<https://doi.org/10.36293/sfj.2019.0043>

SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL STUDIES OF TRANSITION METAL(II) COMPLEXES OF L-TYROSINE AMINO ACID

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Abstract

Complexes of Cu(II), Fe(II), Mn(II), Cr(II), Ni(II), Co(II) and Zn(II) of L-tyrosine amino-acid were synthesized and characterized by physicochemical methods based on their solubility, metal analysis, infrared and UV-Visible techniques. Through N- atoms of the amino group and O- atom of the carboxylic group L-tyrosine acts as a bidentate ligand. The proposed octahedral geometries for Cu(II), Ni(II), Co(II), Zn(II) and square planar geometries for Fe(II), Mn(II) and Cr(II) tyrosine complexes are in agreement with their electronic spectra. The antimicrobial sensitivity of $[\text{Cu}(\text{Tyr})_2 \cdot 2\text{H}_2\text{O}]$, $[\text{Co}(\text{Tyr})_2 \cdot 2\text{H}_2\text{O}]$ and $[\text{Ni}(\text{Tyr})_2 \cdot 2\text{H}_2\text{O}]$, studied, show promising activities against, *Bacillus subtilis* ATTC 33923, *Bacillus cereus* ATTC14579, *Candida albicans* MTTC 227, *Proteus mirabilis* ATTC 21784 and *Salmonella typhi* ATTC 14028 standard strains of microorganisms used. From the results obtained, the enhanced antimicrobial activities of the complexes showed the contributory effects of the metals as a result of the increase lipophilicity, which subsequently favored permeation through the lipid layer of cell membrane to the target organisms.

Keywords: Amino acid, Antimicrobial, L-Tyrosine, bidentate.

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Introduction

Chemical species that are indispensable which perform a major biological functions in living things may be linked to twenty amino acids called building blocks proteins (Howland *et al*, 2003). Tyrosine (Tyr) (Fig. 1) is one of the twenty standard amino acids present in the body and used by cells to synthesize proteins. It is a non-essential amino acid, meaning that it is not only ingested from diet but also synthesized by the body (Kapalka, 2010). This amino acid is synthesized in human body from phenylalanine

by the enzyme phenylalanine hydroxylase, which has tetrahydrobiopterin as a cofactor (De Meer, 2003). This enzyme is essential in conditions related to the metabolism of phenylketonuria and defective biopterin, during the impairment of hydroxylation of the phenyl ring in phenylalanine. Hydrogen bonds in tyrosyl play an important role in stabilizing both secondary and tertiary protein structure and is also an active contributor to site substrate such as carboxypeptidase A and lactate dehydrogenase a coenzyme binder. A number of transmembrane signaling pathways an ingredient

for cell growth are being regulated by the of peptide-bound tyrosine residues through phosphorylation regulates. Thus, defects in tyrosine catabolism results in broad physiological impact (Gary and Smith, 2017).

Figure 1: Structure of L-Tyrosine

The presence of a phenolic hydroxyl group on tyrosine is responsible for its exceptional reactivity (Seim *et al.*, 2011), in addition to this, it also has a carboxylic group, and an amino group. It can be found deep within the protein structure because of its nonpolar nature (Spicer and Davis, 2014). Vital biological molecules, such as thyroxine, dopamine, adrenaline, and melanin herald from tyrosine. Transition metals Complexes especially those with amino acids present in proteins or peptides have varying degrees of biological processes involving oxidation, electron transfer and oxygen conveyer (Stanila *et al.*, 2007). In recent times, there is significant interest in the complexes of amino acids which have catecholic or phenolic side chains (Refat *et al.*, 2008). It was reported that the metal complexes of L-β-(3,4-dihydroxyl phenylalanine) (DOPA), formation of the complex was through chelation of the amino acid using the deprotonated catecholic -OH group. (Ares-Santos *et al.*, 2013; Bagheri *et al.*, 2008; Amirov *et al.*, 2014), this inferred the role of metal ions, in the biological reactions of DOPA and tyrosine.

