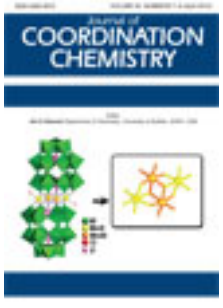

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Mohamed R. Shehata [a], Mohamed M. Shoukry [a] & Sara ali [a]
[a] Department of Chemistry, Faculty of Science, University of Cairo, Cairo, Egypt
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Mono- and binuclear complexes involving $[Pd(N,N\text{-dimethylethylenediamine})(H_2O)_2]^{2+}$, 4,4′-bipiperidine and DNA constituents†

MOHAMED R. SHEHATA, MOHAMED M. SHOUKRY* and SARA ALI

Department of Chemistry, Faculty of Science, University of Cairo, Cairo, Egypt

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The $Pd(dmen)Cl_2$, where dmen = *N*,*N*-dimethethylenediamine, was synthesized and characterized by elemental analysis and spectroscopy. The complex-formation equilibria in the reaction of $[Pd(dmen)(H_2O)_2]^{2+}$ with 4,4′-bipiperidine (Bip) and DNA constituents were investigated at 25°C and 0.1 mol L^{-1} ionic strength. The results show the formation of $[(H_2O)(dmen)Pd(Bip)Pd(dmen)(H_2O)]^{4+}$. Inosine, uracil, and thymine interact with the previously mentioned complex by the substitution of two-coordinated water molecules. The formation constants of all possible mono- and binuclear complexes were determined and their speciation diagrams were evaluated.

Keywords: Palladium(II) complexes; 4,4′-Bipiperidine; DNA constituents; Binuclear complexes; Equilibrium constants

1. Introduction

Attempts to overcome the drawbacks (severe side effects, development of resistance) of cis-$[Pt(NH_3)_2Cl_2]$, cisplatin, in cancer therapy have focused on two different approaches: (1) modification of the chloride leaving groups to alter the pharmacodynamic and -kinetic properties and thereby reduce the toxicity and (2) fundamental changes in the structure of the complex or substitution of primary amine ligands by chelating amines to influence the repair processes that are involved in the development of resistance, i.e., the cell response. In addition to new mononuclear complexes with improved properties in terms of toxicity (carboplatin) or cross-resistance to cisplatin (oxaliplatin), a new class of binuclear Pt(II) complexes has been developed by Farrell's group [1–4]. The apparent advantage of these complexes is the high charge (+4), compared to the neutral mononuclear complexes, resulting in good solubility, efficient electrostatic interaction with polyanionic DNA (the major pharmacological target of platinating agents), and fast uptake [5]. Furthermore, they form structurally different Pt-DNA adducts that may lead to a unique pattern of DNA.

*Corresponding author. Email: shoukrymm@hotmail.com
†Dedicated to Prof. Dallas L. Rabenstein on the occasion of his 70th birthday.

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Pd(II)- and Pt(II)-amine complexes have the same general structures and thermodynamic properties. However, the former complexes are five orders of magnitude more reactive than their platinum counterparts. Therefore, Pd(II) complexes are good models for the analogous Pt(II) complexes in solution. Current research in our laboratories is focused on the equilibria of complex-formation reactions of (diamine)$PdCl_2$ [6–12] and dinuclear palladium(II) [13, 14] complexes with bio-relevant ligands.

In this investigation, *N*,*N*-dimethylethylenediamine is used. It has two methyls attached to one nitrogen of ethylenediamine. The two methyls create steric hindrance with incoming ligands such as DNA, slowing the reactivity of the complexes to the same level as for platinum-amine analogs. The present investigation describes the synthesis and characterization of the Pd(II) complex with *N*,*N*-dimethylethylenediamine and the interaction of $[Pd(dmen)(H_2O)_2]^{2+}$ with the studied DNA constituents and 4,4′-bipiperidine. Binuclear complexes involving $Pd(dmen)^{2+}$ and 4,4′-bipiperidine linking two $Pd(dmen)^{2+}$ species were investigated.

