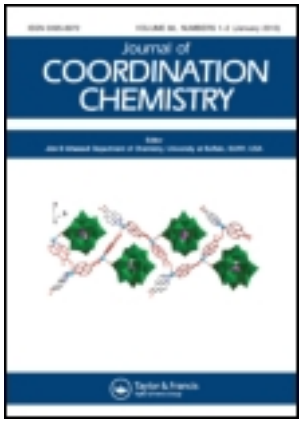

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Amine-bridged binuclear palladium(II) complexes with inosine. Equilibrium studies and DFT calculations

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Amine-bridged binuclear palladium(II) complexes with inosine. Equilibrium studies and DFT calculations

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Complex-formation equilibria involving *trans*-diamine palladium(II) (Pd^{II}), 4,4′-bipyridine (bpy), and inosine were investigated at 25 °C and 0.1 M ($NaNO_3$) ionic strength. The stability constants of all possible mono-nuclear and binuclear complexes were determined. The concentration distribution diagram for the binuclear complexes of Pd^{II}-bpy-inosine reveals the complexes that predominate in the physiological pH range and the quite feasible interaction of the binuclear complex Pd^{II}-bpy-Pd^{II} with inosine as a DNA constituent. On the basis of DFT calculations (B3LYP/LANL2DZp), the structures of the investigated equilibrium species show typical bond lengths for Pd–O and Pd–N bonds. The C–C bond in $[Pd(4,4'\text{-bpy})(NH_3)_2(OH_2)]^{2+}$ is clearly shortened to 1.47 Å, leading to reduced aromaticity in bpy. Comparison with model compounds suggests that the uncoordinated aromatic ring can be understood as an electron donating group.

Keywords: Palladium; 4,4'-bipyridine; Kinetic; DFT; Aromaticity

1. Introduction

Cis-diammine dichloroplatinum (*cisplatin*) is one of the most widely used anticancer drugs [1, 2] and highly effective in the treatment of testicular and ovarian cancer [3]. However, some drawbacks in the clinical treatment still remain, such as serious nephrotoxicity [4] and drug resistance [5]. A variety of bridged platinum complexes with potential cytostatic activity were developed [6]. The goal was to generate more effective substances than the already established *cisplatin*. Whereas complexes that follow the originally determined *cisplatin* structure-activity relationship, which for instance require atleast one NH moiety within the ligand sphere, were synthesized first [7–10], but gradually platinum complexes that violated

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the structure-activity relationship were developed. One of these non-classical complexes is BBR3464 [8, 11] that consists of three platinum centers bridged by an aliphatic chain and the platinums are coordinated by primary amines. The aliphatic chain is a flexible bridge and leads to interstrand cross links with DNA, which persist longer than intrastrand cross links and are considered to be less susceptible to repair as both the strands are affected by the damage [8, 11].

Complex-formation equilibria of binuclear Pt^{II} complexes can provide insight into the behavior of these complexes in biological fluids. In general, Pd(II) and Pt(II) amine complexes have similar structures and thermodynamic properties. However, Pd(II) complexes are five orders of magnitude more labile than their platinum counterparts. Therefore, Pd(II) complexes are good models for analogous Pt(II) complexes in solution.

Recent work in our laboratories focused on the complex-formation equilibria of amine-bridged binuclear palladium(II) and *cis*-(diamine) palladium(II) complexes with DNA, the major target in chemotherapy of tumors, and, bio-relevant ligands such as amino acids, peptides, and dicarboxylic acids [12–17]. The substitution behavior of the binuclear Pt(II) complex [{*trans*-$Pt(NH_3)_2Cl\}_2$(4,4′-bipyridyl)](ClO_4)·DMF with biologically relevant ligands such as thiourea, glutathione, and guanosine-5'-monophosphate was studied [18]. In the present study, the complex-formation reactions involving *trans*-diamminepalladium(II), 4,4′-bipyridine and inosine were investigated. While aware of its toxicity, 4,4′-bipyridine, was selected as it has two hetero-aromatic nitrogen bases (pyridines) which possess π-accepting properties that are involved in π-π stacking effects with nitrogen bases of DNA.

We do not see any indications for potential arrangement of supramolecular systems as initially investigated by the research team of Fujita [19], probably as the concentrations of Pd(II), bpy, and inosine are too low to allow formation of these species.

2. Experimental

2.1. *Materials and reagents*

Trans-diamminepalladium(II) chloride, *trans*-$Pd(NH_3)_2Cl_2$ (Pd^{II}), and 4,4′-bipyridine (bpy) were obtained from Aldrich Chem. Co. Inosine (Ino) was provided by Sigma Chem. Co. All other reagents were of analytical grade. *Trans*-$Pd(NH_3)_2Cl_2$ was converted into the diaqua complex by treating it with two equivalents of $AgNO_3$ as described before [18] and fresh solutions were used to avoid the isomerization of *trans*-$Pd(NH_3)_2Cl_2$. 4,4′-bpy was prepared in the diprotonated form with standard HNO_3 solution. All the solutions were prepared in deionized water.

