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Study on the interaction of porphyrin with G-quadruplex DNAs

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ABSTRACT

Interactions of 5,10,15,20-Tetrakis(*N*-propylpyridinium-4-yl)-21*H*,23*H*-porphyrin (TPrPyP4) with dimer hairpin $(G_4T_4G_4)2$ and parallel four-stranded $(TG_4T)4$ G-quadruplex DNAs in Na^+-containing buffer were studied. The results show that two TPrPyP4 molecules bind to both G-quadruplexes by a noncooperative and nonequivalent binding mode, and there are one high affinity site and one low affinity site, the respective binding constants are 8.06×10^8 and 1.13×10^6 M^{-1} for $(G_4T_4G_4)2$-TPrPyP4, 8.04×10^7 and $9.08\times10^5 M^{-1}$ for $(TG_4T)4$-TPrPyP4. TPrPyP4 presents two lifetimes of about 5.8 and 12.0 ns in the complexes of G-quadruplexes-TPrPyP4. The primary results suggest that two TPrPyP4 molecules bind to both G-quadruplexes by terminal stacking and outside binding mode.

1. Introduction

Guanine-rich DNA sequences of the telomeric ends can form a wide variety of G-quadruplex structures in the presence of certain ions, notably Na^+ and K^+ [1,2]. G-quadruplex DNAs can inhibit the activity of telomerase in cancer cell and have drawn a considerable attention by acting as a promising anticancer drug target [3–5]. The porphyrin derivative 5,10,15,20-Tetrakis(*N*-methylpyridinium-4-yl)-21*H*,23*H*-porphyrin (TMPyP4) has been extensively studied as a quadruplex-binding ligand since it can inhibit the activity of telomerase upon binding to human telomeric G-quadruplex DNAs [6].

G-quadruplex DNAs contain multiple guanine quartets, which are planar arrangements of four Hoogsteen hydrogen-bonded guanines (Scheme 1A). The size of porphyrin ring are similar to that of guanine quartet, hence the stability of G-quadruplex DNA by porphyrin is due mainly to π–π stacking interaction between the porphyrin ring and guanine quartet. Two main models have been proposed for binding of TMPyP 4 to different types of G-quadruplexes, namely, intercalative binding between adjacent G-quartets [7–9] and end-stacking on the G-quartets [9–12]. However, some other binding modes except π–π stacking interaction between the porphyrin ring and G-quartet have also been suggested. For example, Neidle, et al. recently reported an X-ray structure of a G-quadruplex-TMPyP4 complex [13], indicating that TMPyP4 molecules fail directly to interact with G-tetrads in the G-quadruplex.

In our previous experiments, we showed that two TMPyP4 molecules are externally stacked at two ends of parallel G-quadruplex $(TG_4T)4$, whereas four TMPyP4 molecules can intercalate within the diagonal loop regions and intervals between G-quartets for dimer hairpin G-quadruplex $(G_4T_4G_4)2$ in Na^+-containing buffer [9]. In order to further understand the interactions of porphyrin bearing different cation side arm with G-quadruplex DNAs, here we synthesized a porphyrin derivative 5,10,15,20-Tetrakis(*N*-propylpyridinium-4-yl)-21*H*,23*H*-porphyrin (TPrPyP4) with N-propyl pyridinium cationic side arms (Scheme 1B). Based on the circular dichroism (CD), visible absorption and steady and time-resolved fluorescence spectroscopies, the binding stoichiometries, binding constants and possible binding modes of TPrPyP4 with G-quadruplexes $(TG_4T)4$ and $(G_4T_4G_4)2$ in Na^+-containing buffer (pH 7.5) were first studied in detail.