2. Experimental

2.1. *Materials*

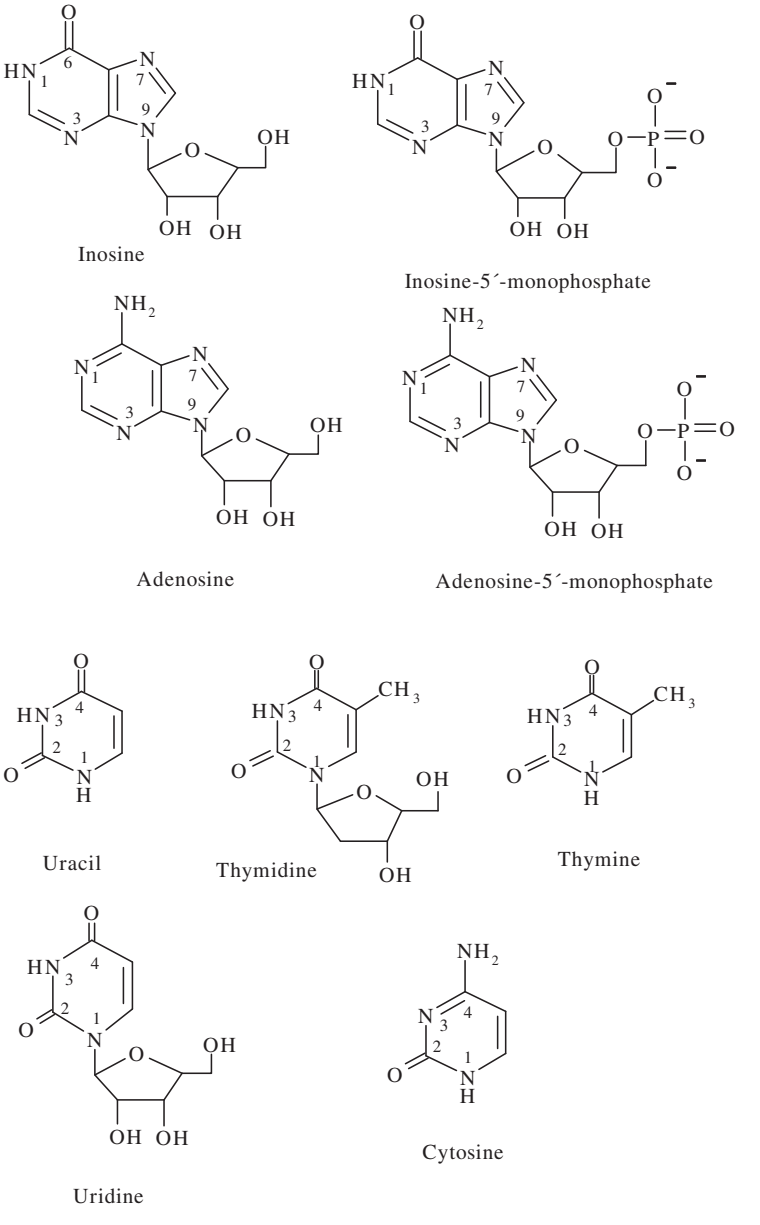
K_2PdCl_4, *N*,*N*-dimethylethylendiamine, 4,4′-bipiperidine · 2HCl (Bip), and cysteine · HCl were obtained from Aldrich. The DNA constituents (inosine, inosine-5′-monophosphate (IMP), adenosine, adenosine-5′-monophosphate, cytosine, thymine, thymidine, uracil, and uridine) were provided by Sigma Chemical Co. For equilibrium studies, $[Pd(dmen)Cl_2]$ was converted into the diaqua complex by treating it with two equivalents of $AgNO_3$, as described [12]. The ligands in the form of hydrochlorides were converted into the corresponding hydronitrates. Cytosine and the nucleotides were prepared in the protonated form with a standard HNO_3 solution. All solutions were prepared in deionized water. The structural formulas of the investigated ligands are given in scheme 1.

2.2. *Synthesis*

$Pd(dmen)Cl_2$ was prepared by dissolving K_2PdCl_4 (2.82 mmol) in 10 mL water under stirring. The clear solution of $[PdCl_4]^{2-}$ was filtered and *N*,*N*-dimethylethylenediamine (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 and/or NaOH. A yellowish-brown precipitate of $Pd(dmen)Cl_2$ was formed and stirred for a further 30 min at 50°C. After filtering off the precipitate, it was thoroughly washed with H_2O, ethanol, and diethyl ether. A yellow powder was obtained. Anal. Calcd for $C_4H_{12}N_2PdCl_2$ (%): C, 18.08; H, 4.52; N, 10.55. Found (%): C, 18.0; H, 5.4; N, 10.3.

2.3. *Characterization of complexes and potentiometric analysis*

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 [15]. All titrations were carried out at 25.0 ± 0.1°C in purified nitrogen using a titration vessel described



Scheme 1. Structural formulas of DNA constituents.

previously [16]. Elemental analysis was done by CHNS Automatic Analyzer, Vario ElIII-Elementar.

The acid dissociation constants of the ligands were determined by titrating 0.05 mmol 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 $[Pd(dmen)(H_2O)_2]^{2+}$ were determined by titrating 0.05 mmol of complex with a standard 0.05 mol L^{-1} NaOH solution. The formation

constants of the complexes were determined by titrating solution mixtures of $[Pd(dmen)(H_2O)_2]^{2+}$ (0.05 mmol) and the ligand in the concentration ratio of 1 : 2 (Pd : ligand) for the DNA constituents. The formation constants of binuclear complexes of Bip were determined by titrating the solution mixture of 0.05 mmol of $[Pd(dmen)(H_2O)_2]^{2+}$ and Bip in the concentration ratio of 2 : 1 (Pd : Bip). The formation constants of the binuclear DNA complexes were determined by titrating the solution mixture of 0.05 mmol of $[Pd(dmen)(H_2O)_2]^{2+}$, Bip, and DNA constituent in the concentration ratio of 2 : 1 : 2 (Pd : Bip : DNA constituent). 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 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}) at 25°C. The pH values, in the range 2–12, were plotted against p[H] values. 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 $[Pd(dmen)(H_2O)_2]^{2+}$, Bip or DNA constituent, and proton, respectively. In the case of the binuclear complex with the DNA constituent, M, L, and H stand for $[(Pd(dmen))_2(Bip)(H_2O)_2]^{4+}$, DNA constituent, and proton, respectively. The calculations were performed using the computer program MINIQUAD-75 [17]. The stoichiometry and stability constants of the complexes formed were determined by trying various possible composition models for the studied systems. The model selected was that which gave the best statistical fit and was chemically consistent with the magnitudes of various residuals, as described elsewhere [17]. Tables 1–3 list the stability constants together with their standard deviations and the sum of the squares of the residuals derived from the MINIQUAD output. The concentration distribution diagrams were obtained with the program SPECIES [18] under the experimental condition used.

