Synthesis and Antifungal Properties of Some Transition Metal Complexes Involving Potentially Active Heterocyclic Ligands

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1 : 1 : 1, M(II)-Npa-TCA/HQ mixed-ligand complexes [M(II) = = Co(II), Ni(II)), Cu(II) and Zn(II); Npa = N-pyridylanthranilic acid; TCA = thiophene-2-carboxylic acid and HQ = 8-hydroxyquinoline] have been prepared and characterized on the basis of elemental analysis, IR and electronic spectral data, conductivity and magnetic measurements. An octahedral environment around the metal ion has been proposed. All the complexes are non--electrolytic in nature. The antifungal activity of the free ligands and their corresponding metal chelates have been determined on some selected fungi.

INTRODUCTION

The importance of mixed-ligand complexes in environmental chemistry,[1] medicinal chemistry,[2] analytical chemistry[3] and industrial chemistry[4] has led to a large number of reports. The information about the role of metal complexes in biological systems, their concentration and presence in different equilibria is of immense importance. Recently, it has been reported[5] that the activity of metal or ligand is considerably increased in the form of metal chelate as compared to that of the free ligand or metal ion. 8-hydroxyquinoline and its derivative have long been establisehd as potential microbial agents and drugs.[6,7] The role of mixed ligand complexes in biological processes has been recognized.[8] It is well established that ternary complexes play a decisive role in the activation of enzymes and also in the storage and transport of active substances through biological membranes.[9,10] In support of the above, the preparation, characterization and antifungal activity of the Co(II), Ni(II), Cu(II) and Zn(II) metal complexes in conjunction with N-pyridylanthranilic acid and thiophene-2-carboxylic acid/8-hydroxyquinoline have been carried out and presented in this communication.

MATERIALS AND METHODS

All the chemicals used were either of AR, BDH or E. Merck grade. The light yellow coloured N-pyridylanthranilic acid was synthesized[11] by condensing sodium salt of o-chlorobenzoic acid and 2-amino-pyridine. The solid metal chelates were synthesized by refluxing a mixture of metal acetates (0.01 M in 30 ml ethanol) with two different ligands (Npa and TCA/HQ) (0.01 M in 50 ml ethanol) for two hours at pH 4—6 adjusted by 1% alcoholic ammonia solution (given in Table I). On concentration the reaction mixture, a coloured precipitate was

obtained. The coloured compound was filtered under suction, washed first with water, ethanol and finally with ether and dried over P_4O_{10} in vacuum. The isolated complexes were tested for purity by running their TLC.

The IR spectra of the complexes and their corresponding ligands were recorded on a Perkin Elmer-521 spectrophotometer. Magnetic susceptibility measurements were carried out at room temperature using Guoy's balance. The electronic spectra were recorded in DMF on a Shimadzu Double beam spectrophotometer UV-150-02. Molar conductance of the complexes was measured in their DMF solutions using the Toshniwal conductivity bridge. Molecular weight of the complexes was determined by the cryscopic method.

RESULTS AND DISCUSSION

The solid metal chelates do not possess sharp melting points and decompose on heating between 230 to 270 °C. The elemental analyses and molecular weight determination of the metal complexes (Table-I) indicate $1:1:1$ (MLL') type stoichoimetry. The values of molar conductance (3.1—4.6 ohm^{-1} cm^2 mol^{-1}) in DMF solution were observed, indicating the non-ionic nature of the complexes.[12]

Magnetic Properties

The magnetic moments of Co(II), Ni(II), Cu(II) and Zn(II) complexes calculated from the corrected magnetic susceptibilities are given in Table I. The observed magnetic moment of Co(II) complexes is within the 4.7—5.2 B. M. range, reported[13] for high spin octahedral complexes. The observed magnetic moment value 3.21 and 3.34 B. M. for Ni(Npa)(TCA) · H_2O and Ni(Npa)(HQ) · H_2O is within the range expected (2.9—3.4 B. M.) for octahedral complexes.[13] The observed magnetic moment 2.12 and 2.01 B. M. of the Cu(Npa)(TCA) · H_2O and Cu(Npa)(HQ) · H_2O complexes agrees well with the spin only value.[14]

