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Speciation studies of mono- and binuclear Pd(II) complexes involving mixed nitrogen–sulfur donor ligand and 4,4′-bipiperidine as a linker

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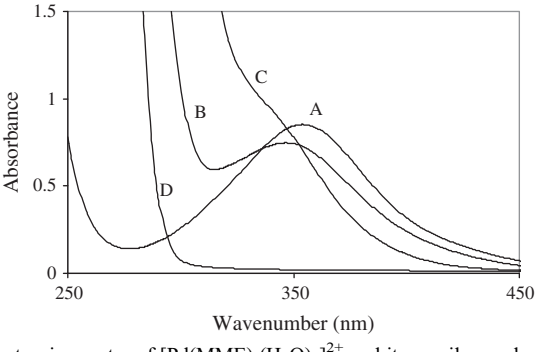

Electronic spectra of $[Pd(MME)(H_2O)_2]^{2+}$ and its uracil complexes

Speciation of mono- and binuclear Pd(II) complexes involving mixed nitrogen–sulfur donor ligand is investigated; 4,4′-bipiperidine is used as a linker.

$Pd(MME)Cl_2$ complex, where MME = methionine methyl ester, was synthesized and characterized by elemental analysis and spectroscopic techniques. $[Pd(MME)(H_2O)_2]^{2+}$ interacts with some DNA constituents giving 1 : 1 and 1 : 2 complexes. The binuclear complexes having 4,4′-bipiperidine as a linker and involving $[Pd(MME)(H_2O)_2]^{2+}$ and DNA constituents were investigated. The results show formation of $[(H_2O)(MME)Pd(Bip)Pd(MME)(H_2O)]^{4+}$. Inosine, uracil, and thymine interact with the previously mentioned complex by substitution of the two coordinated water molecules. Formation constants of all possible mono- and binuclear complexes were determined and their speciation diagrams were evaluated.

Keywords: Palladium(II) complexes; Methionine methyl ester; 4,4′-bipiperidine; DNA constituents; Binuclear complexes; Equilibrium constants

1. Introduction

Since Rosenberg [1] discovered the antitumor activity of *cis*-diamminedichloroplatinum(II), significant contributions were made to produce new platinum-containing compounds to

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Dedicated to Prof. Rudi van Eldik on the occasion of his 70th birthday.

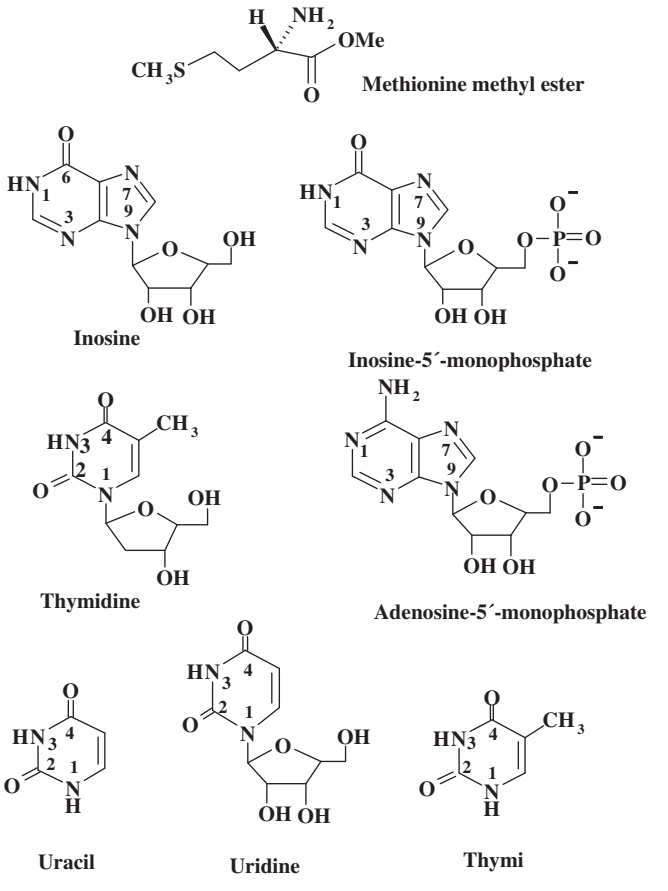
overcome the physiological disadvantages, such as several side effects, drug resistance, and limitation in the field of application. Most of the developed and studied platinum complexes include nitrogen-containing monodentate, bidentate, or tridentate ligands [2–8]. The ultimate aim of the modifications of the parent drug is to make related analogs that produce a different spectrum of DNA lesions and so circumvent the problem of resistance to cisplatin [2, 9]. Therefore, nonclassical platinum derivatives were also investigated, which may violate the classical structure–activity relationship [2]. Complexes are known that include sulfur-containing ligands and show antitumor activity [10]. An example is [Pt($CH_3SCH_2CH_2SCH_3$)Cl_2], Pt(dt), a sulfur analog of the well-studied [Pt($H_2NCH_2CH_2NH_2$)Cl_2], Pt(en) complex [10]. Baltić *et al.* examined the antitumor activity of Pt(dt) against the human breast cancer cell line and found the complex to inhibit the growth of MCF-7 cells in a dose and time-dependent manner [10]. Another example is dichloro(2-methylthiomethylpyridine)platinum(II), Pt(mtp)Cl_2, a complex with nitrogen as well as sulfur donors. In the literature, different synthetic pathways are described [11–13] and the bidentate mixed N,S-complex was found to be a promising cytostatic agent [14, 15]. In addition to new mononuclear complexes with improved properties in terms of toxicity or cross-resistance to cisplatin, a new class of binuclear Pt(II) complexes has been developed by Farrell's group [16–19]. 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 target of platinating agents) and fast uptake [20].