2. Materials and methods

2.1. Materials

The DNA oligonucleotides TG_4T and $G_4T_4G_4$ were purchased from the SBS Genetech Co., Ltd. (China) in a PAGE-purified form. Single-strand concentrations were determined by measuring the absorbance at 260 nm at a high temperature. Single-strand extinction coefficients at 260 nm are 57800 and 115200 M^{-1} cm^{-1} for TG_4T and $G_4T_4G_4$, respectively [9]. The formation of G-quadruplexes was carried out as follows: the oligonucleotide samples, dissolved in a buffer solution consisting of 10 mM Tris–HCl, 1 mM EDTA and 100 mM NaCl at pH 7.5, were heated to 90 °C for 5 min, gently cooled to room temperature, and then incubated at 4 °C overnight. Single-strand concentrations of TG_4T and $G_4T_4G_4$ are divided by 4 and 2 to obtain the concentrations of folded G-quadruplexes of $(TG_4T)4$ and $(G_4T_4G_4)2$, respectively.

Abbreviations: TPrPyP4, 5,10,15,20-Tetrakis(*N*-propylpyridinium-4-yl)-21*H*,23*H*-porphyrin; TMPyP4, 5,10,15,20-Tetrakis(*N*-methylpyridinium-4-yl)-21*H*,23*H*-porphyrin; CD, Circular dichroism.

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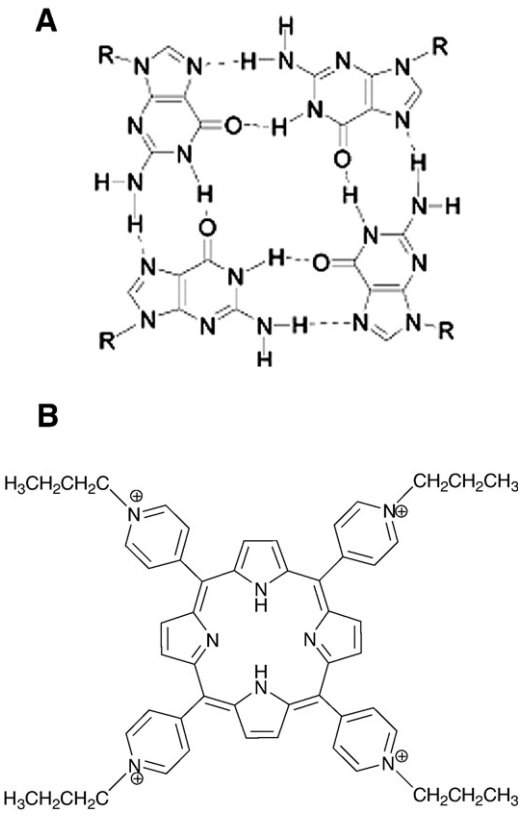

Scheme 1. The structures of G-quartets (A) and TPrPyP4(B).

TPrPyP4 was synthesized according to the literature procedure with small modifications [14]. A detail synthesis procedure was given in the supporting information. The concentration of TPrPyP4 was determined by measuring the absorbance at 423 nm with an extinction coefficient of 2.1×10^5 M^{-1} cm^{-1} [15].

2.2. Absorption spectroscopy

Absorption spectra were measured on a HP 8453 ChemStation with 1 cm-path-length quarter cell. Visible absorption titrations were terminated when the wavelength and intensity of the absorption band for TPrPyP4 did not change any more upon three successive additions of G-quadruplexes. The percent hypochromicity of the Soret band of TPrPyP4 can be calculated using hypochromicity $\%=[(\varepsilon_f-\varepsilon_b)/\varepsilon_f]\times100$, where $\varepsilon_b=A_b/C_b$ [9].The titration data obtained were applied to construct the binding plots of r against C_{free} using the Eq. (1) that is the expression of scatchard analysis with a noncooperative and nonequivalent two-site binding model [16], where r is the moles of TPrPyP4 bound to per mole of G-quadruplex, n_1 and n_2 are numbers of equivalent binding sites, C_{free} is the molar concentration of free TPrPyP4, and K_1 and K_2 are equilibrium constants for two types of binding sites.

$$r=\frac{n_1K_1C_{free}}{1+K_1C_{free}}+\frac{n_2K_2C_{free}}{1+K_2C_{free}} \quad (1)$$

Two series of solutions were used for the continuous variation analysis experiments: one with a varying mole fraction of TPrPyP4 and G-quadruplex and another with varying concentration of TPrPyP4, while the sum of the TPrPyP4 and G-quadruplex concentration was kept at 10 μM. Absorption difference spectra were obtained by subtraction of the absorption spectrum for TPrPyP4 in the absence of G-quadruplexes from that in the presence of G-quadruplexes. The difference in the maximum absorbance values at two wavelengths (between 443 and 420 nm for $(TG_4T)4$, 440 and 420 nm for $(G_4T_4G_4)2$) was plotted versus the TPrPyP4 mole fraction to generate a Job plot [9,17,18].

