Crystal and molecular structure of *cis*-dichloroethionineplatinum(II) and its interaction with adenine, hypoxanthine, cytosine and their nucleosides

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Abstract

The crystal and molecular structure of parent compound *cis*-dichloroethionineplatinum(II) was determined by X-ray diffraction method. The complex crystallises with 4 molecules in the monoclinic space group $P2_1/n$ with a cell of dimensions $a=7.223(1)$, $b=14.435(1)$, $c=11.012(2)$ Å, $\beta=97.69(2)°$. The structure was solved by the heavy atom method and has been refined to an R value of 0.031 for 1573 observed reflections. In *cis*-dichloroethionineplatinum(II), the ethionine molecule coordinates to the platinum through the amino nitrogen and sulfur atoms to form a six-membered ring which adopts a skewed chair conformation. The predominant force of packing in this complex is the intermolecular hydrogen bonding between the two free carboxylic acid groups of adjacent molecules of ethionine. These are reinforced by weak N–H...Cl bonds to stabilise crystal packing. Mixed ligand complexes of Pt(II)ethionine with adenine, adenosine, hypoxanthine, ionosine, cytosine and cytidine were synthesised and characterised by elemental analysis, conductivity measurements, IR and ^{1}H NMR spectral studies. In the complexes of adenine, adenosine, hypoxanthine and ionosine the ligand binding site to the metal ion is N_7, whereas in the case of cytosine and cytidine the binding site is N_3.

Introduction

The synthesis of platinum group metal complexes of nucleic acid bases and their derivatives has acquired much importance recently because of their antitumor and antibacterial activity [1–5]. The discovery of cisplatin (*cis*-dichlorodiammineplatinum(II)) as an effective anticancer drug has given a lot of impetus to the search for new antitumor agents of platinum and other transition metals [6–9]. Ethionine is a biologically important amino acid and is known to inhibit the growth of microorganisms [10] and leukemia in mice [11]. Even though considerable work has been done on S-containing amino acids [12–19], very little is known about ethionine complexes [20–23].

In our earlier communications [24, 25] we have reported the mixed ligand complexes of platinum group metal ions with α-amino acids and purines, pyrimidines and nucleosides. In this paper we report the crystal structure of *cis*-dichloroethionineplatinum(II) and synthesis and characterisation of its mixed ligand complexes with adenine, adenosine, hypoxanthine, ionosine, cytosine and cytidine.

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Experimental

Chromatographically pure DL-ethionine, adenine, adenosine, hypoxanthine, ionosine, cytosine, cytidine and potassiumtetrachloroplatinate(II) were obtained from Sigma Chemical Company, U.S.A. *cis*-Dichloroethionineplatinum(II) was prepared by the published procedure [21].

All solvents used were of high purity and distilled in the laboratory before use. Elemental analyses were obtained from Central Drug Research Institute, Lucknow, India. Conductivity measurements were carried out on conductivity meter no. Dl 909. The IR spectra were recorded in KBr pellets on a Shimadzu 435 spectrophotometer. The ^{1}H NMR spectra of the complexes were recorded on a JEOL 100 MHz spectrometer at Central Salt and Marine Chem-

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icals Research Institute, Bhavnagar. All the ^{1}H NMR spectra were recorded in D_2O solvent.

Preparation of complexes:

cis-Dichloroethionineplatinum(II), [Pt(DL-ethionine)Cl_2] (**1**); chloroadenineethionineplatinum(II) chloride, [Pt(DL-ethionine)(adenine)Cl]Cl (**2**); chloroadenosineethionineplatinum(II) chloride, [Pt(DL-ethionine)(adenosine)Cl]Cl (**3**); chlorohypoxanthineethionineplatinum(II) chloride monohydrate, [Pt(DL-ethionine)(hypoxanthine)Cl]Cl·H_2O (**4**); chloroionosineethionineplatinum(II) chloride, [Pt(DL-ethionine)(ionosine)Cl]Cl (**5**); chlorocytosineethionineplatinum(II) chloride monohydrate, [Pt(DL-ethionine)(cytosine)Cl]Cl·H_2O (**6**); chlorocytidineethionineplatinum(II) chloride, [Pt(DL-ethionine)(cytidine)Cl]Cl (**7**).