Palladium(II) complexes show discrete antitumor activity *in vitro* compared to the platinum-based drugs because of their extremely high liability in biological fluids. We have a long-standing interest in equilibria of complex-formation reactions of (diamine)$PdCl_2$ [21–27] and dinuclear palladium(II) [28, 29] complexes with bio-relevant ligands. It will be of interest to extend these investigations and study the mono- and binuclear complexes with N,S-donor ligands. In this investigation, a chelated methionine methyl (MME) ester was used. It has nitrogen and sulfur sites for chelation. The present investigation describes the synthesis and characterization of a Pd(II) complex with MME. The interaction of [Pd(MME)$(H_2O)_2$]$^{2+}$ with DNA constituents and 4,4′-bipiperidine was studied. Also, the binuclear complexes involving Pd(MME)$^{2+}$ and 4,4′-bipiperidine linking two Pd(MME)$^{2+}$ species were investigated.

2. Experimental

2.1. *Materials*

K_2PdCl_4, MME, 4,4′-bipiperidine·2HCl (Bip), and cysteine·HCl were obtained from Aldrich. The DNA constituents (inosine, inosine-5′-monophosphate (IMP), adenosine-5′-monophosphate, thymine, thymidine, uracil, and uridine) were provided by Sigma Chemical Co. For equilibrium studies, Pd(MME)Cl_2 was converted into the diaqua complex by treating it with two equivalents of $AgNO_3$ as described before [23]. The ligands in the form of hydrochlorides were converted into the corresponding hydronitrates. The nucleotides were prepared in the protonated form with standard HNO_3 solution. All solutions were prepared in deionized water. The structural formulas of the investigated ligands are given in scheme 1.



Scheme 1. Structural formulas of ligands.

2.2. *Synthesis*

$Pd(MME)Cl_2$ was prepared by dissolving K_2PdCl_4 (2.82 mmol) in 10 mL water with stirring. The clear solution of $[PdCl_4]^{2-}$ was filtered and MME (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-brown precipitate of $Pd(MME)Cl_2$ 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 $C_6H_{13}NSO_2PdCl_2$ (F. Wt. = 340.380: C, 21.16; H, 3.81; N, 4.11; S, 9.40. Found: C, 21.2; H, 4.0; N, 3.7, S, 9.1%).

2.3. *Equipment 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 [30]. All titrations were carried out at 25.0

