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ANTIBACTERIAL ACTIVITY AND STRUCTURAL ELUCIDATION OF ORGANORUTHENIUM COMPLEXES LIGATED WITH BIOACTIVE THIOBARBITURIC ACID

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ABSTRACT

Mononuclear arsine complexes of ruthenium (II & III) legated with 2-thiobarbituric acid were prepared using precursors $[RuH(CO)(As\phi_3)_3Cl]$ and $[RuX_2(As\phi_3)_3]$ (X = Cl/Br) with composition $(RuCl(CO)(As\phi_3)_2(TBA)]$ and $[RuX(As\phi_3)(TBA)_2]$ (X = Cl/Br; HTBA = 2-thiobarbituric acid). The compositions of the complexes have been established by CHN elemental analysis, magnetic susceptibility, Conductometric measurement, IR, UV-Vis and ^{1}HNMR spectral data. The thioamide ligand acts as mononegative bidentate (N, S) anion. The ligand and metal complexes were screened for their antimicrobial activity against gram-negative bacteria, *E.coli* and gram-positive bacteria, *S.aureus*. Metal-complexes exhibits more activity than free thioamide ligand.

Keywords: Ruthenium-complexes, mono-nuclear, secondary thioamide, triphenylarsine, anti-microbial activity.

INTRODUCTION

This work is undertaken to the synthesis, structural elucidation and antibacterial studies of some ruthenium chelates with bioactive thiobarbituric acid. Thiobarbituric acid (HTBA) is in use for the determination of the lipid peroxidation in biological system[1-2]. The derivative of thiobarbituric acid has vast medicinal importance showing antifungal[3], antimicrobial[4], antitubercular[5], herbicides[6], antioxidant[7] and other activities[8]. The coordination complexes and mode of bonding of this bioactive molecule is examined by various workers[9-11]. The increasing interest in the bio-inorganic chemistry of organoruthenium compounds are applications as anti-cancer drugs[12-13]. The resurgence of our interest in this ligand, the structure of its synthesized complexes are deduced using various physico-chemical measurements and their antibacterial activity is examined against gram positive bacteria *S. aureus* and gram negative bacteria *E.coli*.

EXPERIMENTAL

All chemicals used in the present work are CP grade or AR grade. Thiobarbituric acid (HTBA) was obtained from E. Merck and its purity was checked spectroscopically. The precursor complexes [RuHCl (CO) $(As\phi_3)_3$] and $[RuX_3(As\phi_3)_3]$ were synthesized by the methods reported in literature[14-16]. All new ruthenium (II) complexes were synthesized using equimolar ratio of precursor and thiobarbituric acid and ruthenium (III) complexes were synthesized using 1:2 molar ratios of precursors and HTBA following our previous methods reported in literature[17-18].

Analyses

1. $[RuCl(CO)(As\phi_3)_2(TBA)]$ (yellow brown) : **Calculated (%)** for $\mathbf{RuC_{41}H_{33}N_2O_3SCl}$ (769.5) : C = 63.93; H = 4.28; N = 3.63; **Found (%)** : C = 64.01; H = 4.30; N = 3.68
2. $[RuCl(As\phi_3)(TBA)_2]$ (green yellow) : **Calculated (%)** for $\mathbf{RuC_{26}H_{31}N_4O_4S_2AsCl}$ (738.42) : C = 42.25; H = 4.19; N = 7.58; **Found (%)** : C = 42.10; H = 4.20; N = 7.56
3. $[RuBr(As\phi_3)(TBA)_2]$ (green brown) : **Calculated (%)** for $\mathbf{RuC_{26}H_{31}N_4O_4S_2AsBr}$ (782.82) : C = 39.85; H = 3.96; N = 7.15; **Found (%)** : C = 39.90; H = 4.01; N = 7.20

Carbon, hydrogen and nitrogen analyses were done at the micro-analytical section of CDRI Lucknow. The infrared spectra of ligand and complexes were recorded with Perkin Elmer Model 577 spectrophotometer in the range of 4000-400 cm^{-1} as KBr pellets. The electronic spectra were recorded with Zeiss (Jena) model and ^{1}HNMR spectra were obtained with Varian EM 390 MHz NMR spectrophotometer. Conductance measurements were made in DMF solutions (10^{-3}M) using Wiss-Werkstatter Weithem obb type LBR conductivity meter.