[Pt(DL-ethionine)Cl₂]

DL-Ethionine (0.250 g, 1.53 mM) was dissolved in 10 ml of warm water and to this a solution of K_2PtCl_4 (0.636 g, 1.53 mM) was added. The solution was warmed on a water bath with stirring when the reddish orange colour of the solution changes to yellow. The heating was continued for a further period of 20 min. On cooling (0 °C), a yellow crystalline solid separated out, which was filtered, washed with cold water, alcohol, ether and dried *in vacuo*. *Anal.* Calc.: C, 16.79; H, 2.81; N, 3.26. Found: C, 16.85; H, 2.87; N, 3.08%.

In a general method for the preparation of complexes **2**–**7**, *cis*-dichloroethionineplatinum(II) (0.582 mM) in water was added to the aqueous solution (0.582 mM) of adenine, adenosine, hypoxanthine, ionosine, cytosine or cytidine. The resulting solution was refluxed on a water bath for 3 h and the solution concentrated to half of its volume, cooled and filtered. On keeping overnight in the refrigerator, the complex separated out. It was washed with acetone and dried *in vacuo*.

Anal. Calc. for [Pt(DL-ethionine)(adenine)Cl]Cl: C, 23.40; H, 3.21; N, 14.88. Found: C, 23.50; H, 3.21; N, 14.71%. Yield ~70%.

Calc. for [Pt(DL-ethionine)(adenosine)Cl]Cl: C, 27.58; H, 3.75; N, 12.06. Found: C, 27.32; H, 3.80; N, 12.22%. Yield ~70%.

Calc. for [Pt(DL-ethionine)(hypoxanthine)Cl]-Cl·H_2O: C, 22.64; H, 3.27; N, 11.99. Found: C, 22.42; H, 3.29; N, 11.58%. Yield ~67%.

Calc. for [Pt(DL-ethionine)(ionosine)Cl]Cl: C, 27.57; H, 3.60; N, 10.03. Found: C, 27.27; H, 3.51; N, 10.16%. Yield ~68%.

Calc. for [Pt(DL-ethionine)(cytosine)Cl]Cl·H_2O: C, 21.50; H, 3.42; N, 10.02. Found: C, 21.32; H, 3.39; N, 10.21%. Yield ~72%.

Calc. for [Pt(DL-ethionine)(cytidine)Cl]Cl: C, 26.78; H, 3.74; N, 8.32. Found: C, 26.61; H, 3.68; N, 8.02. Yield ~69%.

X-ray structure determination of [Pt(DL-ethionine)Cl₂]

Slow evaporation of an aqueous solution of the complex yielded pale yellow needle-like crystals suitable for X-ray studies. A crystal of size 0.04×0.04×0.20 mm was used for the preliminary examination and collection of the intensity data. Accurate cell dimensions were obtained using 25 arbitrarily closer higher order reflections and were $a=7.223(1)$, $b=14.435(1)$, $c=11.012(2)$ Å, $\beta=97.69(2)°$. Extinction conditions served to define the space group unequivocally as $P2_1/n$. The density calculated on the basis of 4 molecules per unit cell is 2.469 g cm^{-3}. Intensity data were collected on Enraf-Nonius automated CAD-4 single crystal diffractometer using graphite monochromatised Cu Kα radiation ($\lambda=1.54018$ Å) in the 2θ range 4–130°, which yielded 1846 reflections, of which 1573 had $I>3\sigma(I)$ and were considered observed. Crystal stability and alignment during data collection was checked using two sets of three control reflections. The intensities were then corrected for Lorentz and polarisation factors. Absorption corrections were applied by Ψ scan method using three reflections near $\chi=90°$ [26].

The structure was solved by the heavy atom method. A difference fourier phased on the Pt atom position followed by a few cycles of least-squares refinement and difference maps led to the location of all the 13 non-H atoms. All the 13 hydrogen atom positions could be located in a difference fourier, computed after a complete convergence anisotropic refinement of non-H atoms. Further cycles of full matrix least-squares refinement with 13 non-H atoms (anisotropic) and 13 hydrogen atoms (isotropic, kept fixed) using the unit weighing scheme with Dunitz–Seiler factor [27] led to the final R value of 0.031 ($R_w=0.034$). All the calculations were carried out on the PDP 11/73 computer using the SDP set of crystallographic programs [28]. The final atomic coordinates are shown in Table 1.

