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SYNTHESIS, CHARACTERIZATION AND ANTIBACTERIAL STUDIES ON SOME ORGANOMETALLIC COMPLEXES OF RUTHENIUM (II) LIGATED WITH 4-AMINO-5-MERCAPTO-3-SUBSTITUTED-1,2,4-TRIAZOLE

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ABSTRACT

Organometallic complexes of ruthenium (II) with the composition $[RuCl(CO)(E\phi_3)_2L]$ and $[Ru(E\phi_3)_2L_2]$ (E = P/As; LH = Phenyl/benzyl derivatives of 4-amino-5-mercapto-3-substituted-1,2,4-triazole) have been isolated using some precursor complexes. The structure of new chelates are deduced by elemental analysis, molar conductance, magnetic moment, IR, UV-vis and ^1H NMR spectral studies. IR spectral studies provides strong evidence in support of the deprotonated ligands with metal ion in a bidentate fashion through both N,S atoms of the thioamide group in octahedral structure. The antibacterial studies of the ligands and their metal chelates have been screened for the selected bacteria, *E. coli*, *B. subtilus* and *S. aureus*. Studies suggest that the metal chelates are more active than ligands but lesser than standard drug streptomycin.

Key words: Organo-ruthenium (II) chelates, Thioamides, Antibacterial studies.

INTRODUCTION

Literature survey reveals that 1,2,4-triazole derivatives have diverse biological potential including antibacterial[1-3], antifungal[4,5], antitumour[6], antitubercular[7], anticancer[8] and anticonvulsant[9]. The current interest in organometallic ruthenium complexes with antitumour activity[10-12] as well as the less amount of work on ruthenium complexes containing heterocyclic chelating secondary thioamide ligands, prompted us to investigate this class of complexes in further detail. We have previously examined reactions, structures and biological evaluation of complexes of Pt-group metals[13-15]. We therefore planned to extend our study by preparing some ruthenium derivatives with heterocyclic thioamides, 4-amino-5-mercapto-3-substituted-1,2,4-triazole (I).

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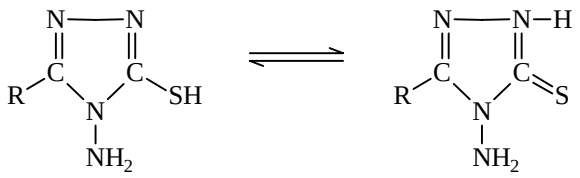


(R = C_6H_5-/$C_6H_5CH_2$-)

All the synthesized compounds are studied for their *in vitro* antibacterial against *Escherichia coli*, *Bacillus subtilis* and *staphylococcus aureus*.

EXPERIMENTAL

All chemicals used were of analar grade. The ligands were prepared by some modified method reported in literature[16]. The precursor complexes [RuHCl(CO)(Eϕ_3)$_3$] and [$RuCl_2$(Eϕ_3)$_4$] (E = P/As) were prepared according to the literature method[17-19].

Preparation of new complexes of ruthenium (II)

Equimolar ratio ligands and [RuHCl(CO)(Eϕ_3)$_3$] (E = P/As) in dry benzene (30 mL) and triethylamine (1.0 mL) as base was refluxed for 4 hr and the progress of reaction was monitored using TLC. At the end the solution was concentrated to ~5 mL and light petroleum ether (60-80^{o}C) was added where by solid complexes separated out. The obtained solid was dried under vacuum over anhydrous $CaCl_2$. Yield = 72.75%. For the preparation of [Ru(Eϕ_3)$_2$)(ligand)$_2$] the precursor complex and ligand were taken in molar ratio = 1:2.

Analysis

1. [RuCl(CO)(Pϕ_3)$_2$(APtT)] (yellow brown): Calculated (%) for $C_{45}H_{37}N_4OSP_2Cl$ Ru (879.70): C = 61.38; H = 4.20; N = 6.36; Ru = 11.48; Found (%): C = 61.02; H = 4.25; N = 6.40; Ru = 11.50.

2. [RuCl(CO)(Asϕ_3)$_2$(APtT)] (yellow brown): Calculated (%) for $C_{45}H_{37}N_4OSAs_2Cl$ Ru (967.34): C = 55.82; H = 3.82; N = 5.78; Ru = 10.44; Found (%): C = 56.61; H = 3.88; N = 5.80; Ru = 10.21.