RESULTS AND DISCUSSION

The analytical data of complexes are in good agreement with the molecular formula proposed. Refluxing a mixture containing [RuHCl (CO) ($As\phi_3$)$_3$] and HTBA in equimolar ratio yielded solid products [RuCl (CO) ($As\phi_3$)$_2$(TBA)] as given below:

$$[RuHCl\ (CO)\ (As\phi_3)_3] + HTBA \xrightarrow[C_6H_6,\ reflux,\ 4\ hr.]{Et_3N/MeOH} [RuCl\ (CO)\ (As\phi_3)_2(TBA)] + H_2(g) + As\phi_3$$

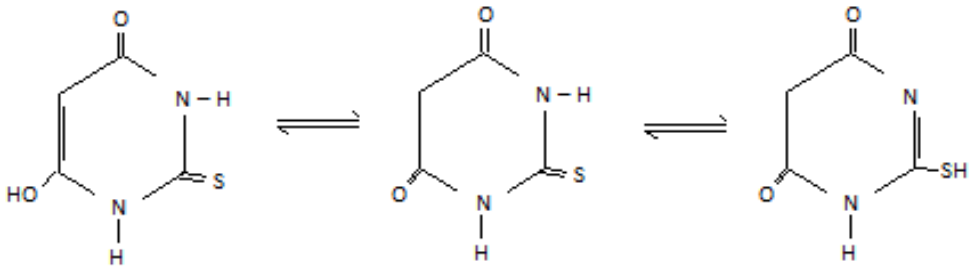
All ruthenium (III) complexes were prepared using precursors, [$RuX_3(As\phi_3)_3$] (X = Cl/Br) and ligand (HTBA) in the molar ratio = 1:2.

$$RuX_3(As\phi_3)_3 + 2HTBA \xrightarrow[C_6H_6,\ reflux,\ 4\ hr.]{Et_3N/MeOH} [RuX\ (As\phi_3)\ (TBA)_2] + 2HX + 2As\phi_3$$

These air-and moisture stable compounds are soluble in chlorinated solvents, acetone, DMF, DMSO but insoluble in water and Et_2O.

Spectral Characterization

Thiobarbituric acid (HTBA) exhibits tautomerism. The purity was checked from ^{1}HNMR and IR spectra. A broad peak was observed at δ4.9 ppm (S, C-H) due to C_5 proton of the Pyrimidine ring and δ3.51 ppm (S, CH) for Str.-I.



Str. I **Str. II** **Str. III**

The sharp signal at δ12.21 ppm with integration corresponds to two N-H and one OH protons as a result of 5-6 enolizaiton also supports the existence of str. I. The appearance of νOH (2895-2810 cm^{-1}), νC=N (1610-1570 cm^{-1}), νC-O (1390-1360 cm^{-1}) and νC-S (795-775 cm^{-1}) in infrared spectra is strong evidence that the ligand is tautomerized to the enol-thiol structure before complexation with metal ions. Morvey et al[19] found that if the structure of thiobarbituric acid does not allow the formation of en-thiol species, a complex formation between thiobarbiturate and the metal ion does not takes place. However,

the systematic shift of four thioamide bands[20-22] of HTBA and the appearance of a weak band at 435-410 cm^{-1} provides a strong evidence for the formation of M-S bond[23].

The thioamide bands of crystalline HTBA undergo major change. Thioamide Band I (1527 cm^{-1}), Band II (1350 cm^{-1}), Band III (1155 cm^{-1}) and Band IV (805 cm^{-1}) of free ligand display red shift of 15-20 cm^{-1} (Band I), 25-30 cm^{-1} (Band III) and 35-40 cm^{-1} (Band IV) respectively on complexation indicating simultaneous M-N and M-S bond[24-26] and the ligand (HTBA) acts as mononegative bidentate anion. The νNH bands are observed at 3210 cm^{-1} and 3105 cm^{-1} in the spectrum of HTBA. The first band was not observed in the spectra of complexes indicating deprotonation of N-H group by metal ion having Ru-N bond. Medium band around 490-505 cm^{-1} also supports the formation of Ru-N bond and assigned to νRu-N mode[27].
Bands around 530, 695, 740, 1450 and 1560 confirmed the presence of coordinated $As\phi_3$ group[28] and at 1920 cm^{-1} due to terminally coordinated C≡O group[29] and is observed at slightly higher frequency than in the precursor complex.

Electronic Spectra and Magnetic Moments
The magnetic moment of [RuCl (CO) $(As\phi_3)_2$(TBA)] is found to be diamagnetic indicating divalent ruthenium having $T_{2g}^{6}\ e_g^{0}$ configuration in octahedral environment[30] and ground state $^1A_{1g}$. The excited state corresponding to the $T_{2g}^{5}\ e_g^{1}$ configuration are $^3T_{1g}$, $^3T_{2g}$, $^1T_{1g}$ and $^1T_{2g}$. Hence, four bands corresponding to the transitions, $^1A_{1g} \rightarrow {}^3T_{1g}$, $^1A_{1g} \rightarrow {}^3T_{2g}$, $^1A_{1g} \rightarrow {}^1T_{1g}$ and $^1A_{1g} \rightarrow {}^1T_{2g}$ are possible in order of increasing energy. The bands observed in the spectrum of [RuCl (CO) $(As\phi_3)_2$(TBA)] at 510 nm ($^1A_{1g} \rightarrow {}^1T_{1g}$), 460 nm ($^1A_{1g} \rightarrow {}^1T_{2g}$) and at 415 nm ($T_{2g} \rightarrow \pi^*$, MLCT) are consistent with octahedral structure[31-32].
The magnetic moment of [RuX $(As\phi_3)$ $(TBA)_2$] (X = Cl/Br) are found in the range of 1.85–1.86 corresponding to one unpaired electron in trivalent ruthenium (d^5) arising from the $t_{2g}^{5}\ e_g^{0}$ configuration in octahedral structure[33]. Hence, two bands corresponding to $^2T_{2g} \rightarrow {}^2A_{2g}$ and $^2T_{2g} \rightarrow {}^2T_{1g}$ are possible.
All the ruthenium (III) complexes display strong band in the visible region in the range 570-565 nm followed by a weak shoulder in the range 450-455 nm which are assigned as $^2T_{2g} \rightarrow {}^2A_{2g}$ and LMCT transition respectively. The band in the 290-295 nm regions are due to $\pi \rightarrow \pi^*$ transition. The pattern of electronic spectra of all ruthenium (III) complexes indicates the presence of an octahedral environment the ruthenium (III) ion.[34-35]