2.4. *Spectrophotometric measurements*

Spectrophotometric measurements of Pd(dmen)–uracil complex (figure 1) were performed by recording the UV-Vis spectra of solutions (A–D), where (A) 2×10^{-4} mol L^{-1} of $Pd(dmen(H_2O)_2^{2+}$, (B) 2×10^{-4} mol L^{-1} of $Pd(dmen)(H_2O)_2^{2+} +$ 2×10^{-4} mol L^{-1} of uracil $+ 2 \times 10^{-4}$ mol L^{-1} of NaOH, (C) 2×10^{-4} mol L^{-1} of $Pd(dmen)(H_2O)_2^{2+} + 4 \times 10^{-4}$ mol L^{-1} of uracil $+ 4 \times 10^{-4}$ mol L^{-1} of NaOH, and (D) 2×10^{-4} mol L^{-1} of uracil.

Spectrophotometric measurements of Pd(dmen)–Bip complex (figure 2) were performed by recording the UV-Vis spectra of solutions (A–D), where (A) 2×10^{-4} mol L^{-1} of $Pd(dmen)(H_2O)_2^{2+}$, (B) 2×10^{-4} mol L^{-1} of $Pd(dmen)(H_2O)_2^{2+} +$

Table 1. Formation constants for complexes of $[Pd(dmen)(H_2O)_2]^{2+}$ with DNA units at 25°C and 0.1 mol L^{-1} ionic strength.

System	M L H[a]	log β[b]	pK_a[c]
Pd(dmen)–OH	1 0 −1	−5.29 (0.02)	5.29
	1 0 −2	−14.74 (0.02)	9.45
	2 0 −1	−2.12 (0.07)	
Inosine	0 1 1	8.80 (0.03)	8.80
	1 1 0	6.51 (0.04)	
	1 2 0	10.48 (0.04)	
	1 1 1	11.19 (0.05)	4.68
Inosine-5′-monophosphate	0 1 1	9.02 (0.02)	9.02
	0 1 2	15.24 (0.03)	6.22
	1 1 0	9.46 (0.03)	
	1 2 0	13.21 (0.04)	
	1 1 1	15.90 (0.03)	6.44
Adenosine	0 1 1	3.60 (0.01)	3.60
	1 1 0	4.74 (0.03)	
	1 2 0	6.62 (0.02)	
Adenosine-5′-monophosphate	0 1 1	7.04 (0.03)	7.04
	0 1 2	11.37 (0.04)	4.33
	1 1 0	5.86 (0.02)	
	1 2 0	9.43 (0.01)	
	1 1 1	11.77 (0.01)	5.91
Cytosine	0 1 1	4.65 (0.02)	4.65
	1 1 0	6.21 (0.02)	
	1 2 0	9.35 (0.03)	
Uracil	0 1 1	9.18 (0.01)	9.18
	1 1 0	8.54 (0.01)	
	1 2 0	14.74 (0.02)	
Thymine	0 1 1	9.65 (0.01)	9.65
	1 1 0	8.80 (0.01)	
	1 2 0	15.29 (0.02)	
Thymidine	0 1 1	9.54 (0.02)	9.54
	1 1 0	7.37 (0.08)	
	1 2 0	10.37 (0.2)	
Uridine	0 1 1	9.01 (0.01)	9.01
	1 1 0	8.09 (0.02)	
	1 2 0	12.65 (0.03)	

[a]M, L, and H are the stoichiometric coefficients corresponding to Pd(dmen), DNA constituent, and H^+, respectively.
[b]log β of Pd(dmen)-DNA complexes. Standard deviations are given in parentheses; sum of square of residuals are less than $5e^{-7}$.
[c]The pK_a of the protonated species ($\log\beta_{111} - \log\beta_{110}$).

