ORIGINAL ARTICLE

# Determination of Stability Constants of Mixed Ligand Complexes of Palladium(II) with Venlafaxine Drug and Sulfur Ligands

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## Abstract

**Aim:** To study complex formation equilibria between [Pd(V)(H2O)2]2+ and sulphur containing amino acids (L). The concentration distribution relations of the various complex species will be evaluated. **Materials and Methods:** [Pd(FLX)Cl2] was prepared by heating PdCl2 (0.89 g, 5 mmole) in 100 mL water and KCl (0.75 g, 10 mmole) to 100.0°C for 30.0 min. After the precipitate was filtered off, it was washed sequentially with water, ethanol and diethyl ether. [Pd(V)Cl2] was converted into the diaqua form treating with two equivalents of AgNO3 overnight, and removing the AgCl precipitate by filtration through a 0.1 µm pore membrane filter. **Results and Discussion:** The acid-based equilibria of [Pd(V)(H2O)2]2+ have been characterized by fitting their potentiometric titration data to various acid–base models. The pKa1 and pK a2 values for [Pd(V)(H2O)2]2+are 4.01 and 8.15, respectively, methionine was found to form a less stable complex than S-methyl cysteine, plausibly due to the fact that the six-membered chelate ring in the former complex is energetically less favoured than the five membered ring in the latter complex. Penicillamine has three binding sites, carboxylic, amino and sulfhydryl groups. It forms the complexes 110 and 111. **Conclusion:** Study indicates that sulphur containing amino acids easily react with Pd(II) because of the great tendency of sulphur (a soft Lewis base) to form bonds with these metals (soft Lewis acids).

**Key words:** Complex formation equilibria, dicarboxylic acids, drug, potentiometric titration, venlafaxine

## INTRODUCTION

Venlafaxine is a cyclohexanol and phenylethylamine derivative that functions as a serotonin and noradrenaline reuptake inhibitor (SNRI) and is used as an antidepressive agent.[1] Venlafaxine inhibits synaptosomal reuptake of both serotonin and noradrenaline and it is also a relatively weak inhibitor of dopamine reuptake.[2] The chemical structure of venlafaxine was depicted in Figure 1.

Cisplatin (cis-[$PtCl_2(NH_3)_2$] also known as cis-DDP) is perhaps the best-known example of a small molecule metal-containing drug. Its use and effectiveness in cancer chemotherapy since the entry into the clinic in the late 1970s has been thoroughly documented.[3-5] Cisplatin is cited for treatment of germ-cell cancers, gestational trophoblastic tumors, epithelial ovarian cancer, and small cell lung cancer as well as for palliation of the bladder, cervical, nasopharyngeal, esophageal, and head and neck cancers.[6-8] In the search for new platinum anticancer 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.

There is also much interest in palladium(II) (Pd(II)) analogues because they are usually isostructural with those of platinum(II) (Pt(II)), which show a very similar coordination process and geometry. However, Pd(II) systems attain equilibrium much more quickly than Pt(II) systems (~$10^4$-$10^5$ faster kinetics). The slow formation kinetics for Pt(II) complexes generally rules out the determination of stability constants. Therefore, Pd(II) complexes are frequently used as model complexes to study

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the interaction of Pt(II) with DNA and to mimic the binding properties of various Pt(II) species.[9] It was also suggested that the faster aquation of Pd(II) compared with Pt(II) *in vitro*, makes the former a better model for studying Pt(II) reactions *in vivo*[10] with biological molecules since these reactions always start with the aquation of the Pt(II) complexes.

Investigations of the stability of the ternary complexes may, therefore, help toward understanding the driving forces which lead to the formation of such complexes in biological systems.[11] Furthermore, the stability constant of metal complexes with drugs is useful to know the proper dose of drug and their effect with all other components of blood stream as well as to measure the strength of metal ligand bonds. The aim of this paper is to study complex formation equilibria between $[Pd(V)(H_2O)_2]^{2+}$ and sulphur containing amino acids (L). The concentration distribution relations of the various complex species will be evaluated.

## EXPERIMENTAL

### Materials and reagent

$PdCl_2$, methionine, penicillamine, mercaptoethylamine, S-methylcysteine, and venlafaxine (V) were obtained from Aldrich Chem. Co. Carbonate-free NaOH (titrant) was prepared and standardized against potassium hydrogen phthalate solution daily. All solutions were prepared in deionized water.

