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SOLID-STATE SYNTHESIS, SPECTRAL AND BIOLOGICAL STUDIES OF Fe (II) COMPLEX DERIVED FROM PARACETAMOL

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ABSTRACT

New solid-state metal complex of Fe (II) with paracetamol (ligand), that is, $[Fe(para)_2Cl_2]$ were synthesized mechanically in 1:2 ratio. The complex has been characterized using physicochemical properties and spectral studies. From the IR and electronic spectral studies, the spectra of the complex were different from that of ligand suggesting the formation of coordination compound. Paracetamol was found to be bidentate ligand in which Fe (II) ion coordinated through the oxygen atom of carbonyl of ketone and nitrogen atom of amide in which the complex is assumed to have octahedral geometry. The complex has shown good antimicrobial activities. The solid-state synthetic method is quick and gives a higher yield, without the need of solvent or heating. Its present higher efficiency in terms of materials, time and energy compared to solution-based synthesis. It is therefore, recommended among others that, solid-state synthesis method should be used in the synthesizing drugs with metals.

***Key words*:** Complex, Solid-State, Paracetamol, Liquid assisting grinding

INTRODUCTION

The term solid-state synthesis is often used to describe the interactions in which reactions are activated mechanically and lead to a variety of molecular or supramolecular compounds, usually starting from solids where neither a solvent medium nor controlled vapour-phase interactions are utilized [1]. Numerous transition metals with drugs molecules complexes show wide-ranging pharmaceutical activity, which place them in several biochemical processes and anti-varies agents. Many methods (such as solution based and solid-state) were published for preparing of the ligand-metal complexes. NMR spectroscopy, IR spectroscopy, UV-visible spectroscopy has been used to elucidate the properties of the complexes [2]. Recently, solid-state synthesis gained more attention, because the reactions most of the times are convenient to use than solution-based synthesis, are cost effective and reduce environmental contamination [3]. Liquid assisted grinding (LAG), also known as solvent drop grinding is an extension of traditional solvent free mechanochemical techniques by which small amount of liquid (LAG liquid assisted grinding solvent) is used as an addictive to enhance or control reactivity [4].

In this article, the solid-state preparation of new transition metal complex of paracetamol, i.e. $[FeCl_2(Para)_2]$ was obtained by grinding together solid paracetamol and the inorganic salt $FeCl_2$ using liquid assisted grinding (LAG) of $(C_2H_5)_2O$ and also to determine the activity of the complex in order to establish how metal-drug binding influence the activity of the drug.

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MATERIALS AND METHODS

Glassware and metal salt used were obtained from department of chemistry Aminu Saleh College of Education, Azare and Active Pharmaceutical Ingredients (API) of Paracetamol was obtained from Buya pharmaceutical industry Azare, Bauchi State, Nigeria and were used without further purification.

Solid State Synthesis (Liquid Assisted Grinding)

The solid-state synthesis, was conducted by 2.0g of the ligand and 1.0g of iron (II) chloride using glass mortar and pestle. Diethyl ether (as LAG) was added in two drops and grinded for 15 minutes until a clear brown powder was obtained which was recrystallized using diethyl ether. [5].

$$FeCl_2.4H_2O + 2Para \xrightarrow[(C_2H_5O)_2O]{\text{Grinding}} [Fe(para)_2Cl_2]$$

Scheme 1: Solid-state synthesis of $[Fe(para)_2Cl_2]$

Physical properties of synthesized complex

Based on the method by [5] the melting point and temperature decomposition was carried out using Stuart melting point apparatus (SMP 10), solubility of the ligand and complex were determined in different solvents ranging from polar to non-polar such as distilled water, methanol, ethanol, CCl_4, benzene, dimethyl formamide (DMF) and diethyl sulfoxide (DMSO) and molar conductivity was carried out using conductivity meter of model DSS-307 in $1x10^{-3}$ DMSO at chemistry department Bauchi State University Gadau. Results are presented in table 1.

Magnetic Susceptibility

$$n = \frac{Xi}{1 - Xi}$$

Where n = number of coordinated ligands

X_1 = mole fraction of maximum absorbance

The prepared metal complex was introduced in to the balance's capillary tube up to a given mark and the reading recorded using magnetic susceptibility balance of Sherwood scientific Cambridge UK. The formula below was used to calculate the magnetic susceptibility (X_g) [2]. That is:

$$X_g = \frac{C\ x\ L\ (R - Ro)}{10^9\ M}$$

Spectral studies

FTIR spectra were recorded in the range of 400-4000cm^{-1} using FTIR by Agilent Technologies and electronic spectra using ultraviolet spectrometer lambda 35 with the range of 200-700nm at Instrumental and central laboratories Bayero University Kano, Nigeria.

