Mixed ligand complexes of palladium(II) and platinum(II) with methionine and purines

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Mixed ligand complexes of Pt(II) and Pd(II) with methionine (MetH) as primary ligand and purines—adenine, guanine and hypoxanthine—as secondary ligands have been prepared by reacting cis-[Pd(MetH)Cl₂] (I) and cis-[Pt(MetH)Cl₂] (2) with adenine, guanine and hypoxanthine in 1:1 molar ratio. The complexes have been characterized on the basis of analytical, conductivity, and IR, electronic and ¹H NMR spectral data. In these complexes methionine is bound to the metal ion through amino nitrogen and sulphur atoms. The purines are bound to the metal ion through nitrogen (N7) of the five-membered ring and are present in a configuration trans to methionine sulphur. This indicates a higher trans directing ability of sulphur compared to that of amino nitrogen of methionine. Conductivity data show that the complexes are 1:1 electrolytes.

The discovery of anticancer activity of certain platinum coordination compounds¹ and use of cis-Pt(NH₃)₂Cl₂ (cis-platin) as a drug in the treatment of several human tumours², have led to an upsurge in research on platinum complexes. Efforts have been directed to synthesize less toxic analogues of cis-platin and to study their interaction with tumours³⁻⁶, and DNA and its constituents⁷⁻¹¹. The preparation of less toxic complexes than cis-platin is possible by the substitution of amine ligands in these complexes by molecules found in biological systems⁷⁻¹¹. Many Pt(II)-amino acid mixed ligand complexes and ternary complexes of Pd(II) and Pt(II) with amino acids and nucleosides¹²⁻¹⁵ were also reported. Earlier we had reported¹⁶ the interaction of cis-dichloroplatinum(II)-amino acid complexes with some purines, pyrimidines and nucleosides. In this paper, we report the interaction of cis-[Pd(MetH)Cl₂] and cis-[Pt(MetH)Cl₂] (MetH = methionine) with adenine, guanine and hypoxanthine.

Materials and Methods
Chromatographically pure DL-methionine and purine bases were obtained from Sigma Chemical Company (USA). Samples of palladium chloride and potassium hexachloroplatinate (AR, 98% pure) were purchased from Johnson Matthey Company (UK) and Alfa Ventron (USA) respectively. Palladium chloride was converted to potassium tetrachloropalladate(II) by heating with potassium chloride solution in 1:2 molar ratio¹⁷. K₂[PtCl₆] was converted to potassium tetrachloroplatinate by reduction with hydrazinium hydrochloride¹⁸. The parent complexes, cis-dichloro(methionine)palladium(II), ¹¹⁹, and cis-dichloro-(methionine)platinum(II), ²²⁰, were prepared by published procedures.

The elemental analyses of the complexes were carried out at the Australian Mineral Development Laboratories, Australia and CDRI, Lucknow, India. The chloride present in the complexes was estimated at Indian Institute of Chemical Technology (IICT), Hyderabad, India, using a published procedure²¹. IR spectra were recorded in KBr on IR-12 Perkin-Elmer 577, 337 and Beckman spectrophotometers. The electronic spectra of the complexes were recorded on a Shimadzu UV 240 instrument at IICT, Hyderabad, India. ¹H NMR spectra were recorded on JEOL 100, 270 and 500 MHz instruments at the University of Hyderabad, IISc, Bangalore and TIFR, Bombay respectively. IR spectra in the region 100-600 cm⁻¹ were recorded on a PE 983 spectrophotometer at RSIC, IIT, Madras, India. A digisun digital conductivity meter No. DI 909 was used to measure the conductivities of the complexes in DMSO/water. The physical, analytical and conductivity data of the complexes are given in Table 1.

