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Stoichiometric Determination of Fe (II), Ni (II) and Cu (II) Complexes of Metronidazole

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Abstract
1-(2-hydroxylethyl)-2-methyl-5-nitroimidazole (metronidazole) complexes of Fe(II), Ni(II) and Cu(II), were prepared in methanol. The complexes were characterized using melting point, infrared, uv/visible spectroscopy while Job's spectroscopic mole fraction method was used to establish the stoichiometries of the complexes (M:L). The increase in the melting point of the complexes compared to the free ligand provided evidence for complexation. The 1-(2-hydroxylethyl)-2-methyl-5-nitroimidazole is a bidentate ligand, which coordinated to the Fe(II), Cu(II) and Ni(II) ions through the oxygen of the hydroxyl group and nitrogen of -C=N group giving the complexes of the form $M(met)_2$(M= Cu) and $M(met)_2.2H_2O$ (M=Fe and Ni) resulting in complexes of mole ratio of 1:2 (M:L). It is found that Fe(II) and Ni(II) formed complexes of octahedral geometries, while Cu(II) formed complexes of square planar geometry, due to the nature and steric disposition of the metronidazole molecule.

Keywords: job's plot, ligand, mole ratio, metronidazole-complexes, stoichiometries

Introduction
It is now a thing of interest to inorganic research chemists over the last few decades due to the capability of metal complexes enhancing biological activity of some medicinal drugs [1]. It is well-known that some drugs act via chelation or by inhibiting metalloenzymes but for most of the drugs act as potential ligands [2]. A lot of studies have been carried out to ascertain how metal binding influences the activities of the drugs viz Co(III) complexes with Vic-Dioxime ligands [3],Nalidixic acid [4], iron (II) chloride complexes with some 2-amino benzimidazole ligands[5] etc, while interest in medical application of metronidazole has been gaining more attention in recent years.

Metronidazole is chemically called, 1-(2-hydroxyethyl)-2-methyl-5-nitroimidazol and the structure displayed in figure 1. It is a well-established antibacterial agent in the treatment of various bacterial infections and antiprotozoal agent. It is a therapeutic agent of choice for amoebiasis and also used in combination with other antimicrobial drugs against yeast infections [6]. 1H-imidazole has both proton donor and acceptor properties [7]. Imidazole functionalities have been used for complex reactions with different molecular components such as carboxylic acids to obtain liquid crystalline assemblies [8].

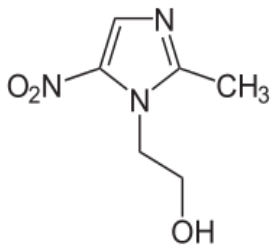

Fig 1: 1-(2-hydroxyethyl)-2-methyl-5-nitroimidazole

Although a few paper have been published on the metal complexes of metronidazole viz Callaghan [9], which reported platinum and copper complexes of metronidazole and 2-methyl–5-nitrobenzimidazole. Another study by Obaleye and Lawal [7], also reported synthesis and characterization of cobalt, iron and nickel complexes of metronidazole. These studies on interaction of metronidazole with metal ions were based mainly on the synthesis and characterization of transition metal complexes of metronidazole and their biological activities as antibacterial agents. The aim of this study was to stoichiometric ally determine Fe (II), Ni (II) and Cu(II) complexes of metronidazole. The complexes prepared were characterized using melting point, infrared, uv/visible spectroscopy while Job's spectroscopic mole fraction method was used to establish the stoichiometries of the complexes (M: L).

Materials and Methods
Metronidazole was purchased from Sam Pharmaceutical Limited, Ilorin, Kwara State, Nigeria. The $FeSO_4.7H_2O$, $CuSO_4.5H_2O$ and $NiSO_4.6H_2O$ were purchased from Finlab, Owerri.

Materials
Magnetic stirrer, pH meter, UV-visible spectrometer v2.30 (UV-2500PC Series), FTIR-8400S Fourier Transform Infrared Spectrophotometer

Procedures
Preparation of stock solution
The stock solution of Fe^{2+} (0.01 M) was prepared by dissolving 0.249 g of $FeSO_4.7H_2O$ in buffer solution. The solutions were made up to the mark in volumetric flask with appropriate buffer solution of the pH range 1-10.

