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Complex Formation Reactions of Palladium(II) and Amlodipine Drug with Biologically Active Ligands

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The stability constants of various complexes of $[Pd(drug)(H_2O)_2]^{2+}$ (drug = amlodipine) with peptides, (L) *viz*. glycylglycine, leucylalanine, glycylvaline, glycinamide and glutamine have been studied using potentiometric measurements. The complexes formation procedure has been predictable according to the pH range studied. A different complexes constants were determined under 0.1 mol/dm^3 $NaNO_3$ and 25 °C conditions such as stability and stoichiometries constants.

Keywords: Drug, Potentiometric studies, Solution equilibria, Stability constants, Peptides.

INTRODUCTION

An increasing in commercial and clinical importance of the therapeutic applications and uses of metal complexes have been reported. Many literature articles gave evidence to the developing significance of the discipline [1-11]. Several chelating agents used clinically may create in most pharmacopoeia [12], while other new one still being sought [13]. Due to Cu(II) free ion toxicity, many medical problems can be improved, such as using of chelating agents in treatment of Wilson's disease [14]. In order to deactivate a metalloenzyme, a wide study on metalloproteinases environment embodies a survey to design a drug from small organic ligands [15,16]. Enzymes containing zinc is related with various ailments like cancer and arthritis. Therefore, drug improvement approach is reasonable for zinc active site inhibition. Actually, because of the catalytic roles in enzymes and the diversity of enzymatic zinc structure, it considers an attractive target [17,18]. The best known example of a small molecule metal-containing drug is cisplatin, chemically (*cis*-$[PtCl_2(NH_3)_2]$. Because both Pt^{2+} and Pd^{2+} are soft Lewis acids, they prefer donors containing sulfur and nitrogen to make stronger bonds than donors containing oxygen atoms. In terms of acid dissociation constants and complex formation, Pt(II) and Pd(II) complexes perform in the identical way. Nevertheless the fact that Pt(II) complexes are less faster than the corresponding Pd(II) complexes by 10^3 to 10^5 times. This property illuminated the high toxicity of *cis*-$Pd(DACH)_2Cl_2$ and *cis*-$Pd(en)Cl_2$ when compared to the analogous Pt(II) complexes, along with their lower antitumor activity [19]. Generally, the medicinal applications of Pd(II) complexes is less. As 10^3 Pd is a radioactive isotope, it can be used as an inhibition for the growing high-grade prostate cancer [20,21]. Conversely, Das and Livingstone suggested that the best activity of N, Pd(II) and S atoms as antitumor agents can be achieved by chelating with inert ligands such as nitrogen and sulfur [22]. They have the suitable liability to transport the metal to the target (DNA) and permit the metal to interact with it. The activity of both tetracycline and Pd(II)-tetracycline complex drug as an inhibitor for growing of two *E. coli* sensitive bacterial strains are almost similar to each other. While this activity is 16 times more powerful against *E. coli* HB101/pBR322, which is resistant to tetracycline [23]. Increasing the importance of the ternary complexes, it is believed worthy to study these complexes for number of amlodipine and peptides as drug with Pd(II). Fig. 1 showed amlodipine compound, chemically 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-

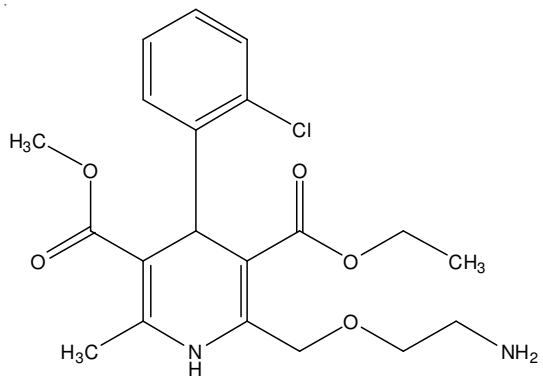

Fig. 1. Structure of amlodipine

1,4-dihydro-6-methyl-3,5-pyridinedicarboxylic acid 3-ethyl 5-methyl ester, which is a second form of the 1,4-dihydropyridine derivative of the proto-typical molecule nifedipine [24]. This compound (amlodipine) can be used in the management of mild-to-moderate essential hypertension and in the treatment of chronic stable angina. In the present study, the formation procedures of $[Pd(drug)(H_2O)_2]^{2+}$ complex with peptides were investigated. The concentration distribution diagram of the several complex species will be estimated.

EXPERIMENTAL

Amlodipine, palladium(II) chloride and peptides *e.g.*, glycylglycine, leucylala-nine, glycylvaline, glycinamide and glutamine were provided by Sigma-Aldrich without any further purification. Solutions were prepared using double distilled water.

Synthesis: $[Pd(drug)Cl_2]$ was prepared as described before [25]. $AgNO_3$ (2 equiv.) was stirred with the chloro complex overnight in order to prepare diaqua complex $[Pd(drug)(H_2O)_2]^{2+}$. The AgCl precipitate was filtrated and the filtrate was diluted in a standard volumetric flask to the required volume.

