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Platinum(II) Complexes with Tetradentate Schiff Bases as Ligands: Synthesis, Characterization and Detection of DNA Interaction by Differential Pulse Voltammetry

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Abstract: Five sterically hindered platinum(II) complexes with tetradentate schiff bases as ligands, [Pt(L)] (L= *N,N'*-bisalicylidene-1,2-ethylenediamine (L^1), *N,N'*-bisalicylidene-1,2-cyclohexanediamine (L^2), N,N'-bis(5-hydroxyl-salicylidene)-1,2-cyclohexanediamine (L^3), *N,N'*-bisalicylidene-1,2-diphenyl-ethylenediamine (L^4) and *N,N'*-bis(3-tert-butyl-5-methyl-salicylidene)-1,2-diphenylethylenediamine (L^5)) have been synthesized and characterized by IR spectroscopy and elemental analysis. The sterical hindrance of antitumor drug candidates potentially makes them less susceptible to deactivation by sulphur containing proteins and helping to overcome resistance mechanisms. The interaction of these metal complexes with fish sperm single-stranded DNA (ssDNA) was studied electrochemically based on the oxidation signals of guanine and adenine. Differential pulse voltammetry was employed to monitor the DNA interaction in solution by using renewable pencil graphite electrode. The results indicate that ligands with different groups can strongly affect the interaction between [Pt(L)] complexes and ssDNA due to sterical hindrances and complex [Pt(L^1)] has the best interaction with DNA among the five complexes.

Keywords: Platinum(II) complexes, Synthesis, DNA interaction, Differential pulse voltammetry.

Introduction

Schiff bases are used as substrates in the preparation of a lot of industrial compounds via ring closure, cycloaddition and replacement reactions[1]. Schiff bases are also important class of compounds in medicinal and pharmaceutical fields such as antimicrobial[2,3], antifungal[4,5] and antitumor activituy[6,7]. The landmark discovery of cisplatin by Rosenberg in 1965 heralded a new era of anticancer drug research based on metallopharmaceuticals[8]. However, it has several limitations including toxicity (nephrotoxicity, neurotoxicity, ototoxicity and

emetogenesis) and intrinsic or acquired resistance[9], for instance, Pt(II) compounds have a strong thermodynamic preference for binding to sulfur donor ligands, hence, before antitumor platinum drugs reach DNA in the nucleus of tumor cells, they may interact with various compounds, including sulfur-containing molecules, these interactions are generally thought to play a primary mechanism underlying tumor resistance to platinum compounds, their inactivation and their side effects[10]. Specific chemical and structural features can be incorporated into new Pt compounds so that they are able to circumvent a specific drug resistance mechanism, such as sterically hindered Pt complexes[11]. There also have been efforts directed at the design of unconventional complexes that violate the original structure-activity relationships, such as trans Pt compounds[12] and binuclear Pt complexes[13]. There has also been interest in Pt(IV) complexes[14] for their potential as orally active agents. It is hoped that they will overcome Pt drug resistance in tumors and be applicable to a broader range of cancers.

In recent years, there has been a gradually attempt in the application of electrochemical techniques[15,16] to understand interactions between DNA and moleculers due to cheapness, simplicity, fast detection and require small amount of sample with respect to the generally used spectroscopic methods[17]. Keeping the above knowledge in mind, the present paper involves preparing and characterizing five new tetradentate sterically hindered platinum(II) complexes with schiff bases as ligands which have more thermodynamic stabilities. In continuation of the study, special attention has been paid to the application of electrochemical measurements based on the interaction of these metal complexes with ssDNA via differential pulse voltammetry using disposable pencil graphite electrode.

Experimental

Reagent grade chemicals were used as received unless otherwise stated. Elemental analysis were determined on a Elemental Vario EL III elemental analyzer. The IR spectra were recorded using KBr pellets and a Perkin-Elmer Model-683 spectrophotometer. The ^{1}H NMR spectra were recorded on a Bruker AVIII 600 NMR spectrometer. Electrochemical experiments are carried on a PC driven PARC 273A potentiostat: galvanostat running with mode 270 electrochemical analysis software or on a CHI 660 workstation. A three-compartment cell contains a working electrode (pencil graphite), a counter electrode (Pt plane) and a calomel reference electrode.

