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Potentiometric and Equilibrium Studies on Complex-Formation Reactions of [Pd(2-aminomethylpyridine)$(H_2O)_2]^{2+}$ with Ligands of Biological Significance and Displacement Reactions of DNA Constituents

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The stability constants of the complexes formed between various biologically relevant ligands (amino acids and DNA constituents) and $[Pd(Pic)(H_2O)_2]^{2+}$ were investigated at 25 °C and 0.1 M ionic strength. The concentration distribution diagrams of the various complex species as a function of pH were evaluated. DNA constituents form 1:1 and 1:2 complexes. The equilibrium constants for the substitution of representative coordinated DNA constituents by mercaptoethylamine, cysteine and glutathione were calculated. The results are expected to contribute to the chemistry of antitumour agents. The thermodynamic parameters ΔH◦ and ΔS◦ calculated from the temperature dependence of the equilibrium constants were determined for adenosine, and adenosinemonophosphate complexes with $[Pd(Pic)(H_2O)_2]^{2+}$. The thermodynamic study of these systems is very important because it can give information about the structural environment of the complexes; moreover, it can help in outlining different noncovalent interactions such as coulombic forces and hydrogen bonds.

Keywords: Potentiometry, Complex-formation, thermodynamics, antitumor, Speciation, glutathione.

1. INTRODUCTION

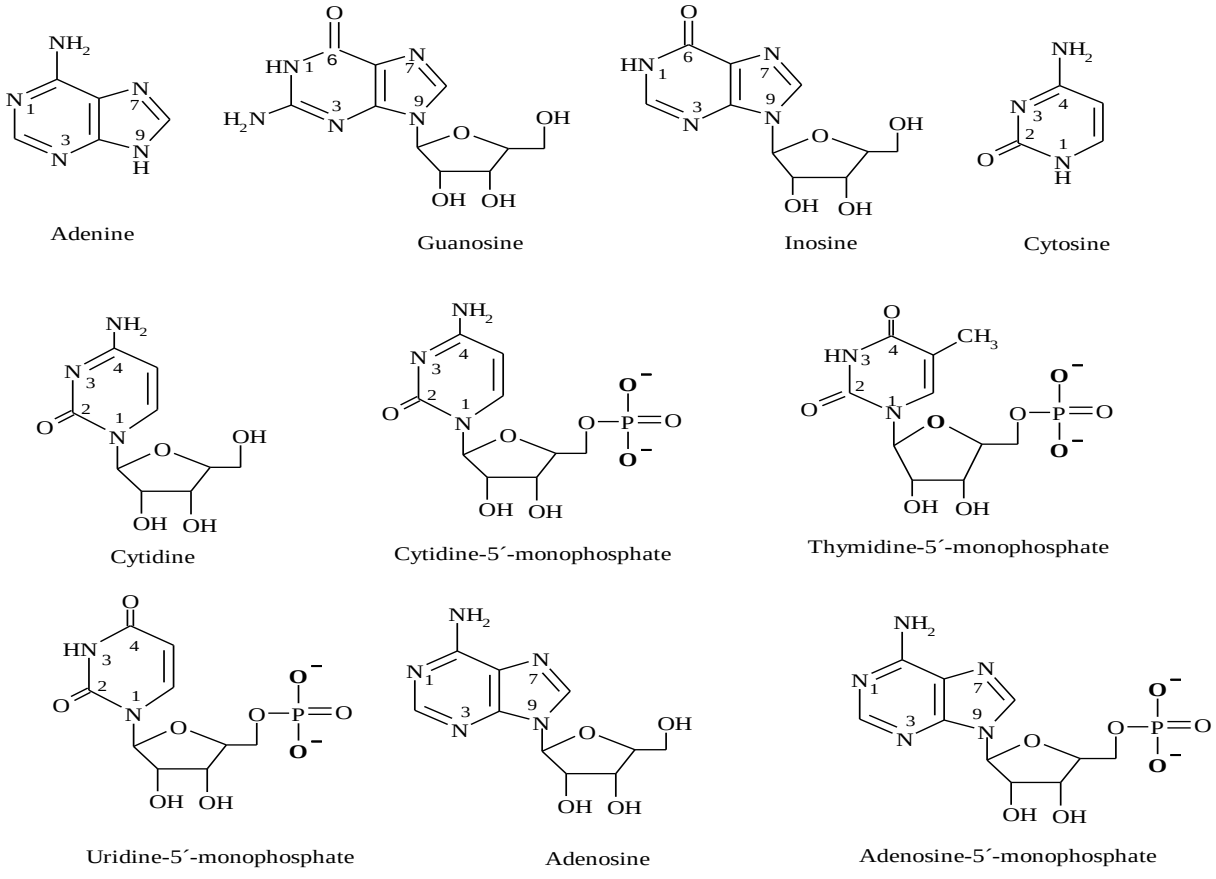
Cisplatin, is one of the most efficient antitumor compounds towards various types of tumors. In spite of the prolonged usage of cisplatin as an antitumor drug, there is still need for progression with reference to reduced toxicity; increased drug effectiveness; expansion of drug activity; increased solubility; acquired resistance during treatment by chemical drugs and removal of side effects like nausea, hearing damage and vomiting [1-3]. 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.

Palladium(II) and platinum(II)-amine complexes have the same structure, with 5-orders of

magnitude higher reactivity in case of palladium(II) complexes, but similar thermodynamic parameters. Palladium(II) complexes act as good models for the analogous platinum(II) complexes in solution. Recent work in our laboratories focused on the equilibria of complex-formation reactions of cis-(diamine)palladium(II) with amino acids, peptides and dicarboxylic acids, esters and DNA, the major target in chemotherapy of tumours [4-9]. In this study, we have investigated the thermodynamic behaviour of palladium(II) complexes with a hetero-aromatic picolylamine that possesses π-acceptor properties, which is believed to favor the reaction with DNA and hence increase the efficiacy of the drug. This is in agreement with the finding that *cis*-Pt(1,4-DACH)Cl_2, is more effective than *cis*-platin and oxaliplatin in *vivo* and in *vitro* tests [10]. Thus, in this context we try to study complex-formation reactions of $[Pd(Pic)(H_2O)_2]^{2+}$ with bioactive ligands in addition to study of the displacement reactions of inosine as a representative example of DNA constituents bound to this complex. Also, the thermodynamics for complex-formation reaction of $[Pd(Pic)]^{2+}$ with adenosine and adenosine monophosphate were calculated and discussed.

2. EXPERIMENTAL

2.1. Materials



Scheme 1. Structural formulae of DNA constituents.

