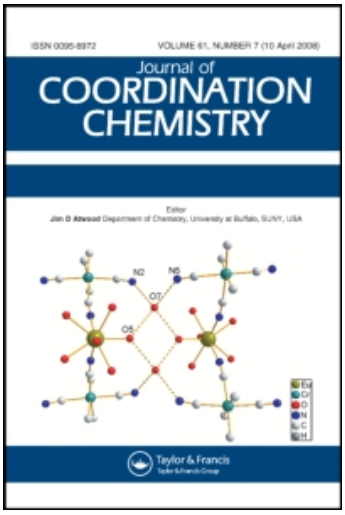

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Complex formation reactions between $[Pd(piperazine)(H_2O)_2]^{2+}$ and biorelevant ligands: synthesis and equilibrium constants

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Complex formation reactions between $[Pd(piperazine)(H_2O)_2]^{2+}$ and biorelevant ligands: synthesis and equilibrium constants

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$[Pd(pip)Cl_2]$, $[Pd(pip)(cbdca)] \cdot 2H_2O$, and $[Pd(pip)(malonate)] \cdot 2H_2O$ complexes were synthesized and characterized, where pip is piperazine and cbdca is cyclobutanedicarboxylate. The stoichiometry and stability of the complexes formed between $[Pd(pip)(H_2O)_2]^{2+}$ and various biologically relevant ligands (amino acids, peptides, DNA constituents, and dicarboxylic acids) were investigated at 25°C and 0.1 M ionic strength. The stability constant of the complexes formed in solution was determined and the binding centers of the ligands were assigned. The concentration distribution diagrams of the complexes were evaluated.

Keywords: Piperazine; Biorelevant ligands; Pd(II) complexes

1. Introduction

For decades, research articles on the subject of antitumor-inhibiting metal compounds have almost stereotypically begun with a reference to Barnet Rosenberg's discovery of the antitumor activity of cis-platin [1]. Increasing numbers of platinum complexes have failed the test of clinical evaluation [2, 3], most close cis-platin analogs. Most of these complexes have a narrow spectrum of activity and clinical use is limited by undesirable side effects [4, 5], including nephrotoxicity, ototoxicity, nausea, vomiting, and myelosuppression. 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, rational design of complexes and the study of relevant structure–activity relationships have been extended to the families of new compounds having high structural diversity [6]. Platinum(II) compounds are inert and consequently difficult to investigate complex formation equilibria. Pd(II)- and Pt(II)-amine complexes have the same structure, with five orders of magnitude higher reactivity in the case of Pd(II) complexes, but similar thermodynamic parameters. Therefore, Pd(II) complexes are good models for analogous Pt(II) complexes in solution.

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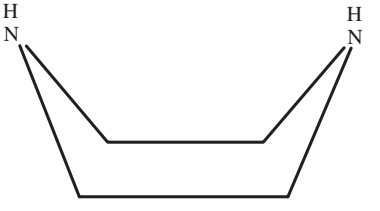
Recent work in our laboratories focused on equilibria of complex formation reactions of cis-(diamine)palladium(II) complexes with DNA, the major target in chemotherapy of tumors, and amino acids, peptides, and dicarboxylic acids and esters [7–13]. In this project, we have synthesized and characterized the $[Pd(pip)Cl_2]$, [Pd(pip)(cbdca)], and [Pd(pip)(malonate)] complexes. Complex formation equilibria between $[Pd(pip)(H_2O)_2]^{2+}$ and biorelevant ligands are investigated. The study of piperazine complexes was performed because (1) piperazine has O_6–N···H [14] and/or phosphate-N···H intramolecular hydrogen bonding [15, 16] with the Pt-DNA adduct, favoring interaction with DNA and (2) the piperazine ring may undergo stacking interactions with the sugar group of DNA, again favoring interaction with DNA. The latter effect is similar to that reported for carboplatin, where the stacking interaction between the cyclobutane ring and the sugar group is part of the increased antitumor activity [17].

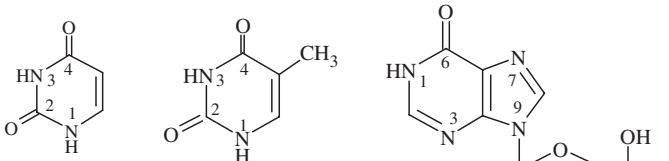


Piperazine (pip)

2. Experimental

2.1. *Materials*

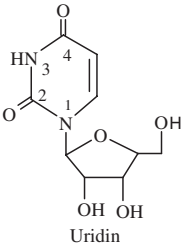
$PdCl_2$ and piperazine were obtained from Aldrich. Amino acids, glycine, alanine,