Antibacterial Activity
All the synthesized compounds were tested against gram positive bacteria *S.aureus* and gram negative bacteria *E.coli* using paper disc method reported in literature[36]. Muller Hinton Agar (Hi-Media Pvt. Ltd. Mumbai, India) was used to culture the test bacteria. The microbial culture was grown at 37^0C for 8 hrs. The concentration of drugs was kept 200 μg/mL in DMF using streptomycin as standard drug for comparison. The complexes show moderate activity on chelation. The increase in the antibacterial activity of ruthenium chelates may be due the effect of the metal ion on the normal cell process. A possible mode of the toxicity increase may be considered in light of Tweedys chelation theory[37].
Chelation considerable reduces the polarity of the metal ion because of partial sharing of its positive charge with the donor groups and possible π-electrons delocalization over the whole chelate ring. Such chelation could enhance the lipophilic character of central metal atom which subsequently favors its permeation through the lipid layers. The mode of action of the compounds may involve formation of hydrogen bond through carbonyl group with active centers of the cell constituents resulting in interference the normal cell processes[38].
Moreover, the complexes possess lower activity than standard drug streptomycin. The variation in the effectiveness of the different complexes against different organism depend either on the impermeability of the cell or the microbe of difference in ribosome of microbial cells[39].

Table–1: Magnetic Moment, Conductometric Measurements, Electronic and ^{1}HNMR spectral data of complexes

Complex	μeff. (BM)	Molar cond. ($\wedge^{-1}cm^2mol^{-1}$)	Electronic Spectra (nm)	1H NMR (δPpm)		
				$As\phi_3$	NH+OH	CH
Ru^{II} (1)	Dia.	10.32	510 ($^1A_{1g}\rightarrow{}^1T_{1g}$) 460 ($^1A_{1g}\rightarrow{}^1T_{2g}$) 420 ($T_{2g}\rightarrow\pi^*$, MLCT)	7.0-8.52 (multiplet)	10.98	4.90
Ru^{III}.Cl (2)	1.85	8.32	570 ($^2T_{2g}\rightarrow{}^2A_{2g}$) 450 (CT Band) 295 ($\pi\rightarrow\pi^*$)	7.20-8.20 (multiplet)	11.2	4.90
Ru^{III}.Br (3)	1.85	8.42	565 ($^2T_{2g}\rightarrow{}^2A_{2g}$) 455 (CT Band) 290 ($\pi\rightarrow\pi^*$)	7.12-8.11 (multiplet)	11.32	4.92

Table- 2: Infrared Spectra of ligand (HTBA) and its complexes (cm^{-1})

Compound	Thioamide Bands				νC=O	νRu-S	νRu-N
	Band I	Band II	Band III	Band IV			
HTBA (ligand)	1527 (s)	1350 (s)	1155 (m)	805 (m)`	1720 (s)	—	—
Ru^{II} (1)	1505 (s)	1365 (s)	1125 (m)	770 (m)	1725 (s)	406 w	490 (m)
Ru^{III}.Cl (2)	1510 (m)	1370 (m)	1120 (m)	772 (m)	1730 (s)	415 w	505 (m)
Ru^{III}.Br (3)	1520 (m)	1375 (m)	1125 (m)	775 (m)	1732 (s)	420 w	500 (m)

Table-3: The zone of inhibition of HTBA, complexes and standard drugs tested for antibacterial activity. Data represent zone of inhibition (mm) and solutions are in μg/mL

Compounds	*E. coli*		*S. aureus*	
	200	100	200	100
HTBA	21	12	20	14
$[RuH(CO)(As\phi_3)_2(TBA)]$	23	15	22	16
$[RuCl(As\phi_3)(TBA)_2]$	23	17	23	15
$[RuBr(As\phi_3)(TBA)_2]$	23	18	22	16
Streptomycin	26		26	

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