Palladium chloride and 2-aminoethylpyridine (Pic) were obtained from Aldrich. The amino acids and related compounds (β-alanine, γ-aminobuteric acid, norvaline, hydroxyproline, lysine.HCl, cysteine, glutamic acid and imidazole) were provided by Sigma Chemicals Company. The DNA units (inosine, adenine, guanosine, adenosine, cytosine, cytidine, cytidine-5'-monophosphate, thymidine-5'-monophosphate, and uridine-5'-monophosphate) (Scheme 1) were provided by Sigma Chemical Co. Mercaptoethylamine was provided by Sigma Chemicals Company. For equilibrium studies, the dichloro complex of palladium(II) with picolylamine was converted into the diaqua complex by treatment with two equivalents of silver nitrate as described before [11,12]. The ligands in the form of hydrochlorides were converted into their corresponding hydronitrates. Cytosine, adenine, guanosine and the nucleotides were prepared in the protonated form with standard nitric acid solution.

2.2. Synthesis

$[Pd(Pic)Cl_2]$ was prepared by heating $PdCl_2$ (0.50 g; 2.82 mmol) and KCl (0.4205 g; 5.64 mmol) in the least amount of water to 70 °C for 30 minutes with stirring. The clear solution of $[PdCl_4]^{2-}$ was cooled to 25 ºC, filtered and 2-aminomethylpyridine (0.3045 g; 2.82 mmol), dissolved in 10 ml H_2O was added dropwise to the stirred solution. The pH was adjusted to 2-3 by the addition of HCl. A yellow precipitate of $[Pd(Pic)Cl_2]$ was formed and stirred for a further 30 minute at 50 °C. After filtering off the precipitate, it was thoroughly washed with H_2O, ethanol and diethylether.

The $[Pd(Pic)Cl_2]$ complex was converted in solution into the diaqua form by treating it with 2 equivalents of $AgNO_3$, as described elsewhere [11,12].

2.3. 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 [13]. All titrations were carried out at 25.0 ± 0.1 ºC in purified nitrogen atmosphere using a titration vessel described previously [14].

2.4. Procedure and measuring technique

The acid dissociation constants of the ligands were determined by titrating 1.25 mmole samples of each with standard NaOH solutions. Ligands were converted into their protonated form with standard HNO_3 solutions. The acid dissociation constants of the coordinated water molecules in $[Pd(Pic)(H_2O)_2]^{2+}$ were determined by titrating 1.25 mmole of complex with standard 0.05 M NaOH solution. The formation constants of the complexes were determined by titrating solution mixtures of $[Pd(Pic)(H_2O)_2]^{2+}$ (1.25 mmole) and the ligand in the concentration ratio of 1:1 for amino acids and in the ratio of 1:2 (Pd:ligand) for the DNA constituents. DNA units were protonated with standard HNO_3 solution. The titrated solution mixtures each had a volume of 40 ml and the titrations were carried out at 25 ºC and 0.1 M ionic strength (adjusted with $NaNO_3$). A standard 0.05 M NaOH solution was used

as 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

$$pM + qL + rH \rightleftharpoons (M)_p(L)_q(H)_r \quad (1)$$

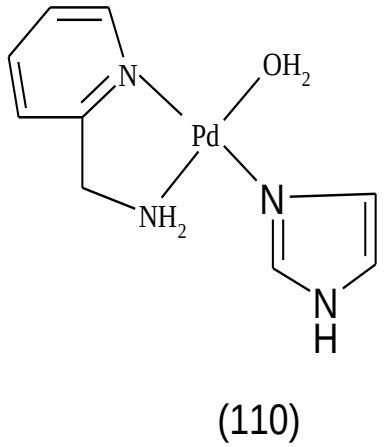
for which the formation constants are given by

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

Where M, L and H stand for $[Pd(Pic)(H_2O)_2]^{2+}$ ion, ligand and proton, respectively. The calculations were performed using the computer program [15] MINIQUAD-75. Various composition models were assumed for the studied systems and the most selected one was that which gave the best statistical fit [15]. Tables 1 and 2 list the stability constants together with their standard deviations from the MINIQUAD output. The concentration distribution diagrams were obtained with the program SPECIES [16] under the experimental condition used.

3. RESULTS AND DISCUSSION

The protonation constants of the investigated ligands were determined under the same experimental conditions of complex formation are used in the calculations of stability constants of the palladium(II) complexes. The values obtained are consistent with data given in the literature [17]. Analysis of the pH-titration data indicated that the formation constant of the $[Pd(Pic)(H_2O)_2]^{2+}$ with amino acids is higher than that for the corresponding monodentate imidazole (Table 1, Scheme 2). This indicates that the amino acids bind as bidentate ligands via the $-NH_2$ and carboxylate groups.



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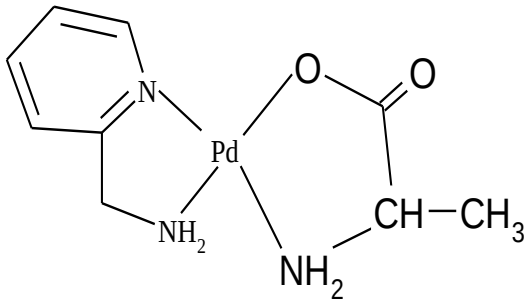

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Scheme 2. Coordination modes of imidazole as monodentate ligand and alanine as bidentate ligand with $Pd(Pic)^{2+}$ complex.

Table 1. Formation constant of $M_pL_qH_r$ species in aqueous solution at 25 ± 0.1 ^oC and I = 0.1 mol-dm^{-3}($NaNO_3$).

