Mixed ligand complexes of cis-dichloroethionineplatinum (II) and cis-dichloroethioninepalladium (II) with substituted pyrimidines

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Received 2 February 1995; revised and accepted 23 May 1995

Mixed ligand complexes of cis-dichloroethionineplatinum (II) and cis-dichloroethioninepalladium (II) with pyrimidines, viz 2-hydroxypyrimidine hydrochloride, isocytosine, 2-mercaptopurine, 5-aminouracil, 2-thiocytosine, and 2-thiouracil have been synthesised and characterised by elemental analysis, conductivity data, IR, UV, 1H and 13C NMR spectra. Based on the spectral data it is found that ethionine coordinates to the metal ion through sulphur and amino nitrogen, leaving a free carboxylic acid group. 2-Hydroxypyrimidine hydrochloride, isocytosine, 2-mercaptopurine act as monodentate ligands and bind to Pt(II) and Pd(II) through N{sub 3}, while 5-aminouracil coordinates to the metal ion through the amino (NH{sub 2}) group. The 2-thiocytosine and 2-thiouracil however act as bidentate ligands, coordinating to the metal ion through nitrogen (N{sub 3}) and sulphur.

Complexes of platinum group metals are being studied extensively because of their antitumour and antibacterial activity{sup 1-5}. Among them cis-platin{sup 1,2} is a potent drug for the treatment of a variety of human tumours. In this regard, attempts have been made to synthesise less toxic and more potent drugs. Several binary and ternary complexes of Pt(II) and Pd(II) were reported with nucleic acid constituents, amino acids and other nitrogen containing ligands{sup 6-14}. More recently B T Khan et al. have reported mixed ligand complexes of Pt(II) and Pd(II) with amino acids, methionine and ethionine and with purines, pyrimidines and nucleosides. Some of these complexes exhibited biological activity{sup 15,16}. Very few complexes with substituted pyrimidines however have been reported{sup 12,17-20}. In view of the importance of these complexes as biologically active compounds, we report in this paper the preparation and characterisation of a series of mixed ligand complexes of Pt(II) and Pd(II) with ethionine and substituted pyrimidines.

Materials and Methods
Chromatographically pure DL-ethionine, 2-hydroxypyrimidine hydrochloride, isocytosine, 2-mercaptopurine, 5-aminouracil, 2-thiocytosine, and 2-thiouracil were obtained from Sigma Chemical Company (USA). Samples of palladium chloride and potassium hexachloroplatinate (AR, 98%) 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 ratio{sup 21}. Potassium hexachloroplatinate was converted to potassium tetrachloroplatinate by reduction with hydrazinium hydrochloride{sup 22}. Solvents used were of high purity and were distilled before use.

The elemental analysis of the complexes were obtained from CDRI, Lucknow. The conductivity data were measured on a digital conductivity meter No. DL 909. The IR and UV spectra were recorded on Shimadzu IR-435 and UV-160 respectively. Far IR was recorded on a PE 983 spectrophotometer at RSIC, IIT, Madras. The 1H NMRs was recorded on 300 MHz spectrometer at CCMB, Hyderabad and 400 MHz spectrometer at RSIC, IIT, Madras respectively. The 13C NMR were recorded on 270 MHz spectrometer at HSc, Bangalore.

The parent complexes cis-(dichloro) (ethionine) platinum (II) and cis-(dichloro) (ethionine) palladium (II) were prepared by published procedures{sup 13,14}. The mixed ligand complexes synthesized were - (Chloro) (2-hydroxypyrimidinehydrochloride) (ethionine) platinum (II) chloride (1), (chloro) (2-hydroxypyrimidinehydrochloride) (ethionine) palladium (II) chloride (2), (chloro) (isocytosine) (ethionine) platinum (II) chloride (3), (chloro) (isocytosine) (ethionine) palladium (II) chloride monohydrate (4), (chloro) (2-mercaptopurine) (ethionine) platinum (II) chloride (5), (chloro) (2-mercaptopurine) (ethionine) palladium (II) chloride (6), (chloro) (2-mercaptopurine) (ethionine) platinum (II) chloride (7), (chloro) (2-mercaptopurine) (ethionine) palladium (II) chloride (8), (chloro) (2-mercaptopurine) (ethionine) platinum (II) chloride (9), (chloro) (2-mercaptopurine) (ethionine) palladium (II) chloride (10).
General procedure for the synthesis of complexes
cis-Dichloroethionineplatinum (II) or cis-dichloroethioninepalladium (II) dissolved in water was added to an aqueous solution of the ligand 2-hydroxypyrimidine, isocytosine, 2-mercaptopyrimidine, 5-aminouracil, 2-thiocytosine, or 2-thiouracil in 1:1 molar ratio, when the colour of the resulting solution changed to light green in case of complex (1), golden yellow in case of complex (2), yellow in case of complexes (3), (4), (7), maroon in case of complex (6), red in case of complex (8), and brown in case of complexes (9) and (10), respectively. The resulting solutions were heated on water bath for 2-3 h, and concentrated to half its volume, cooled, filtered and precipitated with ice cold acetone. The complexes were washed with ice cold acetone and vacuum dried. In case of complexes (5), (11) and (12) when the metal complex solution was added to the ligand solution, a mustard coloured precipitate for complex (5), a green coloured precipitate for complex (11) and a red coloured precipitate for complex (12) was obtained. This was refluxed for 4 h, filtered, washed and vacuum dried.

