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Coordination compounds of n-phthaloylglycine and n-phthaloyltyrosine and their antimicrobial activities

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ABSTRACT
Coordination compounds derived from N-phthaloylglycine and N-phthaloyltyrosine were synthesized. The ligands were formed by 1:2 molar condensation of phthalic anhydride with tyrosine and glycine respectively. The complexes were formulated as $[Zn(PHG)_2(H_2O)_2](OAc)_2$[1], $[Ni(PHG)_2(H_2O)_2](OAc)_2$ [2] and $[Cu(PHT)_2](OAc)_2$ [3] characterized by melting point, conductivity, AAS , IR, Uv-Visible spectroscopies. Both ligands were found to be bidentate. For complexes [1] and [2] the metal ions coordinate through both oxygen of OH and C=O in the carboxylic group to give octahedral geometry whereas in the [3] the coordination of metal ion occurs through both oxygen of phenoxyl and carbonyl group resulting in tetrahedral geometry. The antimicrobial studies using four test organisms(*P.aerugenosa, E.Coli, S. aureus and C. albicans*) revealed that the metal complexes exhibit higher activity than their respective ligands.

Introduction

Glycine and Tyrosine are among the amino acids needed in the body and very important in biology[1-5]. Amino acid has been repeatedly shown to produce wide complexes with transition metals[6-12]. N-phthaloylglycine and N-phthaloyltyrosine have a variety of application in medicinal chemistry, pharmaceuticals as dietary supplements, analytical and are used as antimicrobial reagents[13-14]. All of naturally occurring α-amino acids bind in what is known as the glycinato way. This showed that a five-membered ring is formed with the metal amine nitrogen and carboxylic oxygen[15]. The N-protected amino acids are used for the synthesis of peptide bonds in the solid phase synthesis[16-17]. The phthalimide group act as a protecting group for amines and amino acids[15, 18-19]. Earlier work had shown that some drugs showed increased activity when administrated as metal chelate rather than as organic compound. The metal complexes of N-protected α-amino acids are of great interest because they may be used as a basis for understanding metal-protein interactions [20]. Coordination chemistry of these amino acids with metals afford great insight for understanding the coordination chemistry for the protein at large[15].

Much kind of proteins within the body need metal ions to work, which can also be activated or deactivated by metal ions. These reversible effects are caused by ligation of the metal ions and the protein. If one has an understanding of the basic metal ion N-protected α- amino acid complexation, then one could better identify the coordination site within the protein much more easily. Then N-protected α-amino acids could be simply used as models of the binding site of various proteins[21-22].

The present study is aimed to investigate the reaction of phthaloylglycine (PHG) and phthalolytyrosine (PHT) derived from the condensation of phthalic anhydride and glycine and tyrosine respectively with copper, nickel and zinc ions. The prepared ligands and metal complexes were characterized by AAS, IR Spectroscopy and melting point.

Experimental

Materials and methods

Phthalic anhydride, Tyrosine and Glycine were purchased from sigma chemical company (USA). All other solvents and reagent were of purity (Aldrich and sigma) and were used without further purification. The metal salts used for complexation : Nickel (II) acetate tetrahydrate, Zinc (II) acetate dehydrate and Copper (II) acetate were obtained from British Drug House (BDH) Chemical Limited Company.

The melting point of the ligands and complexes were determined using Barlowords scientific melting point apparatus model NOSMP10, the Infra red (IR) Spectra were recored on Fourier Transform Infrared Spectrophometer (FTIR 8400S) with KBr pellet in range 4000 – 400cm^{-1}. The solubility test were carried out on the ligands and their complexes using varied solvents and the percentage of metal content in the complexes were determined using Atomic Absorption Spectrophometer (AAS) from Department of Chemistry, Ladoke Akintola University, Ogbomoso, Nigeria. The antimicrobial activity of the ligands and complexes were carried out at Department of Microbiology, University of Ilorin, Nigeria using the following organisms (bacteria and fungi): *Pseudomonas aeroginosa, Escheriachia coli, Staphylococcus aureus and Candida albican*.

