http://www.e-journals.in
DOI:10.7598/cst2015.929

Chemical Science Transactions
2015, **4(1),** 81-88

RESEARCH ARTICLE

Synthesis and Characterization of Complexes of Rh(II) with Purines and Pyrimidines

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Received 8 August 20014/ Accepted 5 September 2014

Abstract: The reactions of nucleobases and aminoacids with rhodium(II) acetate resulted in the isolation of the complexes of the types $Rh_2(CH_3COO)_4$ $L(H_2O)$ and $Rh_2(CH_3COO)_4L_2$. The binding sites of nucleobases towards rhodium(II) and the affinity of heteroatoms in nucleobases towards the metal ion were studied by various characterization techniques. Theoretical calculations have been done on the ligands such as $C_6H_5CH_2$-ade, hypoxan, Cl-gua, S-gua, cyt and S-url employing modified neglect of differential overlap (MNDO) method to understand their reactivity towards the metal and to compare with the experimental results.

Keywords: Metal nucleobase complexes, TG, Electronic, ESCA studies, Theoretical studies

Introduction

There has been significant interest in the complexes of rhodium with nucleobases, nucleosides and nucleotides[1-3] due to the potential antitumour activity of the compounds. Adducts of the Rh_2 $(CH_3COO)_4$ L_2 where L is theophylline and caffeine have been prepared and the ligands occupy the axial positions and are bonded through N9 to Rh^{2+} ions[4]. The kinetics of the interaction of 3 glycine containing dipeptides namely Glycyl–*L*-tyrosine, glycyl-*L*-alanine and glycyl-*L*-asparagine has been studied spectrophotometrically in aqueous medium as a function of the molar concentration of $[Rh(H_2O)_5OH]^{2+}$, dipeptide, pH and temperature at constant ionic strengths[5]. The reactions studied showed that the variation in size and bulkiness of the entering dipeptides reflects their properties as nucleophiles. The Rh(II) $(isobutyrate)_4L_2$, an antitumor drug[6] was shown to react with nucleic acid base derivatives, A, G, U and C in $CHCl_3$ solution. When these derivatives were treated with novel metal compound, the rhodium carboxylate in $CHCl_3$ forms fairly strong complex. The metallointercalator Rh(Phi) 2 DMB3+, (Phi,9,10-phenanthrenequinone diimine :DMB, 4,4' –dimethyl -2,2'-bipyridine) catalysed the repair of a thymine dimer incorporated site specifically in a 16-base pair DNA duplex by means of visible light and is accomplished with rhodium noncovalently bound to the complex with the rhodium intercalator tethered to either end of the duplex assembly[7]. The present note reports the synthesis and characterization of the complexes of Rh(II) with nucleic acid derivatives.

Experimental

Rhodium(II) complexes $[Rh_2(CH_3COO)_4L(H_2O)]$, L=Cl-gua, S-gua or hypoxan; $[Rh_2(CH_3COO)_4L_2]$, L=$C_6H_5CH_2$-ade, S-url or cyt have been synthesized and characterized by chemical and thermal analyses, infrared, electronic and ^{1}H NMR studies. The method of syntheses of the complexes is outlined below.

Synthesis of Rh(II) Complexes

Tetrakis - μ - acetatoaquo (6-chloroguanine-N7) dirhodium(II),[$Rh_2(CH_3COO)_4$C1-gua(H_2O)]

Rhodium(II) acetate (1.0 mmol in 20 mL of H_2O) was added to an aqueous solution of Cl-gua (1.0 mmol in 50 mL of H_2O) and stirred continuously for a day. After concentrating the reaction mixture to half of its original volume, the stirring was continued until the precipitation of the product was achieved. The resultant precipitate was filtered, washed with hot water, acetone and air-dried. Similarly the other complexes, namely, tetrakis -μ- acetatoaquo (6-thioguanine-*S*) dirhodium(II), $Rh_2(CH_3COO)_4$ *S*-gua(H_2O), tetrakis -μ- acetatoaquo (hypoxanthine-N7) dirhodium(II), $Rh_2(CH_3COO)_4$ hypoxan(H_2O), tetrakis-μ-acetatobis(N6-benzylademine-N7) dirhodium(II), $Rh(CH_3COO)_4(C_6H_5CH_2\text{-ade})_2$, tetrakis-μ-acetatobis(2-thiouracilato-S) dirhodium(II), $Rh(CH_3COO)_4$(S-ur1)$_2$ and tetrakis-μ-acetatobis (cytosine-O2)dirhodium(II), $Rh_2(CH_3COO)$ (cyt)$_2$ are synthesized using the corresponding nucleobases. The preparation of cytosine complex involved refluxion (8 h). Yields are in the range of 70-75%.