Results and discussion

Crystal structure of [Pt(DL-ethionine)Cl₂]

A perspective view of the molecules is shown in Fig. 1(a). Tables 2 and 3 list the bond lengths and angles in the molecules and Table 4 the torsion angles, with their estimated standard deviations (e.s.d.s) which are only slight underestimates because

TABLE 1. Positional and thermal parameters of non-hydrogen atoms in [Pt(DL-ethionine)Cl_2] with e.s.d.s in parentheses

Atom	*x*	*y*	*z*	*B* (Å^2)[a]
Pt	0.80418(4)	0.44185(2)	0.04830(2)	2.525(4)
Cl1	0.9258(4)	0.4159(1)	0.2496(1)	4.26(4)
Cl2	0.7485(3)	0.5972(1)	0.0855(2)	3.59(3)
S1	0.8485(3)	0.2893(1)	0.0246(1)	3.05(3)
O1	0.538(1)	0.5241(5)	−0.3523(5)	3.8(1)
O2	0.667(1)	0.4087(5)	−0.4480(5)	4.0(1)
N1	0.690(1)	0.4695(5)	−0.1279(5)	3.5(1)
C2	0.736(1)	0.4132(5)	−0.2345(6)	3.3(1)
C3	0.635(1)	0.4554(5)	−0.3504(6)	3.4(1)
C4	0.690(1)	0.3144(6)	−0.2211(6)	3.6(1)
C5	0.835(1)	0.2585(5)	−0.1350(6)	3.4(1)
C6	0.632(2)	0.2384(6)	0.0676(8)	4.0(2)
C7	0.650(2)	0.1308(6)	0.0668(8)	4.5(2)

[a]Anisotropically refined atoms are given in the region of the isotropic equivalent displacement parameter defined as: $(4/3)[a^2B(1,1)+b^2B(2,2)+c^2B(3,3)+ab(\cos\gamma)B(1,2)+ac(\cos\beta)B(1,3)+bc(\cos\alpha)B(2,3)]$.

TABLE 2. Bond distances (Å) in [Pt(DL-ethionine)Cl_2]

Atom 1	Atom 2	Distance
Pt	Cl1	2.302(2)
Pt	Cl2	2.325(2)
Pt	S1	2.244(2)
Pt	N1	2.042(6)
S1	C5	1.802(7)
S1	C6	1.85(1)
O1	C3	1.22(1)
O2	C3	1.31(1)
N1	C2	1.50(1)
C2	C3	1.51(1)
C2	C4	1.48(1)
C4	C5	1.55(1)
C6	C7	1.56(1)

Numbers in parentheses are e.s.d.s in the least significant digits.

TABLE 3. Bond angles (°) in [Pt(DL-ethionine)Cl_2]

Atom 1	Atom 2	Atom 3	Angle
Cl1	Pt	Cl2	92.31(7)
Cl1	Pt	S1	84.85(6)
Cl1	Pt	N1	177.5(2)
Cl2	Pt	S1	175.83(8)
Cl2	Pt	N1	85.5(2)
S1	Pt	N1	97.3(2)
Pt	S1	C5	111.4(2)
Pt	S1	C6	102.8(3)
C5	S1	C6	102.3(4)
Pt	N1	C2	122.2(5)
O2	C2	N1	139.6(6)
N1	C2	C3	108.0(7)
N1	C2	C4	111.5(6)
C3	C2	C4	112.6(6)
O1	C3	O2	124.8(7)
O1	C3	C2	123.9(7)
O2	C3	C2	111.4(9)
C2	C4	C5	115.1(7)
S1	C5	C4	114.5(6)
S1	C6	C7	108.9(8)

Numbers in parentheses are e.s.d.s in the least significant digits.