Preparation of ligands (Phthaloyltyrosine and Phthaloylglycine)

The ligands were prepared by condensation of Phthalic anhydride and Tyrosine or Glycine. A mixture of (2.9624g, 0.02mole) phthalic anhydride and (1.8119g, 0.01mole) Tyrosine (or 0.7507g, 0.01 mole) Glycine were melted at temperature range of 195 – 200°C on a oil bath for fifteen minutes. The mixture was stirred occasionally and phthalic anhydride which sublimed and deposited on the wall of the tube was pushed down

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into the reaction mixture by means of a glass rod. The product was cooled and the liquid mass solidified. It was then recrystallized using 10% v/v of ethanol in water. The white crystalline precipitate formed was dried over in a dessicator over anhydrous calcium chloride. The equation of the reactions are shown in Figs.1 and 2

Phthaloyltyrosine (PHT)

Yield : 85%, M.wt = 299.28, M. pt = 150 – 151°C, IR(KBr , cm^{-1}) : 3411, 1771, 1733, 1396, 1268.UV-vis(methanol): λ, nm: 220, 284

Phthaloylglycine (PHG)

Yield : 96%, M.wt = 205.17, M. pt = 191 – 192°C, IR(KBr, cm^{-1}) : 3560, 1770, 1731, 1713, 1217, 995. UV-vis(methanol): λ, nm: 235, 289

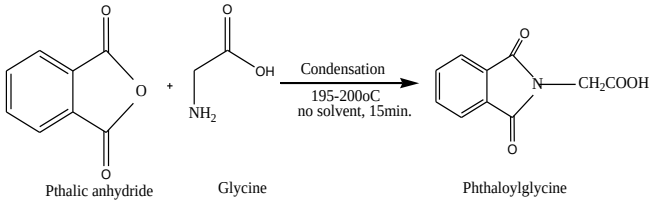

Fig. 1: Synthesis of Phthaloylglycine

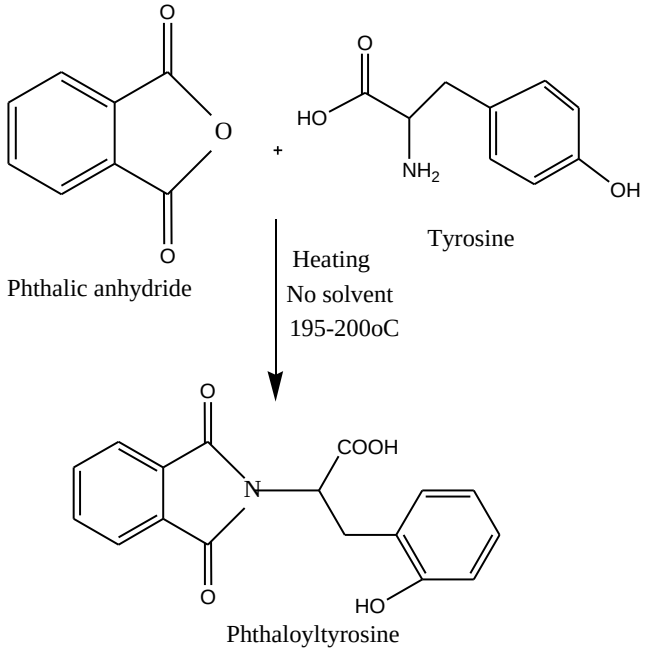

Fig.2: Synthesis of Phthaloyltyrosine

General procedure for Synthesis of Metal Complexes

Metal complexes of Phthaloylglycine (PHG) and Phthaloyltyrosine(PHT)

1mmol of each of ($Zn(CH_3COO)_2 .2H_2O$), ($Ni(CH_3COO)_2.4H_2O$)and $Cu(CH_3COO)_2. H_2O$) in 10ml methanol was added into stirring solution of 2mmol of Phthaloylglycine (0.410g) or Phthaloyltyrosine (0.599g) in 10ml methanol. The resulting mixture was heated under reflux on water bath for 1 hour and white , green and dark green precipitate formed for $[Zn(PHG)_2 (H_2O)_2] (OAc)_2$[1], $[Ni(PHG)_2 (H_2O)_2] (OAc)_2$ [2] and $[Cu(PHT)_2] (OAc)_2$ [3] respectively. Each precipitate was formed on cooling the mixture in an ice bath for two days. The precipitate was filtered, washed severally with methanol and dried over $CaCl_2$ in a dessicator.