System	p	q	r[a]	logβ[b]	S[c]
Pd(Pic)-OH[d]	1	0	-1	-4.81 (0.07)	2.5E-7
	1	0	-2	-13.27 (0.02)	
	2	0	-2	-6.45(0.01)	
Alanine[d]	0	1	1	9.69 (0.01)	9.2E-8
	0	1	2	11.88 (0.02)	
	1	1	0	10.89 (0.03)	3.1E-7
1,1-Cyclobutane dicarboxylic acid[d]	0	1	1	5.68(0.004)	1.6E-8
	0	1	2	8.80 (0.006)	
	1	1	0	8.09(0.006)	4.6E-7
	1	1	1	10.91(0.04)	
β-alanine	0	1	1	10.08(0.01)	2.8E-7
	0	1	2	13.68(0.02)	
	1	1	0	10.18 (0.03)	
	1	1	1	13.64 (0.05)	4.2E-7
γ-aminobuteric acid	0	1	1	9.89(0.01)	4.5E-7
	0	1	2	13.52(0.04)	
	1	1	0	8.02 (0.01)	
	1	1	1	13.37(0.03)	1.8E-7
Imidazole	0	1	1	7.04 (0.01)	2.6E-9
	1	1	0	7.69(0.03)	
	1	2	0	13.91(0.04)	1.8E-7
Glutamic acid	0	1	1	9.42 (0.01)	2.2E-8
	0	1	2	13.50 (0.02)	
	1	1	0	10.32 (0.02)	
	1	1	1	14.11 (0.05)	4.7E-9
Cysteine	0	1	1	10.32 (0.02)	4.9E-8
	0	1	2	18.55 (0.04)	
	0	1	3	20.49 (0.05)	
	1	1	0	16.64 (0.05)	4.4E-9
	1	1	1	20.51 (0.07)	
Glutathione	0	1	1	9.62(0.01)	1.5E-7
	0	1	2	17.63(0.01)	
	0	1	3	20.85 (0.03)	
	1	1	0	15.32 (0.05)	2.7E-7
	1	1	1	19.02 (0.06)	
	1	1	2	22.32(0.08)	
Mercaptoethylamine	0	1	1	10.37(0.01)	3.7E-8
	0	1	2	18.64(0.02)	
	1	1	0	16.51(0.06)	2.4E-7
	1	1	1	20.69 (0.07)	
Lysine	0	1	1	10.51(0.01)	1.4E-8
	0	1	2	19.71(0.02)	
	0	1	3	21.99(0.02)	
	1	1	0	10.82(0.04)	2.5E-7
	1	1	1	19.51(0.06)	

[a] p, q and r are the stoichiometric coefficients corresponding to $Pd(Pic)^{2+}$, L, H^+, respectively. [b] Standard deviations are given in parentheses, [c] Sum of square of residuals. [d] taken from ref. 12.

3.1. Complex-formation equilibria involving amino acids

3.1.1. Complex-formation equilibria of $[Pd(Pic)(H_2O)_2]^{2+}$ with β-alanine

The potentiometric data for the Pd(Pic)-β-alanine system indicated formation of complex species with the stoichiometric coefficients 110 and 111. Comparison of the stability constant of the α-alanine (log $\beta_{Pd(Pic)-\alpha-Ala}$ = 10.89 at 25 ^{o}C) and β-alanine (log $\beta_{Pd(Pic)-\beta-Ala}$ = 10.18 at 25 ^{o}C) complexes indicates that the extra stability of five-membered chelate rings for α-alanine complex compared to six membered chelate rings for β-alanine complex (see scheme 3) i.e., formation of five and five membered chelate rings in case of α-alanine are more stable than formation of 5- and 6-membered chelate rings in case of β-alanine. This is in accord with the data reported for the effect of ring size on the stability of Cu(II) complexes with amino alcohols [18].

Scheme 3. Structural formulae of Pd(Pic)-β-Ala and Pd(Pic)-α-Ala complexes.

3.1.2. Complex-formation equilibria of $[Pd(Pic)(H_2O)_2]^{2+}$ with glutathione

Treatment of the potentiometric data for the Pd(Pic)-glutathione system showed the formation of 110, 111 and 112 complex species. Glutathione has various binding sites, viz. oxygen atom of COOH group, nitrogen atom of NH_2 group and sulphur atom of SH group. The stability constant of the (110) complex (log β = 15.32) is higher than those of α-amino acids (log $\beta_{[Pd(Pic)(glycine)]}$ = 9.95). This indicates that glutathione interacts with palladium(II) ion by the amino and deprotonated SH groups and not by the amino and caboxylate groups like simple α-amino acids. Also, this is in accordance with the fact that palladium(II) has a high affinity for S-donor ligands. Additionally, the stability constant of the 110 complex is in a fair agreement with that of mercaptoethylamine, (where the binding sites are the -NH_2 and sulfhydryl groups) supporting our assumption that glutathione reacts with palladium(II) ion by the -NH_2 and deprotonated sulfhydryl groups.

3.1.3. Complex-formation equilibria of $[Pd(Pic)(H_2O)_2]^{2+}$ with glutamic acid

Glutamic acid has two COOH and one -NH_2 group as potential coordinating centers. It may coordinate either by the two carboxylate groups or by the NH_2 and one carboxylate group. The formation constant of the aspartic acid complex is in the range of those for α- amino acids (log

$\beta_{[Pd(Pic)(glycine)]}$ = 9.95). This may reveal that glutamic acid coordinates via the amino and one carboxylate group.

The pKa of the protonated species is calculated by Eq. (3) [12,19-21]:

$$pK_a = \log \beta_{111} - \log \beta_{110} \quad (3)$$

The pK_a of the protonated species of Pd(Pic)-glutamic acid is (3.79), being more close to that of the protonated carboxylate group (pK_a = 4.08), assuming the proton in the protonated complex would be located on the carboxylate group. This value corresponds to a protonated carboxylate group of glutamic acid considering the increase in acidity due to complex formation.

The speciation diagram given in Fig. 1 shows the formation of the protonated complex 111 with a formation degree of 57 % at pH 3.2. By rising of pH the complex species (110) is formed with a concentration 96 % at pH 7.0 i.e. the reaction of $[Pd(Pic)]^{2+}$ goes to completion in the physiological pH range. However, the species 11-1 has a lower percent (~ 7 %) in the physiological pH range and the species 11-2 predominates after pH 10 attaining the maximum concentration of ~ 99 % at pH ~11.2.