### Preparation of $[Pd(V)(H_2O)_2]^{2+}$ complex

$Pd(FLX)Cl_2$ was prepared by heating $PdCl_2$ (0.89 g, 5 mmole) in 100 mL water and KCl (0.75 g, 10 mmole) to 100.0°C for 30.0 min. After the $K_2[PdCl_4]$ solution was cooled, venlafaxine (1.39 g, 5 mmole), dissolved in 10.0 mL water, was added dropwise to the stirred solution. A yellow precipitate formed and the mixture was stirred for a further 1 h at 25.0°C. After the precipitate was filtered off, it was washed sequentially with water, ethanol, and diethyl ether. $Pd(V)Cl_2$ was converted into the diaqua form treating with two equivalents of $AgNO_3$ overnight and removing the AgCl precipitate by filtration through a 0.1 µm pore membrane filter. Great care was taken to ensure that the resulting solution was free of $Ag^+$ ions and that the chloro complex had been converted into the aqua species, the filtrate made up to the desired volume in a standard volumetric flask.

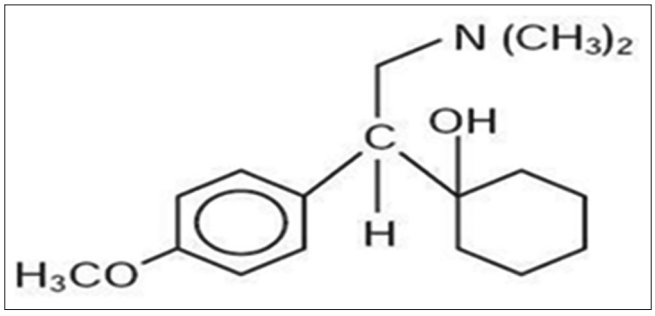



**Figure 1:** Chemical structure of venlafaxine

### Apparatus

Potentiometric titrations were performed at 25°C ± 0.1°C in a double-walled glass vessel using a Griffin pH J-300-010 G Digital pH meter. The electrode was calibrated with standard buffer solutions (pH4.0 and 10.0) before the pH measurements. The ionic strength was kept constant (0.10 mol . $dm^{-3}$) using a $NaNO_3$ solution, and a total volume of 40 $cm^{-3}$ was used for each titration. The $pk_w$ of water was calculated at 0.1 mol/L ionic strength to be 13.87 (0.05).

### Procedure and measuring technique

The acid dissociation constants of the ligands were determined potentiometrically by titrating 40 $cm^3$ of ligand solution ($1.25 \times 10^{-3}$ mol · $dm^{-3}$). The acid dissociation constants of the coordinated water molecules in $[Pd(V)(H_2O)_2)]^{2+}$ were determined by titrating a ($1.25 \times 10^{-3}$ mol · $dm^{-3}$) solution of the complex. The formation constants of the complexes were determined by titrating solution mixtures of $[Pd(V)(H_2O)_2]^{2+}$ ($1.25 \times 10^{-3}$ mol · $dm^{-3}$) and the ligand in concentration ratios

**Table 1:** Formation constants of Pd (V) complexes with S-containing amino acids at 25°C and 0.1 mol/$dm^3$ $NaNO_3$ ionic strength

| System | p | q | r[a] | logβ[b] | $pK_a$[c] |
|---|---|---|---|---|---|
| Pd (V)-OH | 1 | 0 | −1 | −4.12 (0.01) | 4.12 |
| | 1 | 0 | −2 | −12.16 (0.02) | 8.04 |
| Methionine | 0 | 1 | 1 | 9.12 (0.01) | |
| | 0 | 1 | 2 | 11.10 (0.04) | |
| | 1 | 1 | 0 | 15.75 (0.02) | |
| | 1 | 1 | 1 | 21.87 (0.03) | 6.12 |
| Penicillamine | 0 | 0 | 1 | 10.10 (0.01) | |
| | 0 | 1 | 2 | 17.97 (0.02) | |
| | 1 | 1 | 0 | 19.76 (0.03) | |
| | 1 | 1 | 1 | 25.76 (0.01) | 6.00 |
| S-methylcysteine | 0 | 1 | 1 | 8.25 (0.01) | |
| | 1 | 1 | 0 | 16.31 (0.01) | |
| | 1 | 1 | 1 | 20.44 (0.01) | 4.13 |
| Mercaptoethylamine | 0 | 0 | 1 | 10.03 (0.04) | |
| | 0 | 1 | 2 | 18.64 (0.02) | |
| | 1 | 1 | 0 | 19.87 (0.02) | |
| | 1 | 1 | 1 | 26.98 (0.03) | 7.11 |

[a]*p*, *q*, and r are the stoichiometric coefficient corresponding to Pd(V), L, and $H^+$, respectively; [b]Standard deviations are given in parentheses; [c]The $pK_a$ of the ligands, the protonated species or the aqua complexes

of 1:1 sulfur ligands. The equilibrium constants evaluated from the titration data [Table 1] are defined by Equations 1 and 2, where M, L, and H stand for the $[Pd(V)(H_2O)_2]^{2+}$ ion, ligand and proton, respectively.

