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Synthesis, Characterization and Complexation of Sc(III) Ion Using Chloroquine Diphosphate Drug

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ABSTRACT

Chloroquine possess lone pairs of electrons that can be donated to central metal ion. Scandium (III) complex of chloroquine was synthesized by reaction of chloroquine diphosphate with scandium (III) oxide. The metal complex was characterized based on melting point, UV, IR, and ^{1}H NMR Spectroscopy. ^{1}H NMR Spectra of the complex further showed the involvement of the amine group in coordination to the metal complex. The IR spectra of the complex showed the involvement of amine and imine group in coordination to the metal. The electronic spectrum of the complex suggested intraligand charge transfer (ILCT), ligand to metal charge transfer (LMCT), and d-d transition. The melting point of the complex was higher than the free ligand. Spectroscopic studies showed that chloroquine acted as a bidentate ligand. These results showed that chloroquine has the ability to sequestrate Sc (III) ion from solution. We recommend the use of chloroquine in scandium extraction and chelation therapy.

Key words: Chelation, ligand, spectroscopy, chromophores, chloroquine

INTRODUCTION

Chelation therapy is mainly used in medical treatment for reducing the toxic effects of metals by binding to toxic metal ions to form complex structures which are easily excreted from the body removing them from intracellular or extracellular spaces (Aaseth *et al.*, 2015). Toxic metals such as lead, mercury, aluminum, and arsenic poses a serious public health concern that ranges from behavioral dysfunction, damaged central and peripheral nervous systems, compromise kidney and liver functions, and damage haemopoietic and cardiovascular systems (Patrick, 2006; Verstraeten *et al.*,2008; Ronnback and Hansson, 1992). Chelation therapy has been proposed for clearing toxic heavy metals from the body as it not only removes contaminating metals but also decreases free radical production (Ratnaike, 2003; Bradberry and Vale 2009; Andersen ,2004). Most of the heavy metals ions are by nature, carcinogens and hence poses various health concerns for both animal and plants. Important metals such as Fe, Mg, Co, Cu, Cr, Mo, Mn, Ni, and Zn are essential nutrients for both plants and animals and also necessary for various biochemical and physiological functions mainly for growth of life system. But when consumed in excess, creates an adverse effect on biological system as well as results in deficiency disease and damage of several organs like brain, liver, kidney, blood circulation and nerve transmission (Jingping *et al.*, 2017).

Chelating with drugs is indicated primarily for acute poisonings by some metals, especially lead, arsenic, mercury, and iron. Though the drugs may have dangerous side effects, the risks are considered worthwhile in the face of toxicity which may be fatal or cause serious, even permanent injury (Kosnett, 2010). Chelation therapy may be indicated in copper toxicity. For copper toxicity due to ingesting grams of copper, prompt gastric lavage followed by daily intra-muscular injections of dimercaprol may prevent death. The oral chelating drug penicillamine binds copper, facilitating its excretion, and may promote excretion of copper absorbed from burned skin. Chronic oral chelation therapy may be necessary in persons with inherited chronic copper toxicity (Knudtson *et al.*, 2002).

Various biological activities such as antibacterial, antifungal, antitumor and antiviral activities are exhibited by nitrogen-containing organic compounds and their metal complexes. Transition metal centers are attractive moieties for reversible recognition of nucleic acids because they exhibit well defined coordination geometries. They also show distinctive electrochemical properties thereby increasing the functionality of the binding agents (Pedrares *et al.*, 2003). Chloroquine (Figure 1) is a medication used to prevent and treat malaria in areas where malaria is known to be sensitive to its effect. Certain types of malaria, resistant strains, and complicated cases typically require

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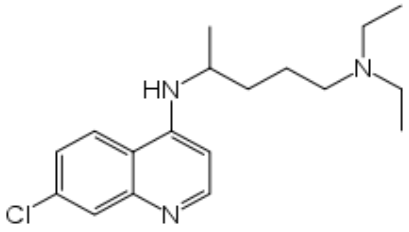

Figure 1: Structure of chloroquine

different or additional medication. Chelation therapy is approaching a turning point that should lead to rapid progress and regain public confidence. The use of chloroquine as a chelating agent is scarcely reported in literature, so the present study communicates the complexation behaviour of chloroquine towards Cr (III) ion.