3. [Ru(Pϕ_3)$_2$(APtT)$_2$] (brown): Calculated (%) for $C_{52}H_{44}N_8S_2P_2Ru$ (1007): C = 61.96; H = 4.36; N = 11.12; Ru = 10.02; Found (%): C = 62.01; H = 4.44; N = 11.01; Ru = 10.20.

4. [Ru(Asϕ$_3$)$_2$(APtT)$_2$] (brown): Calculated (%) for $C_{52}H_{44}N_8S_2As_2Ru$ (1094.84): C = 56.99; H = 4.01; N = 10.23; Ru = 9.22 Found (%): C = 56.40; H = 4.12; N = 9.22; Ru = 9.02.

5. [RuCl(CO)(Pϕ$_3$)$_2$(ABtT)] (yellow brown): Calculated (%) for $C_{46}H_{39}N_4OSP_2Cl$ Ru (893.5): C = 61.77; H = 4.36; N = 6.26; Ru = 11.30; Found (%): C = 61.80; H = 4.40; N = 6.30; Ru = 11.20.

6. [RuCl(CO)(Asϕ$_3$)$_2$(ABtT)] (yellow brown): Calculated (%) for $C_{46}H_{39}N_4OSAs_2Cl$ Ru (981.34): C = 56.24; H = 3.97; N = 5.70; Ru = 10.29; Found (%): C = 56.52; H = 4.01; N = 5.80; Ru = 10.30.

7. [Ru(Pϕ$_3$)$_2$(ABtT)$_2$] (brown): Calculated (%) for $C_{54}H_{48}N_8S_2P_2Ru$ (1035): C = 62.60; H = 4.63; N = 10.82; Ru = 9.75; Found (%): C = 62.56; H = 4.72; N = 10.88; Ru = 9.70.

8. [Ru(Asϕ$_3$)$_2$(APtT)$_2$] (brown): Calculated (%) for $C_{54}H_{48}N_8S_2As_2Ru$ (1122.84): C = 57.71; H = 4.27; N = 9.97; Ru = 8.99; Found (%): C = 57.82; H = 4.48; N = 10.01; Ru = 9.02.

APtTH = 4-amino-5-mercapto-3-aryl-1,2,4-triazole (M. Pt = 203^{o}C) and ABtTH = 4-amino-5-mercapto-3-benzyl-1,2,4-triazole (M. Pt = 206^{o}C).

The analysis of C, H and N were performed at CDRI, Lucknow, India. IR spectra of ligands and complexes were recorded on a Perkin-Elmer 577 spectrophotometer in the range of 4000-200 cm^{-1} as KBr pellet technique. Electronic spectra of ligands and complexes were performed on a Backmann DU-6 spectrophotomer and ^{1}H NMR spectra was recorded on Bruker 400 MHz using TMS as reference. The molar conductance of complexes (10^{-3} M) were measured in DMF using Wiss-Werkstatter Weihem obb type LBR conductivity meter. The magnetic susceptibility was measured on a gouy balance using Hg[Co(SCN)$_4$] as calibrant.

RESULTS AND DISCUSSION

The reaction of precursors with thioamide ligands in 1:1 molar ratio in dry benzene afforded new hexa-coordinated diamagnetic ruthenium (II) complexes of general formula [RuCl(CO)(Eϕ$_3$)$_2$L] (E = P/As; LH = APtTH/ABtTH) and ligands behaves as deprotonated mononegative bidentate ligand (**Scheme I**). However, precursor complexes [RuCl$_2$(Eϕ$_3$)$_4$] (E = P/As) yieleded brown solid products when metal : ligand ratio was 1 : 2 in dry benzene

(**Scheme II**). All solid products were neutral molecules, almost non-conducting in DMF (10^{-3} M). All complexes were air-stable, non-hygroscopic in nature, insoluble in water and highly soluble in DMF, DMSO, acetone and acetonitrile producing coloured solution. The analytical data are in good agreement with general formula assigned.

