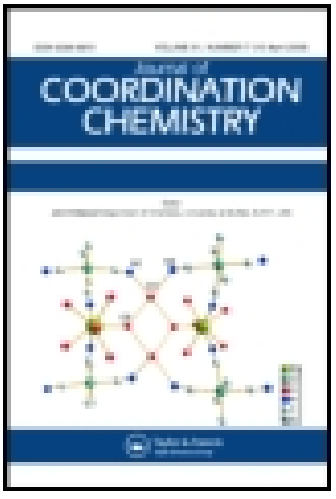

Journal of Coordination Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gcoo20

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Accepted author version posted online: 30 Mar 2015.Published online: 29 Apr 2015.

To cite this article: Perihan A. Khalaf Alla, Mohamed M. Shoukry & Rudi van Eldik (2015): Amine-bridged binuclear complexes involving [Pd(ethylenediamine)$(H_2O)_2]^{2+}$, 4,4′-bipiperidine and DNA constituents, Journal of Coordination Chemistry, DOI: 10.1080/00958972.2015.1035263

To link to this article: http://dx.doi.org/10.1080/00958972.2015.1035263

Journal of Coordination Chemistry, 2015
http://dx.doi.org/10.1080/00958972.2015.1035263

Amine-bridged binuclear complexes involving [Pd(ethylenediamine)$(H_2O)_2]^{2+}$, 4,4′-bipiperidine and DNA constituents

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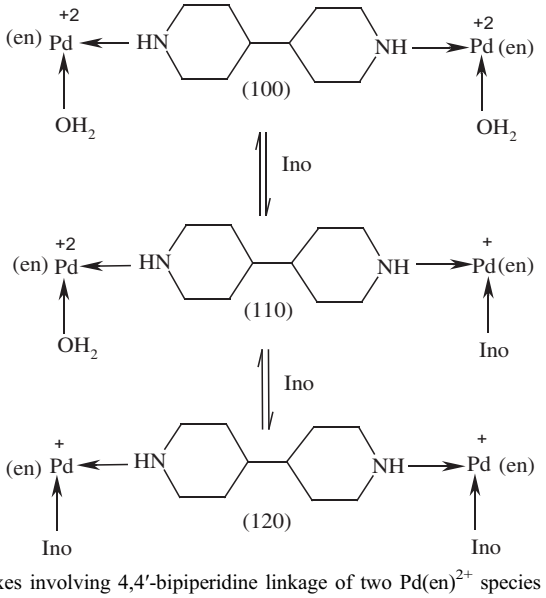
(*Received 9 January 2015; accepted 18 March 2015*)



Binuclear complexes involving 4,4′-bipiperidine linkage of two $Pd(en)^{2+}$ species were investigated. The binding of DNA constituents to the binuclear complex was studied.

The complex formation equilibria in the reaction of $[Pd(en)(H_2O)_2]^{2+}$ with 4,4′-bipiperidine (Bip) and DNA constituents such as inosine, inosine-5′-monophosphate, uracil, uridine, thymine, and thymidine were investigated at 25 °C and 0.1 M ionic strength. The $[(H_2O)(en)Pd(Bip)Pd(en)(H_2O)]^{4+}$ complex and its hydrolyzed species were formed. Substitution of coordinated water by inosine (Ino) as DNA constituent formed the complexes $[(Ino)(en)Pd(Bip)Pd(en)(H_2O)]^{3+}$ and $[(Ino)(en)Pd(Bip)Pd(en)(Ino)]^{2+}$. The formation of the binuclear complexes was further supported by spectral

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measurements. 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

Platinum complexes such as cisplatin, carboplatin, and oxaliplatin are used for treatment of different types of cancer [1, 2]. Drawbacks during treatment, such as vomiting, drug resistance, nephrotoxicity, ototoxicity, neurotoxicity, and cardiotoxicity, encouraged researchers to design new classes of platinum complexes with improved anti-tumor properties. The recent generation of anti-tumor complexes such as orally active polynuclear Pt(II) complexes are now being tested in preclinical trials [3, 4]. These polynuclear Pt(II) complexes consist of either two or three platinum centers that are linked through a flexible bridge such as an aliphatic chain [5–7] or a rigid bridge that consists, for instance, of 4,4′-bipiperidine molecules [8]. The reason for increasing interest in multinuclear complexes is their ability to form DNA adducts that differ significantly from those formed by cisplatin and related complexes [9], resulting in a completely different anti-tumor behavior. Some of the dinuclear platinum(II) complexes are highly effective *in vitro* in cisplatin-resistant cell lines as well as in several tumor cells [10, 11].