Electronic Spectra

The electronic spectra of Co(Npa)(TCA) · H_2O and Co(NPa)(HQ) · H_2O complexes show three absorption bands at 7624, 16366, 19950 and 7636, 16393, 19000 cm^{-1}, respectively, assignable to $^4T_{1g} \rightarrow {}^4T_{2g}$ (F) (ν_1), $^4T_{1g} \rightarrow {}^4A_{2g}$ (F) (ν_2) and $^4T_{1g} \rightarrow {}^4T_{1g}$ (P) (ν_3) transitions in distorted octahedral geometry around the metal ion. The ligand field parameters are consistent with the octahedral configuration of cobalt complexes. The value of ν_2/ν_1 ratio (2.15 for Co(Npa) (TCA) · H_2O and 2.14 for Co(Npa)(HQ) · H_2O) is within the range of theoretical values 2.1—2.2 (Table II). The value of Racah interelectronic repulsion parameter B (903, 891 cm^{-1}) is less than the free ion value (971 cm^{-1}) suggesting a considerable covalent character of the bond. The three bands observed at 9670, 16339, 24630 and 10095, 16670, 24840 cm^{-1} for Ni(Npa)(TCA) · H_2O and Ni(Npa)(HQ)·H_2O complexes may be assigned to $^3A_{2g} \rightarrow {}^3T_{2g}$ (F) (ν_1), $^3A_{2g} \rightarrow {}^3T_{1g}$ (F) (ν_2) and $^3A_{2g} \rightarrow {}^3T_{1g}$ (P) (ν_3) transitions, respectively, in an octahedral geometry.[15] The ligand field parameters Dq, B, β and $LFSE$ have been calculated. The Racah parameter B (797 cm^{-1} for Ni(Npa)(TCA)·H_2O and 748 cm^{-1} for Ni(NPa)(HQ) · H_2O) is less than the free ion value (1040 cm^{-1}). The calculated value of ν_2/ν_1 ratio is within the range expected for an octahedral geometry. The copper complexes show a single broad asymmetric absorption band around 14000 cm^{-1} due to the distorted octahedral environment around copper

TABLE I

Analytical, Molar Conductance and Magnetic Susceptibility Data of Complexes

Metal complex	Colour	Analysis: Found/(Calculated)					Molar conductance* ohm⁻¹ cm² mol⁻¹	μ_{eff} B. M. at 303°K	pH of isolation	Molecular weight: Found (calculated)
		C	H	N	S	M				
Co(Npa)(TCA)·H₂O	Pink	48.68 (48.93)	3.33 (3.38)	6.62 (6.71)	7.63 (7.68)	14.06 (14.12)	3.48	4.92	6.45	401 (417)
Ni(Npa)(TCA)·H₂O	Light green	48.32 (48.96)	3.31 (3.38)	6.69 (6.72)	7.61 (7.69)	13.95 (14.08)	3.21	3.21	6.05	398 (417)
Cu(Npa)(TCA)·H₂O	Black	48.27 (48.39)	3.25 (3.34)	6.52 (6.64)	7.41 (7.60)	14.92 (15.06)	3.12	2.12	5.15	406 (421)
Zn(Npa)(TCA)·H₂O	White	48.08 (48.18)	3.25 (3.33)	6.59 (6.61)	7.51 (7.75)	14.35 (14.43)	3.51	diam.	6.20	410 (423)
Co(Npa)(HQ)·H₂O	Reddish Brown	57.89 (58.07)	3.85 (3.94)	9.57 (9.67)	—	13.49 (13.57)	4.60	5.02	6.30	412 (434)
Ni(Npa)(HQ)·H₂O	Green	57.85 (58.10)	3.81 (3.94)	9.62 (9.68)	—	13.45 (13.52)	4.12	3.34	6.15	408 (434)
Cu(Npa)(HQ)·H₂O	Brown	57.38 (57.46)	3.83 (3.90)	9.54 (9.57)	—	14.37 (14.48)	3.25	2.01	5.05	419 (438)
Zn(Npa)(HQ)·H₂O	White	57.13 (57.22)	3.84 (3.89)	9.41 (9.53)	—	14.76 (14.83)	4.42	diam.	6.25	421 (440)

* At 25 °C of 10⁻³ M solution in dimethylformamide (DMF)