MATERIALS AND METHODS

All chemicals and reagents used in the experimental work were of analytical grade. Pure chloroquine diphosphate drug and Sc_2O_3 were obtained from E. Merck Company, Germany. Melting point of the complex was determined using MPA160 melting point apparatus. Infrared spectra were collected 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 (200-800nm) using DMSO as solvent.The ^1H Nuclear Magnetic Resonance (NMR) spectra were obtained using 499.8 MHz NMR spectrometer from Agilent Technologies.

Synthesis of sulfathiazole - Sc complex

The complex was prepared following a reported procedure (Nadira *et al.,* 1987). Sc (III) salt solutions was prepared by dissolving 5.516 g (0.04 mol) Sc_2O_3 in 25 ml ethanol. The solution of the metal salt was added slowly with stirring in a separate 20 ml of ethanol solution of 12.79 g of chloroquine diphosphate (0.04mol) at room temperature maintaining the pH between 6.0 and 6.5 by adding 10% methanol ammonia solution. On refluxing the mixtures for 2 hours and cooling, the complex separated out. The complex was recrystallized using ethanol, filtered and finally dried in vacuum and weighed.

RESULTS AND DISCUSSION

Physical Properties

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. It has been reported that complexes have higher melting points than the corresponding free ligand (Reiss and Mureseanu, 2012). The melting point of [Sc(CQ)] complex as compared to chloroquine suggests that new products were formed.

Table 1.Physical properties of chloroquine and its Sc complex

Ligand/Metal complex	Color	Yield (%)	Melting point (^oC)
CQ	white	-------	203
[Sc(CQ)n]	white	98.7	235

CQ = Chloroquine

Infrared spectra

The infrared spectrum of chloroquine was compared with that of the metal complex. In the spectrum of chloroquine (Figure 2), the vibrational frequency at 3260 cm^{-1} is assigned N-H stretching (Table 2). In the spectrum of [Sc(CQ)n] (Figure 3), the vibrational frequency shifted to 3217.09 cm^{-1}. This shift suggest that coordination occurred through the N-H functional group because increase in electron density increases the NH bond length and consequently slow down the vibrational frequency (Odiaka, 2004). In the infrared spectrum of chloroquine, the C=N functionality appeared at 1120 cm^{-1} while in [Sc(CQ)], the C=N functionality shifted to 1090.30 cm^{-1}. This shift suggests that coordination occurred through the C=N functional group because increase in electron density increases the C-N bond length and consequently slows down the vibrational frequency (Odiaka, 2004). The aromatic C-C, the aromatic C-H, the aliphatic

C-H, the C-Cl vibrational frequencies of the metal complexes remained unchanged which suggests that these functionalities did not participate in coordination.

Table 2: Infrared spectra of chloroquine and its Sc complex

Ligand/Metal complex	**ν(NH)** cm^{-1}	**ν(C=N)** cm^{-1}
CQ	3260.00	1120.00
[Sc(CQ)n]	3217.09	1090.30

CQ = Chloroquine

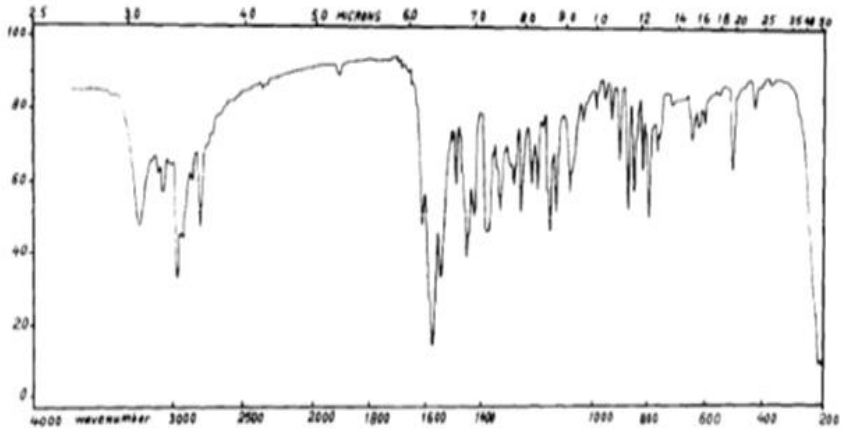

Figure 2: FT-IR spectrum of chloroquine, Source: (Mohammad and Abdullah, 1984).