$[Zn(PHG)_2 (H_2O)_2] (OAc)_2$[1] , White solid , yield : 85%, M.wt 425, M.pt 296-300°C, Zn 10.51% (calcd), Zn 10.87% (found),IR(KBrcm^{-1}): 3507, 1768, 1704, 1565. 562.

UV-vis(methanol): λ, nm: 230, 284

$[Ni(PHG)_2 (H_2O)_2] (OAc)_2$[2] Green solid, Yield : 80%, M.wt = 454, M.pt. 290°C, IR(KBrcm^{-1}): 3493. 1771, 1701, 1595, 574.

UV-vis(methanol): λ, nm: 295, 595

$[Cu(PHT)_2] (OAc)_2$ [3] Dark Green solid, 75%, M. wt : 435, M.pt.: 268°C, Cu 7.45% (Calcd), Cu 7.93% (found), IR(KBrcm^{-1}) 3482, 1701, 1736, 1385, 532.

UV-vis(methanol): λ, nm: 295, 620

Antimicrobial studies

Antibacterial and Antifungal activities of the ligands and their complexes Invitro antibacterial and antifungal activities assays were performed against *P.aerugenosa, E.Coli, S. aureus and C. albicans* by using an agar well diffusion method described by Tella and Obaleye(2010) [23]. All the ligands and their complexes were tested in triplicate at concentration of 25µg methanol was used as control. The Zones of inhibition formed were measured in mm and shown in Table 4.

Results and Discussion

The complexes are of various colours varied from white , green and dark green different from the colour of ligand indicating that the colours formed depend on the metal ions. . The melting points/decomposition temperature of the complexes are different (higher) than that of respective ligand. which is a confirmation of the formation of the complexes The sharpness of the melting points is an indication of the purity of the compounds. Job's method for stoichiometric determination of the complexes indicate a 1.2 mole ratio with respect to the metal and ligand, The complexes were completely insoluble in water but soluble in methanol and ethanol, The theoretical metal content (%) were found to compete favourably to experimental values obtained. The molar conductance values in methanol(10^{-3}) for these compounds are 100-125$\Omega^{-1}mol^{-1}cm^2$. According to these results, the complexes are electrolytes. The presence of acetate ions outside the coordination sphere was detected by addition of 1:1 (H_2SO_4: H_2O) to the complexes which gave an odour of vinegar. Both ligands were found to be bidentate. Spectra data showed that in compounds $[Zn(PHG)_2 (H_2O)_2] (OAc)_2$[1], $[Ni(PHG)_2 (H_2O)_2] (OAc)_2$ [2]metal ion coordinated to the oxygen atom from hydroxyl and carbonyl group of phthaloylglycine to give an octahedral geometry whereas in $[Cu(PHT)_2] (OAc)_2$ [3] metal ion coordinated to oxygen of phenoxyl and carbonyl group of Phthaloyltyrosine resulting in tetrahedral geometry. From spectroscopic studies and analytical data, suggested structures of the complexes are shown in figure 3 and 4.

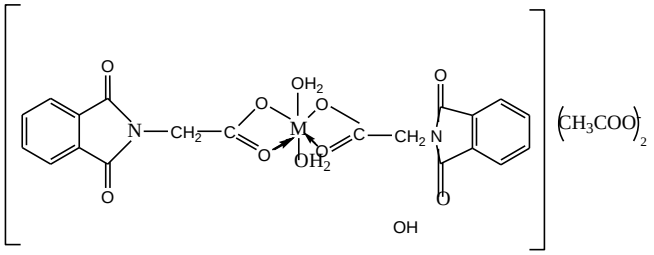

Fig.3: Proposed Structure of $[M(PHG)_2(H_2O)_2](CH_3COO)_2$

M=Zn(II) or Ni(II)