TABLE 4. Torsion angles (°) in [Pt(DL-ethionine)Cl_2]

Atom 1	Atom 2	Atom 3	Atom 4	Angle
Cl1	Pt	S1	C5	−164.84(0.37)
Cl1	Pt	S1	C6	86.21(0.30)
Cl2	Pt	S1	C5	148.05(1.03)
Cl2	Pt	S1	C6	39.10(1.10)
N1	Pt	S1	C5	16.31(0.44)
N1	Pt	S1	C6	−92.63(0.38)
Cl1	Pt	N1	C2	179.64(5.07)
Cl2	Pt	N1	C2	154.82(0.67)
S1	Pt	N1	C2	−28.30(0.67)
Pt	S1	C5	C4	−35.64(0.73)
C6	S1	C5	C4	73.64(0.69)
Pt	S1	C6	C7	−175.02(0.53)
C5	S1	C6	C7	69.31(0.66)
Pt	N1	C2	C3	−177.33(0.58)
Pt	N1	C2	C4	58.46(0.96)
N1	C2	C3	O1	1.25(1.24)
N1	C2	C3	O2	−179.16(0.75)
C4	C2	C3	O1	124.83(0.95)
C4	C2	C3	O2	−55.58(1.06)
N1	C2	C4	C5	−79.81(0.94)
C3	C2	C4	C5	158.61(0.71)
C2	C4	C5	S1	68.70(0.86)

of the use of the full matrix least-squares. Pt(II) displays a square planar geometry in the complex. The ethionine molecule coordinates to the metal atom through the amino nitrogen and sulfur atoms to form a six-membered ring; a view of this chair is shown in Fig. 1(b).

The coordination sphere of complex **1** contains two chlorides, sulfur and α-amino nitrogen of ethionine. The known preference of platinum for a soft donor sulfur over a hard donor oxygen atom makes the coordination of sulfur possible in the complex in spite of the formation of a less stable six-membered ring compared to the formation of a five-membered ring, if amino nitrogen and carboxyl oxygen are pulled into the coordination sphere. Because of the occurrence of atoms of different sizes in the coordination sphere of the metal ion, the square planar geometry gets distorted which is reflected in the significant deviation of bond angles in the complex from 90°. It is interesting to note that the angle N–Pt–S opens upto 97.3(2)° which is compensated