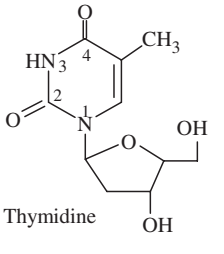
Uracil

Thymine

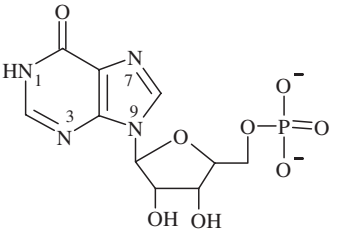
Inosine



Uridin



Thymidine



Inosine-5′-monophosphate

DL-β-phenylalanine, DL-valine, DL-proline, methylamine hydrochloride, ethanolamine hydrochloride, L-histidine, histamine dihydrochloride, L-Threonine, imidazole, tryptophan, and methionine were provided by Sigma Chemical Co. The peptides used (glycinamide, glycylglycine, asparagine, and glutamine) and the dibasic acids used (cyclobutane dicarboxylic acid, malonic acid, oxalic acid, succinic acid, and adipic acid) were all provided by BDH Biochemicals Ltd, Poole, England. The DNA constituents (inosine, inosine-5′-monophosphate, uracil, thymine, thymidine, and uridine) were provided by Sigma Chemical Co. Ligands in the form of hydrochlorides were converted into the corresponding hydronitrates. The nucleotides were prepared in the protonated form with standard HNO_3 solution. All solutions were prepared in deionized water.

[Pd(pip)Cl_2] was prepared by heating $PdCl_2$ (0.177 g, 1.0 mM) and KCl (0.149 g, 2.0 mM) in 10 mL water to 70°C with stirring. The clear solution of $[PdCl_4]^{2-}$ was filtered and piperazine (0.086 g, 1.0 mM) dissolved in 10 mL H_2O was added dropwise to the stirred solution. The pH value was adjusted to 2–3 by the addition of HCl and/or NaOH. An yellowish-brown precipitate of [Pd(pip)Cl_2] formed and was stirred for an additional 30 min at 50°C. After filtering off the precipitate, it was thoroughly washed with H_2O, ethanol, and diethylether. Yellow powder was obtained. $C_4H_{10}N_2PdCl_2 \cdot 1/2H_2O$: Calcd (%): C, 17.61; H, 4.03; N, 10.2. Found (%): C, 17.42; H, 4.02; N, 10.1. [Pd(pip)Cl_2] was converted into the corresponding aqua complex [11] in solution by the addition of two equivalents of $AgNO_3$, heating to 40–50°C for 3 h, and removing the precipitated AgCl by filtration.

[Pd(pip)(cbdca)] and Pd(pip)(malonate) complexes were synthesized by mixing [Pd(pip)Cl_2] (0.112 g, 0.41 mM) with $AgNO_3$ (0.139 g, 0.82 mM) in 10 mL H_2O; the mixture was stirred in the dark for 24 h. White precipitate (AgCl) was filtered off and the filtrate was added to the dicarboxylic acid, dissolved in 10 mL H_2O (0.059 g, 0.41 mM) for cyclobutanedicarboxylic acid and (0.043 g, 0.41 mM) for malonic acid. The pH value was adjusted between 4 and 5 with NaOH and the solution was stirred for an additional 2 h at 60°C and stored at 4°C overnight. The precipitated complexes were isolated by filtration, washed with water, ethanol, and finally diethylether. The analytical data for Pd(pip)(cbdca) $\cdot 2H_2O$ ($C_{10}H_{18}N_2O_6Pd$): Calcd (%): C, 32.3; H, 4.8; N, 7.5. Found (%): C, 31.8; H, 4.4; N, 7.2. The analytical data for Pd(pip)(malonate) $\cdot 2H_2O$ ($C_7H_{16}N_2O_6Pd$): Calcd (%): C, 23.9; H, 4.5; N, 7.9. Found (%): C, 23.8; H, 4.3; N, 7.6.

2.2. *Apparatus*

Potentiometric titrations were performed with a Metrohm 686 titroprocessor equipped with a 665 Dosimat. The titroprocessor and electrode were calibrated with standard buffer solutions, prepared according to NBS specification [18]. All titrations were carried out at 25.0 ± 0.1°C in purified nitrogen using a titration vessel described previously [19]. IR spectra were measured on a 8001-PC FT-IR Shimadzu spectrophotometer using KBr pellets. A Shimadzu TGA-50H thermal analyzer was used to record simultaneously TGA and the differential curves. The measurements were carried out in N_2 (20 mL min^{-1}) with a heating rate of 10°C min^{-1} from 20 to 800°C using platinum crucibles.