Results and Discussion

Rhodium(II) complexes of purines and pyrimidines

The complexes are insoluble in water and in common organic solvents like acetone, alcohol, chloroform and benzene but are soluble in DMSO. However, $Rh_2(CH_3COO)_4$ S-gua (H_2O) is insoluble even in DMSO. The analytical and conductivity data of the complexes are tabulated in Table 1. The complexes of Rh(II) show a molar conductance of 6-11 ohm^{-1} cm^2 in 10^{-3} M DMSO and indicate that the complexes are non-ionic. The compounds do not show any EPR signal suggesting them to be diamagnetic which is also confirmed by magnetic measurements in accordance with the expected dimeric nature of the rhodium(II) systems[8]. Thus, the complexes are possibly dimeric in nature with the bridging of the acetato group and the formation of Rh-Rh bond.

Table 1. Analytical and conductivity data of Rh(II) complexes

S.No	Complexes	C%	H%	N%	Rh%	Molar conductance ohm^{-1} cm^2
1	$Rh_2(CH_3COO)_4$ Cl-gua(H_2O)	24.39 (24.80)	2.96 (2.88)	10.51 (11.13)	33.43 (32.69)	7
2	$Rh_2(CH_3COO)_4$ S-gua(H_2O)	24.80 (24.89)	2.14 (3.05)	10.49 (11.17)	33.31 (32.81)	-
3	$Rh_2(CH_3COO)_4$ hypoxan (H_2O)	26.99 (26.19)	2.19 (3.04)	10.26 (9.40)	34.47 (34.53)	6
4	$Rh_2(CH_3COO)_4$ ($C_6H_5CH_2$-ade)$_2$	41.21 (41.41)	3.12 (3.91)	15.15 (15.09)	22.52 (22.18)	6
5	$Rh(CH_3COO)_4$ (S-url)$_2$	26.92 (27.53)	1.91 (2.31)	8.88 (8.03)	29.67 (29.48)	6
6	$Rh_2(CH_3COO)_4$ (cyt)2	28.90(28.93)	3.14 (3.33)	12.96 (12.66)	29.21 (30.99)	11

Calculated values are given in parenthesis

Thermal analysis studies

The TGA and DTA plots of the rhodium(II) complexes are given in Figures 1 and 2. The thermoanalytical data are presented in Table 2. As seen from the plots, the complexes (1-3) start decomposing around 130 °C and about 2.9% of the initial mass is lost by 150 °C. This is attributed to loss of water. Calculated weight for the dehydration of one molecule of water is 3.03% which agrees well with the observed value. This dehydration process is confirmed by endothermic peak maxima observed at 130 °C in the DTA plot. Increase in temperature, resulted in further loss in weight in the temperature range 250-415 °C and the decomposition is due to the organic moieties. The TG curves indicate that the decomposition process of acetate and nucleobase overlap though there are two distinct DTA peaks around 320 and 395 °C. The final residue obtained around 410 °C is found to be 40.3% of the initial weight of the complex, which is in agreement with the calculated value of 42.11% for the formation of Rh_2O_3 which is confirmed by its powder x-ray diffraction patterns with d_{hkl} values 2.621, 2.725 and 2.572 Å (reported values 2.623, 2.722 and 2.574 Å respectively)[9].

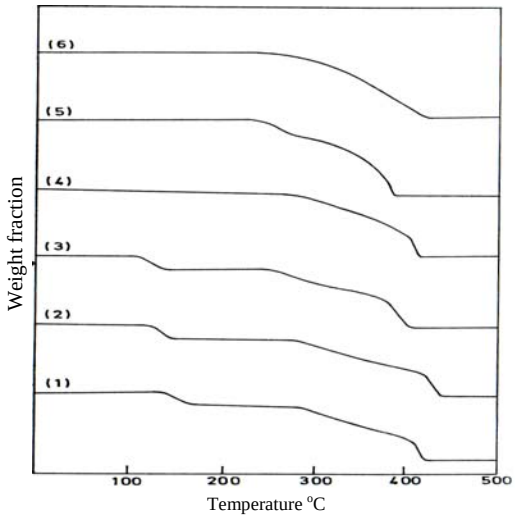

Figure 1. TG curves of $Rh_2(CH_3COO)_4L(H_2O)$, L = (1) Cl-gua(2) *S*-gua(3) hypoxan; $Rh_2(CH_3COO)_4L_2$, L = (4) $C_6H_5CH_2$=ade (5) S-url (6) cyt