$$[RuH(CO)(E\phi_3)_3Cl] + LH \xrightarrow[\text{Reflux, 4 hr}]{C_6H_6/\text{Triethylamine}} H_2(g)\uparrow + E\phi_3 + [RuCl(CO)(E\phi_3)_2(L)]$$

(E = P/As; LH = APtTH/ABtTH)

Scheme I

$$[RuCl_2(E\phi_3)_4] + 2LH \xrightarrow[\text{Reflux, 4 hr}]{C_6H_6/\text{Triethylamine}} 2HCl + 2E\phi_3 + [Ru(E\phi_3)_2L_2]$$

Scheme II

Spectroscopic characterization

UV-Vis spectra

The electronic spectra of complexes were recorded in DMF solution in the range of 800-200 nm (Table 2). The complexes exhibit three bands in the region 215-485 nm. The high intensity bands around 215-270 nm ($\pi\rightarrow\pi^*$) and 300-310 nm ($n\rightarrow\pi^*$) are assignable to ligand centred (LC) transitions. The lowest energy bands observed in the region 480-490 nm are attributed to the $Ru(d\pi) \rightarrow L(\pi^*)$ metal to ligand charge transfer (MLCT) transitions[20]. The pattern of the electronic spectra of all complexes indicated the presence of an octahedral environment around the ruthenium (II) ion, similar to other octahedral ruthenium (II) complexes[21,22].

Infrared spectra

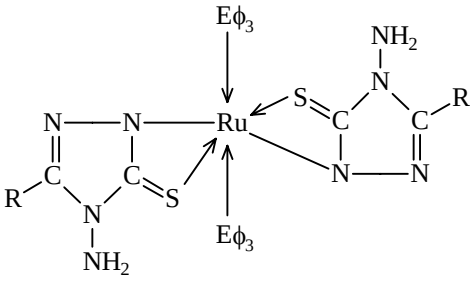
The ligands 4-amino-3-substituted-5-mercapto-1,2,4-triazole display three bands at 3270, 3185 and 3100 cm^{-1} for phenyl substitution (APtTH) and at 3260, 3180 and 3105 cm^{-1} benzyl substitution (ABtTH) due to interaction between $–NH_2$ and –NH groups. These bands are perturbed on coordination with ruthenium (II) ion in position with diminished intensity probably due to replacement of N-H hydrogen and formation of N-Ru bond. The formation ruthenium – N bond is also supported by red shifting of thioamide band I to lower frequency by 35-20 cm^{-1}. The formation of simultaneous Ru-S and Ru-N bond is indicated by blue shift (15-20 cm^{-1}) of thioamide band II to higher frequency and red shift of thioamide band III (20-30 cm^{-1}) and band IV (25-30 cm^{-1}) due to increase in CN bond order and decrease of CS bond order on complexation[23-25]. Formation non-ligand bands at 500-470 cm^{-1} (Ru-N)

and 385-410 cm^{-1} (Ru-S) due to stretching mode confirmed bonding of thioamide ligands through both nitrogen and sulphur and ligands acts as mononegative bidentate anion. The terminal coordinated C ≡ O group appeared at 1965-1980 cm^{-1} slightly higher frequency than in precursor complexes[26]. New bands around 532, 690, 745 and 1560 cm^{-1} due to coordinated $As\phi_3$ and near 530, 685, 745 and 1550 cm^{-1} due to coordinated $P\phi_3$ are agreement with previous literature[27,28].

^{1}H NMR Spectra

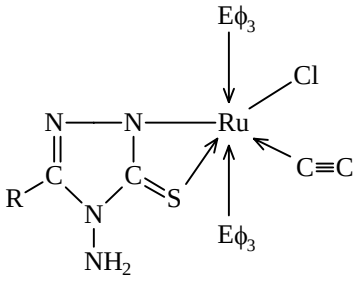
The ^{1}H NMR spectra of all complexes in $CDCl_3$/TMS to confirm bonding of these thioamide ligands to the ruthenium (II) ion. Multiplets observed in the region δ 8.10-8.33 PPM in all the complexes have been assigned to the aromatic protons of $P\phi_3/As\phi_3$ and ligands[29]. All other protons, NH_2 (4.30-4.42 PPM), CH_2 (2.23-2.24 PPM) and Ar-H (7.69-7.89 PPM) of ligands overall under went down field shifting by 0.10-0.25 PPM due to shielding effect on coordination. The absence of imino proton on complexation due to formation of Ru-N bond and deprotonation of N-H group of ligands. These observations are consistent with IR spectral results.