Results and Discussion
The analytical and conductivity data of the complexes (1-12) are given in Table 1. Complexes (1-8) are 1:1 electrolytes and complexes (9-12) are 1:2 electrolytes

The IR spectra of the complexes, in general showed a broad band in the region 3400-3100 cm⁻¹, which may be assigned to ν(OH), ν(NH) and ν(CH) stretching frequencies of coordinated pyrimidines and ethionine. A sharp peak at 1710 cm⁻¹ is assigned to the free COOH group of ethionine and is also due to ν(C = O) group of isocytosine, 5-aminouracil, 2-thiocytosine, and 2-thiouracil, which are not involved in the coordination to the metal. The ν(C = C) and ν(C = N) are important frequencies of pyrimidines and are observed in the region 1600-1400 cm⁻¹.

### Table 1—Characterization data of the complexes

<table>
<thead>
<tr>
<th>Complex No.</th>
<th>Complex</th>
<th>Found (Caled.), %</th>
<th>Molar conductivity (mho cm⁻² mol⁻¹)</th>
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<tr>
<td>1</td>
<td>[Pt(Ethio) (2-hypyHCl)Cl]Cl</td>
<td></td>
<td>21</td>
</tr>
<tr>
<td>2</td>
<td>[Pd(Ethio) (2-hypyHCl)Cl]Cl.H₂O</td>
<td></td>
<td>23</td>
</tr>
<tr>
<td>3</td>
<td>[Pt(Ethio) (Isocyt)Cl]Cl</td>
<td></td>
<td>24</td>
</tr>
<tr>
<td>4</td>
<td>[Pd(Ethio) (Isocyt)Cl]Cl.H₂O</td>
<td></td>
<td>20</td>
</tr>
<tr>
<td>5</td>
<td>[Pt(Ethio) (2-mercaptop)Cl]Cl</td>
<td></td>
<td>26</td>
</tr>
<tr>
<td>6</td>
<td>[Pd(Ethio) (2-mercaptop)Cl]Cl</td>
<td></td>
<td>23</td>
</tr>
<tr>
<td>7</td>
<td>(Pt(Ethio) (5-amura)Cl)Cl</td>
<td></td>
<td>26</td>
</tr>
<tr>
<td>8</td>
<td>[Pd(Ethio) (5-amura)Cl]Cl</td>
<td></td>
<td>19</td>
</tr>
<tr>
<td>9</td>
<td>[Pt(Ethio) (2-thiocy)Cl]₂</td>
<td></td>
<td>40</td>
</tr>
<tr>
<td>10</td>
<td>[Pd(Ethio) (2-thiocy)Cl]₂</td>
<td></td>
<td>44</td>
</tr>
<tr>
<td>11</td>
<td>[Pt(Ethio) (2-thioura)Cl]₂</td>
<td></td>
<td>45</td>
</tr>
<tr>
<td>12</td>
<td>[Pd(Ethio) (2-thioura)Cl]₂</td>
<td></td>
<td>37</td>
</tr>
</tbody>
</table>

Abbreviations: Ethio = Ethionine, 2-hypyHCl = 2-hydroxyprymidine hydrochloride, Isocyt = Isocytosine, 2-mercapto = 2-mercaptopyrimidine, 5-amura = 5-aminouracil, 2-thiocy = 2-thiocytoine, 2-thioura = 2-thiouracil.
cm$^{-1}$, but on complexation shift to lower frequencies by 30-40 cm$^{-1}$ as compared to the ligand, indicating the involvement of ring nitrogens in coordination to the metal ion$^{22}$. For complexes (9-12), the $\nu(C=S)$ stretching frequency is shifted to lower frequency by about 80 cm$^{-1}$ and is observed at 1000 cm$^{-1}$ indicating that the ligand coordinates to the metal ion through sulphur. The peaks observed at 590 and 500 cm$^{-1}$ are assigned to $\nu(M-N)$ and $\nu(M-S)$ stretching frequencies, respectively.