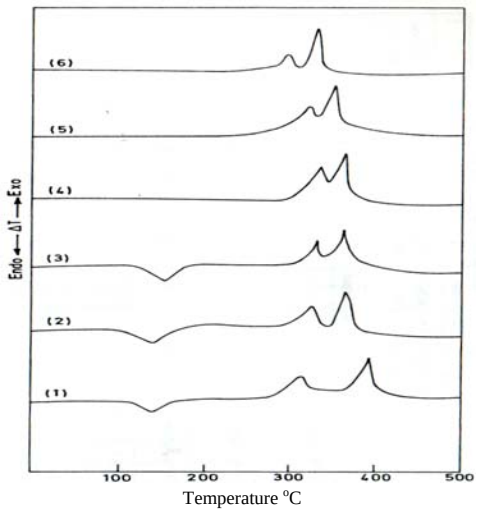

Figure 2. DTA curves of $Rh_2(CH_3COO)_4L(H_2O)$, L = (1) Cl-gua(2) *S*-gua(3) hypoxan; $Rh_2(CH_3COO)_4L_2$, L = (4) $C_6H_5CH_2$=ade (5) S-url (6) cyt

Table 2. Thermoanalytical data of Rh(II) complexes

S.No.	Complexes	Dehydration				Formation of Rh_2O_3			
		Temp. range °C	Weight loss, %		DTA peak temp. °C	Temp. range °C	Weight loss, %		DTA Peak Temp. °C
			Calc.	Found			Calc.	Found	
1	$Rh_2(CH_3COO)_4$ (C1-gua)(H_2O)	130-150	3.03	2.9	-130	290-410	57.89	59.7	+320 +395
2	$Rh_2(CH_3COO)_4$ (*S*-gua)(H_2O)	125-140	3.13	2.9	-130	280-415	58.12	59.5	+330 +375

Contd…

3	$Rh_2(CH_3COO)_4$ (hypoxan)(H_2O)	125-140	3.04	3.0	-135	250-400	58.13	57.4	+330 +370
4	$Rh_2(CH_3COO)_4$ ($C_6H_4O_2$-ade)$_2$	-	-	-	-	270-405	71.19	72.7	+330 +355
5	$Rh_2(CH_3COO)_4$ (S-url)$_2$	-	-	-	-	250-390	63.12	63.6	+310 +360
6	$Rh_2(CH_3COO)_4$ (Cyt)$_2$	-	-	-	-	250-400	61.78	61.8	+310 +350

– endotherm, + exotherm

The TG curves of the complexes 4, 5 and 6 of type $[Rh_2(CH_3COO)_4L_2]$, L=$C_6H_5CH_2$-ade, S-url or cyt suggest that the complexes decompose in the temperature range 250 to 405 °C with exothermic peak maxima around 310 and 360 °C. The observed weight losses are in good agreement with those of calculated weights for the formation of Rh_2O_3. The different slopes of the decompositions curves and two prominent exothermic peaks suggest that the decomposition occurs with different rates.

Electronic spectral studies

The UV-visible absorption spectra of the complexes were recorded in solution medium and as nujol mull with insoluble complexes. Rhodium(II) acetate exhibits absorption bands around 584 and 450 nm in 10^{-3} M DMSO and are assigned to dimeric Rh-Rh and Rh-$OOCCH_3$ interactions[10]. The rhodium(II) complexes isolated in the present study show absorption bands at lower wavelength around 500 nm. In general, the band seen at lower wavelength indicates the adduct formation by the replacement of water molecules in the axial position. The bands around 290 nm observed in the complexes are assigned to $\pi \rightarrow \pi^*$ of nucleobases in the complexes.