TABLE II

Electronic Spectral Data of Co(II), Ni(II) and Cu(II) Complexes at 25 °C of 10^{-4} M Solution in Dimethyformamide (DMF)

Complex	Band maxima cm^{-1}	Assignment	Dq/cm^{-1}	B/cm^{-1}	β	ν_2/ν_1	LFSE $kcal \cdot mol^{-1}$
Co(Npa)(TCA)·H_2O	7624	$^4T_{1g} \rightarrow {}^4T_{2g}$ (F)	874	903	.92	2.15	14.98
	16366	$\rightarrow {}^4A_{2g}$ (F)					
	19950	$\rightarrow {}^4T_{1g}$ (P)					
Ni(Npa)(TCA)·H_2O	9670	$^3A_{2g} \rightarrow {}^3T_{2g}$ (F)	967	797	.76	1.69	33.15
	16339	$\rightarrow {}^3T_{1g}$ (F)					
	24630	$\rightarrow {}^3T_{1g}$ (P)					
Cu(Npa)(TCA)·H_2O	14200	$^2E_g \rightarrow {}^2T_{2g}$	1420	—	—	—	24.34
Co(Npa)(HQ)·H_2O	7636	$^4T_{1g} \rightarrow {}^4T_{2g}$ (F)	875	891	.91	2.14	15.00
	16393	$\rightarrow {}^4A_{2g}$ (F)					
	19900	$\rightarrow {}^4T_{1g}$ (P)					
Ni(Npa)(HQ)·H_2O	10095	$^3A_{2g} \rightarrow {}^3T_{2g}$ (F)	1009	748	.72	1.65	34.61
	16670	$\rightarrow {}^3T_{1g}$ (F)					
	24840	$\rightarrow {}^3T_{1g}$ (P)					
Cu(Npa)(HQ)·H_2O	14050	$^2E_g \rightarrow {}^2T_{2g}$	1405	—	—	—	24.09

ion.[16] The spectral studies, along with the colour and magnetic moment of the complex, point out the distorted octahedral stereochemistry.

Infrared Spectra

For the sake of brevity, only shifted or altogether new peaks appearing in the spectra of metal chelates have been discussed. The free ligand (Npa) shows a band around 3300—3080 cm^{-1} which is shifted to the lower frequency region in the case of their complex, suggesting coordination through N of -NH group. The IR spectra of free ligand (Npa and TCA) showing band at 1680 cm^{-1} which is shifted to the lower frequency region in the metal complexes confirm the coordination of the ligand to metal ion through carboxylic acid moiety.[17] A strong band at 1500 cm^{-1} in the free 8-hydroxyquinoline may be assigned to C=N bond. In complexes, this band is shifted to a lower wave number, ~1390 cm^{-1}, indicating coordination through nitrogen of the ligand.[18] Further, the strong bands in the region 1170—1110 cm^{-1} probably indicate the presence of coordinated 8-hydroxyquinoline in the M(Npa)(HQ)·H_2O complexes.[19] Ring breathing modes[20] at 840 cm^{-1} in the case of thiophene-2-carboxylic acid are lowered in the case of metal complexes. This clearly indicates the involvement of sulphur of thiophene ring in complexation. The presence of coordinated water molecule in the complex is revealed by stretching modes occurring at 3600—3525 cm^{-1} and bending modes of H—O—H appearing around 1580 cm^{-1}. The appearance of bands at ~485 (M—N)[21], ~435 (M—O)[21] and 380—360 cm^{-1} (M—S) support the coordination through N, O and S donor sites of the ligand.
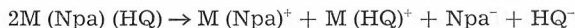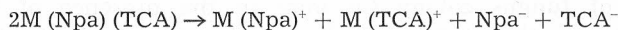
TABLE III

