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Interaction of cationic phthalocyanines with DNA. Importance of the structure of the substituents

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ABSTRACT

The interaction of novel zinc (II) cationic phthalocyanines with CT-DNA was studied using absorption and fluorescence spectroscopy, as well as thermal denaturation profiles. Results showed an electrostatic interaction between the phthalocyanines and CT-DNA. The properties of these phthalocyanines were compared taking the structure of the macrocycle peripheral substituents into account. 2,9(10),16(17),23(24)-tetrakis [(N-butyl-N-methylammonium)ethylsulfanyl]phthalocyaninatozinc(II) tetraiodide (**Pc6**) had a greater affinity for the CT-DNA helix than its bioisoster 2,9(10),16(17),23(24)-tetrakis[(N-dibutyl-N-methylammonium)ethoxy]phthalocyaninatozinc(II) tetraiodide (**Pc7**). 2,9(10),16(17),23(24)-tetrakis[(2-trimethylammonium)ethyl-sulfanyl]phthalocyaninatozinc(II) tetraiodide (**Pc13**) also carried a sulfur atom like **Pc6**, but linked to bulky substituents such as trimethylammonium groups. The planar aromatic region of the cationic phthalocyanines in this study appears to be unable to facilitate their intercalation with CT-DNA.

1. Introduction

The search of novel drugs that may be associated with nucleic acids is a very interesting target in pharmaceutical design. It has been reported that cationic metalloporphyrins exhibit a good affinity for nucleic acids, capable of oxidizing the C–H bonds of the deoxyribose units of DNA that occur as a result of DNA cleavage [1]. In the presence of visible light and oxygen, such water soluble cationic metalloporphyrins induce single-strand scission of DNA [2]. It has also been established that the nature of phthalocyanine substituents and central metal atom affects the biological activity of the molecule [3].

More recently it has been reported that the absence of intercalation by new porphyrins carrying N-methylpyridinium (N-Mepy) groups is due to the requirement of the direct attachment of N-Mepy groups to the porphyrin core [4]. The binding of cationic phthalocyanines to DNA has also been recently studied [5–7]. The interaction between calf thymus (CT)-DNA and an octacationic zinc(II) phthalocyanine has been recently studied by UV/Vis and fluorescence titration, as well as by thermal denaturation, and the results showed strong binding to CT-DNA in a non-intercalative mode [8].

Titrimetric investigations have indicated that electrostatic binding between tetrasubstituted cationic phthalocyanine and anionic DNA phosphate groups occurs to a large extent and that π–π stacking between DNA and phthalocyanine moieties takes place afterward [9].

In a recent study we found that a sulfur-linked cationic dye named: 2,9(10),16(17),23(24)-tetrakis[(2-trimethylammonium) ethylsulfanyl]phthalocyaninatozinc(II) tetraiodide (**Pc13**) was the most active of the four sensitizers assayed with a singlet oxygen quantum yield of 0.58 and a higher bathochromic shift of 10 nm for the Q-band than the isosteric oxygen-linked cationic aliphatic phthalocyanine [10]. When we increased the lipophilicity of **Pc13**, we found that the photosensitizers 2,9(10),16(17),23(24)-tetrakis[(N-butyl-N-methylammonium)ethylsulfanyl]phthaloc-yaninatozinc(II) tetraiodide (**Pc6**) and 2,9(10),16(17),23(24)-tetrakis[(N-dibutyl-N-methylammonium)ethoxy]phthalocyaninatozinc(II) (**Pc7**) had better photodynamic behavior [11]. Our photobiological assays using KB cells indicated that the above-mentioned dyes partially localized in lysosomes, inducing apoptosis after photodynamic treatment [10,11].

Based on the above-mentioned results, here we investigated the interaction of our novel zinc (II) cationic phthalocyanines with CT-DNA by using absorption and fluorescence spectroscopy, and the changes in CT-DNA thermal denaturation profile.

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The properties of these phthalocyanines were compared taking into account the structure peripheral substituents of the macrocycle.

