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Synthesis of some multi-β-substituted cationic porphyrins and studies on their interaction with DNA

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Abstract—A series of multi-β-substituted cationic porphyrins, 2,3,12,13-tetraphenyl-5-(*N*-trimethyl-4-ammoniumphenyl)-10,15,20-triphenylporphyrin **2**; 2,3,12,13-tetramethyl-5-(*N*-trimethyl-4-ammoniumphenyl)-10,15,20-triphenylporphyrin **3**; 2,3,7,8,12,13,17,18-octaphenyl-5-(*N*-trimethyl-4-ammoniumphenyl)-10,15,20-triphenylporphyrin **4**, and 2,3,7,8,12,13,17,18-octaphenyl-5,10-di(*N*-trimethyl-4-ammoniumphenyl)-15,20-diphenylporphyrin **5**, have been synthesized. Their photooxidative abilities and interaction with DNA were investigated by UV, fluorescence, CD, and gel electrophoresis. It is found that substituents at β-position of the porphyrins have significant effect on interactions and binding mode of the porphyrins with DNA. Increasing positive charges in the porphyrins strengthen their interactions with DNA.

1. Introduction

Interactions of a variety of drugs and other relatively small molecules with DNA have aroused great interest of many groups.[1–4] Among these agents, porphyrin family has caused particular attention.[5–8]

Fiel and collaborators[9] had studied the interaction of porphyrins with nucleic acid and found that a variety of porphyrins could bind to DNA.[10–12] As the backbone of nucleic acid has many negative charges, cationic porphyrin derivatives will be more easy to bind to DNA. One widely investigated cationic porphyrin is tetra-(4-*N*-methylpyridium)porphyrin [T4MPyP]. T4MPyP and its analogues have been known to bind to DNA.[13–17]

Natural porphyrin derivatives such as the photosynthetic centers, vitamin B_{12} and P-450[18–20] are β-substituted porphyrins. Their nonplanar conformation was affected by the β-substituents. We could imagine that interactions of nonplanar porphyrins with DNA will have different binding modes compared to that of planar T4MpyP. This assumption was made and supported by Neidle's group.[21] They found that Ni^{2+}-T4MPyP had a highly nonplanar conformation whereas T4MPyP was a typically planar, and the binding mode to DNA was totally changed from intercalation (for planar T4MPyP) to minor groove binding (for nonplanar NiT4MPyP). It suggests that porphyrin structure change can induce their DNA binding mode. Recently, several groups have intensively studied the effect of β-substituents on porphyrin properties.[22–25] It is found that substituents at β-position of porphyrins exerted much larger steric and electronic effects on the porphyrin ring than those at *meso*-aryl position.[26] Therefore, synthesis of β-substituted cationic porphyrins and study on their interaction abilities to DNA will be of great significance for biological and clinical applications. In our previous paper,[27] we synthesized two kinds of β-tetrasubstituted cationic porphyrins and preliminarily investigated their photocleavage abilities to plasmid DNA. Herein, we shall report in detail our synthesis of β-octa-substituted cationic porphyrins and their interactions with DNA.

2. Results

2.1. Synthesis of β-substituted cationic porphyrins

Four β-substituted cationic porphyrins **2**, **3**, **4**, and **5** have been synthesized and shown in Scheme 1.

β-Tetrasubstituted cationic porphyrins **2** and **3** were prepared from β-tetrabromo porphyrin as starting material by following the general method shown in Scheme 2. After bromination of compound **6** with NBS, tetrabromo porphyrin **7** was obtained.[28] Mono-4-nitro-phenyl porphyrin **8** was obtained by reacting fuming HNO_3 with porphyrin **7** in $CHCl_3$ at 5 °C.[29] After coupling boronic acids with compound **8** by

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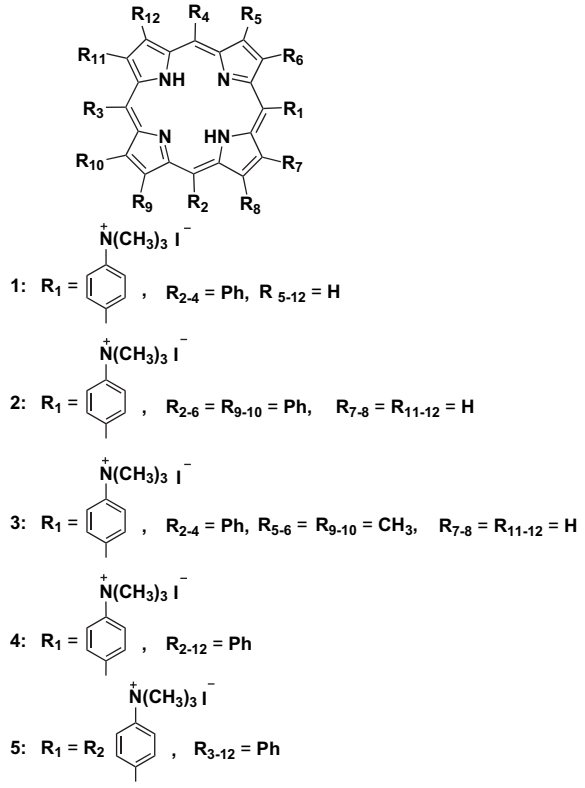
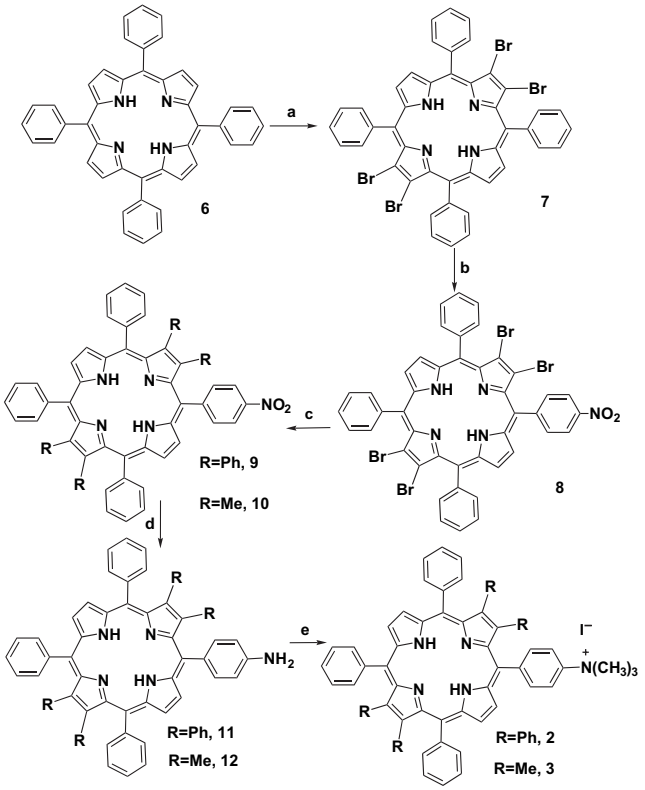


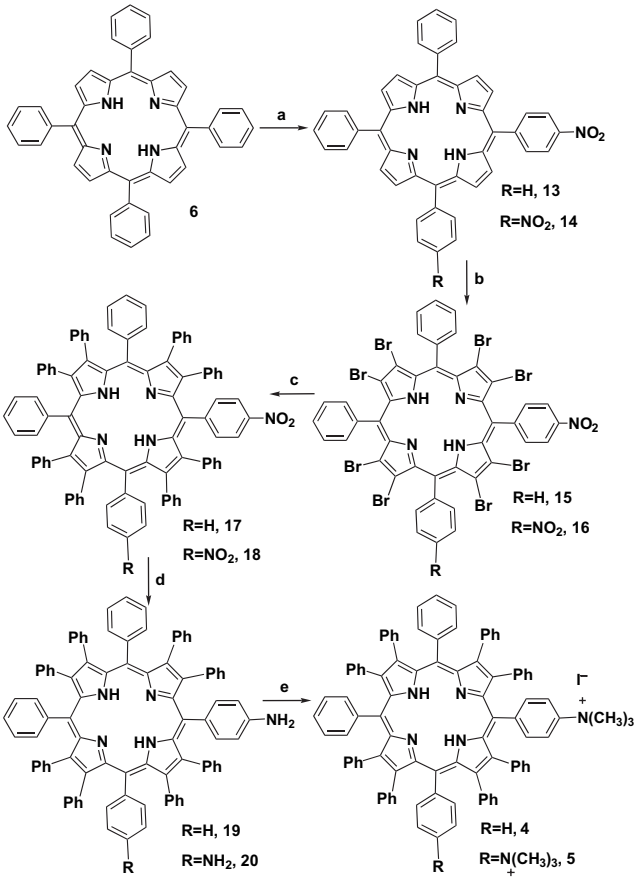
Scheme 1. Structures of the β-substituted cationic porphyrins.



