Biological Important Ni(II) Ternary Complexes Derived from 2-Substituted Benzothiazoles and Amino Acids

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Abstract: Biological important ternary complexes of the type $[\text{NiCl}(\text{L-L})(\text{A-A})(\text{H}_2\text{O})]$ and $[\text{Ni}(\text{L-L}')(\text{A-A})(\text{H}_2\text{O})_2]$, where A-A = Glycine (Gly), Alanine (Ala), L-L = 2-(2'-aminophenyl)benzothiazole (APBT) and L-L' = 2-(2'-hydroxyphenyl)benzothiazole (HPBT), 2-(2'-mercaptophenyl)benzothiazole (MPBT) have been synthesized. These complexes have been characterized by elemental analysis, molecular weight determination, conductivity, magnetic measurements, infrared, electronic spectral and TGA studies. On the basis of above described studies an octahedral geometry has been suggested for these complexes. All these complexes are coloured, thermally stable, monomeric and non-electrolytic in nature. The ligands and their metal complexes were tested against pathogenic fungi *Aspergillus niger* and *Fusarium oxysporum* to assess their fungicidal properties, the antifungal activity data reveals that these metal complexes are found more fungitoxic than the parent ligands.

Keywords: Benzothiazole, Spectral studies, Amino acids, Antifungal activity.

Introduction

Compounds with a benzothiazole moiety have received considerable attention because of their widespread occurrence in biologically active molecules such as antitumor, antimalaria, fungicide, anti-HIV, antiviral and analgesic agents^{1,3}. Recently, radiolabeling of benzothiazole derivatives have been developed for PET imaging in the detection of alzheimer diseases⁴. These compounds also have many industrial applications; for example some 2-substituted benzothiazole are utilized as fluorescence agents in textile dyeing, antioxidants and vulcanization accelerators of rubber.

A large number of benzimidazole derivative have been synthesized and patented as fungicide^{5,6}. The formation and structural aspects of some transition metal complexes of 2-substituted benzimidazole derivatives have been reported by Seth *et al.*⁷ and various other

workers^{8,9}. We describe here the synthesis, characterization and biological activity of Ni(II) ternary complexes derived from 2-substituted benzothiazole *viz.* 2-(2'-aminophenyl)-benzothiazole (APBT), 2-(2'-hydroxyphenyl)benzothiazole (HPBT), 2-(2'-mercaptophenyl)-benzothiazole (MPBT) and amino acids *viz.* glycine (Gly) and alanine (Ala) ligands. As the biological activity is often augmented when a ligand form complexes. The resulting mixed ligand complexes may be of potential biological importance. The structure of ligands used to synthesize the Ni(II) ternary complexes are shown in Figure 1 and 2.

Figure 1. Structure of the ligands APBT, HPBT, MPBT, Gly and Ala

Figure 2. The suggested chemical structures of the Ni(II) ternary complexes

Experimental

All the solvents were distilled prior to use, *o*-aminothiophenol, anthranilic acid, salicylic acid, thiosalicylic acid, NiCl₂·6H₂O were purchased from Merck and used as such.

Physical measurements

Microanalysis was carried out at the CDRI Lucknow, India. Melting points were determined on a capillary melting point apparatus and are uncorrected, IR spectra were recorded (with KBr pellets) on a SHIMADZU 8400 SPIR spectrophotometer. Electronic spectra were recorded on a Varian-Cary UV-visible spectrometer. Magnetic moments were measured on a Gouy balance. Molar conductance were measured in 10⁻³ M DMF on a Systronics conductivity bridge model 305. Molecular weights were determined by the Rast camphor method. Nitrogen was determined by the Kjeldahl's method and sulfur was estimated by the Messenger's method. Chloride was determined by the Volhard's method. nickel was estimated gravimetrically¹⁹.

Synthesis of 2-substituted benzothiazoles (APBT, HPBT, MPBT)

The 2-substituted benzothiazoles *viz.* 2-(2'-aminophenyl) benzothiazole (APBT), 2-(2'-hydroxyphenyl) benzothiazole (HPBT), 2-(2'-marceptophenyl)benzothiazole (MPBT)

were prepared by condensation *o*-aminothiophenol (1.25 g, 0.01 mol) with anthranilic acid (1.37 g, 0.01 mol), salicylic acid (1.38 g, 0.01 mol) and thiosalicylic acid (1.54 g, 0.01 mol) in polyphosphoric acid (20 mL) using the method reported in literature²⁰. The reaction mixture was heated to 250° C under reflux with constant stirring for 4 h. The temperature was brought down to 100 °C and the contents were poured into a large volume of rapidly stirred water. The resultant slurry was made alkaline with 50% NaOH. The crude product was collected by filtration and washed with sufficient amount of water, dried *in vacuo* and recrystallized from ethanol.