2.3. *Procedure and measuring technique*

Acid dissociation constants of the ligands were determined by titrating 0.20 mM samples of each with standard NaOH solutions. Ligands were converted into their protonated form with standard HNO_3 solutions. Acid dissociation constants of the coordinated water in $[Pd(pip)(H_2O)_2]^{2+}$ were determined by titrating 0.20 mM of complex with standard 0.05 M NaOH solution. The formation constants of the complexes were determined by titrating solution mixtures of $[Pd(pip)(H_2O)_2]^{2+}$ (0.20 mM) and the ligand in the concentration ratio of 1 : 1 for amino acids, peptides, and dicarboxylic acids and in the ratio of 1 : 2 (Pd : ligand) for DNA constituents. The titrated solution 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 $NaNO_3$). A standard 0.05 M NaOH solution was used as a titrant. The pH meter readings were converted to hydrogen ion concentration by titrating a standard HNO_3 solution (0.01 M), the ionic strength of which was adjusted to 0.1 M with $NaNO_3$, with standard NaOH (0.05 M) at 25°C. The pH was plotted against p[H]. The relationship pH–p[H] = 0.05 was observed. The species formed were characterized by the general equilibrium

$$pM + qL + rH \rightleftharpoons (M)_p(L)_q(H)_r$$

For which the formation constants are given by

$$\beta_{pqr} = \frac{[(M)_p(L)_q(H)_r]}{[M]^p[L]^q[H]^r}$$

where M, L, and H stand for $[Pd(pip)(H_2O)_2]^{2+}$ ion, ligand, and proton. The calculations were performed using MINIQUAD-75 [20]. The stoichiometry and stability constants of the complexes formed were determined by trying various composition models for the systems studied. The model selected was that which gave the best statistical fit and was chemically consistent with the magnitudes of various residuals, as described elsewhere [20]. Tables 1–4 list the stability constants together with their standard deviations (SDs) and the sum of the squares of the residuals derived from the MINIQUAD output. The concentration distribution diagrams were obtained with the program SPECIES [21] under the experimental condition used.

3. Results and discussion

The acid dissociation constants of the ligands were determined at 25°C and constant 0.10 M ionic strength (adjusted with $NaNO_3$), as were the stability constants of the Pd(II) complexes. The results obtained are in good agreement with literature data [7, 10].

3.1. *Hydrolysis of $[Pd(pip)(H_2O)_2]^{2+}$*

The $[Pd(pip)(H_2O)_2]^{2+}$ may undergo hydrolysis. Its acid–base chemistry was characterized by fitting the potentiometric data to various acid–base models. The best-fit model was consistent with formation of three species: 10-1, 10-2, and 20-1, as given in reactions (1)–(3). Trials were made to fit the potentiometric data assuming the

Table 1. Formation constants for complexes of $[Pd(pip)(H_2O)_2]^{2+}$ with amino acids at 25°C and 0.1 M ionic strength.

System	M	L	H[a]	log β[b]	pK_a[c]	S[d]
$[Pd(pip)]^{2+}$-OH	1	0	−1	−4.95(0.015)	4.95	1.6E-8
	1	0	−2	−14.78(0.03)	9.83	
	2	0	−1	−1.43(0.031)		
Glycine	0	1	1	9.60(0.01)	9.6	1.6E-7
	0	1	2	11.93(0.02)	2.33	
	1	1	0	9.54(0.04)		8.6E-8
Alanine	0	1	1	9.96(0.01)	9.96	9.3E-8
	0	1	2	11.89(0.01)	1.93	
	1	1	0	9.71(0.03)		1.3E-7
β-Alanine	0	1	1	10.11(0.02)	10.11	9.3E-8
	0	1	2	13.75(0.03)	3.64	
	1	1	0	9.45(0.03)		5.8E-8
	1	1	1	13.86(0.05)	4.41	
β-Phenylalanine	0	1	1	9.12(0.01)	9.12	9.3E-8
	0	1	2	11.01(0.03)	1.89	
	1	1	0	8.86(0.10)		3.6E-8
DL-Valine	0	1	1	9.57(0.01)	9.57	9.9E-8
	0	1	2	11.70(0.03)	2.13	
	1	1	0	8.437(0.07)		7.6E-8
DL-Proline	0	1	1	10.52(0.01)	10.52	4.4E-8
	0	1	2	12.03(0.03)	1.51	
	1	1	0	10.00(0.03)		6.3E-8
Methylamine	0	1	1	10.03(0.04)	10.03	4.4E-7
	1	1	0	8.73(0.08)		2.9E-8
	1	2	0	15.04(0.10)		
Tryptophan	0	1	1	9.52(0.01)	9.52	3.2E-8
	1	1	0	8.52(0.11)		4.1E-8
L-Threonine	0	1	1	9.11(0.01)	9.11	7.0E-8
	0	1	2	11.32(0.02)	2.21	
	1	1	0	8.84(0.03)	7.82	9.3E-8
	1	1	−1	1.02(0.06)		
Ethanolamine	0	1	1	7.94 (0.01)	7.94	5.5E-8
	1	1	0	6.65(0.03)	5.81	5.4E-8
	1	1	−1	0.84(0.03)		
L-Histidine	0	1	1	9.53(0.01)	9.53	1.8E-8
	0	1	2	15.81(0.01)	6.28	
	1	1	0	12.58(0.06)		1.6E-7
Histamine	0	1	1	9.88(0.01)	9.88	2.4E-8
	0	1	2	15.97(0.01)	6.09	
	1	1	0	11.19(0.13)		1.7E-8
Imidazole	0	1	1	7.04(0.01)	7.04	1.7E-8
	1	1	0	6.15(0.04)		7.1E-9
	1	2	0	11.86(0.03)		
Methionine	0	1	1	8.76(0.01)	8.76	3.4E-8
	1	1	0	7.18(0.06)		1.4E-7