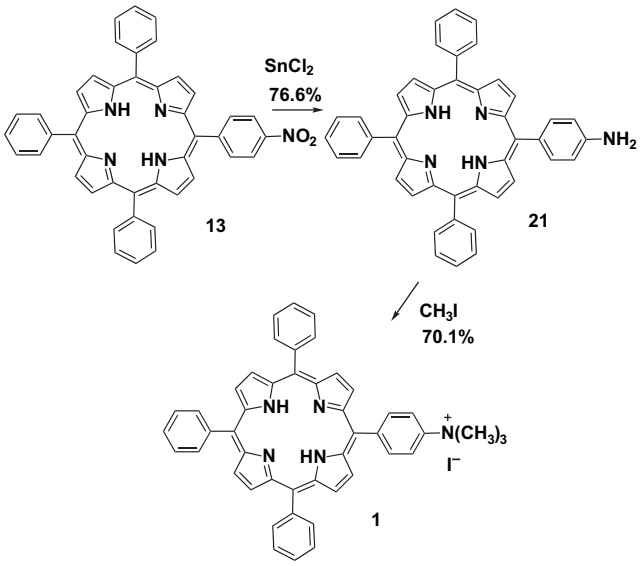
Scheme 2. Synthesis of quaternary ammonium porphyrins **2** and **3**: (a) NBS, $CHCl_3$, reflux 3 h, 75.5%; (b) fuming HNO_3, 5 °C, 3 h, 24.3%; (c) $MeB(OH)_2$, K_2CO_3, $Pd(Ph_3P)_4$, toluene, 95–105 °C, 3 days, 87.2%; $PhB(OH)_2$, Na_2CO_3, $Pd(Ph_3P)_4$, DMF, 12 h, 75.9%; (d) $SnCl_2\cdot 2H_2O$, concd HCl, 70 °C, 3 h (for Me, 87.7%), 12 h (for Ph, 82.6%); (e) CH_3I, DMF, 40 °C, 5 h, 61.1% (Me), 42.3% (Ph).

Suzuki coupling reaction,[30] porphyrins **9** and **10** were obtained in good yields.[31] $SnCl_2$ was chosen as the reducing agent to nitro porphyrin by Kruper[29] because it was moderate to the porphyrin ring but effective to nitro group. It took long time to convert the nitro group into amino group. After methylation of the amino group of compounds **11** and **12**, the desired β-tetrasubstituted cationic porphyrins **2** and **3** were obtained.

β-Octaphenyl substituted cationic porphyrins **4** and **5** were prepared from β-octabromo substituted porphyrins by following the general method shown in Scheme 3. Mono nitrated porphyrin **13** was obtained in high yield by mixing starting material TPP **6** with fuming HNO_3[29] with dinitrated porphyrin **14** obtained in low yield (<20%) by over nitration. Because of the strong oxidizing property of fuming HNO_3, many by-products would be formed as increase of the quantity of fuming HNO_3 and the reaction time. $NaNO_2$ in TFA is a moderate alternative nitrating agent. Dinitrated porphyrin was obtained easily and rapidly under this condition with good yield (>45%).[32] Octabromination of porphyrin **13** and **14** was realized by adding Br_2[28] because of its strong brominating ability. Nitro group increases the acidity of the proton on the central nitrogen, allowing the metalation at room temperature. After metalation by



Scheme 3. Synthesis of quaternary ammonium porphyrins **4** and **5**: (a) fuming HNO_3, 5 °C, 3 h (for 13, 50.5%); $NaNO_2$, TFA, rt, 90 s (for **14**, 45.7%); (b) (1) $Cu(OAc)_2$, $CHCl_3$, rt, 1 h; (2) Br_2, $CHCl_3$, rt, 1 day; (3) $HClO_4$, $CHCl_3$, rt, 12 h, 64.2% (**15**), 67.3% (**16**); (c) $PhB(OH)_2$, K_2CO_3, $Pd(Ph_3P)_4$, toluene, 95–105 °C, 7 days, 55.6% (**17**), 52.3% (**18**); (d) $SnCl_2\cdot 2H_2O$, concd HCl, 80 °C, 2 h, 60.8% (**19**); 58.4% (**20**); (e) CH_3I, DMF, 45 °C, 1 day, 85.5% (**4**), 78.9% (**5**).



Scheme 4. Synthesis of quaternary ammonium porphyrin **1**.

superfluous copper salt, Br_2 was added without removal of the remnant copper salt to complete the bromination of porphyrin **13** and **14**. This process prevents the demetalation and induce the completion of octabromination. After demetalation by $HClO_4$, β-octabromo porphyrins **15** and **16** were obtained. Seven days were taken to complete the coupling reaction. Because of the strong steric effect of the β-phenyl group and the poor water solubility, the nitro group on the *meso*-phenyl was difficult to be reduced in concd HCl. Therefore, addition of a small quantity of DMF as co-solvent in the reaction would solve this problem by increasing the solubility of porphyrin to obtain the desired product in good reduction yield. Finally, methylation of the amino groups in porphyrin **19** and **20** was performed by mixing with methyl iodide in DMF, respectively. Porphyrins **4** and **5** were obtained in the yields of 85.5 and 78.9%.

For control experiments, we synthesized cationic porphyrin **1** without β-substituents by mixing porphyrin **21**[29] with methyl iodide in DMF and the yield was 70.1% (Scheme 4).[33] New compounds have been fully characterized by ^{1}H NMR, HRMS, and UV.

2.2. Binding studies

UV–vis absorption spectroscopy, CD and fluorescence were used to determine the bindings of β-substituted cationic porphyrins **1–5** to DNA. In general, hypochromic shift and

