Interaction of carbonylchlorohydridotris (triphenylphosphine) ruthenium (II) with purine, adenine, cytosine and cytidine

Ranjana Ghose*

Department of Applied Chemistry, Institute of Technology, Banaras Hindu University, Varanasi – 221005, India

Complexes of the type [RuH(Cl)(CO)(L)PPh_3] (L=purine, adenine, cytosine or cytidine) have been prepared and their spectroscopic properties are reported.

Keywords: ruthenium, carbonyl, hydride, adenine, cytosine, cytidine

Many heavy metal ions are toxic in nature and certain complexes show antineoplastic activity. The interaction of the metal ions with DNA constituents might cause these. The biologically important nucleic acids constituents provide potential binding sites for metal ions.

As a number of factors are responsible for the ability of the various donor atoms of nucleosides and nucleotides to act as sites of complexation, it is difficult to predict the binding sites for metal ions in a metal complex. The present paper deals with studies of carbonylchlorohydridotris (triphenylphosphine) ruthenium (II) complex with purine (PUR), adenine (ADN), cytosine (CTS) and cytidine (CTD). Investigations were undertaken to examine any change in the potential binding sites of the ligands which were reported for simple metal ions due to the presence of the triphenylphosphine ligands which could create steric restrants.

Experimental

Materials: The chemicals used were of AnalaR grade. PUR, ADN, CTS, CTD and $[(C_6H_5)_3P]_3Ru(CO)(Cl)H$ were obtained from Aldrich Chemicals Company, Inc., U.S.A. Solvents were dried before use. All the reactions were carried out under dry N_2. The light petroleum used had b.p. 60–80° C.

Methods: IR spectra (KBr) were recorded on a Perkin–Elmer 783 spectrometer and electronic spectra ($CHCl_3$) on a Shimadzu UV 190 spectrometer. ^1H NMR and ^{13}C NMR spectra were measured with a JEOL spectrometer model FX 900 FTNMR using TMS in DMSO–d_6 as internal standard.

Chloride and phosphorus were estimated gravimetrically. C, H and N analyses were determined by a Perkin–Elmer model 240c elemental analyser.

Preparation of complexes: All the reactions were carried out under dry dinitrogen. All the ruthenium (II) complexes were prepared by a similar procedure.

The complex was prepared by the addition of the appropriate ligand suspended in 25ml methanol to a continuously stirred solution of 0.500 g [RuHCl(CO)(PPh_3)] in 5 ml dichloromethane in 1:1 ratio under nitrogen atmosphere. The mixture was refluxed for 30 min, then allowed to cool, filtered off and the resulting solid was washed with methanol and finally with petroleum ether and dried under reduced pressure. Yields were 80–90 %.

Results and discussion†

The new complexes were obtained according to the general reaction

$$[RuHCl(CO)(PPh_3)] \xrightarrow[CH_2Cl_2,\ CH_3OH]{L} [RuHCl(CO)(PPh_3)]$$

One of the three coordinated PPh_3 molecules is replaced by one of the ligand (L) molecules.

The analytical data for the complexes are given in Table 1.† The complexes are dark green in colour and are stable in alcoholic solution as well as in aerobic conditions.

Infrared studies

Purine and adenine complexes: The presence of characteristics ν NH bands in both of these complexes suggest the binding of neutral PUR and ADN ligands in the complexes.[1] Significant shifts and occasional splittings of various vibrational modes of the pyrimidine (pym) and imidazole(im) fragments of ligands are observed when complex formation between PUR[1] or ADN[1-4] and the metal ion takes place. The participation of ligand ring nitrogens in coordination is interpreted.[1-9] On the other hand, the NH_2 deformation modes of free ADN are only slightly shifted in the IR spectrum of the complex indicating the non–participation of the exocyclic N(6) nitrogen of the NH_2 group in coordination.

The imidazole nitrogen which is protonated in the neutral PUR is considered as the most likely binding site.[10] Although a crystal structure determination of PUR places the labile proton at N(7) in the crystal,[11] it is equally well established from ^{13}C NMR studies that the N(7)–H and N(9)–H tautomers of PUR are of comparable energies.[12,13] The labile proton resides on a non–coordinated imidazole nitrogen in metal complexes with neutral PUR or ADN showing the vibration ν NH (im) ≈ 2690 W for PUR and ≈ 2910 W, 2595 W for AND.[5,14,15]

The participation of imidazole nitrogen in coordination is suggested by shifts of several characteristic ring vibrational modes attributable to this fragment of PUR upon metal complex formation (Table 2).