Infrared spectral studies

The characteristic infrared frequencies with the probable assignments are tabulated in Table 3. The infrared spectra of the complexes are compared with those of nucleobases[11] and rhodium(II) acetato complexes in order to find out the mode of nucleobase bonding to rhodium. The vibrational frequencies due to the pyrimidine ring of nucleobases (C_6H_5-ade, Cl-gua and hypoxan) appear in the same region as in the spectra of complexes indicating the non-involvement of the pyrimidine nitrogens in bonding. On the other hand, the bands around 1430, 1345 and 1310 cm^{-1} in $C_6H_5CH_2$-ade, Cl-gua and hypoxan are assigned to the vibrational modes of imidazole moiety and these are located around 1410, 1335 and 1310 cm^{-1} in the complexes, which is suggestive of coordination through imidazole nitrogen N7. The vibrational frequencies of *S*-gua at 1590, 1535, 1480, 1425 and 1330 cm^{-1} due to pyrimidine and imidazole moieties appear nearly at the same positions in the spectra of the complexes which indicate the absence of coordination of ring nitrogen atoms to rhodium(II). Strong absorption at 1550 cm^{-1} in *S*-gua has been assigned to ν_{cs} and it undergoes a shift to lower wave numbers by 15 cm^{-1} in the complex suggesting the sulfur coordination to the metal.

In free cytosine, the absorption at 1675 cm^{-1} is assigned to ν_{co} and strong absorptions at 1615, 1590, 1512 and 1480 cm^{-1} are assigned to the ring vibrations. The latter set of bands are not affected much in the spectra of complexes while ν_{co} undergoes a negative shift of 25 cm^{-1} suggesting coordination to the metal through the exocyclic oxygen, O_2. In the *S*-url complex[12], the bands due to ν_{NH} and ι_{NH} observed around 3100 and 700 cm^{-1} respectively are observed in the same region as in the ligand spectrum, but the intensities of the bands are found to be lowered suggesting that the NH groups are not deprotonated. The band at 1672 cm^{-1}

due to $\nu_{c=o}$, is located at more or less in the same position as that of the ligand indicating the non-involvement of its coordination to the metal. The characteristic thiocarbonyl frequencies at 1550, 1160 and 805 cm^{-1} underwent negative shifts by about 20 cm^{-1} confirming sulphur coordination in the complex .Thus from the infrared studies, it is observed that in the complexes of type $Rh_2(CH_3COO)_4L(H_2O)$ where L= Cl-gua and hypoxan, the coordination is through N7 and through S6 in $Rh_2(CH_3COO)_4$ (*S*-gua)(H_2O). In complexes of type $Rh_2(CH_3COO)_4L_2$, the coordination of the nucleobases is through N7, where L= C_6H,CH_2-ade, through S2 where L = S-url, through O2 when L = cyt. In the far infrared spectra of the complexes, the weak absorption at around 520 cm^{-1} is assigned to ν_{Rh-N} and the band at 450 and 390 cm^{-1} are assigned to and ν_{Rh-s} respectively[10].

Table 3. Principal infrared spectral data of rhodium(II) complexes (cm^{-1})

S.No	Complexes	$V_{C=C}$, V_{C-N} (Pyrimidine ring)	$V_{C=C}$, V_{C-N} Imidazole ring	V_{asy} COO	V_{sym} COO	$V_{C=0}$ (nucleobases)	$V_{C=S}$ (nucleobases)	V_{Rh-N}	V_{Rh-O}, V_{Rh-S}
1	$Rh_2(CH_3COO)_4$ (Cl-gua)(H_2O)	1579m	1420m	1592s	1430s	---	---	521m	460m
		1550m	1335m 1300s						
2	$Rh_2(CH_3COO)_4$ (*S*-gua)(H_2O)	1574m	1430m	1590s	1430s	--	1525m	---	450w, 380m
		1547m	1430s 1320s 1300w						
3	$Rh_2(CH_3COO)_4$ (hypoxan)(H_2O)	1589m	14 I 5m	1590s	141 Is	1680s	---	512s	450s
		1552m	1327m 1310w						
4	$Rh_2(CH_3COO)_4$ $(C_6H_5CH_2\text{-ade})_2$	1571s	1405m	1590s	1427s	---	---	512s	440s
		1531s	1327m 1293s						
5	$Rh_2(CH_3COO)_4$ (*S*-url)$_2$	1520s	---	1590s	1435s	1672s	1530m	---	4505
		1480s					1145w		390s
6	$Rh_2(CH_3COO)_4$ (cyt)$_2$	1520s	---	1600s	1425s	1675s	---	---	440s
		1478m							

