Biometals (2009) 22:385–392
DOI 10.1007/s10534-008-9175-2

Electrochemical and spectroscopic evidences of the interaction between DNA and Pt(II)(dppf)-complex

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Received: 3 March 2008 / Accepted: 14 October 2008 / Published online: 4 November 2008

Abstract The interaction of Pt(II)(dppf)-complex, namely $[Pt(dppf)(H_2O)_2]^{2+}$ with DNA was investigated by DPV and ^{1}H-NMR techniques. The results showed that the interaction process has been characterized by changes in the electrochemical parameters of both compounds and the formation of a new anodic current peak close to the anodic current peak of the $[Pt(dppf)(H_2O)_2]^{2+}$. In addition, the ^{1}H-NMR spectra show that the coordination of Pt(II)(dppf)-complex to dsDNA occurs via N(7) of guanine. Others parameters like pH and ionic strength that affect the interaction process were also investigated.

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Keywords DNA · Platinum · Transition metal complexes · DNA–metal complex interaction

Introduction

The study of the interaction between DNA with complex natural products or inorganic compounds is of primary scientific interest, since DNA is the main target molecule for most anticancer and antiviral therapies according to cell biology. These studies are relevant to help the understanding of the action mechanism of some DNA-target drugs and toxic agents as well the origins of some diseases like gene mutation (Aslanoglu et al. 2000).

Several studies for new clinical drugs involving metal complexes have been reported, in special, platinum derivates. In this sense the development of metal complexes as anticancer drugs has been facilitated by the extensive knowledge of the inorganic chemists in the coordination and redox properties of metal ions (Sherman and Lippard 1987). Metal centers being positively charged are favored to bind to negatively charged molecules such as DNA. The constituents of proteins and nucleic acids offer adequate sites for metal binding in a specific way and it can be related to the pharmacological properties of the complexes. As a result, metal coordination compounds relevantly affect cellular processes such as cell division and gene expression,

as well as others like carcinogenicity and antitumor chemistry (Kostova 2006).

Platinum (II) complexes, notably cisplatin and carboplatin (Fig. 1a, b) are now among the most widely used compounds as chemotherapeutic agents. The first one, cisplatin, reacts with DNA in the cell nucleus, but the mechanism of its anticancer activity is still unclear. It is believed to exert its potent biological activity through covalent modification of DNA followed by disruption of the replication or transcription events (Kennard 1993). Hypotheses have been cited to describe its action, which include proteins in the biological mechanism such as: natural proteins might protect the platinum-DNA adducts from repair or proteins could be diverted from their normal processes by platinum adducts. A hypothesis has been assumed that bifunctional adducts are the strongest contributor in cisplatin anticancer activity. In vitro, the aqua species, $[Pt(NH_3)_2Cl(H_2O)]^+$ reacts with DNA, that is the primary biological target of the drug and as a result is formed covalent adducts preferentially through the N7 atoms of guanine residues (Fig. 1c). The cationic platinum complex is formed when a water molecule attacks the platinum metal center, thus eliminating a chloride ion, which acts as a non-coordinating anion. After losing two Cl^- ions, hydrolyzed cisplatin reacts with DNA, forming coordinative bonds to nitrogen atoms of the nucleobases (Kostova 2006; Wang and Lippard 2005).

The preferential adduct formation with G-N7 has been suggested to be an effect of G-N7 basicity combined with the establishment of a hydrogen bonds between ligands in the coordination sphere of the Pt(II) complex and G-O6. The relative amounts of adducts formed by cisplatin upon binding to double-stranded DNA are usually 90% intrastrand cross-links between adjacent purines and around 10% of monofunctional adducts, interstrand cross-links or intrastrand cross-links between non-adjacent purine residues (Kostova 2006; Wang and Lippard 2005).

However, the usefulness of the drugs like cisplatin for clinical use is limited by some factors; the spectrum of its anticancer activity, which is not active enough against several types of cancer and show the development of resistance after continued treatment. Another aspect is that these compounds are highly toxic to some normal cells (Brabec and Kasparkova 2005). In this direction, there is a trend to find similar substitutes.

It is important to investigate the underlying of antitumor, antimutagenic and anticarcinogenic actions of news platinum compounds to understand how these compounds affect DNA. Moreover, the introduction of new platinum antitumor drugs is based on known mechanistic DNA-binding event.