Potentiometric measurements: The titrations were carried out for 40 mL solution mixtures at 25 °C with a gentle and constant stream of N_2 over the test solutions. The ionic strength was maintained constant at 0.1 mol/L with $NaNO_3$ in all titrations. A titrant of 0.10 mol/dm^3 NaOH solution was used. A solution of 1.25×10^{-3} mol/dm^3 of the complex was titrated in order to determine the constants of acid dissociation for the coordinated water molecules in $[Pd(drug)(H_2O)_2)]^{2+}$. While a 1.25×10^{-3} mol/dm^3 of $[Pd(drug)(H_2O)_2)]^{2+}$ was titrated with a ligand solution mixture to measure the constants of complexes formation in concentration ratio of 1:1. A titrant of 0.10 mol/dm^3 of NaOH solution was used. The equilibrium constants were calculated from the titration data (Table-1) are defined by eqns. 1 and 2, where M, L and H stand for the $[Pd(drug)(H_2O)_2)]^{2+}$ ion, peptides and proton, respectively.

TABLE-1
FORMATION CONSTANTS OF Pd (DRUG) COMPLEXES WITH PEPTIDES AT 25 °C AND 0.1 mol/dm^3 $NaNO_3$ IONIC STRENGTH

System	p	q	r[a]	log β[b]	pK^H
Pd(drug)-OH	1	0	-1	-4.48 (0.01)	–
	1	0	-2	-12.15 (0.02)	
Glycylglycine	0	1	1	7.97 (0.00)	5.96
	1	1	0	9.09 (0.01)	
	1	1	-1	3.13 (0.02)	
Leucylalanine	0	1	1	8.13 (0.02)	6.91
	1	1	0	10.34 (0.01)	
	1	1	-1	3.43 (0.03)	
Glycylvaline	0	1	1	8.24 (0.01)	6.12
	1	1	0	10.23 (0.02)	
	1	1	-1	4.11 (0.01)	
Glutamine	0	1	1	8.98 (0.00)	10.45
	1	1	0	12.77 (0.02)	
	1	1	-1	2.32 (0.01)	
Glycinamide	0	1	1	7.88 (0.00)	4.67
	1	1	0	10.52 (0.02)	
	1	1	-1	5.89 (0.01)	

[a]p, q and r are the stoichiometric coefficient corresponding to Pd (drug), L and H^+ respectively.
[b]Standard deviations are given in parentheses.

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

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

A potentiometric titrations were done by Griffin pH J-300-010 G Digital pH meter at 25 ± 0.1 °C using double-walled glass vessel. A constant temperature bath was used for fixing the temperature by circulating water through the jacket. Hydrogen-ion concentrations were used to calibrate the electrode system instead of activities.

Calculations: The computer program HYPERQUAD was used for calculating the results using about 100 data points for each titration [26]. The stability constants and stoichiometries of the complexes formed were measured by trying different possible composition simulations. The results obtained are shown in Table-1. The program HYSS was used in order to obtain the concentration distribution diagrams [27] with the experimental condition used.

RESULTS AND DISCUSSION

The stability constant of the Pd(II) complexes and acid dissociation constant for the ligand were evaluated using the constant ionic strength of 0.1 mol/dm^3 $NaNO_3$ at 25 °C.

Acid–base equilibria of $[Pd(drug)(H_2O)_2]^{2+}$: Because the complex $[Pd(drug)(H_2O)_2]^{2+}$ could suffer from hydrolysis [28], the potentiometric records were fitted to numerous acid-base simulations in order to evaluate its acid-base chemistry. The results showed that the appropriate model was set up to be reliable with species composition 10-1 and 10-2 as given in eqns. 3 and 4.

$$\underset{100}{[Pd(drug)(H_2O)_2]^{2+}} \rightleftharpoons \underset{10\text{-}1}{[Pd(drug)(H_2O)(OH)]^{+}} + H^+ \quad (3)$$

$$\underset{10\text{-}1}{[Pd(drug)(H_2O)(OH)]^{+}} \rightleftharpoons \underset{10\text{-}2}{[Pd(drug)(OH)_2]} + H^+ \quad (4)$$

The distribution diagram for $[Pd(drug)(H_2O)_2]^{2+}$ and its hydrolyzed species is displayed in Fig. 2. The maximum mono-hydroxo concentration increase as the pH increase, it is reached 51.63 at pH range from 6 to 8, that means they are the key species existing in solution in the physiological pH range. Furthermore, as concentration of monohydroxo species decrease, as pH increase, the main species above a pH of about 10 (dihydroxo species) will be increased.