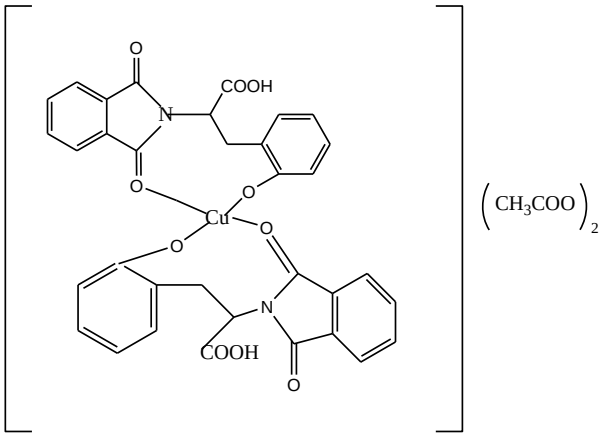

Fig.4: Proposed Structure of $[Cu(PHT)_2](CH_3COO)_2$

Infrared spectra

The importance bands in the IR Spectra of the ligand N-phthaloylglycine as well as its metal complexes are shown in Table 2. The broad band that appeared at 3560cm^{-1} in the spectrum of free ligand (phthaloylglycine) is assigned to stretching frequency ν(OH) of the acid. This disappeared in the spectra of metal complexes confirmed that, the hydrogen ion of carboxylate group in the free ligand was replaced by metal ion via deprotonation[15, 35]. The presence of broad medium bands at 3493 and 3507 cm^{-1} for Ni(II) and Zn(II) complexes respectively can be assigned to ν(OH) vibration of lattice water molecules [24-27] suggesting the coordination of water molecule to metal. The ν(M-O) band observed between 850-780cm^{-1} also confirmed coordinated H_2O or OH. The free ligand also exhibited two strong bands at 1731 and 1713cm^{-1} which is assigned to stretching frequency ν(C=O) of carboxylic group. In case of respective metal complexes, one of these two bands was disappeared and the other one shifted to 1701cm^{-1} and 1704cm^{-1} in Ni(II) and Zn(II) complexes respectively [15]. The band that appeared at 1770cm^{-1} which undergone no remarkable shift in the complexes is assigned to ν(C=O) of the carbonyl. This confirmed that coordination did not take place at ν(C=O) of carbonyl group but at ν(C=O) of carboxylic group. The infrared spectra of metal complexes showed new bands characteristic to ν(COO). These bands appeared at 1595cm^{-1} and 1565 cm^{-1} for Ni(II) and Zn(II) complexes respectively. The absence of stretching frequency ν(C-OH) at 1217cm^{-1} and its bending frequency δ(C-OH at 995cm^{-1} in the spectra of all metal complexes further proved the carboxylate coordination [28-34]. In phthaloyltyrosine metal complex, a strong band at 3411cm^{-1} in the ligand undergone hypsochronic shift in the complexes (3482cm^{-1}) due to the complexation is assigned to stretching frequency of ν(OH) of the phenoxyl group. The band due to carbonyl ν(C=O) stretching vibration which appeared in 1771cm^{-1} in the ligand has shifted bathochromically in the complex. This band shifted to lower frequency by 70cm^{-1} and this suggest the involvement of carbonyl ν(C=O) in the complexation. The band which appeared at 1268cm^{-1} in ligand is assigned to phenolic ν(C-O) stretching vibration and this has no corresponding band in the metal complex which further suggested the coordination of the phenolate anions with the metal ion via deprotonation [35]. In the low frequency region, the new absorption bands obseved in the complexes in the region 532-574cm^{-1} is attributed to ν(M-O) stretching vibration [36].

The Electronic Spectra

The Uv-visible spectra of the ligands and their complexes in methanol are presented in Table 3. Bands between 220-289 nm are attributed to $\pi \rightarrow \pi^*$, $n \rightarrow \pi^*$ transitions within organic ligands. Two bands 230 and 284nm are observed for Zn(II) which confirms the absence of any (d-d) transitions.

Apart from this bands extra bands (595 and 620nm) have been observed for Ni(II) and Cu(II) complexes which attributed to d-d transitions.

Antimicrobial activity

The observation showed that the synthesized metal complexes have more inhibitory activity against bacteria as compared to parental ligands as contained in Table 4. In some cases, ligands and their complexes have similar activity against bacteria. Chelation may enhance or suppress the biochemical potential of bioactive organic species. The higher activity of the metal complexes may be due to effect of metal ions on the normal cell membrane. Metal chelates bear polar and nonpolar properties together; this makes them suitable for permeation to the cells and tissues [37]. Similar correlation and increase in antibacterial activity of ligands on complexation with reference to parent ligands has been well cited [38- 40]. Such increased activity of the metal chelates can be explained on the basis of overtone's concept of and chelation theory [41].