2.2. *Apparatus*

Potentiometric titrations were performed with a Metrohm 751 GPD Titrino equipped with internal dosimat and stirrer. The Titrino and electrode were calibrated with standard buffer solutions, prepared according to NBS specification [20]. The pH meter readings were converted to hydrogen ion concentrations 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 of pH − p[H] = 0.05 was observed. All titrations were carried out at 25.0 ± 0.1 °C in purified nitrogen using a titration vessel, described previously [21].

2.3. *Procedure and measuring technique*

The acid dissociation constants of inosine and protonated bpy were determined by titrating 0.1 mM samples of each with standard NaOH solution. The acid dissociation constants of coordinated water in $[Pd(NH_3)_2(H_2O)_2]^{2+}$ were determined by titrating 0.1 mM of the complex with 0.05 M NaOH. The formation constants of the *trans*-$[Pd(NH_3)_2(H_2O)_2]^{2+}$ complexes with bpy or inosine were determined by titrating a solution of 0.1 mM of the Pd^{II} complex and ligand in the concentration ratio of 1 : 2 and 2 : 1 (metal : ligand) for inosine and bpy, respectively. The formation constant of the binuclear complex inosine-Pd^{II}-bpy-Pd^{II}-inosine was determined by titrating solution mixtures of *trans*-$[Pd(NH_3)_2(H_2O)_2]^{2+}$ (0.2 mM), bpy (0.1 mM), and inosine (0.2 mM). 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 species formed were characterized by the following general equilibrium, where charges have been omitted for simplicity.

$$l\mathrm{Pd} + p(\mathrm{bpy}) + q(\mathrm{ino}) + r(\mathrm{H}) \rightleftharpoons (\mathrm{Pd})_l(\mathrm{bpy})_p(\mathrm{ino})_q(\mathrm{H})_r$$

The complex-formation constant is given by the expression:

$$\beta_{lpqr} = \frac{[\mathrm{Pd}_l(\mathrm{bpy})_p(\mathrm{Ino})_q(\mathrm{H})_r]}{[\mathrm{Pd}]^l[\mathrm{bpy}]^p[\mathrm{Ino}]^q[\mathrm{H}]^r}$$

Pd, bpy, ino, and H represent *trans*-$[Pd(NH_3)_2(H_2O)_2]^{2+}$, 4,4′-bipyridine, inosine, and protons, respectively. The calculations were performed using the computer program MINIQUAD-75 [22]. 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 [22]. Table 1 lists the stability constants together with their standard deviations as obtained from the MINIQUAD output. The concentration distribution diagrams were obtained with the program SPECIES [23] under the experimental conditions used.

Table 1. Formation constants of the binary and binuclear complexes $(Pd)_l(bpy)_p(Ino)_qH_r$ at 25 °C and 0.1 M $NaNO_3$; standard deviations are given in parentheses.

System	l	p	Q	r	$\log\beta$
trans-$[Pd(NH_3)_2(H_2O)_2]^{2+}$	1	0	0	−1	−5.90(0.04)
	1	0	0	−2	−16.16(0.05)
bpy	0	1	0	1	4.86(0.02)
	0	1	0	2	7.60(0.04)
trans-$[Pd(NH_3)_2(H_2O)_2]^{2+}$-bpy	1	1	0	0	4.99(0.06)
	1	1	0	1	10.03(0.02)
	2	1	0	0	8.39(0.06)
	2	1	0	−1	2.43(0.07)
	0	0	1	1	8.64(0.01)
Ino	1	0	1	0	6.71(0.03)
trans-$[Pd(NH_3)_2(H_2O)_2]^{2+}$-Ino	1	0	1	1	10.84(0.10)
	1	0	2	0	10.25(0.02)
	1	0	1	−1	−2.50(0.01)
trans-$[Pd(NH_3)_2(H_2O)_2]^{2+}$-bpy-Ino	1	1	1	0	13.67(0.09)
	1	1	1	1	18.70(0.06)
	2	1	1	0	18.62(0.02)

2.4. *Quantum chemical calculations*

We performed B3LYP/LANL2DZp hybrid density functional calculations, i.e. with the Hay-Wadt-Los Alamos pseudo-potentials on elements heavier than Neon and the D95V-valence basis set augmented with polarization functions for non-hydrogen atoms [24, 25]. In addition, the resulting structures were characterized as minima by computation of the vibrational frequencies. DFT, in particular B3LYP has been shown to provide accurate geometries, good harmonic vibrational frequencies, and is wellsuited for NMR [26] and Nucleus-independent chemical shift (NICS) [27] calculations. The GAUSSIAN 03 suite of programs was used [28].