An apparent advantage of these types of complexes is the high charge (+4) compared to the neutral mononuclear complexes, resulting in good solubility, efficient electrostatic interaction with the poly-anionic DNA (the major pharmacological target of platinating agents), and fast uptake [12]. Understanding of the chemical equilibria of these binuclear complexes is of special concern for pharmaceutical and biomedical research.

Pd(II) and Pt(II) complexes have the same general structures and thermodynamic properties. However, the complexes formed by Pd(II) 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 focused on the complex formation equilibria of (diamine)$PdCl_2$ [13–19] and those of dinuclear palladium (II) [20–22] complexes with bio-relevant ligands.

The present investigation involved the interaction of $[Pd(en)(H_2O)_2]^{2+}$ with DNA constituents and 4,4′-bipiperidine. Also, the binuclear complex involving 4,4′-bipiperidine linking two $Pd(en)^{2+}$ units was investigated. The binding of DNA constituents to the latter complex were studied using potentiometric and spectrophotometric techniques.

2. Experimental

2.1. *Materials*

K_2PdCl_4, ethylenediamine (en), and 4,4′-bipiperidine 2HCl (Bip) were obtained from Aldrich Chemical Co. The DNA constituents (inosine, inosine-5′-monophosphate (IMP), thymine, thymidine, uracil, and uridine) were provided by Sigma Chemical Co. For equilibrium studies, $[Pd(en)Cl_2]$ was converted into the diaqua complex by treating it with two equivalents of $AgNO_3$ as described before [15]. All solutions were prepared in deionized water. The structural formulas of the investigated ligands are given in scheme 1.

2.2. *Synthesis*

$Pd(en)Cl_2$ 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 ethylenediamine (2.82 mmol), dissolved in 10 mL H_2O, was added dropwise to the stirred solution. The pH was adjusted to 2–3 by addition of HCl and/or NaOH. A yellowish-orange precipitate of $Pd(en)Cl_2$ 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 $C_2H_8N_2PdCl_2$: C, 10.11; H, 3.37; N, 10.55. Found: C, 10.0; H, 4.25; N, 10.3%. $Pd(en)Cl_2$ was converted into the diaqua complex $[Pd(en)(H_2O)_2](NO_3)_2$ by stirring the chloride complex with two equivalents of $AgNO_3$ overnight, and removing the AgCl precipitate by filtration through a 0.1 μm pore membrane filter. Great care was taken to ensure that the resulting solution was free of Ag^+ ions and that the chloride complex had been converted into the aqua species. The filtrate was diluted to the desired volume in a standard volumetric flask.

2.3. *Potentiometric measurements*

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 [23]. All titrations were carried out at 25.0 ± 0.1 °C in purified nitrogen atmosphere using a titration vessel described previously [24].

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 $[Pd(en)(H_2O)_2]^{2+}$ were determined by titrating 0.05 mmol of complex with standard 0.05 M NaOH solution.

2.3.1. Preparation of potentiometric samples for mononuclear complexes. The formation constants of the complexes were determined by titrating solution mixtures of $[Pd(en)(H_2O)_2]^{2+}$ (0.05 mmol) and the ligand in the concentration ratio of 1 : 2 (Pd : ligand) for the DNA constituents.