NMR spectral studies

The ^1H NMR spectral data of the complexes are given in Table 4. The NMR spectra assist in evaluating the binding site(s) of the ligands. The ^1H NMR spectrum of free $C_6H_5CH_2$-ade in d_6-DMSO exhibits two singlets at 7.88 and 8.10 ppm corresponding to H2 and H8 resonances respectively. In the complex $Rh_2(CH_3COO)_4(C_6H_5CH_2\text{-ade})_2$, the H8 resonance is observed at 8.25 ppm and the downfield shift of H8 by 0.15 ppm indicates the coordination of $C_6H_5CH_2$-ade to the metal[13] through N7. The same trend is seen in hypoxan

and Cl-gua complexes. Thus, the NMR data confirm the coordination of N7 to rhodium(II). The spectrum of cytosine in d_6-DMSO exhibits two doublets at 6.4 and 7.28 ppm due to H5 and H6 resonances, which do not shift their positions in the spectrum of the complex.

Table 4. Proton NMR data of Rh(II) complexes (TMS - standard, solvent - d_6 - DMSO)

S.No	Complexes	Acetate Protons (8 in ppm)	Nucleobase Protons (8 in ppm)		
		CH_3	H5 / H8	H6 / H2	NH/NH_2
1	$Rh_2(CH_3COO)_4$(Cl-gua)(H_2O)	2.12	8.01	-	12.08 6.98
2	$Rh_2(CH_3COO)_4$(hypoxan)(H_2O)	2.12	8.31	8.0	12.05
3	$Rh_2(CH_3COO)_4(C_6H_5CH_2\text{-ade})_2$	2.10	8.25	7.96	-
4	$Rh_2(CH_3COO)_4(cyt)_2$	2.11	6.40	7.28	12.08

X-ray photoelectron spectroscopic studies

The XPS spectra of the $Rh_2(CH_3COO)_4(C_6H_5CH_2\text{-ade})$ in the 3d region of Rh (Figure 4a), O_{1s} region of acetate (Figure 4b) and N_{1s} region of $C_6H_5CH_2$-ade (Figure 4c) are shown. The rhodium $3d_{5/2}$ and $3d_{3/2}$ core level binding energies are found to be 309.0 and 313.3 eV respectively. The energy separation between rhodium spin-orbit doublet levels is 4.3 eV[14]. Thus the sharp peak at 313.3 eV shows the presence of one type of rhodium atom. A single 01s peak at 533.2 eV indicates the equivalent oxygen atoms in the complex. Three peaks are observed at 397.0, 397.5 and 397.9 eV with an intensity ratio of 2:2:1. In the complex, similar results are observed with a higher shift (0.5 eV) in the binding energy of N7. This suggests N7 coordination of $C_6H_5CH_2$-ade to Rh(II).

