Compounds Based on *meso*-Tri(4-pyridyl)-*p*-acrylamidophenylporphyrin Able to Interact with DNA

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A new type of porphyrinyl-nucleoside was synthesized by the Heck reaction of *meso*-tri(4-pyridyl)-*p*-acrylamidophenylporphyrin with (+)5-iodo-2'-deoxyuridine. The porphyrin used in this reaction was also applied in obtaining a water soluble porphyrin polymer and a copolymer with acrylamide. The porphyrinyl-nucleoside and the polymer and copolymer were investigated for their interaction with ds DNA, oligonucleotides and oligonucleotide duplexes. The extend of the red-shift of the Soret band of porphyrins and the slowing of the mobolity of DNA during electrophoresis of the interacting systems suggested that intercalation of cationic porphyrin units into ds DNA cannot be solely responsible for the observed phenomena.

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Introduction.

The problem of intercalation of cationic porphyrins into ds DNA has been a subject of intensive investigation [1]. The prevailing concept that intercalation is an important phenomenon in cationic porphyrin-DNA interactions has been argued based on a theoretical approach [2,3]. Our investigations of the interaction of *N*-methylpyridiniumporphyrins with ss DNA, in which interacalation is impossible if secondary structure is not present, showed that the observed red-shifts take place and are similar to those characteristic for the interacalation with ds DNA [4]. This prompted us to extend our research with new types of compounds, the synthesis of which started with *meso*-tri(4-pyridyl)-*p*-acrylamidophenylporphyrin **2** obtained from *meso*-tri(4-pyridyl)-*p*-aminophenylporphyrin **1**. These substances are: 1) *meso*-*p*-(5-(2'-deoxyuridyl)acrylamido)phenyltri(4-pyridyl)porphyrin **3**, representing a specific porphyrinylnucleoside, 2) a polymer of the mentioned acrylamidoderivative of porphyrin **4**, and 3) the respective copolymer **5** with acrylamide. After *N*-methylation of the pyridyl *meso*-substituents, the derivatives designated **2-Me**, **3-Me**, **4-Me** and **5-Me**, became water soluble, which was essential for their interactions with DNA.

The importance of the synthesis of the new porphyrinylnucleosides **3**, **3-Me**, became obvious to us after we had synthesized a series of porphyrinylnucleosides in which the nucleoside unit was connected to a *meso*-phenylporphyrin core exclusively through the -O-C(5') centers of the 2-deoxyribofuranose subunits [5,6]. Since the 5'-OH was already blocked, it was not possible to elongate the nucleoside unit into an oligonucleotide or DNA strand. In the case of **3** and **3-Me**, the 3',5'-OH groups remain unsubstituted allowing these compounds to serve as precursors for porphyrinyloligonucleotide/DNA systems in which a number of porphyrin units are attached to the biopolymer chain. On the other hand, the new polymers **4-Me** and **5-Me** contain similar porphyrin units attached to the polyethylene chain. The application of porphyrin **2-Me** as a monomer allowed polymerization and copolymerization either in presence of the DNA or before the addition of DNA. This allowed us to draw new conclusions on the role of intercalation in the porphyrinyloligonucleotide/DNA interactions.

Results and Discussion.

The acrylamidophenylporphyrinylnucleoside **3** was obtained from acrylamidophenylporphyrin **2** by the Heck reaction using (+)-6-iodo-2'-deoxyuridine, and was then transformed by *N*-methylation with methyl iodide into the water soluble tri(*N*-methyl-4-pyridinium) derivative **3-Me**, which was able to interact with oligonucleotides and DNA. In similar *N*-methylation reaction **2-Me** was obtained from **2**. The *N*-methylation reaction also transformed the water insoluble polymer and copolymer into water soluble polymers **4-Me** and **5-Me** with molecular weights of 9,000 and 12,000 daltons, respectively. Solubility in water made them substantially different from previously reported porphyrin-polymers, like those of Kajiwara *et al.* [7,8].