2.3.2. Preparation of potentiometric samples for binuclear complexes. The formation constants of the binuclear complexes of Bip were determined by titrating a solution mixture of 0.05 mmol of $[Pd(en)(H_2O)_2]^{2+}$ and Bip in a concentration ratio of 2 : 1 (Pd : Bip). The formation constants of the binuclear DNA complexes were determined by titrating solution mixtures of 0.05 mmol of $[Pd(en)(H_2O)_2]^{2+}$, Bip, and DNA constituents in a concentration ratio of 2 : 1 : 2 (Pd:Bip:DNA constituent). The each titrated solution mixtures 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 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 a standard NaOH (0.05 M) solution at 25 °C. The pH values 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 represents the $[Pd(en)(H_2O)_2]^{2+}$ ion concentration, L stands for Bip or DNA, and H for the proton. In case of the binuclear complex with DNA constituents, M, L, and H stand for $[(H_2O)(en)Pd(Bip)Pd(en)(H_2O)]^{4+}$, DNA constituent, and proton, respectively. The calculations were performed using the computer program MINIQUAD-75 [25]. The stoichiometry and stability constants of the complexes formed were determined by trying various possible 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 [25]. 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 (Pettit, L., Personal Communication, University of Leeds, 1993) under the experimental condition used.

2.4. *Spectrophotometric measurements*

Spectrophotometric measurements on Pd(en)–Bip complexes were performed by recording the UV–visible spectra of solutions (A–D), where (A) 2×10^{-4} M of $Pd(en)(H_2O)_2^{2+}$; (B) 2×10^{-4} M of $Pd(en)(H_2O)_2^{2+}$ + 1×10^{-4} M of Bip + 2×10^{-4} M of NaOH; (C) 2×10^{-4} M of $Pd(en)(H_2O)_2^{2+}$ + 1×10^{-4} M of Bip + 4×10^{-4} M of NaOH; and (D) 1×10^{-4} M of Bip. The spectral measurements on binuclear complex of thymine, taken as example for DNA, were performed by recording the UV–visible spectra of solutions (E–H), where (E) 2×10^{-4} M of $[Pd(en)(H_2O)_2]^{2+}$, 1×10^{-4} M of Bip and 2×10^{-4} M of NaOH; (F) 2×10^{-4} M of $[Pd(en)(H_2O)_2]^{2+}$, 1×10^{-4} M of Bip, 1×10^{-4} M of thymine and 3×10^{-4} M of NaOH; (G) 2×10^{-4} M of $[Pd(en)(H_2O)_2]^{2+}$, 1×10^{-4} M of Bip, 2×10^{-4} M of thymine and 4×10^{-4} M of NaOH; and (H) 2×10^{-4} M of thymine. Under these prevailing experimental conditions and after neutralization of the hydrogen ions released during complex formation, it was assumed that the complexes were completely formed. In each mixture, the volume was increased to 10 mL by addition of deionized water and the ionic strength was kept constant at 0.1 M $NaNO_3$.

3. Results and discussion

3.1. *Acid–base equilibria of the ligands*

The acid dissociation constants of the ligands were determined in a solution of constant ionic strength of 0.1 M ($NaNO_3$) at 25 °C. The results obtained are in good agreement with the literature data [26].

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

System	M L H[a]	$\log_{10}\beta$[b]	pK_a[c]
Pd(en)-OH	1 0 −1	−6.11 (0.03)	6.11
	1 0 −2	−15.35 (0.05)	9.24
	2 0 −2	−8.76 (0.09)	
Inosine	0 1 1	8.80 (0.03)	8.80
	1 1 0	6.83 (0.04)	
	1 2 0	11.26 (0.04)	
	1 1 1	12.10 (0.05)	5.27
Inosine-5′-monophosphate	0 1 1	9.02 (0.02)	9.02
	0 1 2	15.24 (0.03)	6.22
	1 1 0	8.76(0.03)	
	1 2 0	12.31 (0.04)	
	1 1 1	15.26 (0.03)	6.50
Uracil	0 1 1	9.18 (0.01)	9.18
	1 1 0	8.35 (0.01)	
	1 2 0	14.88 (0.02)	
Thymine	0 1 1	9.65 (0.01)	9.65
	1 1 0	8.56 (0.01)	
	1 2 0	15.14 (0.02)	
Thymidine	0 1 1	9.54 (0.02)	9.54
	1 1 0	8.84 (0.08)	
	1 2 0	14.69 (0.08)	
Uridine	0 1 1	9.01 (0.01)	9.01
	1 1 0	8.70 (0.02)	
	1 2 0	14.37 (0.03)	

[a]M, L and H are the stoichiometric coefficients corresponding to Pd(en), DNA constituent and H^+, respectively.
[b]log β of Pd(en)–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 ($\log \beta_{111} - \log \beta_{110}$).

