Thermodynamics of the interaction of Pd(dmen)(H₂O)₂²⁺ with bio-relevant ligands with reference to the deactivation of metal-based drug by thiol ligands

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1. Introduction

The use of platinum coordination compounds in cancer chemotherapy has been extensively studied following the fortuitous discovery of the therapeutic properties of cisplatin [cis-diaminedichloroplatinum(II)] by Rosenberg et al. [1,2]. First approved for the treatment of testicular cancer in 1978, cisplatin is one of the most widely utilized antitumour drugs, exhibiting high efficacy against solid tumours, particularly testicular and ovarian cancer [3–8]. Despite the remarkable success of cisplatin, several problems have been found in clinical use. First, cisplatin treatment is often accompanied by severe side effects, including cumulative toxicities of nephrotoxicity, neurotoxicity, and emetogenesis [5,6,9–11]. In addition, cisplatin activity is limited to a relatively narrow range of tumours as a result of inherent or treatment-induced tumour resistance [6,12]. In the search for new platinum anticaner drugs, great efforts are devoted to the design of complexes more efficient and less toxic than the reference drugs already in clinical use. For this purpose, the rational design of complexes and the study of relevant structure–activity relationships have been extended to families of new compounds having high structural diversity.

Pd(II) and Pt(II)-amine complexes have the same general structures and thermodynamic properties. However, the former complexes are five orders of magnitude more reactive than their platinum counterparts. Therefore, Pd(II) complexes are good models for the analogous Pt(II) complexes in solution. Recent work in our laboratories focused on the equilibria of complex-formation reactions of (diamine)palladium(II) complexes with bio-relevant ligands as amino acids, peptides and dicarboxylic acids and esters [13–17]. As an extension of the research conducted in our laboratory, the Palladium(II) complex with N,N-dimethylethylenediamine (dmen) was investigated. The ligand dmen has two methyl groups attached to one nitrogen atom of ethylenediamine. The two methyl groups will create steric hindrance for the incoming ligand. This will slow down the reactivity of the complexes to the same level as its platinum-amine analogues. Also, the methyl group substituents may undergo hydrophobic interaction with DNA, such effect may favour the interaction with DNA, which is the main target for the antitumour agent. The thiol ligands as cysteine have high affinity for Pd(II) and Pt(II) complexes. These ligands will compete with the DNA for the reaction with any antitumour agent. Therefore, it is of biological significance to calculate the equilibrium constants for the displacement reaction of model ligands as inosine, glycine or methionine by cysteine. These equilibrium constants may give a measure of the effectiveness of the antitumour agent.

2. Experimental

2.1. Materials

The complex [Pd(dmen)Cl₂] was prepared by heating PdCl₂ (0.1773 g; 1.0 mmol) and KCl (0.1491 g; 2.0 mmol) in the least...
amount of water to 70 °C with stirring. The clear solution of [PdCl4]2− solution was cooled to 25 °C filtered and N,N-
dimethylethyleenediamine (0.0881 g; 1.0 mmol), was added to the
stirred solution. The pH of the solution was adjusted to 2–3 by
addition of HCl. The solution was evaporated to a small vol-
ume (20 ml) under vacuum then an orange crystalline precipitate
of [Pd(dmen)Cl2] was formed on cold. The precipitate was
filtered off and washed with H2O. An orange crystalline precipitate
was obtained; yield 92%. For C6H12N2PdCl4 (F.wt = 265.48) (Anal.
Found: C; 18.04; H; 5.40; N; 10.29. Calc.: C; 18.08; H; 4.52; N; 10.55%.)
The complex was converted in solution into the diaqua form by
|treating it with 2 equivalents of AgNO3, as described elsewhere
[18]. The ligands in the hydrochloride form of the corresponding
hydrochloride form using the procedure described before. The amino acids used were glycine, alanine, β-alanine, β-phenylalanine, proline, valine, isoleucine, serine, threonine, histidine, histamine dihydrochloride, lysine 2HCl, ornitine 2HCl,
ethanolamine HCl, imidazole, S-methylcysteine, methionine and
varamic acid. The amino acid with an amide group are asparagine
and glutamine. The peptides studied were glycaminide and gly-
cylglycine. The dicarboxylic acids investigated are cyclobutane
dicarboxylic acid, malonic acid, oxalic acid, succinic acid, adipic
acid. The amino acid esters investigated were glycine methyl ester,
histidine methyl ester and methionine methyl ester. These materi-
als were all obtained from Sigma Chem. Co.