Determination of Metals to Ligand Ratio

The number of ligands coordinated to the metal ion was determined using Job's method of continuous variation. Method of [6] was modified in which 3.0 mmol of DMSO solution of the ligand and the metal were prepared. The ratio (in ml) 00:16, 01:15, 03:13, 05:11, 07:09, 09:07, 11:05, 13:03 of ligand to metal salt were taken from the ligand solution and the metal chloride respectively. A total volume of 16ml was maintained (in order) throughout the process and the male fraction of the ligand was calculated in the mixture. The solution of the metal salt was scanned (as blank) to find the wavelength of maximum absorbance (λ_{max}) for particular metal ion [6]. The machine new fixed at λ_{max} before taken the absorbance values. The absorbance values were extrapolated against mole fraction of the ligand and the number of coordinated ligands was determined using:

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Antimicrobial Activity

Sensitivity discs were punched from Whatman no.1 filter paper, sterilized in bijous bottles by autoclaving at 121^0C for 15 mins. Sensitivity discs of 0.008g of the extract were prepared and dissolved in 1 ml of DMSO using doubling dilution to give a stock solution of 500μg, 1000μg, 2000μg and 4000μg. Standardized inoculate of each isolated were swabbed on to the surface of Mueller Hinton agar in separate petri dishes and the disc of the standard extract of ciprofloxacin (30μg). The plates were inverted and allowed to stand for 30mins, then incubated aerobically at 35^0C for 18hours. This was followed by measurement of the zone of inhibition formed by the test organisms around each of the extract and standard antibiotic discs [7].

RESULTS AND DISCUSSION

The solid-state synthesis (LAG) was completed within a shorter time of 10-15 minutes.

Table 1. ***Physical properties of paracetamol and its metal (II) complex***

Ligand/ Compounds	Molecular formula	Molar Mass ($gmol^{-1}$)	Colour	Melting point (^{o}C)	Decomposition temperature (^{o}C)
Paracetamol	$C_8H_9NO_2$	151	White	174	-
[Fe(Para)Cl_2]	$C_6H_{17}NO_3Cl_2$	428	Brown	-	243

The reactions of ligand and metal salt produce brown colour of [Fe(para)$_2$Cl$_2$].[5]. The complex decomposed at 243^0C compare with the ligand that melted at 174^0C, the higher value proves evidence of coordination and more stability nature of the complex as presented in table 1. The value agreed with similar complex reported by [8].

Table 2. ***Solubility of Paracetamol and its metal (II) complex***

Ligand/ Complex	Distilled water	CCl_4	Benzene	Diethyl ether	Acetone	Ethanol	Methanol	DMF	DMSO
Para	IN	SS	IN	SS	SS	IN	IN	S	S
[Fe(Para)Cl_2]	IN	IN	IN	IN	IN	IS	IN	SS	S

Key: S = soluble, IN = insoluble and SS = slightly soluble

From table 2 both paracetamol and its complex [Fe(para)$_2$Cl$_2$)] are soluble in DMSO, insoluble in ethanol, methanol and water and slightly soluble in other organic solvents, this agreed with the saying of "like dissolves like". [9].

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Table 3. ***Electronic spectra, conductance in DMSO solvent and magnetic moment (B.M) for prepared metal complex with their suggested geometry***

Compounds	Electronic Spectra			Conductance in DMSO ($\Omega^{-1}cm^2\ mol^{-1}$)	Magnetic moment (BM)	Suggested Geometry
	Wavelength (nm)	Energy (cm^{-1})	Assignments			
Paracetamol	208	48077	$n \rightarrow \pi^*$			
	219	4662	$\pi \rightarrow \pi^*$			
	233	44843	C-T band			
[Fe(Para)Cl_2]	242	41322	$\pi \rightarrow \pi^x$	30.5	5.69	Octahedral
	247	40486	MLCT band			
	251	39840	$^5T_2 \rightarrow {}^5T_{2g}$			
	301	33223	$5T_g \rightarrow {}^5E_g$			

The molar conductance in $1x10^{-3}$ DMSO presented in table 3. Conductivity measurement have frequently been used in elucidating the structure of complexes within their limit of their solubility in a particular solvent, as reported in the literature [9]. Fe (II) complex has a molar conductance value of 30.5 $\Omega^{-1}cm^2\ mol^{-1}$ which indicate that it is non-electrolyte that lie within octahedral geometry in DMSO as reported by [9].

The electronic spectra of the free ligand (paracetamol) exhibited three main bands appeared at 208nm, 219nm and 233nm which was assigned in the assignment of $n \rightarrow \pi^*$, $\pi \rightarrow \pi^*$ and C-T band and its complex shows the bands in the region of 242nm, 247nm, 251nm and 301nm respectively.[10]. These are interpreted to $\pi \rightarrow \pi^x$, MLCT band, $^5T_2 \rightarrow {}^5T_{2g}$ and $5T_g \rightarrow {}^5E_g$ respectively, which indicate an octahedral geometry around Fe (II) ion, as reported by [10].

