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Synthesis, Characterization and Complexation Behaviour of Chloroquine towards Ti (II) Ion

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Authors' contributions

This work was carried out in collaboration among all authors. Author IEO designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors LOO, KCA, COA and AO managed the analyses of the study. Author FCN managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Aims: Chloroquine is a member of the drug class 4-aminoquinoline used for the prevention and treatment of malaria in areas where malaria is known to be sensitive to its effects.
Our aim is to synthesize the chloroquine – titanium complex and to study its coordination behavior.
Place and Duration of Study: Department of Chemistry, Michael Okpara University of Agriculture, Umudike, 2019.
Methodology: Ti(II) complex of chloroquine was synthesized by the reaction of chloroquine phosphate with titanium(IV) oxide. The metal complex was characterized based on UV, IR and 1H NMR Spectroscopy.
Results: The UV spectrum of the complex suggested intra ligand charge transfer (ILCT), ligand to metal charge transfer (LMCT), and d-d transition. The IR spectrum of the complex showed the involvement of amine and imine group in coordination to Ti. This showed that chloroquine acted as a bidentate ligand. 1H NMR of the spectrum further showed the involvement of the amine group in coordination.

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Conclusion: The ability of chloroquine to sequestrate Ti (II) ion has been assured. This drug can be used to chelate Ti ions from solution, environment, and biological system.

Keywords: Coordination; ligand; spectrum; malaria; chloroquine; titanium.

1. INTRODUCTION

Metals are an integral part of many structural and functional components in the body, and the critical role of metals in physiological and pathological processes has always been of interest to researchers. Metal toxicity may occur due to essential metal overload or exposure to heavy metals from various sources. Most metals are capable of forming covalent bonds with carbon, resulting in metal-organic compounds. Metals and metal compounds interfere with functions of various organ systems like the central nervous system (CNS), the hematopoietic system, liver, kidneys, etc. Diagnostic testing for the presence of heavy metals, and subsequently decreasing the body's burden of these substances, should be an integral part of the overall treatment regimen for individuals with a metal poisoning symptomatology or a known exposure to these substances [1-5].

If heavy metals enter and accumulate in body tissue faster than the body's detoxification pathways, a gradual buildup of these toxins will occur. Human exposure to heavy metals has risen dramatically in the last 50 years as a result of an exponential increase in their use in industrial processes and products [6]. The transition metal ions inevitably exist as metal complexes in biological systems by interaction with the numerous molecules possessing groupings capable of complexation or chelation. Hence we find essential metals such as Cu, Zn, Cr, Fe, Mn, and Co existing as binary and ternary chelates of amino acids, carboxylic acids, and proteins. The carcinogenic metals all have the ability-via complexation or ternary complex formation-to, interact with DNA and other nuclear constituents so to alter such cellular properties as membrane integrity.Chelation phenomena enable metals to be transported to or away from vulnerable target sites, and to facilitate nor hinder those intracellular interactions which may ultimately lead to cancer [7-10].

Exposure to toxic metals like cadmium (Cd), lead (Pb), mercury (Hg), chromate (CrO_4^{2-}), arsenite (As) (III), and arsenate ($AsO_4^{3-)}$ are known to induce various diseases that are detrimental to human health. Complete chelation therapies encompass chelating the metal ions in the gastrointestinal fluids in order to limit systemic absorption of ingested materials and chelating the metal ions in the blood that have been absorbed systemically from all routes of exposure (oral, dermal, and inhalation). Since the 1940s, *in vivo* toxic metal immobilization has involved the use of ethylenediamine-tetraacetate (EDTA) or dimercaptosuccinic acid (DMSA) following metal exposures. However, these chelation agents still have many disadvantages and low efficacy. They are also not effective in removing Cd and toxic anions such as chromate and arsenate [11-14].

Titanium-based compounds are routinely used in the treatment of bone fractures as well as dental work. These compounds have the ability to corrode and degrade, generating metallic debris. There is great concern over the increased concentrations of titanium compounds degradation because of the toxic effect over a period of time. They may cause hepatic injury and renal lesions. Based on the harmful effect of titanium, we decided to study the complexation behavior of titanium towards chloroquine.

2. MATERIALS AND METHODS

2.1 Chemicals and Solvents

Chloroquine diphosphate drug and titanium dioxide (TiO_2) were imported from E. Merck Company, Germany. The melting point of the complex was determined using MPA160 melting point apparatus and was uncorrected. Infrared spectra were recorded on Perkin Elmer Paragon 1000 FT-IR spectrophotometer (spectrum BX) equipped with cesium iodide window (4000-350 cm^{-1}) in KBr pellets. The UV-visible spectra were obtained on a Perkin Elmer (lambda 25) spectrometer (200-800 nm) using DMSO as solvent. The ^1H Nuclear Magnetic Resonance (NMR) spectra were obtained using Varian 400 MHz Unity INOVA using TMS as internal standard.