$$pM+qL+rH \rightleftharpoons MpLqHr \quad (1)$$

$$\beta_{pqr} = \frac{[M_pL_qH_r]}{[M]^p[L]^q[H]^r} \quad (2)$$

(charges are omitted for simplicity)

### Data processing

The stoichiometries and stability constants of the complex species formed in solution were determined by examining various possible composition models for the systems studied. About 110-150 experimental data points were available for evaluation in each run. All the dissociation and the complex formation constants were determined using the HYPERQUAD program[12] and the speciation as a function of pH using the HYSS program.[13]

## RESULTS AND DISCUSSION

The proton dissociation constants of the ligands studied have been redetermined at 25.0°C and $I$ = 0.1 mol $dm^{-3}$ $NaNO_3$ to obtain values using the same experimental procedures as used in the determining of stability constants of the Pd(II) complexes and are in good agreement with data found in the literature.[14-17]

### Determination of the acid–base equilibria of $[Pd(V)(H_2O)_2]^{2+}$ complex

The acid–base equilibria of $Pd(V)(H_2O)_2^{2+}$ have been characterized by fitting their potentiometric titration data to various acid–base models. The fitted model, according to the aforementioned method of calculation, was found to be consistent with deprotonation of two coordinated water molecules (Equations 3 and 4).

$$[Pd(V)(H_2O)_2]^{2+} \rightleftharpoons [Pd(V)(H_2O)(OH)]^{+} + H^{+} \quad (3)$$

100 10-1

$$[Pd(V)(H_2O)(OH)]^{+} \rightleftharpoons [Pd(V)(OH)_2] + H^{+} \quad (4)$$

10-1 10-2

The $pK_{a1}$ and $pK_{a2}$ values for $[Pd(V)(H_2O)_2]^{2+}$ are 4.01 and 8.15, respectively, which are comparable with the literature values of similar systems.[18] The species distribution diagram for the hydrolyzed species is shown in Figure 2. The maximum monohydroxo concentration increases as the pH increases, it is reached 99.3 at pH range ca. from 4.8 to 7.6 that means they are the key species existing in solution in the physiological pH range. A further increase in pH is accompanied by a decrease in the monohydroxo species and an increase in dihydroxo species.

### Complex formation reactions of $[Pd(V)(H_2O)_2]^{2+}$ with amino acids containing sulfur atom in the side chain

Calculations of the stability constants of the complex species of Pd(V) with (L) are allotted in Table 1. The potentiometric titration curves for the Pd(V)-methionine system, representative, are significantly lower than the methionine titration curve [Figure 3]. This corresponds to the formation