The stock solution of Ni^{2+} (0.01 M) was prepared by

dissolving 0.2629 g of $NiSO_4.6H_2O$ in buffer solution. The solutions were made up to the mark in volumetric flask with appropriate buffer solution of the pH range 1-10.
The stock solution of Cu^{2+} (0.01 M) was prepared by dissolving 0.249g of $CuSO_4.5H_2O$ in buffer solution. The solution was made up to the mark in volumetric flask with appropriate buffer solution of the pH range 1-10.
Similarly, (0.01M) solution of the ligand was made by dissolving 0.171g of metronidazole in 100 cm^3 in methanol. The absorbance of the stock solution of Fe^{2+}/ metronidazole, Ni^{2+}/ metronidazole, and Cu^{2+} / metronidazole were checked between 200-750nm.

Preparation of working solution
The dilute solutions of Fe^{2+}, Ni^{2+}, Cu^{2+} and the ligand ($1x10^{-5}$ M) were obtained by the appropriate serial dilution of the stock solution. 1.0 cm^3 of the solution was diluted and made up to 100 cm^3.

Preparation of Fe (II) metronidazole complex
Exactly 0.68 g (4 mmol) of metronidazole was dissolved in 10 $cm^3$of methanol on warming, and 0.55 g (2 mmol) of $FeSO_4.7H_2O$ was dissolved in 1 cm^3 of water, both solutions were mixed and stirred for 5 minutes using magnetic stirrer. The resulting reddish-brown solution/mixture was left for four days. This was filtered, washed and rinsed with methanol and distilled water, the crystals were dried in a desiccator containing a drying agent.

Preparation of metronidazole Ni (II) complex
Exactly 0.68 g (4 mmol) of metronidazole was dissolved in 10 $cm^3$of methanol on warming, and 0.53 g (2 mmol) of $NiSO_4.6H_2O$ was dissolved in 1 cm^3 of water, both solutions were mixed and stirred for 5 minutes using magnetic stirrer. The resulting pale green solution was left for four days until crystals were formed. This was filtered, washed and rinsed with methanol and distilled water, the crystals were dried in a desiccator containing a drying agent.

Preparation of Cu (II) metronidazole complex
Exactly 0.68 g (4 mmol) of metronidazole was dissolved in 10 $cm^3$of methanol on warming, and 0.49 g (2 mmol) of $CuSO_4.5H_2O$ was dissolved in 1 cm^3 of water, both solutions were mixed and stirred for 5 minutes using magnetic stirrer. The resulting deep blue solution was left for four days until crystals were formed. This was filtered, washed and rinsed with methanol and distilled water, the crystals were dried in a desiccators containing a drying agent.

Spectroscopic analysis
The infrared spectra of the ligand, metronidazole (Met) and its complexes were recorded in solid state as KBr pellets from 500 – 4500 cm^{-1} using FTIR-8400S Spectrophotometer. The uv/visible spectral of the ligand, metronidazole (Met) and its complexes were recorded on UV-visible spectrometer v2.30 (UV-2500PC Series) using methanol as solvent [5].

Results and discussion
The reactions of the metronidazole with the metal ions gave coloured complexes in good yields according to the equations:

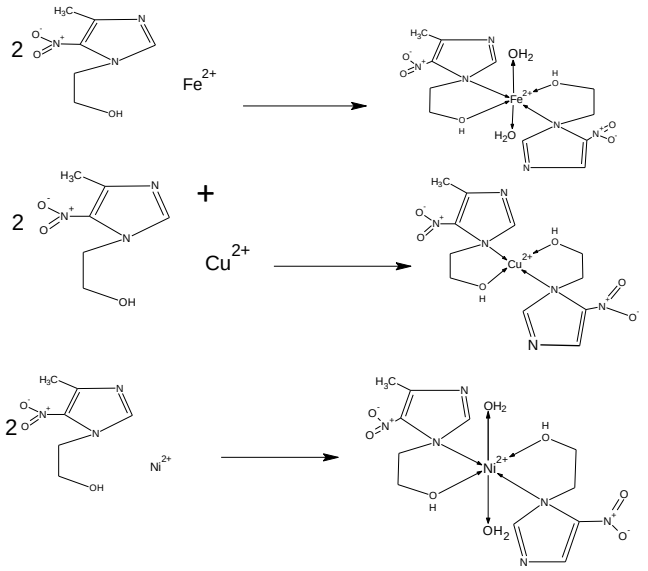

Fig 2: Reaction equations of metronidazole with the metal ions

Physical analysis data of metronidazole and its Fe (II), Ni(II) and Cu(II) complexes are presented in table 1. The complexes are of various colours, which varied from brown, pale green and pale blue different from the colour of the ligand indicating that the colours formed depend on the metal ions (Table 1).