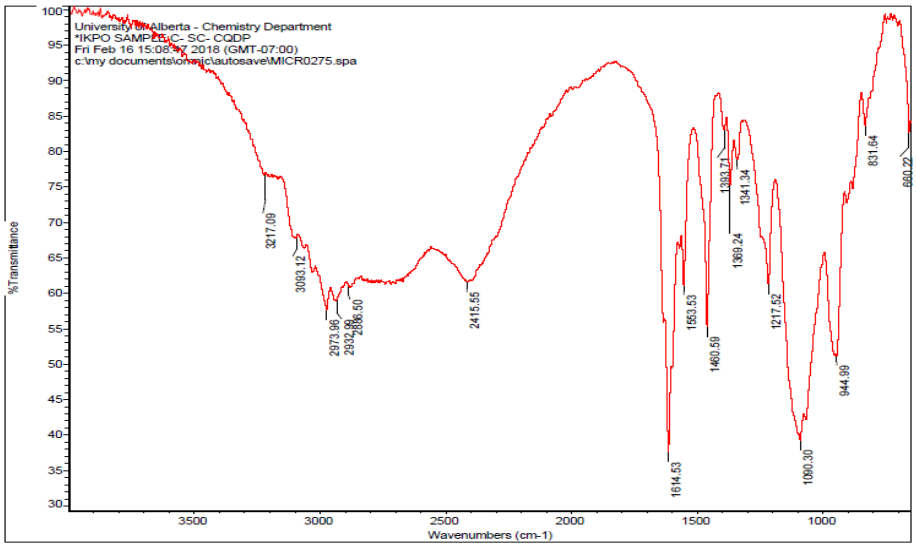

Figure 3: FT-IR spectrum [Sc(CQ)n]

Electronic spectra

The UV absorption bands of the ligand and the complex have been summarized in Table 3. The ultraviolet spectrum of chloroquine in neutral methanol solution in the region of 200 – 400 nm exhibits maxima at 218, 253 and 328 (Mohammad & Abdullah, 1984) as shown in Figure 4. These transitions have been assigned intra ligand charge transfer (ILCT). The chromophores that may exhibit these transitions are C=N and C=C. For the Sc complex, the absorption band at 200, 210, 220, 260, 280 and 290 nm as seen in Figure 5, 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 and above suggests d-d transition. The LMCT and d-d transition suggests that complexation occurred.

Table 3: Electronic spectra of chloroquine and its Sc complex

Ligand/Metal complex	λmax (nm)	Assignments
CQ	218	π-π^* (ILCT)
	253	π-π^* (ILCT)
	328	π-π^* (ILCT)
[Sc(CQ)n]	200	π-π^* (ILCT)
	210	π-π^* (ILCT
	220	π-π^* (ILCT)
	260	π-π^* (ILCT)
	280	π-π^* (ILCT)
	290	LMCT
	680	d-d Transition

CQ = Chloroquine

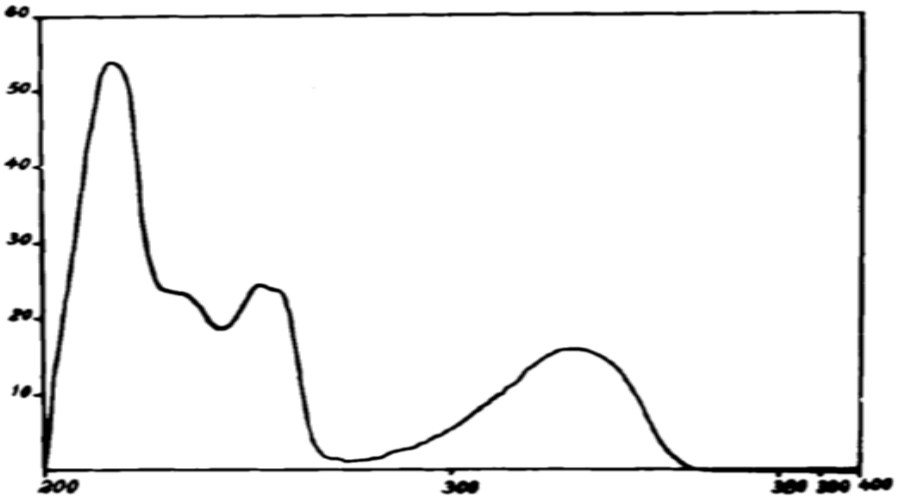

Figure 4: UV spectrum of chloroquine, Source: (Mohammad and Abdullah, 1984)