2.2 Synthesis of Chloroquine-titanium Complex

The complex was prepared following a reported procedure [15]. Ti (II) salt solutions were prepared by dissolving 3.1952 g (0.04 mol) TiO_2 in 25 ml ethanol. The solution of the metal salt was added slowly with stirring in a separate 20 ml of ethanol solution of 20.63 g chloroquine diphosphate (0.04 mol) at room temperature maintaining the $_pH$ between 6.0 - 6.5 by adding 10% ammonia in methanol solution. On refluxing the mixtures for 2 hours and cooling, the complex separated out. The complex was recrystallized in ethanol, filtered dried in a desiccator and weighed.

3. RESULTS AND DISCUSSION

The physical properties of the metal complex have been summarized in Table 1. The change in melting point also indicates the formation of a new complex. The melting point of $[Ti(CQ)_n]$ complex as compared to chloroquine suggests that new product was formed.

Table 1. Physical properties of chloroquine and its titanium complex

Ligand/Metal complex	Color	% Yield	Melting point (°C)
CQ	White	-------	203
$[Ti(CQ)_n]$	White	74.72	250

CQ = Chloroquine

3.1 Infrared Spectra

The infrared spectrum of chloroquine was compared with that of the metal complex. The infrared spectrum of chloroquine as reported in the literature [16] showed N-H stretching vibration frequency at 3260 cm^{-1}. In the spectrum of chloroquine-Ti complex (Fig. 1), the N-H stretching vibration frequency shifted to 3191.26 cm^{-1}. This shift suggests that coordination occurred through the N-H functional group because an increase in electron density will increase the N-H bond length and consequently slow down the vibration frequency [17]. In the infrared spectrum of chloroquine [16], the C=N functionality appeared at 1120 cm^{-1} while in chloroquine-Ti complex, the C=N functionality shifted to 1089.95 cm^{-1}. This shift suggests that coordination occurred through the C=N functional group because an increase in electron density increased the C-N bond length and consequently slowed down the vibration frequency [17]. The aromatic C-C, the aromatic C-H, the aliphatic C-H, the C-Cl vibration frequencies of chloroquine-Ti complex remained unchanged which suggests that these functionalitiesdid not participate in coordination.

3.2 Electronic Spectra

The ultraviolet spectrum of chloroquine in neutral methanol solution in the region of 200 – 400 nm exhibits maxima at 218 nm, 253 nm, and 328 as reported in the literature [16]. These transitions have been assigned intra ligand charge transfer (ILCT). The chromophores that may exhibit these transitions are C=C and C=N. For chloroquine-Ti complex, the absorption bands, 200, 220, 240, 260, 280, 300, and 320 nm as seen in Fig. 2, have been assigned intra ligand charge transfer (ILCT), the band at 340 nm has been assigned ligand to metal charge transfer (LMCT), while the band at 680 nm suggests d-d transition. The LMCT and d-d transition suggest that the complexation occurred successfully.

3.3 ^{1}H-NMR Spectral Studies

The proton NMR of chloroquine as reported in the literature [16] was compared with the proton NMR spectrum of its titanium complex. In the spectrum of the chloroquine, the N-H proton appeared as a doublet at 5.64 ppm, while the N-H stretch of its titanium complex shifted to 4.81 ppm. This shift suggests the involvement of N-H functional group in complexation. Also, in the chloroquine spectrum, $CH_{3,}$ $CH_{2,}$ and CH appeared as multiplets between 0.83-1.33 ppm. These protons also appeared in the complex at 0.83-1.33. This suggests that there was no coordination through these sites. Again in the proton NMR of the chloroquine, $-CHCH_2CH_2CH_2-$, $-CH_3-NCH_2CH_2-_,$ $-CH_3CH-_,$ and aromatic protons appeared at 1.66 ppm (triplet), 2.33-2.67 ppm (multiplets), 3.66 ppm (quartet), and 6.4-8.43 ppm (multiplets). These chemical shifts remained unchanged in the proton NMR of the chloroquine-Ti complex. This suggests that coordination did not occur through these functionalities.

Based on the melting point, UV, IR, and ^{1}H NMR spectral studies, the structure chloroquine-Ti complex has been proposed in Fig. 4.