Novel ferrocenyl-based platinum compounds with geometry cis at the platinum center have been produced and tested as an attempt replacement drugs for cisplatin for clinical use. Earlier studies have shown that this class of compounds exhibits promising antineoplasic and antimicrobial activity (Scarcia et al. 1988; Mason et al. 1999).

In this paper, the $[Pt(dppf)(H_2O)_2]^{2+}$, (diaquo-1,1′ bis (diphenylphosphino)-ferroceno platinum (II) complex, with analogous structure of cisplatin is evaluated in terms of the reactivity towards DNA. This compound is an inorganic square-planar coordination complex, which contain *cis* phosphine configuration;

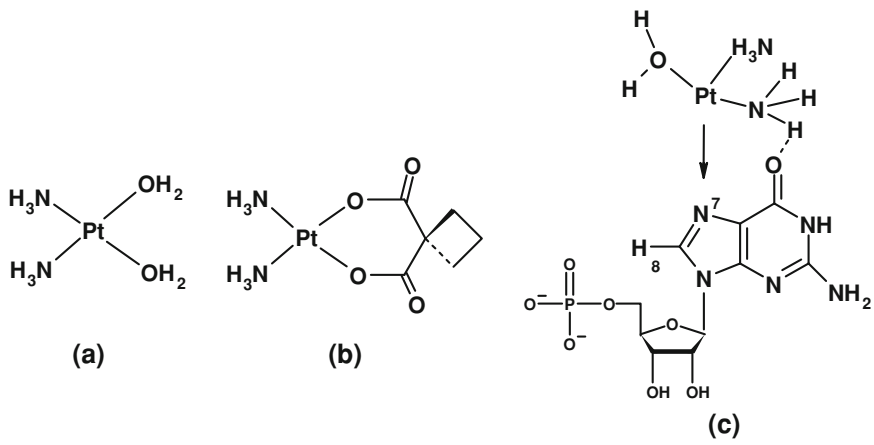

Fig. 1 Structure of cisplatin (**a**), carboplatin (**b**) and adduct formation of cisplatin with guanidine base (**c**)

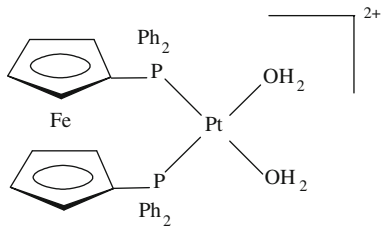

Fig. 2 Structure of the Pt(II)(dppf)-complex, $[Pt(dppf)(H_2O)_2]^{2+}$. Ph denotes phenyl group

a central platinum atom surrounded by ferrocene moiety and two water molecules (Fig. 2). This platinum (II) complex has been known as catalyst (Cullen and Woollins 1981) in homogenous catalysis, especially in Grignard cross coupling reactions (Hayashi et al. 1984). However, no study was performed with this complex in biological system, but the presence of labile water molecules in the platinum coordination sphere, could make it possible to interact with DNA.

The interaction process of metal complex with DNA was studied by electrochemical and spectroscopic approach. The use of the voltammetric technique provides a useful complement to spectroscopic methods and yields information about drug-DNA interactions mechanisms (Lu et al. 2002; Longato et al. 1988).

Materials and methods

Materials

Sodium acetate and sodium chloride were purchased from Merck (Darmstadt, Germany), $AgNO_3$ was purchased from Aldrich (USA) and the complex $[Pt(cod)Cl_2]$ was prepared as described in literature (Longato et al. 1988). Double-stranded calf thymus DNA D4522 (dsDNA activated and lyophilized) was supplied by Sigma (St Louis, USA). Graphite powder (purity 99.9%) was acquired from Aldrich (Milwaukee, USA). All aqueous solutions were prepared using ultrapure water ($\rho > 18$ MΩ/cm) from a Milli-Q system (Millipore, system). Nitrogen saturated solutions were obtained by bubbling of N_2 high purity in the solution for 15 min and continuing with a flow of the pure gas over the solution during the voltammetric measurements. DNA stock solutions (nominally 1,000 μg l^{-1}) were prepared in purified water after dividing and storing in a freezer.