Table 1: Results of some physical data of metronidazole and its Fe (II), Ni (II) and Cu(II) complexes

Compounds	Colour	Melting point ^0C	Conductivity Ω^{-1}
Metronidazole	Cream	163-167	-
$Fe(met)_2.2H_2O$	Dirty Brown	158-161	0.01
$Ni(met)_2.2H_2O$	light green	188-191	0.01
$Cu(met)_2$	Pale blue	190-192	0.22

The melting points of the complexes were different (higher) than that of the ligand, except for $Fe(met)_2$ which was lower by 2^{o}C compared to the ligand, this is an evidence for complexation [19]. All complexes were soluble in methanol on warming but insoluble in acetone, ethanol and water. The molar conductivity from Table 1 for the metal complexes in methanol indicates non-electrolytic behavior of the complexes [12].

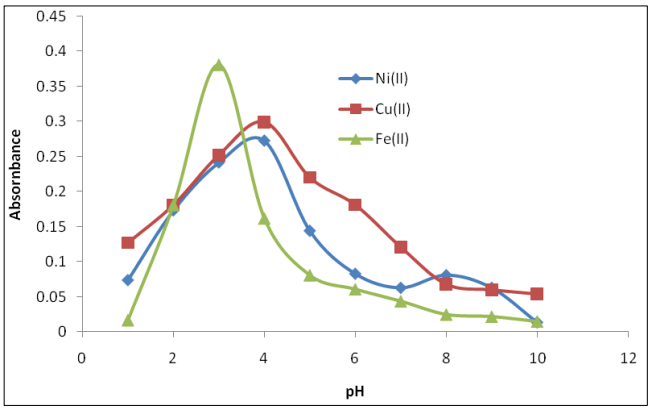

Fig 3: Plot of absorbance of metal/metronidazole complexes as a function of pH values.

The pH variation on the complex formation shows there is maximum formation of Fe^{2+}/metronidazole complex at pH 3, Ni^{2+}/metronidazole complex at pH 4 while Cu^{2+}/metronidazole complex at pH 4 (Figure 3).

Table 2: Data for Job's plot for Fe^{2+}, Ni^{2+}, Cu^{2+} and the ligand at λ_{max} 425 and λ_{max} 350

Metal volume Vm (cm^2)	Ligand volume Vl (cm^2)	Mole fraction Vm/Vm + Vl	Absorbance		
			Fe(II) complex	Ni(II) complex	Cu(II) complex
1.0	9.0	0.1	0.122	0.230	0.301
2.0	8.0	0.2	0.325	0.501	0.504
3.0	7.0	0.3	0.535	0.781	0.675
4.0	6.0	0.4	0.601	0.790	0.683
5.0	5.0	0.5	0.530	0.740	0.600
6.0	4.0	0.6	0.351	0.631	0.471
7.0	3.0	0.7	0.300	0.551	0.390
8.0	2.0	0.8	0.202	0.432	0.271
9.0	1.0	0.9	0.110	0.383	0.190