Thus, on the basis of aforesaid observations the structure of complexes may be deduced as –



(R = C_6H_5-/$C_6H_5CH_2$; E = P/As)

Oh-str. of [Ru $(E\phi_3)_2L_2$]



(R = C_6H_5-/$C_6H_5CH_2$; E = P/As)

Oh-str. of [RuCl(CO) $(E\phi_3)_2L$]

Biological activity

Antibacterial studies

The antibacterial activity of ligands and their ruthenium (II) complexes were studied against Gram-negative (*E. coli*) and two gram-positive (*S. aureus*, *B. Subtilis*) bacterial strains according to the literature protocol and their results were recorded in Table 3. The obtained results are compared with standard drug Streptomycin.

The bacteria were cultured in nutrient ager medium in petri plates and used inoculums for the study using disc diffusion method[30]. The complexes to be tested were dissolve in DMSO to a final concentration of 0.25%, 0.50% and 1% and soaked in the filter paper disc of 5 mm diameter and 1 mm thickness. The discs were placed on the previously seeded plate and incubated at 37°C for 24 hr. The diameter of inhibitory zone around each disc was measured.

The antibacterial activity data show that the complexes exhibit weak to moderate activity. The toxicity of ruthenium chelates increases on increasing the concentration[31-33]. The increase in the antimicrobial activity of the metal chelates may be due to the effect of the metal ion on the normal cell process. The increase in activity on complexation agreement with Tweedys chelation theory[34]. The comparison of the average activity value of thioamide ligands and average activity value of their corresponding ruthenium (II) complexes revealed[35] that the activity of the ruthenium (II) complexes is increased upon coordination with metal ion.

Table 1: Major IR bands of ligands and ruthenium (II) complexes (cm^{-1})

Compounds	ν C≡O	Thioamide Bands$^{\Psi}$				ν Ru-N	ν Ru-S
		Band I	Band II	Band III	Band IV		
APtTH ($C_8H_8N_4S$)	—	1525 (s)	1245 (s)	1140 (m)	760 (m)	—	—
[RuCl(CO)($P\phi_3$)$_2$(APtT)]	1980 (m)	1490 (m)	1255 (m)	1025 (m)	742 (m)	490 (m)	410 w
[RuCl(CO)($As\phi_3$)$_2$(APtT)]	1965 (m)	1485 (m)	1260 (m)	1020 (m)	730 (m)	470 (m)	405 (w)
[Ru($P\phi_3$)$_2$(APtT)$_2$]	—	1495 (m)	1265 (m)	1010 (m)	745 (m)	465 m	400 (m)
[Ru($As\phi_3$)$_2$(APtT)$_2$]	—	1505 (m)	1270 (m)	1015 (m)	740 (m)	475 (m)	410 (w)
ABtTH ($C_9H_{10}N_4S$)	—	1530 (s)	1240 (s)	1145 (m)	780 (m)	—	—
[RuCl(CO)($P\phi_3$)$_2$(ABtT)]	1980 (m)	1515 (ms)	1235 (m)	1130 (m)	740 (m)	480 m	385 w
[RuCl(CO)($As\phi_3$)$_2$(ABtT)]	1980 (m)	1510 (m)	1240 (m)	1135 (m)	742 (m)	485 (m)	405 w
[Ru($P\phi_3$)$_2$(ABtT)$_2$]	—	1495 (m)	1235 (m)	1125 (m)	750 (m)	490 (m)	402 w
[Ru($As\phi_3$)$_2$(ABtT)$_2$]	—	1490 (m)	1230 (m)	1120 (m)	745 (m)	500 (m)	405 w

$^{\Psi}$Mixed Bands: Band I = δ NH + δ CH + νC=N; Band II = νC-N + νC-S + δCH + δNH;
Band III = νC – N + νC – S; Band IV = νC⎓S.