Schiff bases ligands (L^1~L^5) were synthesized according to a published procedure[18]. To a solution of the amine (1 equiv.) in ethanol was added the relevant aldehyde derivatives (1 equiv.). The resulting yellow/orange solution was refluxed for 1.5 h. After cooling to room temperature the solution was concentrated in vacuo to yield a yellow solid product.

Synthesis of N,N'-bisalicylidene-1,2-ethylenediamine (L^1)

Yellow solid product (406 mg, 91%): mp 120-122 ºC. IR(KBr, pellet)υ/cm^{-1}: 1632, 1578, 1498, 1283, 1149, 1042, 1021, 857, 749, 741. ^{1}H NMR (600M Hz, DMSO-d_6), δ: 6.850-7.438 (m, 8 H, Ar-*H*), 8.600 (s, 2 H, -C*H*=N-), 13.380 (s, 2 H, -O*H*), 3.932 (s, 4H, -CH_2-CH_2-). Anal. Calc. for $C_{16}H_{16}N_2O_2$ (268.31): C, 71.62; H, 6.01; N, 10.44. Found: C, 71.54; H, 6.13; N, 10.41.

Synthesis of N,N'-bisalicylidene-1,2-cyclohexanediamine (L^2)

Yellow solid product (195 mg, 93%): mp 118-119 ºC. IR(KBr, pellet)υ/cm^{-1}: 1629, 1579, 1501, 1280, 1148, 1095, 1045, 767, 758. ^{1}H NMR (600M Hz, DMSO-d_6), δ: 13.325 (s, 2 H, -O*H*), 8.490 (s, 2 H, -C*H*=N-), 6.790-7.350 (m, 8 H, Ar-*H*), 3.400-3.450 (m, 2 H, -C*H*-**),**

1.440-1.910 (m, 8 H, -C*H*$_2$-C*H*$_2$-). Anal. Calc. for $C_{20}H_{22}N_2O_2$ (322.40): C, 74.51; H, 6.88; N, 8.69. Found: C, 74.43; H, 6.75; N, 8.62.

Synthesis of N,N'-bis(5-hydroxyl-salicylidene)-1,2-cyclohexanediamine (L^3)

To a 100 mL three-neck flask, equipped with a reflux condenser, thermometer, a nitrogen source and magnetic stirrer was added hydroquinone (2.0 g, 0.018 mol), sodium hydroxide (4.0 g, 0.10 mol), distilled water 40 mL, and chloroform 8.0 mL (98 mmol). The mixture was heated to reflux for 8 h. After cooling, the reaction mixture was acidified to PH 2~3 with 2N hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate extract was treated with vacuum distillation, dried and obtained crude 5-hydroxylsalicylaldehyde (1.7 g). The crude product was purified by column chromatography gave yellow solid product (a_2) (0.41 g, 32.6 %): mp: 94-97 ºC; IR(KBr, pellet)υ/cm^{-1}: 3441, 1660, 1631, 1582, 1486, 1398, 1278, 1151, 1039, 943, 881, 801, 769, 641,484. ^{1}H NMR (600M Hz, DMSO-d$_6$), δ: 6.812-6.974(m, 3H, Ar-*H*), 10.199(s, 1H, -C*H*O).

Yellow solid product (159 mg, 90%): mp 216-218 ºC. IR(KBr, pellet)υ/cm^{-1}: 3329, 1641, 1630, 1483, 1300, 1157, 1047, 804, 788. ^{1}H NMR (600M Hz, DMSO-d$_6$), δ: 12.460 (s, 2 H, -O*H*), 8.365 (s, 2 H, -C*H*=N-), 8.930 (s, 2H, -O*H*), 6.662-6.728 (m, 6H, Ar-*H*), 1.430-1.880 (m, 8 H, -C*H*$_2$-C*H*$_2$-). Anal. Calc. for $C_{20}H_{22}N_2O_4$ (354.40): C, 67.78; H, 6.26; N, 7.90. Found: C, 67.85; H, 6.13; N, 8.11.

