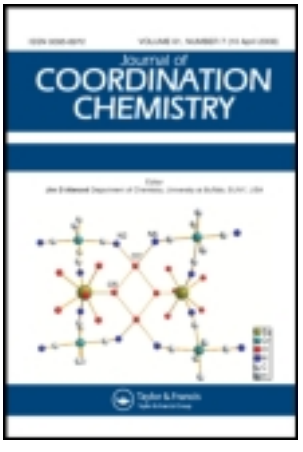

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Potentiometric studies of the interaction of amine-bridged dinuclear palladium(II) complex with nitrogen bases

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Potentiometric studies of the interaction of amine-bridged dinuclear palladium(II) complex with nitrogen bases§

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Complexes formed by interaction of *trans*-diamminepalladium(II) chloride (Pd^{II}) with 1,6-hexanediamine (HDA) and nitrogen bases (B) (imidazole derivatives or methylamine) are investigated at 25°C and 0.1 mol L^{-1} $NaNO_3$ ionic strength using potentiometric measurements. The stability constants of all possible mononuclear and binuclear complexes were determined. The concentration distribution diagram of the binuclear Pd^{II}-HDA-Im derivative reveals the complexes predominating in the physiological pH range; the reaction of the binuclear Pd^{II}-HDA-Pd^{II} with imidazole derivatives is quite feasible.

Keywords: Binuclear complexes; Pd(II); Stability constant

1. Introduction

Cis-platin [cis-diamminedichloroplatinum(II)] is one of the most active anti-tumor agents in clinical use [1]. However, it has a narrow spectrum of activity, and its clinical use is limited by undesirable side effects, including nephrotoxicity, ototoxicity, neurotoxicity, nausea, vomiting, and myelosuppression [2, 3]. In the search for new platinum anticancer drugs, efforts are devoted to complexes more efficient and less toxic than the 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 structural diversity [4, 5].

Recently a variety of bridged platinum complexes with potential cytostatic activity were developed [6] to generate more effective substances than *cisplatin*. Di and trinuclear platinum structural motifs offer a series of potent anticancer compounds with a variety of DNA binding modes [7, 8]. Their chemistry and biological activities may be modulated by the geometry and number of leaving groups in the coordination sphere as well as the nature of the di/polyamine linking the platinum centers. The first of these complexes to enter clinical trials, BBR3464, [{*trans*-$PtCl(NH_3)_2$}$_2$-meo-{*trans*-$Pt(NH_3)_2(NH_2(CH_2)_6NH_2)_2$}]$(NO_3)_4$, showed some responses in cancers not usually

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§Dedicated to Prof. M.H. Elnagdi on the occasion of his 70th birthday.

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sensitive to cisplatin [7, 8]. The high activity of this class of complexes may be explained on the assumption that the aliphatic chain of 1,6-diaminohexane is a flexible bridge leading to interstrand cross-links with Im, which persist longer than intrastrand cross-links and are considered to be less susceptible to repair as both strands are affected by the damage.

Complex-formation equilibria of binuclear Pt^{II} complexes are of biological significance giving a model for the behavior of these complexes in biological fluids. Pt^{II}- and Pd^{II}-amine complexes have the same structures, with five orders of magnitude higher reactivity for Pd^{II} complexes but similar thermodynamic parameters. Therefore, Pd^{II} complexes are considered good models for the analogous Pt^{II} complexes in solution.

Recent work in our laboratories has focused on equilibria of complex-formation reactions of *cis*-(diamine)palladium(II) complexes with bio-relevant ligands, such as amino acids, peptides, dicarboxylic acids, and DNA constituents [9–15]. In this study of complex formation involving *trans*-diamminepalladium(II), 1,6-hexanediamine (HDA), imidazole derivatives and methylamine are investigated.