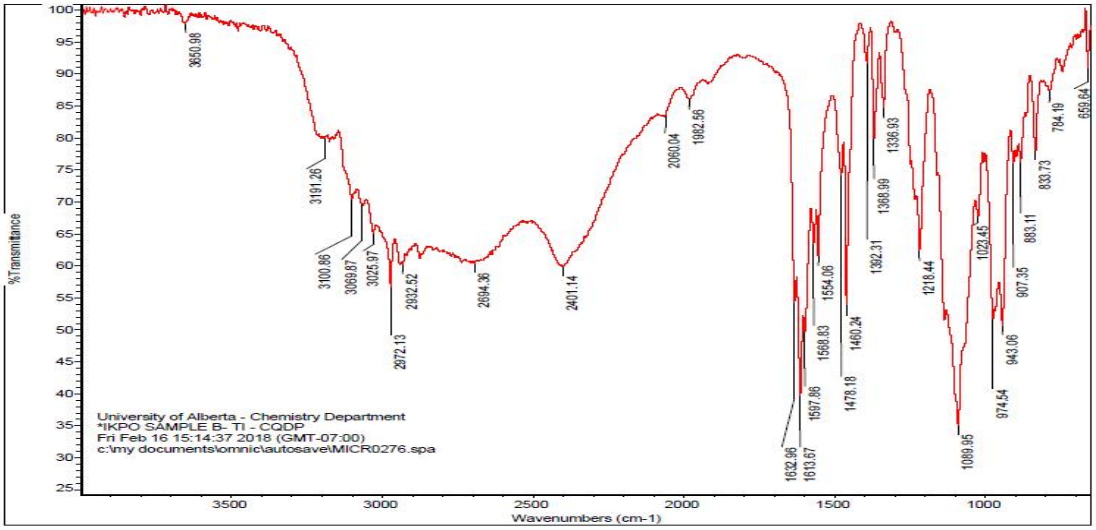

Fig. 1. IR spectrum of chloroquine-Ti complex

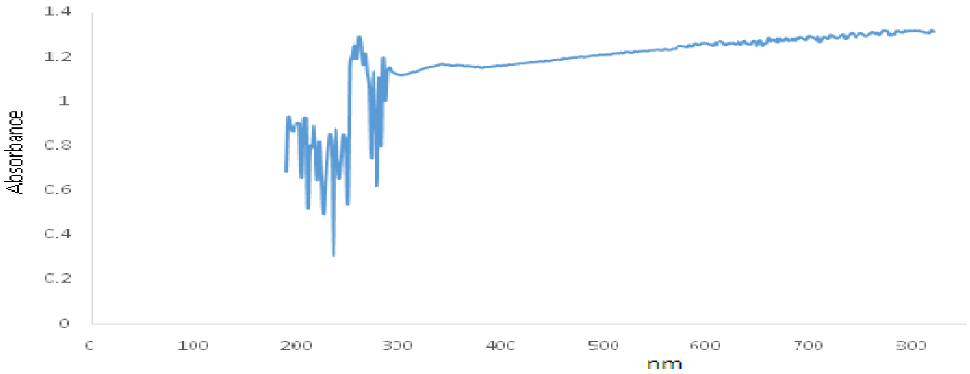

Fig. 2. UV spectrum of chloroquine Ti complex

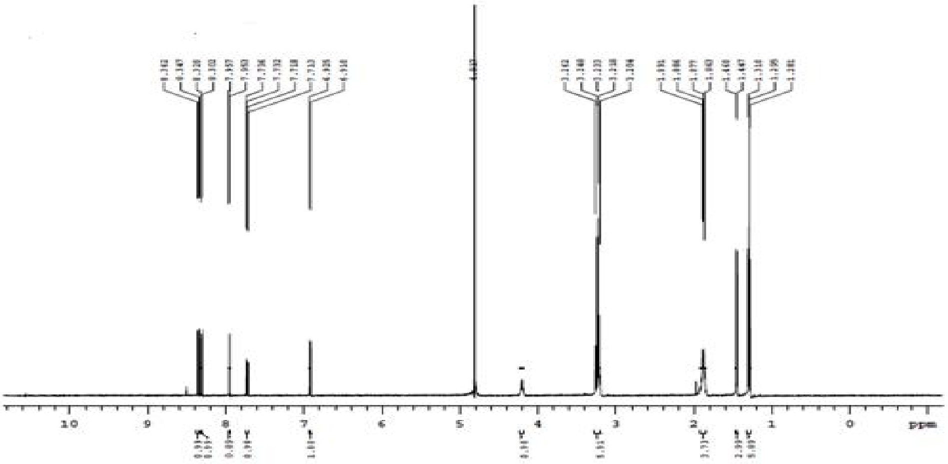

Fig. 3. ^{1}H NMR spectrum of chloroquine-Ti complex

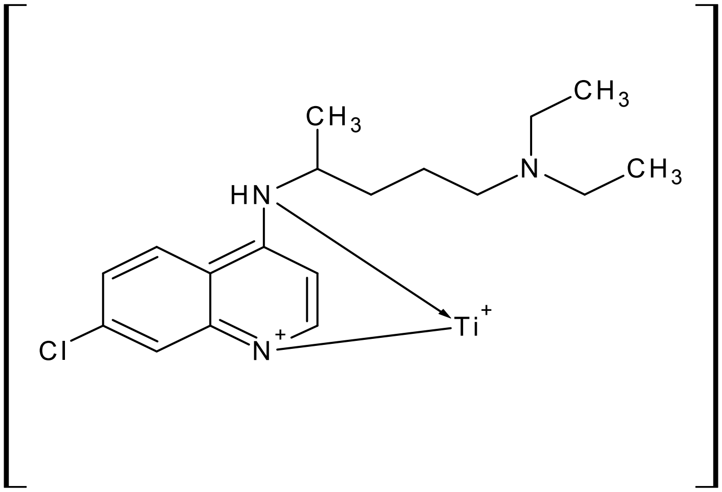

Fig. 4. Proposed structure of chloroquine-titanium complex

4. CONCLUSION

The ability of chloroquine to sequestrate Ti (II) ion has been assured. Chloroquine behaved as a bidentate ligand towards Ti (II) ion. This drug can be used to chelate Ti ions from solution, environment, and biological system.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Flora JS, Pachauri V. Chelation in metal intoxication. International Journal of Environmental Research and Public Health. 2010;7:2745-2788.
2. Andersen O. Chemical and biological considerations in the treatment of metal intoxications by chelating agents. Mini-Reviews in Medicinal Chemistry. 2004;4:11-21.
3. Flora SJ, Mittal M, Mehta A. Heavy metal induced oxidative stress & its possible reversal by chelation therapy. Indian Journal of Medical Research. 2008;128:501-523.
4. Flora S. Metal poisoning: Threat and management. Al Ameen Journal of Medical Sciences. 2009;2.
5. Kalia K, Flora JS. Strategies for safe and effective therapeutic measures for chronic arsenic and lead poisoning. Journal of Occupational Health. 2005;47:1-21.
6. Florea AM, Busselberg D. Toxic effects of metals: Modulation of intracellular calcium homeostasis. Matwiss. u. Werkstofftech. 2005;36:1-4.