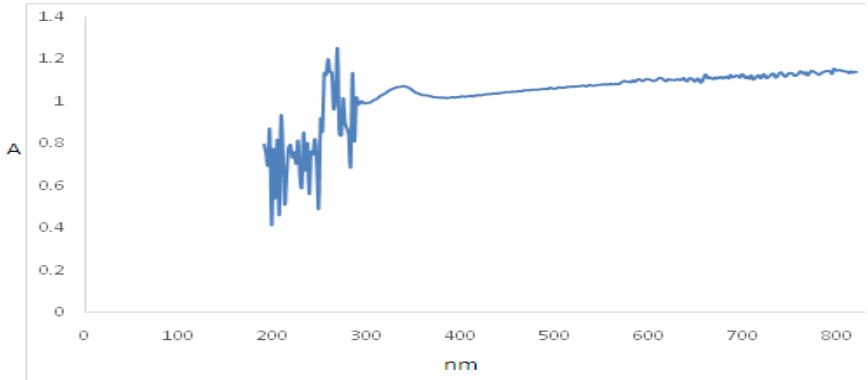

Figure 5**:** UV spectrum [Sc(CQ)n]

^{1}H-NMR spectral studies

The ^{1}H-NMR spectral data of chloroquine and [Sc(CQ)n have been presented in Table 4.The proton NMR of chloroquine was compared with the proton NMR of [Sc(CQ)n]. In the spectrum of the chloroquine (Figure 6), the N-H proton appeared as a doublet at 5.64 ppm, while the N-H stretch of [Sc(CQ)n] complex (Figure 7)

shifted to 4.81 ppm. This shift suggests the involvement of N-H functional group in complexation. Also, in the ^{1}H-NMR spectrum of chloroquine, 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 suggesting that there was no coordination through these sites. Again in the ^{1}H-NMR spectrum of chloroquine, -$CHCH_2CH_2CH_2$-, -CH_3-NCH_2CH_2-, -CH_3CH-,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) but remained unchanged in the spectrum of the metal complex. This suggests that coordination did not occur through these functionalities.

Table 4**:** ^{1}H-NMR spectra of chloroquine and its metal complex

Ligand/Metal complex	N-H (δ ppm)	Aliphatic Proton (δ ppm)	Aromatic Protons (δ ppm)
CQ	5.64	0.83-1.33	6.40-8.43
[Sc(CQ)n]	4.81	0.83-1.33	6.40-8.43

CQ = chloroquine ,

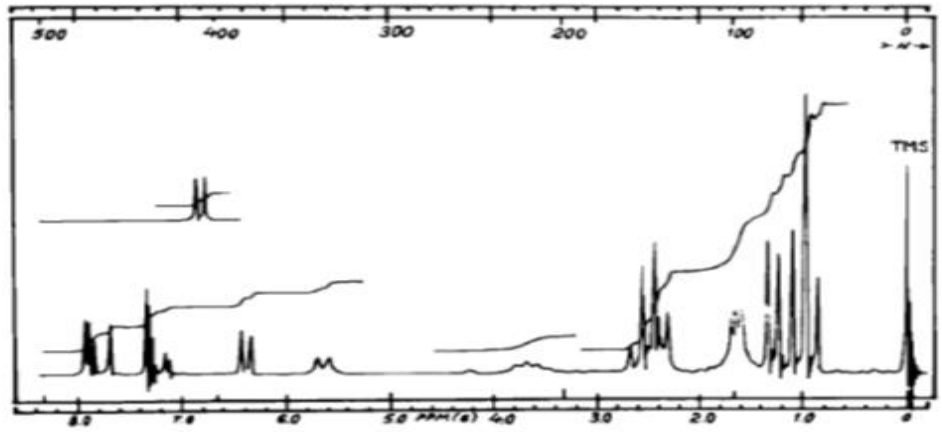

Figure 6**:**^{1}H NMR spectrum of chloroquine, source: (Mohammad and Abdullah, 1984)

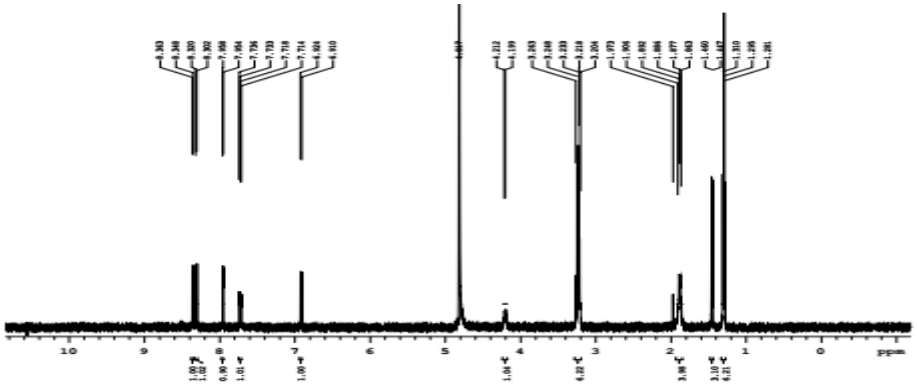

Figure 7: ^{1}H NMR spectrum of [Sc(CQ)n]

Based on the UV, IR and ^{1}H NMR spectra, the structure of chloroquine-Sc complex have been proposed in Figure 8.

