RJC

RASĀYAN *J. Chem.*
Vol. 12 | No. 2 |450 - 454| April - June | 2019
ISSN: 0974-1496 | e-ISSN: 0976-0083 | CODEN: RJCABP
http://www.rasayanjournal.com
http://www.rasayanjournal.co.in

SYNTHESIS AND CHARACTERIZATION OF HETEROTRIMETALLIC FERROCENETHIOSEMICARBOZONERU(III) COMPLEXES WITH ASPH$_3$ FOR APPLICATION AS AN CHEMOTHERAPEUTIC DRUG

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ABSTRACT

Developing a heterometallic system enclosing three different spin carriers has enunciated a wider interest in research as it possesses characteristic features for being photo magnets and with combined features like magneto-luminescence and magneto-chirality. These results in greater prospects in developing molecular "prototypes" for quantum computing and drug delivery. This study aims to synthesize the Heterotrimetallic complexes [RuCl(AsPh$_3$)(L)$_2$](where L=bidentate Schiff base ligand of Ferrocenyl thiosemicarbazone and Ferrocenyl-N-phenylthiosemicarbazone) and characterize them using physicochemical analysis and spectroscopic techniques. The results confirm that in the synthesized complexes, ligands are coordinated with Ruthenium atom via NS. Also, the biological studies ascertain its activity towards biomolecules as a potential antibacterial material and could also find its use as a precursor for some chemotherapeutic drugs and also in supramolecular material research.

Keywords: Ru(III) Heterotrimetallic complexes, Ferrocenylthiosemicarbazone, Ferrocenyl-N-phenylthiosemicarbazone

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INTRODUCTION

The heterometallic system containing multinuclear transition metal complexes leading to the formation of supra-molecular material needs to be explored. These systems are found to be well suited for medical applications which are developed on the properties like good exchange ligand rate, different accessible oxidation states and its capability to mimic iron in binding to biological molecules[1,2].The Ruthenium complexes due to their extreme stability and catalytic behavior have enunciated an interest in converting the molecule into material leading to several applications[1].These are also found to exhibit photochromism–a photochemical phenomena[3]. Investigation with ferrocene and its derivatives has led their application as color pigments and also as a high burning rate catalyst[4,5].Its application as a chemotherapeutic drug has found to have less lethal dosage (LD$_{50}$)compared to others, which are in vogue[6,7]. Transition metal complexes of thiosemicarbazone are found to enhance the cytotoxic activity that has led to screening for pharmacological usage[8]. Ferrocenyl thiosemicarbazone containing transition metal compounds are active against microbiological organism[9]. So this paper focuses on the utilization of ferrocenyl thiosemicarbazones ligand in the synthesis of heterotrimetallic Fe(II) - Ru(III) - Fe(II) complexes with AsPh$_3$ as co-ligand. Further, the antimicrobial activity of the free ligand and the synthesized complexes were analyzed against the selected pathogens and fungi.

http://dx.doi.org/10.31788/RJC.2019.1225006

EXPERIMENTAL

Materials and Methods

Analar or chemically pure grade reagents were used. Ruthenium trichloride trihydrate ($RuCl_{3}.3H_2O$), was procured from Himedia. Standard procedure was used to purify solvents. Vario EL III elemental analyzer was used to record C, H and N analysis. Loba India melting point apparatus was used for Melting point determination.IR Spectrum in the 400-4000 cm^{-1} range was recorded using KBr pellet technique with a Shimadzu/Nicolet instrument and the electronic spectra on Evolution 201- UV-Visible spectrophotometer in DMSO solvent with 200-600 nm. EI mass spectrum was recorded on a JEOL GCMATE II mass spectrometer.

Synthesis of Acetyl Ferrocene[10,11]

A stirred solution of 5.5 gm (0.054 mol) of acetic anhydride in 50 ml of CH_2Cl_2, cooled in an ice bath, with 5 gm (0.027 mol) of ferrocene was saturated with gaseous boron trifluoride.The amber colored solution that soon turned into deep purple was obtained. After stirring for 30 min, the reaction mixture was left intact for 4 h at room temperature. To separate the two layers, with constant stirring, excess sodium acetate solution was added The$CH_2Cl_{2,\text{ the}}$ layer was separated and washed with water, followed by addition of saturated solution of sodium bicarbonate which was then dried over magnesium sulphate. The solvent was removed after filtration and the residue recrystallized with hexane to give orange needles of acetylferrocene with a melting point of 86°C.[10,11]

Synthesis of Bidentate Schiff Base Ligands

Following Schiff bases was synthesized and reacted with starting complexes to obtain new complexes.