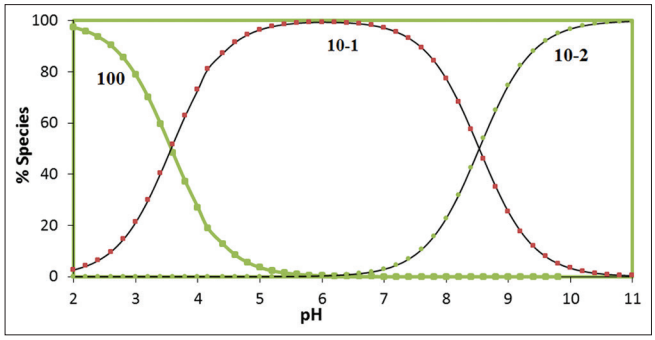



**Figure 2:** Distribution of different species as a function of pH in the hydrolysis of $Pd(V)(H_2O)_2$ system

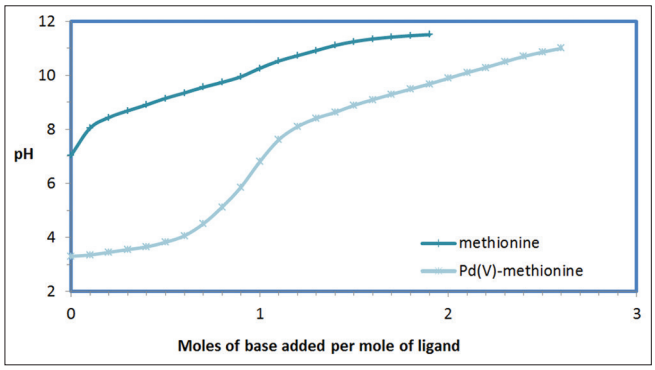



**Figure 3:** Potentiometric titration curves of Pd(V)-methionine system

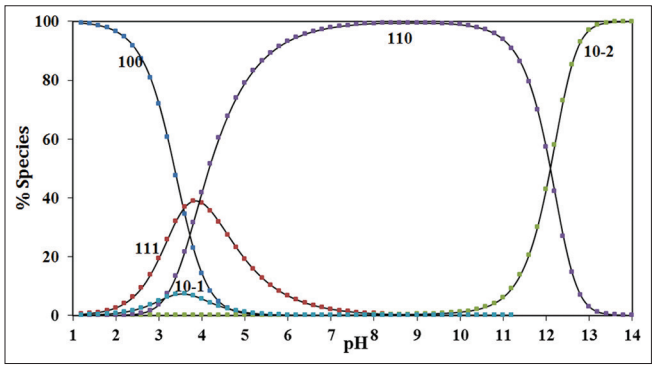
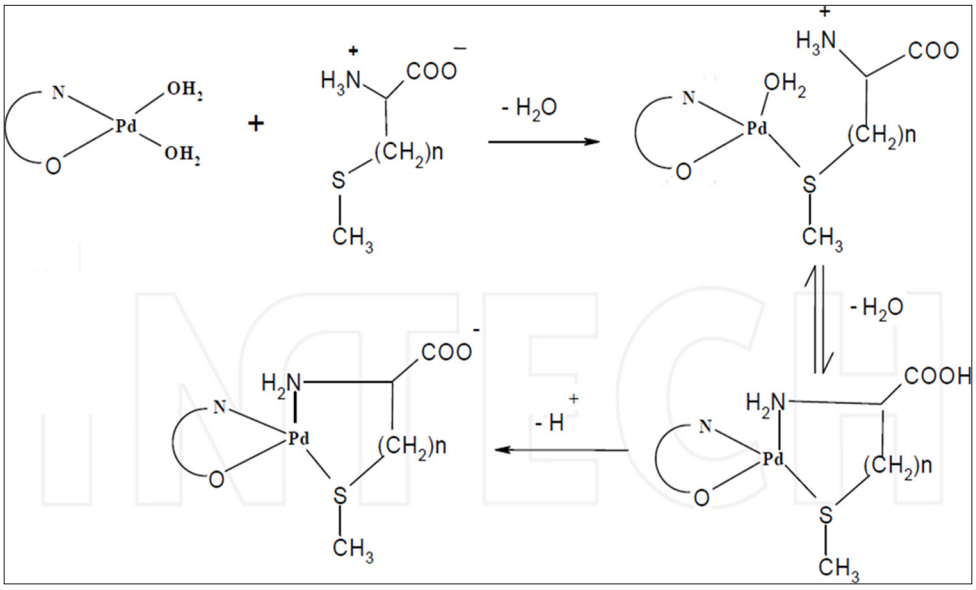



**Figure 4:** Concentration distribution of various species as a function of pH in the Pd(V)–penicillamine system




**Scheme 1:** Interaction of $[Pd(V)(H_2O)_2]^{2+}$ with S-containing amino acids

of a complex species through via release of a hydrogen ion. The stoichiometry and stability constants of the complexes formed have been determined by trying different possible composition models for the system.

Methionine was found to form a less stable complex than S-methyl cysteine, due to the fact that the six-membered chelate ring in the former complex is energetically less favored than the five-membered ring in the latter complex.

Penicillamine has three binding sites, carboxylic, amino, and sulfhydryl groups. It forms the complexes 110 and 111. The stability constant of the 110 complex is in fair agreement with that of mercaptoethylamine (where the binding sites are the amino and sulfhydryl groups) and higher than those for $\alpha$-amino acids (where the binding sites are the amino and carboxylate groups). This indicates that penicillamine interacts with Pd(II) ion by the amino and deprotonated-SH groups.

The acid dissociation constants of the protonated complexes ($pK_a = \log \beta_{111} - \log \beta_{110}$) are 6.12, 6.00, 4.14, and 7.11 for methionine, penicillamine, S-methylcysteine, and mercaptoethylamine, respectively. These values are less than the previously reported microscopic acid dissociation constants[19] of $[-NH_3]^+$ and –SH groups revealing that the $[-NH_3]^+$ and –SH groups most likely take part in complex formation.

### Species distribution curves

In all species investigated the concentration of the complex increases with increasing pH. That makes complex formation more favorable in the physiological pH range. The protonated ternary complex species have been found to be most favored at lower pH values. In order to indicate the main features observed in the species distribution plots in these system, the speciation diagram obtained for Pd-V-penicillamine is shown in Figure 4.

The reaction between $[Pd(V)(H_2O)_2]^{2+}$ and S-containing amino acids is showed in Scheme 1. At low pH values, the coordination site is through S-atom, slowly forming bidentate ligand followed by deprotonation of the carboxylic group.[20]

## CONCLUSIONS

The present investigation describes the formation equilibria of $[Pd(V)(H_2O)_2]^{2+}$, with amino acids containing sulfur atom in the side chain (L). Sulfur-containing amino acids easily react with Pd(II) because of the great tendency of sulfur (a soft Lewis base) to form bonds with these metals (soft Lewis acids). The stability constants of complexes in solution have been calculated and their concentration distributions are evaluated.

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