Free PUR exists in the N(7)–protonated form (I) in the crystal, with the 7H–purine planar molecules joined together

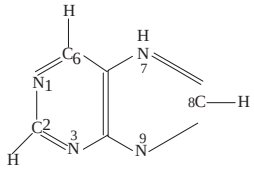
Table 1 Analytical results (%) for the complexes

Complex	Found						Calculated					
	Ru	Cl	P	C	H	N	Ru	Cl	P	C	H	N
$RuHClCO(C_5H_4N_4)[P(C_6H_5)_3]_2$	12.36	4.22	3.86	61.26	4.36	8.60	12.30	4.30	3.75	61.13	4.40	8.49
$RuHClCO(C_5H_5N_5)[P(C_6H_5)_3]_2$	12.52	4.42	3.77	62.20	4.38	6.87	12.47	4.38	3.82	62.27	4.35	6.91
$RuHClCO(C_4N_3H_5O)[P(C_6H_5)_3]_2$	12.65	4.50	3.80	61.89	4.50	5.21	12.68	4.45	3.89	61.77	4.55	5.27
$RuHClCO(C_9N_3H_{13}O_3)[P(C_6H_5)_3]_2$	11.11	3.81	3.56	61.14	4.88	4.56	11.21	3.93	3.44	61.30	4.92	4.66

* Correspondence. E-mail: ranjana_ghose@sify.com

† Tables 2–7 inclusive are not included for reasons of space, but may be inspected by application to the author.

in infinite chains by relatively short (2.85 Å)[11] N(7) – H … N(9) – H bonds. Lautié and Novak pointed out that the N(1), N(3) and N(9) nitrogen atoms are particularly susceptible to act as electron-pair donor sites in donor–acceptor interactions between 7H – purine and Lewis acids.[1] On the basis of IR data (Table 2) it is concluded that neutral PUR coordinates through the N(7) site while retaining the N(9) – protonated form.



The IR spectrum of PUR complex shows a shift in the high frequency region for the bands appearing at 1499, 1568 and 1613 cm^{-1}. These observations suggest a decrease in electron density in the pyrimidine ring due to the binding of metal ion to the imidazole ring. The band due to the C(5)–N(7)–C(8) bonds stretching motions also shifts to higher frequency (1388 cm^{-1}) in the spectrum of ruthenium complex. The Ru(II) complex exhibits shift in the frequency of ν N(7) bands of PUR with respect to free PUR, as compared to N(9) bands suggesting the participation of the N(7) atom in complexation.

The non–participation of the exocyclic NH_2 group nitrogen is indicated by slightly or no shift of the ν NH_2, δ NH_2 and ρ NH_2 bands of ADN in the spectra of the complex (Table 3). The larger shifts and occasional splitting of some of the ν C = C, νC = N and ring vibrations of ADN in the spectra of the complex suggest the binding of ADN through ring nitrogens.[1,4,14,16,17] The protonation site of free ADN (II) is the N(9) atom. When ADN acts as terminal unidentate ligand[10] N(9) is preferred site of bonding. Also the exocylclic NH_2 group present at C(6) increases the electron density at N(9) relative to PUR and blocks the N(1) site sterically making N(9) site more favourable for coordinating with the metal ion.

On comparing the IR spectra of free ADN and its complex it is found that the medium intensity ν N–H band of ADN loses its intensity (Table 3). There is a sharp decrease in intensity of the imidazole N–H rocking mode (~ 1250 cm^{-1}) in the spectrum of the complex suggesting the coordination of the N(9) atom with Ru(II) ion. Also the out-of-plane wagging mode appearing at 871 cm^{-1} in free ADN spectrum loses its intensity in the spectrum of the complex. It is found that a relatively strong band at ~ 1290 cm^{-1} appears in the spectrum of the complex. It appears that it may be a component of the ν N(9)–C(8) + ν N(3)–C(2) + δ C–H vibration.

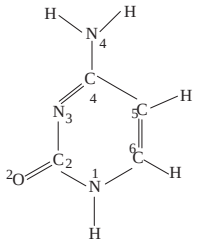
The electronic distribution within the ADN moiety changes on substitution of the proton on N(9) of ADN by a metal ion. These changes may be observed by the changes in vibrations which are related to the imidazole ring. The downward frequency shift of the 1309 cm^{-1} band (Table 3) is observed in the spectrum of the complex while the band at 1331 cm^{-1} is slightly shifted and loses its intensity on substitution at the N(9) atom by the Ru(II) ion since the N(7) atom gets protonated in the complex. The band appearing at 1125 cm^{-1} in the spectrum of ADN shifts to lower frequency in the spectrum of the complex.