In spite of the biological significance of tyrosine, few works have done on its transition metal complexes. X-rayed structures of tyrosine derivatives of copper(II) complexes were reported (Reddy and Sastry, 2005; Reddy *et al.*, 2006; Raymond and Cossy, 2008). Antimicrobial activity of Ni(II) tyrosine complex against medically essential bacteria and

fungi was demonstrated by Islam *et al* (Islam *et al.*, 2007). Milan Remko *et al* used computational chemistry for the study involving conformations and energetic synthesized transition metal cations complexes such as Ni(II), Cu(II) and Zn(II) with phenylalanine, tyrosine and tryptophan (Remko *et al.*, 2011). In order to increase the data base, here, we expand the scope of tyrosine synthesis to include more transition metal(II) salts to give their corresponding complexes, characterisation and antimicrobial studies against some standard strains of microorganisms.

Experimental

Materials and Reagents.

Reagents and solvents used were of analytical grade with no further purification. L-tyrosine, nickel(II) chloride hexahydrate, copper sulphate pentahydrate, manganese(II) chloride, ferrous acetate anhydrous, zinc sulphate heptahydrate, chromium(II) sulphate, cobalt(II) chloride hexahydrate were obtained from Aldrich chemicals.

Physical measurements

The electronic spectra of the complexes in methanol were recorded on UVD- 2960 Double Beam PC Scanning spectrophotometer between 190-900nm and solid reflectance was recorded on Genesis 10S v1.200 spectrophotometer at the Ladoke Akintola University, Ogbomosho, Nigeria. Infra- red spectra were recorded using Perkin Elmer FT-IR Spectrophotometer equipped with KBr disc in the range 4000-400cm⁻¹, and melting points were determined with Stuart SMP10 Melting point apparatus.

Synthesis of Metal(II)tyrosine complexes [M(Tyr)₂].nH₂O where M = Ni, Cu, Cr, Fe, Mn, Zn: The metal(II) tyrosine complexes were prepared according to published procedure (Stanila *et al.*, 2007) except cobalt tyrosine complex. 2 mmol of the ligand [Tyr] was dissolved in 20 ml distilled water, this was followed by the addition of 0.33 ml of 30% NaOH to cause deprotonation. 1mmol of the metal salts in 2 ml of distilled water was added

to the deprotonated amino acid solution under stirring and stirring continued for an hour. The precipitates were filtered off, washed with distilled water several times, dried in air and latter dried over silica gel in vacuo. Yield: (Ni, 0.2070 g (45.52%), Cu, 0.2770 g (60.28%), Cr, 0.2184 g (53.01%), Fe, 0.2360 g (56.73%), Mn, 0.2040 g (49.16%) and Zn, 0.2130 g (46.16%).

Preparation of [Co(Tyr)₂]: This was prepared by a little modification of the published procedure (Stanila *et al.*, 2007). 1mmol of the metal salt in methanol was added to 2 mmol of the ligand in methanol. 0.33ml of 30% NaOH was added to the ligand to bring about deprotonation. After stirring for an hour, the solution was treated with an equal amount of diethyl ether until complete precipitation. The brown precipitate formed was filtered and quickly transferred into a dessicator due to its hygroscopic nature. Yield: 0.4027g (88.51%)

Antimicrobial susceptibility test: Disc diffusion method was employed to determine the inhibition zones of these compounds (Bisno *et al.*, 2003). The samples were tested against *Bacillus subtilis* ATTC 33923, *Bacillus cereus* ATTC14579, *Candida albicans* MTTC 227, *Proteus mirabilis* ATTC 21784 and *Salmonella typhi* ATTC14028 standard strains microorganisms using Nutrient agar medium. Dissolved complexes and controls were then absorbed on filter paper discs (6mm). Sterilized swabs were dipped into inoculum tubes of the microorganism used. These were used to

