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Interactions of DNA with H_2TMPyP^{4+} and Ru(II)$TMPyP^{4+}$: Probable Lead Compounds for African Sleeping Sickness

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Abstract

Interactions of DNA with free base porphyrin, tetrakis(1-methylpyridium-4-yl)porphyrin (H_2TMPyP^{4+}) and its metallo-derivative of ruthenium(II) have been investigated by UV-Vis, fluorescence and circular dichroism (CD) spectroscopy at 0.1 M NaCl, 7.5 pH and 25 °C. The results suggest that Ru(II)$TMPyP^{4+}$ interacts with DNA via outside binding in self-stacking manner as indicated by UV-Vis data, a small red shift ($\Delta\lambda$ = 3 nm) and a minimal hypochromicity (10%) upon addition of DNA. CD spectra showed the presence of a new peak in the Soret region on addition of Ru(II)$TMPyP^{4+}$ to DNA solution. On the other hand, the interaction of free base porphyrin, H_2TMPyP^{4+} with DNA revealed a significant hypochromicity (30%) and a large red shift ($\Delta\lambda$ = 20 nm) in the UV-Vis results which conforms intercalation of free base porphyrin with DNA. In this case, the CD results showed only a negative peak developed in the Soret region during titration with DNA. Fluorescence spectroscopy revealed that initially aggregated porphyrin species were de-aggregated after addition of DNA. This phenomenon has been verified with the fluorescence experiments for the porphyrins in the presence of different concentrations of NaCl and ethanol. Ru(II)$TMPyP^{4+}$ showed enhanced DNA cleavage in the presence of *Eco*R1 restriction enzyme, where the enzyme did not cleave DNA. Metallo-porphyrins having the ability to cleave DNA could be used as chemotherapeutic agents for the treatment of African sleeping sickness (*Trypanosomiasis*).

Key words: Porphyrins, plasmid DNA, UV-Vis spectra, CD, outside binding.

Introduction

Interaction between cationic porphyrins and DNA has been an interesting subject since the first synthesis and the prior discovery by Fiel (1989). Porphyrins and metalloporphyrins are found widely in nature and are used by organisms as cofactors for a variety of enzymes and specialized proteins (Li *et al*., 1996). Biological effects of porphyrin-derivatives depend strongly on their physico-chemical properties (Woynarowski, 2002). The porphyrin core is planar but shielded by peripheral substituents (Lee *et al*., 2001). This makes porphyrins as a photosensitizer that can localize in tumor cells and is phototriggred to damage tumor cells (He *et al*., 2004; Lottner *et al*., 2004; Zhang *et al*., 2003). The recent interest in porphyrins-nucleic acid interaction stems from porphyrin's application in photodynamic therapy. Cationic porphyrins are considered as double functional compounds that strongly bind to DNA and photodynamically modify the target site of a DNA molecule by its cleavage, a mechanism similar to that of some anti-cancer antibiotics (Drain *et al*., 1999). Interestingly, insertion of metal ion into porphyrins core drastically enhances the photo nuclease activity of the porphyrins (Aoki *et al*., 2003).

Metalloporphyrins are extraordinarily versatile and involved in oxygen transport, electron transfer and a variety of redox reactions, such as those associated with catalases, peroxidases and mono-oxygenases (Konorev *et al*., 2002; Perez *et al*., 2002; Yang *et al*., 2001). Cationic porphyrins act as inhibitor of human telomerases, a receptor for peptides and a specific probe of DNA structures (Tjahjono *et al*., 2001; Woynarowski, 2002). They have been found to associate with DNA in various modes (Fiel, 1989; Lee *et al*., 2002; Pasternack and Gibbs, 1989). The three major categories of porphyrin-DNA bindings are intercalation, outside binding without self-stacking, and outside binding with self-stacking along the DNA surface (Fiel, 1989; Marzilli, 1990). Partial intercalation has also been suggested (Ford *et al*., 1987). The binding mode or modes of a specific

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porphyrin-DNA system are highly dependent on the substituents of the porphyrin as well as central metal ions. Generally, the free base porphyrins and square planar complexes such as Ni(II), Cu(II) Pt(II) and Pd(II) intercalate between DNA base pairs (Dougherty, 1988). In the case of intercalation, favorable aromatic π-π stacking interactions between the porphyrins macro-cycle and the base pair of nucleic acids are also invaded (Tjahjono *et al*., 2001). On the other hand, the metalloporphyrins having axial ligands such as Co(III), Mn(III) and Fe(III) or those with bulky substituents, on the periphery of structure, intercalation is blocked and outside binding occurs (Dougherty, 1988).