2.3. Circular dichroism

CD experiments were performed at room temperature using a Jasco-820 spectropolarimeter. For each sample, at least three spectrum scans were accumulated in a 1 cm-path length cell at a scanning rate of 50 nm/min. CD spectra were collected in units of millidegrees versus wavelength and normalized to the total species concentrations. The concentrations of G-quadruplexes are 10 μM. The scan of the buffer alone was subtracted from the average scan for each sample.

2.4. Steady and time-resolved fluorescence spectroscopy

Steady and time-resolved fluorescence measurements were performed using FL920 fluorescence lifetime spectrometer (Edinburgh Instruments, Livingston, UK) operating in the time-correlated single photon counting (TCSPC) mode. Excitation wavelength is set at 430 nm, and the slit width is 3 nm for both excitation and emission for steady fluorescence experiment. The samples were excited by 406.8 nm picosecond pulsed diode laser with pulse width 64.2 ps for time-resolved fluorescence measurement. All decay traces were measured using 4096-channel analyzer. The time resolution per channel was 24 ps. The number of peak counts was approximately 7000. For data analysis commercial software by Edinburgh Instruments was used. The data were fitted using a reconvolution method of the instrument response function (IRF) producing χ^2 fitting values of 1–1.3.

3. Results and discussion

3.1. Structural characterization of G-quadruplex DNAs

CD has been used to examine the structures of quadruplex DNAs [19]. In order to get the exact information on the structures of $(TG_4T)4$ and $(G_4T_4G_4)2$ in Na^+ buffer, their structures were characterized by CD spectra (Fig. 1). CD spectrum of $(TG_4T)4$ presents the positive and negative peaks near 260 and 240 nm, respectively, which is the typical parallel-stranded tetramolecular G-quadruplex [20]. $(G_4T_4G_4)2$ exhibits a typical dimer hairpin antiparallel structure, with the strong positive and negative peaks at 295 and 265 nm, respectively [21].

3.2. Binding modes of TPrPyP4 to G-quadruplexes

To investigate the binding behaviors of TPrPyP4 to G-quadruplexes, we first measured the visible absorption titration spectra of TPrPyP4 by addition of the different concentrations of G-quadruplexes (Fig. 2).

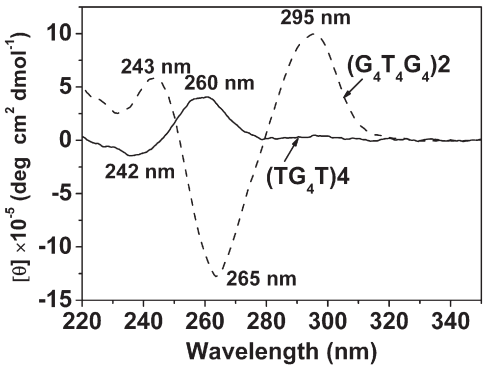

Fig. 1. CD spectra of $(TG_4T)4$ and $(G_4T_4G_4)2$ at a concentration of 10 μm in 10 mM Tris-HCl (pH 7.5) and 1 mM EDTA buffer containing 100 mM Na^+.