2. Experimental

2.1. *Materials and reagents*

All reagents were of analytical grade. *trans*-Diamminepalladium(II) chloride, *trans*-$Pd(NH_3)_2Cl_2$ and 1,6-HDA were obtained from Aldrich Chem. Co. The nitrogen base used (B), imidazole (Im), methylimidazole (MeIm), dimethylimidazole (Me_2Im) and methylamine (MeA) were provided by Sigma Chem. Co. *trans*-$Pd(NH_3)_2Cl_2$ was converted into the diaqua complex by treating it with two equivalents of $AgNO_3$ as described before [16]; fresh solution was used to avoid isomerization of *trans*-$Pd(NH_3)_2(H_2O)_2^{2+}$. 1,6-HDA, imidazole derivatives and methylamine solutions were prepared in the protonated form with standard HNO_3 solution. All solutions were prepared in deionized water.

2.2. *Apparatus*

Potentiometric titrations were performed with a Metrohm 751 GPD titrino equipped with an internal dosimat and 728 stirrer. The titrino and electrode were calibrated with standard buffer solutions prepared according to NBS specification [17]. The pH meter readings were converted to hydrogen ion concentration by titrating a standard HNO_3 solution ($0.01\,mol\,L^{-1}$), the ionic strength of which was adjusted to $0.1\,mol\,L^{-1}$ with $NaNO_3$, with standard NaOH ($0.05\,mol\,L^{-1}$). The pH was plotted against p[H]. The relationship $pH - p[H] = 0.05$ was observed. All titrations were carried out at $25.0 \pm 0.1^{\circ}C$ in purified nitrogen using a titration vessel described previously [18].

2.3. *Procedure and measuring technique*

The acid dissociation constants of the protonated imidazole derivatives and protonated HDA were determined by titrating 0.1 mmol samples of each with standard

NaOH solution. The acid dissociation constants of coordinated water in *trans*-$[Pd(NH_3)_2(H_2O)_2]^{2+}$ were determined by titrating 0.1 mmol of the complex with 0.05 mol L^{-1} NaOH. The formation constants of *trans*-$[Pd(NH_3)_2(H_2O)_2]^{2+}$ with HDA or B were determined by titrating mixture of 0.1 mmol of *trans*-$Pd(NH_3)_2^{2+}$ and ligand in concentration ratios of 1 : 2 and 2 : 1 for B and HDA, respectively. The formation constant of B-Pd^{II}-HDA-Pd^{II}-B was determined by titrating solution mixtures of *trans*-$[Pd(NH_3)_2(H_2O)_2]^{2+}$ (0.2 mmol), HDA (0.1 mmol) and B (0.2 mmol). The titrated solution mixtures each had a volume of 40 mL and the titrations were carried out at 25°C and 0.1 mol L^{-1} ionic strength (adjusted with $NaNO_3$). A standard 0.05 mol L^{-1} NaOH solution was used as titrant. The species formed were characterized by the general equilibrium:

$$lPd + p(HDA) + q(B) + r(H) \rightleftharpoons (Pd)_l(HDA)_p(B)_q(H)_r,$$

$$\beta_{lpqr} = \frac{[Pd_l(HDA)_p(B)_q(H)_r]}{[Pd]_l[HDA]_p[B]_q[H]_r},$$

where charges are omitted for simplicity. Pd, HDA, B, and H represent *trans*-$[Pd(NH_3)_2(H_2O)_2]^{2+}$, 1,6-hexanediamine, nitrogen base, and proton, respectively. The calculations were performed using the computer program MINIQUAD-75 [19]. The stoichiometry and stability constants of the complexes formed were determined by trying various possible composition models. The model selected was that which gave the best statistical fit and was chemically consistent with the magnitudes of various residuals, as described elsewhere [19]. Table 1 lists the stability constants together with their standard deviations and the sum of the squares of the residuals derived from the MINIQUAD output. Concentration distribution diagrams were obtained with the program SPECIES [20] under the experimental conditions used.

3. Results and discussion

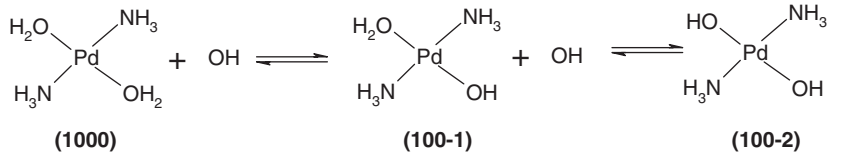
Acid dissociation constants of the protonated form of HDA and B have been reported. These constants were redetermined under the experimental conditions 25°C and constant ionic strength, which were used for determining the stability constants of the Pd(II) complexes.