2.2. Potentiometric measurements

Potentiometric measurements were performed using a
Metrohm 751 Titroprocessor. The electrode and titropro-
cessor were calibrated with standard buffer solutions prepared
according to NBS specifications [19]. pH meter readings were
converted to hydrogen ion concentration by titrating a standard
HNO3 solution (0.01 M), the ionic strength of which was adjusted
to 0.1 M with NaNO3, with standard NaOH (0.05 M) at 25 °C. The
pH was plotted against pH[H]. The relationship pH = p[H] = 0.05 was
observed. IR spectrum was measured on a 8001-PC FT-IR Shimadzu
spectrophotometer using KBr pellets.
The acid dissociation constants of the ligands were determined
by titrating 0.625 mmol samples of each with standard NaOH solu-
tions. The acid dissociation constants of the coordinated water
molecules in [Pd(dmen)](H2O)2]2+ were determined by titrating
0.625 mmol of the complex with standard 0.05 M NaOH solution.
The formation constants of the complexes were determined by
titrating solution mixtures of [Pd(dmen)](H2O)2]2+ (0.625 mmol)
and the ligand in the concentration ratio of 1:1 for amino acids,
peptides and dicarboxylic acids. Imidazole was converted into its
protonated form with standard HNO3 solutions). The titrated solu-
tion mixtures, each had a volume of 40 ml and the titrations
were carried out at 25 °C and 0.1 M ionic strength (adjusted with
NaNO3). A standard 0.05 M NaOH solution was used as titrant.
The equilibrium constants evaluated from the titration data are
defined by Eqs. (1) and (2)

\[ pM + qL + rH^+ \rightarrow [M]_p [L]_q [H]^r \]  

\[ K_{eq} = \frac{[M]_p [L]_q [H]^r}{[M]^p [L]^q [H]^r} \]  

where the charges are omitted for simplicity.

M, L and H represent [Pd(dmen)](H2O)2]2+, ligand and proton,
respectively. The calculations were performed using the program
MINQUAD-75 [20]. Stoichiometric and stability constants of
the complexes were determined by fitting various possible composi-
tion models. The selected model gave the best statistical fit and was
chemically consistent with the titration data without giving any system
drift in the magnitude of various residuals, as described
elsewhere [20]. The stability constants of the complexes formed in
solution are given in Tables 1–3 Tables 1–3. Distribution diagrams
were obtained using the program SPECIES [21].

2.3. Spectrophotometric measurements

Spectrophotometric measurements of Pd(dmen)-OH, amino
acid, peptide or dicarboxylic acid complexes were performed
by recording the UV–visible spectra of solution mixtures of
[Pd(dmen)](H2O)2]2+, ligand and NaOH. Under these prevailing
experimental conditions and after neutralization of the hydrogen
ions released, associated with complex formation, it is supposed
that the complexes have been completely formed. In each mixture
the volume was brought to 10 ml by addition of deionized water
and ionic strength is kept constant at 0.1 M NaNO3.

3. Results and discussion

3.1. Characterization of the solid complex

The analytical data indicates that the complex is of 1:1 stoichiometry of and formula Pd(dmen)Cl2. The IR spectrum of the
Pd(dmen)Cl2 complex exhibits bands in the region 3300–3400 cm−1, attributed to stretching vibrations of NH2 group.
The complex exhibits bands for (NH2) bending at 1465 and
1562 cm−1 and bands for the stretching vibration corresponding to
Pd–N at 480 and 523 cm−1 [22].