inoculate the dried surface of the agar plates by streaking the swab three times over the entire agar surface, the plates were rotated each time at 60°C to make sure there were even distribution of the inoculum. The inoculated plates were left at room temperature for 5 mins. The metal complexes were dissolved in pure DMSO to make a solution of 10 mg / ml concentration which was impregnated on 6 mm Whatman discs. The discs impregnated were placed on the surface of the agar using forceps. Similarly, impregnated discs with 0.8 mg/mL gentamycin and DMSO was also placed on the surface of the agar separately. The agar plates were inverted and incubated at 35° C and 37° C for 24 hours for the bacteria and 72 hours for the fungi respectively. Gentamycin and ketocanazole were used as reference. The experiment was carried out in triplicate and the zones of inhibition measured in millimeter.

Results and Discussion

The reaction of L-tyrosine with metal(II) salt of Mn, Cu, Co, Fe, Zn, Cr and Ni resulted in complexes (Fig 3.) which are stable at room temperature and exhibit variety of colours with good yields as shown in Table1. The complexes melt at temperature above 200°C except Zinc complex which decomposes at 198°C, and are mostly insoluble in most widely known solvents, although few showed varying degree solubility. The analytical data are summarized in Table1 below.

Table 1: Analytical data for the complexes

Compound	Mol.Wt (g/mol)	Colour	% Yield	M.Pt (°C)	%Metal Exp (Calc)
[Cu(Tyr) ₂].2H ₂ O	459.54	Deep blue	60.28	211	13.97 (13.82)
[Fe(Tyr) ₂]	415.93	Brick red	56.73	227	13.21 (13.44)
[Mn(Tyr) ₂]	414.93	Brown	49.16	245	13.78 (13.23)
[Cr(Tyr) ₂]	411.99	Light green	53.01	200	12.48 (12.61)
[Ni(Tyr) ₂].2H ₂ O	454.69	Light green	45.52	202	13.78 (12.90)
[Co(Tyr) ₂].2H ₂ O	454.93	Brown	88.51	232	8.10 (7.71)
[Zn(Tyr) ₂].2H ₂ O	461.40	White	46.16	198	14.91 (14.59)

Tyr = Tyrosine

Infra- red spectra of synthesized compounds

The IR spectra obtained from the analysis of the ligand and the metal complexes were evaluated and were assigned through comparison with the reported in the literature. The IR data is presented in Table 2. The observed $\nu(\text{NH}_2)$ band at 3205cm^{-1} , $\nu(\text{NH})_{\text{as}}$ at 1611cm^{-1} and $\nu(\text{NH})_{\text{sy}}$ at 1511cm^{-1} in tyrosine spectrum were shifted to higher wave number in most complexes prepared indicating the coordination through the $-\text{NH}_2$ end of tyrosine (McAuliffe and Murray, 1973; Rosu *et al.*, 2003; Batiu *et al.*, 2005). There are two ways by which tyrosine can lose one of its protons i.e from carboxylic acid group or phenolic group. However, carboxylic acid group deprotonate easily since the α -amino acid moiety acts as a chelating agent (McAuliffe and Murray, 1973). Thus, the absorption bands at 1587cm^{-1} and 1435cm^{-1} in the spectrum of L-tyrosine are ascribed to $\nu(\text{COO}^-)_{\text{as}}$ asymmetric and $\nu(\text{COO}^-)_{\text{sy}}$ symmetric stretching vibration. These are moved to higher frequencies in the

spectra of the complexes displaying the participation of the carboxylic group in coordination to the metal ion (Socrates, 2001). The difference between the symmetry and asymmetry stretching vibration of COO^- group ($\Delta\nu$ which is equal to $187\text{--}207\text{cm}^{-1}$) gave indication about the manner of coordination of carboxylic group, this value indicated that amino acid coordinated through COO^- group behaved as monodentate donor (Abdel-Rahman *et al.*, 2016).