Synthesis of N,N'-bisalicylidene-1,2-diphenylethylenediamine (L^4)

Yellow solid product (195.1 mg, 93%): m.p. 201~202 ºC; IR(KBr, pellet)υ/cm^{-1}: 1623, 1576, 1496, 1279, 1211, 1151,1052, 859,760. ^{1}H NMR (600M Hz, DMSO-d$_6$), δ: ppm: 5.0513 (s, 2H, Benzyl-*H*), 6.8181-6.8650 (m, 8 H, Ar-*H*), 7.1947-7.3197 (m, 10H, Ph-*H*), 8.4195 (s, 1H, -C*H*=N-), 8.4244 (s, 1 H, -C*H*=N-), 13.1777 (s, 2 H, -O*H*). Anal. Calc. for $C_{28}H_{24}N_2O_2$ (420.18): C, 79.98; H, 5.75; N, 6.66. Found: C, 79.93; H, 5.86; N,6.47.

Synthesis of N,N'-bis(3-tert-butyl-5-methyl-salicylidene)-1,2- diphenylethylenediamine (L^5)

The reaction mixture with p-methylphenol (10.8 g, 0.1 mol) and tert-butyl alcohol (8.9 g, 0.12 mol) was stirred on a 50 ºC oil bath for 6.5 hour, then 50 mL water was added, the oil layer was separated, and the water layer was extracted with ether. The combined organic layer was washed with water, Na_2CO_3/H_2O and H_2O. The products were separated by silica gel chromatography to give 2-t-butyl-2-methylphenol (10.3618 g, 71%): ^{1}H NMR (600 M Hz, DMSO-d$_6$), δ: ppm: 1.3981 (s, 9 H, t-Bu-*H*), 2.2699 (s, 3 H, Me-*H*), 4.2456 (br, 1 H, -O*H*), 6.5568 (d, 1H, Ar-*H*), 6.8696 (d, 1H, Ar-*H*), 7.0654 (s, 1 H, Ar-*H*).

To a 50 mL three-neck flask, equipped with a reflux condenser, thermometer, a nitrogen source and magnetic stirrer was added anhydrous toluene 4 mL, 2-tert-butylcresol (1.6456 g, 10 mmol), tin(IV) tetrachloride 0.6003 g and 2,6-lutidine 0.547 g. The reaction was exothermic. The mixture was stirred for 20 min at room temperature, then paraformaldehyde (0.66 g, 22 mmol) was added. The mixture was heated to about 100 ºC for 5 h. After cooling, the reaction mixture was poured into water, acidified to pH 2~3 with 2N hydrochloric acid and extracted with ether. The ether extract was washed with a saturated sodium chloride solution, dried (Na_2SO_4) and concentrated to leave crude 3-t-butyl-5-methylsalicylaldehyde. Purification by column chromatography (ethyl acetate/petroleum ether) gave the light yellow solid product (a_1) (1.1535 g, 60%): mp 67-69 ºC. ^{1}H NMR (600M Hz, DMSO-d$_6$), δ: ppm: 1.4109 (s, 9 H, t-Bu-*H*), 2.3240 (s, 3 H, Me-*H*), 7.1781 (d, 1 H, Ar-*H*), 7.3308 (d, 1 H, Ar-*H*), 9.8246 (s, 1 H, -C*H*O), 11.6025 (s, 1 H, -O*H*).

Yellow solid product (122.9 mg, 88%): m.p. 179-181 ºC; IR(KBr, pellet)υ/cm^{-1}: 2957, 1625, 1601, 1440, 1263, 1165, 1047, 862, 788. ^{1}H NMR (600M Hz, DMSO-d$_6$), δ: ppm:

1.4252 (s, 18 H, t-Bu), 2.2170 (s, 6 H, -C*H*$_3$), 4.8339 (s, 2 H, Benzyl-*H*), 6.7873 (d, 2H, 2-Ar-*H*), 7.1183 (d, 2H, 4-Ar-*H*), 7.2187-7.3744 (m, 10H, Ph-*H*), 8.0995 (s, 2H, -C*H*=N-), 12.3400 (br, 2H, -O*H*). Anal. Calc. for $C_{38}H_{44}N_2O_2$ (560.34): C, 81.39; H, 7.91; N, 5.00. Found: C, 81.25; H, 7.83; N,4.82.