The interaction of transition metal complexes with DNA or RNA has been the subject of intense interest from different perspectives (Dandliker *et al.*, 1997). Many complexes of this kind with different ligands have been synthesized and investigated during the past decades (Erkkila *et al*., 1999; Moucheron *et al*., 1998; Xiong and Ji, 1999). The studies revealed that the modification of the ligands leads to subtle or substantial changes in the binding modes, location and affinities, giving opportunities to explore various valuable conformation- or site-specific DNA probes and potential chemotherapeutic agents (Carter *et al.*, 1989). However, few studies have been paid on the potential uses of ruthenium and gold porphyrins as chemotherapeutic agents. Nyarko *et al.* (2002, 2004) have studied possible potential uses of some metalloporphyrins on *Trypanosomia* that causes African Sleeping Sickness.

In the present work, interactions between Ru(II)TMPyP^{4+} (metallo-derivative of tetrakis(1-methylpyridium-4-yl)porphyrin) in comparison to free base porphyrin (H_2TMPyP^{4+}) with DNA were studied to understand the manner in which the metallo-porphyrins bind to DNA.

Materials and Methods

Reagents: Tetrakis(1-methylpyridium-4-yl)porphyrin (H_2TMPyP^{4+}, Figure 1) was purchased from Dojindo Laboratories as a tosylate and its metallo-derivatives were prepared by standard procedure (Hambright, 2002). The purity of the synthesized porphyrin was confirmed by its absorption maximum (λ_{max}) at 422 nm (Heilig, 1987). The prepared metalloporphyrin was found to be stable, as they did not dissociate in 1 M HCl or 1M HNO_3. Concentration of free-base porphyrin was determined by titration using a standard copper (II) solution. Buffer solution was prepared from a 2-[4-(2-hydroxyethyl)piperazinyl]ethanesulfonic acid (HEPES) (0.1 M, pH 7.4) and ultrapure sodium hydroxide solution (Merck Chemical Co.). The pBluescript II plasmid DNA was prepared from plasmid bearing the *Escherichia coli* strain by standard procedure (Gibbs *et al*., 1988). A stock solution of DNA was prepared by dissolving pBluescript plasmid DNA in sterilized deionized water and the concentration in base pairs was determined by its known molar extinction coefficient at 260 nm (6600 M^{-1} cm^{-1}) (Nyarko *et al*., 2004). All other reagents were used without further purification. Sterilized deionized water treated by a Milli-QSP TOC (Nippon Millipore Ltd., Japan) was used for making solutions.

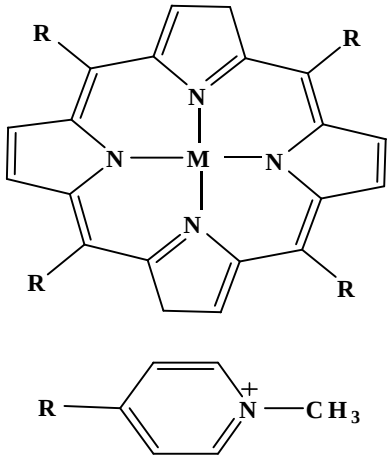

Figure 1. Porphyrin complex of tetrakis(1-methylpyridium-4-yl)porphyrin (H_2TMPyP^{4+}).

Methods: UV-Vis spectra were recorded on a Shimadzu spectrophotometer (model UV-2100, Japan) coupled with a temperature controller (Model RTE-100, Neslab Instruments, USA) at 25°C. CD spectra were measured using spectropolarimeter (JASCO J700). The CD spectra were scanned five times and then averaged. Fluorescence spectra of the free base and metalloporphyrins were recorded on a Hitachi (model F-4500) fluorescence spectrophotometer. The fluorescence emission wavelength was scanned from 550 to 800 nm by setting the excitation wavelength at 430 nm for

Ru(II)TMPyP^{4+} because the isosbestic points for the binary system of Ru(II)TMPyP^{4+}-DNA was observed at 430 nm. Under the present experimental conditions, at 3.6 x 10^{-6} (free base porphyrin) and 3.6 x 10^{-6} M metalloporphyrin, the absorbance and fluorescence spectra of the porphyrin solutions were not affected by the species on the surfaces of the cell walls. Moreover, the results obtained in the fluorescence spectra for these porphyrins on addition of ethanol and NaCl were confirmed by UV-Vis spectroscopic measurements (spectra not shown). All the experiments were done under room light. ION 85 analyzer (Radiometer, Denmark) was used to measure pH of the solutions.