3.2. *Complex formation equilibria of $[Pd(en)(H_2O)_2]^{2+}$*

The reaction of $[Pd(en)(H_2O)_2]^{2+}$ with some DNA constituents was previously studied [27]. Its complex formation equilibria were investigated under the experimental condition used for the formation of binuclear complexes.

$[Pd(en)(H_2O)_2]^{2+}$ may undergo deprotonation. Its acid–base chemistry was characterized by fitting the potentiometric data to various acid–base models. The best-fit model was consistent with the formation of three species: 10-1, 10-2, and 20-2. The first two species, 10-1 and 10-2, are due to deprotonation of the two coordinated water molecules, as given in equations (1) and (2). The third species, 20-2, is the dimeric di-μ-hydroxy-bridged complex of two 10-1 species according to equation (3). The dimeric species 20-2 was detected by El-Sherif [28] for a related system.

$$\underset{100}{[Pd(en)(H_2O)_2]^{2+}} \overset{pK_{a1}}{\rightleftharpoons} \underset{10-1}{[Pd(en)(H_2O)(OH)]^{+}} + H^{+} \quad (1)$$

$$\underset{10-1}{[Pd(en)(H_2O)(OH)]^+} \overset{pK_{a2}}{\rightleftharpoons} \underset{10-2}{[Pd(en)(OH)_2]} + H^+ \quad (2)$$

$$\underset{10-1}{[Pd(en)(H_2O)(OH)]^+} + \underset{10-1}{[Pd(en)(H_2O)(OH)]^+} \overset{\log K_{dimer}}{\rightleftharpoons} \underset{20-2}{[Pd(en)(OH)_2Pd(en)]^{2+}} + 2H_2O \quad (3)$$

The pK_{a1} and pK_{a2} values for $[Pd(en)(H_2O)_2]^{2+}$ are 6.11 and 9.24, respectively. The equilibrium constant for the dimerization reaction (3) can be calculated by equation (4) [29] as $\log K_{dimer} = 3.46$.

$$\log K_{dimer} = \log \beta_{20-2} - 2\log \beta_{10-1} \quad (4)$$

DNA constituents such as uracil, uridine, thymine, and thymidine have basic nitrogen donors (N3) in the measurable pH range [30, 31] and as a consequence form 1 : 1 and 1 : 2 complexes with $Pd(en)^{2+}$ species. As a result of the high pK_a values of pyrimidines ($pK_a > 9$), complex formation predominates above pH 8.5. The thymine complex is more stable than that of uracil, probably due to the higher basicity of the N3 site of thymine resulting from the inductive effect of the extra electron-donating methyl group. Cytosine undergoes N3 protonation under mild acidic conditions. The value obtained for its protonation constant is pK_a 4.65. The lower values of the stability constants of its complexes, table 3, reflect the difference in the basicity of the donor site.

Inosine and nucleotides such as inosine-5′-monophosphate form the monoprotonated complex, in addition to formation of 1 : 1 and 1 : 2 complexes. The pK_a value of the protonated inosine complex is 5.27. This value corresponds 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 [32, 33]. The IMP complex is more stable than that of inosine. This may be accounted for on the basis of different coulombic forces operating between the ions resulting from the negatively charged phosphate group. Hydrogen bonding between the phosphate group and the exocyclic amine is also thought to contribute to the increased stability. Such hydrogen bonding was reported previously for similar systems [34, 35].

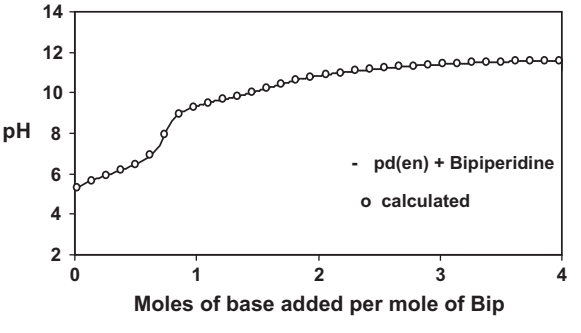


Figure 1. Potentiometric titration curve for 0.05 mmols of $[Pd(en)(H_2O)_2]^{2+}$ and 0.025 mmols of Bip at 25 °C and 0.1 M $NaNO_3$.