Synthesis of [Pt(L^1)]

K_2PtCl_4 (15 mg, 0.036 mmol) was dissoved in 1 mL distilled water, then L^1 (9 mg, 0.034 mmol) dissolving in absolute methanol was added. The reaction mixture was stired in room temperature for 72 h. The complex [Pt(L^1)] was purificated by column chromatography (ethanol/petroleum ether) gave the yellow solid product (12 mg, 77.5%):m.p. >300 ºC; IR(KBr, pellet)υ/cm^{-1}: 1625, 1129, 563,485. Anal. Calc. for $C_{16}H_{14}C_2O_2Pt$ (461.37): C, 41.65; H, 3.06; N, 6.07. Found: C, 40.97; H, 2.59; N, 6.41.

Synthesis of [Pt(L^2)]

The synthesis of [Pt(L^2)] was carried out in an identical manner to [Pt(L^1)] starting from K_2PtCl_4 (15 mg, 0.036 mmol) and L^2 (12 mg, 0.037 mmol). Yellow solid (13 mg, 70.12%). IR(KBr, pellet)υ/cm^{-1}: 1620, 1124, 566, 468. Anal. Calc. for $C_{23}H_{21}N_2O_2Pt$ (530.50): C, 47.54; H, 4.37; N, 5.28. Found: C, 47.35; H, 4.31; N, 5.19.

Synthesis of [Pt(L^3)]

The synthesis of [Pt(L^3)]was carried out in an identical manner to [Pt(L^1)] starting from K_2PtCl_4 (13 mg, 0.031 mmol) and L^3 (11 mg, 0.031 mmol). Yellow solid.(13 mg, 76.5%) IR(KBr, pellet)υ/cm^{-1}: 1620, 1125, 560, 462. Anal. Calc. for $C_{20}H_{20}N_2O_4Pt$ (547.46): C, 43.88; H, 3.68; N, 5.21. Found: C, 43.81; H, 3.52; N, 5.37.

Synthesis of [Pt(L^4)]

The synthesis of [Pt(L^4)] was carried out in an identical manner to [Pt(L^1)] starting from K_2PtCl_4 (15 mg, 0.036 mmol) and L^4 (13mg, 0.031mmol). Yellow solid (14 mg, 73.4%). IR(KBr, pellet)υ/cm^{-1}: 1619, 1121, 527, 474. Anal. Calc. for $C_{29}H_{25}N_2O_2Pt$ (628.60): C, 55.41; H, 4.01; N, 4.46. Found: C, 55.24; H, 4.13; N, 4.37.

Synthesis of [Pt(L^5)]

The synthesis of [Pt(L^5)]was carried out in an identical manner to [Pt(L^1)] starting from K_2PtCl_4 (12 mg, 0.036 mmol) and L^5 (18 mg, 0.036 mmol). Yellow solid (16 mg, 64%). IR(KBr, pellet)υ/cm^{-1}: 1619, 1121, 534, 484. Anal. Calc. for $C_{34}H_{33}N_2O_2Pt$ (696.72): C, 58.61; H, 4.77; N, 4.02. Found: C, 58.44; H, 4.53; N, 4.21.

DNA interaction procedure

Three replicate measurements were carried out for each electrochemical experiment. All data were obtained at room temperature.

