Asian Journal of Chemistry; Vol. 25, No. 2 (2013), 767-770

ASIAN JOURNAL OF CHEMISTRY

http://dx.doi.org/10.14233/ajchem.2013.12888

Interaction of DNA with Cu(II) and Co(II) Complexes with Fused Aromatic N-Containing Ligand

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(*Received*: 19 October 2011; *Accepted*: 20 August 2012) AJC-11974

Three new complexes of fused aromatic N-containing ligands such as $[CuL]Cl_2$ (**1**) and $[CoL]Br_2$ (**2**) (L = 3,10-*bis*(2-(*p*-nitrophenyl))-1,3,5,8,10,13-hexaazacyclotetradecane) and $[CuL^1]Cl_2$ (**3**) [L^1 = 3,10-bi-phenyl-1,3,5,8,10,13-hexaazacyclotetradecane) have been synthesized and characterized by UV-VIS and IR spectra. The interactions of DNA with $[CuL]Cl_2$, $[CoL]Br_2$ and $[CuL^1]Cl_2$ complexes in 1 mM *Tris*-HCl aqueous neutral complex-DNA molar ratio have been carried out by UV absorption spectrometry and fluorescence spectroscopy. The results support for an intercalative reaction of three complexes with DNA, showing $[CuL^1]Cl_2$ has an affinity of *ca.* 10 times higher than $[CuL]Cl_2$ and $[CuL]Cl_2$ ten times higher than $[CoL]Br_2$.

Key Words: Transition metal, DNA intercalation, Fluorescence, Copper, Macrocyclic.

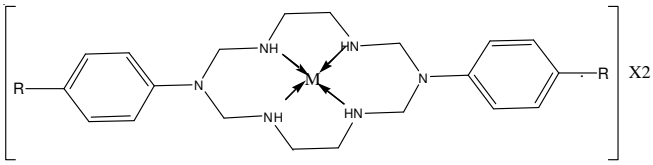
INTRODUCTION

In the past few years, transition metal macrocyclic complexes have received much attention as an active part of metalloenzymes[1,2] as biomimic model compounds[3-6] due to its resemblance with natural proteins like hemerythrin and enzymes. Synthetic macrocycles are a growing class of compounds with varying chemistry[7-15]. Many macrocyclic polyamine and their derivatives have been studied because of their good solubility under physiological conditions and strong coordination ability toward metal ion[16-18]. It is well known that the metal complexes bind to DNA through a variety of modes and each may be exploited in probe development. The reactivity of a metal complex will depend obviously on the nature of the metal complex as well as on the potential supramolecular interactions it can have with the DNA[19]. Copper and cobalt are biologically relevant transition metals and their complexes are of particular interest because they possess biologically accessible redox potentials. Copper and cobalt complexes with N-containing ligands have shown binding and cleavage activities[20-22]. These metal complexes have been found to be useful for design and development of synthetic restriction enzymes[23], new drugs[24] and DNA foot printing agents.

In this paper, we report the synthesis and characterization of new copper(II) and cobalt(II) complexes of fused N-containing ligands. The interaction between (**1**), (**2**) and (**3**) with DNA was studied by UV and florescence spectroscopy. The results showed that these complexes exhibited different DNA binding.

EXPERIMENTAL

All materials and solvents were purchased commercially and were used as supplied. DNA of yem's leaves was purchased from Qiagem. The complexes (Fig. 1) were synthesized by the reaction of 3,10-*bis* (2-(*p*-nitrophenyl))-1,3,5,8,10,13-hexaazacyclotetradecane (L) or 3,10-bi-phenyl-1,3,5,8,10,13-hexaazacyclotetradecane (L^1)with copper(II) chloride or cobalt(II) bromide in a 1:1 molar ratio, respectively, in methanol. L and L^1 ligands were prepared from formaldehyde, ethylenediamine and *p*-nitroaniliine or aniline, respectively in methanol[24]. IR spectra were obtained using KBr discs (4000-500 cm^{-1}) on Bruker tensor 27 FTIR spectrophotometer. The optical absorption was examined on a Perkin Elmer, lambda UV-VIS spectroscopy. Fluorescence was determined on a Cary Eclips spectrophotomete



M= Cu, Co
R= H, NO2
X= Cl, Br

Fig. 1. Chemical structure of the macrocyclic metal complexes

Preparation of $[CuL]Cl_2$ (1) and $[CoL]Br_2$ (2): To a 10 mL stirred MeOH solution of $MX_2{\cdot}2H_2O$ [M = Cu, Co] (5 mmol) was added $H_2NCH_2CH_2NH_2$ (0.7 g, 10 mmol), CH_2O