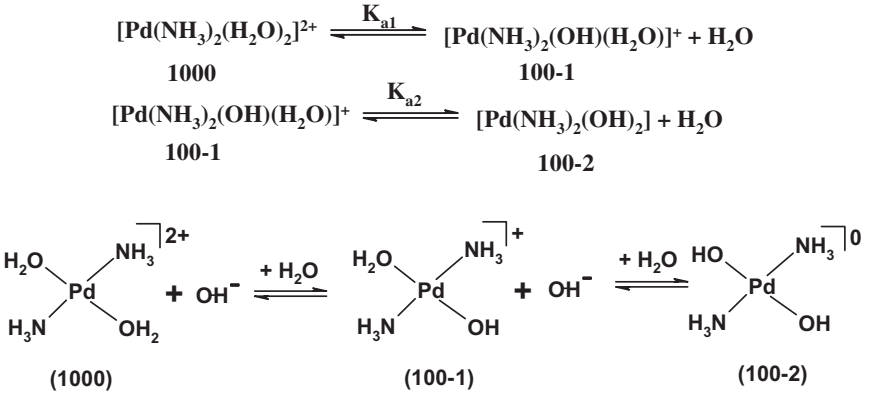
3. Results and discussion

The acid dissociation constants of bpy and Ino were re-determined under the experimental conditions at 25 °C and constant ionic strength used in the determination of the stability constants of the Pd(II) complexes.

3.1. *Hydrolysis of $[Pd(NH_3)_2(H_2O)_2]^{2+}$*

The *trans*-$[Pd(NH_3)_2(H_2O)_2]^{2+}$ may undergo hydrolysis. Its acid-base chemistry was previously [17, 18] characterized by fitting the potentiometric data to various acid–base models. The best fit model was consistent with the formation of two species: 100–1 and 100–2, as given in scheme 1. Trials were made to fit the potentiometric data considering the formation of the bridged dimer [29], 200–2, as in the case of *cisplatin*, but this resulted in very poor fit to the data. This may be due to the fact that the geometrical structure of the *trans*-$[Pd(NH_3)_2(H_2O)_2]^{2+}$ does not allow the formation of a stable dimeric species under the selected conditions.

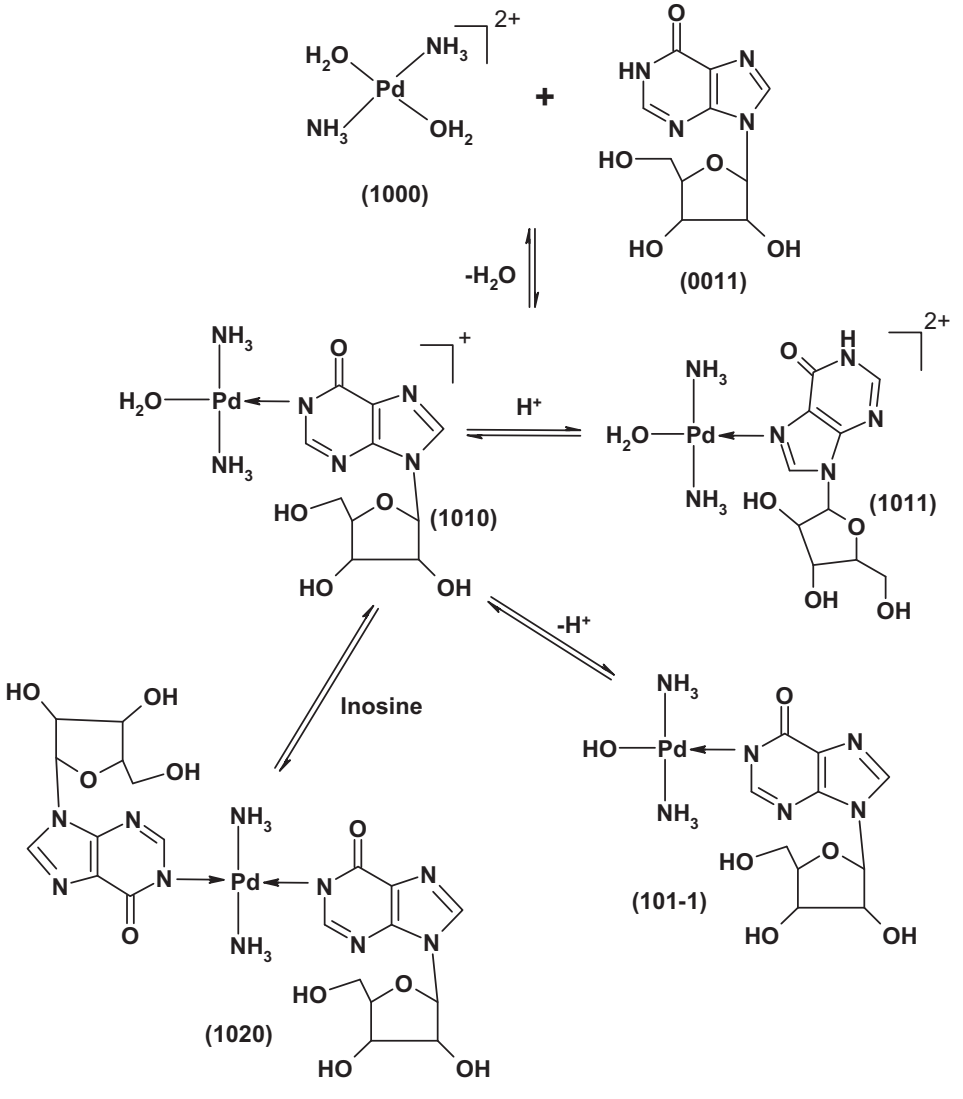
The pK_{a1} and pK_{a2} values for *trans*-$[Pd(NH_3)_2(H_2O)_2]^{2+}$ were 5.90 and 10.26, respectively. The pK_{a1} value is in good agreement with that obtained for *cis*-$[Pd(en)(H_2O)_2]^{2+}$



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

[30] and *cis*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$ [31, 32], where the corresponding values are 5.6 and 5.4, respectively.