Table 4. ***The IR spectra (4000-400 cm^{-1}) of paracetamol and its metal (II) complex***

Ligand/complex	υ(OH)	υ(N-H)	υ(C =O)	(M-O)	(M-N)	(M-Cl)
Paracetamol	3163.40	1566.35	1655.39	-	-	-
[Fe(Para)Cl_2]	3156.40	1562.36	1651.43	478.10	605.11	713.30

The IR data of the ligand and its complex are presented in table 4. The bands at 1655cm^1 and 1566cm^{-1} in the free ligand is assigned to υ(C =O) and υ(N-H) carbonyl of amide which was shifted to 1651cm^{-1} and 1562cm^{-1} for the complex which suggested there is a coordination between the metal and the oxygen atom in both the carbonyl. The bands at 478.10cm^{-1}, 605cm^{-1} and 713cm^{-1} in [Fe(para($_2Cl_2$] which could not be traced in the free ligand is assigned to M-O, M-N and M-Cl respectively. These values prove the formation of a new compound. Similar results have been reported by [11].

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Table 5. ***Mole fraction of the ligand (paracetamol) and Absorbance of Fe^{2+} with the ligand***

Mole fraction X (total volume = 9ml)	Fe: $L_2\lambda_{max}$ = 580nm
0.060	0.102
0.191	0.098
0.315	0.177
0.440	0.210
0.565	0.251
0.688	0.224
0.810	0.227
0.940	0.130
1.000	0.098

Metal-ligand ratio (1:2) as presented in table 5 was estimated using Job's method of continuous variation where a plot of the absorbance against mole fraction gives a curve with maximum absorbance corresponding to the ligand. Mole fractions was used in calculating the number of ligands coordinated to metal ion which suggested 1:2. [6].

Antibacterial studies as presented in table 6, revealed that the complex $[Fe(para)_2Cl_2]$ is active against all bacteria isolates in higher concentrations with the exception of the inactivity in lower concentration (S. Aureus and E. Coli at both 500 $\mu g/agar$ [12].

Table 6. ***Antibacterial test of paracetamol and its metal (II) complex***

Compounds	Concentration ($\mu g/agar$ −well	S. Aureus (mm)	E-Coli (mm)
Paracetamol	4000	18	16
	2000	15	14
	1000	13	11
	500	10	8
$[Fe(Para)Cl_2]$	4000	13	11
	2000	10	9
	1000	8	7
	500	-	-
Standard Ciprofloxacin	500	35	30
	200	-	-

Keys: S. Aureus = staphylococcus Aureus **E. Coli = Escherichia coli**

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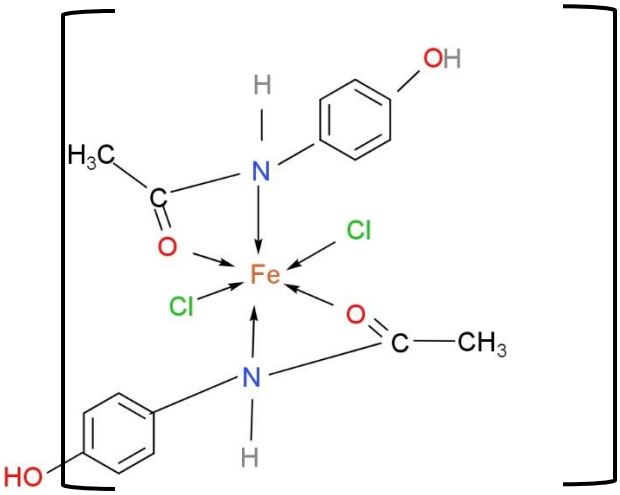
On the basis of the analytical data obtained viz: melting point, conductivity measurement, magnetic susceptibility (effective magnetic moment), Job's method, UV and FTIR spectral studies, the tentatively structure of proposed metal (II) complex of paracetamol as follow: -



Proposed structure of [Fe(para)$_2$Cl$_2$]

CONCLUSION

Paracetamol is very interested ligand in which so many researchers synthesized such as [13] using solution-based synthesis. This work has demonstrated the use of solid-state method (as reliable method) to obtained the same result.

From the values obtained in spectral studies, conductivity and magnetic measurement suggested octahedral geometry. In the spectral studies of both IR and UV-Visible spectroscopy the ligand is coordinated to the metal ion to form a complex of [Fe(para)$_2$Cl$_2$] through υ(C =O) and υ(N-H) of amide given rise to octahedral geometry.

RECOMMENDATION

This research work encourages on the important of solid-state method over solution-based synthesis for the production of metal (II) drugs complexes, because it give higher yield, promote reactions very quickly, cost effective, reduce environmental contamination etc.

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CONFLICT OF INTEREST

The authors agreed and accepted that, no conflict of interest.

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