Results and Discussion

UV-vis spectral studies: Figure 2 shows the UV-Vis spectral change of the free base porphyrin and its metallo-derivatives, Ru(II)TMPyP^{4+}. Figure 2(a) shows UV-Vis spectra of the free base porphyrin (H_2TMPyP^{4+}) upon addition of DNA. In the concentration range of 0 - 2.30 x 10^{-5} M base pairs, the absorption spectra of H_2TMPyP^{4+} showed substantial hypochromicity at 422 nm and a large red shift of $\Delta\lambda$ = 20 nm, whereas Ru(II)TMPyP^{4+} displayed small hypochromicity (10%) and a small red shift ($\Delta\lambda$ = 3 nm) at 417 nm as shown in Figure 2(b). From the UV-vis spectroscopic studies, it has been considered that a substantial hypochromicity and large red shift indicate intercalation whereas small hypochromicity and a small red shift indicate outside binding. Therefore from the UV-Vis spectroscopic results, it may conclude that the free base porphyrin (H_2TMPyP^{4+}) interacts with DNA as intercalation, on the other hand, Ru(II)TMPyP^{4+} interacts as outside binding. The binding modes are confirmed by CD spectroscopy as discussed in the following section. The interaction studies of the porphyrins with DNA are also conducted using fluorescence spectroscopy.

Induced CD spectral studies: In general, DNA bound porphyrins do not possess a chiral center and are optically inactive. However, the CD spectrum in the drug absorption region, especially at the Soret region, is induced when it forms a complex with polynucleotides. Although, the origin of induced CD of the achiral porphyrin-DNA complex is not clear, it is believed to be induced by the coupling of the transition moments of achiral drug and chirally arranged nucleobase transition or by excitonic interaction of the DNA-bound drug. The shape and magnitude of induced CD depends on the binding mode and location of the drug, and the nature of the nucleobases (Erkkila *et al*., 1999; Moucheron *et al*., 1998; Xiong and Ji, 1999).

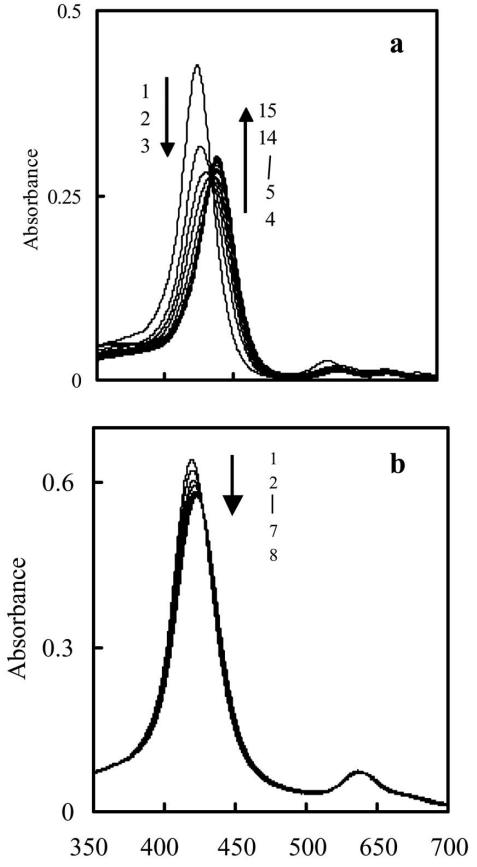

Figure 2. Changes in UV-visible spectra of (a) H_2TMPyP^{4+} in the presence of DNA of (1) 0, (2) 0.15, (3) 0.30, (4) 0.45, (5) 0.60, (6) 0.75, (7) 0.90, (8) 1.10, (9) 1.30, (10) 1.45, (11) 1.60, (12) 1.75, (13) 1.95, (14) 2.25, (15) 2.50 M base pairs, and (b) Ru(II)TMPyP^{4+} in the presence of (1) 0, (2) 0.40, (3) 075, (4) 1.10, (5) 1.55, (6) 1.90, (7) 2.25, (8) 2.50 x10^{-5} M in base pairs. Total concentration of the porphyrins is 3.6 x10^{-6} M. Cell path length is 10 nm.