Methods

Synthesis of the $[Pt(dppf)(H_2O)_2]^{2+}$ complex

The ferrocenylphosphino derivative complex was prepared and characterized according to Noh et al. (2001), but its synthesis is briefly described. A Schlenk flask of 50 ml was charged with 0.183 g (0.330 mmol l^{-1}) of 1′,1′-bis(diphenylphosphino) ferrocene (dppf), 0.112 g (0.300 mmol l^{-1}) of dichloro (cycloocta-1,5-diene) platinum (II) ($[Pt(cod)Cl_2]$), and 20 ml of CH_2Cl_2. The resulting yellow solution was stirred at room temperature for 2.5 h, until the solution become orange. Then, 3.5 g of $AgNO_3$ in 1 ml of H_2O were added to the Schlenk flask. The solution was stirred for more 1 h. The solution was then transferred into a flask of 100 ml and reduced to a volume of 2 ml. Diethyl ether was then added, and the orange yellowish precipitate was filtered off, washed with ether and dried in vacuum. The resulting compound 0.273 g, diaquo-1,1′bis (diphenylphosphino)-ferrocene platinum (II) is a salt of nitrate, $[Pt(dppf)(H_2O)_2](NO_3)_2$ and was obtained 94% yield. ^{1}H-NMR ($CDCl_3$, ppm): $\delta = 7.54$ (dd, 8 H, o-H, Ph), 7.43 (*t*, 4 H, p-H, Ph), 7.25 (*t*, 8 H, Ph), 4.47 (brs, 4 H, Cp, dppf), 4.27 (brs, 4 H, Cp, dppf), 1.69 (brs, 4 H, H_2O); ^{31}P $\{^1$H$\}$ NMR ($CDCl_3$, ppm): $\delta = 9.38$ (s + brd, $J_{P-Pt} = 3.795$).

NMR measurements

The ^{1}H and ^{31}P$\{^1$H$\}$ NMR were recorded at 298 K on Gemini—300 MHZ spectrophotometer in $CDCl_3$ for characterization of $[Pt(dppf)(H_2O)_2]$ complex with 3-(trimethylsilyl)-propanesulfonic acid sodium salt. The interaction studies between 5′GMP and the $[Pt(dppf)(H_2O)_2]^{2+}$ complex by ^{1}H-NMR were recorded at 298 K on Gemini—300 Mz spectrophotometer in DMSO/D_2O mixture as a solvent. The chemical shifts are referred to D_2O signal at 4.8 ppm. The concentration of guanine base and Pt(II)-dppf complex solutions were 32 and 10 mmol l^{-1}, respectively. The all chemical shifts (δ) are relative to the residual peak of the deuterated solvent and given in parts per million.

Electrochemical measurements

The electrochemical measurements were carried out at room temperature and using a conventional

electrochemical cell based on Ag/AgCl as reference, platinum wire as auxiliary and carbon paste as working electrode. The carbon past electrode was prepared in the usual way by hand-mixing 20 mg of graphite and $[Pt(dppf)(H_2O)_2]^{2+}$ powder in different ratio and after dropping 25 µl mineral oil until get a homogeneous paste. The paste was put into a cavity of 1 mm deep consisting of a platinum disk sealed into the extremity of a glass tube (4 mm i.d.) and pressed to smooth the surface. The blank electrode is the electrode without complex and it was prepared by mixing 20 mg of graphite powder and 25 µl mineral oil.

The interaction between dsDNA and $[Pt(dppf)(H_2O)_2]^{2+}$ complex was investigated by using differential pulse voltammetry (DPV). The experimental conditions were: pulse amplitude 50 ms; pulse width 50 ms; scan rate 10 mV s^{-1} and the current sampling time was set at 0.5 s. A potentiostat from Eco Chemie Autolab® PGSTAT30 connected to a PC (software GPES 4.8) was employed in the electrochemical measurements.

The voltammetric signal transduction was performed by subtracting the background electrolyte curve obtained at CPE from the subsequent curves. The electrochemical data presented were obtained in three replicates.