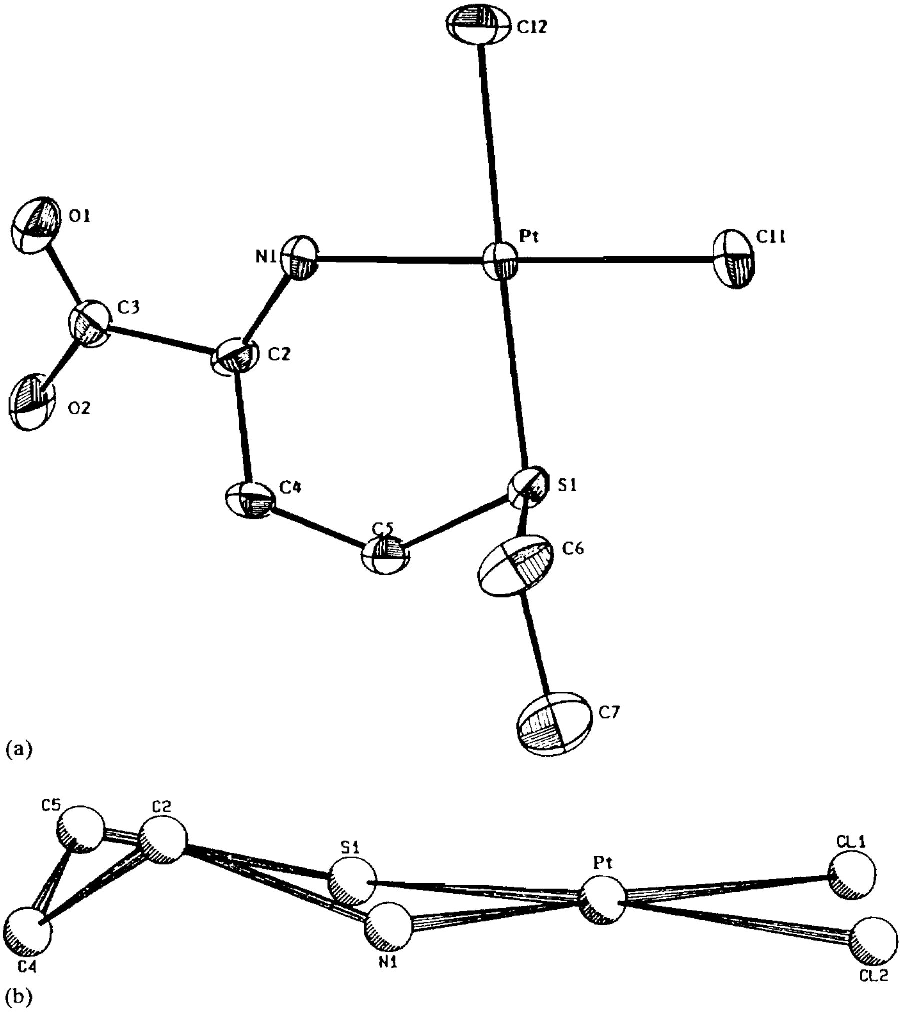


Fig. 1. (a) Perspective view of the [Pt(DL-ethionine)Cl_2]; (b) view of the six-membered chair conformation in complex [Pt(DL-ethionine)Cl_2].

by closing up of the angles S–Pt–Cl to (84.8°). Angles subtended by the *trans* atoms also significantly differ from 180°, i.e. N–Pt–Cl (177.5°) and S–Pt–Cl_2 (175.8°). The corresponding values in [Pd(DL-ethionine)Cl_2] [22] are 96.9, 84.5 and 178.4, 175.7°, respectively.

The structure of complex **1** can be compared with those of [Pt(L-methionine)Cl_2] [29] and [Pd(DL-ethionine)Cl_2] [22] complexes. In the palladium complex, a six-membered skewed chair conformation involving S and N results; a similar situation is observed in our complex (Fig. 1(b)). In complex **1** and [Pd(DL-ethionine)Cl_2], deviations of metal and C_3 from the chair conformation are −0.449 and 0.718 Å and −0.440 and 0.711 Å, respectively, and the other four atoms have a mean deviation of 0.07 Å. One way of measuring the puckering of the *n*-membered rings is through the calculation of torsion angles. The torsion angles within the six-membered ring system of complex **1** vary from 16.30 to 79.81° (Table 4) showing that this ring system is severely puckered.

The Pt atom in complex **1** is 0.041 Å away from the plane defined by N1, S1, Cl1 and Cl2 (σ=0.02 Å). The four ligand atoms and the metal ion deviate from the square plane by a maximum of 0.03 Å. In the related [Pd(DL-ethionine)Cl_2], the deviation of the five atoms from the square plane is 0.04 Å; Pd atom deviates by 0.084 Å from the mean plane of N1, S1, Cl1, Cl2. In [Pd(DL-methionine)Cl_2] the corresponding values are 0.11 and −0.07 Å, respectively.

The Pt–S distance of 2.244 Å in complex **1** can be compared with the values found for *trans*-[Pt$(NH_3)_2$(DMSO)Cl]$(ClO_4)_{0.8}Cl_{0.2}$ (Pt–S of 2.204 Å) [30] and bis-(μ-2-mercaptopyridinato)bis(ethylenediamine)platinum(II) chloride (Pt–S of 2.300 Å)

[31]. The Pt–Cl lengths of 2.302 and 2.325 Å in complex **1** are in the same range as those reported for *trans*-$[Pt(NH_3)_2(DMSO)Cl_4)_{0.8}Cl_{0.2}$ (Pt–Cl 2.302 Å), dichloro(*N*,*N*-dimethylethylenediamine)platinum(II) (Pt–Cl of 2.303 and 2.317 Å) [30]. The Pt–N distance in complex **1** is comparable to that found for *trans*-$[Pt(NH_3)_2(DMSO)Cl](ClO_4)_{0.8}Cl_{0.2}$ (Pt–N of 2.11 and 2.03 Å) [32], dichloro(*N*,*N*-dimethylethylenediamine)platinum(II) (Pt–N of 2.039 and 2.067 Å), *cis*-$[PtCl_2(cyclobutamine)(NH_3)]$ (Pt–N of 2.053 and 2.037 Å) [33] and bis-(μ-2-mercaptopyridinato)bis(ethylenediamine)platinum(II) chloride (Pt–N of 2.08 and 2.05 Å) [31].