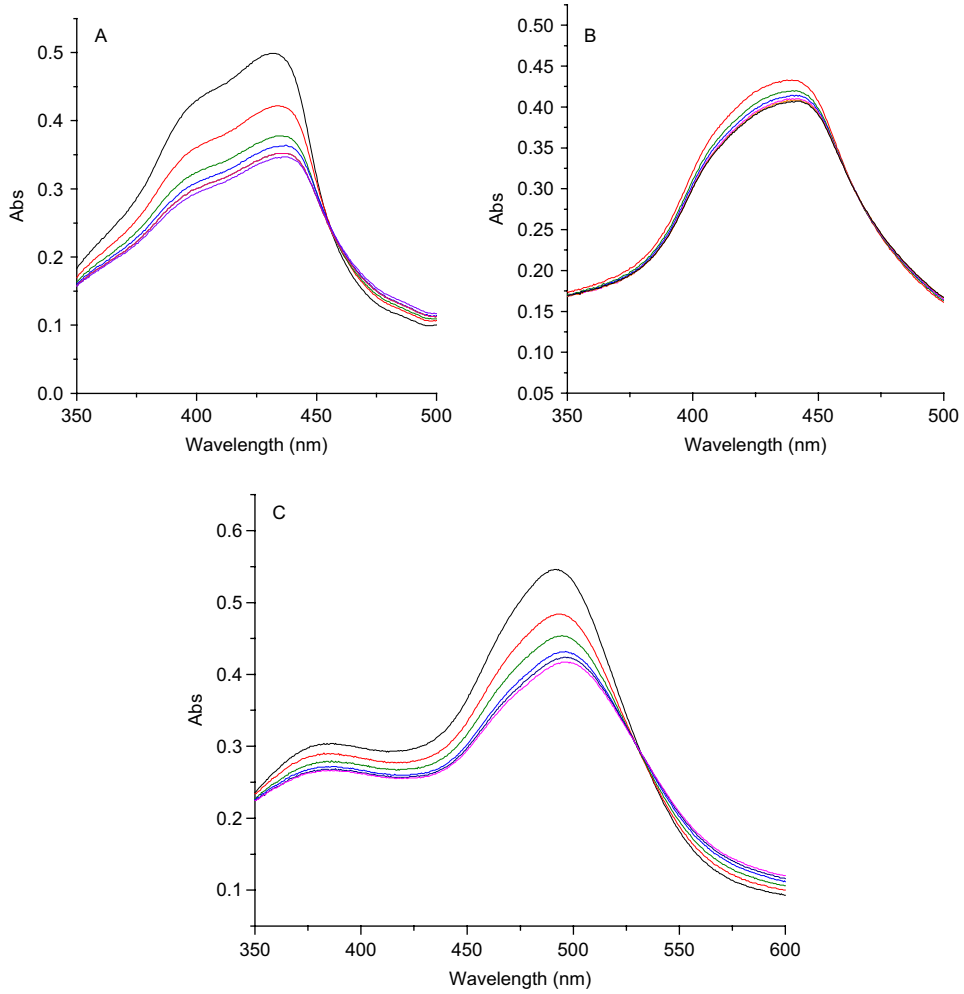


Figure 1. UV–vis absorbance spectra of 10 μM porphyrin **1** (A), **3** (B), and **5** (C) with increasing concentrations of calf thymus DNA base pair from 0, 1.16, 3.32, 4.48, 8.96, and 17.92 μM, respectively. (from upper to lower). The spectra were recorded in 0.05 M Tris–HCl, (pH 7.3), 2% DMF, containing 0.1 M NaCl.

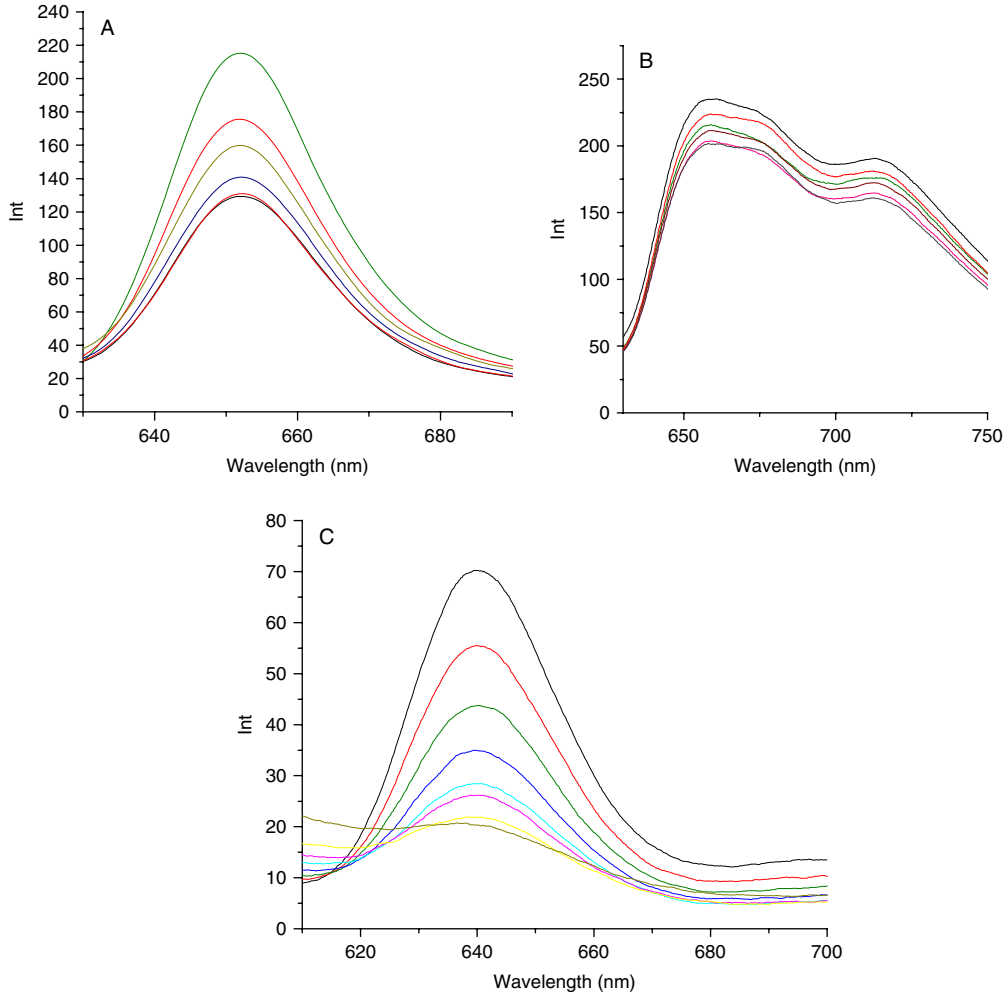


Figure 2. Fluorescence emission spectra of porphyrin **1** (A), 10 μM; **3** (B), 10 μM; **5** (C), 20 μM with increasing concentrations of calf thymus DNA. [Bp]=0, 1.16, 2.32, 3.48, 4.64, 6.96 μM for A and B. [Bp]=0, 0.58, 1.16, 1.74, 2.32, 2.90, 3.48, 4.06 μM. All curves decreased with the addition of DNA. The spectra were recorded in 3 mM Tris–HCl, 0.3 mM EDTA (pH=8.0), 2% DMF.

bathochromic shift in the Soret band, and the change of CD signal of porphyrins upon interaction with DNA indicate binding modes of porphyrins to DNA. The change of the fluorescence emission spectra of porphyrins upon mixing with DNA can point to the nature of the binding.[34]

2.3. UV–vis absorption spectroscopy

The effect of stoichiometric addition of calf thymus DNA on the UV–vis absorption spectra of porphyrins **1**, **3**, and **5** was shown in Figure 1. Increasing the concentration of CT DNA resulted in a hypochromic shift at the Soret band of porphyrins.

In Figure 1, isosbestic point can be observed in the titration curve for each porphyrin, which suggests the formation of a well-defined porphyrin-DNA complex.[35]

As for binding affinity, the most steric hindered porphyrin **5** with two positive charges exhibits the largest binding constant, suggesting that the number of positive charge is essential for the binding. The Columbic force between the cation of porphyrin and the phosphate of nucleotide could favor the interaction of porphyrin with DNA. It is interesting to find that β-phenyl substituted porphyrin **2** and **4** possess stronger binding ability than the less steric hindered β-methyl substituted porphyrin **3**. Probably, electronic effect, at this time, exerts its influence to compensate the disadvantage caused by steric effect on the binding.

2.4. Fluorescence studies[36]

The effect of stoichiometric addition of calf thymus DNA on the fluorescence spectrum of porphyrins **1**, **3**, and **5** is shown in Figure 2, these three porphyrins display distinct fluorescence emission spectrum.

β-Unsubstituted porphyrin **1** (Fig. 2A) displays an intermediate decrease by about 40.3% during the DNA titration, indicating intermediate binding ability compared to porphyrin **3** and **5**. β-Tetramethyl porphyrin **3** (Fig. 2B) exhibits a weak binding by the result of 15.1% maximum hypochromicity. Although the weakest among all the cationic porphyrins, the fluorescence of the dicationc β-octaphenyl porphyrin **5** (Fig. 2C) is quenched rapidly and dramatically (70.1%) by CT DNA, suggesting the strongest binding affinity, that is in good accordance with the result obtained by EB competitive method.