The potentiometric data for the *trans*-$[Pd(NH_3)_2(H_2O)_2]^{2+}$-inosine system were fitted considering the formation of the 1 : 1 (1010) and 1 : 2 (1020) complexes, in addition to the protonated species of the 1 : 1 complex (1011) and its hydrolyzed form (101–1). The crucial question in applying inosine and similar bases as ligands is the mode of coordination [33]. In earlier studies, some of us showed convincingly that the coordination mode on N^1 in the six-member ring or N^7 in the five-member ring depends on the pH of the solution [34, 35]. In weakly acidic medium, coordination of inosine predominantly occurs *via* N^7, whereas under more basic conditions coordination occurs *via* N^1 [34]. Thus, the protonated

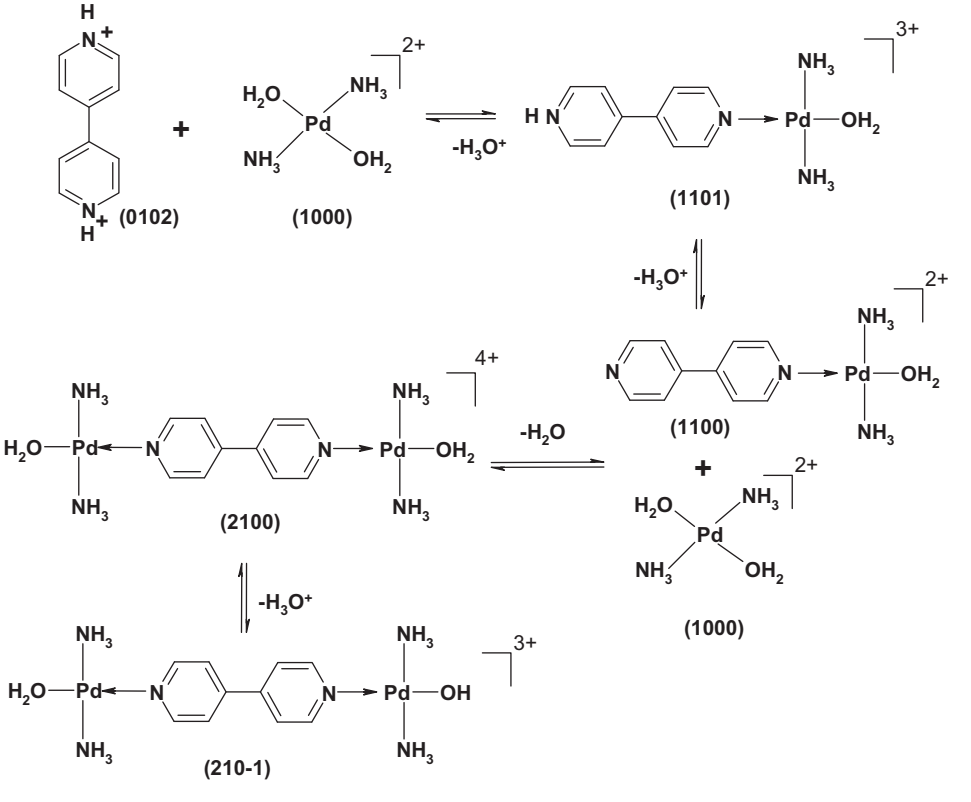


Scheme 2. Complex-formation equilibria in the *trans*-$[Pd(NH_3)_2(H_2O)_2]^{2+}$-Ino system.

complex (1011) is formed by binding to the N^7 site of inosine. The deprotonated complexes (1010) and (1020) are formed by binding to the N^1 site of inosine followed byionization of N_1H. The complex-formation equilibria with inosine are presented in scheme 2. The pK_a value of the protonated species [34] ($\log\beta_{1011} - \log\beta_{1010}$) is 4.13. This value corresponds to N^1H of inosine. The lowering of this value with respect to that of free inosine (pK_a = 8.86) is due to acidification upon complex formation, in accord with previous reports on similar systems [33, 36, 37].

Analysis of the titration data for *trans*-$[Pd(NH_3)_2(H_2O)_2]^{2+}$-bpy system showed the formation of the 1 : 1 complex (1100) in addition to its protonated form (1101) and the 2 : 1 complex (2100) in addition to its hydrolyzed species (210–1). The complex-formation equilibria are presented in scheme 3. The pK_a value of the protonated complex ($\log\beta_{1101} - \log\beta_{1100}$) is 5.04. This value is in agreement with pK_{a1} of free protonated bpy (4.86). The pK_a of coordinated water in the 2 : 1 complex ($\log\beta_{2100} - \log\beta_{210-1}$) is 5.98, in agreement with the pK_a of coordinated water in $[Pd(NH_3)_2(H_2O)_2]^{2+}$.