± 0.1 °C in purified nitrogen using a titration vessel described previously [31]. 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 waters in $[Pd(MME)(H_2O)_2]^{2+}$ were determined by titrating 0.05 mmol of complex with standard 0.05 M NaOH solution. The formation constants of the complexes were determined by titrating solution mixtures of $[Pd(MME)(H_2O)_2]^{2+}$ (0.05 mmol) and the ligand in the concentration ratio of 1 : 2 (Pd : ligand) for the DNA constituents. The formation constants of the binuclear complexes of Bip were determined by titrating solution mixture of 0.062 mmol of $[Pd(MME)(H_2O)_2]^{2+}$ and Bip in concentration ratio of 2 : 1 (Pd : Bip). The formation constants of the binuclear DNA complexes were determined by titrating solution mixtures of 0.062 mmol of $[Pd(MME)(H_2O)_2]^{2+}$, Bip and DNA constituent in 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 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 values from 2 to 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 $[Pd(MME)(H_2O)_2]^{2+}$ ion, Bip or DNA constituent, and proton, respectively. In case of binuclear complex with DNA constituent M, L, and H stand for $[(Pd(MME))_2(Bip)(H_2O)_2]^{4+}$, DNA constituent and proton, respectively. The calculations were performed using the computer program MINIQUAD-75 [32]. 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 [32]. 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 [33] under the experimental condition used.

2.4. *Spectrophotometric measurements*

Spectrophotometric measurements of Pd(MME)-uracil complex (figure 1), were performed by recording the UV–visible spectra of solutions (A-D), where (A) 2×10^{-4} M of Pd(MMA)$(H_2O)_2^{2+}$; (B) 2×10^{-4} M of Pd(MME)$(H_2O)_2^{2+}$ + 2×10^{-4} M of uracil + 2×10^{-4} M of NaOH, (C) 2×10^{-4} M of Pd(MME)$(H_2O)_2^{2+}$ + 4×10^{-4} M of uracil + 4×10^{-4} M of NaOH and (D) 2×10^{-4} M of uracil.

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

System	M	L	H[a]	log β[b] Pd(MME)	pK_a[c]
Pd(MME)-OH	1	0	−1	−5.29 (0.01)	5.29
	1	0	−2	−12.96 (0.05)	7.67
	2	0	−1	−2.46 (0.07)	8.43
Inosine	0	1	1	8.43 (0.01)	
	1	1	0	7.98 (0.02)	4.01
	1	2	0	12.63 (0.03)	
	1	1	1	11.99 (0.03)	
Inosine-5′-monophosphate					
	0	1	1	8.95 (0.02)	8.95
	0	1	2	15.27 (0.03)	6.32
	0	1	3	17.10 (0.01)	
	1	1	0	9.34 (0.01)	
	1	2	0	13.44 (0.01)	
	1	1	1	16.12 (0.01)	6.78
	1	1	2	20.16 (0.02)	4.04
Uracil					
	0	1	1	9.28 (0.01)	9.28
	1	1	0	8.74 (0.01)	
	1	2	0	15.32 (0.02)	
Uridine					
	0	1	1	9.01 (0.01)	9.01
	1	1	0	8.55 (0.02)	
	1	2	0	14.61 (0.03)	
Thymidine					
	0	1	1	9.55 (0.02)	9.55
	1	1	0	9.04 (0.006)	
	1	2	0	15.62 (0.01)	
Thymine					
	0	1	1	9.58 (0.01)	9.58
	1	1	0	9.12 (0.004)	
	1	2	0	15.78 (0.008)	
Adenosine-5′-monophosphate	0	1	1	6.39 (0.02)	6.39
	0	1	2	11.01 (0.03)	4.62
	1	1	0	9.11 (0.06)	
	1	1	1	13.21 (0.1)	4.1
	1	1	2	15.72 (0.1)	2.51

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

Spectrophotometric measurements of Pd(MME)-Bip complex were performed by recording the UV–visible spectra of solutions (A-D), where (A) 2×10^{-4} M of Pd(MME)$(H_2O)_2^{2+}$; (B) 2×10^{-4} M of Pd(MME)$(H_2O)_2^{2+}$ + 1×10^{-4} M of Bip + 2×10^{-4} M of NaOH, (C) 2×10^{-4} M of Pd(MME)$(H_2O)_2^{2+}$ + 1×10^{-4} M of Bip + 4×10^{-4} M of NaOH and (D) 1×10^{-4} M of Bip. The spectral measurements of the binuclear complex of uracil, taken as an example for DNA, were performed by recording the spectra of solutions (E–H) (E) 2×10^{-4} M of $[Pd(MME)(H_2O)_2]^{2+}$, 1×10^{-4} M of Bip and 2×10^{-4} M of NaOH; (F) 2×10^{-4} M of $[Pd(MME)(H_2O)_2]^{2+}$, 1×10^{-4} M of Bip, 1×10^{-4} M of uracil and 3×10^{-4} M of NaOH; (G) 2×10^{-4} M of $[Pd(MMA)(H_2O)_2]^{2+}$, 1×10^{-4} M of Bip, 2×10^{-4} M of uracil and 4×10^{-4} M of NaOH; and (H) 2×10^{-4} M of uracil. Under these prevailing experimental conditions and after neutralization of the hydrogen ions released, associated with complex formation, it is supposed that the complexes have been completely

