Inorganic Chemistry Communications 55 (2015) 30–35

Contents lists available at ScienceDirect

Inorganic Chemistry Communications

journal homepage: www.elsevier.com/locate/inoche

Feature article

Photocleavage of DNA and adenine–thymine inclined binding by a novel ruthenium(II) complex with 3,4-dibromo-imidazo[4,5-*f*][1,10] phenanthroline ligand

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ARTICLE INFO

Article history:
Received 7 January 2015
Received in revised form 12 February 2015
Accepted 22 February 2015
Available online 25 February 2015

Keywords:
Ruthenium(II) complex
DNA sequence-inclined selectivity
Intercalation
Photocleavage

ABSTRACT

A new ruthenium(II) complex $[Ru(phen)2(ODBIP)]^{2+}$ (phen = 1,10-phenanthroline; ODBIP = 3,4-dibromo-imidazo[4,5-*f*][1,10]phenanthroline) has been synthesized. Binding of this complex to poly(dG–dC) DNA, supercoiled pBR322 plasmid DNA, calf thymus DNA (CT DNA), and poly(dA–dT) DNA was investigated by spectroscopic methods. The photocleavage on pBR322 DNA was also studied by agarose gel electrophoresis, and the cleavage mechanisms were further explored. The results indicated that $[Ru(phen)2(ODBIP)]^{2+}$ preferentially bound to DNA at adenine–thymine base pairs by intercalation, and the complex exhibited higher DNA cleavage efficiency under visible light irradiation than under UV light irradiation. The singlet oxygen may be responsible for the DNA photocleavage.

Contents

The discovery and application of cisplatin have advanced the transition of metal complex in the field of chemotherapy and artificial nucleases [1,2]. Ruthenium(II) complexes have attracted special attention due to their good thermodynamic stability, rich photochemical and photophysical properties, and good DNA-binding properties [3,4]. Unlike the square planar structure of cisplatin, ruthenium(II) polypyridyl complexes usually possess a structure of three spatial dimensions of octahedral configuration. The aromatic heterocyclic ligands of ruthenium(II) complex can be designed to intercalate into the DNA base pairs, and generate structure perturbations of DNA [5]. Some ruthenium(II) complexes have been reported to exhibit efficient DNA cleavage activity upon irradiation [6], implying their potential applications as photosensitizers in photodynamic therapy (PDT) for malignant cancers. Investigations on the mechanisms of such photocleavage of DNA are of great value to develop new photo-nucleases and drugs.

Octahedral ruthenium(II) complexes generally bind to DNA non-covalently through three binding modes: intercalation, hydrophobic groove binding, and electrostatic adsorption [1,7]. The structure and planarity of the intercalative ligand play important roles in DNA-binding properties. The substituents in the intercalative ligand also take great effects on DNA-binding behaviors of complex. Changing the substituents in the intercalative ligand can not only cause different DNA-binding behaviors, but also bring various biological activities of ruthenium(II) complexes, which could be helpful to understand the DNA-binding mechanism of ruthenium(II) polypyridyl complex, as well as to develop new complexes with photocleavage activities as potential PDT agents.

In our previous studies, we have reported a ruthenium(II) complex $[Ru(phen)_2(ODCIP)]^{2+}$ with two chloride substituents in the phenyl ring of intercalative ligand [8]. Here we introduced two bigger bromide substituents to 3 and 4 positions of phenyl ring to form a new ligand ODBIP. The ligand ODBIP and its corresponding ruthenium(II) complex $[Ru(phen)_2(ODBIP)]^{2+}$ were prepared according to the routes in scheme S1.

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http://dx.doi.org/10.1016/j.inoche.2015.02.024
1387-7003/