The water soluble porphyrins **2-Me** and **3-Me** were exposed to aqueous solutions of oligonucleotide 20-mers, the $(dG)_{20}$-$(dC)_{20}$ and $(dA)_{20}$-$(dT)_{20}$ duplexes, and to the DNA plasmid-pRIT6. In every case, the porphyrin Soret band was red-shifted by 6-14 nm, accompanied by hypochromicity in the range of 10-64%, see Table 1. However,

Scheme

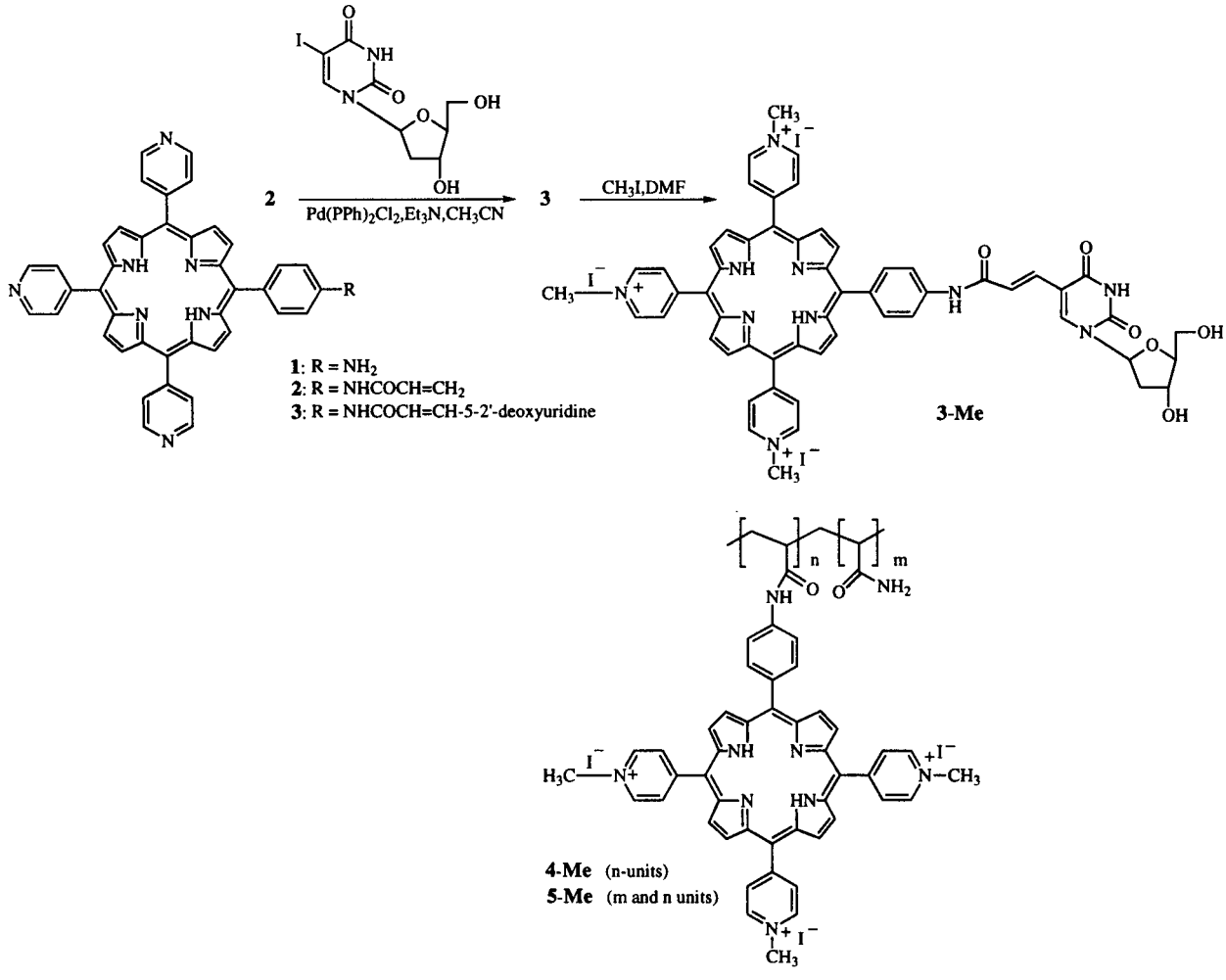

Table 1

γ_0		Soret band shift (nm)		Hypochromicity (%)		Oligonucleotide	γ_0		Soret band shift(nm)		Hypochromicity (%)	
2-Me	3-Me	2-Me	3-Me	2-Me	3-Me	Compound	4-Me	5-Me	4-Me	5-Me	4-Me	5-Me
7.3	11.3	12	14	27	17	dA	3.6	7	10	10	21	25
7.8	10.5	10	12	15	13	dT	9	12.3	8	8	7	19
7.6	9.8	6	14	54	38	dG	13.4	26	10	14	42	45
8.1	9	6	10	40	28	dC	9.5	9.2	8	8	27	36
3.3	4	10	12	10	12	$(dA)_{20}$-$(dT)_{20}$	4.6	0.8	8	8	4.6	0.8
3.8	3.2	14	12	41	35	$(dG)_{20}$-$(dC)_{20}$	9.0	5	12	10	36	42
3.3	6	10	10	42		Plasmid DNA	2.2	1.5	10	10	30	28