Results and discussion

The procedure reported to evaluate the interaction between $[Pt(dppf)(H_2O)_2]^{2+}$ complex with dsDNA consisted in studies performed by DPV with the complex immobilized on CPE and DNA in sodium acetate buffer solution. It was carried out considering that voltammetric approach has shown to be a very powerful technique for characterizing the ferrocene-derived compounds related to its biological activity mainly in studies involving redox process in vivo (Han et al. 2003). Besides, in previous tests it was observed the poor aqueous solubility of $[Pt(dppf)(H_2O)_2]^{2+}$ complex which limit, in part, the characterization of a possible interaction with DNA. The electrochemical behavior of the compound in the absence of DNA is shown in Fig. 3.

The behavior of the platinum complexes containing 1,1′bis (diphenylphosphino) ferrocene are influenced greatly by the Lewis-acid character of the Pt(II) center and mainly by the properties of the dppf ligand. The redox active ferrocene backbone of dppf has been proposed to influence the electron transfer properties of dppf containing compounds. However, unlike ferrocene, the oxidation of dppf is not completely reversible. This bidentate ligand is well-known redox ligand and in this sense its complexes are expected to exhibit a ferrocene-centered oxidation process, together with the additional redox process at other metal centers in the molecule (Nataro et al. 2003). Variation of these complexes, with $X = Cl$ or thiolate show different redox behavior in organic electrolyte solutions, which is related directly to the electron-donor ability of terminal ligands (Nataro et al. 2003; Vrana and Brabec 1986; Sequaris et al. 1984). The electrochemical characterization of $[(dppf)PtX_2]$

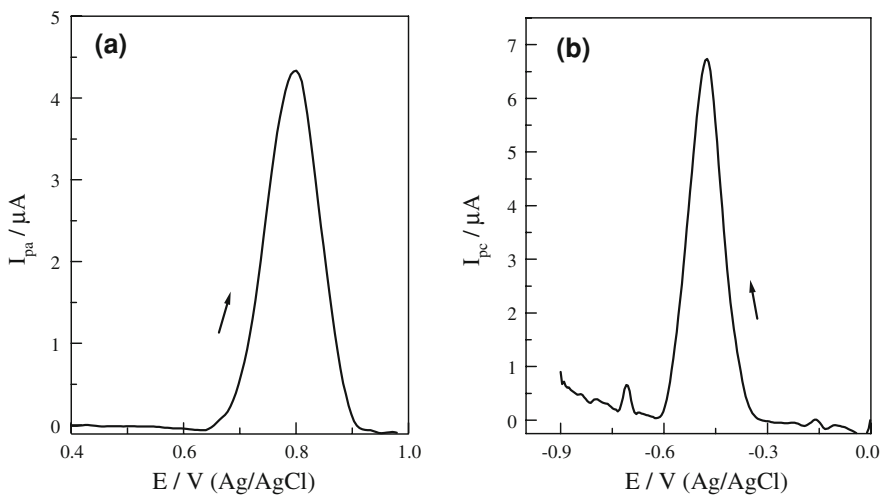

Fig. 3 Anodic (**a**) and cathodic (**b**) differential pulse voltammograms of the $[Pt(dppf)(H_2O)_2]^{2+}$ complex modified CPE in sodium acetate buffer 0.25 mol l^{-1} (pH = 4.5). DPV parameters: pulse amplitude 50 ms; pulse width 50 ms; scan rate 10 mV s^{-1}

heterobimetallic complex in aqueous solutions has not been reported. The redox behavior of the [Pt(dppf)$(H_2O)_2]^{2+}$ in acetate buffer is characterized by two peaks, one anodic peak at +0.8 V (versus Ag/AgCl) (voltammogram 3a) and other cathodic peak at −0.47 V (versus Ag/AgCl) (voltammogram 3b). This reaction could be an oxidation/reduction process of the dppf ligand within the complex with the possibility of the oxidation event of $Pt^0 \rightarrow Pt^1$ couple, type $[Pt\,L]^{0/+}$ and $[Pt\ L]^{+/2+}$, respectively where L = [(dppf)$(H_2O)_2$] as suggested for analogous complexes (Noh et al. 2001).

In this study, the electrochemical transduction of the interaction between $[Pt(dppf)(H_2O)_2]^{2+}$ complex and DNA was performed exploiting the distinct well-defined oxidation peaks of both compound at the CPE surface.