Synthesis of 1-Acetyl ferrocenethiosemicarbazone (FL)

To 1:1 molar ratio of acetylferrocene and thiosemicarbazone refluxed in anhydrous ethanol for 5h, glacial acetic acid (few drops) were added and refluxing continued for 1h. This was cooled and decanted into ice. The granulated product obtained after filtration was recrystallized using absolute ethanol and dried in vacuum to give 1-acetylferrocenethiosemicarbazone with a melting point of 130 ^{0}C.[11,12]

Synthesis of 1-Acetylferrocene-4-phenylthiosemicarbazone (FPL)[11, 12]

To1:1 molar ratio of acetylferrocene and 4-phenylthiosemicarbazone refluxed in anhydrous ethanol for 5h, glacial acetic acid was added and refluxing continued for 1h.This was cooled and decanted into ice. The granulated product obtained, recrystallized from absolute ethanol and vacuum dried to give 1-acetylferrocene-4-phenylthiosemicarbazone (FPL) whose melting point was found to be 175 ^{0}C.[11, 12]

Synthesis of Trichlorotris(triphenylarsine)ruthenium(III) [$RuCl_3(AsPh_3)_3$]

A mixture of $RuCl_{3}.3H_2O$(0.2 g) in methanol (25 ml) and conc. HCl (25 ml) was refluxed for 30 min. To this triphenylarsine (1.2 g) in methanol (25 ml) was added and refluxing continued for 30 min. The oily mass which separates out was left in a mortar for a day under atmospheric conditions and then crushed. This was washed with methanol and vacuum dried to obtain trichlorotris(triphenylarsine)ruthenium(III) of melting point 146^{o}C.

Synthesis of Ruthenium(III) Complexes

[$RuCl(AsPh_3)(FL)_2$]

[$RuCl_3(AsPh_3)_3$] (0.108 g; 0.1 mmol) in dry benzene (20 ml) and the Schiff base FL (0.060 g; 0.2 mmol) was refluxed for 6 h. The obtained brown color solution was concentrated and treated with petroleum ether at (60-80^{o}C) to yield the complex [$RuCl(AsPh_3)(FL)_2$].This was then recrystallized from CH_2Cl_2 / petroleum ether (60-80 ^{o}C)and vacuum dried. A brown color crystal of [$RuCl(AsPh_3)(FL)_2$]with a melting point of 298^{o}Cwas obtained and the yield was found to be 70%.

[$RuCl(AsPh_3)(FPL)_2$]

[$RuCl_3(AsPh_3)_3$] (0.108 g; 0.1 mmol) in dry benzene (20 ml) and the Schiff base FPL 0.064 g (0.2 mmol) was refluxed for 6 h. A Black color solution obtained was concentrated. The complex obtained was separated using petroleum ether (60-80^{o}C). The resulting complex was recrystallized from CH_2Cl_2 /

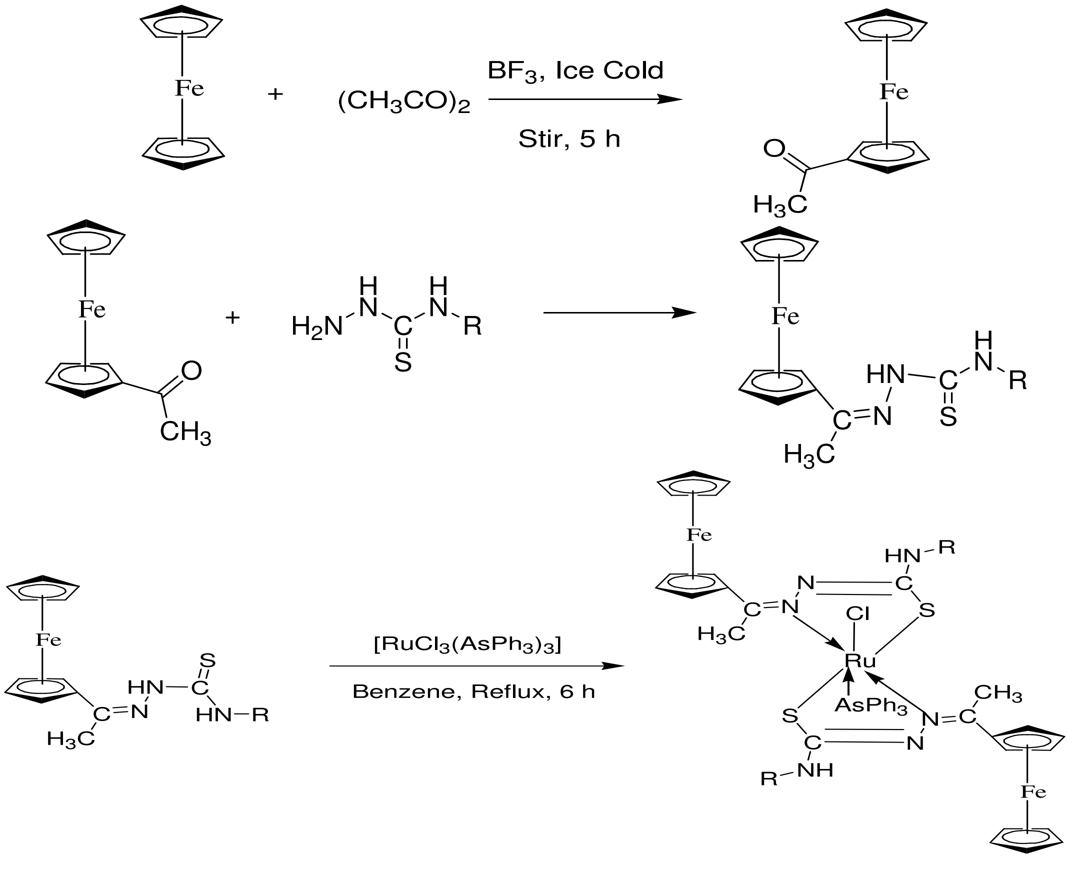
petroleum ether (60-80°C)and dried in vacuum to yield [RuCl(AsPh$_3$)(FPL)$_2$]. The color of the complex was found to be Grey with a melting point of 311 °C and the yield obtained was 75%.

