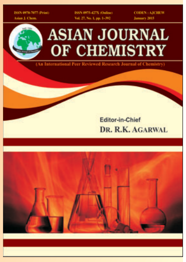
Asian Journal of Chemistry; Vol. 27, No. 10 (2015), 3567-3570

ASIAN JOURNAL OF CHEMISTRY

http://dx.doi.org/10.14233/ajchem.2015.18838



Synthesis, Characterization and Electrochemical Studies on the Interaction Mechanism of Ternary La(III) Complex with DNA

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Received: 4 November 2014; *Accepted*: 6 April 2015; *Published online*: 22 June 2015; AJC-17304

A new Schiff base ligand (KGOV) was synthesized using potassium salt of glycine and *o*-vanillin. A ternary complex of lanthanum(III) with this ligand and 1,10-phenanthroline, $[La(GOV)(phen)(NO_3)](NO_3)\cdot 3H_2O$ was synthesized and characterized by elemental analysis, IR, TG-DTG, ^{1}H NMR spectra and molar conductance. The fundamental electrochemical characteristics of the La(III) ternary complex have been studied and the interactivity of La(III) complex with DNA was also studied by cyclic voltammetry. The results suggest that the complex combined with DNA in the form of intercalative binding. The binding ratio between the La(III) ternary complex and DNA was calculated to be 1:1 and the binding constant was 1.13×10^5 L mol^{-1}.

Keywords: Schiff base, La(III) complex, Cyclic voltammetry, DNA.

INTRODUCTION

Some Schiff base complexes derived from amino acids are particularly active biology. Recently, studies of such complexes of transition metal and rare earth ions with Schiff base have been reported[1-5]. It is known that some rare earth complexes with Schiff base possess antifungal and antibacterial properties[6,7]. The numerous biological experiments performed so far suggest that DNA is the primary intracellular target of anticancer drugs because the interaction between small molecules and DNA can cause DNA damage in cancer cells, blocking the division of cancer cells and resulting in cell death[8-10]. Of those studies, the interaction of transition metal complexes with DNA has gained much attention, owing to their possible applications as new therapeutic agents and their photochemical properties that make them potential probes of DNA structure and conformation[11-17].

It is necessary to understand the binding properties in developing new potential DNA targeting antitumor drugs. Basically, metal complexes interact with double helix DNA in either non-covalent or covalent way. The former way includes three binding modes, *i.e.*, intercalation, groove binding and external static electronic effects. Among these interactions, intercalation is one of the most important DNA binding modes. It was reported that the intercalating ability appeared to increase with the planarity of ligands[18,19]. Additionally, the coordination geometry and ligand donor atom type also play key roles in determining the binding extent of complexes to DNA[20,21]. The metal ion type and its flexible valence, which are responsible for the geometry of complexes, also affect the intercalating ability of metal complexes to DNA[22,23]. In this paper the La(III) complex with glycine-*o*-vanillin and 1,10-phenanthroline was synthesized and the interaction of the complex with DNA was studied by cyclic voltammetry The aim of this research is to investigate the interaction of the rare earth Schiff base complex with DNA and we synthesized the La(III) complex with glycine-*o*-vanillin and 1,10- phenanthroline.

EXPERIMENTAL

Glycine was BR (Biochemical Reagent). The other reagents were AR (Analysis Reagent) grade and were used without further purification. Salmon sperm DNA was purchased from Shanghai Huashun Biological Engineering Company ($A_{260}/A_{280} > 1.8$). The concentration was determined by the ultraviolet absorption at 260 nm (Z = 6600 M^{-1} cm^{-1}).

Elemental analyses were carried out with a model 2400 Perkin-Elmer analyzer. Infrared spectrum was recorded in KBr pellets using a Nicolet 170SX spectrophotometer in the 4000-400 cm^{-1} region. Molar conductivity at room temperature was measured in 10^{-3} mol L^{-1} DMSO solution using a DDSJ-308A type conductivity meter at 25 °C. The thermo gravimetric measurements were made using a Perkin-Elmer TGA7 thermo gravimeter. The heating rate was programmed to be 10 °C/min with the protecting stream of N_2 flowing at 40 mL/min. ^{1}H NMR spectra were recorded in DMSO-d_6 as the solvent at 600 MHz with a JNM ECP-600 spectrometer using tetramethyl silane (TMS) as an internal reference. All electrochemical measurements were carried out with Model CHI 832 voltammetric analyzer. A three-electrode, Ag/AgCl/KCl(salt) as reference electrode and glass carbon electrode (GCE) as working electrode.