As shown in Figure 3, DNA did not show any spectra at the Soret region, but on addition of cationic porphyrin or its metallo-derivatives, either positive or negative peak was developed. The development of positive or negative peak depends on the binding modes of the porphyrins with DNA. Figure 3(a) shows the CD spectra of DNA upon addition of free base porphyrin. The results indicate that a significant hypochromicity was observed at 270 nm with the development a negative peak at the Soret region. Both the UV-Vis and CD spectroscopy results indicated that the free base porphyrin, H_2TMPyP^{4+} interacted with DNA as

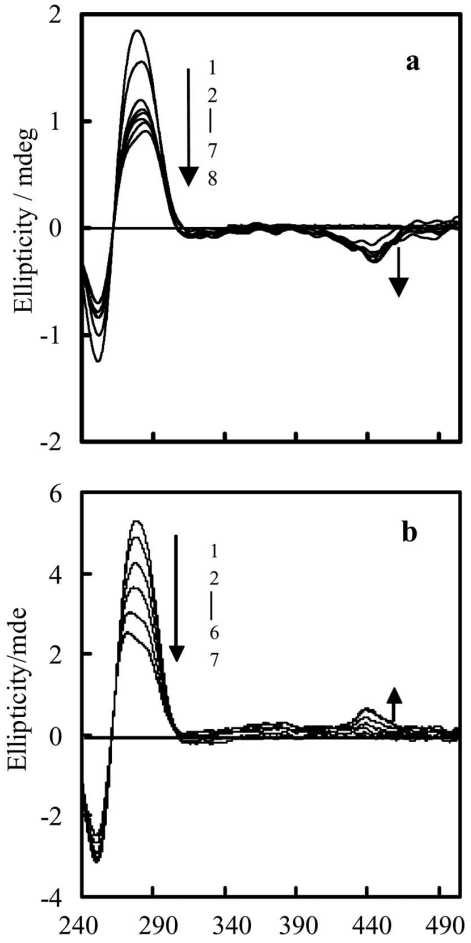

Figure 3. CD spectral changes of DNA (1.0 x10^{-4} M base pairs) upon the addition of the porphyrins. Arrows indicate spectral increase or decrease with addition of (a) H_2TMPyP^{4+} of (1) 0, (2) 0.15, (3) 0.30, (4) 0.45, (5) 0.65, (6) 0.85, (7) 1.10, (8) 1.35, (9) 1.70 M, and (b) Ru(II)$TMPyP^{4+}$ of (1) 0, (2) 0.20, (3) 0.40, (4) 0.60, (5) 0.90, (6) 1.30, (7) 1.70 x10^{-5} M. Cell path length is 10 mm.

intercalation since the development of negative peak is a signature of intercalation. On the other hand, a positive peak at the Soret region with hypochromicity at 270 nm, was observed upon addition of Ru(II)$TMPyP^{4+}$ into the DNA solution as shown in Figure 3(b). Therefore, both the UV-Vis and CD results indicated the outside binding of Ru(II)$TMPyP^{4+}$ with DNA. In the previous study (Nyarko *et al.*, 2004), we observed both positive and negative peaks at the Soret region with hypochromicity at 270 nm upon addition of Au(III)$TMPyP^{5+}$ into DNA solution. It has been reported that Au(III)$TMPyP^{5+}$ interacted with DNA via outside binding with a partial intercalation. The development of either positive or negative peak at the Soret region indicated the formation of porphyrin-DNA binary complexes because only porphyrin did not give any peak at that region. Therefore, it is concluded that an induced chirality is developed when porphyrins are bound to DNA.

