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Synthesis and Characterisation of Some Mixed Artemisinin-Nicotinamide and Artemisinin-Ascorbic Acid: Metal Complexes and their Antimicrobial Activity Studies

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Abstract

Metal complexes of Zn^{2+}, Mn^{2+}, Cu^{2+} and Fe^{3+} with mixed artemisinin-nicotinamide and artemisinin-ascorbic acid have been synthesised and characterised using infrared and electronic spectroscopic analysis, melting point determination and conductivity measurements. The two ligands have been found to act as bidentate chelating agents with artemisinin-nicotinamide coordinating through the carbonyl and amide groups, while artemisinin-ascorbic acid coordinated through the hydroxyl and carbonyl groups. Antibacterial screening of the complexes against five bacteria- *Escherichia coli*, *Stapphylococcus aureus*, *Klebsiella pneumonia*, *Pseudomonas aureginosa* and *Proteus mirabilis*, was also investigated. The metal complexes were found to have varied degree of inhibitory effect against the bacteria.

Keywords: Artemisinin, Nicotinamide, Ascorbic acid, Metal complexes, Antimicrobial activities.

Introduction

A vitamin is an organic compound required by an organism as a vital nutrient in limited amounts (Lieberman and Bruning, 1997). Until the 1900s, vitamins were obtained solely through food intake, and changes in diet especially during a particular growing season can alter the types and amounts of vitamins ingested (Lieberman and Bruning, 1997). Hence vitamins have been produced as commodity chemicals and made widely available as inexpensive pills for several decades which allow supplementation of the dietary intake (Kirk-Othmer, 1984).

On the other hand, artemisinin is a new class of anti-malarial drug that combat malaria caused by a parasite known as *Plasmodium falciparum* usually carried by a female anopheles mosquito. As the name implies, antimalarials attack the different stages of the parasite growth and development such as killing the sexual form of the parasite in the bloodstream (Okie, 2008). Artemisinin has a strong blood schizonticidal action and it reduces gametocyte transmission of the parasite (Crutcher and Hoffman, 1996). It is used for therapeutic treatment of cases of resistant and uncomplicated *P. falciparum*.

However, research has shown that complexing drugs to metal ions could enhance their activities (El Guindi, *et al*. 1988). Synthesis of metal-drug complexes has therefore continued to be a subject of continued research. We hereby report the synthesis of more antimalarial-vitamin- drug-metal complexes in order to contribute to the effort being made to produce drugs that can be used against drug-resistant diseases.

Materials and Experimental

Materials

The reagents and the solvents used for this research were of analytical grade and used as received without further purification. The ligands – Artemisinin and vitamins (nicotinamide and ascorbic acid) were respectively obtained from Bond Chemical industries, Oyo State and Peace Pharmaceuticals, Kwara State, Nigeria. Zinc(II)chloride dihydrate ($ZnCl_2.2H_2O$), manganese(II)chloride tetrahydrate ($MnCl_2.4H_2O$), copper(II)chloride dihydrate ($CuCl_2.2H_2O$), and iron (III)chloride hexahydrate ($FeCl_3.6H_2O$) and various solvents used were obtained from the Department of Chemistry University of Ilorin. The bacteria test organisms (*Escherichia coli*, *Staphylococcus aureus*, *Klebsiella pneumonia*, *Pseudomonas auriginosa* and *Proteus mirabilis*) were obtained from University of Ilorin Teaching Hospital, Ilorin, Nigeria. The melting points were determined using the Gallenkamp melting point apparatus and the open capillary method. The solubility of the complexes was studied in various solvents such as distilled water, acetone, ethanol, methanol, toluene, ethyl acetate and benzene. The conductivity measurements for the ligands and complexes were also carried out using the WTW conductometer Bridge with cell constant $0.82cm^{-1}$. The infrared spectra of the samples were recorded on Nicolet iS5 Fourier Transform Infrared spectrophotometer. The electronic spectra of the complexes in

solution run in the range 200-1000 nm on Beckman Coulter DU 730 life Science Ultraviolet-visible spectrophotometer. The Nuclear Magnetic Resonance analysis for some of the compounds was also carried out. The antimicrobial screening of the ligands and complexes was carried out at the Department of Serology, University of Ilorin Teaching Hospital, Ilorin.