The electronic spectra of the complexes (1-12) show peaks in the region 241-324 nm, which are assigned to $\pi-\pi^*$ transitions of coordinated pyrimidines with the $\epsilon_{\text{max}}$ value of $2.33 \times 10^3$ to $7.35 \times 10^3$ M$^{-1}$ cm$^{-1}$, respectively.

The $d-d$ transitions in complexes 2, 4, 5, 6, 7, 8, 9, 10, 11 and 12 occur at 314 nm ($\epsilon_{\text{max}} = 6.19 \times 10^3$), 814 nm ($\epsilon_{\text{max}} = 1.21 \times 10^4$), 377 nm ($\epsilon_{\text{max}} = 1.87 \times 10^4$), 379 nm ($\epsilon_{\text{max}} = 1.90 \times 10^4$), 699 nm ($\epsilon_{\text{max}} = 1.04 \times 10^4$), 291 nm ($\epsilon_{\text{max}} = 5.04 \times 10^3$), 386 nm ($\epsilon_{\text{max}} = 2.15 \times 10^4$), 361 nm ($\epsilon_{\text{max}} = 5.28 \times 10^3$), 368 nm ($\epsilon_{\text{max}} = 1.21 \times 10^3$) and 418 nm ($\epsilon_{\text{max}} = 2.42 \times 10^3$), respectively.

The $^1$H NMR spectra of the complexes were recorded to determine the binding sites of the ligand to the metal ion. The $^1$H NMR spectrum of complex (1) shows a triplet at 6.62 ppm due to C$_6$H proton, and a doublet [J(H$_2$-H$_3$) = 12 Hz] for C$_4$H proton at 8.15 ppm with a doublet due to coupling of $^{195}$Pt with C$_4$H proton [J$^{195}$(Pt-H$_4$) = 40 Hz] and a doublet for C$_3$H proton at 8.76 ppm. An upfield shift for the C$_4$H proton by 0.57 ppm as compared to the ligand, and also an upfield shift in C$_5$H proton by 0.34 ppm, implies that 2-hydroxypyrimidine hydrochloride coordinates to the metal ion through N$_3$. The ethionine protons are observed between 1.26 to 4.65 ppm.

The $^1$H NMR spectrum of complex (2) shows a downfield shift of 0.17 ppm for C$_4$H proton and a small shift of 0.05 ppm for C$_3$H as compared to the ligand. The downfield shift in C$_2$H protons implies that 2-hydroxypyrimidine hydrochloride is coordinated to the metal ion through N$_3$. The ethionine protons are observed between 1.5 to 4.8 ppm. The $^{13}$C [$^1$H] NMR spectrum also supports the coordination of 2-hydroxypyrimidine hydrochloride to metal ion through N$_3$. There is a downfield shift in C$_2$ and C$_4$ carbons by 2 ppm and 4 ppm, respectively indicating that 2-hydroxypyrimidine hydrochloride coordinates to the metal through N$_3$. The ethionine protons are observed between 13 to 51 ppm. The resonance due to carboxylic group is observed at 176 ppm.

The $^1$H NMR spectrum of complex (3) shows a doublet [J(H$_2$-H$_3$) = 11 Hz] for C$_3$H proton with $^{195}$Pt satellites due to coupling of C$_3$H with $^{195}$Pt [J$^{195}$(Pt-H$_3$) = 20 Hz] and a doublet for C$_4$H proton [J(H$_2$-H$_4$) = 14 Hz] at 7.59 ppm. An upfield shift in the C$_3$H proton by 0.11 ppm as compared to the ligand and its interaction with $^{195}$Pt and no shift in case of C$_4$H proton indicates that isocytosine coordinates to the metal ion through N$_3$.