The C–C distance in L-threonine [34] and DL-methionine [35] showed a marked variation from 1.54 Å and alternations including those of C–S bonds. In both these cases, it was argued that the presence of a Zwitterionic form and asymmetrical packing due to hydrogen bonding are responsible for this alternation. The C–S distance in complex **1** is comparable with those found for $[Pd(DL\text{-methionine})Cl_2]$ [17] and $[Pd(DL\text{-ethionine})Cl_2]$ [22] with the same marked alternations. Variations from the value of 1.54 Å exist for the C–C bonds in complex **1**, but the pattern of alternation is irregular.

The packing of the molecules in three dimensions is shown in Fig. 2. The amino nitrogen is tetrahedrally surrounded by Pt, one carbon and two hydrogens. An inspection of the intermolecular distances reveals that the hydrogens of the amino group may probably be involved in weak N–H...Cl hydrogen bonding, though this possibility was discarded in the case of $[Pd(DL\text{-methionine})Cl_2]$. However, as the X-ray data on the $[Pd(DL\text{-methionine})Cl_2]$ complex is of low

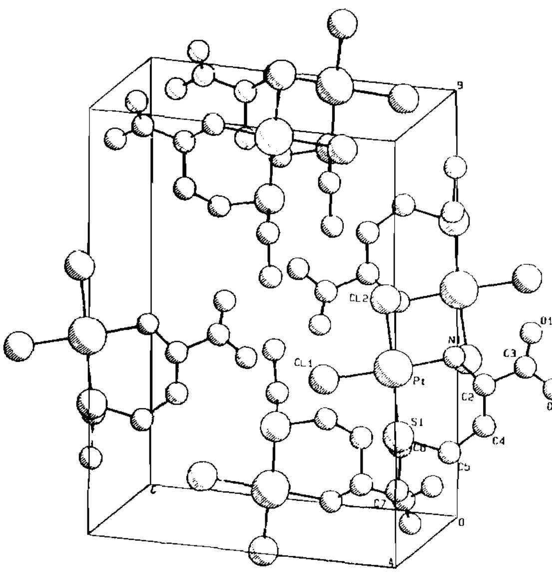
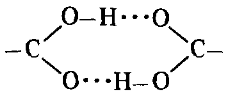


Fig. 2. Molecular packing of $[Pt(DL\text{-ethionine})Cl_2]$.

accuracy and as the hydrogens could not be located from the difference map, the conclusions arrived at are questionable. An inspection of the difference map in complex **1** shows that the atom H11 is probably involved in a hydrogen bonding, namely N1–H11...Cl2 of length 2.97 Å with an angle of 126.8°. A N1–H12...Cl2 bond of length 3.40 Å with N1–H12–C2 angle of 136.4° also occurs. However, the predominant force in the packing of the molecules is the hydrogen bonding of the type

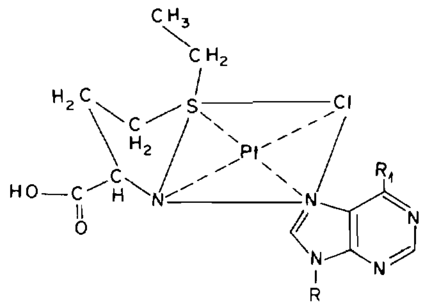


leading to a dimer formation between adjacent carboxylic acid groups. The O–H...O distance is 2.69 Å and O–H–O angle is 143.0 Å. This situation is similar to that found for $[Pd(DL\text{-methionine})Cl_2]$ [17], $[Pt(L\text{-methionine})Cl_2]$ [29] and $[Pd(DL\text{-ethionine})Cl_2]$ [22]. It should be noted that this feature is characteristic of the packing in carboxylic acids and is found in simple carboxylic acids, such as pthalic acid [36] and succinic acid [37]. Such a kind of packing has been obviously forced by the occurrence of a neutral ethionine moiety in the structure and resulting unionised carboxylic groups. We believe the weak N–H...Cl bonds give additional reinforcement for the packing forces. The situation is very similar to that found in the packing of $[Pd(DL\text{-ethionine})Cl_2]$.