(2.0 mL) and *p*-nitro-aniline (1.9 g, 16 mmol). The mixture was refluxed for 26 h, then the solution was filtered hot and the filtrate allowed standing at room temperature. The green (**1**) and yellow (**2**) precipitates which formed were filtered off, washed with MeOH and further dried *in vacuo*. Yield (%): 65 (**1**), m.p. 125 ºC, IR (KBr, ν_{max}, cm^{-1}): 3480(s), 3359(m), 3215 (m), 2960 (m), 1632 (s), 1595 (s), 1392 (m); yield (%): 81 (**2**), m.p. 128 ºC IR (KBr, ν_{max}, cm^{-1}): 3364(m), 3074(m), 2923(m), 2702, 1666(m), 1601(s), 1466(m).

Preparation of $[CuL^1]Cl_2$ (3): To a 10 mL stirred MeOH solution (10 mL) of $CuCl_2{\cdot}2H_2O$ (5 mmol) was added $H_2NCH_2CH_2NH_2$ (0.7 g, 10 mmol), CH_2O (2.0 mL) and aniline (1.1 g, 12 mmol). The mixture was refluxed for 26 h, then the solution was filtered hot and the filtrate allowed standing at room temperature. The purple precipitate which formed was filtered off, washed with MeOH and further dried *in vacuo*. Yield (%): 53 (**3**), m.p. 102 ºC, IR (KBr, ν_{max}, cm^{-1}): 3417 (s), 3355 (m), 3215 (m), 2926 (m), 1666 (w), 1599 (s), 1500 (s).

DNA binding experiments: The solution of DNA gave a ratio UV absorbance at 260 and 280 nm, A_{260}/A_{280} of 1.7-1.8, indicating that DNA was sufficiently free of protein. The stock solution of DNA was prepared in 50 mM Tris-HCl/Nacl buffer. pH 7.2 (stored at 4 ºC). The concentration of DNA was determined from its absorption intensity at 260 nm with a molar extinction coefficient of 6600 M^{-1} cm^{-1} with respect to base[25]. The binding constant K_b was determined using reported procedure[26].

RESULTS AND DISCUSSION

Electronic absorption spectroscopy is usually employed to determine the binding of complexes with the DNA helix. A complex bound to DNA through interaction is characterized by change in absorbance (hypochromism or hyperchromism) and change in wavelength, due to the intercalative mode involving a strong stacking interaction between the aromatic chromophore and the DNA base pairs. The extent of hypochromism or hyperchromism is commonly consistent with strength of intercalative interaction[27-31].

Absorption titration experiments were carried out by varying the DNA concentration while maintaining the complex concentration constant. Absorbance values were recorded after each successive addition of equipment equilibration (Ca), the absorption data were analyzed for an evaluation of the intrinsic binding constant K_b using reported procedure[32].

The absorption spectra of all the three complexes in the absence and presence of DNA are shown in the Figs. 2-4. In the UV region, complexes (**1**) and (**2**) exhibit one instance absorption at 370-380 nm which is assigned to the ligand-to-metal charge-transfer absorption (LMCT) and complex (**3**) exhibits two instance absorption bands: one at *ca*. 233 nm which is assigned to the intra ligand (π-π^*) transition of aromatic chromophore and the other at *ca*. 320 nm which is assigned to (LMCT). With increasing DNA, the absorption band of complexes are affected, resulting in the obvious tendency of hypochromism and slight shift to longer wavelengths, which indicates that all the three aromatic N-containing Cu(II) and Co(II) complexes can interact with DNA.