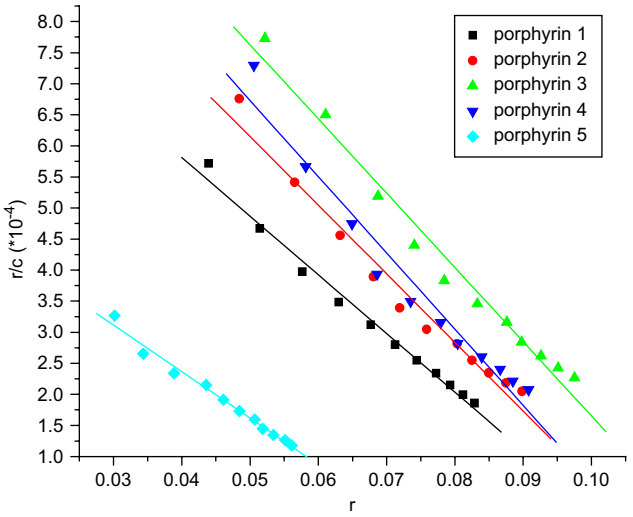


Figure 3. The Scatchard plot drawn by EB fluorescence competitive method. All [porphyrin]=2 μM, DNA [bp]=5.80 μM in 0.05 M Tris–HCl, (pH 7.3), 2% DMF, containing 0.1 M NaCl.

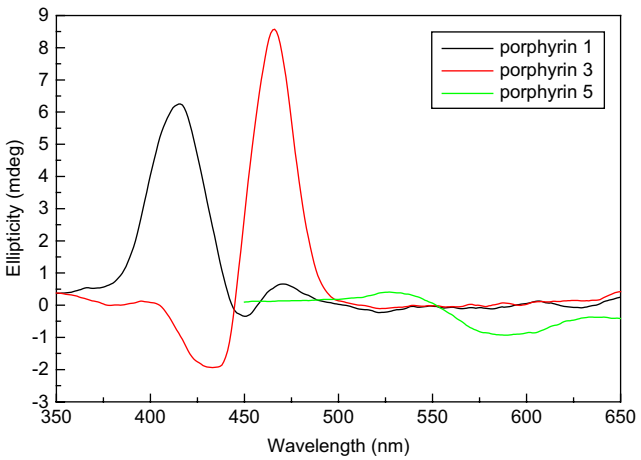


Figure 4. Induced CD spectra of 20 μM porphyrin **1**, **3**, and **5** in the presence of calf thymus DNA at R=0.5. The spectra were recorded in 3 mM Tris–HCl, 0.3 mM EDTA (pH 8.0), 4% DMF.

The binding affinity between porphyrin and DNA is expressed as shown by the apparent binding constants (K_{app}). It is calculated and determined by ethidium bromide (EB) fluorescence competitive method. In this method, EB is usually used as DNA probe and competed DNA binding sites with porphyrin. The results can be reflected by variation of fluorescence intensity. All measurements and calculation methods were performed by the reported methods.[37,38] The Scatchard plot is drawn by this method and had been shown in Figure 3.

Data of UV-titration and K_{app} are summarized in Table 1. As shown in Table 1, porphyrin **1** displays the largest hypochromicity of 32.0%, but its moderate bathochromic shift (6 nm) implies that this compound adopts a nonintercalation mode with CT DNA. The bathochromic shift values obtained for the interactions of porphyrin **2**, **3**, **4**, and **5** with calf thymus DNA are small and suggested that the binding mode of these four β-substituted porphyrins should not be intercalation.[39] Obviously steric hindrance of these porphyrins controls their binding mode with CT DNA.

Table 1. Values of hypochromicity, bathochromic, and binding constant

Por	% Hypochromicity with CT DNA	Bathochromic shift (nm)	K_{app}
1	32.0	6	2.00×10^5
2	10.7	<3	1.77×10^5
3	14.3	6	3.53×10^4
4	16.5	<3	1.01×10^5
5	24.0	5	7.54×10^5

2.5. Circular dichroism (CD) studies

To further clarify the binding mode, the induced CD spectra of the porphyrins were recorded at the presence of calf thymus DNA. Figure 4 shows the induced CD spectra of porphyrins **1**, **3**, and **5** bound to calf thymus DNA. In the case of duplex DNA, a positive induced CD band in the Soret region indicates its groove binding, and a negative induced CD band indicates intercalation.[6–8] Conservative CD signal is a signature of self-stacked porphyrins bound externally on the polymer surface.[6–8] Porphyrin **1** shows a strong positive peak and a weak positive peak (black); porphyrin **3** shows a strong positive peak and a weak negative peak (red), whereas porphyrin **5** shows conservative CD profiles (green). No ellipticity is in the CD of either porphyrins or DNA alone as control experiment. Porphyrins **1** and **3** should be located at the groove of calf thymus DNA and might interact with DNA in groove binding mode. Conservative CD signal of porphyrin **5** suggests its external binding mode on the DNA surface.

2.6. Structural optimization

The structural optimization of porphyrin **1**, **2**, **3**, **4**, and **5** was calculated by semiempirical AM1 method and shown in Figure 5. Porphyrin **1** without β-substituents has a nearly planar ring (Fig. 4A), whereas the steric effect of nonplanar porphyrins **2**, **3**, **4**, and **5** might block their intercalations into the base pair of DNA. Tetramethyl substituents at β-positions of porphyrin (Fig. 5C) might display moderate steric hindrance, and the porphyrin ring has a little distortion. Phenyl substituted porphyrins (Fig. 5B, D and E) show much more intense steric effect. Porphyrin **5** has eight phenyl groups at its β-position, so the steric hindrance effect is the largest and the porphyrin ring adopts a saddle conformation. Further computational research on the binding mode of these porphyrins with DNA is underway.

2.7. Photosensitized cleavage of DNA

A convenient way to test the ability of porphyrins to photodamage DNA is to measure the conversion of supercoiled DNA (form I) to form II.[40] The cleaving abilities of porphyrins **1**, **2**, **3**, **4**, and **5** to plasmid DNA (pBR322) upon illumination were investigated using agarose gel electrophoresis. All experiments were performed in buffer (pH=8.0, 3 mM Tris–HCl, 0.3 mM EDTA, 2% DMF) and the samples were irradiated by high-pressure mercury lamp 50-W for 60 min at room temperature and the distance from the sample to the filament of the mercury lamp was 20 cm. Results of DNA cleavage are illustrated in Figure 6.