The DPV of $[Pt(dppf)(H_2O)_2]^{2+}$ complex modified electrode (voltammogram 4a) and dsDNA in solution (voltammogram 4b) are shown in Fig. 4. Voltammograms of native DNA in acetate buffer solution at unmodified CPE produces two well-defined peaks related to the oxidation signal of the purines bases, guanine at +0.9 V (versus Ag/AgCl) and adenine at +1.18 V (versus Ag/AgCl). In the same anodic potential range, the signal of $[Pt(dppf)(H_2O)_2]^{2+}$ complex modified electrode in contact with dsDNA solution show changes in the electrochemical parameters of both compounds, in special DNA where the peaks corresponding to guanine and adenine were significantly affected by the presence of [Pt(dppf)$(H_2O)_2]^{2+}$ complex. In the obtained voltammogram is observed only a small peak (voltammogram 4c) close to the anodic peak of the complex, which show the interaction between $[Pt(dppf)(H_2O)_2]^{2+}$ complex and dsDNA has take place. It can be observed by the decrease of the peak current (around 68%) with a small shift of the peak potential (by 38 mV) in relation to the peak potential observed for the complex. On the other hand in Fig. 5 in the cathodic potential range, the peak current of the [Pt(dppf) $(H_2O)_2]^{2+}$ complex in the presence of dsDNA solution decrease in around 54%, but was not observed displacement of its peak potential as well as no signal of the individual dsDNA solution.

The ability of DNA to bind with a number of platinum complexes with aromatic ligands is well

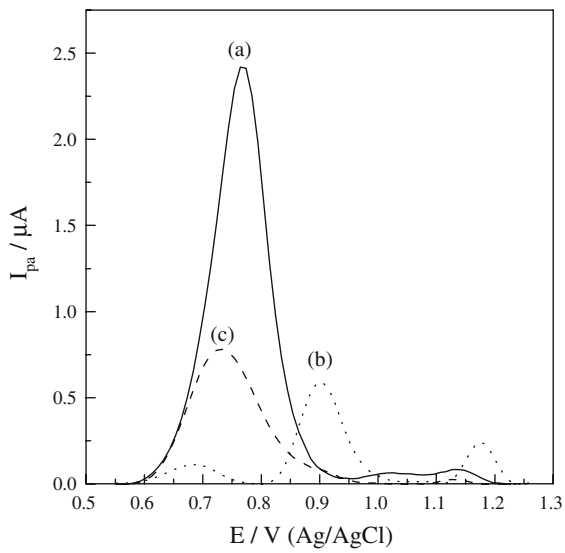

Fig. 4 Differential pulse voltammograms obtained in 0.25 mol l^{-1} acetate buffer for (**a**) (—) $[Pt(dppf)(H_2O)_2]^{2+}$ complex modified CPE; (**b**) (•••) unmodified CPE in dsDNA solution and for (**c**) (- - -) $[Pt(dppf)(H_2O)_2]^{2+}$ complex adsorbed on the CPE in the presence of dsDNA solution. Concentration of the $[Pt(dppf)(H_2O)_2]^{2+}$ complex on the CPE = 1.3×10^{-8} mol mg^{-1}, concentration of dsDNA solution = 30 μg l^{-1}

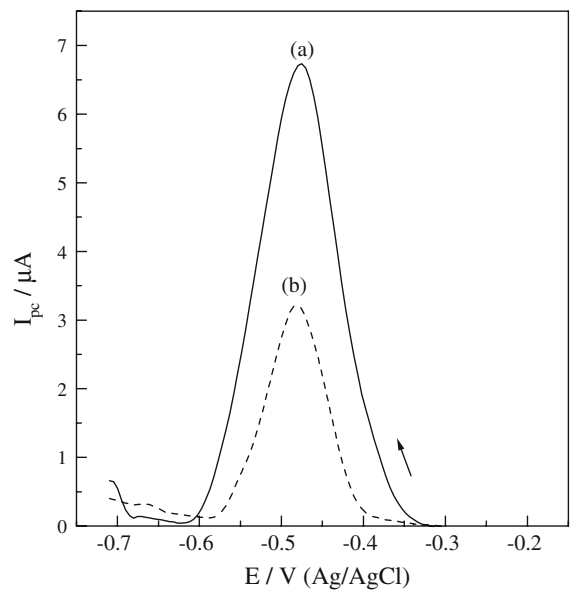

Fig. 5 Differential pulse voltammograms obtained in 0.25 mol l^{-1} acetate buffer for (**a**) (—) $[Pt(dppf)(H_2O)_2]^{2+}$ complex modified CPE and (**b**) (- - -) $[Pt(dppf)(H_2O)_2]^{2+}$ adsorbed on the CPE in the presence of dsDNA solution. Concentration of the $[Pt(dppf)(H_2O)_2]^{2+}$ complex on the CPE = 1.3×10^{-8} mol mg^{-1}, concentration of dsDNA solution = 30 μg l^{-1}