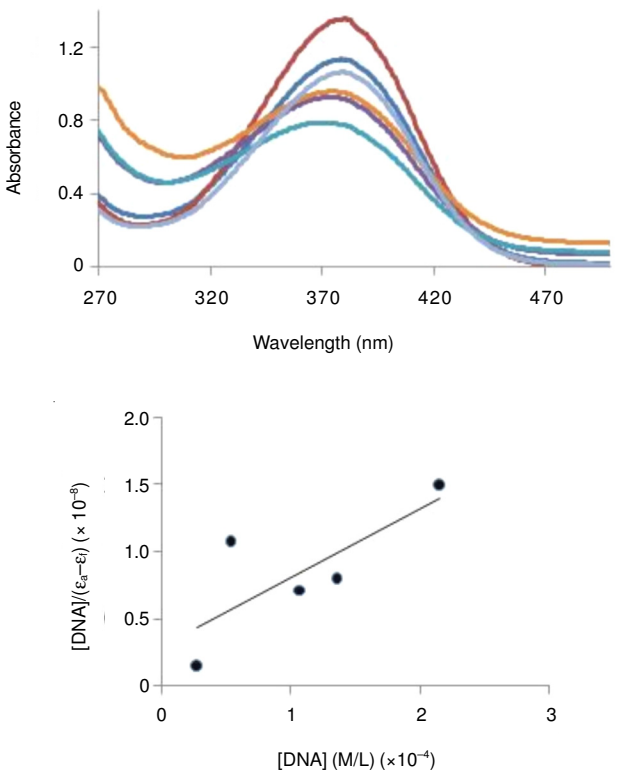


Fig. 2. Absorption spectra and the plot of $[DNA/\varepsilon_a - \varepsilon_f$ *versus* [DNA] for the titration of DNA with complex (**1**)

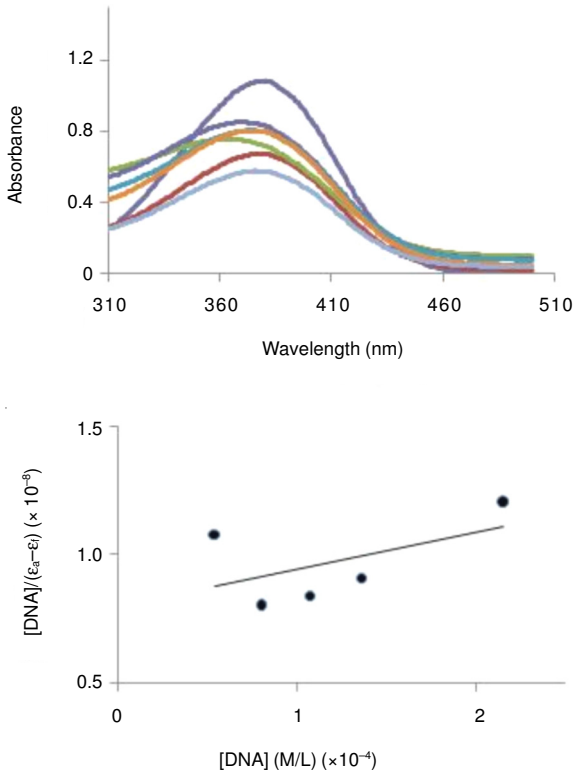


Fig. 3. Absorption spectra and the plot of $[DNA/\varepsilon_a - \varepsilon_f$ *versus* [DNA] for the titration of DNA with complex (**2**)

The $[DNA]/\varepsilon_a - \varepsilon_f$ ratio were plotted against [DNA] and intrinsic constant K_b were obtained from the ratio of the slop to the intercept. The K_b value obtained for complexes (**1**), (**2**) and (**3**) are 1.6×10^4, 1.2×10^3 and 1.5×10^5 M^{-1}, respectively.

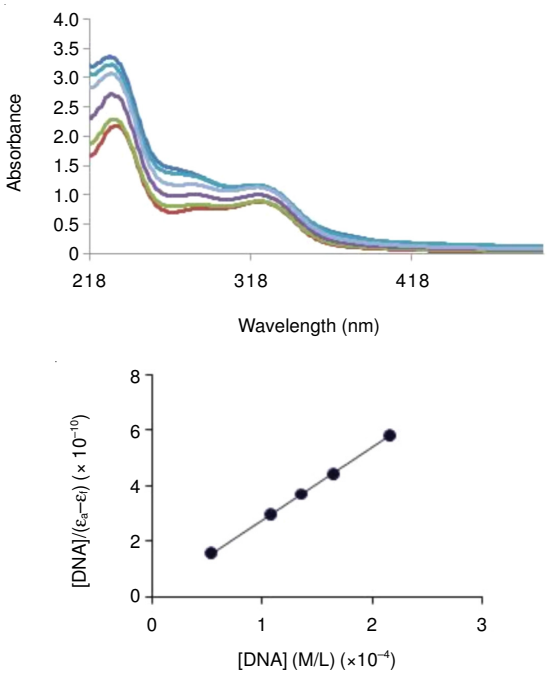
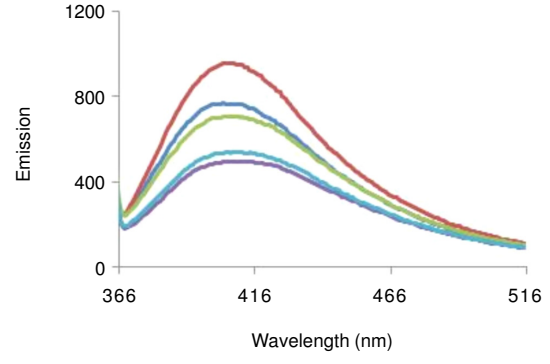