The mixed ligand complexes (chloro)(adenine)-
Table I—Analytical and conductivity data of Pd(II) & Pt(II)-methionine-purine mixed ligand complexes

<table>
<thead>
<tr>
<th>Complex No.</th>
<th>Complex (Colour)</th>
<th>Found (Calc.), %</th>
<th>Molar conductivity (mho cm(^{-2}) mol(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>C</td>
<td>H</td>
</tr>
<tr>
<td>1</td>
<td>[Pd(MetH)Cl(_2)] (Yellow)</td>
<td>24.67</td>
<td>3.98</td>
</tr>
<tr>
<td>2</td>
<td>[Pt(MetH)Cl(_2)] (Yellow)</td>
<td>21.60</td>
<td>2.42</td>
</tr>
<tr>
<td>3</td>
<td>[Pd(MetH)(Ade)Cl,Cl(_2)H(_2)O] (Yellow)</td>
<td>23.70</td>
<td>4.20</td>
</tr>
<tr>
<td>4</td>
<td>31.20</td>
<td>2.84</td>
<td>12.88</td>
</tr>
<tr>
<td>5</td>
<td>[Pd(MetH)(Gua)Cl,Cl(_2)H(_2)O] (Yellow)</td>
<td>21.35</td>
<td>2.62</td>
</tr>
<tr>
<td>6</td>
<td>21.18</td>
<td>2.48</td>
<td>12.45</td>
</tr>
<tr>
<td>7</td>
<td>[Pd(MetH)(Hypo)Cl,Cl(_2)H(_2)O] (Yellow)</td>
<td>21.32</td>
<td>2.30</td>
</tr>
<tr>
<td>8</td>
<td>[Pt(MetH)(Gua)Cl,Cl(_2)H(_2)O] (Yellow)</td>
<td>24.60</td>
<td>3.37</td>
</tr>
</tbody>
</table>

(methionine)palladium(II) chloride dihydrate (3), (chloro)(adenine)(methionine)platinum(II) chloride (4), (chloro)(guanine)(methionine)(palladium) (II) chloride hydrate (5), (chloro)(guanine)(methionine)platinum(II) chloride monohydrate (7) and (chloro)(hypoxanthine)(methionine)platinum(II) chloride monohydrate (8) were prepared by reacting cis-(dichloro)(methionine)palladium(II) (1) or cis-(dichloro)(methionine)platinum(II) (2) with adenine/guanine/hypoxanthine in a 1:1 mole ratio in aqueous medium. When the purine was added to 1 or 2 and the contents heated on a water bath for 0.5-3.0 hr, the colour of the solution changed from yellow to light yellow. The reaction mixtures were cooled and filtered to remove unreacted traces of the parent complex and the ligand. The solution was further concentrated when pale yellow complexes 3-8 were precipitated which were washed with ethanol and dried with ether; yield, 70%.

Results and Discussion
The analytical data of the complexes (Table I) are in agreement with the stoichiometries proposed for the complexes. The infrared spectra of the parent complexes cis-[Pd(MetH)Cl\(_2\)] and cis-[Pt(MetH)Cl\(_2\)] show strong peaks at 1705 and 1710 cm\(^{-1}\) respectively, which are characteristic of the uncoordinated carboxylic acid group of methionine. Due to the hydrogen bonding interactions in these complexes, broad peaks were observed in the region 3000-3245 cm\(^{-1}\). In the far IR region, peaks were observed at 570-592 cm\(^{-1}\) which are assigned to vM – N mode arising due to the coordination of methionine to Pd(II) or Pt(II) through amino nitrogen. Peaks observed in the region 485-505 cm\(^{-1}\) are assigned to vM – S which indicate coordination of ether sulphur atom of methionine. The two absorptions in the region 320-395 cm\(^{-1}\) are characteristic of cis configurations for the chloro ligands. These assignments are in agreement with the coordination mode of methionine with Pt(II) established by Freeman et al.23, 24.