Conclusion

Three complexes of N-phthaloylglycine and N-phthaloyltyrosine were synthesized and isolated. They were characterized using IR, AAS and melting point. Both ligands were found to be bidentate . For complexes $[Zn(PHG)_2(H_2O)_2](OAc)_2]$ and $[Ni(PHG)_2(H_2O)_2](OAc)_2]$ the metal ions coordinate through both oxygen of OH and C=O in the carboxylic group to give octahedral geometry whereas in the $[Cu(PHT)_2](OAc)_2]$ the coordination of metal ion occurs through both oxygen of phenoxyl and carbonyl group resulting in tetrahedral geometry. The N-Phthaloyl ligands and their complexes were screened against bacteria and fungi to assess their potential as antimicrobial agent. The complexes showed greater activity against the three microorganisms compared to N-Phthaloyl ligands

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Table 1: Analytical Data and Some Physical Properties of the Ligand and Metal Complexes

Complexes/ Ligands	Colour	Formular weight	Conductivity $\Omega^{-1}mol^{-1}cm^2$.	M.pt	% Metal Calc(Found)
PHT	White	299	3	150-151	-
PHG	White	205	2	191-192	-
$[Cu(PHT)_2](OAc)_2$	Dark green	455	104	268	7.45(7.93)
$[Zn(PHG)_2(H_2O)_2](OAc)_2$	White	554	112	290	-
$Ni(PHG)_2(H_2O)_2](OAc)_2$	Green	425	125	298	10.51(10.87)

Table 2 : Infrared Spectra of Ligands and their Complexes (cm^{-1})

Ligands/ Complexes	ν(OH)	ν(OH)/ lattice water	ν(C=O) carboxylic	ν(C=O) carbonyl	ν_{as}(COO)	ν(C-OH)	δ(C-OH)	ν(M-O)
PHG	3560m,br	-	1731vs,1713vs	1770vs	-	1217vs	995m,br	-
$Ni(PHG)_2(H_2O)_2](OAc)_2$	-	3493m,br	1701 s	1771s	1595br	-	-	574m
$[Zn(PHG)_2(H_2O)_2](OAc)_2$	-	3507m,br	1704vs	1768s	1565br	-	-	562s
PHT	3411m,br	-	1733s	1770vs	-	-	-	-
$[Cu(PHT)_2](OAc)_2$	3482m,br	-	1736s	1701vs	-	-	-	532s

v = stretching, s = strong, br = broad, m = medium, vs = very strong, δ= bonding, as = asymmetrical

Table 3: Uv-Visible spectra of free ligands and their complexes 10^{-3}M in methanol

Compounds	Λ max, nm	Wavenumber(cm^{-1})	Assignment
PHG	235, 289	42553, 34602	$\pi \rightarrow \pi^*$, $n \rightarrow \pi^*$
PHT	220, 284	45455 , 35211	$\pi \rightarrow \pi$, $n \rightarrow \pi^*$
$[Zn(PHG)_2(H_2O)_2](OAc)_2$	230, 284	43478, 35211	$\pi \rightarrow \pi^*$, $n \rightarrow \pi^*$
$[Ni(PHG)_2(H_2O)_2](OAc)_2$	295, 595	33898, 16806	C.T, d-d
$[Cu(PHT)_2](OAc)_2$	292 , 620	34247, 16129	C.T, d-d

Table 4: Effect of Ligand and Metal Complexes on the Growth of Bacteria

Ligands/ Complexes	Diameter of Inhibition Zone (mm)			
	P. aerugenosa	*E. coli*	*S. aureus*	*C. albicans*
PHG	11	13	10	12
PHT	13	10	11	15
$Ni(PHG)_2(H_2O)_2](OAc)_2$	15	20	16	13
$[Zn(PHG)_2(H_2O)_2](OAc)_2$	2.1	1.2	1.2	1.2
$[Cu(PHT)_2](OAc)_2$	2.0	1.5	1.0	1.5