIBI [L_2]: 2-N-(4-methylphenylethanimine) benzimidazole.

Equimolar aqueous ethanolic solution of 4-methylacetophenone (10mmol) and 2-aminobenzimidazole (10mmol) were prepared. Same procedure was followed as above. Yellowish White crystals obtained with yield 51.7% (m.p. 287.2 ^{o} C) Scheme-II.

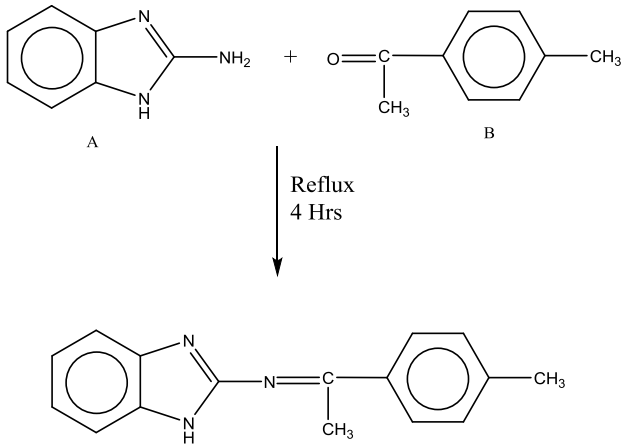
(B) SYNTHESIS OF COMPLEX [Ni L_1 L_2 Cl_2].nH_2O

Conventional thermal procedure was employed for synthesis of complex. 10ml of ethanolic solution of ligand L_1 (10mmol) was added to 10ml of ethanolic solution of ligand L_2 (10mmol) with constant stirring. Now, aqueous solution of $NiCl_2.6H_2O$ (10mmol) was added to above solution with constant stirring. No precipitate seen. Reaction mixture was refluxed for 3 hours (progress & completion of reaction monitored by TLC). After completion, reaction mixture was concentrated, cooled at room temperature. Solid product obtained was filtered, washed, recrystallized and dried in vacuo Scheme-III.

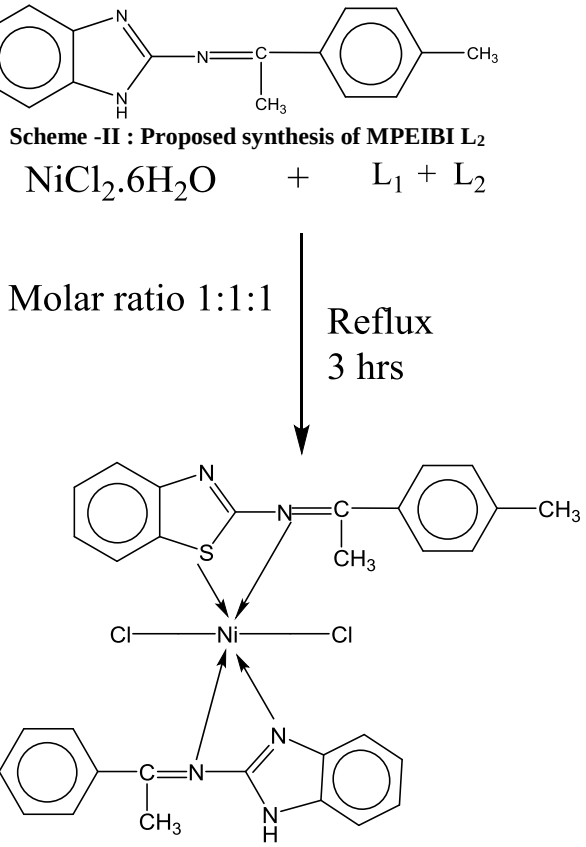
All above synthetic procedures were repeated using microwave assisted technique and results were compared.