3.2. Acid–base equilibria of the ligands and [Pd(dmen)(H2O)2]2+ complex

The acid dissociation constants of the ligands were determined
under the same experimental conditions of ionic strength and tem-
perature used to study the Pd1 complexes. The acid–base equilibria
of [Pd(dmen)(H2O)2]2+ given in Eq. (3a–c) were investigated and
the equilibrium constants were determined and given in Table 1. These values were taken into account in determining the stability
constants of the Pd1 complexes.

\[ [\text{Pd(dmen)}(\text{H}_2\text{O})]^{2+} + \text{H}^+ \rightarrow [\text{Pd(dmen)}(\text{H}^+)(\text{H}_2\text{O})]^{2+} \]  

\[ [\text{Pd(dmen)}(\text{H}_2\text{O})(\text{OH})]^+ + \text{H}^+ \rightarrow [\text{Pd(dmen)}(\text{H}^+)(\text{H}_2\text{O})(\text{OH})]^{2+} \]  

\[ [\text{Pd(dmen)}(\text{H}_2\text{O})]^2+ + \text{H}^+ \rightarrow [\text{Pd(dmen)}(\text{H}^+)(\text{H}_2\text{O})]^2+ \]  

The pK\text{aq} and pK\text{pK} values for [Pd(dmen)](H2O)2]2+ are 5.29 and
9.45, respectively, which are comparable with the literature values
of similar systems [23]. The equilibrium constant for the dimer-
ization reaction (3c) can be calculated by Eq. (4) and amounts to
3.17

\[ \log K_{\text{dimer}} = \log \beta_{10.1} – \log \beta_{20.1} = -2.12 – (-5.29) = 3.17 \]  

The spectra of the hydrolysed forms of [Pd(dmen)](H2O)2]2+,
given in Fig. 1, show that the band at 353 nm corresponding to
[Pd(dmen)](H2O)2]2+ undergoes a blue shift to 334 nm upon forma-
tion of [Pd(dmen)OH] (10-1 species) by addition one equivalent of
NaOH. This is due to ligand field splitting as a result of substitu-
tion of coordinated H2O molecule by OH−. This band is further
shifted to 328 nm by addition of two equivalents of NaOH forming
the dihydroxy–species, [Pd(dmen)(OH)2]. (10-2 species).
Table 1
Formation constants for complexes of [Pd(dmen)(H2O)2]2+ with amino acids at 25 °C and 0.1 M ionic strength.

<table>
<thead>
<tr>
<th>System</th>
<th>MLH4</th>
<th>logβb</th>
<th>pKαc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pd(dmen)—OH</td>
<td>1</td>
<td>−5.29(0.02)</td>
<td>5.29</td>
</tr>
<tr>
<td>Glycine</td>
<td>0</td>
<td>9.61(0.02)</td>
<td>9.61</td>
</tr>
<tr>
<td>Alanine</td>
<td>0</td>
<td>12.02(0.03)</td>
<td>2.41</td>
</tr>
<tr>
<td>S-Methylcysteine</td>
<td>0</td>
<td>10.25(0.02)</td>
<td></td>
</tr>
<tr>
<td>β-Alanine</td>
<td>0</td>
<td>9.71(0.01)</td>
<td>9.71</td>
</tr>
<tr>
<td>β-Phenylalanine</td>
<td>0</td>
<td>9.12(0.01)</td>
<td>9.12</td>
</tr>
<tr>
<td>Valine</td>
<td>0</td>
<td>9.58(0.01)</td>
<td>9.58</td>
</tr>
<tr>
<td>Proline</td>
<td>0</td>
<td>10.52(0.01)</td>
<td>10.52</td>
</tr>
<tr>
<td>Isoleucine</td>
<td>0</td>
<td>11.14(0.05)</td>
<td>3.64</td>
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<td>Ethanolamine</td>
<td>0</td>
<td>9.95(0.01)</td>
<td>9.95</td>
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<tr>
<td>Serine</td>
<td>0</td>
<td>9.14(0.01)</td>
<td>9.14</td>
</tr>
<tr>
<td>Threonine</td>
<td>0</td>
<td>9.06(0.01)</td>
<td>9.06</td>
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<tr>
<td>Histidine</td>
<td>0</td>
<td>9.15(0.01)</td>
<td>9.15</td>
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<tr>
<td>Histamine</td>
<td>0</td>
<td>9.58(0.01)</td>
<td>9.59</td>
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<tr>
<td>Imidazole</td>
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<td>6.85(0.02)</td>
<td>6.85</td>
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<td>Ornithine</td>
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<td>10.58(0.02)</td>
<td>10.58</td>
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<tr>
<td>Lysine</td>
<td>0</td>
<td>19.66(0.03)</td>
<td>2.92</td>
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<tr>
<td>S-Methylcysteine</td>
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<td>10.61(0.03)</td>
<td>1.96</td>
</tr>
<tr>
<td>Methionine</td>
<td>0</td>
<td>9.12(0.02)</td>
<td>9.12</td>
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</table>