1×10^{-4} mol L^{-1} of Bip + 2×10^{-4} mol L^{-1} of NaOH, (C) 2×10^{-4} mol L^{-1} of $Pd(dmen)(H_2O)_2^{2+}$ + 1×10^{-4} mol L^{-1} of Bip + 4×10^{-4} mol L^{-1} of NaOH, and (D) 1×10^{-4} mol L^{-1} of Bip. The spectral measurements of the binuclear complex of uracil, taken as an example for DNA (figure 2) were performed by recording the spectra of solutions (E–H) (E) 2×10^{-4} mol L^{-1} of $[Pd(dmen)(H_2O)_2]^{2+}$, 1×10^{-4} mol L^{-1} of Bip, and 2×10^{-4} mol L^{-1} of NaOH; (F) 2×10^{-4} mol L^{-1} of $[Pd(dmen)(H_2O)_2]^{2+}$, 1×10^{-4} mol L^{-1} of Bip, 1×10^{-4} mol L^{-1} of uracil, and 3×10^{-4} mol L^{-1} of NaOH; (G) 2×10^{-4} mol L^{-1} of $[Pd(dmen)(H_2O)_2]^{2+}$, 1×10^{-4} mol L^{-1} of Bip, 2×10^{-4} mol L^{-1} of uracil, 4×10^{-4} mol L^{-1} of NaOH, and (H) 2×10^{-4} mol L^{-1} of uracil. Under these experimental conditions and after neutralization of the hydrogen ions released with

Table 2. Formation constants for complexes of $[Pd(dmen)(H_2O)_2]^{2+}$ with bipiperidine at 25°C and 0.1 mol L^{-1} ionic strength.

System	M L H[a]	log β[b]	pK_a[c]
Bipiperidine	0 1 1	10.96 (0.02)	10.96
	0 1 2	21.12 (0.01)	10.16
	1 1 0	13.82 (0.06)	
	1 1 1	19.92 (0.05)	6.10
	2 1 0	20.04 (0.06)	

[a]M, L, and H are the stoichiometric coefficients corresponding to Pd(dmen), Bip, and H^+, respectively.
[b]log β of Pd(dmen)–Bip complexes. Standard deviations are given in parentheses; sum of square of residuals are less than $5e^{-7}$.
[c]The pK_a of the ligand or the protonated complex.

Table 3. Formation constants for the binuclear complexes of $[(H_2O)(dmen)Pd(Bip)Pd(dmen)(H_2O)]^{4+}$ with some DNA constituents at 25°C and 0.1 mol L^{-1} ionic strength.

System	M L H[a]	log β[b]	pK_a[c]
$[(H_2O)(dmen)Pd(Bip)Pd(dmen)(H_2O)]^{4+}$			
	1 0 −1	−9.62 (0.02)	9.62
	1 0 −2	−19.17 (0.01)	9.55
Inosine	0 1 1	8.80 (0.02)	8.80
	1 1 0	5.27 (0.05)	
	1 2 0	9.09 (0.05)	
Uracil	0 1 1	9.18 (0.01)	9.18
	1 1 0	5.57 (0.04)	
	1 2 0	9.74 (0.06)	
Thymine	0 1 1	9.65 (0.01)	9.65
	1 1 0	5.73 (0.03)	
	1 2 0	10.38 (0.05)	

[a]M, L, and H are the stoichiometric coefficients corresponding to $[(H_2O)(dmen)Pd(Bip)Pd(dmen)(H_2O)]^{4+}$, DNA constituent, and H^+, respectively.
[b]log β of binuclear complexes. Standard deviations are given in parentheses; sum of square of residuals are less than $5e^{-7}$.
[c]The pK_a of the ligands or the aqua complexes.

complex-formation, it is supposed that the complexes have been completely formed. In each mixture, the volume was brought to 10 mL by the addition of deionized water and ionic strength is kept constant at 0.1 mol L^{-1} $NaNO_3$.

3. Results and discussion

3.1. *Characterization of the solid complexes*

The analytical data indicates that the complex is of 1 : 1 stoichiometry and of formula $Pd(dmen)Cl_2$. The IR spectrum of $Pd(dmen)Cl_2$ exhibits bands at 3300–3400 cm^{-1}, attributed to stretching vibrations of NH_2. The complex exhibits bands for (NH_2)

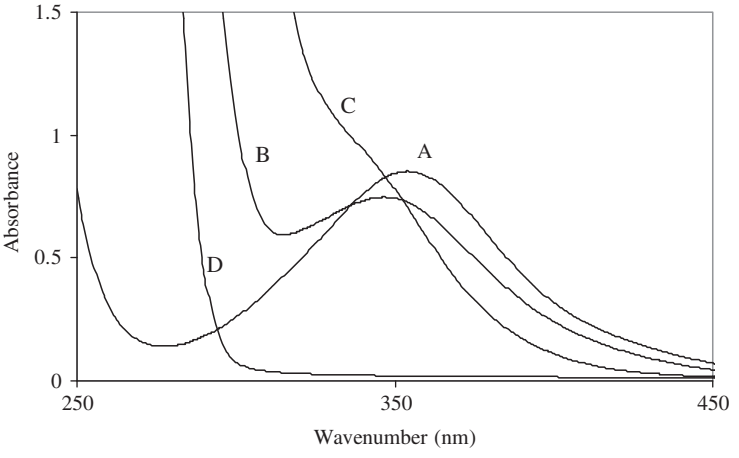


Figure 1. Electronic spectra of $[Pd(dmen)(H_2O)_2]^{2+}$ and its uracil complexes. Composition of solution mixtures A, B, C, and D are given in section 2.