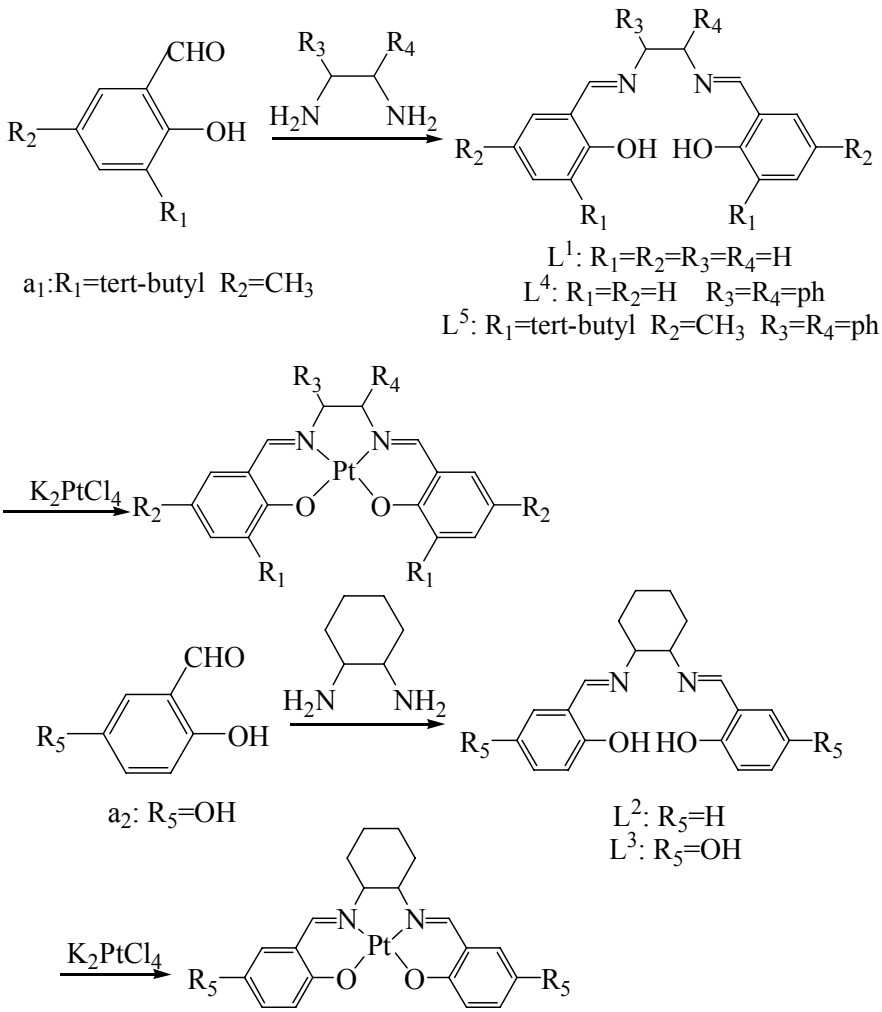
Interaction of DNA with metal complexes: Metal complex in the concentration level of 100 μg/mL (unless otherwise indicated) was added to supporting electrolyte containing 100 μg/mL DNA. A pencil graphite electrode was first pre-treated as described above and subsequently immersed into the mixture solution. The accumulation of the mixture was performed for 3 min while holding the potential at +0.50 V under stirred conditions. The electrode was then washed with a clean supporting electrolyte for 8 s.

Signal transduction: The oxidation signals of guanine and adenine were measured by using differential pulse voltammetry with the following parameters: amplitude 50 mV, step potential 8 mV, pulse width 0.06 s, pulse period 0.2 s, setting time 4 s, between +0.45 and +1.40 V in a fresh supporting electrolyte. Successive measurements were carried out by repeating the above assay protocol.

Results and Discussion

Chemistry

The symmetric schiff bases ligands L^1-L^5 and their complexes were prepared as shown in **Scheme 1.** The platinum complexes [Pt(L^1)]~[Pt(L^5)] have been prepared by the reaction of K_2PtCl_4 with symmetric schiff bases in a mixture of CH_3OH/H_2O. Unfortunately, there is no clear NMR data of the complex due to the low intensity of the signals.



Scheme 1. Synthesis of L^1-L^5 and Pt complexes.