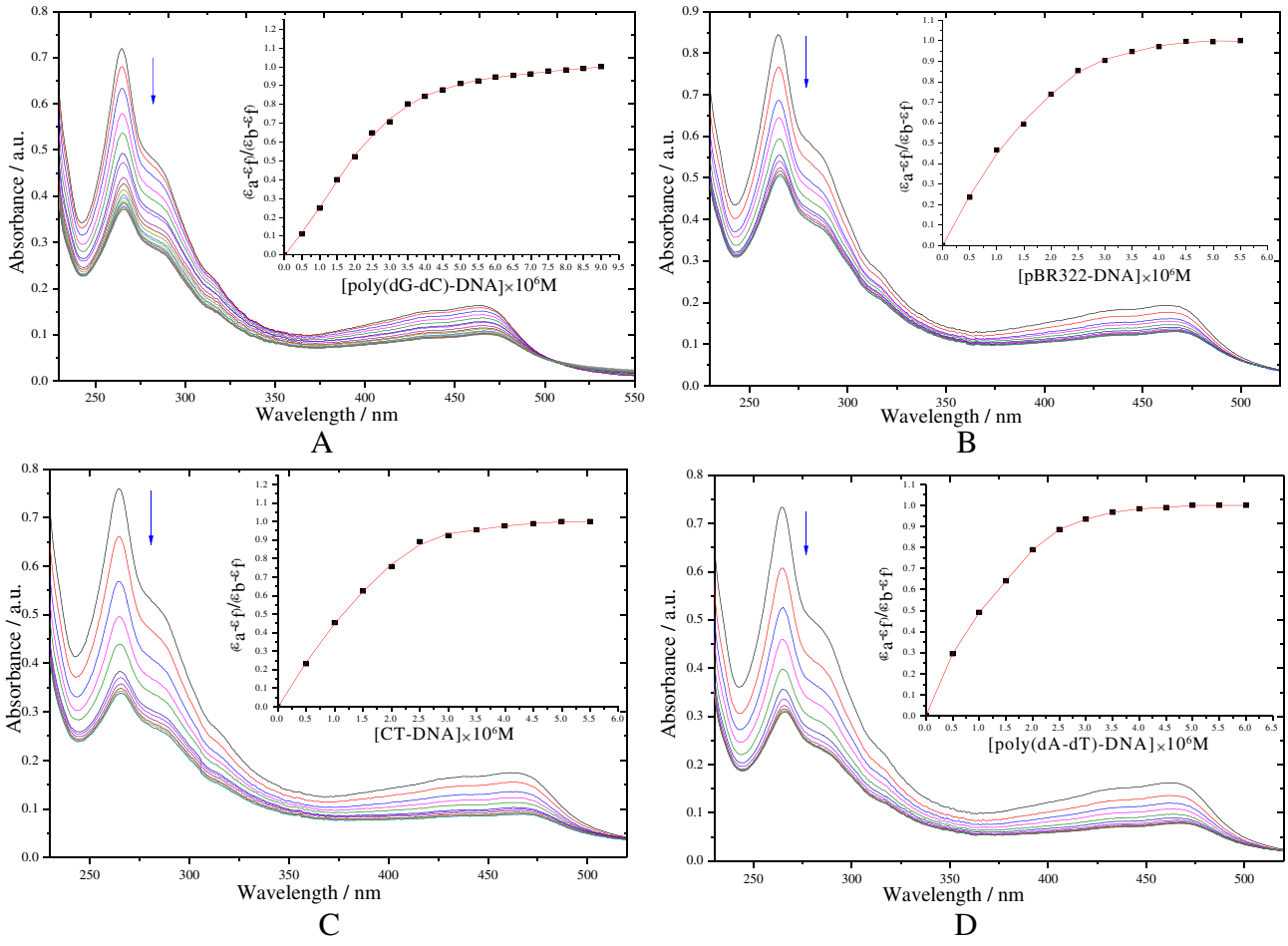

Fig. 1. Absorption spectra of $[Ru(phen)_2ODBIP]^{2+}$ in Tris–HCl buffer upon addition of increasing amount of DNA. (A) poly(dG–dC), (B) pBR322 DNA, (C) CT DNA, (D) poly(dA–dT) DNA. [Ru] = 10 μM, [DNA] = 0–6.0 μM with the interval of 0.5 μM, the temperature is 298 K. Inset: plots of $(\varepsilon_a - \varepsilon_f) / (\varepsilon_b - \varepsilon_f)$ vs. [DNA].

Compared with $[Ru(phen)_2(ODCIP)]^{2+}$, the two bigger bromide substituents in the intercalative ligand may bring some interesting differences in DNA binding behaviors. The interactions of $[Ru(phen)_2(ODBIP)]^{2+}$ with four kinds of DNA (containing different percents of adenine–thymine (A–T) base pairs) were studied by spectroscopic methods. The absorption spectra of complex with increasing amount of DNA were shown in Fig. 1. The equilibrium binding constants (K) were obtained using the following Eqs. (1) and (2) [9,10]:

$$\left(\varepsilon_a - \varepsilon_f\right) / \left(\varepsilon_b - \varepsilon_f\right) = \left(b - \left(b^2 - 2K^2 C_t [DNA]/s\right)^{1/2}\right) / 2KC_t \quad (1)$$

$$B = 1 + KC_t + K[DNA]/2s \quad (2)$$

s is the binding site size of small molecule interacting with DNA. ε_b and ε_f are the extinction coefficients at the maximum absorption of the DNA fully bound and free complex, respectively. ε_a is the apparent extinction coefficient of complex observed at a given DNA concentration. [DNA] denotes the concentration of DNA in nucleotide. C_t is the total ruthenium complex concentration.

The absorption spectra of complex in the absence and presence of different DNA (at constant concentration of complex) are given in Fig. 1. The absorption spectra data are also listed in Table 1. The bands at 264.5 nm are assigned to the intraligand (IL) π–π* transitions, the shoulder bands around 290 nm can be attributed to the two phen ligands, and the bands between 460 and 470 nm are attributed to the metal-to-ligand charge transfer (MLCT). Upon addition of poly(dA–dT), the complex exhibited obvious red shift and hypochromism in the MLCT band, the hypochromism in the MLCT band was 51.6% and the red shift was 6 nm. However, the complex exhibited less hypochromism upon addition of pBR322, CT-DNA and poly(dG–dG). The binding constants of the complex with poly(dG–dC) DNA (0% AT), supercoiled pBR322 plasmid

Table 1
Absorption spectra data and DNA binding constants of $[Ru(phen)_2ODBIP]^{2+}$ with four kinds of DNA.

DNA	AT (%)	λ_{max} (nm)				Δλ (nm)		H (%)[a]		K_b (M^{-1})
		Free		Bound						
		IL	MLCT	IL	MLCT	IL	MLCT	IL	MLCT	
Poly(dG–dC)	0	265.0	464.0	266.0	467.0	1.0	3.0	48.5	38.1	2.0×10^5
pBR322 DNA	46	264.5	463.5	266.0	468.5	1.5	5.0	40.4	33.0	5.5×10^5
CT DNA	58	264.5	464.0	265.5	468.5	1.0	4.5	55.7	49.1	6.3×10^5
Poly(dA–dT)	100	264.5	464.0	266.5	470.0	2.0	6.0	58.2	51.9	8.1×10^5

[a] $H\% = [(\varepsilon_f - \varepsilon_b) / \varepsilon_f] \times 100\%$.