documented (Sherman and Lippard 1987; Puxty et al. 2005; Bjelosevich et al. 2006). Usually, these complexes coordinate to DNA by the interaction of a planar molecule between neighbor base pairs of DNA, which it is held by the Van der Waal forces. Classical intercalators in platinum complexes like bypyridine, terpyridine and o-phenanthroline ligands have been investigated and their biological activity related to intercalating ability usually with adduct formation. It was also observed that for some platinum complexes, in particular those in the oxidation state of +2, cause major conformational changes during DNA interaction (Lu et al. 2002; Vrana and Brabec 1986). Others studies revealed that under normal conditions, these complexes coordinates to DNA preferentially by base residues in single or double-stranded DNA. Binding sites are N7 atom of guanine, N7 and N1 atoms of adenine and N3 atom of cytosine (Sequaris et al. 1984; Swiatek 1994), respectively.

Using the ^{1}H-NMR spectroscopy and evaluating the changes in the chemical shifts of the protons is possible to obtain specific information about the interaction sites. The interaction between 5′GMP (32 mmol l^{-1}) and $[Pt(dppf)(H_2O)_2]^{2+}$ complex (5 mmol l^{-1}) in D_2O/DMSO (pH 6.80) was investigated by the ^{1}H-NMR as displayed in Fig. 6. In Fig. 6a the signal of H8 of 5′GMP at δ8.32 was observed. When the complex was mixed with 5′GMP a new signal of H8 went downfield (δ8.82), proving the interaction via N7 of 5′GMP (Petrovic et al. 2007). As shown in the ^{1}H-NMR spectra of the mixture (Fig. 6c), the downfield displacement of the H(8) proton of 5′GMP, indicated that the coordination site of $[Pt(dppf)(H_2O)_2]^{2+}$ to DNA occurred via N(7) of guanine residues on adjacent strands of DNA.

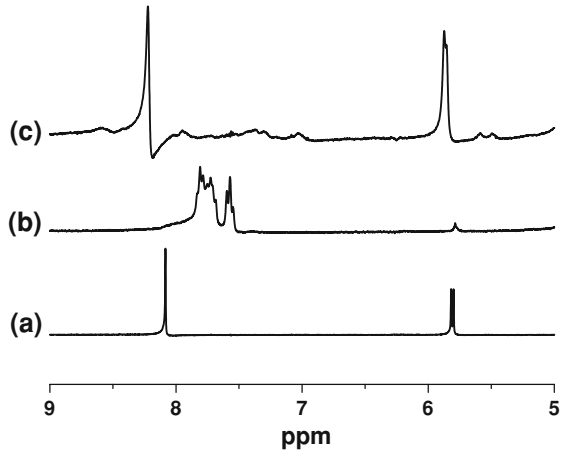

Fig. 6 ^{1}H-NMR spectra at 298 K. **a** 5′GMP, (**b**) $[Pt(dppf)(H_2O)_2]^{2+}$ complex and (**c**) mixture of the 5′GMP and $[Pt(dppf)(H_2O)_2]^{2+}$ complex. The solvent used was DMSO/D_2O mixture. The concentration of 5′GMP and $[Pt(dppf)(H_2O)_2]^{2+}$ complex solutions were 32 and 10 mmol l^{-1}, respectively