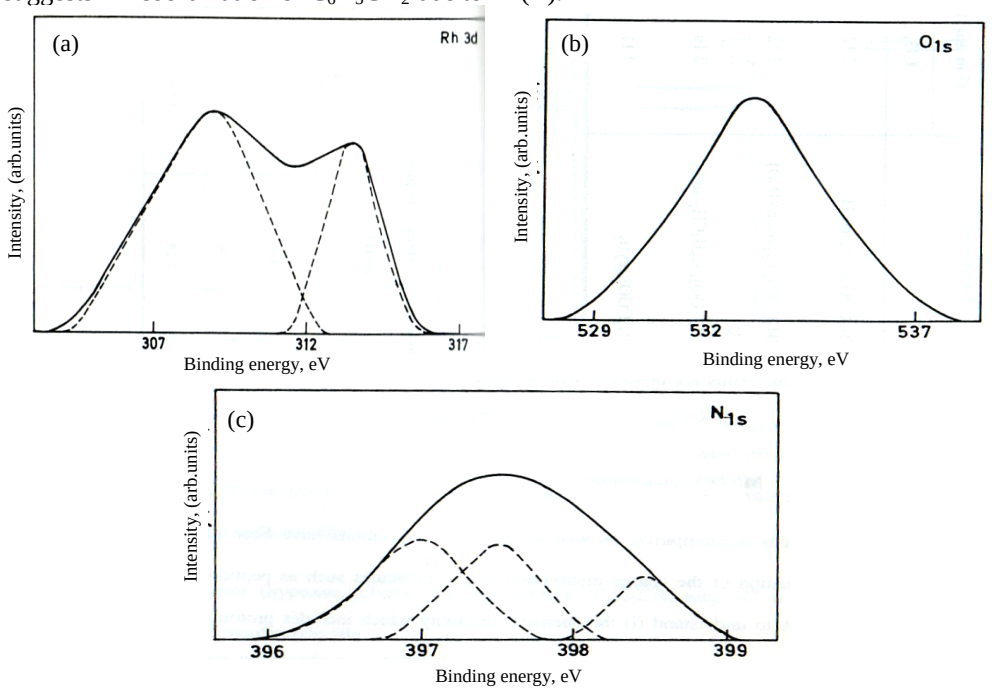

Figure 4. X-Ray photoelectron spectra (a) 3d region of Rh, (b) O1s region of acetate and (c) N1s region of $C_6H_5CH_2$-ade

MNDO calculations

Various semiempirical as well as *ab initio* calculations have been reported for the evaluation of the charge distribution in the molecules such as peptides, proteins and DNA to understand (i) the chemical reactivity which includes protonation, alkylation and metallation, (ii) the observed experimental electronic absorption spectra and x-ray photoelectron spectra, (iii) the energy requirement for the interconversion of the various possible tautomeric forms and (iv) the structure and functions of DNA .

In the MNDO calculations, the various interatomic distances, bond angles and dihedral angles of the molecules are needed for the calculation of the cartesian coordinates which are arrived from the geometry of the molecules after optimization. The optimization of geometry is done by using PC MODEL. The trend in the values of charge densities calculated in the present studies are employed to support the assignments of the bands observed in the XPS spectra and to understand the ligating properties of the molecules to metals. The molecules studied are (1) $C_6H_5CH_2$-ade (2) hypoxan (3) Cl-gua (4) *S*-gua (5) Cyt and (6) *S*-url.

Table 5 gives the charge densities at various nitrogen and sulfur sites of the molecules. The complex $Rh_2(CH_3COO)_4(H_2O)_2$ add one or two ligand molecules and the experimental studies indicated various coordination sites in the molecule to rhodium(II).

Table 5. Atomic charges at the various nitrogen and Sulfur sites of different ligands

S.No.	Molecules	N1	N3	N7	N9	S/O
1	N6-Benzyladenine	-0.34	-0.24	-0.17	-0.28	-
2	Hypoxanthine	-0.39	-0.28	-0.15	-0.22	-
3	6-Chloroguanine	-0.30	-0.29	-0.30	-0.26	-
4	6-Thioguanine	-0.2	-0.30	-0.32	-0.23	-0.11
5	Cytosine	-0.36	-0.36	-0.36	-	-0.19
6	2-Thiouracil	-0.32	-0.36	-0.32	-	-0.18

The results indicate that the N1 site is the most electron rich and the order is found to be N1 > N3 > N9 > N7> O, S. Therefore, it is expected that N1 may be the preferred metal binding site in these molecules. In the present study, it may be seen from the experimental results that purines and pyrimidines use various sites for their coordination to rhodium(II) and indicated that in oxopurine (hypoxan, Cl-gua) and aminopurine ($C_6H_5CH_2$-ade), N7 is the preferred coordination site whereas O2 in cytosine, sulfur in *S*-gua and *S*-url are the preferred coordinating sites. From the MNDO results, it is seen that N7 in purines, O2 and S in pyrimidines are favourable electronically for the binding to rhodium(II).

Conclusion

The nucleobases ($C_6H_5CH_2$-ade, Cl-gua and hypoxan) bind to rhodium through N7 and the thio-nucleobases (*S*-url and *S*-gua) through sulfur and cytosine through O2. The adenine derivative ($C_6H_5CH_2$-ade) and pyrimidine nucleobases (*S*-url and cyt) are found to occupy the axial positions of square plane of each rhodium(II) formed by the bridging of acetate, whereas the guanine derivatives (Cl-gua, *S*-gua and hypoxan) occupy one of the axial sites and the other by a water molecule. Rhodium(II) appears to have a greater affinity towards sulfur atom than other heteroatoms.

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