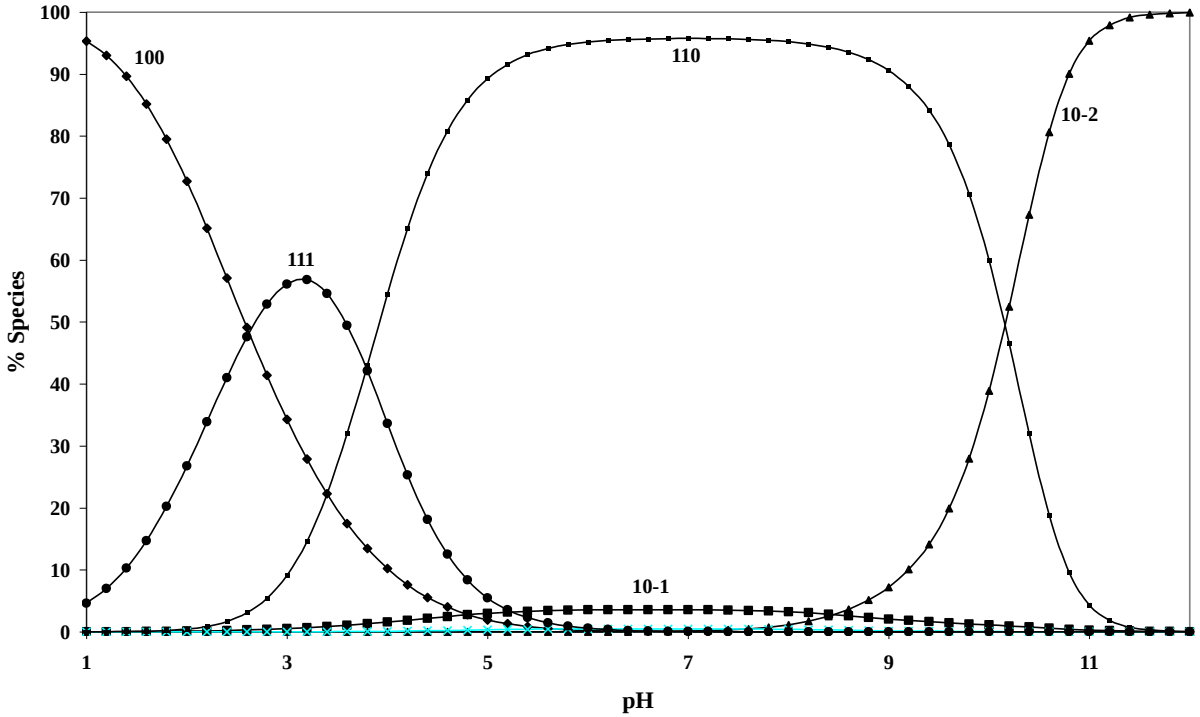


Figure 1. Species distribution of various species as a function of pH in the Pd(Pic)-Glutamic acid system

3.1.4. Complex-formation equilibria of $[Pd(Pic)(H_2O)_2]^{2+}$ with lysine

Analysis of the titration data for the Pd(Pic)-lysine amino acid system showed the formation of 1:1 species in addition to the monoprotonated species (Table 1). The stability constant of the Pd(Pic)-lysine complex ($\log\beta_{110}$ = 10.82) is extremely fair with those of α- amino acids. This may indicate that lysine most likely chelates by the amino and carboxylate groups (glycine-like), due to chelates formed

by coordination via the two NH_2 groups will form unstable 8-membered ring. The pK_a value of the protonated species is 8.69 for lysine amino acid.

3.2. Complex-formation equilibria involving DNA complexes

DNA constituents such as adenosine, adenine, cytosine and cytidine form 1:1 and 1:2 complexes with the $Pd(Pic)^{2+}$ ion. However, inosine, guanosine, adenine and nucleotides such as adenosine-5′-monophospate, cytidine-5′-monophosphate, uridine-5′-monophosphate and thymidine-5′-monophosphate form the monoprotonated complex in addition to the formation of 1:1 and 1:2 complexes.

Protonated adenine has two pK_a's at 4.23 and 9.58 corresponding to the N1 and N9 sites, respectively. Hodgson [23] and Marzilli [24] discussed both solution and solid complex studies and concluded that N9 is the coordination site of adenine in the palladium(II) complex. The data in Table 2 indicates the presence of protonated species 111 and 122, which confirms a site change upon varying the pH. At low pH, the N9H is still protonated, as is further confirmed by the higher pK_a value, 9.33 for the 121 species. The pK_a value of the protonated species (111) of the adenine complex is 5.24 ($\log\beta_{111}$-$\log\beta_{110}$). Thus, acidification of the N9H in the species 111 occurs by 4.34 (9.58-5.24). At higher pH, as soon as N9H is deprotonated, the binding site may shift to N9.

Inosine may protonate at N7 forming a (N1H-N7H) monocation. In the present study, the pK_a of N1H was determined (pK_a = 8.70). The pK_a of N7H is 1.2 [25]. It was reported [11] that, in the acidic pH range, N1 remained protonated, while the metal ion is coordinated to N7. In inosine, the pK_a of the protonated species is 3.88, which means that N1H is still protonated and is acidified by 4.82 pK units, (8.70-3.88) upon complex formation, Table 1. The binding site at the higher pH was disputed and a gradual change from N7-binding to N1-binding with an increase of pH was suggested [26].

The speciation diagram for the Pd(Pic)-inosine system, taken as a model for DNA binding (Fig. 2), shows that in the physiological pH range the inosine complex (110) predominates with a maximum concentration of 96.8 %, i.e. the interaction between $Pd(Pic)^{2+}$ and inosine as a DNA constituent is feasible. The protonated complex (111) exists at low pH < 2 with 93 %. The (120) species exists with a concentration of 64.0 % at pH 9.2.

The complexes with DNA constituents are stabilized by intramolecular stacking between the pyridine aromatic ring structure and the purine rings [22]. The concentration distribution diagrams, (Fig. 2), show that complex-formation between $[Pd(Pic)(H_2O)_2]^{2+}$ and inosine as a representative example of DNA subunits suppresses dramatically the hydoxo species, shifting them to higher pH.

Inosine complex ($\log\beta_{110}$ = 8.81) is less stable than inosine-5′-monophosphate complex ($\log\beta_{110}$ =10.42) [11]. This may be explained on the basis of different coulombic forces between the ions resulting from the -vely charged PO_4^{3-} group i.e., the extra stabilization may be attributed to the triply -vely charged 5′-IMP^{3-} ion.