Changes in the Soret band of porphyrins and porphyrin polymer and copolymer resulting from the interaction with oligonucleotides/DNA. γ_0 = molar ratio of oligonucleotide/DNA (in bases) to porphyrin or porphyrin polymer/copolymer (in porphyrin units) measured at the highest hypochromicity value.

the bathochromic effect was more advanced and hypochromic effect less advanced when caused by porphyrinyl-nucleoside **3-Me** than porphyrin **2-Me**. The porphyrinyl-nucleoside generated the same Soret band shifts and hypochromicity when interacting with single-stranded oligonucleotides (into which intercalation cannot take place) as when interacting with double stranded oligonucleotides. The same results were observed for **2-Me**, only its red-shift resulting from interaction with dG and dC was reduced to 60%. The results of interaction of polymer **4-Me** and copolymer **5-Me** with DNA are also presented in Table 1. The Soret band red shifts ranged in this case from 8 to 14 nm (from the starting position at 426 nm), and were of approximately the same magnitude for both the polymer and copolymer. Hypochromicity was seen to be greater for the copolymer by 7-33%. The red shift of the porphyrin IV(Q) band from its 522 nm value (compare values from [9] was in every case the same, 4 nm. Values of the molar ratio of oligonucleotide/DNA (in base pairs or bases) to porphyrin derivative (in porphyrin units), γ_0, decreased for oligonucleotides in the order of dG>dC>dT>dA. Similar results were seen for oligonucleotide duplexes, $(dG)_{20}$-$(dC)_{20}$>$(dA)_{20}$-$(dT)_{20}$, while for plasmid DNA the γ_0 values were much lower. Values γ_0 for **2-Me** and **3-Me** interacting with different oligonucleotides were much more alike than for interaction of polymers **4-Me**, **5-Me** and they are 10-20% higher for the porphyrinylnucleoside **3-Me** than for the porphyrin **2-Me**. Similarly, the red shifts are as a rule higher for **3-Me** than for **2-Me** but both were higher than for polymers (with the exception of dG and dC interactions with **2-Me**). The similarity of the Soret band red shifts and rather low ratios of oligonucleotide/DNA to porphyrin at which saturation took place may imply that the assumption of intercalation as the main reason for the Soret band red shift of porphyrins interacting with ds DNA is an overstatement (an appropriate γ_0 ratio is necessary for intercalation as demonstrated for the acridine-DNA system [10,11]).

Additional evidence was provided by experiments in which the porphyrin **2-Me**, representing a monomer of **4-Me** and **5-Me**, was either mixed with DNA and then polymerized or was first polymerized or copolymerized with acrylamide and then mixed with DNA. As shown by the contours of the electrophoretic separation presented in Figure 1, the mobility on the electrophoresis gel of supercoiled plasmid DNA (lane 7) changed only slightly when it interacts with the porphyrin polymer **4-Me** (lane 4) or its copolymer with acrylamide **5-Me** (lane 5). Since slowing of the DNA mobility is a result of unwinding caused by intercalation or/and "fattening" (grafting) by the bulky intercalator, the small changes which took place testify against unwinding or grafting under the applied conditions. However, since a red shift of the Soret band up to 10 nm has been observed for the DNA-porphyrin system in the absence of apparent unwinding, these results may suggest that the red shift of such a size does not necessarily result from intercalation into DNA. Mixing and incubation of monomeric porphyrin **2-Me** with the same DNA substantially slows down the DNA mobility (lane 6) but polymerization following mixing and incubation causes only minimal effect (lane 2). This could suggest that at the beginning intercalation took place which resulted in unwinding of DNA under the influence of monomeric porphyrin and that the latter polymerized only to a small degree (if at all) because of the rigid placement of the monomeric units in the DNA backbone. Characteristically, the red shift of the monomer-DNA system, 10 nm, (see also, lane 6) is the same as of the polymer-DNA system (see also, lane 4) in which the decrease of DNA mobility was less advanced. This again suggests that the red shift of the Soret band of porphyrin interacting with DNA can be caused by other type of interactions than intercalation, for instance by simple electrostatic interactions. With acrylamide present in the porphyrin (**2-Me**)-DNA system before the copolymerization took place, the mobility of DNA (lane 1) was slowed even more than in the absence of acrylamide (lane 2), probably because of the enhancement by acrylamide of the templating effect primarily due to DNA.