3.1. *Acid-base equilibria of trans-*$[Pd(NH_3)_2(H_2O)_2]^{2+}$

trans-$[Pd(NH_3)_2(H_2O)_2]^{2+}$ may undergo hydrolysis. Its acid–base chemistry was characterized by fitting the potentiometric data to various acid–base models. The data were fitted considering the formation of two species: **100-1** and **100-2**, as shown in scheme 1. Trials were made to fit the potentiometric data considering the formation of the bridged-dimer, **200-2**, as in $[Pd(diamine)(H_2O)_2]^{2+}$ [21] and Be(II) complex [22], but this resulted in a very poor fit to the data. This may be explained on the premise that the concentration range of *trans*-$[Pd(NH_3)_2(H_2O)_2]^{2+}$ used in this investigation is too low to allow formation of this species.

Table 1. Formation constants of the binary and binuclear complexes of general formula $(Pd)_l(HDA)_p(B)_q(H)_r$ at 25°C and $I = 0.1\ mol\ L^{-1}NaNO_3$; standard deviations are given in parentheses.

System	l	p	q	r	logβ
trans-$[Pd(NH_3)_2(H_2O)_2]^{2+}$	1	0	0	−1	−5.90(0.04)
	1	0	0	−2	−16.16(0.05)
1,6-HDA	0	1	0	1	9.95(0.06)
	0	1	0	2	19.69(0.02)
trans-$[Pd(NH_3)_2(H_2O)_2]^{2+}$-HDA	1	1	0	1	17.67(0.02)
	1	1	0	0	12.63(0.04)
	2	1	0	0	14.74(0.05)
	2	1	0	−1	7.40(0.02)
	2	1	0	−2	−1.67(0.02)
Imidazole (Im)	0	0	1	1	6.48(0.01)
trans-$[Pd(NH_3)_2(H_2O)_2]^{2+}$-Im	1	0	1	0	6.02(0.06)
	1	0	2	0	11.28(0.04)
trans-$[Pd(NH_3)_2(H_2O)_2]^{2+}$-HDA-Im	2	1	1	0	20.740.09)
	2	1	2	0	24.96(0.08)
Methylimidazole (MeIm)	0	0	1	1	6.94(0.04)
trans-$[Pd(NH_3)_2(H_2O)_2]^{2+}$-MeIm	1	0	1	0	5.49(0.07)
	1	0	2	0	9.56(0.08)
trans-$[Pd(NH_3)_2(H_2O)_2]^{2+}$-HDA-MeIm	2	1	1	0	20.48(0.06)
	2	1	2	0	24.12(0.07)
Dimethylimidazole (Me_2Im)	0	0	1	1	7.25(0.02)
trans-$[Pd(NH_3)_2(H_2O)_2]^{2+}$-$Me_2Im$	1	0	1	0	5.34(0.07)
	1	0	2	0	10.00(0.05)
trans-$[Pd(NH_3)_2(H_2O)_2]^{2+}$-HDA-$Me_2Im$	2	1	1	0	20.21(0.06)
	2	1	2	0	21.20(0.05)
Methylamine (MeA)	0	0	1	1	10.03(0.04)
trans-$[Pd(NH_3)_2(H_2O)_2]^{2+}$-MeA	1	0	1	0	9.63(0.02)
	1	0	2	0	15.85(0.08)
trans-$[Pd(NH_3)_2(H_2O)_2]^{2+}$-HDA-MeA	2	1	1	0	25.22(0.09)
	2	1	2	0	33.89(0.07)