Main IR absorptions of ligands and complexes were shown in **Table 1.** Comparison of the IR spectra of the free ligands with that of their Pt(II) complexes, the $(CH=N)_{imine}$ stretching frequencies were found in free ligand at 1632, 1629, 1630, 1623 and 1625 cm^{-1}, while in complexes shifted to low wavenumbers at 1625, 1620, 1620, 1619 and 1619 cm^{-1}. On the other hand, in the spectra of a metal complexes, the bands for the phenolic group (C-O)

shifted from 1149, 1148, 1157, 1151 and 1165 cm^{-1} to 1129, 1124, 1125, 1121 and 1121 cm^{-1}, comparing to the free ligands. New bands appeared at about 460-485 and 530-565 cm^{-1} and were may assigned to υ_{Pt-O} and υ_{Pt-N}, respectively. All of these indicated that nitrogen atoms of the imine groups and oxygen atoms of the phenolic groups are coordinated to the metal ion. Elemental analysis also confirms the named stoichiometries of all the complexes.

Table 1. Main IR absorptions of ligands and complexes (cm^{-1}).

	ν (C=N)	ν (C-O)	ν (Pt-N)	ν (Pt-O)
L^1	1632	1149		
L^2	1629	1148		
L^3	1630	1157		
L^4	1623	1151		
L^5	1625	1165		
$Pt(L^1)$	1625	1129	563	485
$Pt(L^2)$	1620	1124	566	468
$Pt(L^3)$	1620	1125	560	462
$Pt(L^4)$	1619	1121	527	474
$Pt(L^5)$	1619	1121	534	484

DNA interaction of the complexes

The oxidation peaks of dsDNA are virtually absent in differential pulse voltammetry, on the contrary, the well-developed voltammetric signals of ssDNA can be readily obtained. The large difference in the oxidation signals of dsDNA and ssDNA was due to the distinctness of accessibility and flexibility of two kinds of DNA[19]. Denaturation of DNA is performed by thermal heat up to 100 °C for about 15 min, following by quick cooling in an ice bath. The redox behavior of tested complexes was investigated by differential pulse voltammetry in 0.5 M acetate buffer pH=4.6 containing 20 mM NaCl, Voltammograms, which were monitored in blank supporting electrolyte (transfer voltammetry), obtained before/after interaction between 100 $\mu g/mL^{-1}$ Pt(II) complex and 100 $\mu g/mL^{-1}$ ssDNA were shown in **Figure 1~5**.

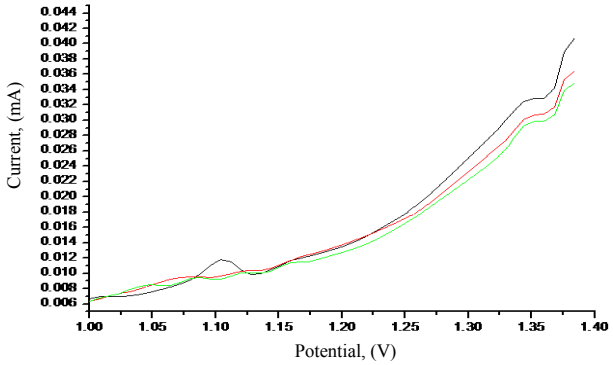


Figure 1. Interaction of ssDNA with $[Pt(L^1)]$. (—) DNA blank. (—) $[Pt(L^1)]$ + DNA stirring after 0.5 h. (—) $[Pt(L^1)]$ + DNA stirring after 12 h.

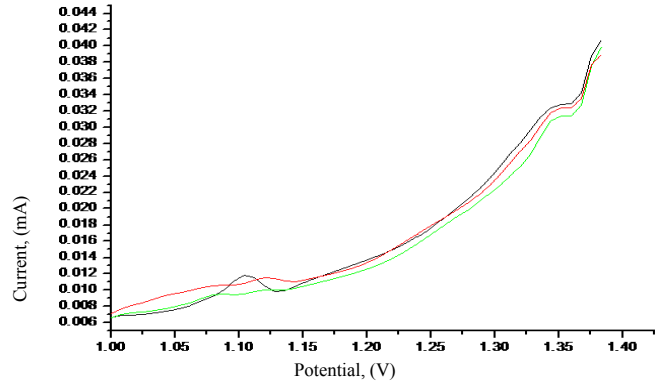


Figure 2. Interaction of ssDNA with [Pt(L^2)]. (—) DNA blank. (—) [Pt(L^2)] + DNA stirring after 0.5 h. (—) [Pt(L^2)] + DNA stirring after 12 h.