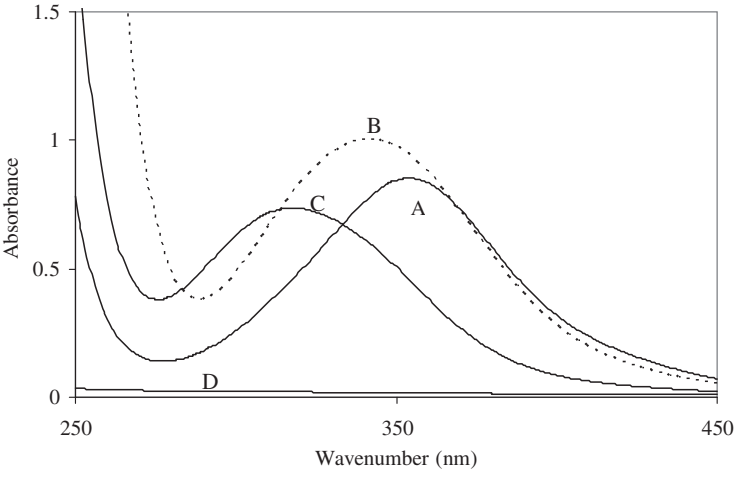


Figure 2. Electronic spectra of $[Pd(dmen)(H_2O)_2]^{2+}$ and its Bip complexes. Composition of solution mixtures A, B, C, and D are given in section 2.

bending at 1465 and 1562 cm^{-1} and bands for the stretching vibration corresponding to Pd–N at 480 and 523 cm^{-1}.

3.2. *Acid–base equilibria of the ligands*

Acid dissociation constants of the ligands were determined in a solution of constant ionic strength (0.1 mol L^{-1} $NaNO_3$) at 25°C. The results obtained are in good agreement with the literature data [19].

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

$[Pd(dmen)(H_2O)_2]^{2+}$ may undergo hydrolysis. Its acid–base chemistry was characterized by fitting the potentiometric data to various acid–base models. The best-fit model was found to be consistent with the formation of three species: 1 0 −1, 1 0 −2, and 2 0 −1, as presented in reactions (1)–(3). Trials were made to fit the potentiometric data assuming the formation of the monohydroxo-bridged dimer, 2 0 −2, but this resulted in a very poor fit of the data. The dimeric species 2 0 −2 was detected by Nagy *et al.* [20] for a similar system.

$$\underset{1\,0\,0}{\left[Pd(dmen)(H_2O)_2\right]^{2+}} \overset{pK_{a1}}{\rightleftharpoons} \underset{1\,0\,-1}{[Pd(dmen)(H_2O)(OH)]} + H^+ \quad (1)$$

$$\underset{1\,0\,-1}{[Pd(dmen)(OH)]^+} \overset{pK_{a2}}{\rightleftharpoons} \underset{1\,0\,-2}{\left[Pd(dmen)(OH)_2\right]} + H^+ \quad (2)$$

$$\underset{1\,0\,0}{\left[Pd(dmen)(H_2O)_2\right]^{2+}} + \underset{1\,0\,-1}{[Pd(dmen)(H_2O)(OH)]^+} \overset{\log K_{dimer}}{\rightleftharpoons} \underset{2\,0\,-1}{[(H_2O)Pd(dmen)(OH)Pd(dmen)(H_2O)]^{3+}} + H_2O \quad (3)$$

The pK_{a1} and pK_{a2} values for $[Pd(dmen)(H_2O)_2]^{2+}$ are 5.29 and 9.45, respectively. The equilibrium constant for the dimerization reaction (3) can be calculated by equation (4) as 3.17.

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

The distribution diagram for $[Pd(dmen)(H_2O)_2]^{2+}$ and its hydrolyzed species reveals that the concentration of the monohydroxo species 10-1 and the dimeric species 20–1 increases with the increase of pH, reaching a maximum concentration of 96% at pH 7.5 for the 10–1 species and 36.6% at pH 5.5 for the 20–1 species. This indicates that in the physiological pH range, i.e., at pH 6–7, the monohydroxo complex (10–1) dominates and can interact with the DNA subunits. At higher pH the inert dihydroxo complex will be the major species, and consequently the ability of DNA to bind will decrease significantly.

3.4. *Complexes of DNA constituents*

DNA constituents such as adenosine, cytosine, uracil, thymine, thymidine, and uridine form 1 : 1 and 1 : 2 complexes with $Pd(dmen)^{2+}$. However, inosine and nucleotides such as inosine-5′-monophosphate and adenosine-5′-monophosphate form the mono-protonated complex, in addition to the formation of 1 : 1 and 1 : 2 complexes. The pK_a value of the protonated inosine complex is 4.68, corresponding to N_1H. The lowering of this value with respect to that of free inosine ($pK_a = 8.80$) is due to acidification upon complex-formation [21,22]. IMP complex is more stable than that of inosine. This may be explained on the basis of different coulombic forces operating between the ions resulting from the negatively charged phosphate. Hydrogen-bonding between the

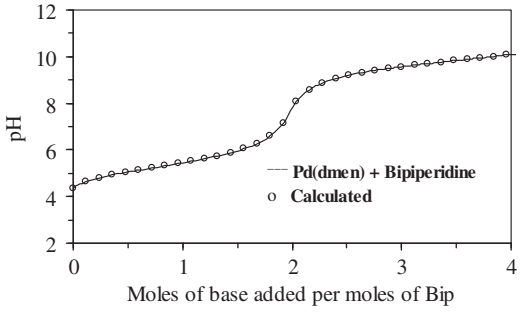


Figure 3. Potentiometric titration curve for 1.25 mmol of $[Pd(dmen)(H_2O)_2]^{2+}$ and 0.0625 mmol of Bip at 25°C and 0.1 mol L^{-1} $NaNO_3$.

phosphate and exocyclic amine is also thought to contribute to the increased stability. Such hydrogen bonding was previously reported for similar systems [23, 24].