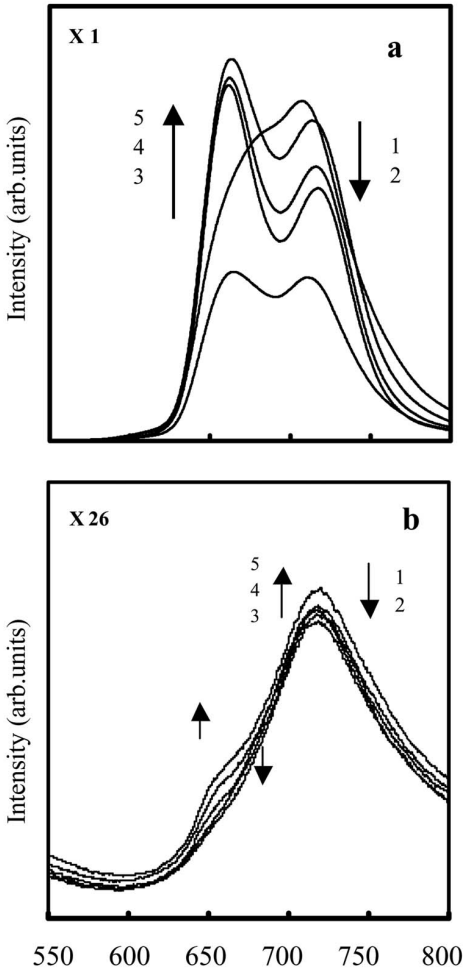

Figure 4. Fluorescence spectra of (a) H_2TMPyP^{4+} and (b) Ru(II)$TMPyP^{4+}$ in the presence of DNA of (1) 0, (2) 0.30, (3) 0.75, (4) 1.20, (5) 1.55x10^{-5} M base pairs at pH 7.4 (HEPES). Concentrations of porphyrin and sodium chloride are 3.6x10^{-6} and 0.1 M, respectively. Magnification was based on comparisons with Fig. 2(a).

Fluorescence spectroscopic studies: Figure 4 shows the fluorescence spectra of free base and metalloporphyrin. Figure 4(a) shows the fluorescence spectra of the free base porphyrin upon addition of DNA. Free base porphyrin exhibited high excitation fluorescence as shown in Figure 4(a) but Ru(II)$TMPyP^{4+}$ showed weak fluorescence emission as shown in Figure 4(b). The week intensity for the metallo-porphyrin is due to heavy atom effect by the ruthenium atom. Similar results were found for Au(III)-,

Pt(II) and Pd(II)TMPyP as we reported previously (Nyarko *et al.*, 2004). Nevertheless, the data obtained for the Ru(II)porphyrin provide good information about its interaction with DNA. In the absence of DNA, the fluorescence of H_2TMPyP^{4+} was quite strong with two main peaks at 663 and 720 nm. Upon addition of a low concentration of DNA, the fluorescence intensity of H_2TMPyP^{4+} decreased due to self-stacking of the free base porphyrin along the DNA surface as a result of the proximity of the neighboring porphyrin molecules to each other (Nyarko *et al*., 2002; Nyarko *et al*., 2004). However, two peaks of the H_2TMPyP^{4+} in the emission spectra began to increase the self-stacking was reduced at higher concentrations of DNA (Figure 4a). Interestingly, the peak intensity at 663 nm was higher than that at 720 nm. At the highest concentration of DNA, the peak intensity at 663 nm was almost equal to the original peak obtained in the absence of DNA, while the peak intensity centered at about 720 nm was much lower. The increased fluorescence emission in excess amount of DNA is therefore attributed to the reduced self-stacking of the porphyrin molecules and their subsequent outside interactions with DNA bases.

On addition of increasing concentrations of NaCl from 0.001 - 0.1 M to H_2TMPyP^{4+} in the absence of DNA, there were marginal increases in the emission spectra with the maximum fluorescence observed at 720 nm (Figure 5(a)) due to aggregation of the porphyrin molecules. The observed fluorescence spectra of the aggregated form of H_2TMPyP^{4+} remained virtually unchanged with increasing concentrations of NaCl (Kano *et al*., 1987; Kano *et al*., 1990). However, the fluorescence intensity increased with increasing concentration of ethanol (from 0 to 40%) and two peaks were development centered at 663 and 720 nm (Figure 5(c)). This indicates that the aggregated form of H_2TMPyP^{4+} was destroyed in the presence of increasing