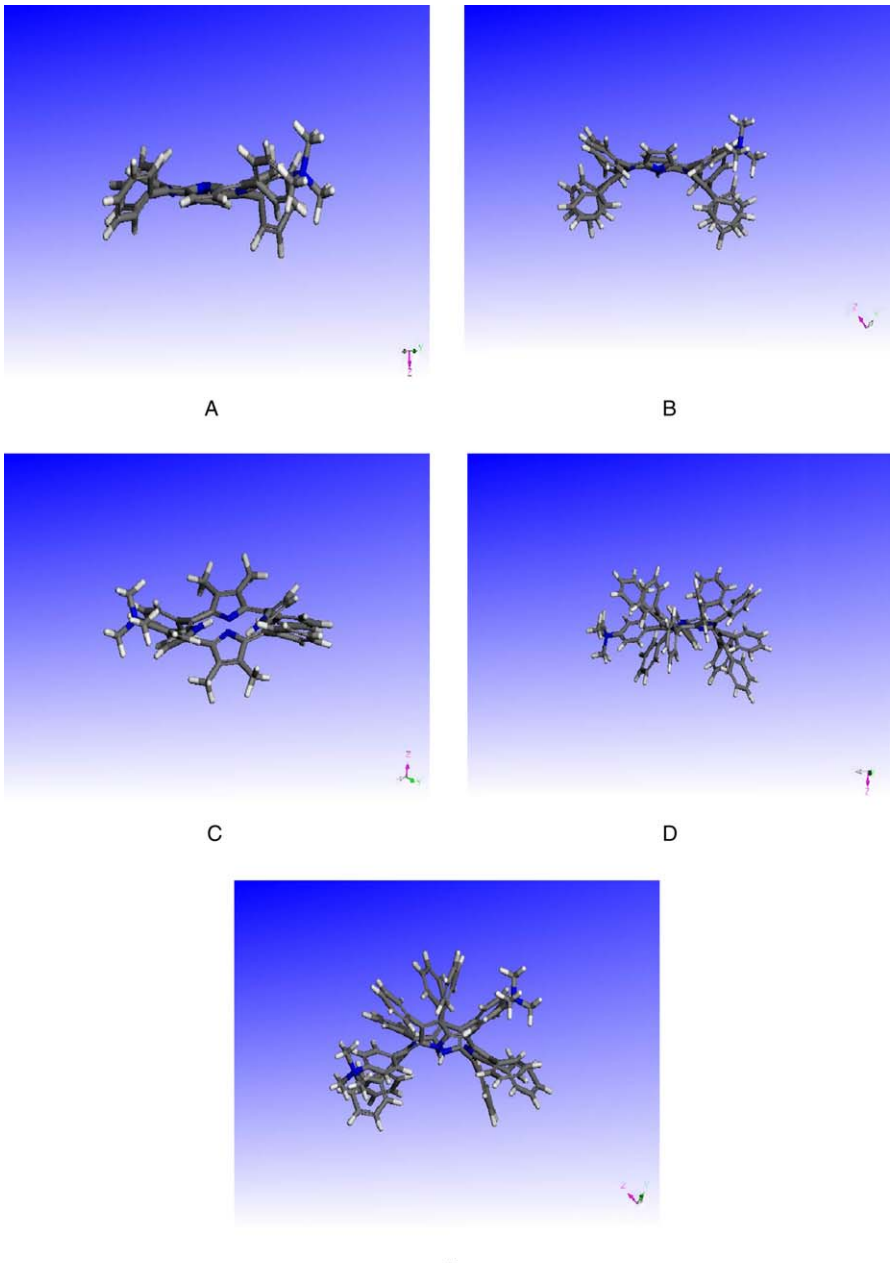


Figure 5. Structural optimization of porphyrin **1** (A), **2** (B), **3** (C), **4** (D), and **5** (E). The geometry of compounds was optimized by semiempirical AM1 method.

Control experiments indicated that no cleavage of DNA happened in the presence of DMF (Fig. 6A, lane 2). No cleavage of DNA was also observed if compound **3** was mixed with DNA without illumination (Fig. 6A, lane 3). In the presence of light, most cationic porphyrins, except β-nonsubstituted porphyrin **1**, were able to convert supercoiled DNA into form II at the concentration of 20 μM. Comparing with the mono-cationic β-substituted porphyrin **2**, **3**, and **4**, tetramethyl substituted porphyrin **3** had the strongest ability to cleave DNA. Tetraphenyl substituted porphyrin **2** had the weakest ability to cleave DNA among these three mono cationic porphyrins (Fig. 6A). Dicationic porphyrin **5** displayed stronger cleavage ability than all mono-cationic porphyrins. For porphyrin **5** (5 μM), the amount of DNA converted to form II in 60 min was almost 90%, but 50% for the strongest mono cationic porphyrin **3** at the same concentration (Fig. 6B). It suggests that charges might be one of important factor to interact with DNA.

3. Discussion

It is reported that the species responsible for causing DNA cleavage is believed to be singlet oxygen.[41–43] Our previous research[27] suggested that the rate of singlet oxygen production for β-nonsubstituted porphyrin and β-tetrasubstituted porphyrin was not significantly different. Measurement of singlet oxygen production by measuring the decomposition of 1,3-diphenylisobenzofuran (DPBF)[44–47] for these porphyrins **1**, **2**, **3**, **4**, and **5** has been carried out and the results are shown in Figure 7. The slope of the plots of bleached absorption versus illumination time is proportional to the rate of

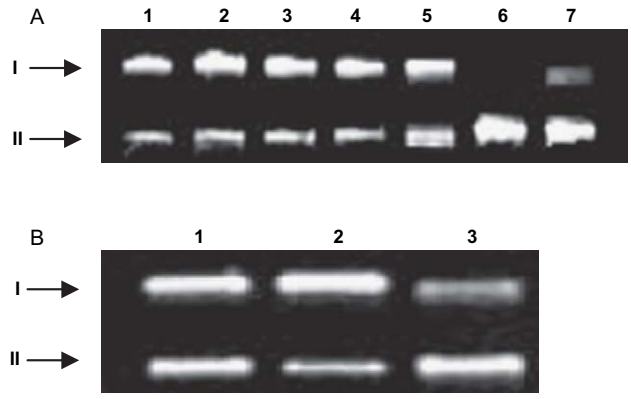


Figure 6. Agarose gel electrophoresis (1%) of supercoiled pBR322 DNA photosensitized with porphyrin **1**–**5**. 10 μL reaction mixtures contained 75 ng of plasmid DNA, 3 mM Tris–HCl, 0.3 mM EDTA (pH 8.0), 2% DMF. (A): lane 1: DNA+*hν* (60 min); lane 2: DNA+DMF (2%)+*hν* (60 min); lane 3: DNA+**3** (20 μM); lane 4: DNA+**1** (20 μM)+*hν* (60 min); lane 5: DNA+**2** (20 μM)+*hν* (60 min); lane 6: DNA+**3** (20 μM)+*hν* (60 min); lane 7: DNA+**4** (20 μM)+*hν* (60 min). (B): lane 1: DNA+**3** (5 μM)+*hν* (60 min); lane 2: DNA+**4** (5 μM)+*hν* (60 min); lane 3: DNA+**5** (5 μM)+*hν* (60 min).

production of singlet oxygen.[44–47] It is found that the rates of singlet oxygen production for these five porphyrins are not significantly different from each other (Table 2). Therefore, substitution at β-position of these porphyrins does not change the yields of singlet oxygen production. It implies that the photocleavge abilities of DNA by these differently β-substituted porphyrins are probably related to their conformations.

Many factors affect the porphyrin's interaction with DNA. In our case, the steric effect of the porphyrin skeleton and the number of charge on the porphyrin are the primary factors to influence their efficiency to bind with and cleave DNA. Since porphyrin **1** has the least hindrance and electronic effect compared to other cationic β-substituted porphyrins, it implies that the unfavor binding position between porphyrin

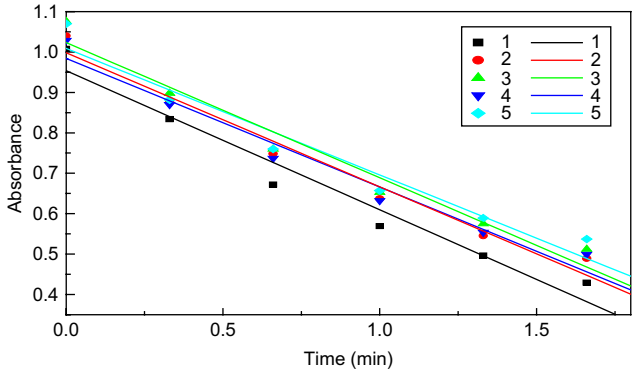


Figure 7. Decomposition of DPBF by compounds **1**, **2**, **3**, **4**, and **5**. Porphyrins (1 μM) and DPBF (100 μM) were irradiated in solution (3 mM Tris–HCl, 0.3 mM EDTA (pH 8.0), 2% DMF).

Table 2. The slopes (*S*) of the plots of bleached absorption of DPBF by photosensitization of **1**, **2**, **3**, **4**, and **5**

	1	**2**	**3**	**4**	**5**
S	−0.34	−0.33	−0.33	−0.32	−0.31

1 and DNA occurs, which induces the weakest ability to cleave DNA. Among porphyrins **2**, **3**, and **4**, all with one positive charge, porphyrin **3** with electron rich methyl groups induces more DNA cleavage under illumination although it has a weaker binding constant.

The number of charges on the porphyrin ring is another important factor to affect the cleavage ability of porphyrin. Obviously, the Columbic force between positive and negative charges strengthen the interaction of porphyrin and DNA.[48] Our experimental data indicates that, compared to other mono cationic porphyrins, dicationic porphyrin **5** upon DNA addition displays strong hypochromic shift in UV–vis absorbance spectra, novel hyperchromic shift in fluorescence emission spectrum and the best DNA cleavage ability. It may have the most efficient binding mode among these five porphyrins.