* M, L and H are the stoichiometric coefficients corresponding to [Pd(dmen) (H2O)2]2+, amino acid, and H+, respectively; the coefficient −1 refers to a proton loss.
* Log β of Pd(dmen)-amino acids. Standard deviations are given in parentheses; sum of square of residuals are less than 5E−7.
* The pKα of the ligands, the protonated species or the aqua complexes.

Table 2
Formation constants for complexes of [Pd(dmen)(H2O)2]2+ with peptides at 25 °C and 0.1 M ionic strength.

<table>
<thead>
<tr>
<th>System</th>
<th>MLH4</th>
<th>Logβb</th>
<th>pKαc</th>
</tr>
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<tr>
<td>Cysteine</td>
<td>0</td>
<td>10.36(0.01)</td>
<td>10.36</td>
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<tr>
<td>Glutamic acid</td>
<td>0</td>
<td>9.54(0.01)</td>
<td>9.54</td>
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<tr>
<td>Glycine</td>
<td>0</td>
<td>7.88(0.02)</td>
<td>7.88</td>
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<tr>
<td>Glycylglycine</td>
<td>0</td>
<td>7.27(0.02)</td>
<td>7.94</td>
</tr>
<tr>
<td>Asparagine</td>
<td>0</td>
<td>8.56(0.01)</td>
<td>8.56</td>
</tr>
<tr>
<td>Glutamine</td>
<td>0</td>
<td>9.50(0.01)</td>
<td>9.50</td>
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</tbody>
</table>

* M, L and H are the stoichiometric coefficients corresponding to [Pd(dmen) (H2O)2]2+, peptides, and H+, respectively; the coefficient −1 refers to a proton loss.
* Log β of Pd(dmen)-peptides. Standard deviations are given in parentheses; sum of square of residuals are less than 5E−7.
* The complex pKα of the peptides or of the peptide NH ionization.

Fig. 1. The electronic spectra of (A) 2 × 10−4 M of [Pd(dmen)(H2O)2]2+; (B) 2 × 10−5 M of [Pd(dmen)(H2O)2]2+ and 2 × 10−4 M of NaOH; (C) 2 × 10−4 M of [Pd(dmen)(H2O)2]2+ and 4 × 10−4 M of NaOH.
Table 3