[a]M, L, and H are the stoichiometric coefficients corresponding to Pd(pip), amino acid, and H^+, respectively; the coefficient −1 refers to a proton loss.
[b]log β of Pd(pip)-amino acids. SDs are given in parentheses.
[c]The pK_a of the ligands, the protonated species or the aquo complexes.
[d]S – sum of square of residuals.

Table 2. Formation constants for complexes of $[Pd(pip)(H_2O)_2]^{2+}$ with peptides at 25°C and 0.1 M ionic strength.

System	M	L	H[a]	$\log\beta$[b]	pK_a[c]	S[d]
Glycinamide	0	1	1	7.88(0.00)	7.88	4.6E-8
	1	1	0	7.41(0.05)	5.02	3.4E-7
	1	1	−1	2.39(0.05)		
Glycylglycine	0	1	1	7.97(0.01)	7.97	2.5E-8
	0	1	2	11.01(0.01)	3.04	
	1	1	0	7.48(0.02)	6.99	3.42E-8
	1	1	−1	0.49(0.04)		
DL-aspargine	0	1	1	8.55(0.01)	8.55	5.9E-8
	0	1	2	10.79(0.03)	2.24	
	1	1	0	9.12(0.03)	6.84	8.46E-8
	1	1	−1	2.28(0.04)		
L-glutamine	0	1	1	9.00(0.01)	9.00	1.1E-8
	0	1	2	11.19(0.02)	2.19	
	1	1	0	8.99(0.02)	7.60	3.7E-8
	1	1	−1	1.39(0.06)		

[a]M, L, and H are the stoichiometric coefficients corresponding to Pd(pip), peptides, and H^+, respectively; the coefficient −1 refers to a proton loss.
[b]$\log\beta$ of Pd(pip)-peptides. SDs are given in parentheses.
[c]The complex pK_a of the peptides or of the peptide NH ionization.
[d]S – sum of square of residuals.

Table 3. Formation constants for complexes of $[Pd(pip)(H_2O)_2]^{2+}$ with dibasic acids at 25°C and 0.1 M ionic strength.

System	M	L	H[a]	$\log\beta$[b]	pK_a[c]	S[d]
Cyclobutane-1,1-dicarboxylic acid (CBDCA)	0	1	1	5.54(0.01)	5.54	9.6E-9
	0	1	2	8.77(0.01)	3.23	
	1	1	0	5.61(0.11)		8.4E-8
	1	1	1	10.04(0.17)	4.43	
Oxalic acid	0	1	1	4.10(0.01)	4.10	1.1E-7
	0	1	2	5.78(0.06)	1.68	
	1	1	0	5.74(0.14)		1.7E-7
	1	1	1	10.61(0.16)	4.87	
Malonic acid	0	1	1	5.42(0.01)	5.42	2.8E-8
	0	1	2	8.19(0.01)	2.77	
	1	1	0	5.11(0.13)		1.4E-7
	1	1	1	9.69(0.17)	4.58	
Succinic acid	0	1	1	5.35(0.00)	5.35	1.8E-8
	0	1	2	9.41(0.01)	4.06	
	1	1	0	4.31(0.05)		2.8E-8
	1	1	1	8.10(0.08)	3.79	
Adipic acid	0	1	1	5.28(0.01)	5.28	1.1E-7
	0	1	2	9.61(0.01)	4.33	
	1	1	0	3.81(0.04)		2.3E-8
	1	1	1	7.92(0.08)	4.11	

[a]M, L, and H are the stoichiometric coefficients corresponding to Pd(pip), dibasic acids, and H^+, respectively.
[b]$\log\beta$ of Pd(pip)-dibasic acids. SDs are given in parentheses.
[c]The pK_a of the protonated species ($\log\beta_{111}$–$\log\beta_{110}$).
[d]S – sum of square of residuals.

Table 4. Formation constants for complexes of $[Pd(pip)(H_2O)_2]^{2+}$ with DNA units at 25°C and 0.1 M ionic strength.