2. Materials and methods

2.1. Materials

The phthalocyanines used in this work 2,9(10),16(17),23(24)-tetrakis[(N-butyl-N-methylammonium)ethylsulfanyl]phthalocyaninatozinc(II) tetraiodide (**Pc6**)[11], 2,9(10),16(17),23(24)-tetrakis[(N-dibutyl-N-methylammonium)ethoxy]phthalocyaninatozinc(II) tetraiodide (**Pc7**) [11,12], 2,9(10),16(17),23(24)-tetrakis[(2-trimethylam-monium)ethylsulfanyl]phthalocyaninatozinc(II) tetraiodide (**Pc13**) [10] (Fig. 1), and tetra-*t*-butyl phthalocyaninatozinc(II) [13] were synthesized in our laboratory. Sodium chloride was obtained from Mallinckrodt (Phillipsburg, NJ, US). Deoxyribonucleic acid sodium salt from calf thymus (CT-DNA), tris (hydroxymethyl) aminomethane hydrochloride, and tetrasodium ethylenediaminetetraacetate dihydrate, were purchased from Sigma–Aldrich. All chemicals were of reagent grade and used without further purification. Distilled water treated in a Milli-Q system (Millipore) was used.

2.2. Instrumentation

Electronic absorption spectra were determined with a Shimadzu UV-3101 PC spectrophotometer and Shimadzu UV-3600 PC coupled to a thermostat MGW LAUDA BRINKMANN RC6 to an ethanol–water bath. Fluorescence spectra were monitored with a Photon Technology International spectrofluorometer. pH was measured with a Thermo pH-meter Altronix TPX-1.

2.3. DNA binding studies

2.3.1. Optical absorption and fluorescence spectroscopy studies

All titrations for DNA-binding experiments were conducted at pH 7.4 in a 10 mM Tris HCl buffer containing 145 mM NaCl. The concentrations of CT-DNA per nucleotide phosphate were calculated by UV absorbance at 260 nm using a DNA extinction coefficient (ε_{DNA}) of 6600 $M^{-1}cm^{-1}$. Absorption spectra were recorded between 200 nm and 800 nm. Titrations of **Pc6**, **Pc7**, and **Pc13** at fixed concentrations of 1.83×10^{-4} M, 1.98×10^{-4} M, and 1.96×10^{-3} M in Tris–EDTA buffer were performed by adding injections between 0 and 260 μL of CT-DNA stock solution concentrations of 6.15×10^{-6} M, 1.00×10^{-4} M, and 2.33×10^{-4} M respectively. Dilution effects were measured by control titrations with buffer instead of CT-DNA.

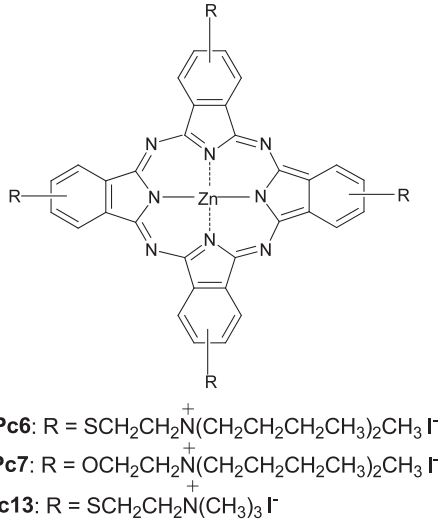

Fig. 1. Chemical structure of phthalocyanines.