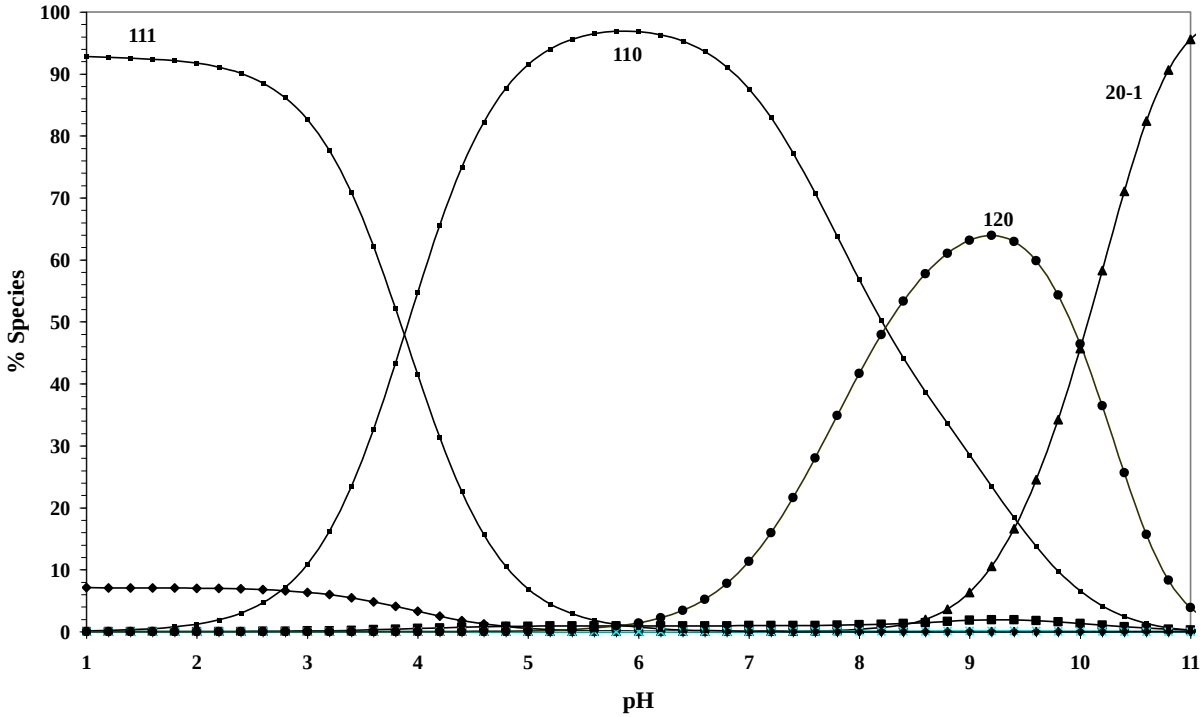


Figure 2. Species distribution of various species as a function of pH in the Pd(Pic)-Inosine system.

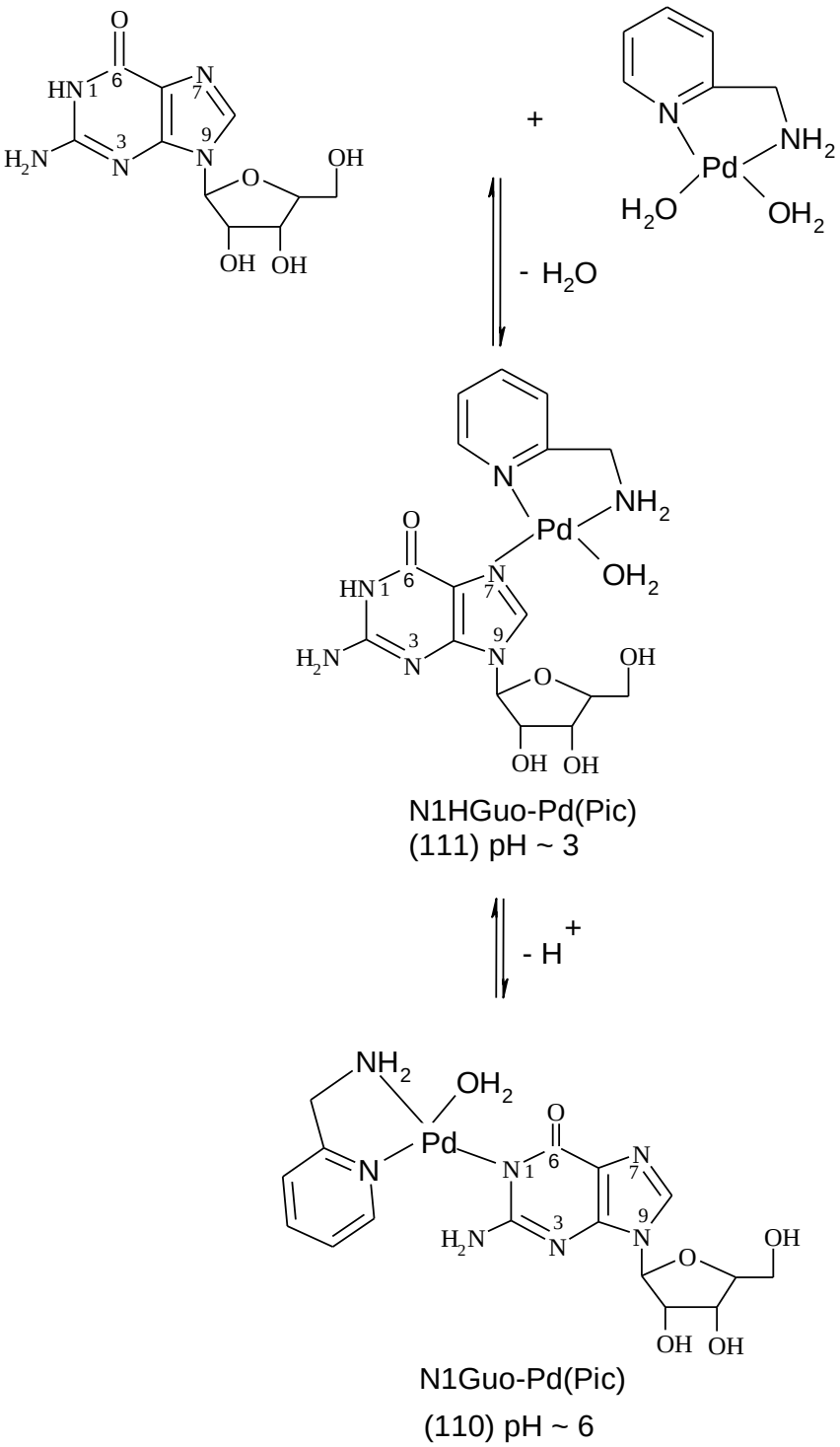
The pyrimidines cytosine, cytidine, cytidine-5′-monophosphate, uridine-5′-monophosphate and thymidine-5′-monophosphate, have basic nitrogen donor atoms (N3) in the measurable pH range and as a consequence they form 1:1 and 1:2 complexes with $Pd(Pic)^{2+}$ species. As a result of the high pK_a values of pyrimidines ($pK_a \approx 9$) and the fact that they are monodentates, the complexes are formed only above pH 8, supporting the view that the negatively charged nitrogen donors of pyrimidine bases are important binding sites in the neutral and slightly basic pH ranges.

Moreover, uridine-5′-monophosphate, cytidine-5′-monophosphate and thymidine-5′-monophosphate form protonated complexes (111) in addition to deprotonated 110 and 120 complexes. The pK_a values of these protonated species are 5.94, 4.73 and 6.02 for uridine-5′-monophosphate, cytidine-5′-monophosphate and thymidine-5′-monophosphate, respectively. These values correspond to the $PO_2(OH)$ group. The lowering of these values with respect to those of the free ligands is due to acidification upon complex formation [27].

Both cytosine and cytidine undergo N3 protonation under mild acidic conditions. The values obtained for the protonation constants are 4.59 and 4.29 for cytosine and cytidine, respectively. The lower basicity of the nucleoside probably results from the electron-withdrawing effect of the ribofuransyl group, which reduces the electron density in the cytosine ring. The lower values of the stability constants of their complexes, Table 2, reflect the difference in the basicity of the donor sites.