Fig. 4. Absorption spectra and the plot of [DNA/$\varepsilon_a - \varepsilon_f$ *versus* [DNA] for the titration of DNA with complex (**3**)

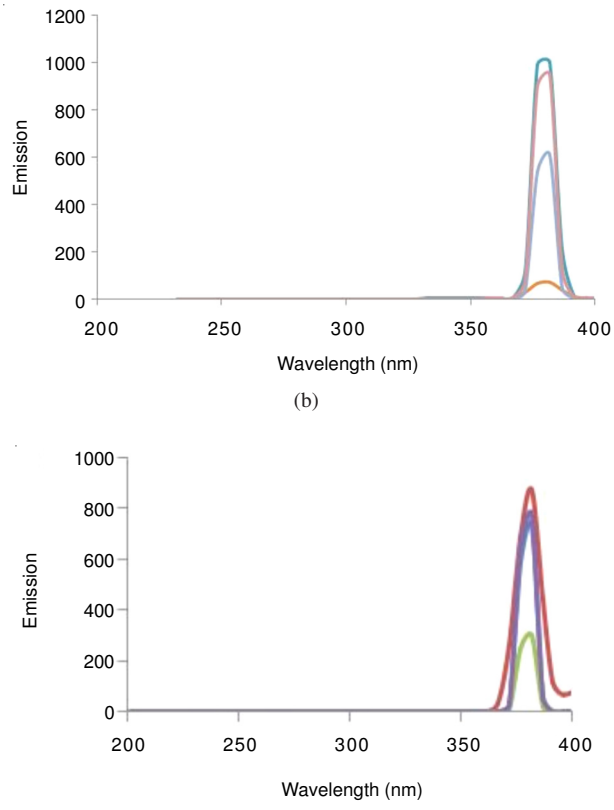
The DNA binding abilities of three complexes were examined by UV-VIS absorption spectroscopy and emission intensity fluorescence.

The stability of all the complexes in 50 mM Tris-HCl/NaCl buffer (pH = 7) at room temperature was monitored by UV-VIS spectroscopy for 24 h and liberation of the ligand was not observed under the conditions. This study suggests that the complexes are stable under the conditions studied and can be titrated with DNA.

Fluorescence spectroscopic studies: Emission band is present in spectrum of the (**1**), (**2**) and (**3**) complexes. It is known that DNA does not give fluorescence, the emission spectra of complexes in *Tris*-HCl, 1 mM; in the presence of increasing amounts of DNA are shown in Fig. 5. It can be noted that the intensity of fluorescence spectrum of complexes is lowered by addition of increasing amount of DNA. The relative intensity values (F_0/F) at 410 nm for (**1**), at 382 nm for (**2**) and 382 nm for (**3**) of the fluorescence spectra of the DNA-complex in the presence of increasing amounts of DNA are illustrated in Fig. 5. It can be seen that a higher excess of DNA leads to more effective quenching of the fluorophore molecule fluorescence.



(a)



(b)

(c)

Fig. 5. Emission quenching spectra of: complexes a (**1**), b (**2**) and c (**3**) with increasing of [DNA] in buffer 5 mM *Tris*-HCl mM NaCl, pH = 7.2 at room temperature

This result confirms that DNA interacts with complexes by an intercalating mechanism.

Conclusion

In this work, we have synthesized and characterized new complexes of Cu(II) and Co(II). Interactions of these complexes with DNA were investigated by absorption and emission spectra. From the experimental results, it shows the UV hypochromism of the absorption band at 320-380 nm in the presence of increasing amounts of DNA. In emission spectrum, the decrease of the fluorescence band of the complexes by the addition of increasing amounts of DNA, confirms intercalation binding of DNA to complexes.

ACKNOWLEDGEMENTS

The authors are grateful to Alzahra-University for providing financial support to undertake this work.

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