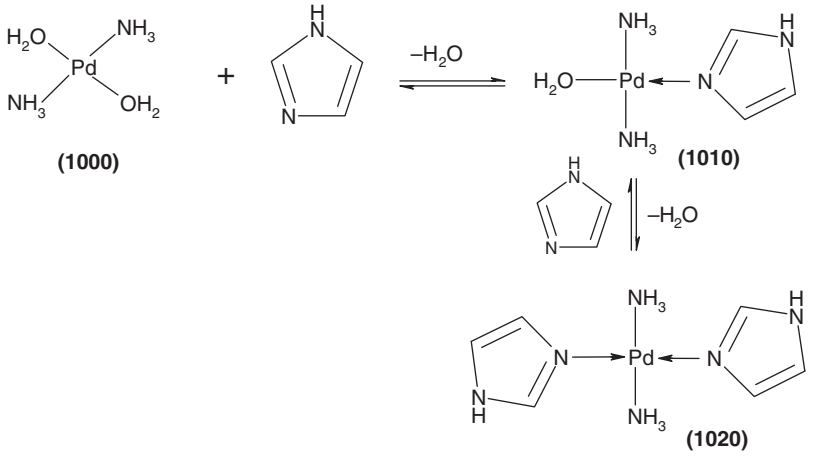


(1000) **(100-1)** **(100-2)**

Scheme 1. Acid-base equilibria of *trans*-$[Pd(NH_3)_2(H_2O)_2]^{2+}$.

The pK_{a1} and pK_{a2} values for *trans*-$[Pd(NH_3)_2(H_2O)_2]^{2+}$ are 5.90 and 10.26, respectively. The pK_{a1} value is in fair agreement with that obtained for *cis*-$[Pd(en)(H_2O)_2]^{2+}$ [23] and *cis*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$ [24, 25], where the corresponding values are 5.6 and 5.37, respectively.

The concentration distribution diagram for *trans*-$[Pd(NH_3)_2(H_2O)_2]^{2+}$ and its hydrolyzed species reveals that the concentration of monohydroxo species (**100-1**) increases with increasing pH and predominates with maximum concentration of 99% at pH 7.8–8.2. A further increase in pH is accompanied by an increase of dihydroxo concentration (**100-2**), which is the main species above pH 10.5.



Scheme 2. Complex-formation equilibria of imidazole.