There will be a reinforcement of the C(6)–NH_2 bond and a weakening of the C(1)–N(6) bond when the proton of N(9) atom gets substituted by a metal ion. It is indicated by the shift of the band appearing at 1420 cm^{-1} in free ADN spectrum (Table 3) due to the transfer of charge from the amino group to the N(1) atom.

On the basis of the above discussion the N(9) atom of ADN is suggested as the site for metallation. The literature survey also reveals the N(9) atom as the coordination site for ADN, guanine and xanthine[10,18-22] and N(9) and N(3) atoms both for AND.[23]

Cytosine and cytidine complexes: There are four different potential binding sites of CTS (III) with metal ions viz. N(1), C(2) = O, N(3) and C(4)–NH_2. CTS acts as bidentate[21,24-27] as well as a monodentate[28] ligand.

The free CTS ligand exihibits[29] the NH, CO, CH and CN vibrations in the range 1700–1800 cm^{-1}. The N(1)–H in-plane and out-of-plane vibrations of CTS occurring at 1540 cm^{-1} and 822 cm^{-1}, respectively, show only slightly shift but their intensities in the complex remain unchanged indicating the non–participation of the N(1) site in coordination to Ru(II) in the complex. In the spectra of the complex the ring stretching frequency (Table 4) is shifted to higher frequency and its intensity is greatly reduced. The stretching frequencies due to C = C and C = N in CTS[30] appearing at 1616cm^{-1} (shoulder) and at 1505 cm^{-1} are shifted towards higher frequencies in the complex. The values of ν (C = O) at 1667 cm^{-1} in free CTS also shifted to higher frequencies. This suggests that the metal is coordinated to the N(3) atom of CTS.



CTD(IV) binds with the metal ion in its complexes both as a monodentate and bidentate ligand due to the presence of its several potential binding sites [C(2) = O, N(3), C(4)–NH_2].

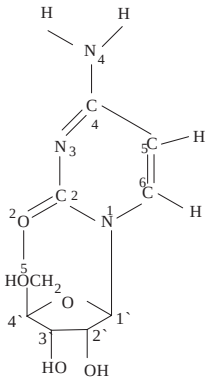


Table 5 presents various IR bands of CTD and its new metal complex. In the spectra of its complex the ring vibration frequency is shifted to the higher frequency with reduced intensity showing the flow of electrons from the ring toward the metal ion. The stretching frequencies appearing at 1463 and 1500 are shifted towards higher frequencies in the complex. Also the ν C(2) = O band at 1660 is shifted to higher frequencies on complex formation.

The other bands do not show any substantial shift suggesting the participation of the N(3) atom of CTD in complex formation with Ru(II).

^{13}C NMR and ^{1}H NMR spectra

PUR and ADN complexes: The binding sites in PUR and ADN can be best interpreted in terms of the resonance shifts which occur for various carbon atoms in ^{13}C NMR spectra. Out of the various possible binding sites in both PUR and ADN, N(3) is weakly basic but has been found as a possible binding site. PUR has no exocyclic group at C(6) site so there is no steric differences between N(1) and N(7) sites.[31] Hence, N(7) or N(9) in PUR, which are the most basic sites, are the possible coordination sites.

^{13}C NMR peak assignment[12] and chemical shift data are tabulated in Table 6. The resonance shifts observed for C(6) (3.2 ppm) is upfield while downfield shifts occur for C(5) (1.7 ppm) and C(8) (1.5 ppm). Similar shifts for C(6) and C(8) have been reported for MeHg(II) complexes of guanosine and inosine[32] when binding occurs at the N(7) atom. Since similar shifts are also noted in the present study for C(6) and C(8) resonances with respect to magnitude and directions, the N(7) atom of PUR is suggested as the binding site for the ruthenium complex. The C(2) resonance shows negligible upfield shifts (0.1 ppm) indicating the non–participation of N(1) and N(3) atoms in coordination.

The ^{1}H NMR data are not useful in assigning the binding site in PUR since the ligand resonances in the complexes are masked by the intense triphenylphosphine resonance. The literature survey[10,14,33–36] also reveals the site of coordination of PUR and its derivatives as N(9) and / or N(7) rather than N(1).