The concentration distribution diagram of *trans*-$[Pd(NH_3)_2(H_2O)_2]^{2+}$-bpy complexes is given in figure 1. The protonated complex (1101) starts to form at pH 2 and reaches a maximum concentration of 52%. The binuclear complex (2100) reaches a maximum concentration of 39% at pH 5.0. The mononuclear complex predominates with a maximum concentration of 20% at pH 6.3.



Scheme 3. Complex-formation equilibria in the *trans*-$[Pd(NH_3)_2(H_2O)_2]^{2+}$-bpy system.

We further studied the influence of aromaticity of the 4,4′-bpy on the structural geometry of the Pd(II) complexes in thermodynamic equilibrium and during the reaction kinetics by quantum chemical calculations (B3LYP/LANL2DZp) (table 2).

A comparison of the structures of the complexes in the studied equilibria reveals a well-known bonding situation (see table 2). All Pd–NH_3 bond lengths *cis* to pyridine (py) or H_2O and OH are 2.09 Å, no matter whether aqua or hydroxo complexes are considered. The water ligands are bound to Pd^{2+} at a distance of 2.13 − 2.16 Å, reflecting small differences that originate from the different *trans* influence of the coordinated NH_3 or pyridine. After deprotonation, the Pd–O bond is clearly shortened to 1.97 Å independent of whether NH_3 or pyridine is in the *trans* position. The

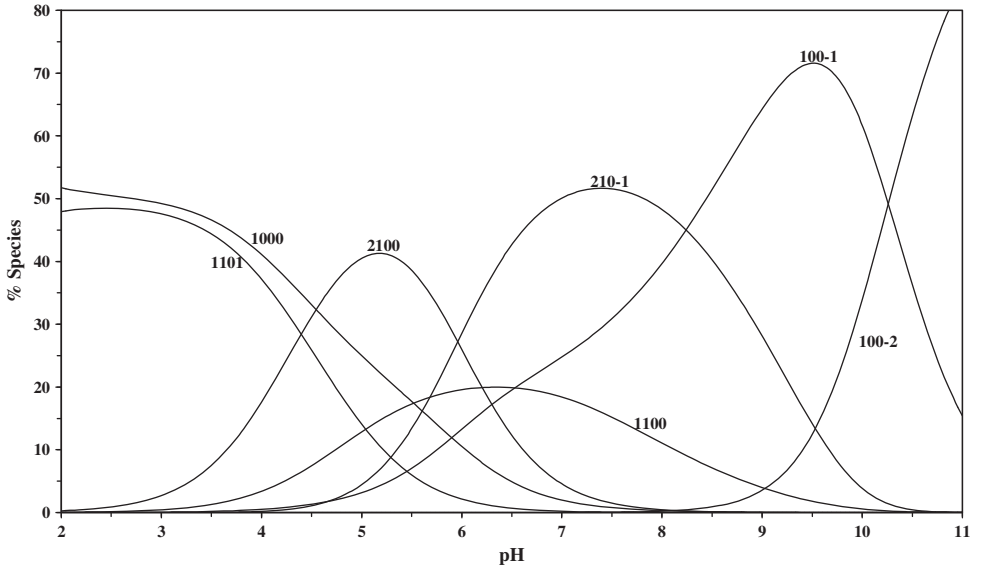


Figure 1. Concentration distribution of *trans*-$[Pd(NH_3)_2(H_2O)_2]^{2+}$-bpy complexes as a function of pH.

Table 2. Calculated (B3LYP/LANL2DZp) structural data for reference species and complexes present in the studied equilibria.

Complex *d* [Å]	*d*(Pd–O)	*d*(Pd–N) (*cis*)	*d*(Pd–N) (*trans*)	*d*(Pd–O)	*d*(Pd–N) (*cis*)	*d*(Pd–N) (*trans*)
$[Pd(NH_3)_3(OH_2)]^{2+}$	2.13	2.09	2.07	-.–	-.–	-.–
$[Pd(NH_3)_3(OH)]^{+}$	1.97^{OH}	2.09	2.16	-.–	-.–	-.–
$[Pd(py)(NH_3)_2(OH_2)]^{2+}$	2.14	2.09/2.10	2.02	-.–	-.–	-.–
$[Pd(py)(NH_3)_2(OH)]^{+}$	1.97^{OH}	2.09	2.11	-.–	-.–	-.–
1000	2.09	2.08	-.–	-.–	-.–	-.–
$[Pd(H_2O)(NH_3)_2(OH)]^{+}$	1.95^{OH}	2.09/2.10	-.–	2.19	-.–	-.–
[Pd(4,5,9,10-tetrahydro-2-azapyrene) $(NH_3)_2(OH_2)]^{2+}$	2.16	2.09/2.10	2.01	-.–	-.–	-.–
$[Pd(pyph)(NH_3)_2(OH_2)]^{2+}$	2.16	2.09/2.10	2.01	-.–	-.–	-.–
1100	2.15	2.09/2.10	2.01	-.–	-.–	-.–
1101	2.13	2.09/2.10	2.05	-.–	-.–	-.–
2100	2.13	2.09/2.09	2.06	2.13	2.09/2.09	2.06
210–1	2.14	2.09/2.10	2.04	1.96^{OH}	$2.10/2.10^{OH}$	2.15^{OH}