The ligand adenine shows vC = N + vC = C at 1335-1460 cm\(^{-1}\) while guanine and hypoxanthine show peaks due to vC = N + vC = C at 1510 cm\(^{-1}\) and 1600 cm\(^{-1}\) respectively in their IR spectra. In all the mixed ligand complexes these peaks were shifted to lower frequencies indicating the involvement of one of the ring nitrogens in coordination to the metal ion.

In the IR spectra of the complexes 3-6 strong and broad peaks occurring in the region 1600-1710 cm\(^{-1}\) are assigned to vC = O of the uncoordinated carboxylic acid group and NH\(_2\) deformation modes of adenine and guanine which overlap with each other. The NH\(_2\) groups of adenine and guanine do not participate in bonding to the metal ion under normal conditions, because the electron pair present on the nitrogen of the NH\(_2\) is delocalized into the ringπ-system and is not available for donation.

In the far IR spectra of mixed ligand complexes the vM – N frequencies that arise due to the coordination
of methionine and purines are observed in the range 507-585 cm⁻¹. The peaks observed in the range 417-490 cm⁻¹ are assigned to vM-S. In all the mixed ligand complexes, a single peak observed in the range 315-370 cm⁻¹ is assigned to the vM-Cl which indicates that only one chloride is present in the coordination sphere of the metal ion.

The electronic spectra of the complexes 3, 4, 5, 6, 7 and 8 show peaks at 265 nm (εₘₐₓ = 9.60 x 10⁴), 268 nm (εₘₐₓ = 1.38 x 10⁴), 248 nm (εₘₐₓ = 1.32 x 10⁴), 274 nm (εₘₐₓ = 4.86 x 10³), 250 nm (εₘₐₓ = 2.07 x 10⁴) and 255 nm (εₘₐₓ = 9.62 x 10³), respectively which can be assigned to π→π* transitions of coordinated purine. The π→π* transitions occur in adenine at 268 nm (εₘₐₓ = 1.13 x 10⁴) and 262 nm (εₘₐₓ = 1.30 x 10⁴). Guanine and hypoxanthine show this transition at 246 nm (εₘₐₓ = 0.94 x 10⁴) and 250 nm (εₘₐₓ = 1.05 x 10⁴) respectively.

The d-d transitions in Pd(II) complexes are extremely weak with ε values less than 10. Therefore, they could not be recorded with reasonable accuracy. In Pt(II) mixed ligand complexes weak d-d transitions occur in the region 240-280 nm.

In ¹H NMR spectrum of methionine a signal at δ 2.08 ppm is assigned to S-CH₃ protons while a triplet centered at δ 2.60 ppm is due to the methylene protons of the methionine. The proton present on the α-carbon atom of the methionine gives a signal at δ 3.30 ppm.

In the ¹H NMR spectra of complexes 1 and 2, a singlet at δ 2.48 and a multiplet centered at δ 2.54 ppm are assigned to S-CH₃ protons. The downfield shift of the signal by 0.4 ppm and 0.46 ppm, respectively in these complexes indicates the involvement of sulphur in coordination to the metal ion. cis-[Pd(MelH)Cl₂] showed peaks due to β-CH₂ and γ-CH₃ protons at δ 2.66 and δ 2.79 ppm, whereas the corresponding signals merged in a peak at 2.80 ppm in cis-[Pt(MelH)Cl₂]. Compared to uncoordinated methionine these signals are shifted downfield which again confirms the coordination of S-CH₃ group of the amino acid to the metal ion. The signal due to α-CH₂ proton occurs at 3.55 and 4.10 ppm observed in the spectra of these complexes, respectively can be assigned to α-CH₂ proton of methionine. These peaks are shifted downfield to the extent of 0.25 and 0.80 ppm respectively in complexes 1 and 2 indicating the coordination of NH₂ group to the metal ion.