The $\nu(\text{O-H})$ stretching vibrations does not appear in the spectrum of the ligand, but do appear as broad in the spectra of some the complexes around 3662cm^{-1} to 3311cm^{-1} , indicating the presence lattice water molecule coordinated to the metal ion. The $\nu(\text{M-O})$ and $\nu(\text{M-N})$ bands were observed at $802\text{--}533\text{cm}^{-1}$ and $450\text{--}351\text{cm}^{-1}$. The bands have been assigned stretching respectively; this indicates ligand participation via the N and O atoms (Aiyelabola *et al.*, 2012).

Table 2: IR data of tyrosine ligand and its metal(II) complexes

Complexes/ Ligand	$\nu(\text{NH}_2)$	$\nu(\text{NH})_{\text{as}}$	$\nu(\text{NH})_{\text{s}}$	$\nu(\text{COO}^-)_{\text{as}}$	$\nu(\text{COO}^-)_{\text{s}}$	$\nu(\text{OH})$	$\nu(\text{M-N})$	$\nu(\text{M-O})$
L-tyrosine	3205_{br}	1611_{s}	1510_{w}	1587_{w}	1435_{m}	-	-	-
$[\text{Cu}(\text{Tyr})_2] \cdot 2\text{H}_2\text{O}$	3299_{br}	1603_{s}	1515_{w}	1568_{w}	1440_{m}	3311_{br}	401_{w}	682_{w}
$[\text{Fe}(\text{Tyr})_2]$	3205_{br}	1608_{s}	1512_{w}	1590_{w}	1454_{w}	-	354_{s}	699_{w}
$[\text{Mn}(\text{Tyr})_2]$	3204_{br}	1609_{s}	1513_{w}	1590_{w}	1453_{s}	-	351_{s}	802_{w}
$[\text{Cr}(\text{Tyr})_2]$	3207_{w}	1615_{s}	1513_{w}	1591_{w}	1454_{m}	-	450_{w}	620_{w}
$[\text{Ni}(\text{Tyr})_2] \cdot 2\text{H}_2\text{O}$	3356_{br}	1658_{s}	1518_{w}	1614_{w}	1460_{m}	3589_{br}	409_{w}	533_{w}
$[\text{Co}(\text{Tyr})_2] \cdot 2\text{H}_2\text{O}$	3443_{br}^*	1633_{s}	1516_{w}	1503_{w}	1441_{m}	-	390_{w}	535_{w}
$\text{Zn}(\text{Tyr})_2 \cdot 2\text{H}_2\text{O}$	3293_{br}	1599_{s}	1515_{w}	1574_{w}	1407_{m}	3550_{br}	410_{w}	534_{w}

Key: w= weak; s= sharp; m= medium; br= broad; sym= symmetric; asy= asymmetric, * band for NH overlaps with OH of water

Electronic spectra of the synthesised complexes

The electronic spectral absorptions of the ligand and complexes (Fig. 3) are presented in Table 3. The electronic spectra of L-tyrosine gave two bands at 210nm (47619cm^{-1}) and 235nm (42553cm^{-1}) and which are assigned to $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ respectively. Cobalt complex with electronic configuration of d^7 having a spectroscopic ground term of 4F , exhibited three bands in the visible region at 490nm (20408cm^{-1}), 505nm (19801cm^{-1}) and 515nm (19417cm^{-1}) ascribed to $^4T_{1g}(F) \rightarrow ^4T_{1g}(P)$, $^4T_{1g}(F) \rightarrow ^4A_{2g}(F)$ and $^4T_{1g}(F) \rightarrow ^4T_{2g}(F)$ which is consistent with a high-spin octahedral geometry (Ackermann, 2011; Sreekanth and Kurup, 2003) which agrees with octahedral geometry [25-26]. The following absorptions exhibited by Nickel tyrosine complex at 48780cm^{-1} , 21367cm^{-1} are ascribed to metal to ligand charge transfer, while the d-d transitions 18867cm^{-1} , 16611cm^{-1} , 15060cm^{-1} which have been assigned to $^3A_{2g} \rightarrow ^3T_{1g}(P)$, $^3A_{2g} \rightarrow ^3T_{1g}(F)$ and $^3A_{2g} \rightarrow ^3T_{2g}$ respectively suggesting an octahedral geometry (Affan *et al.*, 2009). The blue complex of Cu

complex gave a single band at 798nm (18348cm^{-1}), which is assigned to $^2E_g \rightarrow ^2T_{2g}$ transition typical of octahedral complex (Manceau and Matynia, 2010; Sarhan *et al.*, 2011).