The pyrimidines uracil, uridine, thymine, and thymidine have basic nitrogen donors (N_3) in the measurable pH range [25] and as a consequence they form 1 : 1 and 1 : 2 complexes with $Pd(dmen)^{2+}$. As a result of the high pK_a values of pyrimidines ($pK_a > 9$), complex-formation dominates above pH 8.5. The thymine complex is more stable than that of uracil, probably due to the higher basicity of the N_3 site of thymine resulting from the inductive effect of the extra electron-donating methyl. Cytosine undergoes N_3 protonation under mild acidic conditions. The value obtained for its protonation constant is 4.65. The lower values for the stability constants of its complexes (table 3) reflect the difference in basicity of the donor site.

The spectra given in figure 1 show that the band at 353 nm corresponding to $[Pd(dmen)(H_2O)_2]^{2+}$ (A) undergoes a blue shift to 345 nm for $[Pd(dmen)(uracil\text{-}H)]^{+}$, 110 (B). This band is further shifted to a shoulder at 336 nm for $[Pd(dmen)(uracil\text{-}H)_2]$, 120 (C). The band appears as a shoulder due to the large absorption of uracil (D).

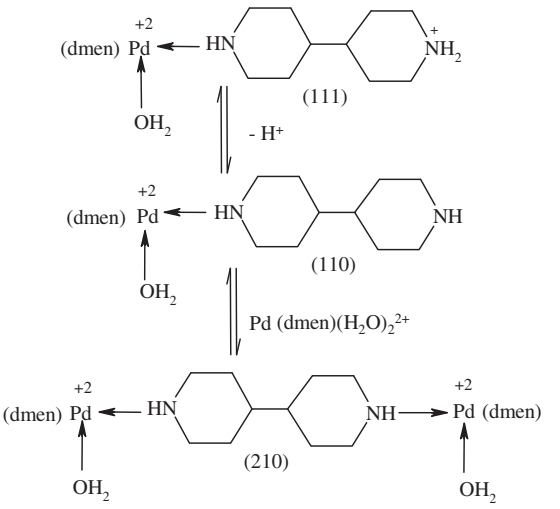
3.5. *Complex formation equilibria of binuclear $Pd(dmen)^{2+}$ involving 4,4′-bipiperidine and some selected DNA constituents*

The titration curve of the solution mixture of $Pd(dmen)(H_2O)_2]^{2+}$ and 4,4′-bipiperidine in the ratio 2 : 1, figure 3, shows a sharp inflection at $a = 1$ (a is moles of base added per mole of 4,4′-bipiperidine), corresponding to the complete formation of $[(H_2O)(dmen)Pd(Bip)Pd(dmen)(H_2O)]^{4+}$ with a formation constant $\log \beta_{210} = 20.04$ (scheme 2, table 2).

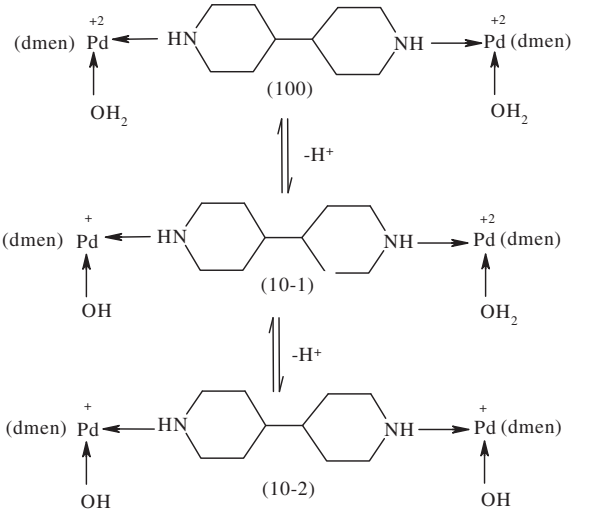
Beyond $a = 1$, the binuclear complex is subjected to hydrolysis. In this region, the titration data are fitted considering the formation of the hydrolyzed species with stoichiometric coefficients 10–1 and 10–2, as given in scheme 3.

The speciation diagram of the Pd(dmen)–bipiperidine system is given in figure 4. The binuclear complex, $[(H_2O)(dmen)Pd(Bip)Pd(dmen)(H_2O)]^{4+}$ (210), starts to form at low pH and on increasing pH, its concentration increases; it is the dominant species up to pH 7.2 and reaches a maximum concentration of 87.5% at pH 5.2.