Table 2. Complex formation constants for the complexes formed between $[Pd(en)(H_2O)_2]^{2+}$ and bipiperidine at 25 °C and 0.1 M ionic strength.

System	M L H[a]	$\log_{10}\beta$[b]	pK_a[c]
4,4′-Bipiperidine	0 1 1	10.96 (0.02)	10.96
	0 1 2	21.12 (0.01)	10.16
	1 1 0	13.31 (0.07)	
	1 1 1	19.66 (0.04)	6.35
	2 1 0	20.00 (0.09)	

[a]M, L and H are the stoichiometric coefficients corresponding to Pd(en), Bip and H^+, respectively.
[b]$\log_{10}\beta$ of Pd(en)–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.

3.3. *Complex formation equilibria of the binuclear $Pd(en)^{2+}$complex with 4,4′-bipipridine*

The titration curve of a solution mixture of 4,4′-bipiperidine and $Pd(en)(H_2O)_2]^{2+}$ in the ratio 1 : 2, figure 1, shows a sharp inflection at $a = 1$ (a is number of mole of base added per mole of 4,4′-bipiperidine), corresponding to the complete formation of the $[(H_2O)(en)Pd(Bip)Pd(en)(H_2O)]^{4+}$ complex with a formation constant of $\log \beta_{210} = 20.00$, see scheme 2 and table 2.

Beyond $a = 1$, the binuclear complex is subjected to deprotonation. In this region, the titration data were fitted considering the formation of the hydrolyzed species with stoichiometric coefficients of 10-1 and 10-2 as given in scheme 3. The pK_{a1} of the bridged complex $[(H_2O)(en)Pd(Bip)Pd(en)(H_2O)]^{4+}$ is significantly higher than that of $Pd(en)(H_2O)_2{}^{2+}$ and in fair agreement with its pK_{a2} value. This may be due to the electron donation of 4,4′-bipiperidine in coordination with the Pd^{II} center. This is expected to decrease the electrophilicity of the Pd^{II} ion, to weaken the Pd–OH_2 bond and consequently increase the pK_a value. Also, the pK_{a1} and pK_{a2} values of the bridged complex $[(H_2O)(en)Pd(Bip)Pd(en)(H_2O)]^{4+}$ are nearly equal. This indicates that the two Pd(en) units behave as two separated species, i.e. the Bip bridge does not allow the two Pd(en) units to communicate electronically with each other. This can be explained on the basis of the absence of π-conjugation in the Bip bridge.

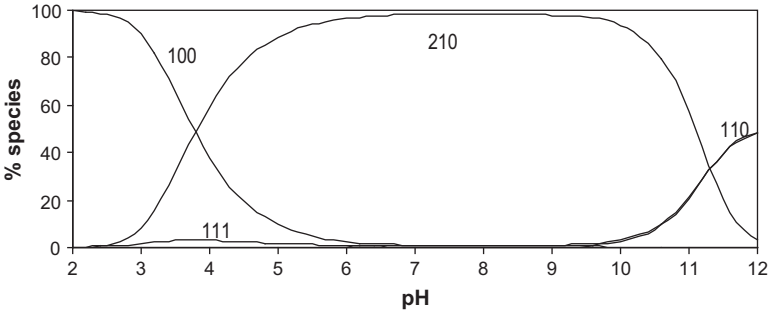


Figure 2. Concentration distribution of various species as a function of pH in the $[Pd(en)(H_2O)_2]^{2+}$-4,4′-bipiperidine system.