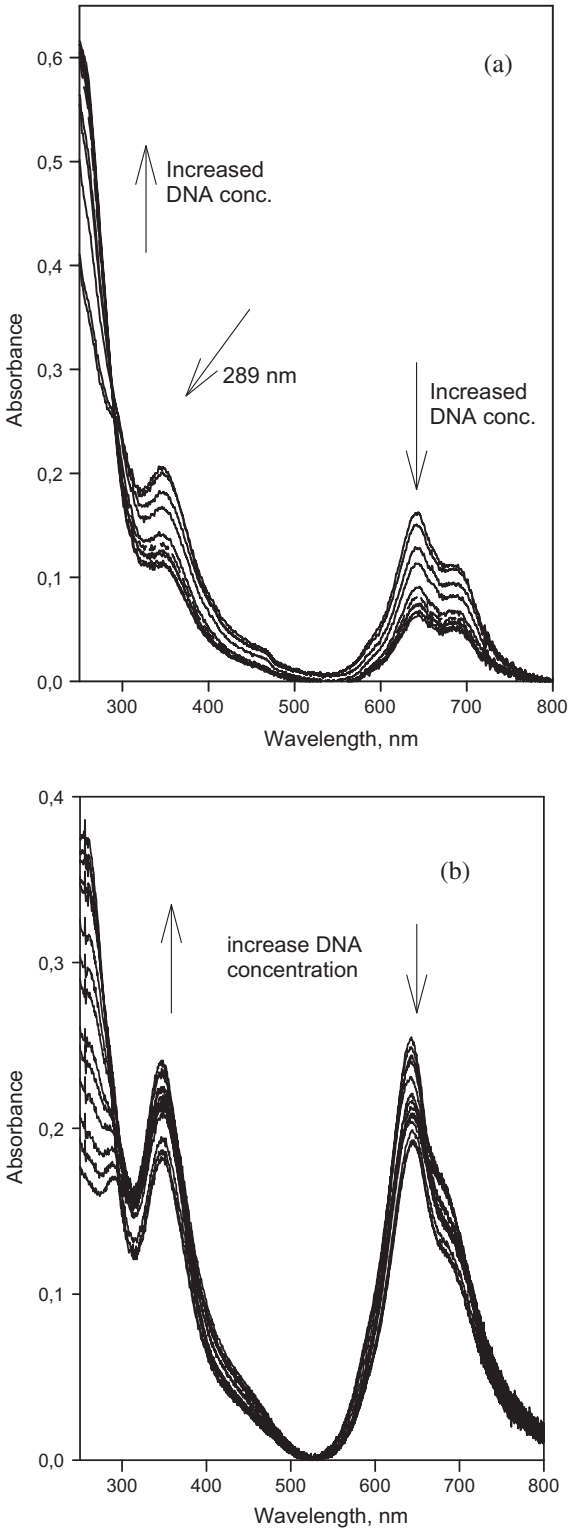

Fig. 2. Effect of CT-DNA on the visible spectra of **Pc6** (a) and **Pc13** (b).

Absorption and emission spectra were recorded with a 10×10 mm quartz cuvette with a 500 μL capacity at room temperature.

Emission spectra were recorded at an excitation wavelength (λ_{exc}) of 610 nm (Q-band) between 640 and 800 nm; a cut-off filter was used to prevent the excitation beam from reaching the detector (Schott RG 630).

2.3.2. Determination of the apparent binding constant of the phthalocyanines to DNA using UV/visible spectrometry

The apparent binding constant (K_{app}) of the phthalocyanines to nucleic acids was determined by means of titration by reading the absorbance of the phthalocyanines at λ_{max} after the addition of the nucleic acid, according to Eq. (1) [7,14,15]:

$$\frac{c}{\Delta\varepsilon_a} = \frac{c}{\Delta\varepsilon} + \frac{1}{K_{app}\Delta\varepsilon} \quad (1)$$

where c is the concentration of CT-DNA, $\Delta\varepsilon_a = |\varepsilon_a - \varepsilon_f|$, $\Delta\varepsilon = |\varepsilon_b - \varepsilon_f|$, and ε_a, ε_b and ε_f correspond to the apparent extinction coefficient, and the extinction coefficient of the bound form and the free form of the phthalocyanines, respectively. ε_a corresponded to A_{obsd}/[Pc] at different concentrations of CT-DNA.

2.4. Fluorescence quantum yields

Relative fluorescence quantum yields were determined by comparison with that of tetra-*t*-butyl phthalocyaninatozinc(II) (Φ_F = 0.30 in toluene, λ_{max} 610 nm) [13]. The quantum yields were calculated as described elsewhere [16]. Studies were conducted at a fixed amount of the phthalocyanines by increasing CT-DNA concentrations according to 2.3.1.

2.5. Thermal denaturation studies

The melting temperatures (T_m) for a CT-DNA concentration of 3.93×10^{-4} M and concentrations of 1.83×10^{-4} M of **Pc6**, 1.98×10^{-4} M of **Pc7**, and 8.81×10^{-5} M of **Pc13**, were measured in Tris–EDTA buffer at pH 7.4. The samples were heated in a temperature range from 15 °C to 98 °C. The melting temperatures were monitored at 260 nm and the absorbance was the average (±SD) of three independent values.

3. Results and discussion

3.1. Phthalocyanine-CT-DNA binding studies

3.1.1. Absorbance studies

Experiments of UV/Vis titration of phthalocyanines with CT-DNA were performed to investigate phthalocyanine-CT-DNA binding. The principal characteristic observed in the absorption spectra of phthalocyanines was the presence of isosbestic points (Fig. 2) between 250 nm and 350 nm, consistent with an equilibrium between the CT-DNA and the phthalocyanine complexes (289 nm, 308 nm, and 281 nm for **Pc6**, **Pc7** and **Pc13** respectively).