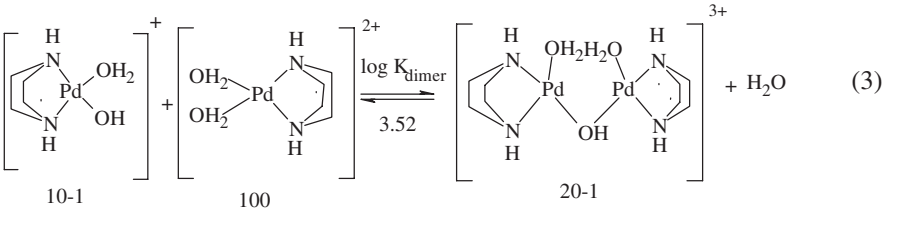
System	M	L	H[a]	log β[b]	pK_a[c]	S[d]
Uracil	0	1	1	9.28 (0.00)	9.28	2.4E-8
	1	1	0	8.69(0.03)		3.9E-9
	1	2	0	15.58(0.04)		
Uridine	0	1	1	9.01(0.01)	9.01	1.1E-7
	1	1	0	8.54(0.03)		6.8E-9
	1	2	0	14.70(0.06)		
Thymine	0	1	1	9.58(0.00)	9.58	8.7E-8
	1	1	0	8.95(0.04)		9.0E-9
	1	2	0	15.86(0.07)		
Thymidine	0	1	1	9.55(0.04)	9.55	6.4E-8
	1	1	0	8.92(0.03)		7.4E-9
	1	2	0	15.26(0.07)		
Inosine	0	1	1	8.43(0.01)	8.43	4.1E-8
	1	1	0	6.87(0.04)		6.5E-9
	1	2	0	11.52(0.06)		
	1	1	1	11.70(0.04)	4.83	
Inosine-5′-monophosphate	0	1	1	8.95(0.01)	8.95	4.8E-8
	0	1	2	15.27(0.02)	6.32	
	0	1	3	17.10(0.06)		
	1	1	0	8.56(0.04)		2.4E-8
	1	2	0	13.54(0.05)		
	1	1	1	14.54(0.03)	5.98	

[a]M, L, and H are the stoichiometric coefficients corresponding to Pd(pip), DNA units, and H^+, respectively.
[b]log β of Pd(pip)-DNA units. SDs are given in parentheses.
[c]The pK_a of the protonated species (log β_{111}–log β_{110}).
[d]S – sum of square of residuals.

formation of the monohydroxo-bridged dimer, 20-2, but this resulted in a very poor fit to the data. The bridged species 20-1 was detected by Nagy *et al*. [22] for a similar system. Also, this hydrolyzed species was formed with Be(II) complex [23].

$$\underset{(100)}{\left[Pd(pip)(H_2O)_2\right]^2} + \overset{pKa_1}{\rightleftharpoons} \underset{(10\text{-}1)}{[Pd(pip)(H_2O)(OH)]^+} + H^+ \quad (1)$$

$$\underset{(10\text{-}1)}{[Pd(pip)(H_2O)(OH)]^+} \overset{pKa_2}{\rightleftharpoons} \underset{(10\text{-}2)}{\left[Pd(pip)(OH)_2\right]} + H^+ \quad (2)$$



(3)

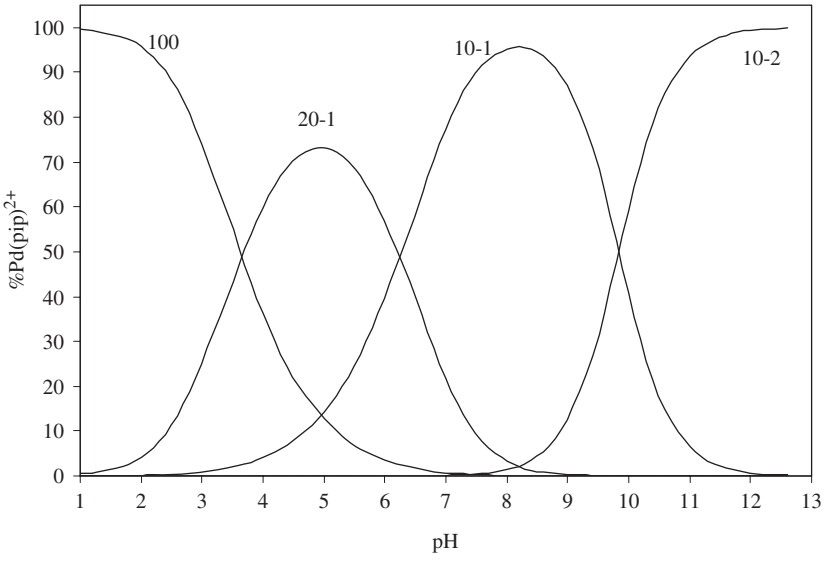


Figure 1. Concentration distribution of various species as a function of pH in the hydrolysis of $[Pd(pip)(H_2O)_2]^{2+}$ complex system (at concentration of 1.25 mM L^{-1} for Pd(pip)).