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

System	M L H[a]	$\log_{10}\beta$[b]	pK_a[c]
$[(H_2O)(en)Pd(Bip)Pd(en)(H_2O)]^{4+}$	1 0 −1	−9.64 (0.04)	9.64
	1 0 −2	−19.03 (0.02)	9.39
Inosine	0 1 1	8.80 (0.02)	8.80
	1 1 0	5.40 (0.03)	
	1 2 0	9.87 (0.05)	
Inosine-5′-monophosphate	0 1 1	9.02 (0.02)	
	0 1 2	15.24(0.03)	9.02
	1 1 0	5.52(0.02)	6.22
	1 2 0	10.00 (0.04)	
Uracil	0 1 1	9.18 (0.01)	9.18
	1 1 0	5.98 (0.04)	
	1 2 0	10.94 (0.06)	
Thymine	0 1 1	9.65 (0.01)	9.65
	1 1 0	6.16 (0.03)	
	1 2 0	11.38 (0.03)	
Thymidine	0 1 1	9.54(0.02)	9.54
	1 1 0	5.25 (0.05)	
	1 2 0	10.49 (0.02)	
Uridine	0 1 1	9.01 (0.01)	9.01
	1 1 0	5.04 (0.02)	
	1 2 0	10.15 (0.03)	

[a]M, L and H are the stoichiometric coefficients corresponding to $[(H_2O)(en)Pd(Bip)Pd(en)(H_2O)]^{4+}$, DNA constituent, and H^+ respectively.
[b]$\log_{10}\beta$ 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.

The speciation diagram for the Pd(en)-bipiperidine system is given in figure 2. The binuclear complex, $[(H_2O)(en)Pd(Bip)Pd(en)(H_2O)]^{4+}$ (210), starts to form at low pH and on increasing pH its concentration increases. It is the predominant species up to pH 7.2 and reaches a maximum concentration of 98.13% at pH 7.6.

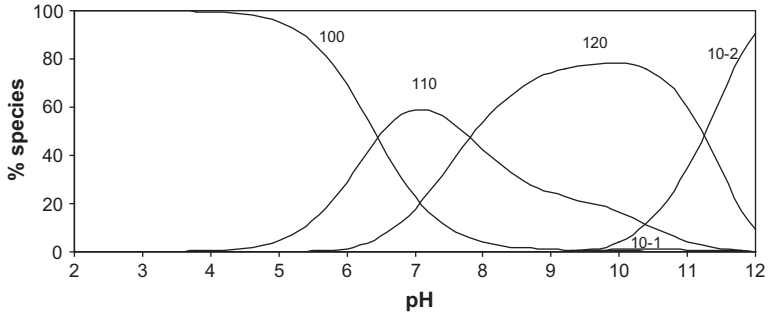


Figure 3. Concentration distribution of various species as a function of pH in the $[(H_2O)(en)Pd\text{-}Bip\text{-}Pd(en)(H_2O)]^{4+}$-inosine system.

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

The complex formation between $[(H_2O)(en)Pd(Bip)Pd(en)(H_2O)]^{4+}$ and inosine, taken as an example for a DNA constituent, showed the formation of 1 : 1 and 1 : 2 complexes, as given in scheme 4. The stability constant of the DNA complexes is of the order thymine > uracil > inosine. The thymidine complex is more stable than that of uridine, see table 3. This may be explained as a result of the difference in the basicity of the donor atom as reflected by the pK_a values.

The speciation diagram of the $[(H_2O)(en)Pd(Bip)Pd(en)(H_2O)]^{4+}$-inosine complex is given in figure 3. The 1 : 1 complex starts to form at pH 4 and on increasing pH its concentration increases and reaches a maximum concentration of 59.11% at pH 7. The 1 : 2 complex attains a maximum degree of formation of 78.17% at pH 10. The hydrolyzed species are formed above 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.

Spectral bands for $Pd(en)(H_2O)_2^{2+}$ and its 4,4′-bipiperidine complex were compared. They are quite different in terms of the position of the maximum wavelength and molar absorptivity, see figure 4. The spectrum of the $[Pd(en)(H_2O)_2]^{2+}$complex (mixture A) shows an absorption maximum at 340 nm. The spectrum obtained for the $[(H_2O)(en)Pd(Bip)Pd(en)(H_2O)]^{4+}$ complex (mixture B) exhibits a band at 322 nm. This band is further shifted to 316 nm by adding 2×10^{-4} M NaOH for the formation of $[(OH)(en)Pd(Bip)Pd(en)(OH)]^{2+}$ (mixture C). There is no UV absorption for free Bip in this region (mixture D).