7. Schubert J. Interaction of metals with small molecules in relation to metal protein complexes. In: Chemical Specificity in Biological Interactions, Gurd FRN, Ed., Academic Press, New York; 1954.
8. Wood JM. Biological cycles for elements in the environment. Naturwiss. 1975;62: 357.
9. Martell AE. Chemistry of carcinogenic metals. Environ. Health Perspect. 1981;40: 207.
10. Sillenand LG, Martell AE. Stability constants of metal-ion complexes. The Chemical Society, London; 1971.
11. Sangvanich T, Morry J, Fox C. Novel oral detoxification of mercury, cadmium, and lead with thiol-modified nanoporous silica. ACS Appl Mater Interfaces. 2014;6:5483-5493.
12. Davidson JD, Wiacek RJ, Burton S. Improved deposition and deprotection of silane tethered 3,4 hydroxypyridinone (HOPO) ligands on functionalized nanoporous silica. Inorg Chem Commun. 2012;18:92-96.

13. Samuels WD, Lafemina NH, Sukwarotwa V. Chloromethylated activated carbon: A useful new synthon for making a novel class of sorbents for heavy metal separations. Sep Sci Technol. 2010;45: 228-235.
14. Yantasee W, Sangvanich T, Creim J. Functional sorbents for selective capture of plutonium, americium, uranium, and thorium in blood. Health Phys. 2010;99: 413-419.
15. Nadira W, Singh HB. Synthesis of metal complexes of antimalaria drugs and *in-vitro* evaluation of their activity. Inorg. Chim. Acta. 1987;135:134–137.
16. Mohammad T, Abdullah A. Analytical profiles of drug substances. King Saud University, Riyadh, Saudi Arabia. 1984;13.
17. Odiaka TI. Modern organometallic chemistry. University Press PLC, Ibadan; 2014.

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