The pK_{a1} and pK_{a2} values for $[Pd(pip)(H_2O)_2]^{2+}$ are 4.95 and 9.83, respectively. The equilibrium constant for the dimerization reaction (3) calculated by equation (4) is 3.52.

$$\log K_{dimer} = \log \beta_{20\text{-}1} - \log \beta_{10\text{-}1} = -1.43 - (-4.95) = 3.52 \quad (4)$$

The distribution diagram for $[Pd(pip)(H_2O)_2]^{2+}$ and its hydrolyzed species is given in figure 1. The dimer with a single hydroxyl bridge reaches a maximum concentration of 73% at pH 5, whereas the concentration of the monohydroxo species (10-1) increases with increasing of pH reaching a maximum concentration of 95% at pH 8. A further increase in pH is accompanied by an increase in the dihydroxo species (10-2), which is the main species with pH above ~10.0. This reveals that in the physiological pH range,that is, at pH 6–7, the monohydroxo complex (10-1) predominates and can interact with the DNA subunits. At higher pH, the less active dihydroxo complex will be the major species, and consequently the ability of DNA to bind the Pd(amine) complex will decrease significantly.

3.2. *Amino acid complexes*

The analysis of the titration data for the Pd(pip)-amino acid system showed the formation of 1 : 1 species. Threonine has an extra binding center on the β-alcoholate group. This group was reported [24] to participate in metal complex formation. The potentiometric data are much better fit assuming the formation of complex species 110 and 11-1. This reveals that the β-alcoholate group participates in complex formation through induced ionization of the alcoholic group forming 11-1. The pK^H of the β-alcoholate incorporated in the Pd(II) complex ($\log \beta_{110}$–$\log \beta_{11\text{-}1}$) is 7.82. Also, ethanolamine forms the complex species 110 and 11-1, and the $\log \beta_{110}$ value for

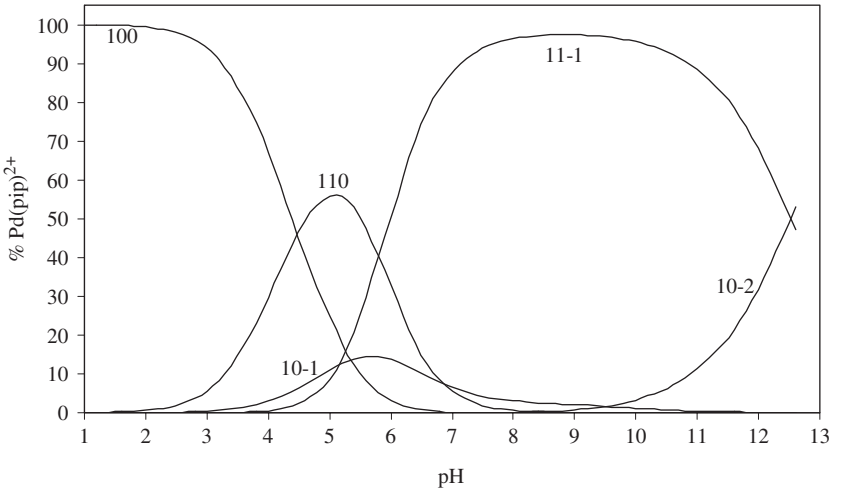


Figure 2. Concentration distribution of various species as a function of pH in the Pd(pip)-ethanolamine system (at concentration of 1.25 mM L^{-1} for $Pd(pip)^{2+}$ and ethanolamine).

ethanolamine complex is smaller than that for threonine. This may be due to the coordination of ethanolamine at low pH occurring through the amino and neutral alcohol groups, while in the case of threonine the coordination is through amino and carboxylate. At high pH, the hydroxyl is coordinated and undergoes induced ionization forming 11-1. The pK^{H} value of the coordinated alcohol in ethanolamine (5.81) is smaller than that of threonine, consistent with the reaction scheme where the alcohol in ethanolamine is coordinated to $Pd(pip)^{2+}$, while the threonine alcohol is competing with the carboxylate in binding to $Pd(pip)^{2+}$. Due to the coordination of the alcohol, the OH bond is considerably weakened and the ionization of a proton occurs at lower pH.

The distribution diagram for the ethanolamine complex, given in figure 2, shows that the complex species with coefficients 110 reaches the maximum degree of formation (58%) at pH 5.0. However, the species 11-1 starts to form after pH 4.0 and attains the maximum concentration of ~98% at pH ~7.0; i.e. in the physiological pH range.

3.3. *Peptide complexes*

The analysis of the potentiometric data for the peptide complexes reveals the formation of complexes with stoichiometric coefficients 110 and 11-1 according to the following equilibria (5) and (6), where HL is glycinamide, glycylglycine, aspargine, and glutamine.

$$\left[Pd(pip)(H_2O)_2\right]^{2+} + L^- \overset{K}{\rightleftharpoons} \underset{(110)}{[Pd(pip)L]^+} + 2H_2O \tag{5}$$

$$[Pd(pip)L]^+ \overset{K^H}{\rightleftharpoons} \underset{(11\text{-}1)}{[Pd(pip)LH_{-1}]} + H^+ \tag{6}$$

The 110 complex is formed *via* the coordination of amine and carbonyl. On increasing pH, the coordination site should switch from carbonyl to amide with the release of