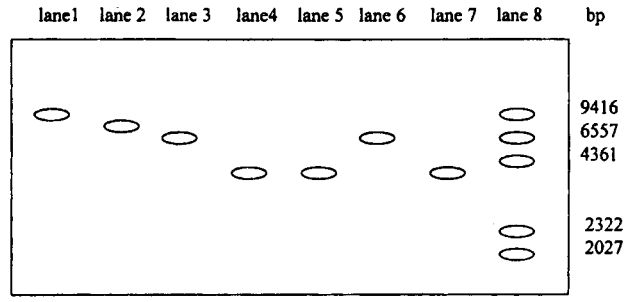

Figure 1. Agaral gel electrophoretic patterns of supercoiled plasmid DNA interacting with monomeric and polymeric porphyrins. Lane 1 - porphyrin **2-Me** and acrylamide mixed and incubated with DNA, then coplymerized. Lane 2 - porphyrin **2-Me** mixed and incubated with DNA, then polymerized. Lane 3 - porphyrin **2-Me** copolymerized with acrylamide and then DNA added. Lane 4 - porphyrin polymer **4-Me** mixed and incubated with DNA. Lane 5 - porphyrin copolymer with acrylamide **5-Me** mixed and incubated with DNA. Lane 6 - porphyrin **2-Me** mixed and incubated with DNA. Lane 7 - DNA as control. Lane 8 - DNA standards: λDNA/HINDIII fragments; bp denote base pairs.

EXPERIMENTAL

Materials and Methods.

The following commercially available chemicals from Aldrich (unless otherwise stated) were used without further purification: 4-pyridinecarboxaldehyde, *p*-acetamidobenzaldehyde,

pyrrole, propionic acid, iodomethane, pyridine, acryloyl chloride, *N,N*-dimethylformamide, acetonitrile (dried over molecular sieves and freshly distilled under nitrogen), (+)-5-iodo-2'-deoxyuridine, bis(triphenylphosphine)palladium(II) chloride, triethylamine (dried and freshly distilled under nitrogen), chloroform (Fisher, dried and freshly distilled), methanol (Fisher), silica gel 70-230 mesh 60A, and tlc plates coated with silica gel $60F_{254}$.

The ^1H nmr spectra were recorded on a Bruker IBM AT 300 MHz Fourier transform spectrometer. Routine measurements were made on Bruker AC 200 MHz Fourier transform spectrometer. Electronic absorption spectra were recorded on a Hewlett-Packard 8452A diode array spectrometer. Fast atomic bombardment mass spectrometry was performed on a 70 E HFVG mass spectrometer with an 11/250 data system, 3-nitrobenzyl alcohol applied as a matrix.

The single stranded (ss) DNA 20-mers of dA, dT, and dG and dC were purchased from Gibco/BRL, Life Technology, Grand Island, NY). The required $(dA)_{20}$-$(dT)_{20}$ and $(dG)_{20}$-$(dA)_{20}$ ds-DNA oligomer duplexes were prepared by mixing, boiling and cooling the same molar amounts of dA and dT or dG and dC 20-mers. The DNA plasmid pRIT-5 was purified from *E.coli.*

Synthesis.

Meso-tris(4-pyridyl)-*p*-aminophenylporphyrin (**1**).

This compound was prepared by the procedure described in our previous article [12].

Meso-tris(4-pyridyl)-*p*-acrylamidophenylporphyrin **2**.