Based on the existing data, Pd-Pic complexes of nucleosides are less stable than the corresponding bases as evident from the stability constants given in Table 2. The presence of sugar residue imposes steric hindrance in nucleosides for their complexation with metal ions and reduces the overall basicity of metal complexes of nucleosides considerably.

Guanosine forms a stronger 110 complex (log β =10.05) in addition to the protonated 111 complex. For Pd(Pic)-guanosine complex, the pK_a value of the protonated species of the guanosine complex (111) is 5.62 ($\log\beta_{111}$ - $\log\beta_{110}$). The former pK_a value for Pd-Pic-guanosine complex corresponds to the N^1H group. The N^1H group was acidified upon complex formation by 3.55 (9.17-5.62) pK units for guanosine. A proposed coordination process of $Pd(Pic)^{2+}$ with guanosine is given in Scheme 4.



Scheme 4. Proposed coordination process of $Pd(Pic)^{2+}$ with Guanosine

Table 2. Formation constant of $M_pL_qH_r$ species in aqueous solution at 25 ± 0.1 ^oC and I = 0.1 $mol.dm^{-3}$($NaNO_3$).

System	p	q	r[a]	logβ[b]	S
Inosine	0	1	1	8.70 (0.01)	5.4E-8
	1	1	0	8.81 (0.01)	3.7E-8
	1	2	0	12.58 (0.03)	
	1	1	1	12.69 (0.07)	
Adenine	0	1	1	9.58 (0.03)	3.5E-8
	0	1	2	13.81 (0.04)	
	1	1	0	9.71 (0.03)	4.9E-8
	1	2	0	14.62 (0.05)	
	1	1	1	14.95 (0.06)	
	1	2	1	23.95 (0.09)	
Guanosine	0	1	1	9.17 (0.04)	2.7E-7
	0	1	2	11.15 (0.05)	
	1	1	0	10.05 (0.02)	5.5E-8
	1	2	0	14.65 (0.04)	
	1	1	1	15.67 (0.08)	
Adenosine	0	1	1	3.67 (0.03)	1.9E-8
	1	1	0	3.52 (0.04)	5.6E-8
	1	2	0	5.96 (0.06)	
Adenosine-5'-monophosphate	0	1	1	7.11 (0.03)	5.6E-8
	0	1	2	11.42 (0.06)	
	1	1	0	4.77(0.05)	3.8E-7
	1	2	0	8.91(0.06)	
	1	1	1	10.77(0.09)	
Cytosine	0	1	1	4.59 (0.04)	1.7E-8
	1	1	0	6.11 (0.03)	7.2E-7
	1	2	0	9.16 (0.05)	
Cytidine	0	1	1	4.29 (0.02)	3.1E-8
	1	1	0	5.35 (0.05)	2.2E-7
	1	2	0	8.87 (0.07)	
Cytidine-5'-monophosphate	0	1	1	6.39(0.02)	4.9E-8
	0	1	2	10.91(0.03)	
	1	1	0	5.95 (0.01)	1.9E-7
	1	2	0	8.74 (0.04)	
	1	1	1	10.68 (0.07)	
Uridine-5'-monophosphate	0	1	1	9.49(0.02)	2.8E-8
	0	1	2	15.58(0.04)	
	1	1	0	8.37 (0.02)	6.1E-7
	1	2	0	14.06 (0.05)	
	1	1	1	14.39 (0.08)	
Thymidine-5'-monophosphate	0	1	1	9.68 (0.01)	1.3E-8
	0	1	2	15.98 (0.02)	
	1	1	0	8.46 (0.03)	7.4E-7
	1	2	0	14.29 (0.05)	
	1	1	1	14.48 (0.08)	

[a] p, q and r are the stoichiometric coefficients corresponding to $Pd(Pic)^{2+}$, L, H^+, respectively, Standard deviations are given in parentheses, [c] Sum of square of residuals.

3.3. Displacement reaction of coordinated inosine

It was shown above that N-donor ligands such as DNA constituents have affinity for $[Pd(Pic)(H_2O)_2]^{2+}$, 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 palladium(II) to coordinate to S-donor ligands was demonstrated as shown in Tables 1 and 2. These results assumed that Pd(II)-N adducts can easily be converted into Pd-S adducts. Thus, the equilibrium constant for such conversion is of biological significance. Consider inosine as a typical DNA constituent (presented by HA) and cysteine as a typical thiol ligand (presented by H_2B). The equilibria involved in complex-formation and displacement reactions are:

$$HA \rightleftharpoons H^+ + A^- \quad (4)$$

$$H_2B \rightleftharpoons 2H^+ + B^{2-} \quad (5)$$

$$[Pd(Pic)]^{2+} + A^- \rightleftharpoons [Pd(Pic)A]^+ \quad (6)$$

$$\beta_{110}^{[Pd(Pic)A]+} = [Pd(Pic)A^+]/[Pd(Pic)^{2+}][A^-] \quad (7)$$

(100 110)

$$[Pd(Pic)]^{2+} + B^{2-} \rightleftharpoons [Pd(Pic)B] \quad (8)$$

$$\beta_{110}^{[Pd(Pic)B]} = [Pd(Pic)B]/[Pd(Pic)^{2+}][B^{2-}] \quad (9)$$

(100 110)

$$[Pd(Pic)(A)]^+ + B^{2-} \overset{K_{eq}}{\rightleftharpoons} [Pd(Pic)(B)] + A^- \quad (10)$$

The equilibrium constant for the displacement reaction given in Eq. (10) is given by

$$K_{eq} = [Pd(Pic)(B)][A^-]/[Pd(Pic)(A)]^+[B]^{2-} \quad (11)$$

Substitution from eq. (7) and (9) in eq. (11) results in:

$$K_{eq} = \beta_{110}^{[Pd(Pic)B]}/\beta_{110}^{[Pd(Pic)A]+} \quad (12)$$

$\log_{10} \beta_{110}$ values for $[Pd(Pic)(A)]^+$ and $[Pd(Pic)B]$ complexes taken from Table 2 amount to 8.81 and 16.64, respectively, and by substitution in Eq. 12 results in $\log_{10} K_{eq} = 7.83$. In the same way the equilibrium constants for the displacement of coordinated inosine by glycine is $\log_{10} K_{eq} = 2.08$. These values indicate how SH ligands like cysteine and glutathione are effective in displacement of the DNA constituents, which is the main target in tumour chemotherapy.