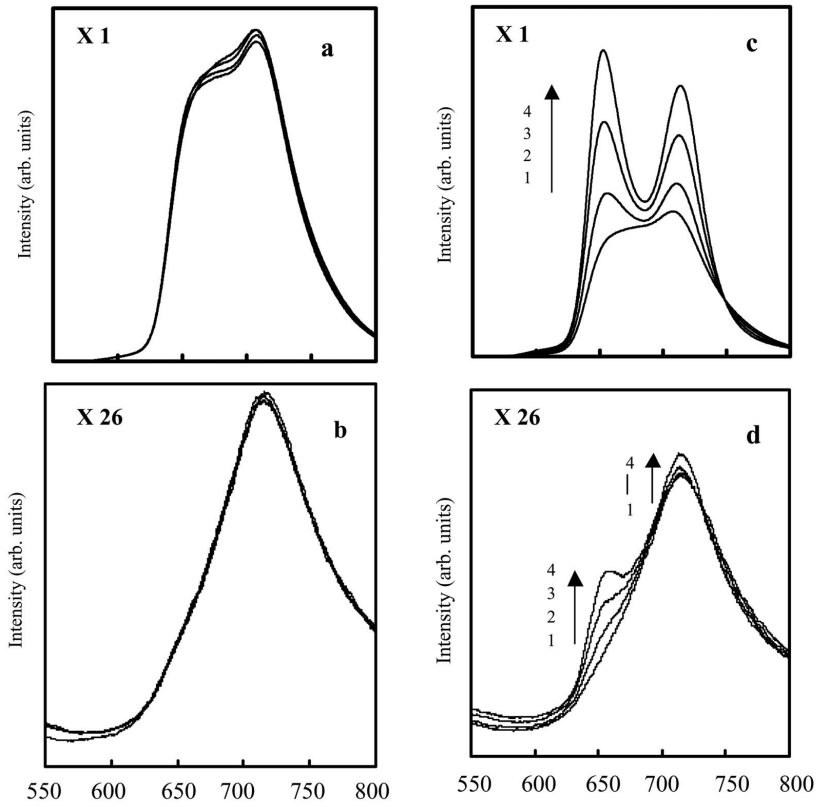

Figure 5. Fluorescence spectra of (a) H_2TMPyP^{4+} and (b) Ru(II)$TMPyP^{4+}$ in the presence of increasing concentrations of NaCl of (1) 0, (2) 0.001, (3) 0.01 and (4) 0.1 M. Fluorescence spectra of (c) H_2TMPyP^{4+} and (d) Ru(II)$TMPyP^{4+}$ in the presence of increasing amounts of ethanol of (1) 0, (2) 10%, (3) 20%, (4) 30% and (5) 40%, respectively. pH of the solutions is 7.4 (HEPES buffer). Concentration of the porphyrins is 3.6 x 10^{-6} M. Cell path length is 10 mm. Magnification was based on comparisons with Fig. 5(a) and (c).

amounts of ethanol leading to the appearance of the monomer bands which led to an increase in their fluorescence intensities. These observations therefore confirm that in the presence of excess amounts of DNA, the free base porphyrin was progressively converted from the aggregate to the monomer form upon intercalating into the DNA bases thereby leading to the enhancement in the fluorescence intensity.

In the case of Ru(II)TMPyP^{4+}, a broad fluorescence spectrum of low intensity was observed between the wavelength range of 650 and 750 nm (Figure 4b). However, upon addition of DNA, ranging from 2.50x10^{-6} to 1.4 x 10^{-5} M in base pairs, the emission spectrum still showed a single peak at 720 nm, but at higher DNA concentration the fluorescence spectrum showed an intense peak at 720 nm with a shoulder at 650 nm (Figure 4(b)). The fluorescence spectra of the metalloporphyrin were unchanged upon addition of a range (0 – 0.1 M) of NaCl in the absence of DNA (Figure 5(b)). However, two sharp peaks were observed with increasing amounts of ethanol (0 – 40%). This is due to de-stacking of Ru(II)TMPyP^{4+} and enhanced the monomer band (Figure 5(d)), just as in the case of the addition of excess amounts of DNA to the Ru(II)porphyrin solution.

Conclusion

UV-Vis, fluorescence and circular dichroism (CD) spectroscopy were used to investigate the interaction of free base porphyrin, tetrakis(1-methylpyridium-4-yl)porphyrin (H_2TMPyP^{4+}) and its metallo-derivatives of ruthenium(II). The results indicated that Ru(II)TMPyP^{4+} interacted with DNA via outside binding with self-stacking manner, while the free base porphyrin, H_2TMPyP^{4+}, interacted with DNA as intercalation. Usually, the metallo-porphyrins having axial ligands interact with DNA as outside binding such as Mn(III)-, Fe(III)TMPyP^{5+}, whereas the square planar, e.g. Ni(II), Pt(II) which have no axial ligands interact with DNA as intercalation. Tabata *et al.*, (2000) demonstrated that metalloporphyrins with axial ligands could enhance DNA cleavage in the presence of low concentration of restriction enzyme where the enzyme does not cleave the DNA. Ru(II)TMPyP^{4+} also shows enhanced DNA cleavage in the presence of low concentration of restriction enzyme (e.g., *Eco*R1, *Hae*III) where the enzymes do not cleave the DNA. Nyarko *et al.* (2002, 2004) verified that the metallo-porphyrins having the ability to cleave DNA could be used as chemotherapeutic agents for the treatment of African sleeping sickness (*Trypanosomiasis*). Therefore, Ru(II)TMPyP^{4+} is to be considered as a potential chemotherapeutic candidate for the treatment of African sleeping sickness.

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