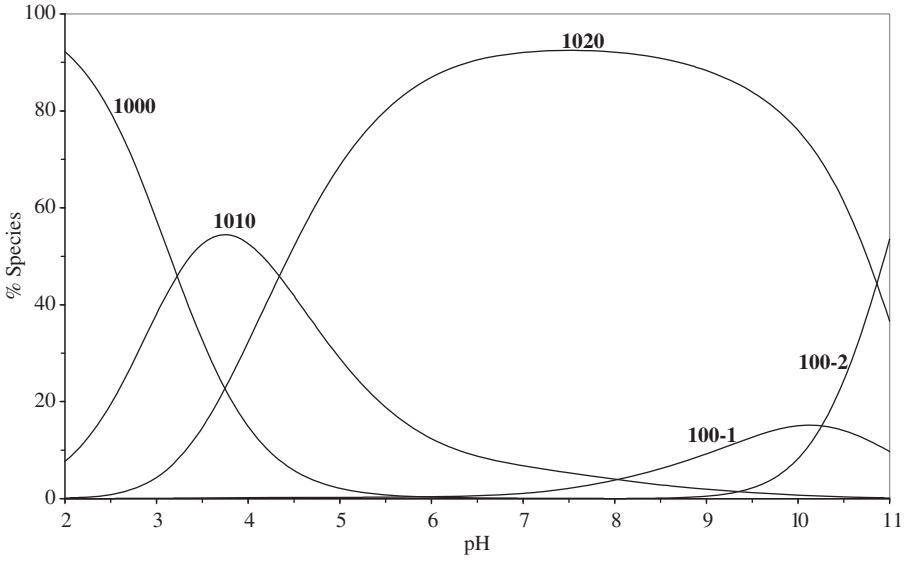
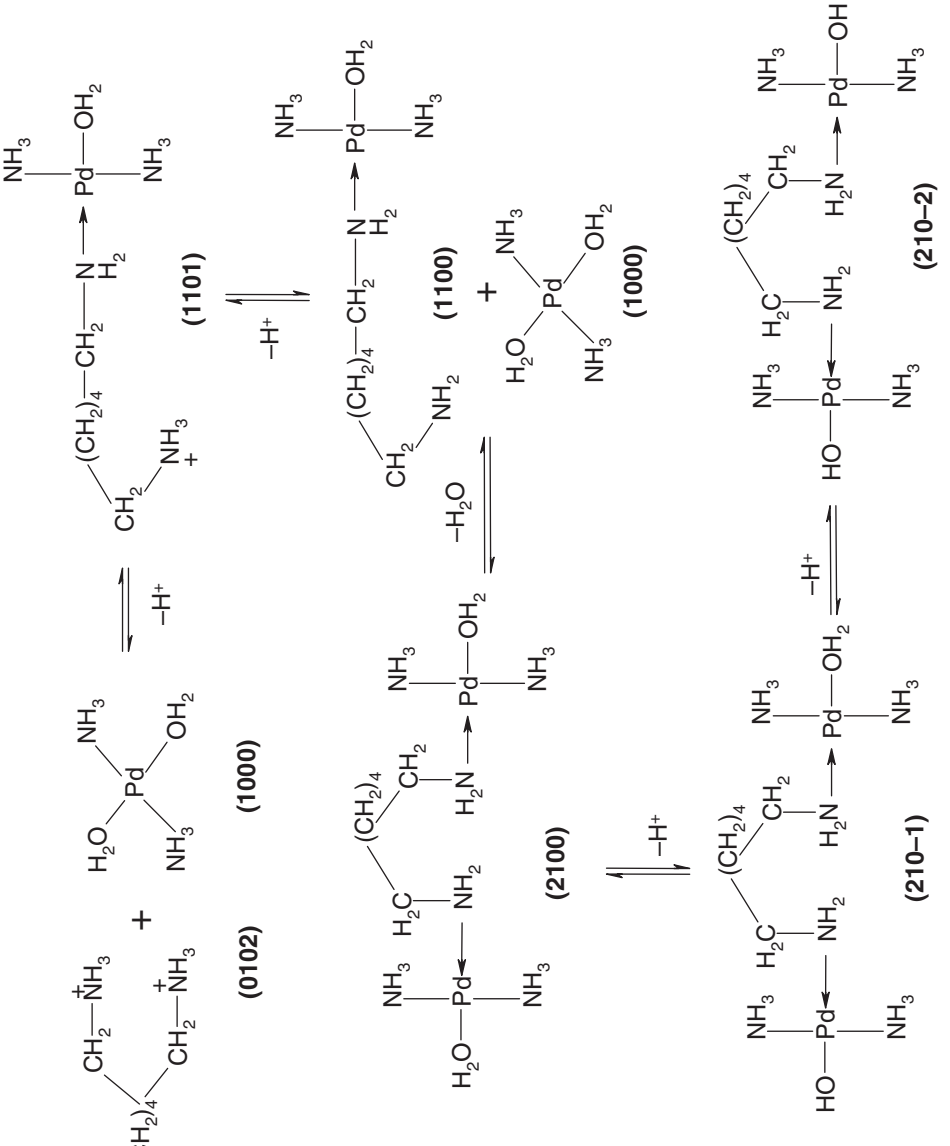


Figure 1. Concentration distribution of *trans*-$[Pd(NH_3)_2(H_2O)_2]^{2+}$-Im system.

3.2. *Complex-formation equilibria*

The potentiometric data of *trans*-$[Pd(NH_3)_2(H_2O)_2]^{2+}$-B system is fitted considering the formation of the 1 : 1 and 1 : 2 complexes. The complex-formation equilibria of imidazole are given in scheme 2. The concentration distribution diagram for the imidazole complex, given in figure 1, shows that the 1 : 1 complex starts to form at pH 2



Scheme 3. Complex-formation equilibria of 1,6-hexanediamine.