The log K_{eq} for the displacement reaction of the chelated cyclobutanedicarboxylate with inosine. amounts to - 0.72. The low value of - 0.72 is of biological significance since it is in line with the finding that carboplatin interacts with DNA through ring opening of chelated CBDCA and not through displacement of CBDCA.

3.4. Effect of Temperature

The values obtained for the thermodynamic parameters $\Delta H°$, $\Delta S°$ and $\Delta G°$ [28], associated with the adenosine, AMP and their complex formation with $Pd(Pic)^{2+}$ species were calculated from the temperature dependence of the data in Tables 3 and 4. $\Delta H°$ and $\Delta S°$ were obtained by linear least square fit of *ln K* versus 1/T ($ln\ K = -\Delta H°/RT + \Delta S°/R$) leading to an intercept $\Delta S°/R$ and a slope –

$\Delta H°/R$, where K is the equilibrium constant. The thermodynamic parameters $\Delta H°$, $\Delta S°$ and $\Delta G°$ were given in Table 5 and the linear relation between log K and 1/T is given in Figs. 3 and 4.

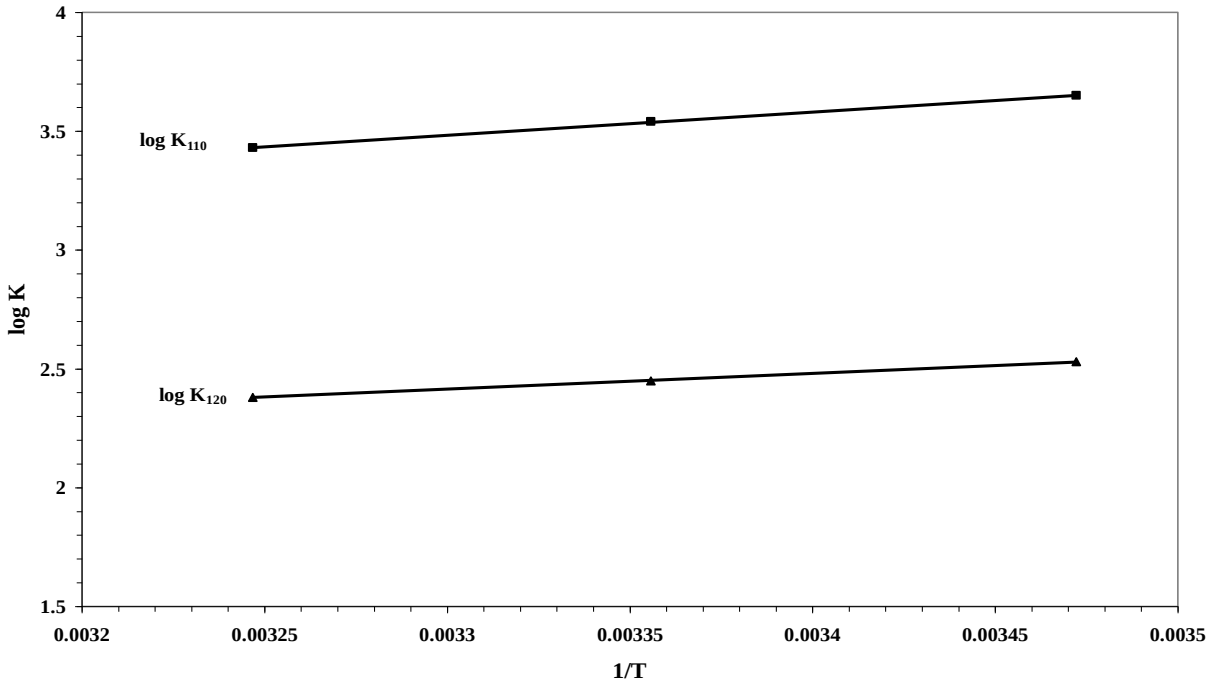


Figure 3. Effect of temperature on the formation constant ($\log_{10} K_{110}$) and ($\log_{10} K_{120}$) of Pd(Pic)-Adenosine system

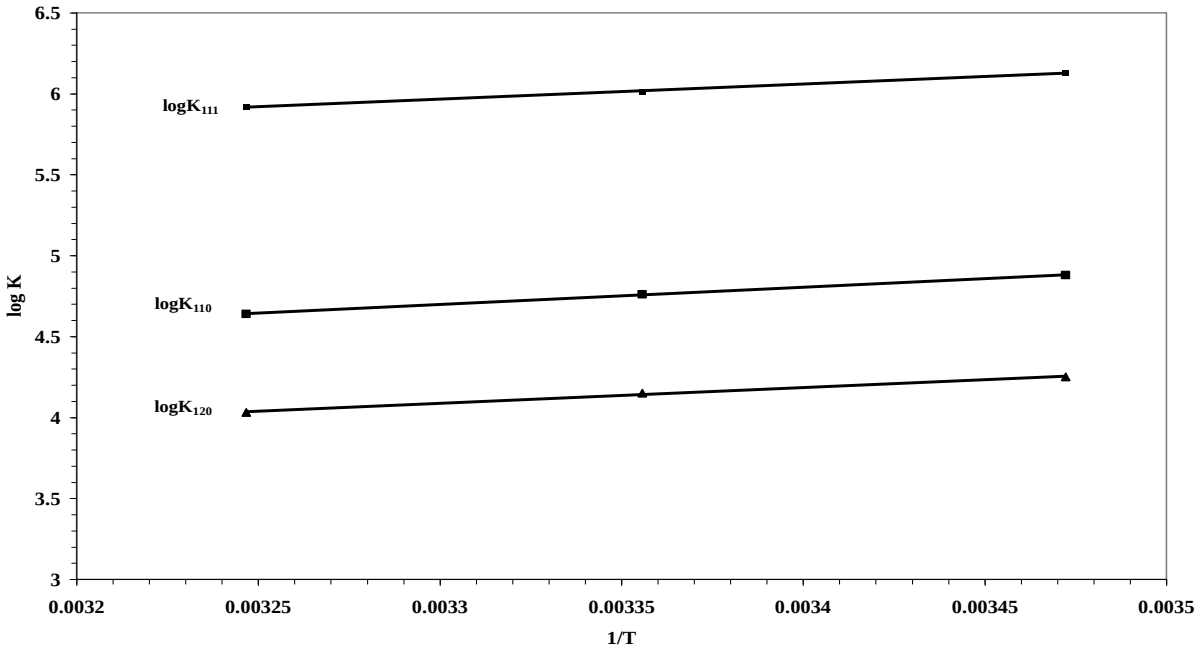


Figure 4. Effect of temperature on the formation constant ($\log_{10} K_{111}$), ($\log_{10} K_{110}$) and ($\log_{10} K_{120}$) of Pd(Pic)-AMP system

The main conclusions from the data can be summarized as follows.