Preparation of nickel(II) ternary complex

To a solution of NiCl₂·6H₂O (0.95 g, 0.004 mol) in dry EtOH (25 mL) was added APBT (0.90 g, 0.004 mol) / HPBT (0.91 g, 0.004 mol) / MPBT (0.97g, 0.004 mol) and glycine (0.30 g, 0.004 mol) / alanine (0.36 g, 0.004 mol) in dry EtOH (25 mL). The reaction mixture was then refluxed in the presence of a drop of pyridine with constant stirring for 4 h, and allowed to stand at room temperature overnight. These were filtered, recrystallized from EtOH and dried *in vacuo*.

Results and Discussion

The Ni(II) ternary complexes were synthesized by NiCl₂·6H₂O with 2-substituted benzothiazoles (APBT, HPBT and MPBT) and amino acids (Gly, Ala) in 1:1:1 molar ratio.

Where

L-L = APBT, L-L' = HPBT, MPBT and A-A = Gly, Ala

These reactions are processed easily and lead to the formation of coloured solids, which are stable to air and moisture. The resulting Ni(II) ternary complexes are soluble in DMSO and DMF. The molar conductance values of 10⁻³ M solutions of these complexes lay in the range 10-20 Ω⁻¹ cm² mol⁻¹ in dry DMF, indicating their non-electrolytic behaviour¹⁰. The monomeric nature of these complexes has been confirmed by the molecular weight determination. The analytical data and physical properties of the ligands and their Ni(II) ternary complexes are given in Table 1. The compounds were characterized on the basis of following studies.

Infrared spectra

The important IR spectral bands and their tentative assignments are presented in Table 2. The ligands APBT, HPBT, MPBT, Gly and Ala act as bidentate ligands in these Ni(II) ternary complexes using nitrogen, oxygen and sulfur as donor atoms. The IR spectra of APBT, Gly/Ala shows two strong bands in the region 3400-3370 cm⁻¹ and 3310-3250 cm⁻¹ due to ν_{as} (N-H) and ν_s (N-H) vibrations of NH₂ of these ligands, respectively. These bands are shifted to lower frequency by 35-80 cm⁻¹ in the respective Ni(II) ternary complexes, suggesting the coordination through nitrogen lone pair of the NH₂ group to the Ni atom without any deprotonation¹¹. It is further supported by appearance of the new bands in the region 436-432 cm⁻¹ due to ν(Ni←N) vibration. The appearance of absorption bands in the region 448-445 cm⁻¹ may be assigned to ν(Ni-O) vibration. The occurrence of non-ligand absorption band in the region 320-315 cm⁻¹ may be attributed to ν(Ni-Cl) vibration¹².

Table 1. The analytical data and physical properties of the ligands and their Ni(II) ternary complexes

S.No	Compound and empirical formula	Colour	Yield %	M.P. °C	Elemental analysis found (calcd.) %						Molecular weight found (calcd.)
					C	H	N	S	Cl	Ni	
1.	[NiCl(APBT)(Gly)(H ₂ O)]NiC ₁₅ H ₁₆ O ₃ N ₃ SCl	Bluish Green	60	225	43.58 (43.67)	3.87 (3.91)	10.12 (10.18)	7.70 (7.77)	8.50 (8.59)	14.18 (14.23)	410.01 (412.54)
2.	[NiCl(APBT)(Ala)(H ₂ O)]NiC ₁₆ H ₁₈ O ₃ N ₃ SCl	Bluish Green	62	230	44.95 (45.05)	4.18 (4.25)	9.72 (9.85)	7.42 (7.52)	8.22 (8.31)	13.65 (13.76)	422.52 (426.57)
3.	[Ni(MPBT)(Gly)(H ₂ O) ₂]NiC ₁₅ H ₁₆ O ₄ N ₂ S ₂	Yellowish Green	61	240	43.71 (43.82)	3.85 (3.92)	6.71 (6.81)	15.52 (15.60)	-	14.22 (14.28)	409.10 (411.15)
4.	[Ni(MPBT)(Ala)(H ₂ O) ₂]NiC ₁₆ H ₁₈ O ₄ N ₂ S ₂	Light Green	65	245	45.12 (45.20)	4.18 (4.27)	6.48 (6.59)	15.01 (15.08)	-	13.70 (13.81)	422.02 (425.18)
5.	[Ni(HPBT)(Gly)(H ₂ O) ₂]NiC ₁₅ H ₁₆ O ₅ N ₂ S	Light Green	68	258	45.52 (45.60)	4.02 (4.08)	7.01 (7.09)	8.04 (8.12)	-	14.75 (14.86)	392.50 (395.08)
6.	[Ni(HPBT)(Ala)(H ₂ O) ₂]NiC ₁₆ H ₁₈ O ₅ N ₂ S	Light Green	64	262	46.92 (46.98)	4.36 (4.43)	6.78 (6.85)	7.77 (7.84)	-	14.27 (14.35)	406.02 (409.11)