<table>
<thead>
<tr>
<th>System</th>
<th>M, L</th>
<th>log K'</th>
<th>pKα/*</th>
</tr>
</thead>
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<tr>
<td>Cyclobutane-1,1,1,1-tetrol acid</td>
<td>0.01</td>
<td>5.57</td>
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<tr>
<td></td>
<td>0.10</td>
<td>5.57</td>
<td>5.57</td>
</tr>
<tr>
<td></td>
<td>1.0</td>
<td>5.57</td>
<td>5.57</td>
</tr>
<tr>
<td></td>
<td>1.0</td>
<td>5.57</td>
<td>5.57</td>
</tr>
<tr>
<td>Malonic acid</td>
<td>0.01</td>
<td>5.57</td>
<td>5.57</td>
</tr>
<tr>
<td></td>
<td>0.10</td>
<td>5.57</td>
<td>5.57</td>
</tr>
<tr>
<td></td>
<td>1.0</td>
<td>5.57</td>
<td>5.57</td>
</tr>
<tr>
<td></td>
<td>1.0</td>
<td>5.57</td>
<td>5.57</td>
</tr>
<tr>
<td>Oxalic acid</td>
<td>0.01</td>
<td>5.57</td>
<td>5.57</td>
</tr>
<tr>
<td></td>
<td>0.10</td>
<td>5.57</td>
<td>5.57</td>
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<tr>
<td></td>
<td>1.0</td>
<td>5.57</td>
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<tr>
<td></td>
<td>1.0</td>
<td>5.57</td>
<td>5.57</td>
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<tr>
<td>Succinic acid</td>
<td>0.01</td>
<td>5.57</td>
<td>5.57</td>
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<tr>
<td></td>
<td>0.10</td>
<td>5.57</td>
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<tr>
<td></td>
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<td>5.57</td>
<td>5.57</td>
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<tr>
<td>Adipic acid</td>
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<td>5.57</td>
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<td></td>
<td>0.10</td>
<td>5.57</td>
<td>5.57</td>
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<td>5.57</td>
<td>5.57</td>
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<tr>
<td>Fumaric acid</td>
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<td>5.57</td>
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<tr>
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<td>5.57</td>
<td>5.57</td>
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<td>1.0</td>
<td>5.57</td>
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<td></td>
<td>1.0</td>
<td>5.57</td>
<td>5.57</td>
</tr>
</tbody>
</table>

* M, L and H are the stoichiometric coefficients corresponding to Pd(N–N), dibasic acids, and H+ respectively.

3.3. Amino acid complexes

Fitting of the potentiometric data for [Pd(dmen)]-amino acid equilibria indicated the formation of 1:1 complexes. Histidine is a tridentate ligand having amino, imidazole and carboxylate groups as binding sites. With [Pd(dmen)](H2O)2]2+ only, two of the three binding sites are involved in complex formation, hence histidine coordinates in either a glycine-like or a histamine-like mode. The stability constant of the histidine complex is in fair agreement with that of histamine and higher than those of amino acids. This indicates that histidine interacts with the PdII complex in the same way as histamine coordinates. The analysis of the titration results for imidazole complex reveals the formation of 1:1 and 2:2 complexes. The stability constant of the 1:1 complex with imidazole has a smaller value than those of amino acids. This gives further support to the proposal that amino acids are coordinating as bidentate ligands. The stability constant values (log β110) of simple amino acid complexes are compared. The proline complex has the highest value. This may be due to the highest basicity of the proline amino group as reflected by the highest pKα value. The stability constant of the alanine complex (log β110 = 9.22) is lower than that of glycine (log β110 = 9.72), although pKα of alanine (9.69) is higher than that of glycine (9.66). This may be due to the steric interaction between the alkyl groups in the dmen and the methyl group in the alanine. The stability constant of the complex with lysine (log β110 = 11.63) is little bit higher than those of α-amino acids. This may be taken to indicate that lysine most likely chelates through the α-amino and carboxylate groups (N, O-donor set). There is another way for coordination of lysine, where the two amino groups are bound to the PdII ion. However, the latter possibility is ruled out as formation of such a complex will involve formation of less stable 8-membered chelate ring, which is thermodynamically unfavoured. The stability constant value of methionine complex (log β110 = 8.77) is lower than those of most simple amino acids. This may be explained by the fact that the amino group of methionine is less basic than those of other amino acids as reflected by pKα values, Table 1.

The electronic spectrum of [Pd(dmen)(H2O)2]2+ in presence and absence of alanine, taken as example for amino acids and given in Fig. 2, are compared. Upon complexation, the band of [Pd(dmen)(H2O)2]2+ complex at 353 nm is shifted to 306 nm for [Pd(dmen)alanine]+, (110 species). This shift is expected as a result of ligand field splitting upon substitution of coordinated water by alanine.