The results can be interpreted as follows.

(1) The protonation reactions of adenosine (Eq.13) and AMP (Eqs 14 and 15) are shown as follow:

$L + H^+ \rightleftharpoons HL^+$ (13)

$L^{2-} + H^+ \rightleftharpoons HL^-$ (14)

$HL^- + H^+ \rightleftharpoons H_2L$ (15)

Table 3. Protonation constants of adenosine and adenosine monophosphate at different temperatures and I = 0.1 mol dm^{-3} $NaNO_3$.

System	*T* (°C)	p	q	r	$\log_{10}\beta$	S	log K_{NH}	log $K_{Phosphate}$
Adenosine	15	0	1	1	3.75±0.05	3.6 E-8	3.75	
	25	0	1	1	3.65±0.03	1.9 E-8	3.65	
	35	0	1	1	3.54±0.07	4.3E-8	3.54	
AMP	15	0	1	1	7.24±0.05	7.3E-8	7.24	4.41
		0	1	2	11.65±0.08			
	25	0	1	1	7.11±0.03	5.6E-8	7.11	4.31
		0	1	2	11.42±0.06			
	35	0	1	1	7.01±0.04	4.9E-8	7.01	4.19
		0	1	2	11.20±0.08			

Table 4. Stability constants of Pd(Pic)-adenosine and Pd(Pic)-AMP at different temperatures and I = 0.1 mol dm^{-3} $NaNO_3$.

System	*T*(°C)	p	q	r	$\log_{10}\beta$	S
Pd-Pic-adenosine	15	1	1	0	3.65±0.06	7.1E-8
		1	2	0	6.18±0.08	
	25	1	1	0	3.54±0.04	5.6E-8
		1	2	0	5.99±0.06	
	35	1	1	0	3.43±0.04	2.1E-8
		1	2	0	5.81±0.08	
Pd-Pic-AMP	15	1	1	0	4.88±0.02	1.6E-7
		1	2	0	9.13±0.06	
		1	1	1	10.98±0.04	
	25	1	1	0	4.76±0.05	3.8E-7
		1	2	0	8.91±0.06	
		1	1	1	10.77±0.09	
	35	1	1	0	4.64±0.03	3.8E-7
		1	2	0	8.67 ±0.05	
		1	1	1	10.56±0.08	

(2) The log K^H values for the protonation reaction of adenosine and AMP as given in Eqs. 13-15 decrease with increasing temperature. This means that, the dissociation constants increase with the increase of the temperature revealing that its acidity increases with increasing temperature.

(3) A negative value of ΔH° for the protonation process of both adenosine and AMP ligands indicates that its association process is accompanied by a release of heat and the process is exothermic.

(4) The protonation reaction of adenosine and AMP ligands has positive entropy; this may be due to increased disorder as a result of desolvation processes and the breaking of hydrogen bonds. On the other hand, the second protonation process is accompanied by less positive entropy than the first one as expected for AMP.

(4) The complex formation reactions of $Pd(Pic)^{2+}$ with adenosine (Eqs. 16 and 17) and AMP (Eqs. 18-20) can be represented as follow:

$$[Pd(Pic)]^{2+} + L \rightleftharpoons [Pd(Pic)L]^{2+} \quad (16)$$

$$[Pd(Pic)L]^{2+} + L \rightleftharpoons [Pd(Pic)L_2]^{2+} \quad (17)$$

$$[Pd(Pic)]^{2+} + L^{2-} \rightleftharpoons [Pd(Pic)L] \quad (18)$$

$$[Pd(Pic)]^{2+} + L^{2-} \rightleftharpoons [Pd(Pic)L_2]^{2-} \quad (19)$$

$$[Pd(Pic)L] + H^{+} \rightleftharpoons [Pd(Pic)LH]^{+} \quad (20)$$

The negative values of ΔH° for complexation reactions show that the chelation processes are exothermic, indicating that the complex formation reactions are favored at low temperatures. This may be attributed to the fact that when a coordinate bond between the ligand and the metal ion is formed, the electron density on the metal ion generally increases. Consequently, its affinity for a subsequent molecule ligand decreases, leading to an increase in ΔG^{o} and ΔH^{o} of complexation.

(5) Table 4 shows that ($\log_{10} K_1$-$\log_{10} K_2$) values are usually positive, since the coordination sites of the metal ions are more freely available for binding of the first molecule than the second one.

(6) The ΔS° value for complexation reactions are positive confirms that complex formation is entropically favourable. This indicates that the increase in entropy by the release of bound solvent molecules on chelation is greater than the decrease resulting from the chelation process itself. This may occur due to the ordered solvent molecules around both the ligand and the metal ion has acquired a more random configuration on chelation i.e., the ordered arrangements of the solvent molecules around the ligand and $[Pd(Pic)]^{2+}$ cation is lost when the complex is formed.

(7) All values of ΔG^{o} for complexation are negative (Table 5), indicating that the chelation process proceeds spontaneously.

(8) It is generally noted that $-\Delta G_1^{o} > -\Delta G_2^{o}$ and $-\Delta H_1^{o} > -\Delta H_2^{o}$ (Table 5). This may be attributed to the steric hindrance produced by the entrance of a second molecule.

Table 5. Thermodynamics for the association of adenosine, AMP, Pd(Pic)-adenosine and Pd(Pic)-AMP systems.

System	**ΔH° ($kJmol^{-1}$)**	**ΔS° ($JK^{-1} mol^{-1}$)**	**ΔG° ($kJmol^{-1}$)**
Adenosine			
$L + H^{+} \rightleftharpoons HL^{+}$	-17.82	9.98	-20.79
AMP			

$L^{2-} + H^{+} \rightleftharpoons HL^{-}$	-19.55	22.59	-27.11
$HL^{-} + H^{+} \rightleftharpoons H_2L$	-18.66	19.89	-24.59
Pd-Pic-adenosine			
$[Pd(Pic)]^{2+} + L \rightleftharpoons [Pd(Pic)L]^{2+}$	-18.68	5.05	-20.18
$[Pd(Pic)L]^{2+} + L \rightleftharpoons [Pd(Pic)L_2]^{2+}$	-12.74	4.17	-13.99
Pd-Pic-AMP			
$[Pd(Pic)]^{2+} + L^{2-} \rightleftharpoons [Pd(Pic)L]$	-20.37	22.59	-27.11
$[Pd(Pic)]^{2+} + L^{2-} \rightleftharpoons [Pd(Pic)L_2]^{2-}$	-18.66	16.68	-23.63
$[Pd(Pic)L] + H^{+} \rightleftharpoons [Pd(Pic)LH]^{+}$	-17.86	55.14	-34.29

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