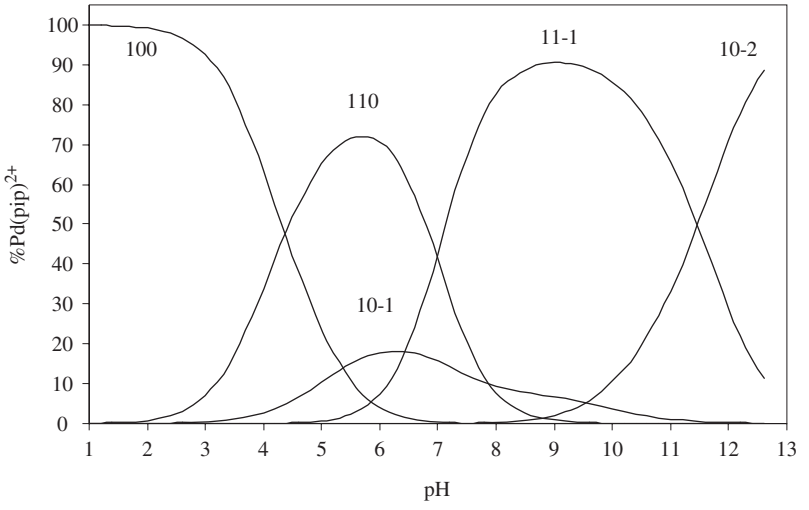


Figure 3. Concentration distribution of various species as a function of pH in the Pd(pip)-glycylglycine system (at concentration of 1.25 mM L^{-1} for $Pd(pip)^{2+}$ and glycylglycine).

amide hydrogen forming [Pd(pip)(LH_{-1})]. Such changes in coordination centers are well documented [25, 26]. The pK^H values of the amide groups incorporated in the Pd(II) complexes ($\log \beta_{110}$–$\log \beta_{11\text{-}1}$) are in the 5.02–7.60 range. The relative magnitude of the pK^H values of the Pd(II) complexes with peptides has interesting biological implications. Under normal physiological conditions (pH 6–7), the peptide would coordinate to $[Pd(pip)(H_2O)_2]^{2+}$ in entirely different fashions. Glutamine and aspargine would exist solely in the protonated form, whereas glycinamide would be present entirely in the deprotonated form. In addition, the slight difference in the side chain of the peptides produces dramatic differences in their behavior towards palladium. pK^H for glycinamide complex is lower than those of other peptides, signifying that the more bulky substituent on the peptide hinders the structural change in going from protonated to deprotonated complexes. The pK^H of the glutamine complex is markedly higher than those for the other peptide complexes. This is ascribed to the formation of a seven-membered chelate ring, which would probably be more strained and therefore less favored.

The speciation diagram of glycylglycine complex is given in figure 3. The $Pd(pip)(L)^+$ (110) species starts to form at pH 2.0, and with increasing of pH its concentration increases reaching 72% at pH 5.5. Further increase of pH is accompanied by a decrease in $Pd(pip)(L)^+$ concentration and an increase of Pd(pip)(LH_{-1}) formation.

3.4. *Dicarboxylic acid complexes*

The potentiometric data of Pd(pip)-dicarboxylic acid complexes is best fitted considering formation of the 1 : 1 species and its protonated form. The results in table 3 show that oxalic acid complex forming a five-membered chelate ring is most stable, which is consistent with recently published results on V(IV) complex [27]. The adipic acid complex is the least stable as the complex involves the formation of the least

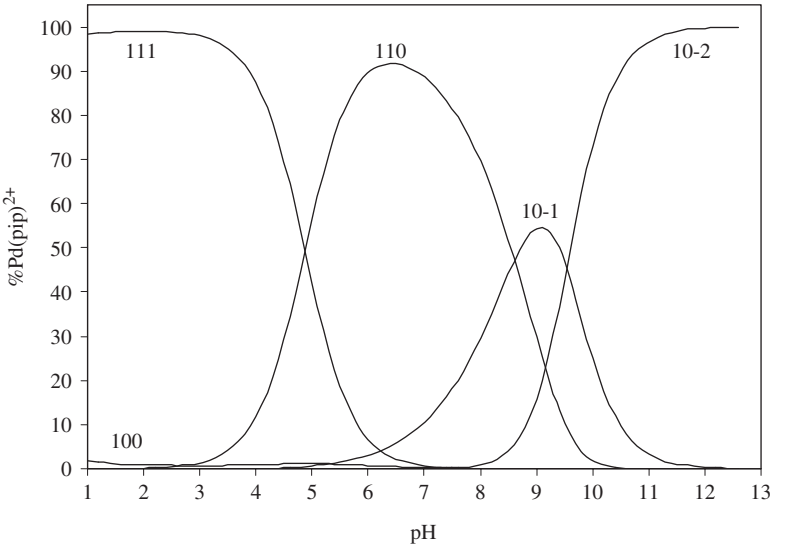


Figure 4. Concentration distribution of various species as a function of pH in the Pd(pip)-oxalic acid system (at concentration of 1.25 mM L^{-1} for $Pd(pip)^{2+}$ and oxalic acid).

stable eight-membered chelate ring. The pK_a values of the protonated species for $[Pd(pip)HL]^+$ are in the range 3.84–4.87, lower than those for HL^-. The lowering of the pK_a is due to the acidification of the second carboxylic acid group upon coordination of Pd(II) to one carboxylate group [28].