Preparation of the ligand: *o*-Vanillin was added (with stirring) to anhydrous ethanol (20 mL) to make a pellucid solution. Then, it was slowly dripped into the anhydrous ethanolic solution (15 mL) containing 0.01 mol glycine (containing 0.01 mol KOH) at 65 °C (pH = 6.0-6.5), a mass of yellow grain was separated out which was collected by filtration and washed several times with anhydrous ethanol, recrystallized with methanol and then dried under vacuum for later use. The yield of the reaction was 85.2 %. Anal. calcd. for $C_{10}H_{10}NO_4K$ (247.3): C, 48.56 %; H, 4.08 %; N, 5.66 %;. Found: C, 48.53 %; H, 4.15 %; N, 5.58 %. IR data (KBr pellets, ν_{max}, cm^{-1}): 1660.5 C=N; 1603.2, 1314.4 COO^-; 1242.2 Ar-O.

Preparation of the complex: 0.5 mmol lanthanide nitrate hexahydrate in 15 mL of anhydrous ethanol was added dropwise into the solution of Schiff-base (0.5 mmol) in 15 mL of anhydrous ethanol and was stirred at 80 °C. After 2 h, 10 mL of anhydrous ethanol containing 0.5 mmol 1,10-phen was dripped into the mixture, continuously to be stirred at the same temperature for 8 h. The yellow solution obtained was filtered and the yellow powder was dried under vacuum. The C, H and N contents were as follows: Anal. calcd. for $C_{22}H_{24}N_5O_{13}La$ (705.4): C, 37.46 %; H, 3.43 %; N, 9.93 %; La, 19.69 %. Found: C, 39.54 %; H, 3.46 %; N, 9.72 %; La, 19.88 %. IR data (KBr pellets, ν_{max}, cm^{-1}): 1642.8 C=N; 1580.2, 1376.4 COO-; 1228.5 Ar-O; 1533.3, 1386.4, 1230.6, 1028.4 NO_3^-.

Electrochemical study on the interaction between the complex and DNA: A definite quantity of $[La(GOV)(phen)(NO_3)](NO_3)\cdot 3H_2O$ solution was transferred into 5 mL colorimetric tubes containing 0.05 mol L^{-1} pH 4.25 B-R buffer solution and then DNA was added. The changes on characteristics of CVs were investigated. For CV scanning, the potential scanning range was from 1.0 to -0.2 V, the scanning rate was 0.062 V/s; the sample interval was 0.001 V and the quiet time was 2 s.

RESULTS AND DISCUSSION

Molar conductance and Spectroscopic studies: The title complex is yellow powder, soluble in DMSO, DMF. The molar conductivity of the complex is 73.08 S cm^2 mol^{-1} in DMSO, which is expected for 1:1 electrolytes[24].

The shift of ν(C=N) from 1660.5 cm^{-1} in the Schiff base ligand and 1636.1 cm^{-1} in 1.10-phen to 1642.8 cm^{-1} in the complex, suggests that La(III) is bonded with N atom in Schiff base and 1.10-phen. The shift of $\nu_{as}(COO^-)$ and $\nu_s(COO^-)$ from 1603.2 cm^{-1} and 1314.4 cm^{-1} in the ligand to 1580.2 cm^{-1} and 1376.4 cm^{-1} in the complex, respectively, suggests the coordination of the oxygen in the carboxylate group to the metal ion. The value of $\nu[\nu_{as}(COO^-)-\nu_s(COO^-)]$ = 203.8 cm^{-1} indicates that the $-COO^-$ group is coordinated to the metal ion in a monodentate fashion[25]. A broad absorption band at the range of 3300-3100 cm^{-1} in the complex was attributed to ν(O-H) of phenol and the water molecules. The vibration of ν(Ar-O) of the ligand occurs at 1242.2 cm^{-1}. The shift to lower frequency by about 14 cm^{-1} in the metal complex indicates the coordination of hydroxyl oxygen to metal ion. In the spectrum of the complex, four additional bands, which are not present in the spectrum of the ligand, were observed. Of these, the bond of 1028.4 cm^{-1} is assigned to the n_2 mode of the nitrate group. The bands of 1533.3 and 1230.6 cm^{-1} in the complex are the two split bands of ν_4 and ν_1, respectively, of the coordinated nitrate group. The magnitude of (ν_4-ν_1) is more than 180 cm^{-1} for the complex, which indicates that the nitrate group in coordinated to the metal ion in a bidentate fashion. The bands 1386.4 cm^{-1} are assigned to the non-coordinated nitrate group[26].