Synthesis of the metal complexes of Artemisinin-ascorbic acid

A 5 mmol metal salts ($ZnCl_2.2H_2O$ (0.034 g), $MnCl_2.4H_2O$ (0.031 g), $CuCl_2.2H_2O$ (0.043 g) and $FeCl_3.6H_2O$ (0.068 g)) each was weighed accurately and dissolved in 20 ml ethanol in a beaker. Artemisinin (0.141 g, 10 mmol) and ascorbic acid (0.088 g, 10 mmol) were weighed and dissolved separately in 30 ml ethanol. The solution of the metal salts and the ligands were then mixed together in a 250ml conical flask. The mole ratio of the metal salt to ligand was maintained at 1:2:2. The solution was then heated to reflux for about two hours at 70^oC. Thereafter the solution was allowed to cool to room temperature and the crystals formed were washed in distilled water and dried in the desiccator.

Antimicrobial Screening of the ligands and metal complexes

The antimicrobial screening of the ligands and complexes was done using Punched hole method. The test organisms are five bacteria- *E. coli*, *S. aureus*, *K. pneumonia*, *P. aureginosa,* and *P. mirabilis*. Nutrient agar was prepared and poured on some petridishes. The petridishes were allowed to dry in the oven. Each organism was dissolved in normal saline water and innoculated separately on the nutrient agar. Six holes were then punched on each plate and the dissolved complexes and ligands were introduced into the holes. The plates were incubated for 24hrs after which some zones of inhibition were seen for some of the organisms. These zones of inhibition were then measured.

Results and Discussion

Table 1 Analytical test data and some physical properties of the complexes

Sample analyzed	Melting point (^{0}C)	Colour	Conductivity µS	Electronic transition λmax(nm)	% Yield
Artemisinin	152 – 156	White	--	293	-
Nicotinamide	118 – 122	White	--	298	-
$Zn(Art)(Nic)Cl_2$	196 – 202	Dirty white	13	299	80.93
$Mn(Art)(Nic)Cl_2$	194 – 197	White	40	295	85.41
$Cu(Art)(Nic)Cl_2$	198 – 201	Green	102	292	84.90
Ascorbic acid	224 – 228	White	--	326	-
$Mn(Art)(Asc)Cl_2$	296 -300	White	9	298	73.08
$Fe(Asc)Cl_3$	290-294	Yellow	16	297	86.54

Table 2 Selected Infrared spectra data of the metal complexes

Ligand /Complex	Infrared spectra assignment				
	$\bar{\upsilon}$(O-H)cm^{-1}	$\bar{\upsilon}$ (C=O)cm^{-1}	$\bar{\upsilon}$(N-H)cm^{-1}	$\bar{\upsilon}$ (C=N)cm^{-1}	$\bar{\upsilon}$ (C=C)cm^{-1}
Artemisinin	3456.55 vw,sh	1737.92 vs,sh	-	-	-
Nicotinamide	-	1701.27 vs,b	3367.82 vs, b	1672.34 vs,b	1620.26 vs,b
$Zn(Art)(Nic)Cl_2$	3227.02 vs,b	1734.06 m,sh	3095.85 vs, sh	1626.05 m,sh	1545.03 vs, sh
$Mn(Art)(Nic)Cl_2$	3425.69 vs,sh	1705.13 vs,sh	3298.38 vs, sh	1672.34 vs,sh	1600.97 vs,sh
$Cu(Art)B_3Cl_2$	3423.76 m,sh	1705.13 vs,sh	3205.80 m, sh	1672.34 m,sh	1600.97 m,sh
Ascorbic acid	3525.99 vs,sh	1755.28 s,sh	-	-	1674.27 vs,b
$Mn(Art)(Asc)Cl_2$	3385.18 vs,b	1654.98 vs,b	-	-	1654.98 vs,b
$Fe(Asc)Cl_3$	3352.39 vs,b	1651.12 vs, b	-	-	1651.12 vs,b

Discussion

It was observed from Table 1 that the complexes had higher melting points than the ligands. This might be attributed to larger carbon atoms in them. The results of the conductivity measurements show that there were electronic transitions from one d-orbital to another in the complex molecules. The electronic spectra data (Table 1) had been interpreted in terms of electron transfer from the metal to the antibonding orbital of the ligands (Williams and Flemming, 1980). Higher bands than those of the ligands were assigned to n-π^* transitions (i.e bathochromic shift) while the lower bands were assigned to π-π^* transitions (i.e hypsochromic shift) (Kamlet and Taft, 1976).