The spectrum of this complex, $[\text{Mn}(\text{Tyr})_2]$ exhibited bands at 35336cm^{-1} which is ascribed to metal- ligand charge transfer and d-d bands at 13315cm^{-1} , 13477cm^{-1} , 13812cm^{-1} to $^6A_{1g} \rightarrow ^4T_{2g}$, $^6A_{1g} \rightarrow ^4E_g$, $^6A_{1g} \rightarrow ^4E_g$ transitions (Aiyelabola *et al.*, 2012). The $[\text{Fe}(\text{Tyr})_2]$ complex spectrum exhibited metal to ligand charge transfer at 30769cm^{-1} and the d-d transition bands at 22472cm^{-1} , 20284cm^{-1} , 18797cm^{-1} correspond to $A_{1g} \rightarrow B_{1g}$, $A_{1g} \rightarrow B_{2g}$ and $A_{1g} \rightarrow E_g$ respectively which is characteristics of square planar geometry (Affan *et al.*, 2009). The electronic spectra of Chromium complexes in $[\text{Cr}(\text{Tyr})_2]$ showed bands at 23255cm^{-1} , 21505cm^{-1} , 11363cm^{-1} ascribed to metal to ligand charge transfer, $A_{1g} \rightarrow A_{2g}$ and $A_{1g} \rightarrow B_{1g}$ respectively. The electronic spectra of Zinc complexes $[\text{Zn}(\text{Tyr})_2] \cdot 2\text{H}_2\text{O}$ showed bands in visible region at 20284cm^{-1} which may be as a result of metal to ligand charge transfer in an octahedral geometry.

Table 3: Electronic spectra of L-tyrosine and its metal complexes.

Complex/Ligand	Energies(cm^{-1})	Tentative Assignment	Probable Geometry
L-tyrosine (Tyr)	47619 42553	$\pi \rightarrow \pi^*$ $n \rightarrow \pi^*$	
$[\text{Cu}(\text{Tyr})_2] \cdot 2\text{H}_2\text{O}$	12531 18348	$^2E_g \rightarrow ^2T_{2g}$	Octahedral
$[\text{Fe}(\text{Tyr})_2]$	30769 22472 20284 18797	Charge transfer $A_{1g} \rightarrow B_{1g}$ $A_{1g} \rightarrow B_{2g}$ $A_{1g} \rightarrow E_g$	Square Planar
$[\text{Mn}(\text{Tyr})_2]$	13315 13477 13812 35336	$^6A_{1g} \rightarrow ^4T_{2g}$ $^6A_{1g} \rightarrow ^4E_g$ $^6A_{1g} \rightarrow ^4E_g$ Charge transfer	Square Planar
$[\text{Cr}(\text{Tyr})_2]$	23255 21505 11363	Charge transfer $A_{1g} \rightarrow B_{2g}$ $A_{1g} \rightarrow B_{1g}$	Square Planar

[Ni(Tyr) ₂].2H ₂ O	48780	Charge transfer	Octahedral
	21367	Charge transfer	
	18867	$^3A_{2g} \rightarrow ^3T_{1g}(P)$	
	16611	$^3A_{2g} \rightarrow ^3T_{1g}(F)$	
	15060	$^3A_{2g} \rightarrow ^3T_{2g}$	
[Co(Tyr) ₂].2H ₂ O	25641	Charge transfer	Octahedral
	20408	$^4T_{1g}(F) \rightarrow ^4T_{1g}(P)$	
	19801	$^4T_{1g} \rightarrow ^4A_{2g}$	
	19417	$^4T_{1g}(F) \rightarrow ^4T_{2g}$	
[Zn(Tyr) ₂].2H ₂ O	20284	Charge transfer	Octahedral