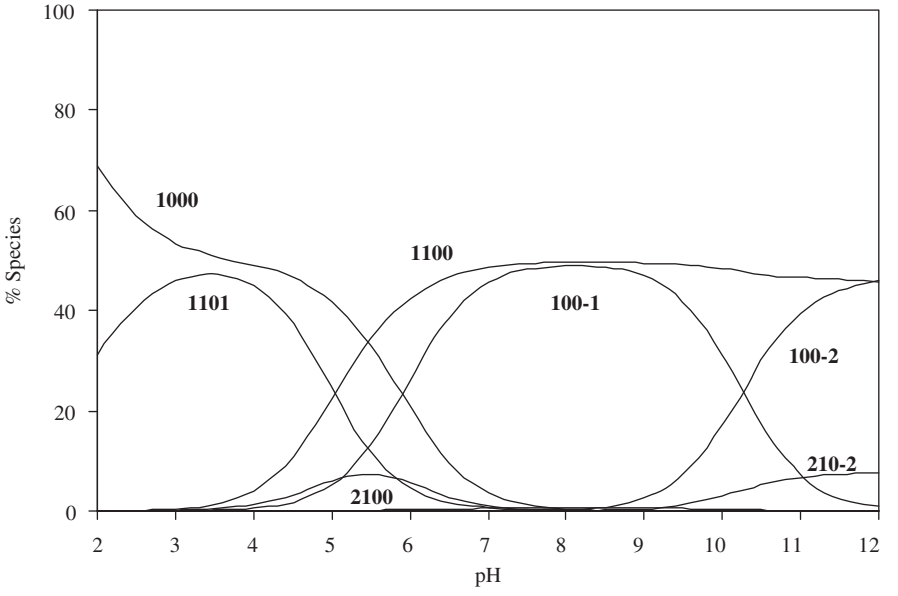
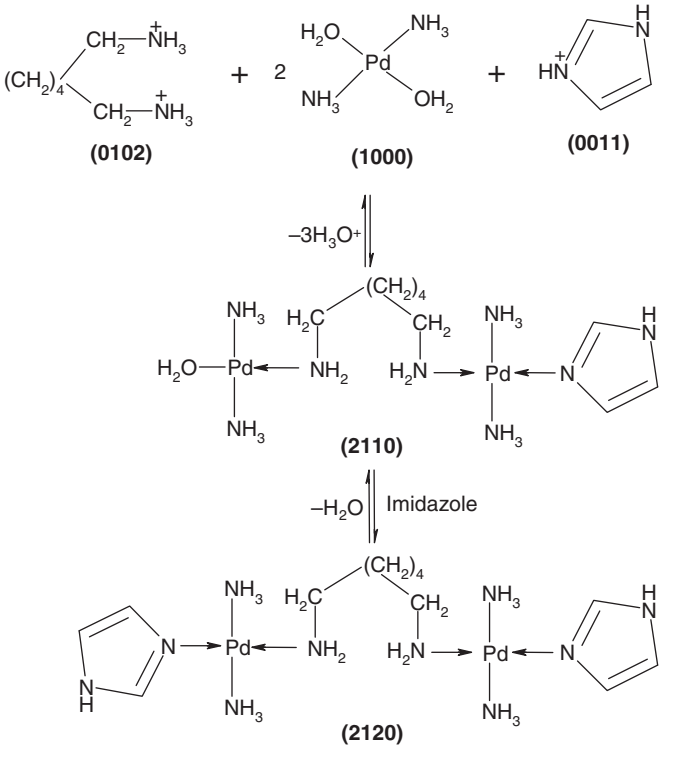


Figure 2. Concentration distribution of *trans*-$[Pd(NH_3)_2(H_2O)_2]^{2+}$-HDA system.

and attains maximum concentration of 55% at pH 3.7. However, the 1 : 2 complex predominates with the formation degree of 92% at pH 7.0–7.5.