^{1}H NMR spectra: The ^{1}H NMR spectra of the Schiff base ligand and complex $[La(GOV)(phen)(NO_3)](NO_3)\cdot 3H_2O$ were recorded in DMSO-d_6. In the spectrum of the ligand the phenolic OH proton appears at 14.21 ppm. This signal shifts to 12.63 ppm in the complex spectrum, which indicates that the coordination of phenolic oxygen to metal ions. The peak at 9.37 ppm in the Schiff base ligand can be assigned to CH=N proton. It shifts to 8.69 ppm in the spectrum of the complex, which confirms the coordination of azomethine group to metal ion. In the spectrum of the complex the multi signals within the 7.36-7.57 ppm range were assigned to aromatic H protons. In the spectrum of the ligand the $-OCH_3$ proton appears at 3.37 ppm and it appears at 3.34 ppm in the complex spectrum, which indicates the $-OCH_3$ is not bound to metal ion.

Thermal decomposition studies: The DTG-TG curves of the La(III) complex were determined in a stream of N_2 at a flowing rate of 40 mL/min. The complex decomposes in four steps. The first weight loss stage have decomposition temperature ranges of 35-157 °C, with weight losses of 7.3 % (calcd. 7.66 %), which corresponds to the loss of three molecules of water. The fact that the water molecule was lost at a low temperature suggests that the water is crystal water. The complex decomposed in three steps after the loss of crystal water. The second, third and fourth subsequent decomposition steps start at 157 °C and continue up to 903 °C, corresponding to the fractional loss of the ligand molecules and the decomposition of metal nitrate. The weight percentage of 23.16 % (calcd. 23.09 %) of the original sample remained, La_2O_3 is the final product.

According to the characterizations enumerated above, the possible structure of the complex is shown as Fig. 1.

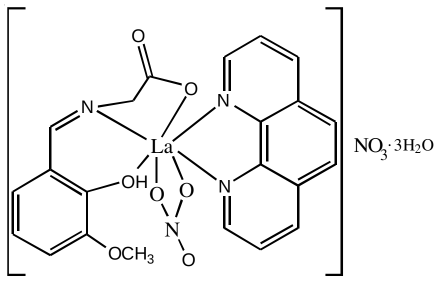

Fig. 1. Suggested structure of La(III) complex

Cyclic voltammetry characteristics of the La(III) complex and its interaction with DNA: Electrochemical study on $[La(GOV)(phen)(NO_3)](NO_3)\cdot 3H_2O$ and its interaction with DNA were performed at 25 °C. The cyclic voltammograms of La(III) complex are shown in Fig. 2. The curve 1 is a cyclic voltammogram of the title complex in the B-R(Britton-Robinson) buffer solution (pH = 4.25). The oxidation peak occurs at the potential 0.478 V. The curve 2 is cyclic voltammogram of the mixed solution of DNA and complex in the B-R buffer solution, the peak potential shifts to 0.530V, the electric current of oxidation peak decreased and had no new oxidation peak occur, through which we can presume DNA and complex formed the new compound that wasn't electric activity compound. Due to the new compound didn't conducted, the concentration of the complex reduced so that the number of the molecule of the complex moved to the surface of electrode declined, which lead to the electric currents became weak. It is generally accepted that there are three kinds of binding modes for small molecules to DNA, which refer to intercalative binding, groove binding and electrostatic binding. Bard *et al.*[27] suggested that when the molecule inserts into the inner of DNA bi-helix structure, the peak currents of the oxidation of the voltammetry decreased with positive shifts of the peak potential. On the other way round, when the molecule interacted with DNA in the form of static effect, the peak currents of the voltammetry curves of the oxidation of the voltammetry decreased with negative shifts of the peak potential. In summary, it is inferred that the complex interact with DNA in the form of intercalative binding.