4. Conclusion

Five cationic porphyrins **1**, **2**, **3**, **4**, and **5** including four β-multisubstituted porphyrins **2**, **3**, **4**, and **5** have been synthesized and characterized. Their structures were optimized by semiempirical AM1 method. The results indicate that β-unsubstituted porphyrin has a planar ring structure while the substituents at β-position convert the porphyrin ring to distorted ones. The UV–vis absorption, fluorescence, CD, and DNA photocleavage evidence from the present study indicates that β-substituted cationic porphyrins bind to and photocleave DNA efficiently. CD spectra indicate that porphyrin **1** interacts with DNA in groove binding mode. Substituents on β-position of the porphyrins change their binding modes and intensify their interaction with DNA. Because of the differences on hypochromicity of Soret band by DNA addition and DNA photocleavage ability, octaphenyl substituents on β-position make porphyrin having a more efficient binding mode than the tetraphenyl substituted one. Our results also suggest that number of positive charge in the porphyrins plays an important role in the interaction with DNA. β-Octaphenyl dicationic porphyrin shows marked change both on UV–vis absorption and fluorescence intensity by adding calf thymus DNA and it therefore has the strongest interaction with DNA. Our further studies on the relationship of DNA site-specific binding with the β-substituted effects are undergoing.

5. Experimental

5.1. General experimental information

All chemicals were of reagent grade. $CHCl_3$ was washed by H_2O, followed by refluxing with CaH_2, distilled over CaH_2, and kept over 4-Å molecular sieves. NMR spectrum was recorded on a Varian Mercury-VX300 spectrometer at 300 MHz, MS was recorded on a Brucker Daltonics APE XII 47e and VG-707V-HF mass spectrometer. UV–vis spectra and binding constant measurement of DNA were carried out on UV–vis Spectrophotometer (Shimadzu). Fluorescence studies were performed on a JASCO fluorescence spectrometer. Circular Dichroism spectrum was recorded on a Jasco J-810 spectropolarimeter. In UV–vis spectra,

fluorescence, CD, and DNA photosensitized cleavage studies, 2–4% DMF was added to increase the solubility of porphyrins in water.

5.2. Synthesis of porphyrins

5.2.1. 2,3,12,13-Tetrabromo-5-(4-nitrophenyl)-10,15,20-triphenylporphyrin (8). Porphyrin **7** (1 g, 1.08 mmol) was dissolved in chloroform and degassed by nitrogen for 10 min. Fuming nitric acid (0.87 mL, 1.3 g, 20.52 mmol) was added dropwise and the solution was stirred at 0–5 °C for 3 h. The reaction mixture was quenched by adding cold water and washed with H_2O. The organic layer was dried (Na_2SO_4) and evaporated to afford a crude product, which was purified by column chromatography on silica gel using $CHCl_3$–hexane (7:3) as eluent. Crystallization from CH_2Cl_2–MeOH gave porphyrin **8** in a yield of 24.3%. ^{1}H NMR ($CDCl_3$, 300 MHz): −2.80 (br s, 2H, pyrrole), 7.78–7.80 (m, 9H, 3,4,5-phenyl), 8.17 (d, J=5.4 Hz, 6H, 2,6-phenyl), 8.38 (d, J=8.4 Hz, 2H, 2,6-nitrophenyl), 8.65 (d, J=8.7 Hz, 2H, 3,5-nitrophenyl), 8.70–8.75 (m, 4H, β-pyrrole); UV–vis ($CHCl_3$): λ_{max} (nm, log ε)=439 (5.29), 505.5 (3.62), 535.5 (4.15), 644.0 (3.53), 687.0 (3.93). FABMS: $C_{44}H_{26}N_5O_2Br_4$ $[M+1]^+$: found 976, calcd 976.

5.2.2. 2,3,12,13-Tetraphenyl-5-(4-nitrophenyl)-10,15,20-triphenylporphyrin (9). A 50-mL telfon-stoppered flask was charged with porphyrin **8** (113 mg 0.1 mmol), $PhB(OH)_2$ (141 mg, 1.1 mmol, 10 equiv), $(Ph_3P)_4Pd$ (54 mg, 0.05 mmol, 0.4 equiv), 2 M Na_2CO_3 (1.2 mL, 2.3 mmol, 20 equiv), and DMF (20 mL). The brown suspension was degassed by freeze-pump-thaw method (three cycles), and then was heated at 90–100 °C under N_2 for 12 h. The reaction mixture was worked up by extracting with 50 mL CH_2Cl_2 and washed with water and brine. The organic layer was dried over anhydrous Na_2SO_4 and rotary evaporated to dryness. The crude product was purified by column chromatography on silica gel using CH_2Cl_2 as eluent to give porphyrin **9** (80 mg, 0.08 mmol). ^{1}H NMR ($CDCl_3$, 300 MHz): −2.14 (s, 2H, pyrrole), 6.76–6.80 (m, 20H, phenyl), 7.08–7.20 (m, 9H, 3,4,5-phenyl), 7.72 (s, 6H, 2,6-phenyl), 7.87 (d, J=7.5 Hz, 2H, 2,6-nitrophenyl), 7.94 (d, J=8.7 Hz, 2H, 3,5-nitrophenyl), 8.20–8.35 (m, 4H, β-pyrrole); UV–vis ($CHCl_3$): λ_{max} (nm, log ε)=436.0 (5.11), 498.5 (3.51), 529.0 (3.98), 642.5 (3.18), 683.5 (3.49); ESI HRMS for $C_{68}H_{46}N_5O_2$ $[M+H]^+$: found 964.3655, calcd 964.3646.

5.2.3. 2,3,12,13-Tetramethyl-5-(4-nitrophenyl)-10,15,20-triphenylporphyrin (10). A 50-mL telfon-stoppered flask was charged with porphyrin **8** (105 mg 0.1 mmol), $MeB(OH)_2$ (65 mg, 1.1 mmol, 10 equiv), $(Ph_3P)_4Pd$ (50 mg, 0.04 mmol, 0.4 equiv), anhydrous K_2CO_3 (297 mg, 2.1 mmol, 20 equiv), and toluene (20 mL). The brown suspension was degassed by freeze-pump-thaw method (three cycles), and then was heated at 90–100 °C under N_2 for 3 days. The reaction mixture was worked up by extracting with 50 mL CH_2Cl_2 and washed with water and brine. The organic layer was dried over anhydrous Na_2SO_4 and rotary evaporated to dryness. The crude product was purified by column chromatography on silica gel using CH_2Cl_2–MeOH (200:1) as eluent to give porphyrin **10** (70 mg, 0.1 mmol). ^{1}H NMR ($CDCl_3$, 300 MHz): −2.82 (s, 2H, pyrrole), 2.28–2.32 (m, 12H, CH_3), 7.58–7.68 (m, 9H, 3,4,5-phenyl), 7.98 (d, J=7.2 Hz, 6H, 2,6-phenyl), 8.13 (d, J=7.5 Hz, 2H, 2,6-nitrophenyl), 8.43 (d, J=7.5 Hz, 2H, 3,5-nitrophenyl), 8.16–8.39 (m, 4H, β-pyrrole); UV–vis ($CHCl_3$): λ_{max} (nm, log ε)=420.5 (5.22), 522.0 (3.95), 567.0 (3.08), 587.0 (3.51), 639.0 (3.18); ESI HRMS for $C_{48}H_{38}N_5O_2$ $[M+H]^+$: found 716.3009, calcd 716.3020.

5.2.4. 2,3,12,13-Tetraphenyl-5-(4-aminophenyl)-10,15,20-triphenylporphyrin (11) and 2,3,12,13-tetramethyl-5-(4-aminophenyl)-10,15,20-triphenylporphyrin (12). Nitroporphyrin (50 mg, 0.052 for **9**, 0.070 for **10**) was dissolved in concd HCl (10 mL) and degassed by nitrogen for 3 min followed by addition of $SnCl_2 \cdot H_2O$ (35 mg for **9**, 47 mg for **10**). The suspension was heated at 65–75 °C under N_2 for 3 h (over night for porphyrin **9**). The reaction mixture was quenched by cold water and concd aqueous ammonia (pH 8.0) and extracted by CH_2Cl_2. The organic layer was dried over anhydrous Na_2SO_4 and rotary evaporated to dryness. The crude product was purified by column chromatography on silica gel using CH_2Cl_2–MeOH (100:1 for **9**, 100:2 for **10**) as eluent to give the aminoporphyrin **11** (yield 82.6%) and **12** (yield 87.2%).