Figure 2: Proposed structure for the octahedral complexes

Figure 3: Proposed structure for the square planar complexes

Antimicrobial studies

The metal complexes (Fig.3) were screened for their antimicrobial activities against *Bacillus subtilis* ATTC 33923, *Bacillus cereus* ATTC 14579, *Candida albicans* MTTC 227, *Proteus mirabilis* ATTC 21784 and *Salmonella typhi* ATTC 14028. The antimicrobial report is summarized on Table 4. The complexes [Zn(Tyr)₂].2H₂O, [Mn(Tyr)₂], [Fe(Tyr)₂] and [Cr(Tyr)₂] are insoluble in DMSO and in nearly all

solvents fit for the screening and this cause a serious challenge to conduct their antimicrobial studies. Antimicrobial screening was only conducted on [Cu(Tyr)₂].2H₂O, [Co(Tyr)₂].2H₂O and [Ni(Tyr)₂].2H₂O as presented in Table 4. The complexes exhibited better antimicrobial activity than L-tyrosine ligand.

The results showed the contributing effect of the metals by the increase antimicrobial activities

exhibited by the complexes. The polarities of the metal ions are greatly reduced through chelation due to the partial sharing of their positive charge with the donor groups and probable p-electron delocalization over the chelate ring. Lipophilic nature of metal ions are enhanced chelation and this will result in easy penetration through the lipid layer of cell membrane. Majority of the complexes gave comparable zones of inhibition

which strengthen the fact that donor atoms and the amount of the chelate ring are comparable for the complexes. Only Copper complex exhibited activity against the fungus used *Candida albicans*. The exhibited antimicrobial activities of the complexes are lower when compared with the positive control gentamycin.

Table 4: Antibacterial screening of metal(II) complexes of L-tyrosine

Compounds/ microorganisms	<i>Bacillus subtilis</i>	<i>Bacillus cereus</i>	<i>Proteus mirabilis</i>	<i>Salmonella typhi</i>	<i>Candida albicans</i>
Gentamycin	26	26	36	25	30
DMSO	NA	NA	NA	NA	NA
L-Tyrosine	NA	15	12	NA	12
Cu(Tyr) ₂ .2H ₂ O	NA	15	15	10	14
Co(Tyr) ₂ .2H ₂ O	13	14	15	12	NA
Ni(Tyr) ₂ .2H ₂ O	10	10	14	NA	NA

NA = no activity, positive control = Gentamycin, negative control = DMSO

Conclusions

Metal (II) complexes of L-tyrosine amino acid were synthesized and characterized using physicochemical method. Based on the evidences from percentage metal analysis, solubility test, infrared spectra and electronic spectra measurement. Through the amine N and carboxylic O atoms, L-tyrosine behaved as a bidentate ligand. From the results obtained, six coordinate octahedral and four coordinate square planar geometries were projected for the synthesised complexes. The antimicrobial sensitivity of [Cu(Tyr)₂.2H₂O], [Co(Tyr)₂.2H₂O] and [Ni(Tyr)₂.2H₂O], study showed promising activities against *Candida albicans* MTTC 227, *Bacillus subtilis* ATTC 33923, *Bacillus cereus* ATTC 14579, *Proteus mirabilis* ATTC 21784 and *Salmonella typhi* ATTC 14028 standard microorganisms used. The results obtained showed the contributing effect of the metals in enhancing antimicrobial activities which was exhibited through increase in lipophilic nature as a result of chelation, which consequently improves the penetration of

the cell membrane through the lipid layer to the intended organisms.

Acknowledgement

The authors thank Professor I. A .Oladosu of Department of Chemistry, University of Ibadan for his useful suggestions

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