Antifungal Activity of Ligand/Metal Complexes

Ligand/metal complex	Aspergillus niger % inhibition			Aspergillus flavus % inhibition			Penicillium citrinum % inhibition		
	Concentration (ppm)			Concentration (ppm)			Concentration (ppm)		
	100	200	500	100	200	500	100	200	500
TCA	40.5	50.3	90.3	30.8	42.4	87.5	35.3	40.6	85.6
HQ	90.0	92.0	100.0	91.0	93.2	100.0	90.8	95.8	100.0
Npa	56.8	68.0	70.3	65.5	72.8	75.7	60.2	69.3	74.4
Co(Npa)(TCA)·H$_2$O	81.3	90.5	100.0	85.5	96.6	100.0	82.3	93.5	100.0
Ni(Npa)(TCA)·H$_2$O	74.8	85.4	100.0	79.7	91.2	100.0	77.3	88.7	100.0
Cu(Npa)(TCA)·H$_2$O	69.5	72.3	90.5	73.5	80.7	93.8	72.6	75.5	92.2
Zn(Npa)(TCA)·H$_2$O	50.3	55.6	62.9	61.5	67.9	70.3	65.7	60.3	65.5
Co(Npa)(HQ)·H$_2$O	99.1	100.0	100.0	99.4	100.0	100.0	99.3	99.0	100.0
Ni(Npa)(HQ)·H$_2$O	96.3	99.5	100.0	97.3	100.0	100.0	96.8	100.0	100.0
Cu(Npa)(HQ)·H$_2$O	93.5	98.2	100.0	94.2	99.0	100.0	93.9	99.0	100.0
Zn(Npa)(HQ)·H$_2$O	91.2	95.6	100.0	92.3	96.4	100.0	91.5	96.0	100.0

Culture media = Agar-Agar. Time = 96 hours. Temperature = 37 °C.

the chelate is transfered to another system with a strong complexing power, such as thiols, thiophenes, porphyrine and the remaining 8-hydroxyquinoline may combine with cresolase or other metal enzymes. It has been indicated[7] that 1 : 2 chelate of M(II)-8-hydroxyquinoline penetrates the cell and dissociates. 1 : 1 half chelate would then become a toxic entity by combining and blocking the metal substances on enzymes. Gershon and Parmegiani[5] supported the above mechanism and indicated that the antimicrobial activity of M(II)-8-hydroquinoline is not due to the release of 8-hydroxyquinoline within the cell but to the dissociated 1 : 1 complex such as the one reported.[7]

The comparable activity of the mixed-ligand complexes to that of ligands (Npa, TCA and HQ) and 1 : 2, metal-Npa, even though the former possess less lipophilic character, may be due to the dissociation of mixed complexes at the site of action as shown below:

$$2M\ (Npa)\ (TCA) \rightarrow M\ (Npa)^+ + M\ (TCA)^+ + Npa^- + TCA^-$$

$$2M\ (Npa)\ (HQ) \rightarrow M\ (Npa)^+ + M\ (HQ)^+ + Npa^- + HQ^-$$

Both the 1 : 1, cationic complexes thus formed may be acting as active moieties at the site of action reinforcing the total activity. Thus, in the mixed complexes, in addition to 1 : 1, metal-Npa, 1 : 1, metal-TCA/HQ may also be acting as an active agent which increases their activity. Binary complexes individually show a low activity due to their low lipid solubility which will not permit considerable amounts of cationic complexes to go to the site of action.

Apart from this, a comparatively faster diffusion of the metal complex as a whole through the cells of fungi may be one of the important factors. It is evident that these complexes are stable and chemically inert having no

specific active centres. Such compounds can exert a powerful inhibitory effect on an intracellular biological process by concentrating at the susceptible site from which it slowly dissolutes. The growth inhibition capacity of the complexes follows the order: $Co(II) > Ni(II) > Cu(II) > Zn(II)$.

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SAŽETAK

Sinteza i antigljivično djelovanje nekih kompleksa prijelaznih elemenata

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Mješoviti kompleksi Ni(II), Cu(II) i Zn(II) s ligandima: N-piridilantranilna kiselina (Npa), tiofen-2-karboksilna kiselina (TCA) i 8-hidroksikinolin (HA), sastava $M^{II}(Npa)(TCA)$ odnosno $M^{II}(Npa)(HA)$ pripravljeni su i karakterizirani elementnom analizom, infracrvenim i elektronskim spektrima, vodljivošću i magnetskim momentima. Predložena je oktaedarska struktura kompleksa.

U otopini u dimetilformamidu ti su kompleksi neelektrolitske prirode. Ispitano je antigljivično djelovanje slobodnih liganada i pripravljenih kompleksa na odabranim vrstama gljivica.