5.2.5. 2,3,12,13-Tetraphenyl-5-(4-aminophenyl)-10,15,20-triphenylporphyrin (11). ^{1}H NMR ($CDCl_3$, 300 MHz): −1.99 (s, 2H, pyrrole), 6.53 (d, J=7.2 Hz, 2H, 3,5-aminophenyl), 6.84–6.89 (m, 20H, phenyl), 7.22 (d, J=11.7 Hz, 9H, 3,4,5-phenyl), 7.62 (d, J=7.8 Hz, 2H, 2,6-aminophenyl), 7.81 (d, J=6.6 Hz, 6H, 2,6-phenyl), 8.34 (s, 3H, β-pyrrole), 8.48 (s, 1H, β-pyrrole); UV–vis ($CHCl_3$): λ_{max} (nm, log ε)=439.0 (5.21), 514.5 (3.94), 533.0 (4.02), 643.5 (2.78), 688.0 (3.81); ESI HRMS for $C_{68}H_{48}N_5$ $[M+H]^+$: found 934.3896, calcd 934.3904.

5.2.6. 2,3,12,13-Tetramethyl-5-(4-aminophenyl)-10,15,20-triphenylporphyrin (12). ^{1}H NMR ($CDCl_3$, 300 MHz): −2.81 (s, 2H, pyrrole), 2.32 (s, 9H, CH_3), 2.43 (s, 3H, CH_3), 6.94 (d, J=8.1 Hz, 2H, 3,5-aminophenyl), 7.61 (d, J=7.2 Hz, 9H, 3,4,5-phenyl), 7.75 (d, J=8.1 Hz, 2H, 2,6-aminophenyl), 7.99 (d, J=5.7 Hz, 6H, 2,6-phenyl), 8.34 (s, 3H, β-pyrrole), 8.44 (s, 1H, β-pyrrole); UV–vis ($CHCl_3$): λ_{max} (nm, log ε)=422.5 (5.35), 503.5 (3.92), 521.0 (4.17), 588.0 (3.87), 650.0 (3.86); ESI HRMS for $C_{48}H_{40}N_5$ $[M+H]^+$: found 686.3277, calcd 686.3278.

5.2.7. 5-(*N*-trimethyl-4-aminiumphenyl)-10,15,20-triphenylporphyrin (1); 2,3,12,13-tetraphenyl-5-(*N*-trimethyl-4-aminiumphenyl)-10,15,20-triphenylporphyrin (2); and 2,3,12,13-tetramethyl-5-(*N*-trimethyl-4-aminiumphenyl)-10,15,20-triphenylporphyrin (3). Aminoporphyrin (40 mg, 0.079 for **21**, 0.043 for **11**, 0.058 for **12**) and CH_3I (1 mL) were dissolved in 10 mL of DMF. The reaction mixture was stirred at 45 °C for 5 h and then added 50 mL of CH_2Cl_2 followed by washing with water and brine. The organic layer was dried over anhydrous Na_2SO_4 and rotary evaporated to dryness. The crude product was purified by crystallization from CH_2Cl_2–Et_2O to give salt **1** (yield 70.1%), **2** (yield 42.3%), and **3** (yield 61.6%).

5.2.8. 2,3,12,13-Tetraphenyl-5-(*N*-trimethyl-4-aminiumphenyl)-10,15,20-triphenyl porphyrin (2). Data provided in our previous paper.[27]

5.2.9. 2,3,12,13-Tetramethyl-5-(*N*-trimethyl-4-aminiumphenyl)-10,15,20-triphenyl porphyrin (3). ^{1}H NMR (DMSO-d_6, 300 MHz): −2.89 (s, 2H, pyrrole), 2.40 (s, 12H, CH_3), 3.88 (s, 9H, methyl), 7.75 (d, J=7.5 Hz, 9H, 3,4,5-phenyl), 7.90 (s, 2H, 3,5-aminophenyl), 8.00 (s, 6H, 2,6-phenyl), 8.30 (s, 4H, β-pyrrole), 8.37 (s, 2H, 2,6-aminophenyl); UV–vis (MeOH): λ_{max} (nm, log ε)=417.0 (5.20), 518.5 (3.90), 562.5 (3.26), 584.5 (3.51), 642.0 (3.30); ESI HRMS for $C_{51}H_{46}N_5$ [M^+-I^-]: found 728.3764, calcd 728.3748.

5.2.10. 2,3,7,8,12,13,17,18-Octabromo-5-(4-nitrophenyl)-10,15,20-triphenylporphyrin (15). Porphyrin **13** (407 mg, 0.62 mmol) was dissolved in 100 mL of chloroform followed by the addition of $Cu(OAc)_2\cdot H_2O$ (617 mg, 3.1 mmol, 5 equiv). The reaction mixture was stirred at room temperature for 1 h. After complete conversion to copper porphyrin as detected by TLC, liquid Br_2 was added to the reaction mixture directly. The solution was continually stirred for about 1 day at room temperature. Aqueous solution of sodium thiosulfate was added to quench the reaction. After removal of the excessive bromine, the reaction mixture was washed by H_2O for several times and then 20 mL of perchloric acid was added to the solution. The reaction mixture was stirred for about 8 h for demetallization. The organic layer was separated and washed with aqueous and solution of sodium bicarbonate and water, and dried over anhydrous Na_2SO_4. The organic mixture was rotary evaporated to give a solid. The crude product was purified by column chromatography on silica gel using CH_2Cl_2 as eluent to give porphyrin **15** (512 mg, 0.4 mmol). ^{1}H NMR ($CDCl_3$, 300 MHz): 7.80–7.87 (m, 9H, 3,4,5-phenyl), 8.23 (d, J=6.0 Hz, 6H, 2,6-phenyl), 8.44 (d, J=8.1 Hz, 2H, 2,6-nitrophenyl), 8.62 (d, J=7.8 Hz, 2H, 3,5-nitrophenyl); UV–vis ($CHCl_3$): λ_{max} (nm, log ε)=473 (5.17), 574 (3.84), 626 (4.00); ESI HRMS for $C_{44}H_{22}N_5O_2Br_8$ [M+H]$^+$: found 1291.5002 (4^{79}Br+4^{81}Br), calcd 1291.5158 (4^{79}Br+4^{81}Br).

5.2.11. 2,3,7,8,12,13,17,18-Octabromo-5,10-di(4-nitrophenyl)-15,20-triphenylporphyrin (16). Porphyrin **16** was synthesized by the same method as for porphyrin **15**. ^{1}H NMR ($CDCl_3$, 300 MHz): 7.70 (d, J=7.2 Hz, 6H, 3,4,5-phenyl), 8.20 (s, 4H, 2,6-phenyl), 8.42 (d, J=6.9 Hz, 4H, 2,6-nitrophenyl), 8.64 (d, J=8.4 Hz, 4H, 3,5-nitrophenyl); UV–vis ($CHCl_3$): λ_{max} (nm, log ε)=475 (5.10), 573 (3.84), 625 (3.92); ESI HRMS for $C_{44}H_{21}N_6O_4Br_8$ [M+H]$^+$: found 1336.4890 (4^{79}Br+4^{81}Br), calcd 1336.5009 (4^{79}Br+4^{81}Br).