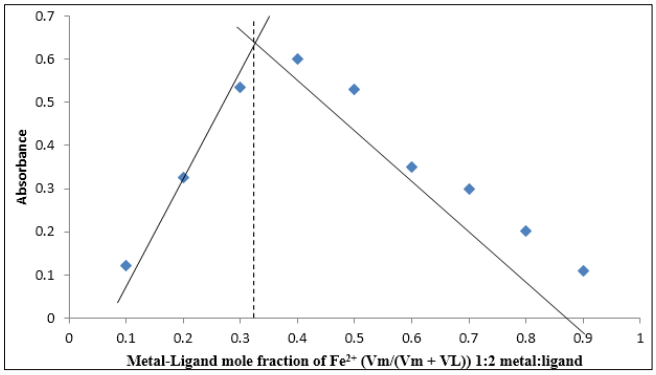

Fig 4: Job's plot for Fe^{2+}/ metronidazole at λ_{max} 350 and pH 3

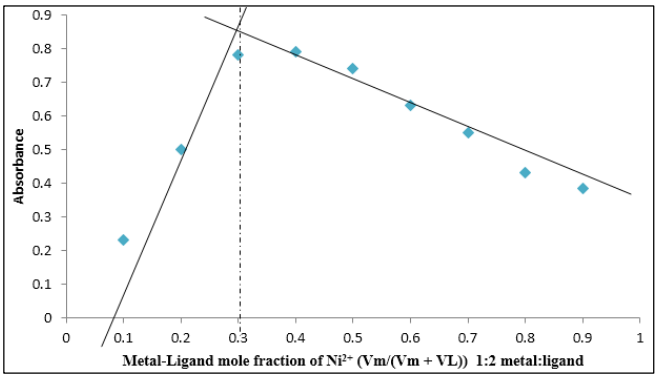

Fig 5: Job's plot for Ni^{2+}/ metronidazole at λ_{max} 350 and pH 4

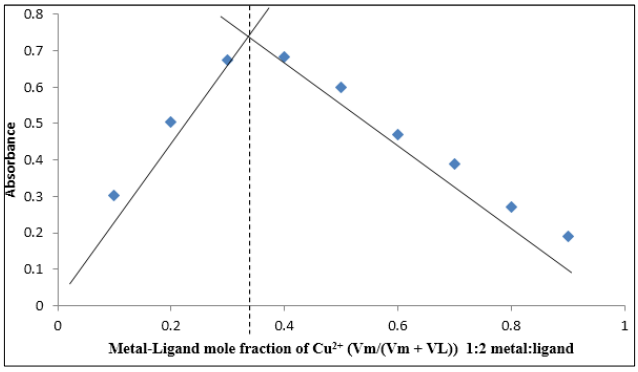

Fig 6: Job's plot for Cu^{2+}/ metronidazole at λ_{max} 350 and pH 4

Job's plots for the complexes formed are presented in figures 4-6. Job's plot for Fe^{2+}/metronidazole complex at $\lambda_{max\ 350\ nm}$ Ni^{2+}/metronidazole complex at $\lambda_{max\ 350\ nm}$ and Cu^{2+}/metronidazole complex at $\lambda_{max\ 425\ nm}$ showed that the formation of 1:2 metal: ligand complexes at the intersection of the straight line thus agreeing with Job's method.