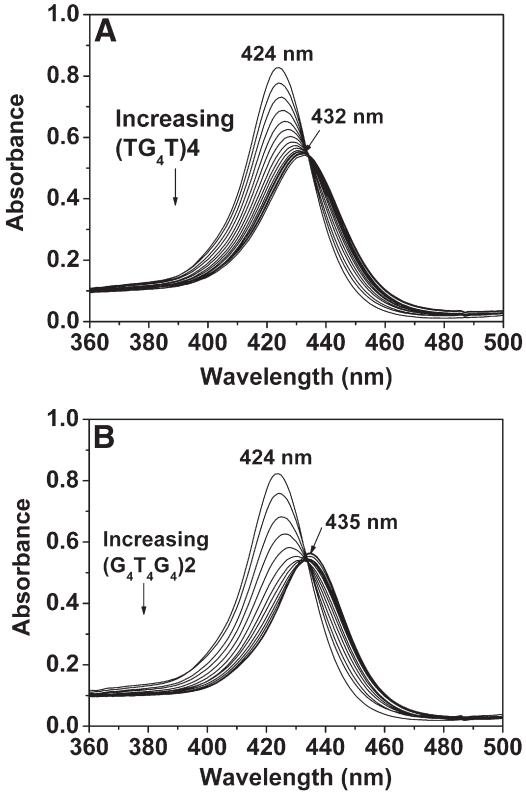

Fig. 2. Absorption titration of 4 μM TPrPyP4 with $(TG_4T)4$ (A) and $(G_4T_4G_4)2$ (B) G-quadruplexes in the presence of 100 NaCl. All spectra were measured in 10 mM Tris–HCl (pH 7.5) and 1 mM EDTA buffer solution.

The results show 8 nm red shift and 48% hypochromicity for $(TG_4T)4$, and 11 nm red shift and 54% hypochromicity for $(G_4T_4G_4)2$ in the Soret band of TPrPyP4 at the end of titration. In the case of duplex DNA, porphyrin intercalation is characterized experimentally by large red shift (>15 nm) and substantial hypochromicity of the Soret band (>35%), and the external groove binding mode of porphyrin is characterized by small red shit (<8 nm) and hypochromicity (<10%) [22]. The observed values of red shifts are smaller than those of the typical intercalation, but the large hypochromicities % are in the range of an intercalative binding. Since the end-stacking is not significant for long duplex DNA when compared with short G-quadruplexes, the above results suggest that terminal stacking on G-quartet should be possible, but we cannot exclude that TPrPyP4 interacts with G-quadruplexes via outside binding mode.

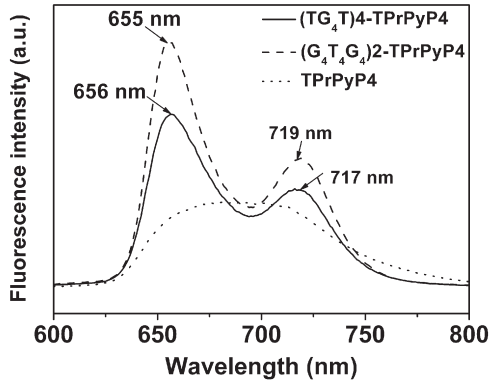

Fig. 3. Steady fluorescence spectra of free TPrPyP4 and G-quadruplex-TPrPyP4 complexes (G-quadruplex/TPrPyP4 = 2:1) in buffer solution containing 10 mM Tris–HCl (pH 7.5), 1 mM EDTA, and 100 mM Na^+.

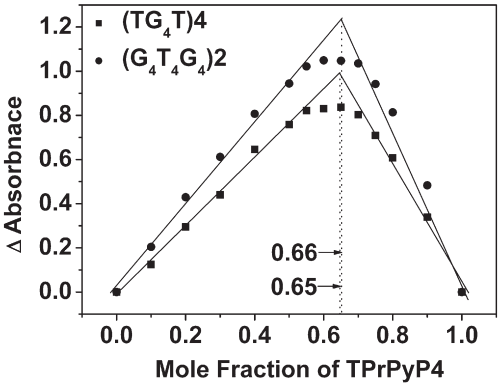

Fig. 4. Job plots of TPrPyP4 versus $(TG_4T)4$ and $(G_4T_4G_4)2$ G-quadruplexes in 10 mM Tris–HCl (pH 7.5), 1 mM EDTA, and 100 mM Na^+ buffer.