5.2.12. 2,3,7,8,12,13,17,18-Octaphenyl-5-(4-nitrophenyl)-10,15,20-triphenylporphyrin (17). A 100-mL telfon-stoppered flask was charged with porphyrin **15** (100 mg 0.08 mmol), $PhB(OH)_2$ (190 mg, 1.5 mmol, 20 equiv), $(Ph_3P)_4Pd$ (72 mg, 0.06 mmol, 0.8 equiv), anhydrous K_2CO_3 (428 mg, 3.1 mmol, 40 equiv), DMF (5 mL), and toluene (50 mL). The brown suspension was degassed by freeze-pump-thaw method (three cycles), and then was heated at 90–100 °C under N_2 for 7 days. The reaction mixture was worked up by extracting with 50 mL CH_2Cl_2 and washed with water and brine. The organic layer was dried over anhydrous Na_2SO_4 and rotary evaporated to dryness. The crude product was purified by column chromatography on silica gel using CH_2Cl_2–MeOH (200:1) as eluent to give porphyrin **17** (55 mg, 0.04 mmol). ^{1}H NMR ($CDCl_3$, 300 MHz): 6.67–6.68(m, 40H, phenyl), 7.12 (s, 9H, 3,4,5-phenyl), 7.89 (d, J=8.4 Hz, 2H, 3,5-nitrophenyl), 7.93–7.99 (t, 6H, 2,6-phenyl), 8.06 (d, J=9.0 Hz, 2H, 2,6-nitrophenyl); UV–vis ($CHCl_3$): λ_{max} (nm, log ε)=469 (4.99), 562 (3.83), 617 (3.81); ESI HRMS for $C_{92}H_{62}N_5O_2$ [M+H])$^+$: found 1268.4884, calcd 1268.4898.

5.2.13. 2,3,7,8,12,13,17,18-Octaphenyl-5,10-di(4-nitrophenyl)-15,20-triphenylporphyrin (18). Porphyrin **18** was synthesized by the same method as for porphyrin **17**. ^{1}H NMR ($CDCl_3$, 300 MHz): 6.68–6.83 (m, 46H, phenyl and 3,4,5-phenyl), 7.53 (d, J=8.7 Hz, 4H, 3,5-nitrophenyl), 7.59 (d, J=7.5 Hz, 4H, 2,6-phenyl), 7.65 (d, J=8.7 Hz, 4H, 2,6-nitrophenyl); UV–vis ($CHCl_3$): λ_{max} (nm, log ε)=493 (4.89), 586 (3.15), 642 (3.56); ESI HRMS for $C_{92}H_{61}N_6O_4$ [M+H]$^+$: found 1313.4755, calcd 1313.4749.

5.2.14. 2,3,7,8,12,13,17,18-Octaphenyl-5-(4-aminophenyl)-10,15,20-triphenyl porphyrin (19). Porphyrin **17** (30 mg, 0.02 mmol) was dissolved in 6 mL of a mixed solvent (DMF–concd HCl=1:5). The mixture was degassed by nitrogen for 3 min followed by addition of $SnCl_2\cdot H_2O$ (16 mg, 0.07 mmol). The suspension was heated to 80 °C under N_2 for 3 h. The reaction mixture was quenched by adding cold water and concd aqueous ammonia (pH 8.0) and extracted by CH_2Cl_2. The organic layer was dried over anhydrous Na_2SO_4 and rotary evaporated to dryness. The crude product was purified by column chromatography on silica gel using CH_2Cl_2–MeOH (100:1) as eluent to give porphyrin **19** (18 mg, 0.01 mmol). ^{1}H NMR ($CDCl_3$, 300 MHz): 6.06 (d, J=8.1 Hz, 2H, 3,5-aminophenyl), 6.68–6.84 (m, 49H, phenyl and 3,4,5-phenyl), 7.38 (d, J=8.1 Hz, 2H, 2,6-aminophenyl), 7.59 (d, J=6.9 Hz, 6H, 2,6-phenyl); UV–vis ($CHCl_3$): λ_{max} (nm, log ε)=490 (4.88), 576 (3.11), 642 (3.51); ESI-MS for $C_{92}H_{63}N_5$ [M]: found 1238.7, calcd 1238.5; ESI HRMS for $C_{92}H_{64}N_5$ [M+H]: 1238.5156, calcd 1238.5158.

5.2.15. 2,3,7,8,12,13,17,18-Octaphenyl-5,10-di(4-aminophenyl)-15,20-triphenylporphyrin (20). Porphyrin **20** was synthesized by the same method as for porphyrin **19**. ^{1}H NMR ($CDCl_3$, 300 MHz): 6.05 (d, J=7.5 Hz, 4H, 3,5-aminophenyl), 6.68–6.74 (m, 46H, phenyl and 3,4,5-phenyl), 7.35 (d, J=7.5 Hz, 4H, 2,6-aminophenyl), 7.55 (d, J=6.6 Hz, 4H, 2,6-phenyl); UV–vis ($CHCl_3$): λ_{max} (nm, log ε)=501 (4.89); ESI HRMS for $C_{92}H_{64}N_6$ [M+H]$^+$: found 1253.5320, calcd 1253.5224.

5.2.16. 2,3,7,8,12,13,17,18-Octaphenyl-5-(*N*-trimethyl-4-aminiumphenyl)-10,15,20-triphenylporphyrin (4). Porphyrin **19** (18 mg, 0.01 mmol) and CH_3I (1 mL) were dissolved in 10 ml DMF. The reaction mixture was stirred at 45 °C for 1 day and then added 50 mL of CH_2Cl_2 followed by washing with water and brine. The organic layer was dried over anhydrous Na_2SO_4 and rotary evaporated to dryness. The crude product was purified by crystallization using DMF–CH_2Cl_2–Et_2O as eluent to give the salt **4** (17 mg, 0.01 mmol). ^{1}H NMR (DMSO-d_6, 300 MHz): 3.54–3.59 (m, 9H, methyl), 6.66–6.99 (m, 40H, phenyl), 7.06–7.21 (m, 9H, 3,4,5-phenyl), 7.31–8.48 (m, 10H, phenyl); UV–vis ($CHCl_3$): λ_{max} (nm, log ε)=498 (4.97), 648 (3.82); ESI

HRMS for $C_{95}H_{70}N_5$ [M−I]: found 1280.5626, calcd 1280.5616.

5.2.17. 2,3,7,8,12,13,17,18-Octaphenyl-5,10-di(*N*-trimethyl-4-aminiumphenyl)-15,20-diphenylporphyrin (5). Porphyrin **5** was synthesized by the same method as for porphyrin **4**. ^{1}H NMR (DMSO-d_6, 300 MHz): 3.50 (s, 9H, methyl), 3.54 (s, 9H, methyl), 6.69–6.86 (m, 40H, phenyl), 7.01–7.10 (m, 6H, 3,4,5-phenyl), 7.26–8.11 (m, 12H, phenyl); UV–vis ($CHCl_3$): λ_{max} (nm, log ε)=493 (4.94), 649 (3.92); ESI-MS for $C_{98}H_{78}N_6$ [(M−2I)/2]: found 669.8, calcd 669.8; ESI HRMS for $C_{98}H_{78}N_6$ [(M−2I)/2]: found 669.3138, calcd 669.3133.

5.3. UV–vis spectroscopy-titration and fluorescence-titration studies

Titration of the porphyrins (10 μM) with calf thymus DNA was performed at room temperature in a buffer (3 mL, pH 8.0, 3 mM Tris–HCl, 0.3 mM EDTA) containing 2% DMF (with 0.1 M NaCl for UV–vis). A stock solution of CT DNA was prepared and stored in distilled water. The total concentration of DNA in the system was from 1 μM to 20 μM.

5.4. Circular dichroism (CD) studies

The spectral bandwidth was 2 nm, and the cell length was 1 cm. Calf thymus DNA was added to the porphyrins (20 μM), and after an incubation period of 15 min, the samples were scanned in the visible region. *R* value, ratio of concentration of the porphyrins to concentration of DNA, was 0.5. Baseline was corrected using the same buffer before scanning the samples. The spectra were recorded in 3 mM Tris–HCl, 0.3 mM EDTA (pH 8.0), 2% DMF.

5.5. Gel electrophoresis

Photocleavage of supercoiled pBR322 (0.15 μg) was performed with the porphyrins in buffer (pH 8.0, 3 mM Tris–HCl, 0.3 mM EDTA, 2%DMF). Samples were exposed to a 50-W high-pressure mercury lamp, which was placed 20 cm away from the samples at room temperature for 60 min and loaded onto 0.9% agarose gel containing 0.1 μg/mL ethidium bromide. The agarose gels were run at 130 V in TAE buffer. The gels were observed and photographed under UV light.

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