Table 2: ^{1}H NMR and electronic spectral data of ruthenium (II) complexes

Complex	^{1}H NMR (δ PPM)					Electronic spectra
	$P\phi_3/As\phi_3$	Ar-H	NH_2	NH	CH_2	λ_{max} (nm)/ (assignments)
$[RuCl(CO)(P\phi_3)_2(APtH)]$	8.0-8.30	7.72-7.80	4.44-4.56	—	2.38	265 ($\pi \rightarrow \pi^*$) 304 ($n \rightarrow \pi^*$) 480 ($T_{2g} \rightarrow \pi^*$)
$[RuCl(CO)(As\phi_3)_2(APtH)]$	8.30-8.32	7.10-7.81	4.40-4.56	—	2.34	312 ($\pi \rightarrow \pi^*$) 272 ($n \rightarrow \pi^*$) 490 ($T_{2g} \rightarrow \pi^*$)
$[Ru(P\phi_3)_2(APtH)_2]$	8.32-8.40	7.22-7.30	4.60-4.62	—	2.42	270 ($\pi \rightarrow \pi^*$) 310 ($n \rightarrow \pi^*$) 480 ($T_{2g} \rightarrow \pi^*$)
$[Ru(As\phi_3)_2(APtH)_2]$	8.33-8.45	7.30-7.41	4.60-4.70	—	2.44	280 ($\pi \rightarrow \pi^*$) 318 ($n \rightarrow \pi^*$) 485 ($T_{2g} \rightarrow \pi^*$)
$[RuCl(CO)(P\phi_3)_2(ABtH)]$	8.10-8.25	7.42-7.42	4.63-4.71	—	2.41	215 ($\pi \rightarrow \pi^*$) 308 ($n \rightarrow \pi^*$) 470 ($T_{2g} \rightarrow \pi^*$)
$[RuCl(CO)(As\phi_3)_2(ABtH)]$	8.12-8.22	7.40-7.33	4.60-4.71	—	2.45	216 ($\pi \rightarrow \pi^*$) 305 ($n \rightarrow \pi^*$) 482 ($T_{2g} \rightarrow \pi^*$)
$[Ru(P\phi_3)_2(ABtH)_2]$	8.10-8.22	7.50-7.60	4.44-4.56	—	2.40	210 ($\pi \rightarrow \pi^*$) 300 ($n \rightarrow \pi^*$) 482 ($T_{2g} \rightarrow \pi^*$)
$[Ru(As\phi_3)_2(ABtH)_2]$	8.12-8.33	7.60-7.62	4.45-4.60	—	2.44	215 ($\pi \rightarrow \pi^*$) 305 ($n \rightarrow \pi^*$) 485 ($T_{2g} \rightarrow \pi^*$)

Table 3: Antibacterial bioassay of ligands and ruthenium (II) complexes diameter of inhibition zones (mm)

Compounds	*E. coli*			*B. subtilus*			*S. aureus*		
	0.25%	**0.50%**	**1%**	**0.25%**	**0.50%**	**1%**	**0.25%**	**0.50%**	**1%**
APtTH ($C_8H_8N_4S$)	08	10	12	09	08	10	09	11	12
[RuCl(CO)($P\phi_3$)$_2$(APtT)]	10	12	13	11	12	14	11	13	14
[RuCl(CO)($As\phi_3$)$_2$(APtT)]	09	12	14	10	12	14	11	13	15
[Ru($P\phi_3$)$_2$(APtT)$_2$]	11	13	14	12	14	15	11	14	15
[Ru($As\phi_3$)$_2$(APtT)$_2$]	10	12	14	12	14	15	10	12	14
ABtTH ($C_9H_{10}N_4S$)	09	12	13	09	10	12	08	10	12
[RuCl(CO)($P\phi_3$)$_2$(ABtT)]	12	13	15	10	11	13	10	12	14
[RuCl(CO)($As\phi_3$)$_2$(ABtT)]	11	13	14	11	13	15	11	12	14
[Ru($P\phi_3$)$_2$(ABtT)$_2$]	11	12	14	10	11	14	10	12	14
[Ru($As\phi_3$)$_2$(ABtT)$_2$]	10	12	14	NT	NT	NT`	NT	NT	NT
Streptomycin (standard drug)	23	24	28	22	28	29	29	29	26

NT = not tested

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