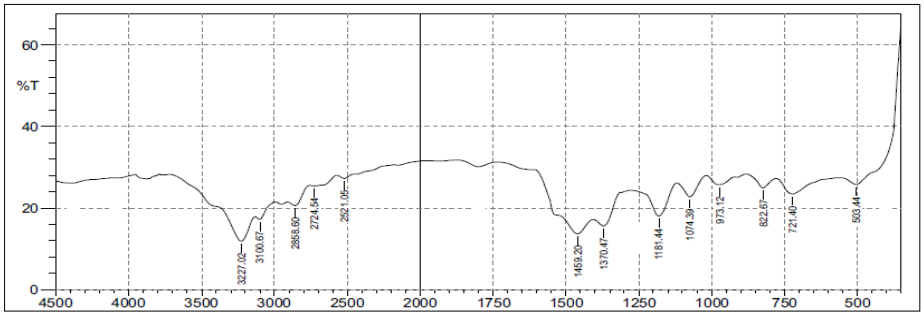

Fig 7: IR spectra for Metronidazole

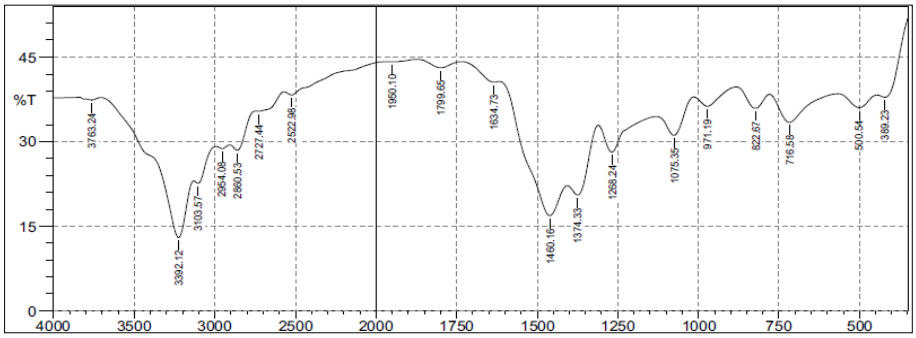

Fig 8: IR spectra for $[Fe(met)_2.2H_2O]$

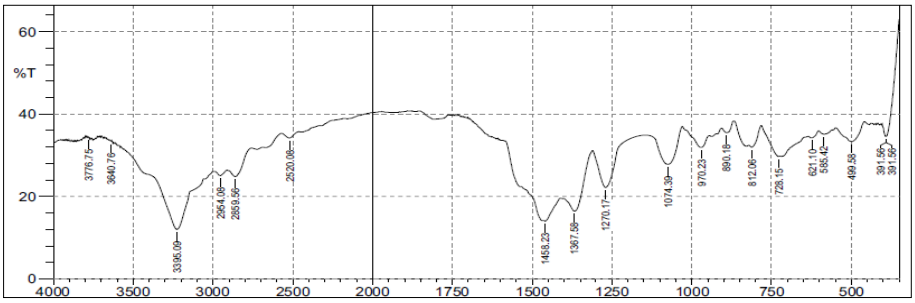

Fig 9: IR spectra for [Ni (met)$_2$.2H$_2$O]

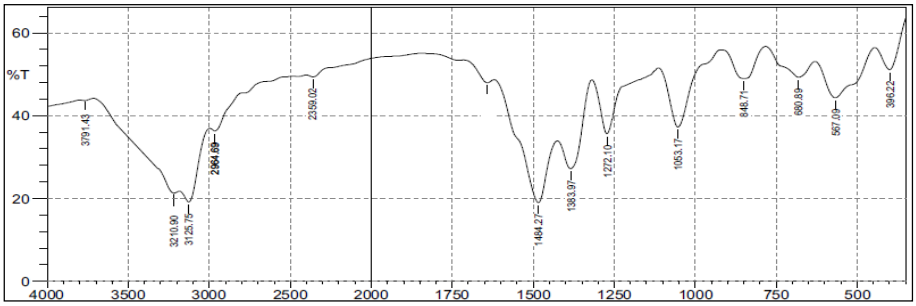

Fig 10: IR spectra for [Cu (met)$_2$]

Table 3: IR spectral data for metronidazole and its Fe (II), Ni(II) and Cu(II) complexes

Metronidazole	[Fe(met)$_2$.2H$_2$O]	[Ni(met)$_2$.2H$_2$O]	[Cu(met)$_2$]	Assignment
-	3392	3395	-	vOH of water
3227	-	-	3210	vOH of alcohol
3100	3103	3100	3125	V=C-H aromatic
1074	1075,1268	1074,1270	1272,1185	vC-N
1269	1268,1374	1270, 1367	1272,1383	=C-N aromatic
1650	1634	1600	1642	-C=N stretch
1650	1634	1600	1642	vC=C aromatic
1459	1460	1458	1484	-CH bend
729	-	-	-	C-H rock
3450	3763	3640,3776	3791	N-H stretch
1550	1634	1650	1642	N-H bend
1370	1374	1367	1383	NO_2 asymmetric
2858 2970	2954 2860	2859 2954	2964	CH_3 rocking
-	389	391	399	V(M-O and M-N-C + chelating ring vibration)

The IR spectral for the ligand and metal complexes are presented in figures 7 – 10, while the data and assignment are presented in Table 3. The observed IR frequency mode has been assigned by comparing published report on metronidazole and their metal complexes [13]. The broad absorption band at the 3227 cm^{-1}, which is absent in the spectra of the metal complexes of Fe^{2+} and Ni^{2+} was assigned to vOH of the enol form of the ligand [13].