Acryloyl chloride (4 mg, 0.044 mmole) in chloroform (10 ml) was added dropwise to the chloroform solution of porphyrin **1** (32 mg, 0.05 mmole) and triethylamine (6 µl, 0.044 mmole) at 0° under nitrogen. The reaction mixture was stirred at room temperature for 6 hours, 30 ml of chloroform was added afterward and washed twice with ice-cooled 5% sodium bicarbonate aqueous solution and ice-water. The chloroform phase was dried over anhydrous sodium sulfate. The residue after removing the solvent was chromatographed on silica gel column, using chloroform:methanol (50:1) as eluent. The first and the second fraction contained the unreacted porphyrin **1** and the product porphyrin **2**, respectively, yield is 75%; ms: (tab) m/z (M+1)+688; ^1H nmr (deuteriochloroform): ppm 9.03 (m, 6H, 2,6-Py), 8.94 (d, 2H, 2,6-CONH-Ph-), 8.83 (m, 8H, β-pyrrole), 8.15 (m, 6H, 3,5-Py), 8.03 (d, 2H, 3,5-CONH-Ph-), 7.99 (s, 1H, NHCO), 6.65 (dd, J_{MX} = 3 Hz, J_{AX} = 27 Hz, 1H, vinyl), 6.47 (dd, J_{AX} = 15 Hz, J_{AM} = 27 Hz, 1H, vinyl), 5.95 (dd, J_{MX} = 3 Hz, J_{AX} = 15 Hz, 1H, vinyl), -2.90 (s, 2H, inner NH of porphyrin); uv-vis (chloroform): λ_{max} nm 420 (Soret), 514, 548, 594, 650; ir (potassium bromide): cm^{-1}; 3295 (ν_{NH}), 1650 ($\nu_{C=O}$), 1610 ($\nu_{C=C}$).

Anal. Calcd. for $C_{44}H_{30}N_{80}O$: C, 76.95; H, 4.40; N, 16.32. Found: C, 76.90; H, 4.55; N, 16.25.

Meso-tris(4-pyridyl)-*p*-(5-(2'-deoxyuridyl)acrylamido)phenylporphyrin **3**.

Porphyrin **2** (35 mg, 0.05 mmole), triethylamine (0.12 ml), (+)-5-iodo-2'-deoxyuridine (19 mg, 0.05 mmole) and bis(triphenylphosphine)palladium(II) chloride (3 mg) were introduced into acetonitrile (25 ml) consecutively under argon. The reaction mixture was refluxed under argon for 36 hours. The residue after removing the solvent under vacuum was chromatographed on silica gel with chloroform/methanol as eluent from 40:1 to 10:1 ratio range. The unreacted starting material was removed as the first fraction while the product was eluted out as the second fraction, yield 50% based on the reacted starting material; ms: (tab), m/z (M+1)+914; ^1H nmr (deuteriochloroform): ppm 11.69 (s, 1H, H-3), 10.65 (s, 1H, NHCO), 9.05 (d, 6H, 2,6-Py), 8.95 (m, 2H, β-pyrrole), 8.88 (m, 6H, β-pyrrole), 8.42 (s, 1H, H-6), 8.26 (d, 6H, 3,5-Py), 8.18 (d, 2H, 2,6-CONH-Ph-), 8.16 (d, 2H, 3,5-CONH-Ph), 7.42 (d, J = 15 Hz, 1H, =CH), 7.48 (d, J = 15 Hz, 1H, =CH), 6.19 (t, 1H, H-1'), 5.29-5.30 (m, 2H, OH-3',5'), 4.28 (m, 1H, H-4'), 3.82 (m, 1H, H-3'), 3.41 (m, 2H, H-5'), 2.24 (m, 2H, H-2'), -3.02 (s, 2H, inner NH of porphyrin); uv-vis (chloroform): λ_{max} nm 308, 420 (Soret), 514, 548, 592, 646.

Anal. Calcd. for $C_{53}H_{40}N_{10}O_6$: C, 69.73; H, 4.42; N, 15.34. Found: C, 69.70; H, 4.51; N, 15.45.

Meso-tris(*N*-methyl-4-pyridiniumyl)-*p*-acrylamidophenylporphyrin **2-Me**.