The conductivity of complex **1** in DMSO (5 mhos) indicates that it is a non-electrolyte. For complexes **2–7** the conductivity values vary from 20–30 mhos indicating that these complexes are 1:1 electrolytes.

In the IR spectra of all these mixed ligand complexes, the presence of the COOH band around 1700 cm^{-1} indicates a free carboxylic acid group of ethionine. The important ligational frequencies of purines, pyrimidines and nucleosides are the $\nu(C{=}C)$, $\nu(C{=}N)$, $\nu(C{=}O)$ modes. The $\nu(C{=}C)$ and $\nu(C{=}N)$ of adenine, adenosine, hypoxanthine, ionosine, cytosine and cytidine are observed around 1450–1600 cm^{-1} and undergo a significant shift of about 60–100 cm^{-1} on complexation compared to the frequencies in the free ligands, indicating the involvement of ring nitrogen in coordination to the metal ion. There is no significant shift in the ligational frequencies of $\nu(C{=}O)$ and NH_2 modes observed around 1710 and 1680 cm^{-1}, respectively, excluding the coordination of the C=O or NH_2 groups of the ligands to the metal ion. The $\nu(OH)$ mode of coordinated water appears as a medium band around 3300 cm^{-1}.

The ^1H NMR spectrum of DL-ethionine gives a triplet centered at 1.50 ppm corresponding to the methyl protons. The quartet centered at 2.95 ppm and a triplet centered at 2.85 ppm can be attributed to the $S\text{–}CH_2\text{–}$ protons. The resonance peak observed



2 [Pt(DL-Ethio)(Adenine)Cl]Cl R_1 = NH_2 R = H

3 [Pt(DL-Ethio)(Adenosine)Cl]Cl R_1 = NH_2, R = Ribose

4 [Pt(DL-Ethio)(Hypoxanthine)Cl]Cl · H_2O R_1 = OH R = H

5 [Pt(DL-Ethio)(Inosine)Cl]Cl R_1 = OH R = Ribose

Fig. 3. The structure of mixed ligand complexes **2**, **3**, **4** and **5**.

as a triplet of doublets centered at 2.38 ppm arises due to the methylene ($-CH_2-$) protons. The resonance peak observed as a triplet at 4.10 ppm corresponds to the $-CH$ protons.

In complex 1, the $S-CH_2$ and $-CH$ resonance peaks are shifted downfield by 0.35 and 0.45 ppm, respectively indicating that the sulfur and NH_2 groups of ethionine are coordinated to the metal ion. This is supported by crystal structure analysis.

In the ^1H NMR spectrum of complex **2** the signals observed at 8.48 and 8.24 ppm are assigned to the C_8H and C_2H protons of coordinated adenine, respectively. The peak corresponding to the C_8H proton is shifted more downfield (0.16 ppm) than that of C_2H (0.05 ppm) indicating that N_7 of adenine is the coordinating site of the metal ion. Such a situation also exists for complex **3** where the C_8H protons are shifted more downfield (0.25 ppm) than the C_2H protons indicating N_7 as the coordinating site in adenosine.

The ^1H NMR spectrum of complex **4** exhibits a downfield shift of 0.20 ppm for the C_8H protons of hypoxanthine which shows N_7 as the site of coordination to the metal ion. In the ^1H NMR spectrum of complex **5**, the signals observed at 8.48 and 8.15 ppm are assigned to the C_8H and C_2H protons of coordinated ionosine, respectively. Since the signal due to the C_8H proton is shifted more (0.26 ppm) than that for the C_2H proton (0.06 ppm), N_7 of ionosine is proposed as the binding site for the metal ion.

Based on the above data the structures shown in Fig. 3 are proposed for complexes **2**, **3**, **4** and **5**.

In the ^1H NMR spectrum of complex **6**, the signals at 6.19 and 7.57 ppm correspond to the C_5H and C_6H resonances of coordinated cytosine. The C_5H proton has a larger downfield shift (0.31 ppm) compared to the C_6H protons (0.10 ppm) which indicates N_3 as the site of coordination. Such a situation also exists for complex **7** where the C_5H protons are shifted more downfield (0.51 ppm) than the C_6H protons indicating N_3 as the coordinating site in cytidine.

In all these mixed ligand complexes nucleobases bind to the metal ion *trans* to S.

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