The ¹H NMR spectrum of adenine shows a doublet at δ 8.32 and 8.20 ppm due to C₈H and C₄H protons (see structure I). The ¹H NMR spectrum of complex 3 shows a doublet at 8.46 and 8.40 ppm whereas in complex 4 these peaks appear at 8.61 and 8.56 ppm respectively. Since signals due to the C₈H and C₄H protons (see structure I) are shifted downfield in complexes 3 and 4 by 0.14, 0.20 and 0.29 and 0.36 ppm respectively, it can be inferred that N₇ or N₁ of adenine is involved in coordination in these complexes. In the complex 3 the signals due to α-CH, β-CH₂, γ-CH₂ and S-CH₃ are observed as a triplet at 4.10, triplets of doublets centered at 2.53 and 2.46, a triplet at 2.68 and a singlet at 2.24 ppm respectively. These signals are observed as a triplet centered at 4.28, triplets of doublets centered at 2.91 and 2.77, a triplet at 2.58 and a singlet at 2.31 ppm, respectively in complex 4. The signal due to the proton of α-carbon is observed as a triplet because of the spin-spin coupling with β-CH₂ protons. The β-CH₂ protons show triplets of doublet due to the spin-spin coupling with adjacent α-CH and γ-CH₂ protons. The γ-CH₂ protons are observed as a triplet due to coupling with β-CH₂ protons. The S-CH₃ protons give a single peak.

The ¹H NMR spectrum of guanine in D₂O (basic) shows a signal at 7.68 ppm due to the C₈H protons. In the ¹H NMR spectrum of complex 6, this signal appears at 8.78 ppm. Since this peak is shifted downfield with respect to the ligand, N₇ of the guanine is proposed as the binding site. The signals due to methionine α-CH, β-CH₂, γ-CH₂ and S-CH₃ protons are observed in the region 4.21-2.51 ppm. The signal due to the proton on the α-carbon is observed at 4.21 ppm. A triplet centered at 3.20 ppm is assigned to the γ-CH₂ protons. A doublet appearing at 2.75 and 2.63 ppm is assigned to β-CH₂ protons. The S-methyl protons are observed at 2.51 ppm.

The ¹H NMR spectrum of hypoxanthine exhibits two signals at 8.08 and 7.87 ppm respectively which are assigned to C₈H and C₄H protons. The ¹H NMR spectrum of complex 7 shows these signals at 8.33 and 7.75 respectively. Since signal due to C₈H protons is shifted more, N₇ of hypoxanthine is proposed as the coordination site. In complex 8 these signals are observed at 8.97 and 8.08 ppm respectively. As the signal due to the C₈H protons is shifted more (0.89 ppm) in comparison to that due to C₄H protons (0.21 ppm), it is proposed that N₇ of hypoxanthine is the coordination site in complex 8. The protons of methionine give peaks in the region 4.18-2.22 ppm.
and 4.11-2.21 ppm respectively in complexes 7 and 8. Based on the above data a general structure (I) is proposed for complexes 3-8.

In all the complexes 1-8, both methionine and purines bind to the metal ion, Pd(II) or Pt(II), through soft donor atoms sulphur and nitrogen, since both metal ions are soft acids28.

The reaction of purines with cis-[Pt(MetH)Cl2] and cis-[Pd(MetH)Cl2] is very fast, as compared to that with cis-[Pt(GlyH)Cl2], cis-[Pt(Ala)Cl2] and K[Pt(His)Cl2]19. This difference in the rates of reaction is solely due to the high trans directing ability of the coordinated sulphur group.

Since trans directing ability of coordinated sulphur in complexes 1 and 2 is greater as compared to that of coordinated nitrogen, it is proposed that purine is occupying a position trans to sulphur group of amino acid eventhough one more site trans to amino group is also available for the purine.

All these complexes show high molar conductivities in water, because of the ionization of the free COOH group in the complex. However, in DMSO some of these complexes show low conductivities (below 40 mhos cm−2 mol−1). On the basis of the conductivity data and chloride estimation of a few complexes, it is proposed that all the complexes are 1:1 electrolytes.

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References

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