The ^{13}C NMR data for ADN and its complex are reported in Table 6. Only four resonances are observed which are assigned to C(6), C(2) C(4) and C(8).[37] Two of these four resonance are exhibited in the spectrum of the complex and they are assigned to C(2) and C(8). The C(8) resonance show a downfield shift of 2.8 ppm in the Ruthenium complex but an upfield shift is observed for C(2) resonance. The site of coordination would be an atom or group adjacent to C(8) atom. Hence, N(7) or N(9) atom is indicated as the coordination site.

On the basis of IR data and ^{13}CNMR data N(7) atom is suggested as the binding site in PUR and N(9) atom in ADN in their ruthenium complexes.

CTS and CTD complexes: To determine the binding site in nucleic bases ^{13}C NMR chemical shift data[32,38,39] and the magnitude of the change in the chemical shifts have been used successfully. It is reported[40] that the downfield shifts in the C(2) resonance of CTD in Me_2 SO–d_6 are caused by alkaline earth salts due to its binding at O(2). Electrophiles known to bind to N(3) atom of CTD cause upfield shifts in both C(2) and C(4) resonances in Me_2SO[38,41,42] and aqueous solutions.

For CTS complex ^{13}C NMR spectra (Table 7) shows the largest upfield shift for C(2) (7.7ppm) resonances. Also on upfield shift of 2.6 ppm is observed for the C(4) resonance in the ruthenium complex. Since the chemical shifts are large for the atoms which are closest to the binding site, N(3) in CTS is the proposed site for metallation in the ruthenium complex.

The ^{13}C NMR spectrum of CTD shows[43] characteristic changes which signal the binding mode in the direction of shift of the C(2) resonance. An upfield shift of the C(2) resonance signifies strong N(3) binding while downfield shifts indicate stronger interaction with O(2).

The ^{13}C NMR spectrum of the ruthenium complex (Table 7) shows upfield shifts in the C(2) (4.4ppm) and C(4) (2.1ppm) resonances. Other carbon resonances exhibit <1ppm shifts. This suggests that Ru(II) coordinates to CTD at the N(3) site. This is in agreement with earlier ^{13}C NMR studies.[33,40,43]

The ^{1}H NMR spectra can not be used to get any fruitful information as H(6) and NH_2 resonances are obscurred by the intense proton resonances of the triphenylphosphine group.

All the characteristic bands[44] of PPh_3, CO, and RuH have been tabulated in Tables 2,3,4,5 in the IR spectra of all the complexes. The carbonyl stretching frequencies are at 1954s, 1950s, 1940s and 1940s for PUR, ADN, CTS and CTD ruthenium complexes respectively. The ν Ru–N bands (Tables 2,3,4,5(of medium intensity appear in the range 370-490cm^{-1} in the IR spectra of the complexes.

All the Ru(II) complexes are diamagnetic in nature indicating spin pairing in Ru(II) (d^6 system) and hence a distorted octahedral geometry could be assigned to the new complexes. The ground state of Ru(II) in octahedral environment is $^{1}A_{1g}$ and hence only two spin-allowed transitions $^{1}A_{1g} \rightarrow {}^{1}T_{1g}$ and $^{1}A_{1g} \rightarrow {}^{1}T_{2g}$ are expected. The new Ru(II) complexes exhibits two bands at 500-520 nm and 460-490 nm corresponding to transitions $^{1}A_{1g} \rightarrow {}^{1}T_{1g}$ and $^{1}A_{1g} \rightarrow {}^{1}T_{2g}$ respectively. Thus a distorted octahedral geometry is proposed for all the new complexes.

The present study demonstrates the interaction of a metal ion which is already sterically crowded with nucleic acid bases. It has been found that Ru(II), inspite of being sterically crowded in carbonylchlorohydridotris (triphenylphosphine) ruthenium(II) prior to the interaction with nucleic acid bases, binds to the bases as usual even in its distorted octahedral complexes *i.e.* binding sites of PUR and ADN are N(7) and N(9) atoms respectively while CTS and CTD bind at their N(3) sites. The binding of Ru(II) at these sites of nucleic acid bases changes the electronic ring system resulting in significant disruptions in the hydrogen bonding between the base pair. Thus the above studies serve as a model for the interactions of platinum metals with nucleic acid base pairs which lead to understand the biological functions of the complexes.

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