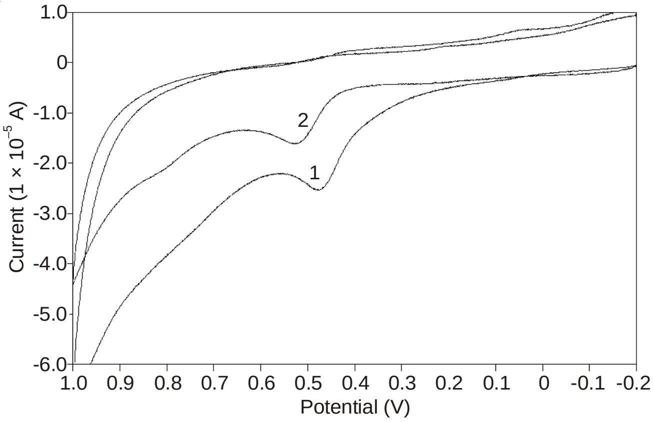

Fig. 2. Cyclic voltammetry of La(III) ternary complex and the interaction of complex and DNA $C_{[La(GOV)(phen)(NO_3)](NO_3)\cdot 3H_2O}$: 1.00×10^{-4} mol L^{-1}, C_{DNA}: (1) 0. (2) 1.40×10^{-4} mol L^{-1}

Binding ratio and the binding constant between the complex and DNA: To study the binding ratio and binding constant between $[La(GOV)(phen)(NO_3)](NO_3)\cdot 3H_2O$ and DNA, it was assumed the interaction of DNA and $[La(GOV)(phen)(NO_3)](NO_3)\cdot 3H_2O$ only produced one single complex: DNA-nML, then the following balance existed in the solution.

$$DNA + nML \rightleftharpoons DNA - nML \quad (n = 1,2,3, \ldots \text{ or } 1,1/2,1/3, \ldots)$$

The equilibrium constant β could be expressed as eqn. 1

$$\beta = \frac{[DNA - nML]}{[DNA][ML]^n} \qquad (1)$$

Following equation can be deduced[28]:

$$\Delta I_{p,max} = KC_{DNA} \qquad (2)$$

$$\Delta I_{pa} = K[DNA - nML] \qquad (3)$$

$$[DNA] + [DNA - nML] = C_{DNA} \qquad (4)$$

$$\Delta I_{p,max} - \Delta I_{pa} = K(C_{DNA} - [DNA - nML]) \qquad (5)$$

$$\Delta I_{p,max} - \Delta I_{pa} = K[DNA] \qquad (6)$$

Substitute (eqns. 3 and 6) into eqn. 1:

$$\frac{1}{\Delta I_{pa}} = \frac{1}{\Delta I_{p,max}} + \frac{1}{\beta \Delta I_{p,max}[ML]^n} \qquad (7)$$

C_{DNA} and [DNA] in the equations denote analysis concentration and equilibrium concentration of DNA, respectively, [ML] denotes equilibrium concentration of metal complexes, ΔI_{pa} and $\Delta I_{p,\,max}$ denote differencing and the maximum differencing of the reduction peak and the oxidation peak current of ML on account of DNA addition, respectively.

According to the eqn. 7, different n might result in different curves of ΔI_{pa}^{-1} *versus* $[[La(GOV)(phen)(NO_3)](NO_3)\cdot 3H_2O]]^{-n}$. With the suitable n, the curve of ΔI_{pa}^{-1} *versus* $[La(GOV)(phen)(NO_3)](NO_3)\cdot 3H_2O]^{-n}$ should be a straight line if there was only one complex formed when $[La(GOV)(phen)(NO_3)](NO_3)\cdot 3H_2O$ bound to DNA. From the slope and intercept of the straight line, the binding constant β could be calculated and the n could be regarded as the binding ratio.

The dependence of the oxidation peak current (I_{pa}) on the analytical concentration of $[La(GOV)(phen)(NO_3)]NO_3\cdot 3H_2O$ in the absence (curve 1) and presence (curve 2) of DNA was shown in Fig. 3. The relationship between ΔI_{pa} (the difference of I_{pa1}, $I_{pa2,}$ $\Delta I_{pa} = I_{pa1}$-I_{pa2}) and the analytical concentration of $[La(GOV)(phen)(NO_3)]\ (NO_3)\cdot 3H_2O$ was also displayed (curve 3).