Antimicrobial Activity

Three pathogens *E.coli, Enterococcus sp and Staphylococcus sp*, selected for the antibacterial study were maintained in respective slants under refrigerated conditions. Similarly, the fungal pathogens were also preserved for the studies. These pathogens with the load of 10^8–10^9cfu/mL were grown in nutrient broth for 18-20 h. Pour plate method was followed and 1 mL of the culture was inoculated on a nutrient agar plate. Agar well diffusion assay was performed. The positive control used was 15ppm of streptomycin. At the end of incubation, the zone of inhibition around each well was measured to determine the antimicrobial activity.[13]

RESULTS AND DISCUSSION

The synthesis of trimetallic complexes involved the preparation of acetylferrocene by the reaction of ferrocene with acetic anhydride in presence of BF$_3$followed by synthesis of ferrocenyl thiosemicarbazone ligands by the condensation of acetylferrocene with appropriate thiosemicarbazone ligands which were further reacted with Ruthenium (III) starting complexes in dry benzene in 1:2 molar ratio. The schematic representation of the synthesis of trimetallic complexes [RuCl(AsPh$_3$)(L)$_2$] (L = bidentate Schiff base ligand)is shown in Scheme-1.



Scheme-1: [RuCl(AsPh$_3$)(L)$_2$] Complex Formation (R = H or Ph)

In these reactions, the ferrocenyl thiosemicarbazone behaves as a monofunctionalbidentate ligand by substituting two of the triphenylarsines and two of the halide ion from the starting complexes. The analytical data are presented in Table-1. These Ruthenium(III) complexes are found to be stable to air as well as light, and soluble in organic solvents. The CHN analyses of these complexes are in accordance with the proposed molecular formula.

Table-1: Analytical Data of the Ru(III) Complexes

Complexes	Melting Point °C	Color	Elemental Analyses Calculated (Found) (%)			
			C	H	N	S
[RuCl(AsPh$_3$)(FL)$_2$]	298	Brown	50.64 (51.22)	4.16 (4.38)	8.06 (8.27)	6.15 (5.92)
[RuCl(AsPh$_3$)(FPL)$_2$]	>300	Grey	56.25 (55.94)	4.30 (4.63)	7.03 (6.94)	5.37 (5.81)

IR Spectral Analysis

The IR spectral bands of ferrocenylthiosemicarbazone and ferrocenyl-N-phenylthiosemicarbazone ligands and that of their Ruthenium(III) complexes are presented in Table-2.