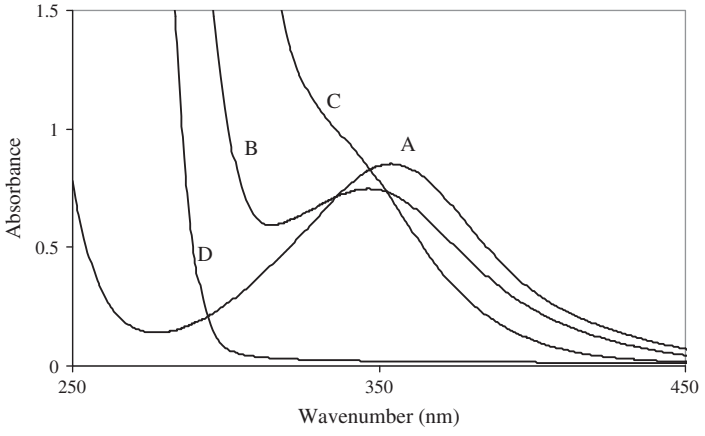


Figure 1. The electronic spectra of $[Pd(MME)(H_2O)_2]^{2+}$ and its uracil complexes. Composition of solution mixtures A, B, C, and D are given in section 2.

formed. In each mixture the volume was brought to 10 mL by addition of deionized water and ionic strength is kept constant at 0.1 M $NaNO_3$.

3. Results and discussion

3.1. *Characterization of the solid complexes*

The analytical data indicates that the complex is of 1 : 1 stoichiometry, $Pd(MME)Cl_2$. The IR spectrum of the $Pd(MME)Cl_2$ complex exhibits bands at 3300–3400 cm^{-1}, attributed to stretching vibrations of NH_2. The complex exhibits bands for (NH_2) bending at 1465 and 1562 cm^{-1} and bands for the stretching vibration corresponding to Pd–N at 480 and 523 cm^{-1}. The ^1H NMR spectrum of the complex is in accordance with previously reported data [34].

3.2. *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 literature data [35].

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

$[Pd(MME)(H_2O)_2]^{2+}$ may undergo hydrolysis. Its acid–base chemistry was characterized by fitting the potentiometric data to various acid–base models. The best-fit model was consistent with the formation of three species: 10–1, 10–2, and 20–1, as given in reactions 1–3. Trials were made to fit the potentiometric data assuming formation of the monohydroxo-bridged dimer, 20–2, but this resulted in a very poor fit to the data. The dimeric species 20–2 were detected by Nagy *et al.* [36] for a similar system. The formation of the

dihydroxo-bridged dimer (20–2), found for most Pd-diimine complexes, is not favored in the case of the Pd-MME complex. This may be accounted for on the basis that the strong labilization effect of the S-donor will cause the dimeric form (20–2) to be strained and consequently energetically not favored [23].

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

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

$$\underset{100}{[Pd(MME)(H_2O)_2]^{2+}} + \underset{10-1}{[Pd(MME)(H_2O)(OH)]^{+}} \overset{\log K_{dimer}}{\rightleftharpoons} \underset{20-1}{[(H_2O)Pd(MME)(OH)Pd(MME)(H_2O)]^{3+}} + H_2O \tag{3}$$

The pK_{a1} and pK_{a2} values for $[Pd(MME)(H_2O)_2]^{2+}$ are 5.29 and 7.67, respectively. The equilibrium constant for the dimerization reaction three can be calculated by equation 4 as 2.83.

$$\log K_{dimer} = \log \beta_{20-1} - \log \beta_{10-1} \tag{4}$$

3.4. *Complexes of DNA constituents*

Inosine and nucleotides such as inosine-5′-monophosphate and adenosine-5′-monophosphate form protonated complexes, in addition to the formation of 1 : 1 and 1 : 2 complexes. Inosine forms a monoprotonated complex (111). The pK_a value of the protonated inosine complex is 4.01. This value corresponds to N1H. The lowering of this value with respect to that of free inosine ($pK_a = 8.43$) is due to acidification upon complex formation [37]. Inosine-5′-monophosphate forms mono- and diprotonated complexes. The pK_a values of the protonated species of the IMP complex (112) are 4.04 ($\log \beta_{112} - \log \beta_{111}$) and 6.78 ($\log \beta_{111} - \log \beta_{110}$).