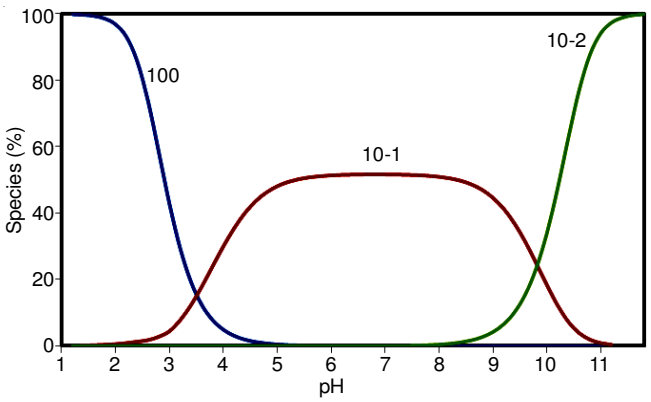

Fig. 2. Distribution of different species as a function of pH in the hydrolysis of $Pd(drug)(H_2O)_2$ system

Ternary Pd(II) complexes: The potentiometric records of the Pd(drug) peptide system were fitted by different simulations. The complexes formation with stoichiometric coefficients 110 and 11-1 give a reliable results for the most suitable model. In the 110 case, the peptide is attached through the carbonyl oxygen and amino groups. Coordination of the carbonyl and amino groups will led to form the complexes. A modification of the coordination centers from carbonyl oxygen to amide nitrogen are well predictable and would be happen after deprotonation of the amide group [29].

The peptides leucylalanine, glycylvaline and glycylglycine may coordinate through carboxyl group with the amide group in the side chain and the terminal amino group. The ligands would then act as a simple amino acid. Otherwise, the carbonyl oxygen of the amide group and the terminal amino group could also be coordinate with ligands. In some cases, existing of the amide and the carboxyl groups, could be act safely since the affinity of palladium to nitrogen donor sites is large. There is no decisive indication to ignore either of these conceivable outcomes. The peptide could be coordinate as a simple amino acids, this can be proved from the fact that the values of log β_{110} for the peptide complexes compare favourably with that of α-amino acids, taking in consideration the difference in their basicities. Considering the fact that glutaminate has a negative charge and glycinamide is neutral, the electrostatic interaction between the twofold positively charged metal complex and the glutaminate would result in a lowering of formation free energy. As a result, the glycinamide complex is less stable than the glutamine complex. The pK^H values of the amide groups, incorporated in the palladium(II) complexes (log β_{110} – log β_{11-1}) are in the range of 4.67-10.45 (Table-1). Reviewing the literature, compounds with seven membered chelate ring are more strained and less favoured, such as in glutamine complex, so its pK^H is relatively much higher than the others and it could coordinate in its protonated form under physiological conditions (pH ~ 7.4).

Previous studies mentioned many thrilling biological applications for the relative magnitudes of pK^H of the palladium(II) complexes with peptides. The deprotonated amide group can be catalyzed with $[Pd(drug)(H_2O)_2]^{2+}$ complex under normal physiological conditions (pH about 7.4) in which the catalytic action would be very explicit. A dramatic differences in peptides actions to the palladium species would be cleared based on the mild difference in their side chains.

Fig. 3 showed the diagram of concentration distribution for [Pd(drug)-glycylglycine] (110) system. As the [Pd(drug)L] complex concentration increase with increasing pH, it starts to be formed at pH.1.4 till it reached a maximum of 93.7 % at a pH of about 6.8. On the other hand, further increase in the pH will yield a decrease in [Pd(drug)L] complex concentration and an increase of [Pd(drug)LH-1] (11-1), reaching a maximum of 96 % at the pH 10.8.

Conclusion

In this work, the potentiometric results for the scheme consisting of [Pd(drug)] and peptides exhibited the formation of the complexes with stoichiometric coefficients 11-1 and 110. Because the glutamine complexes have a chelate with seven-membered ring, which could be more strained and less

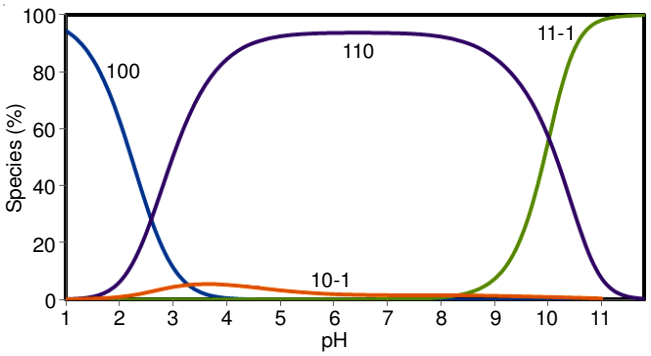

Fig. 3. Concentration distribution of different species as a function of pH in the Pd(drug)-glycylglycine system

favoured, they have a higher pK^H value, (log β_{110} – $\log_{10}\beta_{11-1}$), than the others peptides complexes. Consequently, coordination in protonated form of glutamine would be the major formula under physiological conditions (pH ~ 7.4). The concentration distribution curves of the several complex species existing in solution were estimated.

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