3.4. Peptide complexes

The potentiometric data of the peptide (HL) complexes were fitted assuming the formation of the species [Pd(dmen)(HL)]+ (110 species) and [Pd(dmen)(HL−)] (11-1 species). The former species is formed by coordination through the amino group and carbonyl oxygen atom. On increasing the pH, the coordination site should switch from the carbonyl oxygen to the amide nitrogen with release of the amide hydrogen, forming the complex [Pd(dmen)(NH2−)]. Such changes in coordination centers are now well documented [24]. The pKα of the coordinated amide group was calculated using Eq. (5) and is given in Table 2. The pKα for the glycine complex is lower than the pKα of the other peptides. This may be explained on the premise that the more bulky substituent group on the peptide may serve to hinder the structural change in going from protonated to deprotonated complexes. Asparagine complex has the highest stability constant value, most probably due to the presence of α-amino group that can coordinate firstly as glycine does. The α-amino group of asparagine is more basic than those of other peptides, which result in an increase of stability constant of its complex.

The concentration distribution diagrams of peptide complexes, indicate that all peptides form the complex species (110) at low pH, and thus prevent the hydrolysis of PdII ion i.e. the hydrolysed species (10-1) and (10-2) are either not formed or formed in very low concentration. The induced ionization of the peptide hydrogen of glycine and tryptophan starts at pH ~3. However asparagine ionization starts above pH ~8. Therefore, under normal physiological condition (pH 6–7), the peptides would coordinate to [Pd(dmen)(H2O)2]2+ in entirely different ways. Glycine and tryptophan are present entirely in the deprotonated form (11-1), whereas asparagine exists soley in the protonated form.

Spectral bands of [Pd(dmen)(H2O)2]2+ and its glycine complex are quite different in the position of the maximum wavelength, Fig. 3. The spectral band of the [Pd(dmen)(H2O)2]2+ complex
appeared at 353 nm and is shifted to 299 nm upon formation of [Pd(dmen)(glycinamide)]⁺ complex (110 species). A further shift of the band to 294 nm in the deprotonation and formation of [Pd(dmen)(glycinamideH⁻)] complex (11-1 species). The progressive shift toward shorter wavelength in the absorption spectrum may be taken as evidence, supporting the potentiometric measurements for the induce ionization of amide upon complex formation.

### 3.5. Dicarboxylic acid complexes

In the case of dicarboxylic acids, the potentiometric data were fitted on the basis of the formation of 110 complex and its monoprotonated form (111). The formation constants of the (110) complexes with oxalic, CBDCA and malonic acids, where fiv- and six-membered chelate rings are higher than those involving seven-membered, as in succinic, and nine-membered chelate rings as in adipic acid. This may be explained on the premise that the five- and six-membered rings are more favored energetically than the seven and the nine-membered rings.

It is interesting to note that 1,1-CBDCA has a higher stability constant than that of malonic acid, although both form 6-membered chelate rings. This may be due to the higher pKₐ values of the former than the latter dicarboxylic acid.

The pKₐ value of the protonated complex species of [Pd(dmen) CBDCA] is 2.13. This value is lower than that of free CBDCAH⁻, which indicates acidification of the second carboxylic group upon coordination of [Pd(dmen)(H₂O)]²⁺ with the first carboxylate group. The pKₐ value of this protonated species in case of [Pd(en)HCBDC]⁺ was estimated before from UV/vis measurements to be ca. 2.5 at 25°C and 0.1 M ionic strength [25]. This species was documented to be the active form in the case of carboplatin [26]. The concentration distribution diagram of CBDCA complex, taken as an example, is given in Fig. 4, shows that the protonated species (111) is stable only at low pH and the species (110) is predominating at the physiological pH. The hydrolysed species (20-1) for all dibasic acids complexes predominates only at high pH.