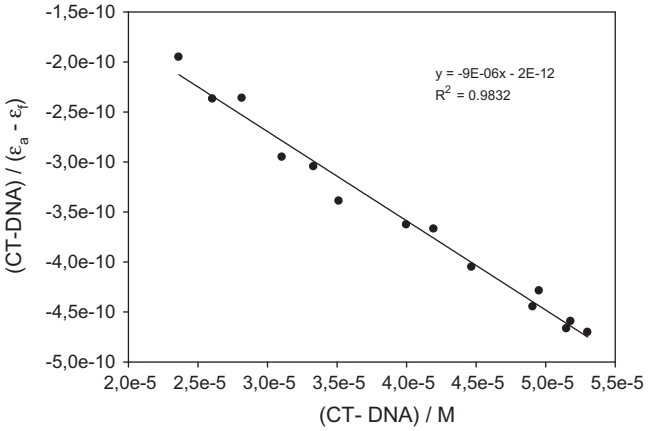

Fig. 3. The plot of [CT-DNA]/$\Delta\varepsilon_a$ versus [CT-DNA] (Eq. (1)) for **Pc13**.

The intensity absorption ratio of the two bands corresponding to the monomer and oligomers was calculated. The higher values of the ratio indicated a disaggregated dye form [17,18]. This ratio was calculated for each Pc-CT-DNA system by using the λ_{max} indicated in Table 1. These values were compared with those obtained in tetrahydrofurane (THF), where aggregation was not observed, and with those obtained in HEPES pH 7.4 and 145 mM NaCl.

Due to their insolubility in aqueous solutions, **Pc6** and **Pc7** were aggregated. When CT-DNA was added, the monomer/oligomer ratio for **Pc6** and **Pc7** increased compared with buffer values, but did not change appreciably over the range of CT-DNA concentrations studied. **Pc13** behaved similarly to **Pc6** and **Pc7**.

A small red shift in the absorption spectra ($\Delta\lambda \approx 3$–6 nm) was obtained for **Pc6** and **Pc7** upon CT-DNA addition**.** However, this value was not sufficient to establish intercalation of phthalocyanines to CT-DNA, and could be attributed to the electrostatic binding between the positive charge of phthalocyanines and the negative charge of phosphate CT-DNA [4,19] .

3.1.2. Determination of the apparent binding constant of the phthalocyanines to CT-DNA using UV/visible spectrometry

The absorbance titration values were used to construct the plot of $[DNA]/(\varepsilon_a - \varepsilon_f)$ versus [DNA] (Fig. 3). The plots were linear and K_{app} values $>10^4$ M^{-1} were obtained (Table 2). The large apparent binding constant indicated that phthalocyanines have a strong interaction with CT-DNA. This result agrees with the changes in the absorption spectra [19]. However, the values obtained ($K_{app} \leqslant 10^6$) were lower than the apparent binding constant, which is currently associated with intercalation. Thus, the results could represent a non-intercalative binding mode [8,20].

3.1.3. Fluorescence studies

The fluorescence spectra of phthalocyanines at different concentrations of CT-DNA were studied. For all phthalocyanines, the fluorescence spectra showed neither significant wavelength shifts nor relevant modifications in shape, indicating that the monomer is the only fluorescence species. In the presence of CT-DNA, the fluorescence intensity at the maximum emission wavelength

Table 1
Photophysical parameters of phthalocyanines.

Pc	$\lambda_{monomer}$/nm	$\lambda_{oligomer}$/nm	Mon/olig (THF)	Mon/olig (HEPES)	Mon/olig*
6	681	642	5.26	–**	0.72–0.78
7	681	636	5.56	–**	≈0.85
13	684	649	7.14	0.58 #	0.70

* At different ratios of [Pc]/[DNA].
** Water insoluble Ref. [11]. #Ref. [10].

Table 2
Apparent binding constant, fluorescence quantum yield and denaturalization temperature of phthalocyanines.