Based on ^{1}H-NMR information, there is the formation of an adduct as new product, with a potential very close to that observed for $[Pt(dppf)(H_2O)_2]^{2+}$ complex, by binding firstly to the guanine residues and not with the DNA phosphate groups. On the basis of the knowledge of DNA interaction studies with platinum coordination compounds, it is possible to consider that the interaction process may take place by intercalation (Bjelosevich et al. 2006; Petrovic et al. 2007). According to the reported to N7 binding site of the guanine, it may be assumed the Pt(II)(dppf)-complex form adduct predominantly the DNA major groove (Collins and Wheate 2004; Sadler and Guo 1998). It is favored because studied square-planar complex coordinate with the plane of the guanine bases, resulting in some restructuring of the double helix. It means that the bound guanine is responsible by the electrochemical oxidation process. The observed low electrochemical signal can be explained considering that for calf thymus DNA (in our case) there is a relatively small number of guanines in the dsDNA sequence, only 20% of the nucleotides are guanine (Sistare et al. 1999) which result in few binding products lead to effective electron transfer. It is also important to consider the occurrence of eventual electrostatic interactions. The partial insertion of the ligands of the complex between adjacent base pairs on the DNA duplex strand allows that remaining ligands disposed along to the major groove of DNA can interact electrostatically with the sugar-phosphate backbone and hydrophobically with the region in the ligand of the paired nucleotide bases.

In order to have more information about the interaction, experiments with other ionic strength of the buffer solution were also performed. In Table 1 is shown that the anodic peak current of the formed adduct is smaller at low ionic strength; reduction around 83% at 0.25 mol l^{-1} in comparison with higher ionic strength; reduction around 70% at 0.5 mol l^{-1}, values in relation to $[Pt(dppf)(H_2O)_2]^{2+}$

Table 1 Effect of the buffer solution concentration on the interaction process between $[Pt(dppf)(H_2O)_2]^{2+}$ and dsDNA in relation to adduct formation

	Concentration of the buffer solution (mol l^{-1})			
	0.25		0.50	
	I_{pa} (μA)	E_{pa} (V)	I_{pa} (μA)	E_{pa} (V)
$[Pt(dppf)(H_2O)_2]^{2+}$	4.0	0.76	3.0	0.73
dsDNA	0.6	0.90	0.7	0.90
$[Pt(dppf)(H_2O)_2]^{2+}$–dsDNA	0.7	0.73	0.9	0.71

pH, 4.5; I_{pa}, anodic peak current; E_{pa}, anodic peak potential

complex. It was also observed that the peak potential shifted to a less positive value increasing the ionic strength. The positively charged $[Pt(dppf)(H_2O)_2]^{2+}$ can be bound to an electronegative group of the guanine base (e.g. N7-guanine) even at low ionic strength. This process is better observed at high ionic strength, which indicates that the surface accessibility of dsDNA to associate with $[Pt(dppf)(H_2O)_2]^{2+}$ ions at the electrode is facilitate increasing the ionic strength.

Conclusions

The study concerning the development of metal complexes as drugs is not an easy task, considering the difficulty of evaluation of its pharmacological specificity related to its clearance and biodistribution. Besides, favorable physiological responses of candidate drugs need to be demonstrated firstly in vitro studies with targeted biomolecule and tissue before any type of in vivo investigation. A mechanistic understanding of how metal complexes can interact with these biomarkers is important to understand its activity as pharmaceuticals.

In this sense, the use of chemical methods that provide information for this purpose is essential. Electrochemical investigation of drug–DNA interaction can provide a useful complement to other methods and in many cases yield information about the mechanism of interaction and the adduct conformation. In case of the $[Pt(dppf)(H_2O)_2]^{2+}$–dsDNA interaction, the use of voltammetric method was possible to probe the interaction by the changes of the electrochemical behavior of the compounds. On the other hand, the information from NMR spectra contributed for the nature of the interaction.

The definitive results performed after a set of experiments provide evidence that the interaction between $[Pt(dppf)(H_2O)_2]^{2+}$ complex and dsDNA has taken place. However, it is still impossible to conclude the mode of interaction.

The recognition mechanism of the antitumor activity of platinum compounds is a complex process involving a number of factors. Considering that DNA is an important and major pharmacological target of these compounds, information about its DNA-binding mode help us to characterize new platinum compounds related to the clinical potential. In this direction, voltammetry may be used as a technique for detection of DNA interaction modes considering that the voltammetric behavior of compounds during the interaction process would be useful in the screening design for new drugs with favorable DNA interaction patterns.

Acknowledgments The authors thank FAPESP for the financial support.

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