The $^1$H NMR spectrum of complex (4) shows two doublets due to C$_2$H and C$_4$H at 6.00 ppm and 7.57 ppm, respectively. As there is a downfield shift in C$_3$H proton by 0.14 ppm as compared to the ligand and a negligible shift in C$_4$H proton by 0.04 ppm, it may be inferred that isocytosine coordinates to the metal ion through N$_3$. The $^{13}$C [$^1$H] NMR also supports this conclusion. There is a downfield shift in the complex in the C$_2$, C$_4$, C$_5$, and C$_6$ carbons by 5.57, 2.12, 1.87, and 0.86 ppm as compared to the ligand. A greater shift in C$_2$ and C$_4$ carbons infers that isocytosine coordinates to the metal ion through N$_3$. The ethionine carbons are observed between 13 to 52 ppm. The resonance due to carboxylic carbon is observed at 189 ppm.

The $^1$H NMR spectrum of complex (5) shows a triplet for C$_5$H proton, a doublet [J(H$_2$-H$_3$) = 13 Hz] for C$_4$H proton with $^{195}$Pt satellites due to coupling of $^{195}$Pt with C$_4$H proton [J$^{195}$(Pt-H$_4$) = 19 Hz] and a doublet for C$_3$H proton at 8.30 ppm. A downfield shift in C$_4$H proton by 0.42 ppm as compared to the ligand and also a shift in C$_6$H proton by 0.47 ppm infers that 2-mercaptopyrimidine coordinates to the metal ion through N$_3$. The C$_6$H proton undergoes a negligible shift. The corresponding palladium complex (6) shows a triplet at 7.04 ppm for C$_6$H proton and a doublet at 8.54 ppm for C$_4$H proton. The downfield shift in C$_5$H and C$_3$H protons by 0.26 ppm and by 0.19 ppm implies that 2-mercaptopyrimidine coordinates to the metal ion through N$_3$.

The $^1$H NMR spectrum of complex (7) shows a triplet centered at 7.4 ppm with 1:4:1 ratio and a coupling constant of 12 Hz. Such a splitting is characteristic of the protons of amino group coordinated to platinum (II)$^{10}$. There is an upfield shift in C$_5$H proton by 0.2 ppm as compared to the ligand showing that the amino group of 5-aminouracil is coordinated to the metal ion. The ethionine protons are observed between 1.4 to 4.4 ppm.

The $^1$H NMR spectrum of complex (8) shows a triplet at 6.8 ppm due to coordinated amino group and a signal at 8.3 ppm for C$_4$H proton. There is a downfield shift in C$_6$H proton by 0.3 ppm indicating that the amino group of 5-aminouracil is coordinated to the metal ion.

The $^1$H NMR spectrum of complex (9) shows a doublet for C$_3$H proton centered at 6.41 ppm and
another doublet at 7.9 ppm for C₆H proton [J(HS-H₆) = 12 Hz]. A downfield shift in C₅H proton by 0.4 ppm and in C₆H proton by 0.17 ppm indicates that 2-thiocytosine is coordinated to the metal ion through N₃ and S₂. In the corresponding Pd(II) complex (10), the ¹H NMR shows a doublet at 6.14 ppm for C₅H proton and 7.73 ppm for C₆H protons. Since the downfield shift in C₅H and C₆H protons is 0.13 ppm and 0.10 ppm, it is concluded that 2-thiocytosine is coordinated to the metal ion through N₃ and S₂.

The ¹H NMR spectrum of complex (11) shows a doublet at 6.04 ppm for C₅H proton and at 7.52 ppm for C₆H proton. A downfield shift in C₅H and C₆H proton by 0.22 ppm and 0.14 ppm respectively shows that 2-thiouracil is coordinated to the metal ion through N₃ and S₂. In the corresponding Pd(II) complex (12), the ¹H NMR spectrum shows two doublets at 5.95 and 7.5 ppm for C₅H and C₆H protons, respectively. A downfield shift in C₅H and C₆H protons by 0.13 and 0.12 ppm respectively, infers that 2-thiouracil is coordinated to the metal ion through N₃ and S₂. The ethionine protons are observed between 4.5 to 1.5 ppm.

Based on the analytical, conductivity and spectral data, the structures shown in I (a), (b) and (c), are proposed for complexes (1-6) respectively, where ethionine acts as a bidentate ligand coordinating to the metal ion through sulphur, amino nitrogen and the secondary ligand acts as a monodentate ligand and coordinates to the metal ion through N₃. In case of complexes (7) and (8), 5-aminouracil is coordinated to the metal ion through amino group (Structure II). The structures for complexes (9), (10), (11) and (12) are shown in III (a) and (b), respectively, where the secondary ligand 2-thiocytosine and 2-thiouracil act as a bidentate ligand and coordinates to the metal ion through N₃ and sulphur.

Acknowledgement
One of us (KA) is grateful to the CSIR, New Delhi, for financial assistance.

References