Pc	K_{app}	Φ_{Fmax}	Φ_F (DMF)	ΔT_m
6	8.9×10^6	0.032 ± 0.006	0.13 *	5.1
7	9.7×10^5	0.035 ± 0.006	0.14 *	5.5
13	4.2×10^6	0.0015 ± 0.0004	0.15 **	4.9

Φ_{Fmax} correspond to the maximum value measured for each phthalocyanine in the presence of CT-DNA.
* Ref. [11].
** Ref. [10].

changed according to the relationship between the phthalocyanines and CT-DNA concentrations (R). This became more evident in the spectra of **Pc6** and **Pc7**. For high ratio values of $R \geqslant 9.99$ and 12.6 for **Pc6** and **Pc7** respectively, fluorescence intensity and fluorescence quantum yields (Table 2) increased, which we attributed to the disaggregation of the phthalocyanines in the presence of CT-DNA binding, since only monomeric form of the dye fluoresce [12,13,16,18]; at low values of R, for example with an excess of CT-DNA, the intensity of the fluorescence signal decreased. This change in emission shows that binding to CT-DNA quenched the fluorescence of the phthalocyanines. Fig. 4 shows a change in the emission spectra of **Pc6** (the same effect was observed for **Pc7**, data not shown). The plot is linear, thus indicating that only static or dynamic quenching occurs. Taking the shape of the absorbance spectra into account, we may be in the presence of static quenching (see Fig. 2).

The fluorescence intensity signal for **Pc13** increased with CT-DNA concentration. We attributed this to the presence of an increased amount of monomeric phthalocyanines bound to CT-DNA. However, the fluorescence quantum yields indicate that the amount of monomeric species is very low in comparison with **Pc6** and **Pc7.**

3.2. Thermal denaturation studies

The profile of the melting temperature (T_m) of DNA is a measure of the stability of the DNA double helix with temperature. When a compound is bound to DNA an increase in T_m indicates the strength of the interaction [8,9]. The T_m value can also be used to distinguish between an intercalative and external binding modes. Generally, classical intercalation gives rise to higher ΔT_m values than either groove binding or outside stacking [8,9]. The values obtained for **Pc6**, **Pc7**, and **Pc13** (Table 2) indicate a moderate bond strength between these phthalocyanines and CT-DNA. However, this value

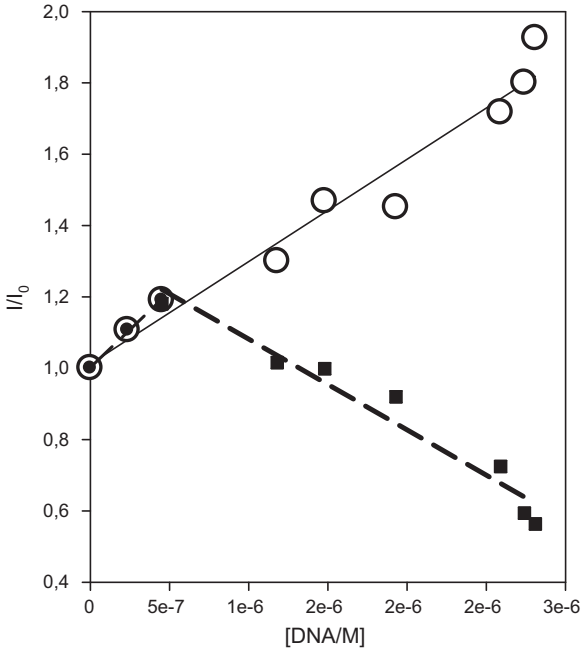

Fig. 4. Fluorescence spectra of **Pc6** (■) and **Pc13**(○) at increasing concentrations of CT-DNA.