Table 2. IR spectral data (cm⁻¹) of ligands (APBT, HPBT, MPBT) and Ni(II) ternary complexes

S.No	Compound	ν (C=C)	ν (C=N)	ν (NH ₂)		ν (O-H)	ν (S-H)	ν (C=O)	ν (Ni-N)	ν (Ni-S)	ν (Ni-O)	ν (Ni-Cl)
				Asym.	Sym.							
1.	APBT	1586	1615	3370	3250	-	-	-	-	-	-	-
2.	HPBT	1590	1620	-	-	3330	-	-	-	-	-	-
3.	MPBT	1582	1618	-	-	-	2560	-	-	-	-	-
4.	[NiCl(APBT)(Gly)(H ₂ O)]	1584	1608	3355	3240	-	-	1662	436	-	448	320
5.	[NiCl(APBT)(Ala)(H ₂ O)]	1580	1606	3352	3235	-	-	1660	432	-	445	315
6.	[Ni(HPBT)(Gly)(H ₂ O) ₂]	1585	1612	3360	3242	-	-	1680	438	-	455	-
7.	[Ni(HPBT)(Ala)(H ₂ O) ₂]	1582	1610	3358	3238	-	-	1675	435	-	452	-
8.	[Ni(MPBT)(Gly)(H ₂ O) ₂]	1580	1606	3350	3230	-	-	1670	430	335	440	-
9.	[Ni(MPBT)(Ala)(H ₂ O) ₂]	1578	1604	3348	3228	-	-	1665	428	332	438	-

The broad band at 3330 cm⁻¹ due to ν (O-H) phenolic mode of HPBT, disappears in the Ni(II) ternary complexes, indicating the deprotonation of the OH group and coordination of phenolic oxygen to the Ni atom with the formation of Ni-O bond. This gets further support by the appearance of band in the region 455-452 cm⁻¹ due to ν (Ni-O) vibrations¹³. The IR spectrum of MPBT shows a band at 2560 cm⁻¹ due to ν (S-H) (thiophenolic) vibration, which disappears in the Ni(II) ternary complexes, suggesting the deprotonation of -SH group and coordination through thiophenolic sulfur with the Ni atom. It is further supported by the appearance of new band in the region 335-332 cm⁻¹ due to ν (Ni-S) vibration.

A medium or relatively weak band in the 1620-1615 cm^{-1} region in the IR spectra of the free ligands (APBT, HPBT and MPBT) is due to $\nu(\text{C}=\text{N})$ vibration. This band is shifted to lower frequency by 10-20 cm^{-1} in Ni(II) ternary complexes indicate the bonding of the benzothiazole tertiary nitrogen with Ni atom¹⁴. It is further confirmed by the appearance of band in the region 438-428 cm^{-1} due to $\nu(\text{Ni} \leftarrow \text{N})$ vibration.)