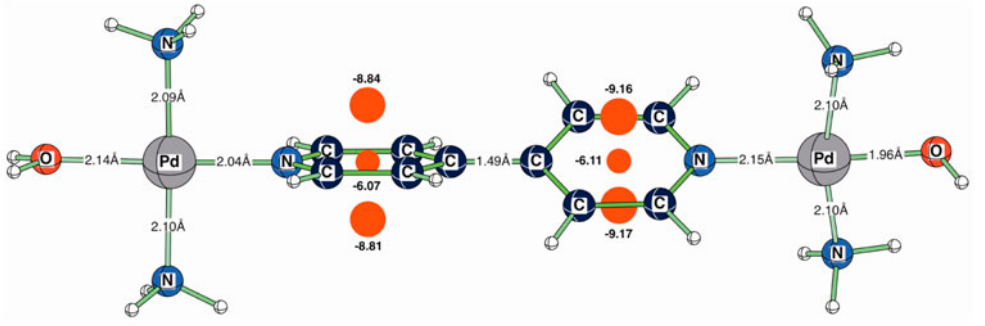


Figure 2. Calculated structure and NICS-values (B3LYP/LANL2DZp) for 210–1.

position *trans* to oxygen in all structures in the investigated equilibria is occupied by a pyridine derivative. Therefore, complexes with pure pyridine ligands were also studied. As expected, the longest Pd–N_{Py} bonds (e.g. 2.11 Å in $[Pd(Py)(NH_3)_2(OH)]^+$, 2.15 Å in 210–1) were found for the hydroxo complexes, as the hydroxo ligand has the largest *trans*-influence, also reflected in $[Pd(NH_3)_3(OH)]^+$ (2.16 Å). The Pd–N_{Py} bond is elongated in both the cases by 0.09 Å (see figure 2).

NICS(1) values are considered to be hardly influenced by σ-effects [27]. Comparison of the NICS(1) values (see table 3) for the coordinated pyridine moieties show no significant influence of the Pd(II) coordination to the pyridine ring beside the polarization effect, which is also observable in the protonated heterocycles and is known from earlier studies [38].

Table 3. Calculated (B3LYP/LANL2DZp) NICS values for references and complexes in the studied equilibra.

Compound	NICS(0)	NICS(1)	NICS(−1)	NICS(0)	NICS(1)	NICS(−1)
Benzene	−8.34	−10.15	−10.15	-.–	-.–	-.–
Pyridine	−6.87	−10.17	−10.17	-.–	-.–	-.–
H^+pyridine	−7.82	−9.72	−9.72	-.–	-.–	-.–
4,4′-bipyridyl	−6.32	−9.55	−9.55	−6.32	−9.55	−9.55
H^+(4,4′-bipyridyl)	-6.34^{H+}	-8.20^{H+}	-8.20^{H+}	−5.81	−9.35	−9.35
$2H^+$(4,4′-bipyridyl)	-7.42^{H+}	-9.13^{H+}	-9.13^{H+}	-7.42^{H+}	-9.13^{H+}	-9.13^{H+}
$[Pd(py)(NH_3)_2(OH_2)]^{2+}$	−6.80	−9.73	−9.70	-.–	-.–	-.–
$[Pd(py)(NH_3)_2(OH)]^+$	−6.70	−9.76	−9.76	-.–	-.–	-.–
$[Pd(pyph)(NH_3)_2(OH_2)]^{2+}$	$-4.19^{Pd^{2+}}$	$-6.97^{Pd^{2+}}$	$-6.94^{Pd^{2+}}$	−5.89	−8.31	−8.28
[Pd(4,5,9,10-tetrahydro-2-azapyrene) $(NH_3)_2(OH_2)]^{2+}$	$-4.22^{Pd^{2+}}$	$-6.77^{Pd^{2+}}$	$-6.71^{Pd^{2+}}$	−4.78	−8.21	−8.21
1100	$-5.29^{Pd^{2+}}$	$-8.06^{Pd^{2+}}$	$-8.02^{Pd^{2+}}$	−5.63	−9.27	−9.27
1101	$-6.45^{Pd^{2+}}$	$-9.23^{Pd^{2+}}$	$-9.19^{Pd^{2+}}$	-7.42^{H+}	-9.16^{H+}	-9.16^{H+}
2100	$-6.45^{Pd^{2+}}$	$-9.23^{Pd^{2+}}$	$-9.24^{Pd^{2+}}$	$-6.45^{Pd^{2+}}$	$-9.23^{Pd^{2+}}$	$-9.24^{Pd^{2+}}$
210–1	−6.07	−8.84	−8.81	-6.11^{OH-}	-9.16^{OH-}	-9.17^{OH-}

Notes: H+: protonated pyridine ring; Pd^{2+}: pyridine ring coordinated to the Pd^{2+} center.