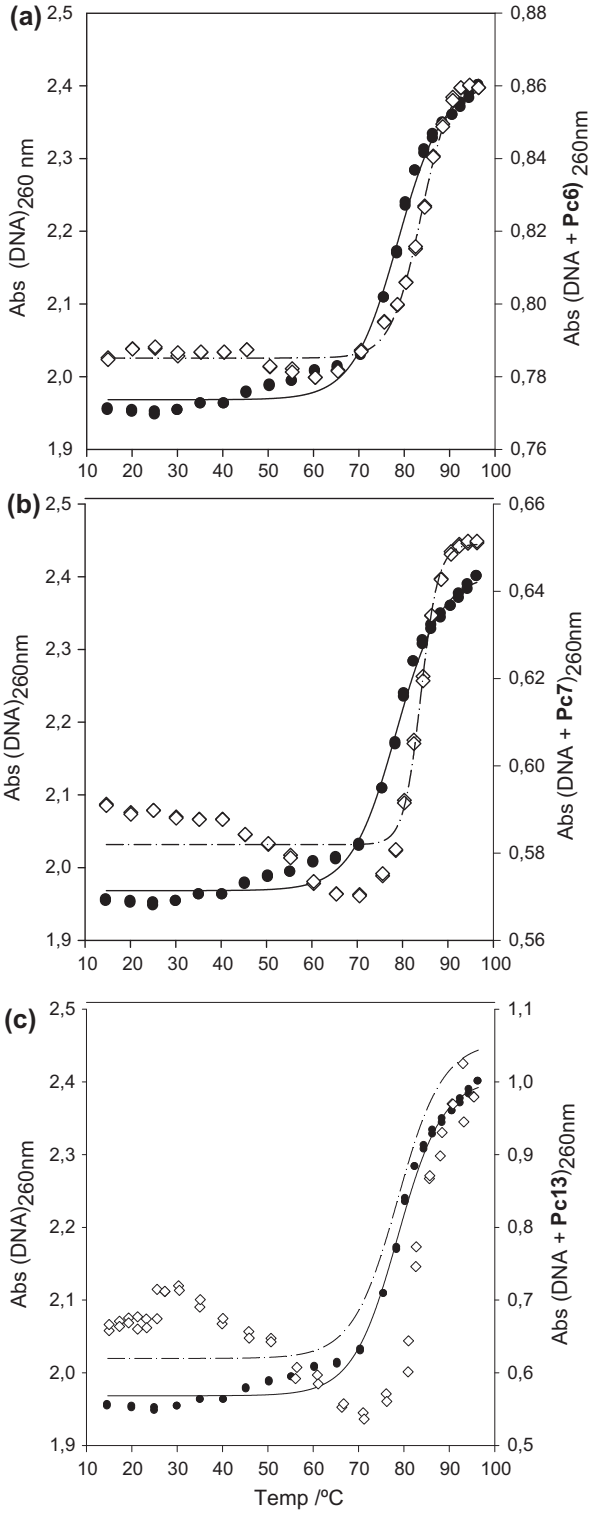

Fig. 5. Qualitative thermal-denaturalization profiles of CT-DNA in the absence (●) and presence (◇) of **Pc6** (a), **Pc7** (b) and **Pc13** (c).

is not high enough to be considered an intercalating binding (see Fig. 5).

4. Conclusions

In water, the cationic phthalocyanines **Pc6** and **Pc7** are aggregated due to their very low solubility. The presence of CT-DNA has a dual effect. On the one hand, it favored phthalocyanine disaggregation (see Table 1) because the monomer/oligomer ratio was higher in the presence of CT-DNA than in buffer solution. On the other hand, it favored a large π–π interaction between the phthalocyanine macrocycle with DNA helix structure. For that reason, in all CT-DNA concentrations tested, the monomer/oligomer ratio was lower than 1 and fluorescence intensity for **Pc6** and **Pc7** decreased as CT-DNA concentrations increased (low *R* values). The phthalocyanine apparent binding constant was higher for **Pc6** than for **Pc7**. **Pc6** had a greater affinity for the DNA helix than its bioisoster **Pc7**, which carried an oxygen atom, due to the presence of a more electropositive atom, as sulfur, linked to the macrocycle. **Pc13** also carried a sulfur atom but linked to higher bulky substituents, such as trimethylammonium groups, than **Pc6**.

Besides, the apparent binding constants and thermal denaturation studies indicate that the intercalation of phthalocyanines and CT-DNA is not involved, at least to a significant extent. Therefore it can be postulated that there is an electrostatic interaction between the phthalocyanines and CT-DNA. Similar results have been reported for tetra(trimethylammonium)phthalocyaninato zinc tetraiodide [5], 2,9(10),16(17),23(24)-tetrakis-[2′,3′.5′,6′,tetrafluoro-4′-(2-diethylaminoetanethio)benzyloxy]phthalocyaninato zinc(II)tetraiodide as well as for 2′,3′,5′,6′-tetrafluoro-4′-(2-dimethylaminoetanethio)benzyloxy peripheral substituted tetra-cationic water soluble zinc (II) phthalocyanine [9].

Preliminary studies of the interactions of porphyrins with CT-DNA allowed to conclude that direct attachment of N-alkylpyridinium groups to the porphyrin ring in such a way that the N-alkylpyridinium group can become nearly coplanar with the porphyrin ring is necessary for intercalation to occur [4]. Also has been reported that bulky porphyrin substituents would not impede interaction with CT-DNA [21–24].

The planar aromatic region of the cationic phthalocyanines in this study appears to be unable to facilitate their intercalation with CT-DNA.

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