Complex-formation between $[(H_2O)(dmen)Pd(Bip)Pd(dmen)(H_2O)]^{4+}$ and inosine, taken as an example of a DNA constituent, showed the formation of 1 : 1 and 1 : 2



Scheme 2. Complex formation equilibria of Pd(dmen)–Bip complexes.



Scheme 3. Acid–base equilibria of $[(H_2O)(dmen)Pd(Bip)Pd(dmen)(H_2O)]^{4+}$.

complexes, as given in scheme 4. The stability constant of the DNA complexes is thymine > uracil > inosine (table 3). This may be explained as a result of the difference in the basicity of the donor as reflected by the pK_a values.

The speciation diagram of $[(H_2O)Pd(dmen)(Bip)Pd(dmen)(H_2O)]^{4+}$-inosine complex is given in figure 5. The 1 : 1 complex starts to form at pH 4 and on increasing pH, its concentration increases and reaches a relative amount of 70% at pH 7–8.5. The 1 : 2 complex attains a maximum formation degree of 27% at pH 10.6. The hydrolyzed species are formed after pH 9.0. From a biological point of view, it is interesting to note that the DNA complex predominates in the physiological pH range, and the reaction of the binuclear complex with DNA is quite feasible.

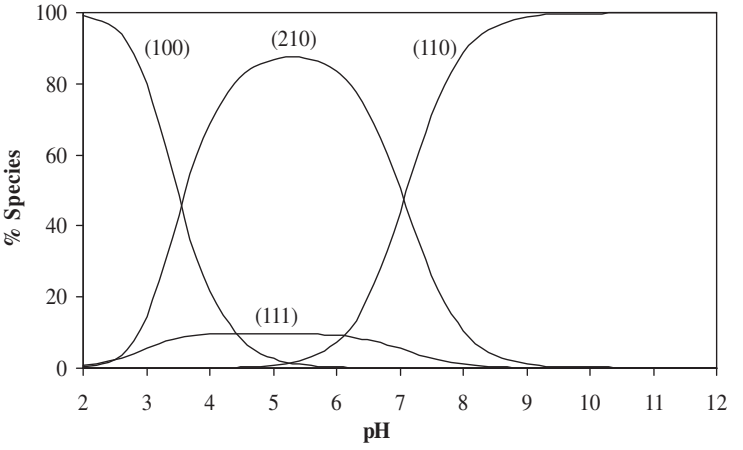
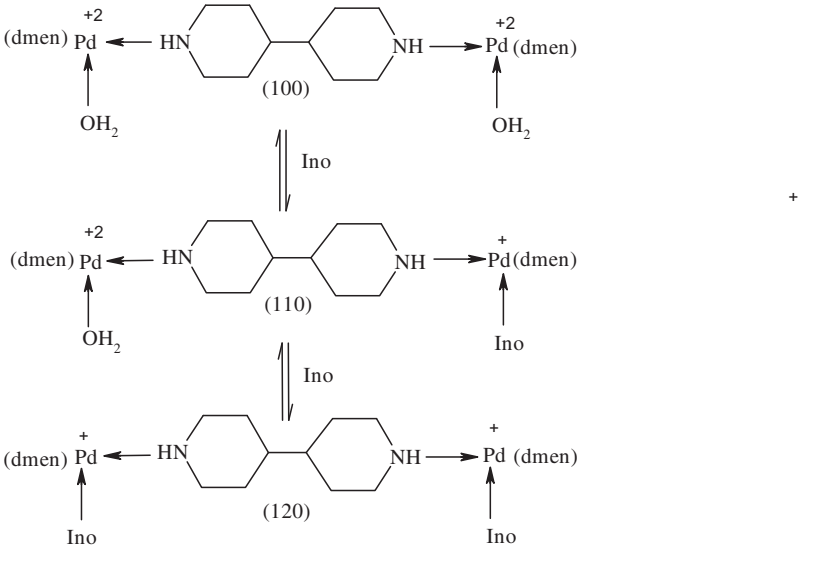


Figure 4. Concentration distribution of various species as a function of pH in the $[Pd(dmen)(H_2O)_2]^{2+}$-bipiperidine system.



Scheme 4. Complex-formation equilibria of the $[(H_2O)(dmen)Pd(Bip)Pd(dmen)(H_2O)]^{4+}$-inosine complex.

Spectral bands of $Pd(dmen)(H_2O)_2^{2+}$ and its 4,4′-bipiperidine complex are quite different in the position of the maximum wavelength and molar absorptivity (figure 2). The spectrum of $[Pd(dmen)(H_2O)_2]^{2+}$ (mixture A) shows an absorption maximum at 353 nm. The spectrum obtained for $[(H_2O)(dmen)Pd(Bip)Pd(dmen)(H_2O)]^{4+}$ (mixture B) exhibits a band at 339 nm. This band is further shifted to 315 nm by the addition of additional 2×10^{-4} mol L^{-1} NaOH for the formation of [(OH)(dmen)Pd(Bip)Pd (dmen)(OH)]$^{2+}$ (mixture C). There is no UV absorption for free Bip in this region (mixture D).