Table-2: IR, Electronic and MS Data of Schiff Base Ligands and Ru(III) Complexes

Complexes	$\nu_{C=N}$ (cm^{-1})	$\nu_{C=S}$ (cm^{-1})	$\nu_{C=N} + \nu_{C=C}$	νAsPh$_3$ (cm^{-1})	UV-Vis λ_{max} (nm)	EI-mass, *m/z* Calculated (found) M$^+$
1-Acetylferrocenethiosemicarbozone (FL)	1651	821	-	-	245,380	-
1- Acetylferrocene-4-phenylthiosemicarbozone (FPL)	1650	815	-	-	256,395	-
[RuClAsPh$_3$(FL)$_2$]	1631	738	1579	1438,1088,704	260,390, 420,468	1042.78 (1042)
[RuClAsPh$_3$(FPL)$_2$]	1608	739	1547	1438,1094,702	261,412, 488, 588	1184.78 (1184)

The mode of coordination is fixed by comparing the IR spectral data of Ruthenium(III) complexes and the ligands. The strong absorption band of free Schiff base ligand (around 1650 cm$^{-1)}$,is characteristic of azomethine group (C=N). In the complexes prepared, the frequency of absorption at 1608–1631 cm^{-1} observed is attributed to(C=N) azomethine. The decrease in absorption frequency observed is indicative of coordination of the azomethine nitrogen of Schiff bases to Ruthenium. The disappearance of the medium intensity band in the region 821-823 cm^{-1}($\nu_{(c=s)}$) of the ligand and appearance of new band in the region 722–739 cm^{-1} in the synthesized trimetallic complex is attributed as reported[9,14] as "the other coordination through the sulphur atom of the ligand occurs after the enolisation of NHC=S group of the ligand followed by coordination through the S atom after deprotonation". Characteristic bands due to triphenylarsineare also present in the expected region.

Electronic Spectral Analysis

Electronic absorption spectral data using the DMSO solvent is presented in Table-2. On comparing the data of free ligands with complexes, in complexes a shift in the π-π* transitions and n-π* transitions occurred that is due to the involvement of molecular orbital of the cyclopentadienyl ring, C=N and enolic -SH chromophore. The presence of shoulder in the region of 430-447nm and band at 468-588 nm in the complexes is attributed to the transition of 3d electron and MLCT from iron respectively to either non-bonding or antibonding orbitals of the cyclopentadienyl ring. The strong band at 420-488 nm in the Ruthenium(III) complexes could be assigned to the LMCT transitions. The lower wavelength bands are characterized as ligand centered transitions occurring within the ligand orbitals[9,12].

Mass Spectral Analysis

The mass spectrum of the complexes (Table-2) reveals the presence of molecular ion peak [M$^+$] at *m/z* =1042 and 1184which authenticates the stoichiometry of the complexes. The spectrum is also in good agreement with the proposed molecular structure.

The antimicrobial activity was screened (Table-3) for three different bacterial species and different fungi. Significant zones of inhibition were not observed for fungi indicating the non-effectiveness of the complex against fungal infections compared to standard Cotrimazole but the varying zones of inhibition were prominent against the bacterial strains. It was observed that it is more effective towards *Staphylococcus sp* than the *E.coli, and Enterococcus sp*. Though the ligand shows cytotoxic activity against the bacteria the coordination with the Ruthenium ions facilitates the significant cytotoxic activity. As reported[14,15]"the improved activity arises from the delocalization of the positive charge between the organic moiety and the metal ion, which favors the drug entering the normal cellular processes of the bacteria". The C=N group present result in a hydrogen bond with the active centers of the constituents of the cell. This influences the antimicrobial activity. The presence of chlorine atom also may influence the cytotoxic activity[14,]The biological activity of metallic Ruthenium complexes suggested in the report[16] on "inhibition of the growth of LoVo human colon adenocarcinoma and MiaPaCa pancreatic cancer cell lines"is the interaction with plasmid pBR 322 DNA. The mode of binding could be either intercalation between base pairs of DNA or involving a covalent bond formation within from the purine base[16].

Table-3: Antimicrobial Activity of the Complexes

Ligands and Complexes	The Diameter of Inhibition Zone (mm)[a] for Bacteria		
	E. coli	*Enterococcus sp*	*Staphylococcussp*
1- Acetyl ferrocenethiosemicarbozone (FL)	12	13	14
1- Acetylferrocene-4- phenylthiosemicarbozone (FPL)	17	18	15
[RuClAsPh$_3$(FL)$_2$]	18	19	27
[RuClAsPh$_3$(FPL)$_2$]	22	21	28
Streptomycine	23	23	26

[a]Values are an average of triplicate runs

CONCLUSION

The heterotrimetallic Fe(II) - Ru(III) - Fe(II) complexes with ferrocenyl thiosemicarbazone(FL), ferrocenyl-N-phenyl thiosemicarbazone(FPL) ligands and AsPh$_3$were synthesized and characterized. The ligands are found to act as NS donors in these complexes. The coordination modes were confirmed by spectral studies. The easy accessibility to catalyze the oxidation and reduction reactions due to the redox potential of ruthenium depending on the physiological environment and the interaction of the organic moiety enables it to preferably be a precursor for chemotherapeutic drugs.

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[RJC-5006/2018]