Electronic absorption spectra and magnetic studies

The electronic spectral data and magnetic moments of the Ni(II) ternary complexes are given in Table 3. The electronic spectra of Ni(II) ternary complexes were recorded in nujol mull. These complexes display three absorption band of low intensity due to d-d transitions in the region 9725-9830 cm^{-1} , 18225-18655 cm^{-1} and 28045-28245 cm^{-1} are assigned to the $^3\text{A}_{2g}(\text{F}) \rightarrow ^3\text{T}_{2g}(\text{F})$ (ν_1); $^3\text{A}_{2g}(\text{F}) \rightarrow ^3\text{T}_{1g}(\text{F})$ (ν_2) and $^3\text{A}_{2g}(\text{F}) \rightarrow ^3\text{T}_{1g}(\text{P})$ (ν_3) transition¹⁵, respectively. The position of these bands are similar to those reported for Ni(II) complexes with an octahedral geometry¹⁶. The room temperature magnetic moments of these complexes indicates the paramagnetic nature of the Ni(II) ion the magnetic moments of these complexes have been found in the range 3.26-3.32 B.M., which are in the consistent with the high spin state at the Ni(II) ion and in the range expected for octahedral complexes.

Table 3. Magnetic moments (μ_B) and electronic spectral data for the Ni(II) ternary complexes of 2-substituted benzthiazole and amino acids

S.No.	Complex	Magnetic moment (μ_B) B.M.	Electronic transition and assignments cm^{-1}		
			$^3\text{A}_{2g}(\text{F}) \rightarrow ^3\text{T}_{2g}(\text{F})$ (ν_1)	$^3\text{A}_{2g}(\text{F}) \rightarrow ^3\text{T}_{1g}(\text{F})$ (ν_2)	$^3\text{A}_{2g}(\text{F}) \rightarrow ^3\text{T}_{1g}(\text{P})$ (ν_3)
1.	[NiCl(APBT)(Gly)(H ₂ O)]	3.30	9740	18250	28060
2.	[NiCl(APBT)(Ala)(H ₂ O)]	3.32	9745	18255	28065
3.	[Ni(HPBT)(Gly)(H ₂ O) ₂]	3.26	9828	18650	28240
4.	[Ni(HPBT)(Ala)(H ₂ O) ₂]	3.27	9830	18655	28245
5.	[Ni(MPBT)(Gly)(H ₂ O) ₂]	3.26	9725	18225	28045
6.	[Ni(MPBT)(Ala)(H ₂ O) ₂]	3.27	9730	18230	28050

TGA studies of Ni(II) ternary complexes

The existence of coordinated water molecule in these Ni(II) ternary complexes is confirmed by TGA studies. The coordinated water molecules are lost in the temperature range 100 to 310 °C. The ultimate product of the thermal decomposition in these complex is nickel oxide. Thus, on the basis of analytical data and above describe studies, an octahedral geometry may be assigned for these Ni(II) ternary complexes.

The toxicity increased as the concentration was increased. The antifungal activity data also reveals that Ni(II) ternary complexes of MPBT and Gly/Ala are more fungitoxic than the complexes of APBT and HPBT¹⁸ ligands, respectively.

Biological activity

The antifungal activity of ligands (APBT, HPBT and MPBT) and their Ni(II) ternary complexes were carried out against pathogenic fungi, namely *Aspergillus niger* and *Fusarium oxysporum* by radial growth methods. The solution of the test compound were prepared (50, 100 and 200 ppm) in dimethylformamide. The linear growth of the fungus was recorded by measuring the diameter of the fungus colony after 72 h and the percentage inhibition was calculated as $100(\text{C}-\text{T})/\text{C}$, where T are the diameter of the fungus colony in the control and test plates respectively. The results of antifungal activity of the ligands and Ni(II) ternary complexes have been compared with the conventional fungicide Bavistin taken as standards (Table 4).

Table 4. Fungicidal screening data for ligands (APBT, HPBT and MPBT) and their Ni(II) ternary complexes

Complex	Concentration, ppm					
	<i>Aspergillus niger</i>			<i>Fusarium oxysporum</i>		
	Inhibition after 72 h, %			Inhibition after 72 h, %		
	50	100	200	50	100	200
APBT	40	52	62	43	55	64
HPBT	34	46	58	36	48	60
MPBT	46	58	68	48	61	70
[NiCl(APBT)(Gly)(H ₂ O)]	62	74	88	65	78	90
[NiCl(APBT)(Ala)(H ₂ O)]	63	75	89	66	79	92
[Ni(HPBT)(Gly)(H ₂ O) ₂]	52	68	78	54	70	80
[Ni(HPBT)(Ala)(H ₂ O) ₂]	53	69	80	55	71	82
[Ni(MPBT)(Gly)(H ₂ O) ₂]	72	85	94	73	87	96
[Ni(MPBT)(Ala)(H ₂ O) ₂]	73	86	96	74	88	98
Bavistin (Standard)	86	98	100	87	99	100

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