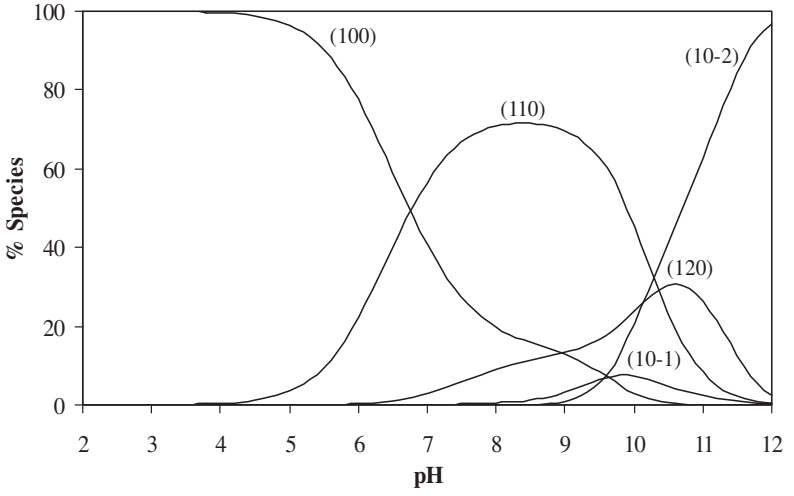


Figure 5. Concentration distribution of various species as a function of pH in the $[(H_2O)(dmen)Pd(Bip)Pd(dmen)(H_2O)]^{4+}$-inosine system.

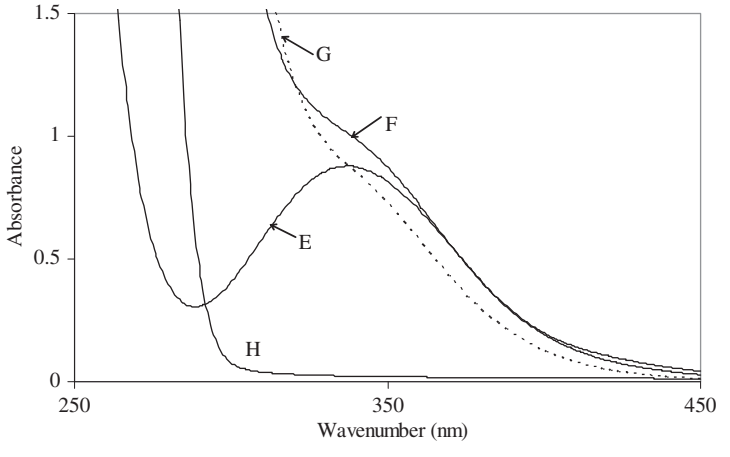


Figure 6. Electronic spectra of binuclear Pd(II) complexes involving Bip and uracil. Composition of solution mixtures E, F, G, and H are given in section 2.

Spectral bands of $Pd(dmen)(H_2O)_2^{2+}$ with 4,4′-bipiperidine and uracil are given in figure 6. The spectrum obtained for $[(H_2O)(dmen)Pd(Bip)Pd(dmen)(H_2O)]^{4+}$ (mixture E) occurs at 339 nm. The spectra obtained for $[(H_2O)(dmen)Pd(Bip)Pd(dmen)(uracil)]^{3+}$ (mixture F) and $[(uracil)(dmen)Pd(Bip)Pd(dmen)(uracil)]^{2+}$ (mixture G) exhibit shoulders at 332 and 315 nm, respectively. The spectral band shifts are evidence for binuclear complex formation, supporting the potentiometric results. Further investigation on binuclear complex formation may require further studies such as mono- and polynuclear NMR measurements.

4. Conclusion

The present investigation describes complex-formation equilibria of $Pd(dmen)(H_2O)_2^{2+}$ with some selected DNA constituents and 4,4′-bipiperidine. The results indicate that the formation of binuclear complexes and the reaction with DNA constituents is feasible. The data support the biological significance of the di- and trinuclear platinum(II) complexes having a potent anti-tumor activity [26]. In this study, $[Pd(dmen)(H_2O)_2]^{2+}$ does not form the dihydroxo-bridged dimer (20–2), as reported for most Pd-diimine complexes. This may be explained on the basis of steric interaction created by the two methyls attached to amino nitrogen. The stability constant of Pd(dmen)-inosine complex is lower than that for the Pd(Pic)-inosine complex (where Pic = 2-picolylamine) [11]. This is attributed to the π-acceptor properties of the pyridyl group of Pic, which leads to an increase in the electrophilicity of Pd(II) and consequently increases the stability constant of its complex. Therefore, the structure of the diimine has an effect on the stability of the DNA adduct. It is interesting to compare the results of this study with those of the previously reported results of similar binuclear Pd(II) complexes. The stability constant of the binuclear inosine complex formed with $[H_2O(NH_3)_2Pd\text{-}Bip\text{-}Pd(NH_3)_2H_2O]^{4+}$ is $\log K = 5.51$, as reported previously [13], in good agreement with that of the binuclear inosine complex formed with $[(H_2O)(dmen)Pd(Bip)Pd(dmen)(H_2O)]^{4+}$ ($\log K = 5.27$), as reported in the present investigation.

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