Compound **2** (6.9 mg, 0.01 mmole) and 10 times excess iodomethane was introduced into DMF (5 ml) and stirred overnight at room temperature. The reaction completion was monitored by tlc using chloroform/methanol (20:1) as eluent and stopped when the starting porphyrin disappeared. Compound **2-Me** was obtained without further purification after removing the excess iodomethane and the DMF; ^1H nmr (DMSO-d_6), ppm 10.60 (s, 1H, NHCO), 9.50 (d, 6H, 2,6-Py), 9.18 (d, 2H, 2,6-CONH-Ph), 9.08 (d, 2H, 3,5-CONH-Ph), 9.00 (d, 6H, 3,5-Py), 8.08 (m, 8H, β-pyrrole), 6.58 (dd, J_{AX} = 15 Hz, J_{AM} = 24 Hz, 1H, vinyl), 6.32 (dd, J_{MX} = 3 Hz, J_{AM} = 24 Hz, 1H, vinyl), 5.82 (dd, J_{MX} = 3 Hz, J_{AX} = 15 Hz, 1H, vinyl), 4.72 (s, 9H, N^+-CH_3), -3.00 (s, 2H, inner NH of porphyrin); uv-vis (water) λ_{max} nm 424 (Soret), 520, 560, 584, 644.

Anal. Calcd. for $C_{47}H_{39}N_8I_3O$: C, 50.74; H, 3.53; N, 10.07. Found: C, 50.80; H, 3.72; N, 10.21.

Meso-tris(*N*-methyl-4-pyridiniumyl)-*p*-(5-(2'-deoxyuridyl)acrylamido)phenylporphyrin **3-Me**.

This compound was made in the same way as compound **2-Me** starting with compound **3**; ^1H nmr (DMSO-d_6): ppm 11.15 (s, 1H, H-3), 10.60 (s, 1H, NHCO), 9.79 (d, 6H, 2,6-Py), 9.18 (m, 2H, β-pyrrole), 8.98 (d, 6H, 3,5-Py), 8.54 (s, 1H, H-6), 8.19 (d, 2H, 2,6-CONH-Ph-), 8.16 (d, 2H, 3,5-CONH-Ph), 7.78 (m, 6H, β-pyrrole), 7.42 (d, J = 15 Hz, 1H, CH=), 7.48 (d, J = 15 Hz, 1H, =CH), 6.15 (t, 1H, H-1'), 4.69 (s, 9H, N^+-CH_3), 4.30 (m, 1H, H-4'), 3.80 (m, 1H, H-3'), 3.45 (m, 2H, H-5'), 2.33 (m, 2H, H-2'), -3.04 (s, 2H, inner NH of porphyrin); uv-vis (water), λ_{max} pm 268, 428 (Soret), 520, 556, 590, 646.

Anal. Calcd. for $C_{56}H_{49}N_{10}I_3O_6$: C, 50.24; H, 3.69; N, 10.46. Found: C, 50.38; H, 3.81; N, 10.28.

Porphyrin Polymer **4**.

Compound **2** (14 mg, 0.02 mmole) was dissolved in 10 ml of DMF (freshly distilled under nitrogen) and 2,2'-azobisisobutylonitrile (1 mole % of the monomer) was added. The solution was stirred under nitrogen at 80° for 60 hours. The residue after removing the DMF under vacuum was chromatographed on silica gel with chloroform/methanol as eluent from 10:1 to 1:1 ratio. The first fraction was the unreacted monomer. The second broad fraction was collected as polymer product with yield of 45% based on the reacted monomer; ^1H nmr (deuteriochloroform): ppm 9.28 (m, 6H, 2,6-Py), 8.92 (m, 8H, β-pyrrole), 8.50 (m, 4H, phenyl), 8.14 (s, 1H, NHCO), 8.07 (m, 6H, 3,5-Py), 2.92 (quint, 2H, CH_2-CO-), 1.67 (m, 2H, -CH_2-), -2.90 (s, 2H,

inner NH of porphyrin); ir (potassium bromide): cm^{-1}; 3295 (ν_{NH}), 1659 ($\nu_{C=O}$); uv-vis (chloroform): λ_{max} nm 420 (Soret), 516, 550, 590, 644.

Anal. Calcd. for $C_{44}H_{30}N_8O$: C, 76.95; H, 4.40; N, 16.32. Found: C, 76.82; H, 4.55; N, 16.50

Cationic Porphyrin Polymer **4-Me**.

The water-soluble porphyrin polymer was obtained by *N*-methylation of the pyridyl groups on the polymer in the same way as described for compound **2-Me**. The average molecular weight measured by Size Exclusion Chromatography was 9,000 Daltons which was determined from the standard curve made with cytochrome c, bluedextrose and albumin.