Scheme -I : Proposed synthesis of MPEIBT L_1



Scheme -II : Proposed synthesis of MPEIBI L_2



Scheme -III : Proposed synthesis of Complex

Antimicrobial Activity

As reported earlier in our work, biological activity(Barry,1986) of both ligands and complex was done ***in vitro*** against selective bacterial and fungal strains for growth inhibiting potential using **Cup-Plate** method. For bacterial study, gram positive bacteria ***S. aureus***

(MTCC-96), gram negative bacteria ***P. aeruginosa*** (MTCC-424) and fungal strain ***C. albicans*** (MTCC-227) were selected. **Nutrient agar** was employed for bacterial studies, whereas **Malt Yeast agar** was employed as culture media for antifungal study. For antibacterial and antifungal studies, **Norfloxacin** and **Clotrimazole** were used as standard drug. Sterilization of culture medias, petridishes and other glasswares was carried out by autoclave. Incubation period for antibacterial study was 48 hours at 37± 2° C whereas for antifungal study, incubation period was 72 hours at 25± 2° C. Test solutions of all compounds (100µg/ml, 50µg/ml) were prepared by dissolving the test compounds in DMF with definite concentration. For different strains, zone of inhibition (mm) was measured after incubation and results are tabulated in **Table-4**.

RESULTS AND DISCUSSIONS

For all synthesized ligands/ complex, physiochemical data, elemental analysis with molar conductance and magnetic moments are tabulated in **Table-1**. Spectral data of FTIR and ^{1}HNMR are tabulated in **Table-2** and **Table-3** respectively. Antibacterial and antifungal activity results are tabulated in **Table-4**.

Table 1 : Physical Proprieties and Elemental Analysis of Synthesized Compounds

Compound (ligand/ complex)	Colour/ M.P.	Mol.wt. Anal. Calcd. (Found)	% Elemental Analysis Anal. Calcd. (Found)						Molar cond. (ohm^{-1} cm^2 mol^{-1})	μ_{eff} (BM) Appr.
			C	H	N	S	Cl	M		
L_1 (MPEIBT)	Pale Yellow/ 248.3^{O}C	266.3 (266.1)	72.1 (72.0)	5.3 (5.2)	10.5 (10.4)	12.0 (12.2)	-	-	NA	-
L_2 (MPEIBI)	Yellowish White/ 287.2 ^{O}C	249.3 (249.1)	77.0 (76.4)	5.6 (5.7)	16.85 (16.80)	-	-	-	NA	-
$NiL_1L_2Cl_2$	Greenish Yellow 297.1 ^{O}C	645.3 (644.8)	59.5 (59.0)	4.5 (4.4)	10.8 (10.0)	4.9 (4.5)	11.0 (10.8)	9.0 (8.9)	12.63	3.17

Table 2 : Selected FTIR spectral data ν (cm^{-1}) of ligand and complexes

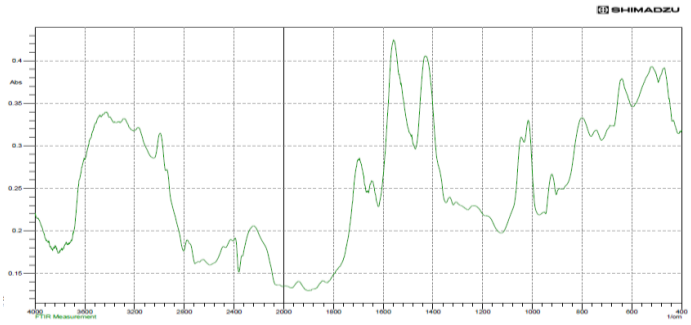
Ligand/complex	ν (C=C) (Str.)	ν (C=C) (Bend.)	ν (C=N)	ν (C-S)	ν (C-H) (Str.)
MPEIBT (L_1)	1446	994	1571	662	3020
MPEIBI (L_2)	1441	812	1550	-	2960
$NiL_1L_2Cl_2$	1436	896	1553	653	2998