The former pK_a value corresponds to N_1H and the second pK_a value to $-PO_2(OH)$. The N_1H group was acidified upon complex formation by 4.91 pK_a units. Acidification of the N_1H group upon complex formation is consistent with previous reports for IMP complex [37, 38]. The phosphate group was not acidified upon complex formation since it is far from the coordination center. IMP complex is more stable than that of inosine, explained on the basis of different Coulombic forces operating between the ions resulting from the negatively charged phosphate. Hydrogen bonding between phosphate and exocyclic amine is also thought to contribute to the increased stability. Such hydrogen bonding was reported previously for similar system [39, 40].

The pyrimidines uracil, uridine, thymine, and thymidine have basic nitrogen donors (N3) in the measurable pH range [41] and as a consequence form 1 : 1 and 1 : 2 complexes with $Pd(MMA)^{2+}$ 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.

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

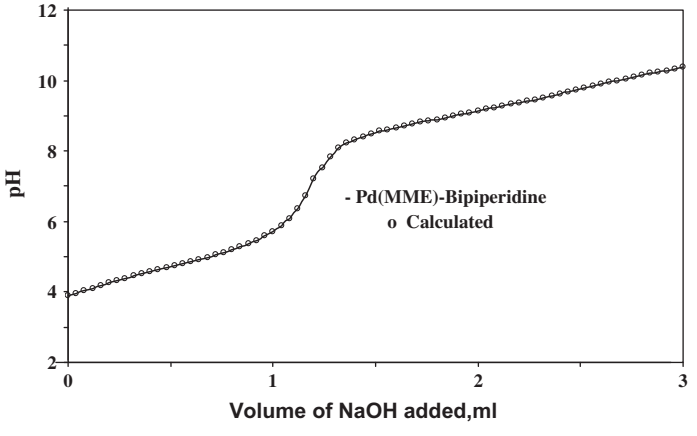
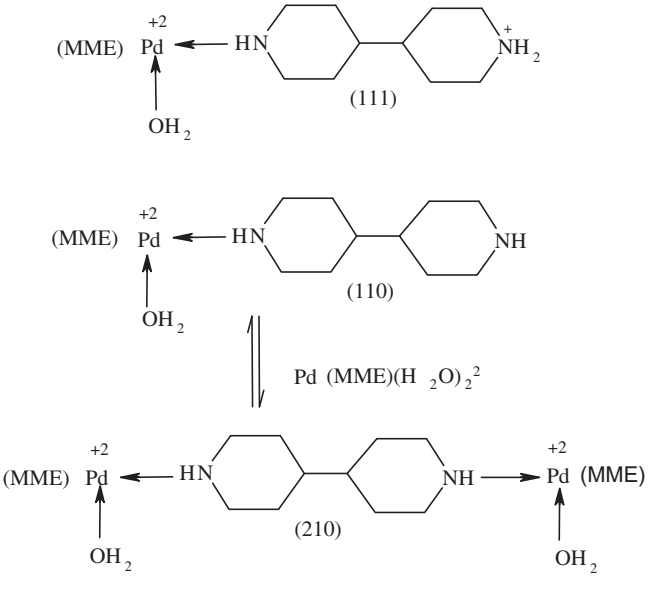


Figure 2. Potentiometric titration curves of $[Pd(MME)(H_2O)_2]^{2+}$-bipiperidine system.



Scheme 2. Complex formation equilibria of Pd(MME)-Bip complexes.

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

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

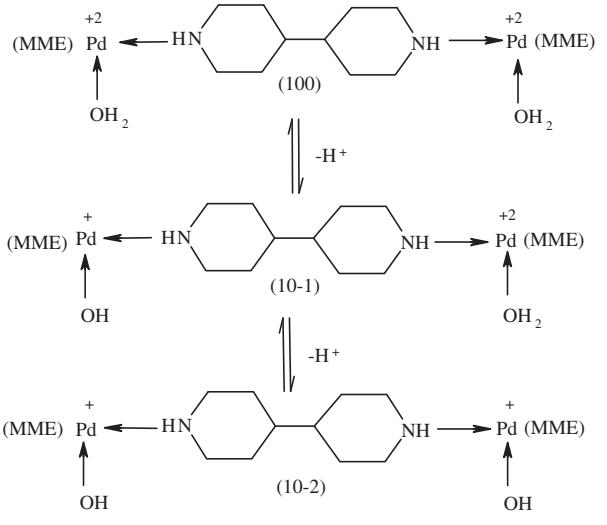
Beyond $a = 1$, the binuclear complex is subjected to hydrolysis. In this region, the titration data are fitted considering the formation of the hydrolyzed species with stoichiometric coefficients 10–1 and 10–2 as given in scheme 3.