The ir spectrum showed the disappearance of the 1618 cm^{-1} C=C band and those at 720 and 620 cm^{-1} (which are the finger-print bands for terminal $CH=CH_2$ groups). Also the signals in the vinyl region of the ^1H nmr spectrum (6.7-5.75 ppm) typical for a monomer disappeared and gave rise to a triplet at 2.92 ppm and a multiple at 3.06 ppm of the respective aliphatic protons; uv-vis (chloroform): λ_{max} nm 426 (Soret), 522, 558, 584, 652.

Anal. Calcd. for $C_{47}H_{39}N_8I_3O$: C: 50.74; H, 3.53; N, 10.07. Found: C, 50.61; H, 3.70; N, 10.21.

Porphyrin Copolymer **5**.

The copolymerization procedure was the same as the polymerization using compound **2** and acrylamide with molar ration at 1:6. The yield was 60% based on the reacted porphyrin; ^1H nmr (deuteriochloroform): ppm 9.06 (m, 6H, 2,6-Py), 8.87 (m, 8H, β-pyrrole), 8.17 (m, 6H, 3,5-Py), 8.08 (m, 4H, -Ph), 3.00 (m, 14H, CH_2-CO-), 2.00 (m, 14H, CH_2), -2.96 (s, 2H, inner NH of porphyrin); ir (potassium bromide): 3312 (ν_{NH}), 3420, 3400, (ν_{NH_2}), 1668 ($\nu_{C=O}$); uv-vis (chloroform): ν_{max} nm 420 (Soret), 516, 550, 590, 646.

Anal. Calcd. for the molar ratio 1:6 of the starting monomer and comonomer $C_{62}H_{60}N_{14}O_7$: C, 66.89; H, 5.43; N, 17.62. Found: C, 67.01; H, 5.62; N, 17.85.

Cationic Porphyrin Copolymer **5-Me**.

This water-soluble cationic porphyrin copolymer was made in the same way as described for compound **2-Me**. The average molecular weight was measured to be 12,000 daltons using the same standard curve as for polymer **4-Me**; uv-vis (chloroform), λ_{max} nm: 426 (Soret), 522, 560, 586, 642.

Anal. Calcd. for the molar ratio 1:6 of the starting monomer and comonomer $C_{65}H_{69}N_{14}I_3O_7$: C, 50.73; H, 4.52; N, 12.74. Found: C, 50.87; H, 4.71; N, 12.92.

Electronic Spectra Determination of Porphyrin-DNA Interaction.

DNA at various concentrations was added to the aqueous solution of porphyrin compounds. The uv-vis spectra were recorded for pure porphyrin compounds and each DNA-porphyrin solution after 5 minutes of mixing. The molar ratio (γ_0:mole of base pair (ds DNA) or base (ss DNA) to the mole of porphyrin unit) was measured at the highest hypochromicity value.

Unwinding of Supercoiled Plasmid DNA.

The following interaction reactions were carried out before the gel electrophoresis was performed.

(1) DNA, porphyrin **2-Me** and acrylamide were mixed and incubated for 5 minutes and copolymerized through radical initialization by ammonium persulfate and *N,N,N',N'*-tetramethylethylenediamine in aqueous medium at room temperature for 40 minutes.

(2) DNA acid porphyrin **2-Me** were first mixed and incubated for 5 minutes. The solution was brought under polymerization conditions as in (1).

(3) Compound **2-Me** and acrylamide were copolymerized first and DNA was added to the solution and incubated for 5 minutes.

(4) DNA and cationic porphyrin polymer **4-Me** were mixed and incubated for 5 minutes.

(5) DNA and cationic porphyrin copolymer **5-Me** were mixed and incubated for 5 minutes.

(6) DNA and porphyrin **2-Me** were mixed and incubated for 5 minutes.

In all cases, the molar ratio of porphyrin unit to DNA base pair were controlled at 1:2. The final concentration of each species was as following: DNA:6 x 10^{-11} *M* [base pairs], porphyrin unit:3 x 10^{-11} *M*, $(NH_4)_2S_2O_8$:8 x 10^{-11} *M*, *N,N,N',N'*-tetramethylethylenediamine:1 x 10^{-10} *M*, acrylamide:3.6 x 10^{-10} *M*.

All reaction solutions as well as unreacted DNA used as control and DNA standards were loaded on a 1% agarose gel. The electrophoresis was run in Tris-EDTA, *p*H = 8.0, at 2.0 volts/cm for 90 minutes.

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