Spectral bands of the $Pd(en)(H_2O)_2^{2+}$ complexes involving 4,4′-bipiperidine and thymine were compared. The spectrum obtained for $[(H_2O)(en)Pd(Bip)Pd(en)(H_2O)]^{4+}$ (mixture E) occurs at 322 nm. The spectrum obtained for $[(H_2O)(en)Pd(Bip)Pd(en)(thymine)]^{3+}$ (mixture F) exhibits a shoulder at 322 nm. The spectra of the binuclear complexes $[(H_2O)(en)Pd(Bip)Pd(en)(thymine)]^{3+}$ (mixture F) and $[(thymine)(en)Pd(Bip)\text{-}Pd(en)(thymine)]^{2+}$ (mixture G) show an isosbestic point at 322 nm, indicating an equilibrium between these complexes. Further information on the binuclear complex formation may require further studies such as mono and polynuclear NMR measurements.

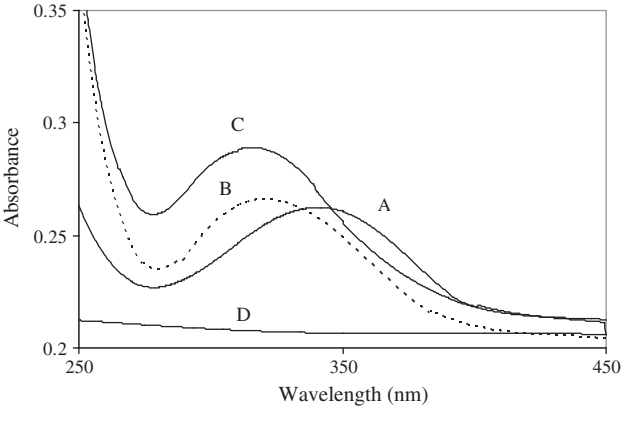
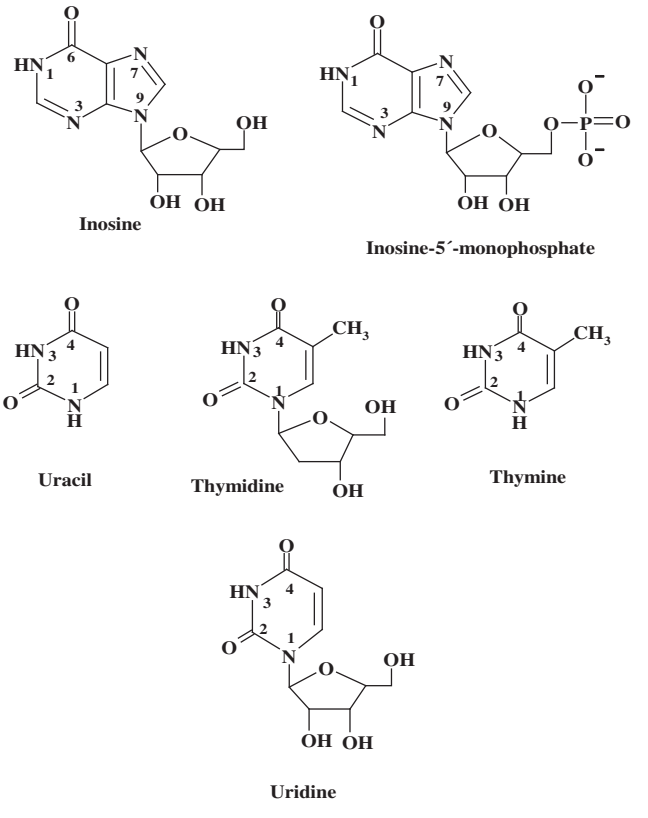
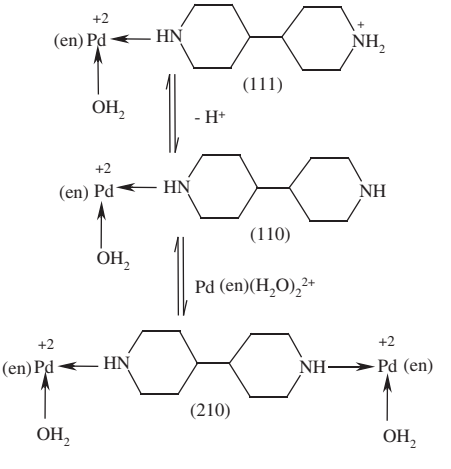