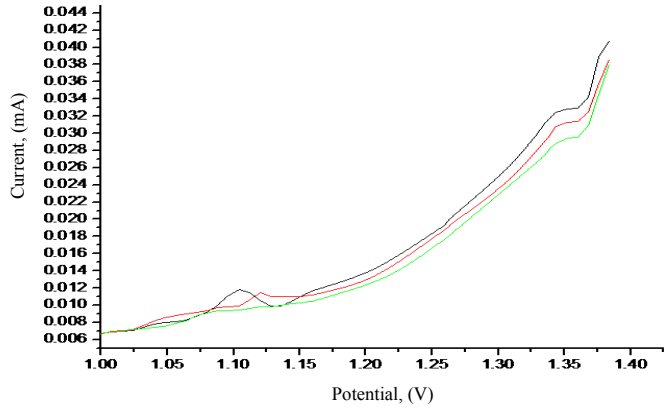


Figure 3. Interaction of ssDNA with [Pt(L^3)]. (—) DNA blank. (—) [Pt(L^3)] + DNA stirring after 0.5 h. (—) [Pt(L^3)] + DNA stirring after 12 h.

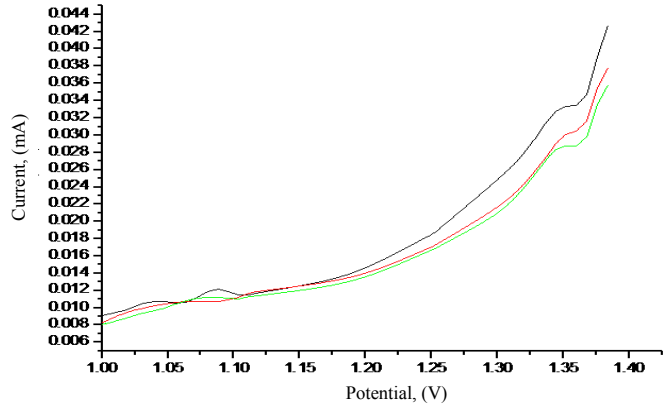


Figure 4. Interaction of ssDNA with [Pt(L^4)]. (—) DNA blank. (—) [Pt(L^4)] + DNA stirring after 0.5 h. (—) [Pt(L^4)] + DNA stirring after 12 h.

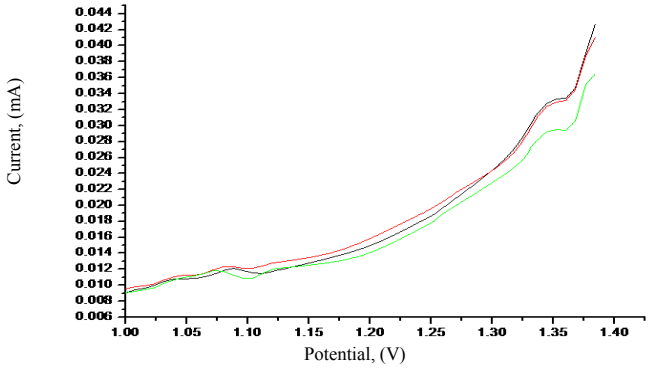


Figure 5. Interaction of ssDNA with [Pt(L^5)]. (—) DNA blank. (—) [Pt(L^5)] + DNA stirring after 0.5 h. (—) [Pt(L^5)] + DNA stirring after 12 h.

Under the conditions of the experiment, the redox behavior of original ssDNA exhibited one positive peak at around +1.10 V due to the oxidation of guanine residues, mean response 0.011± 0.00025 mA (n =3) and the second at around +1.34 V due to the oxidation of adenine residues, mean response 0.032 ±0.00036 mA (n =3). In the blank supporting electrolyte, we can see one clearly positive peak around +1.50 V, mean response 0.486 mA, which is attributed to the oxidation of Cl^{-1}. But unfortunately we could not see any positive peak singles about Pt(II) complexes.