The speciation diagram of Pd(MME)-bipiperidine system is given in figure 3. The binuclear complex, $[(H_2O)(MME)Pd(Bip)Pd(MME)(H_2O)]^{4+}$ (210), starts to form at low pH and on increasing pH, its concentration increases to the predominant species up to pH 7.2 and reaches a maximum concentration of 87.5% at pH 5.2.

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

System	M	L	H[a]	log β[b]	pK_a[c]
Bipiperidine	0	1	1	10.96 (0.01)	10.96
	0	1	2	21.12 (0.02)	10.16
	1	1	0	13.33 (0.08)	
	1	1	1	19.98 (0.03)	6.65
	2	1	0	20.06 (0.10)	

[a]M, L, and H are the stoichiometric coefficients corresponding to Pd(MME), bipiperidine and H^+, respectively.
[b]log β of Pd(MME)-Bip. 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.



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

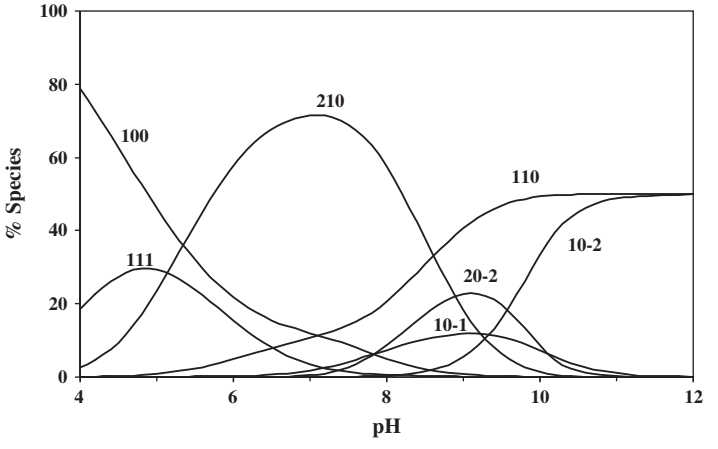
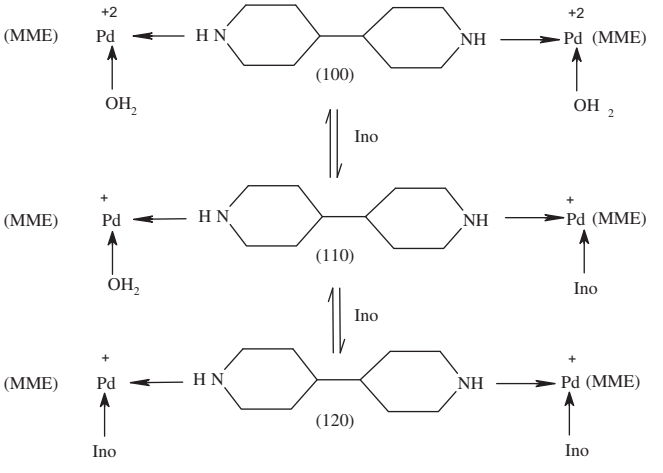


Figure 3. Concentration distribution of various species as a function of pH in the $[Pd(MME)(H_2O)_2]^{2+}$-bipiperidine system.



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

The complex formation between $[(H_2O)(MME)Pd(Bip)Pd(MME)(H_2O)]^{4+}$ and inosine, taken as an example of 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 thymine > inosine > uracil (table 3).

The speciation diagram of $[(H_2O)Pd(MME)(Bip)Pd(MME)(H_2O)]^{4+}$-inosine complex is given in figure 4. The 1 : 1 complex starts to form at pH 2 and on increasing pH, its concentration increases, reaching a relative amount of 94% at pH 5.6. The 1 : 2 complex attains a maximum formation degree of 89% at pH 10.1. The hydrolyzed species are formed after pH 10.0. From the biological point of view, the DNA complex predominates in the physiological pH range and the reaction of the binuclear complex with DNA is quite feasible.