Table 4. Calculated (B3LYP/LANL2DZp) C–C bond length between the aromatic rings.

C–C bond [Å]	1.49	1.48	1.50	1.47		
Compound	4,4′-bipyridyl	H^+(4,4′-bipyridyl)	$2H^+$(4,4′-bipyridyl)	$[Pd(PyPh)(NH_3)_2(OH_2)]^{2+}$		
C–C bond [Å]	1.45		1.47	1.50	1.50	1.49
Compound	[Pd(4,5,9,10-tetrahydro-2-aza-pyrene)$(NH_3)_2(OH_2)]^{2+}$		1100	1101	2100	210–1

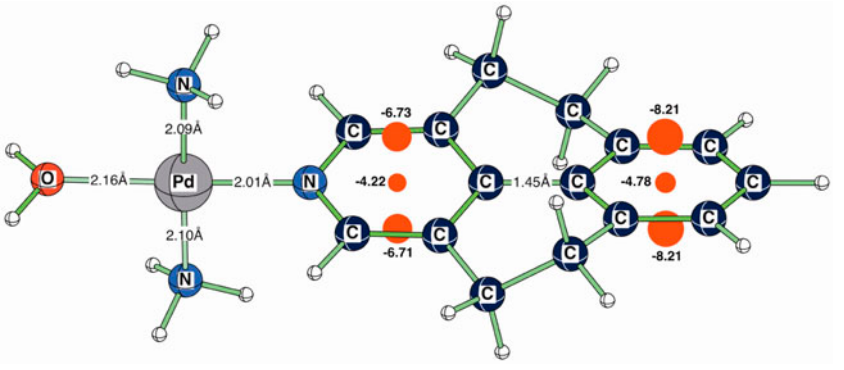
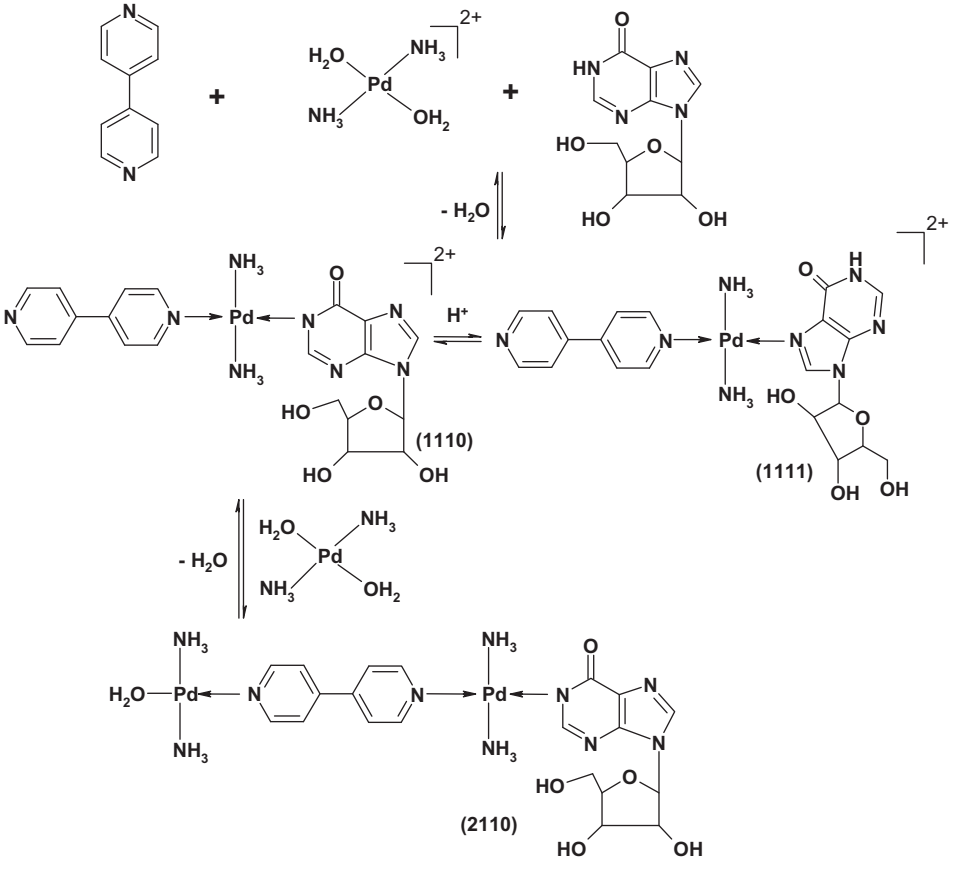


Figure 3. Calculated structure and NICS-values (B3LYP/LANL2DZp) for [Pd(4,5,9,10-tetrahydro-2-azapyrene)$(NH_3)_2(OH_2)]^{2+}$.



Scheme 4. Complex-formation equilibria in the *trans*-$[Pd(NH_3)_2(H_2O)_2]^{2+}$-bpy-Ino system.