The formation of CBDCA complexes is confirmed by spectral measurements, Fig. 5. The band corresponding to [Pd(dmen)(H₂O)]²⁺ complex, appeared at 353 nm is shifted to 332 nm in the formation of [Pd(dmen)(HCBDCA)]⁺ complex (111 species). This band is shifted to 328 nm upon deprotonation and formation of [Pd(dmen)(CBDCA)] complex (110 species). Displacement reaction of coordinated isonine, glycine or methionine

It was shown above that N-donor ligands such as DNA constituents have affinity for [Pd(dmen)(H₂O)]²⁺, which may have important biological implications since the interaction with DNA is thought to be responsible for the anti-tumour activity of related complexes. However, the preference of Pd(I) to coordinate to S-donor ligands suggests that Pd(I)-N adducts can easily be converted into Pd-S adducts [27,28]. Consequently, the equilibrium constant for such conversion is of biological significance. Consider isonine as a typical DNA constituent (presented by HA) and cysteine as a typical thiol ligand (presented by H₂B). The equilibria involved in complex-formation and displacement reactions are

$$\text{HA} = \text{H}^+ + \text{A}^-$$

$$\text{H}_2\text{B} = 2\text{H}^+ + \text{B}^{2-}$$

$$\beta_{110}^{[\text{Pd(dmen)A}]^+} = \frac{[\text{Pd(dmen)A}]^+}{[\text{Pd(dmen)}^2+][\text{A}^-]}$$  \hspace{1cm} (6b)

$$\beta_{110}^{[\text{Pd(dmen)A}]^+} = \frac{[\text{Pd(dmen)A}]^+}{[\text{Pd(dmen)}^2+][\text{A}^-]}$$  \hspace{1cm} (6b)

$$[\text{Pd(dmen)]}^2+ + \text{B}^{2-} = [\text{Pd(dmen)B}]_\text{110}$$  \hspace{1cm} (7a)

$$\beta_{110}^{[\text{Pd(dmen)B}]^+} = \frac{[\text{Pd(dmen)B}]^+}{[\text{Pd(dmen)}^2+][\text{B}^{2-}]}$$  \hspace{1cm} (7b)

$$[\text{Pd(dmen)(A)]}^+ + \text{B}^{2-} \rightleftharpoons [\text{Pd(dmen)(B)]} + \text{A}^-$$  \hspace{1cm} (8)
The equilibrium constant for the displacement reaction given in Eq. (9) is given by

$$K_{eq} = \frac{[\text{Pd(dmen)}(B)][A^-]}{[\text{Pd(dmen)}(A)^+][B^2^-]} \quad (9)$$

Substitution from Eq. (6b) and (7b) in Eq. (10) results in:

$$K_{eq} = \frac{[\text{Pd(dmen)}B]}{[\text{Pd(dmen)}A^+]^{110}} \quad (10)$$

The potentiometric data of inosine complex is fitted considering the formation of 1:1 and 1:2 complexes and the protonated species of the 1:1 complex. The log β values are 6.51(0.04), 10.48(0.04) and 11.19(0.05) for 110, 120 and 111 species respectively. Cysteine forms 1:1 complex and its protonated species. The log β values are 16.33(0.03) and 20.59(0.03) for 110 and 111 species. Log β110 values for [Pd(dmen)(A)]⁺ and [Pd(dmen)B] complexes amount to 6.51 and 16.33, respectively and by substitution in Eq. (10) results in log $K_{eq}$ = 9.72. In the same way the equilibrium constants for the displacement of coordinated inosine by glycine and methionine are log $K_{eq}$ = 3.74 and 2.91, respectively. These values clearly indicate how sulphide ligands such as cysteine and by analogy glutathione are effective in displacing the DNA constituent, i.e., the main target in tumour chemotherapy.

4. Conclusion

In comparison of stability constants of [Pd(dmen)(H₂O)$_2$]²⁺ complexes with biorelevant ligands as amino acids, peptides and dicarboxylic acids, it would be possible to evaluate the speciation of Pd(II) complexes in biological fluid. The competition between cysteine and DNA (inosine) for reaction with DNA was investigated. The equilibrium constant for displacement of DNA by cysteine measures the deactivation of the Pt/Pd based-drug by the sulphur containing biomolecules.