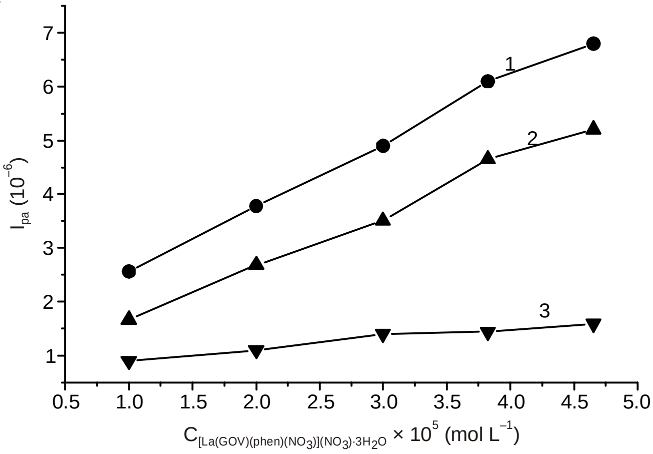

Fig. 3. Relationship curve of I_{pa1}, I_{pa2} and ΔI_{pa} *vs.* $C_{[La(GOV)L_2(NO_3)](NO_3)\cdot 3H_2O}$; 1.$C_{DNA}$:0 2.$C_{DNA}$: 1.4×10^{-4} mol L^{-1} 3. $I_{pa} = I_{pa1} - I_{pa2}$

The curves of ΔI_{pa}^{-1} *versus* $[[La(GOV)(phen)(NO_3)](NO_3)\cdot 3H_2O]^{-0.5}$, ΔI_{pa}^{-1} *versus* $[[La(GOV)(phen)(NO_3)]NO_3\cdot 3H_2O]]^{-1}$ and ΔI_{pa}^{-1} *versus* $[[La(GOV)(phen)(NO_3)](NO_3)\cdot 3H_2O]]^{-2}$ were displayed in Fig. 4, where $[[La(GOV)(phen)(NO_3)](NO_3)\cdot 3H_2O]$ represented the equilibrium concentration of $[La(GOV)(phen)(NO_3)](NO_3)\cdot 3H_2O$ and calculated from data in Fig. 4, For n = 0.5 and 2, the curves bent down and up, respectively. While

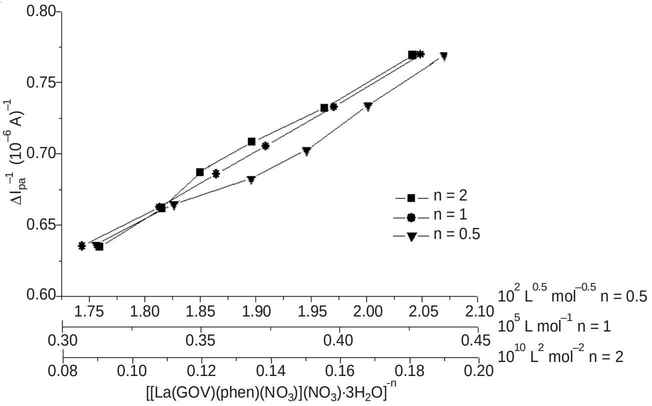

Fig. 4. Relationship curve of ΔI_{pa}^{-1} *vs.* $[[La(GOV)(phen)(NO_3)](NO_3)\cdot 3H_2O]^{-n}$

for n = 1, the curve was a straight line ($\gamma = 0.998$), indicating the forming of a 1:1 association between $[La(GOV)(phen)(NO_3)](NO_3)\cdot 3H_2O$ and DNA. From the slope and intercept of the straight line, the binding constant β was calculated to be 1.13 × 10^5 L mol^{-1}.

Conclusion

The results presented here indicate that La(III) can form stable solid ternary complex with Schiff base *o*-vanillylideneglycine (KGOV) and 1,10-phenanthroline. The composition of the complex is confirmed to be $[La(GOV)(phen)(NO_3)](NO_3)\cdot 3H_2O$. The interaction of the La(III) ternary complex with DNA was also studied by cyclic voltammetry. The results of the cyclic voltammetry showed that the La(III) complex had an oxidation peak with the oxidation potential at 0.478 V. After the DNA was added, the peak current declined with the peak potential shifting positively. This suggested that the complex combined with DNA in the form of intercalative binding. The binding ratio between the La(III) ternary complex and DNA was calculated to be 1:1 and the binding constant was 1.13 × 10^5 L mol^{-1}.

ACKNOWLEDGEMENTS

This work was supported by the National Natural Science Foundation of China to C.F. Bi (No. 21371161 and No. 21071134), the Specialized Research Fund for the Doctoral Program of Higher Education of China to Y.H. Fan (No. 20120132110015).

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