However, the broad band appearing in the 3392 cm^{-1} and 3395 cm^{-1} of the IR spectra region for Fe^{2+} and Ni^{2+}complexes have been attributed to vOH of adduct of water molecules coordinated to the central metal ion or residing in the crystal lattices of the complexes [14, 15]. The IR spectra of the metal complexes gave strength to our opinion that the hydrated bischelates of Fe^{2+} and Ni^{2+}complexes where formed, by showing vibrational frequencies of water at 3392 cm^{-1} for Fe^{2+} complex and 3395 cm^{-1} for Ni^{2+}complexes. Having established a mole ratio of 1:2 for both complexes, it implies that two water molecules must have coordinated to the 4-coordinate complexes of Fe^{2+} and Ni^{2+}complexes to bring about coordination saturation to give an octahedral geometry of the form $ML_2.2H_2O$ for each.

The band centered around 1650 cm^{-1} in the IR spectrum of the ligand is assigned to C=N stretch. The assignment also showed a shift of the vC=N from 1650 cm^{-1} recorded for metronidazole to the band appearing at lower frequency at 1634 cm^{-1} (Fe), 1600 cm^{-1} (Ni) and 1642 cm^{-1} (Cu) for the metal complexes, these bathochromic shift in the complexes provided evidence that (i) the -C=N group is a coordinating site of the [14, 16]. (ii) the chelation process is essentially that of the displacement of H ion from the OH group of the ligand by the metal ion and the formation of M-O and M-N-C bonding system by the reaction type

$$M^{n+}_{(aq)} + nmet_{(org)} \rightarrow M(met)_{n(org)} + nH^{+}_{(aq)}$$

Where n is the number of ligand involved

The band at 1370 cm^{-1} in the ligand was assigned to the NO_2 stretching which also appeared in the complexes but with a slight shift in all the complexes. The vibration frequency mode of interest in the 600-200 cm^{-1} region of IR are those due to metal – ligand and chelate ring vibrations. Hence, the

unique bands in the IR spectra of the metal complexes appearing at 389 cm^{-1} (Fe), 391 cm^{-1} (Ni) and 399 cm^{-1} (Cu) and absent in the IR spectrum of the ligand, have been assigned to vM-O and vM-N-C of the metal complexes [12, 18, 15].

The M-O, M-N-C and chelate ring vibration frequency mode follow the order Fe < Ni< Cu which is the order of decreasing atomic weight of the metals, and in accordance with the Irving-Williams order of stability for divalent first row transition metal ions complexing with various ligands [20].

Table 4: UV spectral data of metronidazole and its Fe (II), Ni (II) and Cu (II) complexes

Compounds	λ_1(nm)	ε_1(L.mol^{-1} cm^{-1})	λ_2(nm)	ε_2(L.mol^{-1} cm^{-1})
Metronidazole	305	316	425	222s
Fe(met)$_2$	350	240	-	-
Ni(met)$_2$	350	238	-	-
Cu(met)$_2$	335	361	425	147

From Table 4 gives the electronic spectral data of the ligand and its metal complexes, the energy absorbed in the ultraviolet/ visible region produced changes in the electronic energy of the compound resulting from transition of valence electrons in the complexes. These transitions consist of the excitation of an electron from a filled molecular orbital (usually a non-bonding (n) or a bonding π π^* molecular orbital to an unfilled molecular orbital. It is not all transition from filled to unfilled molecular orbital is allowed [18].

As revealed in the Table, the metal complexes appear to have virtually identical spectra, and absorb in the near visible region around λ_1=305 nm, λ_2 =425 nm for the ligand and 350 nm for Fe (met)$_2$, 350 nm for Ni(met)$_2$and 335 nm,λ_2 = 425 nm for Cu(met)$_2$ complexes. These absorption are ascribed to intraligand π π^* transition [19, 15]. The close absorption spectra of the ligand and the metal complexes suggest that the π-bonding system of the free nitroimidazole is intact in the ligand of the metal complexes [19]. Indicating that there are no interaction between the metal ions and π-bonding system of the ligand. The coordination between the ligand and the metal ions is therefore through $^{\delta}$ bond formation between the metal ions and the O atom of the hydroxyl group of the ligand.

The maximum absorption of peaks of metronidazole at λ (425, 305) nm correspond mainly to π π^* transfer transition [19, 15].

Conclusion

Job's plot for Fe^{2+}/metronidazole complex, Ni^{2+}/metronidazole complex and Cu^{2+}/metronidazole complex revealed the formation of 1:2 metal: ligand complex formation.

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