Table 3. Formation constants for binuclear complexes of [(H2O)(MME)Pd(Bip)Pd(MME)(H2O)]$^{4+}$ and some DNA constituents at 25 °C and 0.1 M ionic strength.

System	M	L	H[a]	log β[b]	pK_a[c]
$[(H_2O)(MME)Pd(Bip)Pd(MME)(H_2O)]^{4+}$					
	1	0	−1	−8.04 (0.07)	8.04
	1	0	−2	−16.87 (0.05)	8.83
Inosine					
	0	1	1	8.80 (0.02)	8.80
	1	1	0	7.89 (0.01)	
	1	2	0	12.84 (0.02)	
Uracil					
	0	1	1	9.18 (0.01)	9.18
	1	1	0	6.62 (0.09)	
	1	2	0	11.95 (0.1)	
Thymine					
	0	1	1	9.65 (0.01)	9.65
	1	1	0	8.66 (0.02)	
	1	2	0	15.59 (0.03)	

[a]M, L, and H are the stoichiometric coefficients corresponding to (MME)Pd(Bip)Pd(MME), DNA units, and H^+, respectively.
[b]log β of (MME)Pd(Bip)Pd(MME)-DNA constituent complex. 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.

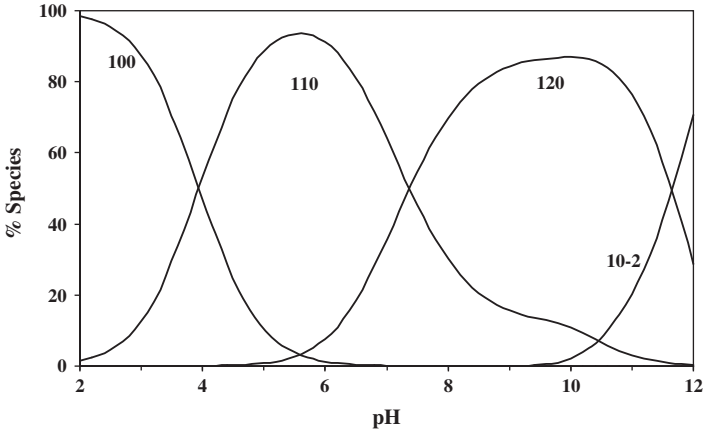


Figure 4. Concentration distribution of various species as a function of pH in the Pd(MME)-bipiperidine-inosine system.

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

Spectra of $Pd(MME)(H_2O)_2^{2+}$ complexes with 4,4′-bipiperidine and uracil are scanned. The spectrum obtained for $[(H_2O)(MME)Pd(Bip)Pd(MME)(H_2O)]^{4+}$ (mixture E) shows a

band at 339 nm. The spectrum obtained for $[(H_2O)(MME)Pd(Bip)Pd(MME)(uracil)]^{3+}$ (mixture F) and $[(uracil)(MME)Pd(Bip)Pd(MME)(uracil)]^{2+}$ (mixture G) exhibit shoulders at 332 nm and 315 nm, respectively. The spectral band shifts are taken as evidence for binuclear complex formation, supporting the potentiometric results. Further investigation on the binuclear complex formation may need further studies as mono- and polynuclear NMR measurements.

4. Conclusion

The present investigation describes complex formation equilibria of $Pd(MME)(H_2O)_2^{2+}$ with some selected DNA constituents and 4,4′-bipiperidine. The results indicate formation of binuclear complex and the reaction with DNA constituents is feasible. The data support the biological significance of the di- and trinuclear platinum(II) complexes having potent antitumor activity [42]. In the present study, $[Pd(MME)(H_2O)_2]^{2+}$ does not form the dihydroxo-bridged dimer (20–2) as reported for most Pd-diimine complexes. This may be explained on the basis that strong labilization of the S-donor will cause the dimeric form (20–2) to be strained and consequently energetically not favored. It is interesting to compare the results of the present study with those of Pd(II) complexes involving N,N-donors. The stability constant of Pd(MME)-DNA complex is higher than those of Pd(II) complexes with N,N-dimethylethylenediamine [43], This same effect arises in the binuclear complexes. This may be due to the hydrogen bonding between the bound DNA constituents and the ester group of the bound MME.

Disclosure statement

No potential conflict of interest was reported by the authors.

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