The concentration distribution diagram of the oxalic acid complex is given in figure 4. The monoprotonated species attains its maximum concentration of 98% at pH 3.2. This form has one coordination site available for binding to DNA. Such species was documented to be the active form in the case of carboplatin [17].

3.5. *DNA complexes*

DNA constituents such as the pyrimidines uracil, uridine, thymine, and thymidine have basic nitrogen donors (N_3) [29] as reflected from the high pK_a values of pyrimidines ($pK_a > 9$). They form 1 : 1 and 1 : 2 complexes predominating above pH 8.5. The thymine complex is more stable than that of uridine, probably due to the high basicity of the N_3 group of thymine resulting from the extra electron-donating methyl. Inosine has two coordination sites, N_1H and N_7H. The pK_a value of N_7H is too low to determine by potentiometry. The pK_a of N_1H group is 8.43, in agreement with that obtained previously [26]. Inosine-5′-monophosphate has, in addition, a phosphate as binding site. The pK_a of the phosphate is 6.32. This value compares favorably with recently published data for phosphates; the pK_a value of phosphate group of adenosine-5′-triphosphate is 6.21 ($I = 0.5$ M $NaClO_4$, $T = 25°C$) [30]. Inosine and its nucleotides inosine-5′-monophosphate form the monoprotonated complex, in addition to the formation of 1 : 1 and 1 : 2 complexes. The pK_a of the protonated inosine complex is

4.83; this value corresponds to N_1H. The lowering of this value with respect to that of free inosine ($pK_a = 8.43$) is due to acidification upon complex formation [31, 32].

3.6. *Characterization of solid complexes*

The dichloro complex is insoluble in water, whereas the cbdca and malonate complexes are soluble in water. All the complexes are stable in air allowing physical measurements. The IR spectra of $[Pd(pip)Cl_2]$, $[Pd(pip)cbdca] \cdot 2H_2O$, and $[Pd(pip)malonate] \cdot 2H_2O$ exhibit bands for $\delta(NH_2)$ at 1448, 1458, and 1567 cm^{-1}, respectively. The stretching vibration bands corresponding to ν_{Pd-N} were assigned at 450, 465, and 525 cm^{-1} for $[Pd(pip)Cl_2]$, $[Pd(pip)cbdca] \cdot 2H_2O$ and $[Pd(pip)malonate] \cdot 2H_2O$, respectively. The $\nu_{C=O}$ and ν_{C-O} are observed at 1704 and 1288 cm^{-1}, respectively, for uncoordinated COOH in cyclobutane dicarboxylic acid with $\nu_{C=O}$ shifting to 1623 cm^{-1} in $[Pd(pip)cbdca] \cdot 2H_2O$ spectrum, while ν_{C-O} shifted to higher frequency at 1377 cm^{-1}. This indicates unidentate coordination [33]. The stretching vibrations of $\nu_{C=O}$ and ν_{C-O} are at 1773 and 1244 cm^{-1}, respectively, for uncoordinated COOH in malonic acid with $\nu_{C=O}$ shifting to lower frequency at 1567 cm^{-1} in $[Pd(pip)malonate] \cdot 2H_2O$ and ν_{C-O} shifting to higher frequency at 1367 cm^{-1}. This also indicates unidentate coordination.

Lattice water of $[Pd(pip)Cl_2] \cdot 1/2H_2O$, $[Pd(pip)cbdca] \cdot 2H_2O$, and $[Pd(pip)malonate] \cdot 2H_2O$ were observed at 3430.7, 3443.1, and 3405.6 cm^{-1}, respectively. They are not removed even by extensive drying in vacuum. The presence of water in the complexes was confirmed by TGA experiments in N_2.

The thermogravimeteric analysis of the complexes exhibits mass loss in the temperature range 50–80°C corresponding to loss of water for the complexes. These results are consistent with analytical data.

4. Conclusion

This study describes the complex formation equilibria of $[Pd(pip)(H_2O)_2]^{2+}$ with biorelevant ligands. From a combination of stability constant data of such diaqua complexes with amino acids, peptides, DNA constituents, and dicarboxylic acids, it is possible to calculate the equilibrium distribution of the complex species in biological fluids. The $[Pd(pip)(cbdca)] \cdot 2H_2O$ and $[Pd(pip)(malonate)] \cdot 2H_2O$ complexes were synthesized and characterized.

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