In order to further understand the binding mode of TPrPyP4 with each G-quadruplex, the steady-state fluorescence spectra were measured. Upon formation of a complex of TPrPyP4 with each G-quadruplex at a G-quadruplex/TPrPyP4 molar ratio of 2, the emission intensity of TPrPyP4 is increased significantly, and its broad fluorescence band is splitted two peaks near 655 and 715 nm (Fig. 3). It was reported that the outside bindings of TMPyP4 to both poly(dAdT)poly(dAdT) and RNA result in a splitting and significant increase in intensity of the emission spectrum of TMPyP4 [23,24]. So our results suggest that TPrPyP4 might interact with G-quadruplexes by outside binding mode.

To further clarify the binding mode, we measured the CD spectra of G-quadruplexes-TPrPyP4 complexes at a G-quadruplex/TPrPyP4 molar ratio of 2. Unfortunately, we did not observe the induced CD spectra of TPrPyP4. However, on the basis of the absorption and fluorescence spectra, we speculate that the bindings of TPrPyP4 to both G-quadruplexes may contain two modes of end-stacking and outside binding.

3.3. Binding stoichiometries and binding constants of TPrPyP4 to G-quadruplexes

In an attempt to determine the number of ligand-binding sites, the continuous variation analysis (Job plot) was performed. Fig. 4 shows that TPrPyP4 forms 2:1 complexes with both $(TG_4T)4$ and $(G_4T_4G_4)2$ G-quadruplexes in Na^+ buffer.

Furthermore, the absorption titration data obtained were fit to the Scatchard model using the Eq. (1) and the fit results are summarized in Table 1. The binding stoichiometries shown in Table 1 are comparable with those obtained by Job plot. The good fit results obtained by Eq. (1) (Fig. S1) indicate that there are two types of binding in the presence of Na^+, and one binding does not influence the binding on another site. Interestingly, a recent crystal structure reported by Neidle et al. also observed two independent binding sites for TMPyP4 in the complex with human telomeric G-quadruplex DNA [13].

The current results are substantial different from our previous results about interactions of TMPyP4 with $(TG_4T)4$ and $(G_4T_4G_4)2$ in Na^+-containing buffer [9], in which the binding stoichiometries are 2 and 4 for $(TG_4T)4$ and $(G_4T_4G_4)2$, respectively, especially, the bindings of TMPyP4 to both G-quadruplexes are cooperative. This comparison

Table 1
The binding stoichiometries (n_1, n_2) and binding constants (K_1, K_2) of free TPrPyP4 to G-quadruplexes in buffer containing 100 mM Na^+

G-quadruplexes	n_1	K_1 (M^{-1})	n_2	K_2 (M^{-1})
$(TG_4T)4$	0.92	8.04×10^7	1.36	9.08×10^5
$(G_4T_4G_4)2$	1.13	8.06×10^8	1.36	1.13×10^6

reveals that both the binding mode and binding stoichiometry of the porphyrins for G-quadruplexes may be modulated by the peripheral groups. It was reported that effects of *N*-methyl and *N*-propyl substituents on the binding interaction of TMPyP4 with duplex DNA are very small [15]. We speculate that *N*-methyl replaced by large *N*-propyl substituent in the porphyrin core inhibits further binding of TPrPyP4 to G-quadruplexes, because G-quadruplex contains four strands that are crowded when compared with duplex DNA containing two strands, it is difficult for G-quadruplex to bind much more porphyrins with the bulkyl *N*-propyl due to steric effect.

According to the fitting results, the binding affinity of TPrPyP4 for site 1 (K_1) exhibits about two orders of magnitude larger than that for site 2 (K_2) for the different forms of G-quadruplexes. This is consistent with the previous reports wherein porphyrin binding was indicated to present one secondary site with lower affinity [25,26]. More recently, the binding constants of some derivatives of porphyrin to c-MYC and telomeric G-quadruplexes have been determined, indicating that there are one higher and one lower affinity sites [27,28]. Combining the binding modes obtained by absorption and fluorescence spectroscopies, herein, we suggest that K_1 and K_2 values should be the binding constants of terminal stacking and outside binding, respectively.