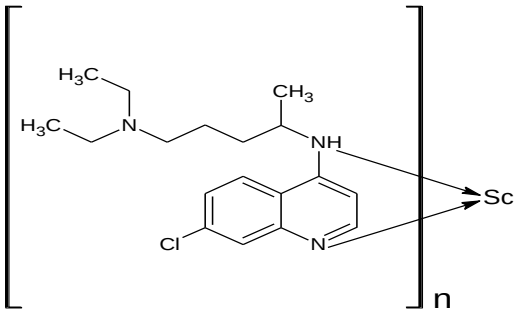

Figure 8. Proposed structure of chloroquine scandium complex, [Sc(CQ)n]

CONCLUSION

Chloroquine can be used to remove carcinogenic metal which are not biologically important from the environment or from the human body. The ability for chloroquine to sequestrate Sc (III) ion is hereby assured.

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REFERENCES

Aaseth J., Skaug M.A., Cao, Y. and Andersen, O., (2015). Chelation in metal intoxication — Principles and paradigms, *Journal of Trace Elements in Medicine and Biology.*31: 260-266.

Andersen, O. (2004). Chemical and biological considerations in the treatment of metal intoxications by chelating agents. *Mini-Reviews in Medicinal Chemistry,* 4:11

Bradberry, S. and Vale A. (2009). A comparison of sodium calcium edentate (edentate calcium disodium) and succimer (DMSA) in the treatment of inorganic lead poisoning. *Clinical toxicology,* 47: 841-858.

Jingping, W., Chengjun, W., Peiqi, W., Xiao, L., Zhang,M. and Zhu, J. (2017). Polypyrrole capacitance characteristics with different doping ions and thicknesses. *Physical Chemistry Chemical Physics*,19: 21165-21173

Knudtson, M. L., Wyse, G. and Galbraith, P. D (2002). Chelation therapy for ischemic heart disease: A randomized controlled trial. *Journal of the American Medical Association*, 287(4): 481-486.

Kosnett, M. J (2010). Chelation for heavy metals (arsenic, lead, and mercury): protective or perilous? *Clinical Pharmaceutical & Therapeutics*, 8: 412-415.

Mohammad,T. and Abdullah,A. A. (1984). Analytical Profiles of Drug Substances, volume 13, King Saud University, Riyadh, Saudi Arabia.

Nadira, W., and Singh, H. B (1987). Synthesis of metal complexes ofantimalaria drugs and *in-vitro* evaluation of their activity. *Inorg. Chim. Acta.* 135: 134-137

Odiaka,T. I (2004). Modern Organometallic Chemistry, University Press PLC, Ibadan.18

Patrick, L. (2006). Lead toxicity, a review of the literature. Part 1. Exposure, evaluation and treatment. *Alternative Medicine Review,* 11: 2-22.

Pedrares, A.S., Romero, J., Vazquez, J.A.G., Duran, M.L. and Casanova, I. (2003). Electrochemical, synthesis and structural characterisation of zinc, cadmium and mercury complexes of heterocyclic bidentate ligands (N, S). *Dalton Transaction* 7: 1379 - 1388.

Ratnaike, R. N. (2003). Acute and chronic arsenic toxicity. *Postgraduate Medical Journal,* 79: 391 - 396.

Reiss, A. and Mureseanu, M. (2012), Transition metal complexes with ligand containing thioamide moiety: Synthesis, characterization and antibacterial studies, *Journal of Chilean Chemical Society*, 57(4):1409 – 1414.

Ronnback, L. and Hansson, E. (1992). Chronic encephalopathies induced by low doses of mercury or lead. *British Journal of Industrial Medicine* 49: 233-240.

Verstraeten, S. V., Aimo, L. and Oteiza, P. I. (2008). Aluminium and lead: molecular mechanisms of brain toxicity. *Archives of Toxicology*, 82: 789-802.