Table 3 : Important ^{1}HNMR spectral data □ (ppm) of ligand and complexes

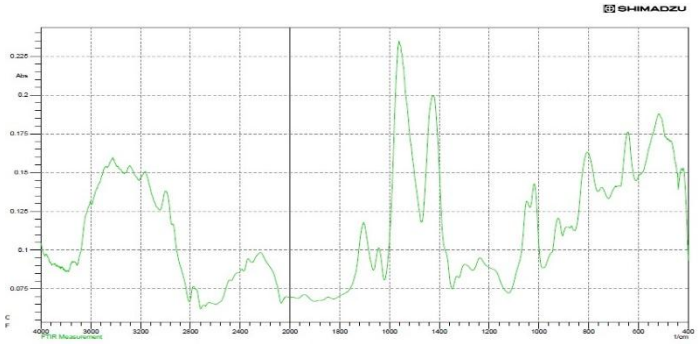
Compound	Ar-H	CH_3 (Azomethine)	CH_3 (Ar-CH_3)
MPEIBT (L_1)	7.6	1.8	2.2
MPEIBI (L_2)	7.7	1.8	2.1
$NiL_1L_2Cl_2$	8.0	2.0	2.3

Table 4 : Antimicrobial Activity of Synthesized Compounds using Cup-Plate Method

Compound	Conc. (µg/ml)	Zone of inhibition (mm)		
		Antibacterial Activity		Antifungal Activity
		S.aureus	*P.aeruginosa*	*C.albicans*
MPEIBT (L_1)	100	29	27	18
	50	20	18	14
MPEIBI (L_2)	100	32	30	24
	50	21	24	15
$NiL_1L_2Cl_2$	100	37	39	24
	50	28	27	22
Norfloxacin (for antibacterial)	50	24	22	NT
Clotrimazole (for antifungal)	50	NT	NT	16



FTIR of L_1



FTIR of L_2

Physiochemical analysis of ligand and complexes compared and it is observed that complexes are coloured with sharp melting points and soluble in ethanol, DMSO, DMF and THF. Elemental analysis revealed that observed values are in good agreement with calculated values. Molar conductance of complex at concentration 0.001 M in DMSO were measured at room temperature. For complex $NiL_1L_2Cl_2$, molar conductance is ~12.63 $\Omega^{-1}cm^2mol^{-1}$

indicating that complex is non-electrolytic in nature. Magnetic moment measurements (μ_{eff} values) for $NiL_1L_2\ Cl_2$ is found ~ 3.17 BM which support octahedral geometry for complex and its paramagnetic nature.

In **FTIR Spectra** (Table-2) shift of absorption frequency of selective bonds to lower frequency supports coordination. New absorption band appeared at 483, 472 cm^{-1} correspond to M-N bond and 521 cm^{-1}, 526 cm^{-1} correspond to M-S bond.

^{1}HNMR (Table-3) spectra of synthesized compounds recorded in $CDCl_3$ and chemical shift expressed in values (ppm) downfield to TMS. Observed peaks at (8.0-7.6 ppm) show the presence of aromatic protons but above peaks in complex compared to ligand was found to be shifted to lower field after complex formation takes place. Methyl protons attached to C=N observed at 1.8 ppm in ligands that show shift to downfield in complexes. In addition, methyl protons attached to phenyl ring observed at 2.1-2.2 ppm that also show shift to downfield in complex.

The peaks in electronic spectrum of complex in DMF solution was studied that was found to shift from 345 nm, 356 nm of ligands to 386 nm in complex (Red Shift) showing complexation behaviour. Electronic spectra of Ni(II) complex shows three additional bands indicating octahedral geometries for both complexes.

On the basis of spectroscopic (FTIR, ^{1}HNMR, electronic) evidences a six coordinated behaviour is expected for complexe with no water molecules either coordinated or lattice held.

In most of the cases, biological screening results for selective bacterial and fungal strains report enhanced zone of inhibition for complex as compared to ligands. This may be due to coordination of ligand to metal ions. Synthesized complex is found to have remarkable antimicrobial activities and are more potent.

CONCLUSIONS

An octahedral geometry has been proposed for synthesized complex. The complex is non-electrolytic in nature with paramagnetic behaviour. No water molecule either coordinated or lattice held are present in complexes because there is no FTIR band related to water.

Our present work reveals that efficiency of metal ions in biological system is increased on complexation with biologically active ligands. Any compound may act either by killing the microbe or by blocking their active sites. The complex is found to have remarkable antibacterial and antifungal activity as compared to respective ligand. It may be further concluded that microwave assisted technique can be more preferred as it is faster,ecofriendly greener approach.

CONFLICT OF INTEREST

There is no conflict of interest.

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