3.4. Fluorescence lifetimes of TPrPyP4 in the different binding sites

In order to provide further insight into the binding sites of TPrPyP4 for each G-quadruplex, the time-resolved fluorescence spectra were measured, which gives the more detailed information of environment around a fluorophore [29]. Fig. 5 shows the fluorescence decays of TPrPyP4 in free form and G-quadruplex-TPrPyP4 complexes at 2:1 molar ratio of G-quadruplex to TPrPyP4. For free TPrPyP4, the fluorescence decay is monoexponential and the lifetime is 4.65 ns (Table 2). However, the fluorescence decays for G-quadruplex-TPrPyP4 complexes are multiexponential, requiring two lifetime components to give a satisfactory fit, which indicates the existence of two binding states of TPrPyP4, in which TPrPyP4 experiences different interactions and environments and hence has different quenching rates. These results further support the existence of two binding modes.

That TPrPyP4 is partitioned between two environments is also in accordance with the fit results obtained by absorption titration. The predominant, longer lifetimes (τ_2) of about 12 ns with fractional amplitudes of about 73% and 79% should be the characteristic of TPrPyP4 in an end-stacking conformation, in which the nonpolar microenvironment may inhibit the intramolecular quenching of the S1 state of TPrPyP4 [30]. The shorter lifetimes of about 6 ns with fractional amplitudes of about 29% and 21% suggest that TPrPyP4 is in an outside binding environment, where a slight decrease in the

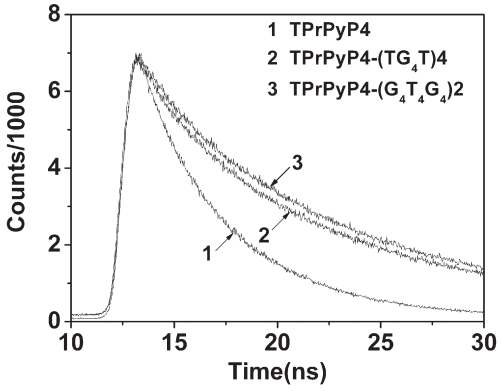

Fig. 5. Fluorescence decay curves of free TPrPyP4 and G-quadruplex-TPrPyP4 complexes (G-quadruplex/TPrPyP4=2:1) in buffer solution containing 10 mM Tris–HCl (pH 7.5), 1 mM EDTA, and 100 mM Na^+.

Table 2
The fluorescence lifetimes of free TPrPyP4 in the presence and absence of G-quadruplexes in buffer containing 100 mM Na^+

Compounds	τ_1(ns)	τ_2(ns)
TPrPyP4	4.65±0.01	0
$(TG_4T)4$-TPrPyP4	5.81±0.04	11.72±0.02
	(27.36±0.36%)	(72.64±0.32%)
$(G_4T_4G_4)2$-TPrPyP4	5.83±0.05	12.57±0.02
	(20.87±0.30%)	(79.13±0.32%)

τ_1 and τ_2 denote the fluorescence lifetimes that were obtained at 703 nm for free TPrPyP4, and 717 and 719 nm for complexes of (TG4T)4 and (G4T4G4)2 with TPrPyP4, respectively. The data in bracket are the respective fractional amplitudes.

polarity of the environment may protect the fluorescence of TPrPyP4 from the quenching action of intramolecular charge transfer state from the macrocycle to the propyl pyridine groups [30]. Based on these results, the major fraction of TPrPyP4 in solution containing G-quadruplexes is an end-stacking binding form, which can be attributed to the larger affinity of TPrPyP4 to the end-stacking binding site than to the outside binding site for G-quadruplexes.

In summary, two distinct nonequivalent binding sites of TPrPyP4 to $(TG_4T)4$ and $(G_4T_4G_4)2$ G-quadruplexes in the presence of Na^+ were confirmed by the Scatchard analysis and fluorescence lifetime measurement. The primary results show that TPrPyP4 interacts with G-quadruplexes by end-stacking and outside binding. The lifetimes and binding constants of TPrPyP4 in the end-stacking mode are larger than those in the outside binding mode for $(TG_4T)4$ and $(G_4T_4G_4)2$ G-quadruplexes.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bpc.2008.06.006.

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