The only exception in the experimentally studied compounds is 1100. Here the NICS(0) and NICS(1) values are more reduced (4,4′-bpy NICS(1): −9.7; 1100 NICS(1): −8.0) than

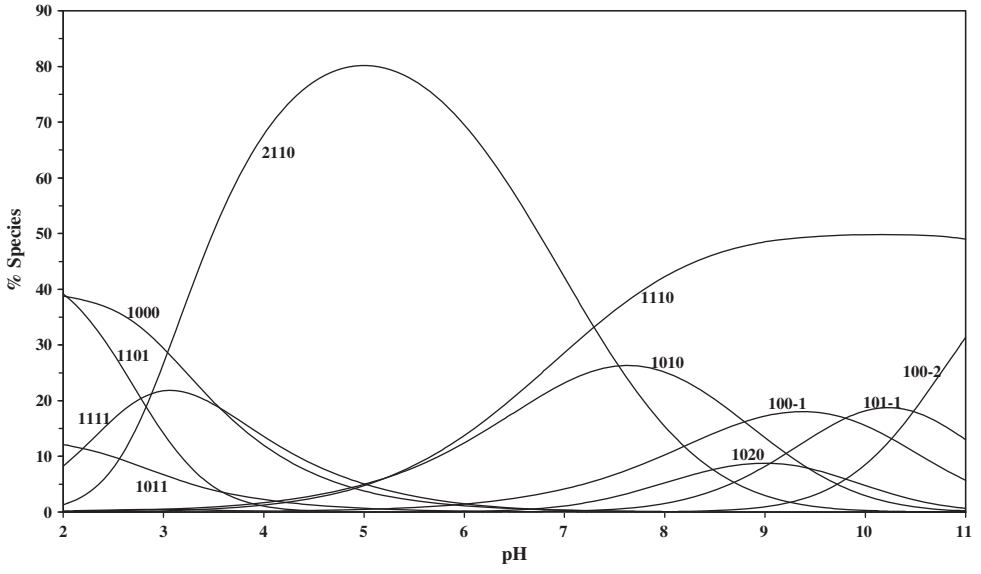


Figure 4. Concentration distribution of *trans*-$[Pd(NH_3)_2(H_2O)_2]^{2+}$-bpy-Inosine complexes as a function of pH.

in the other cases. An inspection of the calculated structures shows that the largest structural difference is found for the C–C bond between the two aromatic units (see table 4).

A comparison between NICS(1) values and the calculated C–C bond length between the aromatic rings shows a good qualitative relationship. As the C–C bond lengths, increase the NICS(1) values decrease ([Pd(4,5,9,10-tetrahydro-2-azapyrene)$(NH_3)_2(OH_2)]^{2+}$: C–C bond: 1.45 Å, NICS(1): −6.8; 2100 C–C bond: 1.50 Å, NICS(1) −9.2) (see figures 2 and 3). The described effect is reduced when protons or palladium cations are bound to both the sides of 4,4′-bpy, which is interpreted in terms of an electron donating effect of the second ring.

For the *trans*-$[Pd(NH_3)_2(H_2O)_2]^{2+}$-bpy-Ino system, the results presented in scheme 4 show the presence of the complex with stoichiometric coefficients 1 : 1 : 1 : 1 (1110) and its protonated form (1111), and the 2 : 1 : 1 : 0 complex (2110). The pK_a value of the protonated species (1111) ($\log \beta_{1111} - \log \beta_{1110}$) is 5.03, which corresponds to the N_1H of coordinated inosine and, as mentioned before, the N_1H group is acidified upon coordination. The concentration distribution diagram of the binuclear complex involving inosine is given in figure 4. The protonated species starts to form at pH 2. The mononuclear complex (1110) predominates with a concentration of 47% at pH 9.0. The binuclear complex (2110) predominates with a maximum degree of formation of 80% at pH 5.0. This reveals that in the physiological pH range the interaction between binuclear Pd^{II}-bpy-Pd^{II} and a DNA constituent such as inosine is quite feasible and consequently supports the anti-tumor activity of this class of complexes.

4. Conclusions

The present investigation reports on the complex-formation equilibria of *trans*-palladium with 4,4′-bipyridine and inosine as an example of a DNA constituent. The results indicate

the formation of a binuclear complex. The reaction with DNA constituents is feasible and consistent with earlier investigations on inosine complex-formation with $[(H_2O)(dmen)Pd(bpy)Pd(dmen)(H_2O)]^{4+}$, where dmen represents N,N-dimethylethylenediamine [39]. The results support the biological significance of bi- and trinuclear platinum(II) complexes that have potent anti-tumor activity. The formation of macromolecules seems to be unlikely as the concentration range of Pd(II), bpy and inosine is too low to allow formation of such species.

The calculated structures of the investigated equilibria show characteristic bond lengths for all Pd^{2+}-ligand interactions. Interestingly, the C–C bond in 1100 is clearly shrunk at 1.47 Å. This is reflected in the reduced aromaticity of 4,4′-bipyridine. The investigation of the related model compounds suggests that the uncoordinated aromatic ring can be interpreted as an electron donating group.

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