Firstly, we reacted with five ligands and ssDNA in the room temperature in solution, and found no change of redox signal values of guanine and adenine residues. After the interaction of complexes and ssDNA in solution, redox signal values of guanine and adenine were shown in **Table 2**. Complex [Pt(L^1)] had strong bonding with guanine and adenine residues after stirring 0.5 h at room temperature, the redox peaks of guanine and adenine residues decreased by 2.3 and 3.2 μA, from 0.0119 and 0.0333 mA to 0.0096 mA and 0.0301 mA. When 1,2- ethylenediamine was replaced by the large ring planar steric 1,2-cyclohexanediamine (L^2), the bond formation of complex [Pt(L^2)] with ssDNA significantly reduced, decreasing by 0.3 and 0.9μA after the stirring of 0.5 h. 1,2-Cyclohexanediamine planar structure might hamper the interaction between Pt complex and ssDNA. In order to improve the water-solubility of complex, we introduced hydroxyl group in aromatic ring (L^3), expecting to enhance coordination of Pt complex [Pt(L^3)] with ssDNA. However, we found the result had almost no change, the redox peaks of guanine and adenine residues only decreased by 0.9 and 2 μA after 0.5 h stirring. To validate whether it was planar structure or not hindering coordination of complexes and DNA, we substituted 1,2-cyclohexanediamine to non-coplanar 1,2-diphenyl-ethylenediamine (L^4). Compared to [Pt(L^2)], [Pt(L^4)] had better interaction with ssDNA after stirring 0.5 h, decreasing by 1.2 and 3.3μA. On the other hand, we discussed the effect of interaction between aromatic substituents of complex and DNA. We joined tert-butyl and methyl to *o*- and *p*- of phenolic hydroxyl group respectively, synthesizing complex [Pt(L^5)], and found that redox peak values of guanine and adenine had no change after 0.5 h stirring. Symmetrical tert-butyl on benzene ring effectively prevented attacking of Pt ion to ssDNA. We also observed the interactions between complexes and ssDNA after 12 h stirring, which were consistent to those after 0.5 h: [Pt(L^1)]~[Pt(L^4)] continued to interact with ssDNA. [Pt(L^5)] almost had no coordination to guanine residues, but had better coordination to adenine residues. So we concluded that substituents on ligands can effectively influence the interaction between Pt complexes and DNA, bulky substituents on ligands can effectually embarrass the coordination of Pt ion to guanine and adenine residues.

Table 2. Redox signal values of guanine and adenine (mA).

	Stirring after 0.5 h		Stirring after 12 h	
	Guanie	Adenine	Guanie	Adenine
DNA blank	0.0119	0.0333		
$Pt(L^1)$ + DNA	0.0096	0.0301	0.0092	0.0293
$Pt(L^2)$ + DNA	0.0116	0.0324	0.0096	0.0308
$Pt(L^3)$ + DNA	0.0110	0.0313	0.0095	0.0294
$Pt(L^4)$ + DNA	0.0107	0.0300	0.0108	0.0288
$Pt(L^5)$ + DNA	0.0120	0.0329	0.0118	0.0299

Conclusion

Rare-earth platinum complexes have proved their effectiveness in tumor cells[20]. In this study five platinum complexes with symmetric tetradentate schiff base as ligands were synthesized and characterized. Compounds were tested for their DNA interaction ability with the fish sperm ssDNA using differential pulse voltammetry at pencil graphite electrode. The determined DNA binding levels for platinum complexes showed that $[Pt(L^1)]$ had the best interaction with DNA, substituents on ligands can effectively influence the interaction between Pt complexes and DNA, bulky substituents on ligands can effectually embarrass the coordination of Pt ion to guanine and adenine residues. However, these are preliminary observations and a more extensive study would be necessary in order to assert that the complexes act as cleavage agents.

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