Analysis of the titration data for *trans*-$[Pd(NH_3)_2(H_2O)_2]^{2+}$-HDA showed the formation of the 1 : 1 and 2 : 1 (Pd^{II}:HDA) complexes in addition to the protonated species of the 1 : 1 complex and the hydrolyzed species (**210-1**) and (**210-2**). The complex-formation equilibria are given in scheme 3. The p*K*a of the protonated complex ($\log\beta_{1101} - \log\beta_{1100}$) is 5.04, and is in good agreement with pK_{a1} of free protonated HDA (4.86). The p*K*a of coordinated water in the 2 : 1 complex ($\log\beta_{2100} - \log\beta_{210\text{-}1}$) is 5.98, and is in good agreement with the p*K*a of coordinated water in *trans*-$[Pd(NH_3)_2(H_2O)_2]^{2+}$. This indicates that the coordination of 1,6-diaminohexane has no effect on the electrophilicity of Pd^{II}. The concentration distribution diagram for *trans*-$[Pd(NH_3)_2(H_2O)_2]^{2+}$-HDA is shown in figure 2. The protonated 1 : 1 complex (**1101**) reaches maximum concentration of 48% at pH 3.5, while the unprotonated form (**1100**) predominates with maximum formation degree of 50% at pH 6.5. The 2 : 1 complex (**2100**) reaches maximum concentration of 9% at pH 5.5. The **2100** complex is formed in the same pH range where **1101** and **100-1** are formed. Therefore, the possibility of formation of **2100** by combination of **1101** and **100-1** could not be excluded. The hydrolyzed species predominate above pH 8.0.

The *trans*-$[Pd(NH_3)_2(H_2O)_2]^{2+}$-HDA-nitrogen base system, represented in scheme 4, shows the presence of complexes with stoichiometric coefficients **2110** and **2120** ($Pd^{II} : HDA : B : H^+$). The concentration distribution diagram of the binuclear complex involving imidazole is given in figure 3. The binuclear complex (**2110**) starts to form at pH 4.5 and dominates with concentration of 38% at pH = 7.1. **2120** starts to form at pH 5.0 and attains maximum formation of 63% at pH = 9.2. This reveals that in the physiological pH range the interaction between binuclear Pd^{II}-HDA-Pd^{II} and imidazole



Scheme 4. Complex formation equilibria of amine-bridged dinuclear complex.

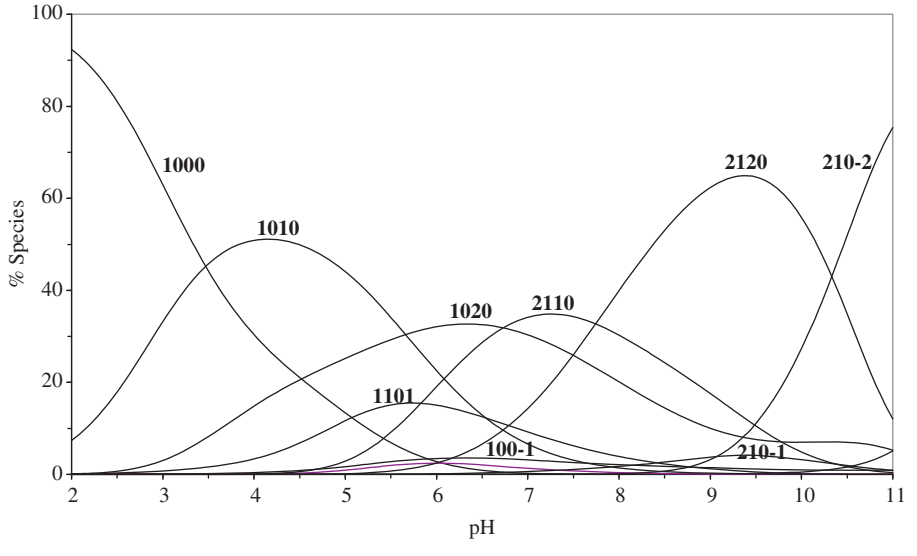


Figure 3. Concentration distribution of *trans*-$[Pd(NH_3)_2(H_2O)_2]^{2+}$-HDA-Im system.

is quite feasible and consequently supports the anti-tumor activity of this class of complexes. The hydrolyzed species **210-1** and **210-2** start to form after pH 8. These species are formed by assuming that the coordinated imidazoles are expelled and replaced by hydroxide.

The stability constant values of the binary and binuclear complexes of methylamine are higher than those of imidazole and its derivatives, due to higher basicity of methylamine nitrogen as reflected from the high p*K*a value [26].

4. Conclusion

The present investigation describes equilibria of binuclear Pd(II) complex with the nitrogen bases, methylamine, and imidazole derivatives. The results support the biological significance of this class of binuclear Pd(II) complex and give a model for the behavior of this interesting class of complexes in biological fluids.

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