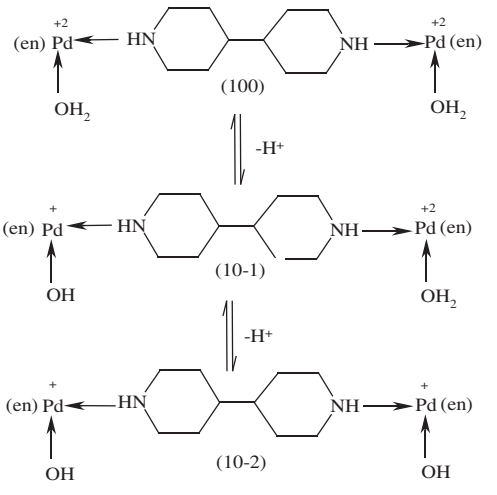
Figure 4. The electronic spectra of Pd(en)–Bip complexes. Compositions of the solution mixtures A, B, C and D are given in the Experimental Section.



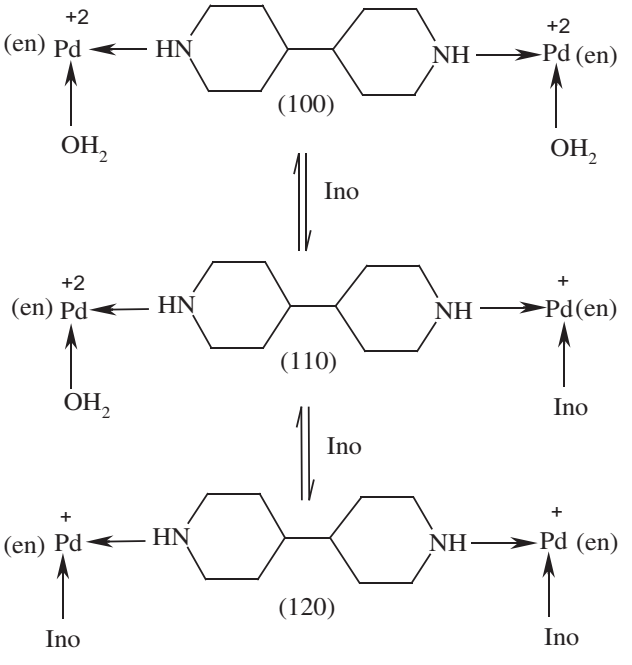
Scheme 1. Structural formulas of the DNA constituents.



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



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



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

4. Conclusions

The present investigation describes complex formation equilibria of $[Pd(en)(H_2O)_2]^{2+}$ with 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 di- and trinuclear platinum(II) complexes having potent antitumor activity [36]. In this study, $[Pd(en)(H_2O)_2]^{2+}$ forms the dihydroxo-bridged dimer (20-2), as reported for most Pd-diamine complexes. The stability constant of the Pd(en)-inosine complex is lower than that for the Pd(pic)–inosine complex, where pic = 2-picolylamine [18]. 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 constants of its complex. Therefore, the structure of the diamine has an effect on the stability of the DNA adduct.

The formation of the binuclear complex through bridging with 4,4′-bipiperidine decreases the electrophilicity of the Pd^{II} centers. This in turn leads to an increase in the pK_a of the diaqua-bridged complex and a decrease in the stability constants of the binuclear DNA complexes. The Bip bridge does not allow the two Pd(en) units to communicate electronically with each other. This is evidenced by the similarity of the pK_a values of the diaqua-bridged complex.

It is interesting to compare the results of this study with those of the previously reported results for similar binuclear Pd(II) complexes. The stability constant of the binuclear inosine complex formed with $[(H_2O)(NH_3)_2Pd(Bip)Pd(NH_3)_2(H_2O)]^{4+}$ is $\log_{10} K = 5.51$, as reported before [20], in good agreement with that of the binuclear inosine complex formed with $[(H_2O)(en)Pd(Bip)Pd(en)(H_2O)]^{4+}$ ($\log_{10} K = 5.40$), as reported in the present study.

Disclosure statement

No potential conflict of interest was reported by the authors.

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