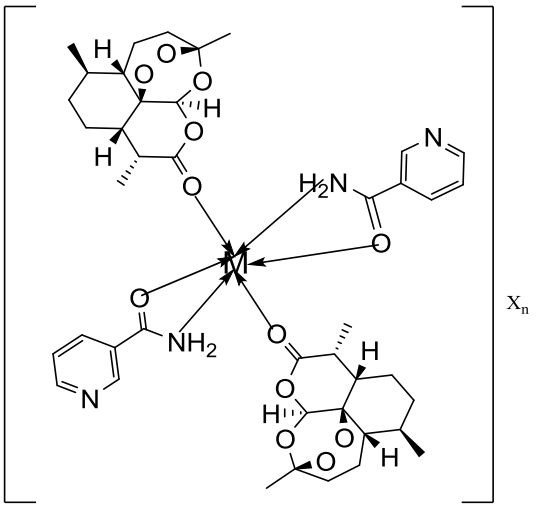
Therefore, only the band at 298nm in free nicotinamide underwent a bathochromic shift in its complex with zinc metal salt. In essence electrons moved from the non-bonding orbital of zinc metal to the antibonding orbital of nicotinamide. On the other hand, the band at 298nm in free nicotinamide underwent hypochromic shift in its complexes with manganese and copper while the band at 326nm in free Ascorbic acid underwent hypochromic shift in its complexes with manganese and iron.

This in essence implies that electrons moved from the bonding orbital of manganese and iron metal to the antibonding orbital of each ligand (Williams and Flemming, 1980). These shifts in bands could be a result of complexation.

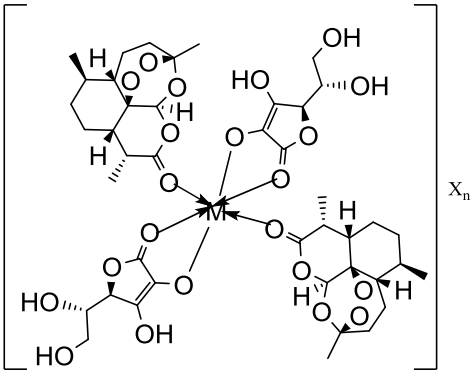
The very strong and sharp absorption band in the infrared spectrum of artemisinin (Table 2) at a wavelength of 1737cm^{-1} might be due to υ(C=O) vibrational stretching of an ester or lactone group (Coartes, 2000). This band experienced a slight shift to a lower frequency in its complexes showing that there was coordination at the (C=O) group of Artemisinin. The very strong but broad band of free nicotinamide at 1701cm^{-1} and 3367cm^{-1} were attributed to υ(C=O) and υ(N-H) stretching frequencies respectively (Kamlet and Taft, 1976). These bands were seen to undergo a shift to a lower frequency at υ(N-H) and a higher frequency at υ(C=O) in the complexes showing coordination of nicotinamide through its (C=O) and (N-H) groups. In the infrared spectrum of free ascorbic acid, the band at 3525cm^{-1} and 1755cm^{-1} were attributed to υ(O-H) and υ(C=O) stretching frequencies respectively (Coartes, 2000). These bands shifted to

lower frequencies in the metal complexes, an indication of coordination of ascorbic acid through its (O-H) and (C=O) groups.

On the basis of analytical data and spectroscopic data, the tentatively proposed structures for the metal complexes are shown below:



Proposed structure for $M(Art)_2(Nic)_2X_n$
$M = Zn^{2+}$, Mn^{2+} and Cu^{2+}; X = Cl and n = 2 Art = Artemisinin and Nic = Nicotinamide



Proposed structure for $M(Art)_2(Asc)_2X_n$
$M = Mn^{2+}$; X = Cl and n = 2; $M = Fe^{3+}$, X = Cl and n = 3;
Art = Artemisinin and Asc = Ascorbic acid

Antimicrobial Studies

Table 4 Result of the percentage zone of inhibition of the ligands and their metal complexes at the concentration of 0.1%w/v on the microbial population.

Ligand/ Complex	E. coli	S. aureus	K. pneumonia	P. mirabilis	P. auriginosa
Artemisinin	18	0	10	0	15
Nic	13	8	15	13	18
$Zn(Art)(Nic)Cl_2$	22	8	17	17	22
$Mn(Art)(Nic)Cl_2$	23	20	15	22	15
$Cu(Art)(Nic)Cl_2$	20	8	20	20	17
Asc	0	10	8	8	0
$Mn(Art)(Asc)Cl_2$	20	15	15	15	17
$Fe(Art)(Asc)Cl_3$	17	20	17	15	17

The determination of various properties of the complexes and their antimicrobial screening could be used to ascertain whether or not the complexes were better than their parent antimalarial drug. The diameter of the zone of inhibition is a measure of antibacterial activity (Barry *et al*. 1979). The increase in the percentage zone of inhibition for metal complexes (Table 4) when compared with Artemisinin and the vitamins was an indication that the metal complexes were able to decrease the population of the bacteria species. It was also an indication that the metal complexes were more effective than their parent drugs.

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