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The stability of DNA–porphyrin complexes in the presence of Mn(II) ions

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ABSTRACT

The complex formation of porphyrins with DNA leads to changes of stability of DNA. In the present study we investigated binding properties and the thermodynamic parameters of a water-soluble, cationic planar Cu(II)-containing meso-tetrakis(4-N-butyl-pyridiniumyl)porphyrin [CuTButPyP4] and nonplanar Co(II)-containing meso-tetrakis(4-N-butyl-pyridiniumyl)porphyrin [CoButPyP4] with calf thymus DNA in the presence of divalent manganese ions. For displaying the changes of thermodynamic parameters (T_m and ΔT) the melting curves of DNA–porphyrin complexes in the presence of Mn^{2+} ions have been obtained. The enthalpy (ΔH) of helix–coil transition has been also evaluated. It was shown that the binding of ions to DNA proceeds in two stages depending on the manganese/DNA phosphates molar ratio [Mn]/[P]. At the first stage ($0.001<[Mn]/[P]<1$), the interaction of manganese ions with DNA phosphates occurs, causing an additional screening of their negative charge and the stabilization of the double helix. As a result, the best conditions for intercalation of CuTButPyP4 or of peripheral rings of CoButPyP4 occur. The significant increase of T_m, but less changes of ΔT were observed. At the second stage ($1<[Mn]/[P]<4$), the ions interact with both the phosphates and the nitrogen bases of DNA. At this stage, it is possible for the manganese ion to coordinate simultaneously to the oxygen atom of the phosphate and the neighboring base of DNA. At a higher [Mn]/[P] ratio, the destabilization of the double helix begins, and partial breakage of the hydrogen bonds between the nitrogen bases occurs. Respectively the destabilization of DNA in the presence of both porphyrins takes place.

1. Introduction

The thermodynamics of binding of small molecules to DNA has both practical and fundamental interests. The practical interest lies in the contribution that thermodynamics can support a rational design for the development of DNA molecules. In recent years, studies on the interaction of cationic porphyrins with DNA have received much attention because of its importance in DNA-probing and photodynamic therapy of cancer [1–3]. As DNA-binding ligands, porphyrins may associate with DNA in three binding modes: intercalation, groove binding, and outside binding with self-stacking along the DNA helix.

The interaction studies of cationic porphyrins with DNA have shown that the intercalation of porphyrin into DNA requires at least temporary existence of planar conformation of porphyrin molecule (i.e. it must have a limited effective thickness). External (groove) binding is typical for porphyrins with bulky peripheral substituents or axial ligands on the central ion, resulting in steric hindrance, thus making intercalation impossible. [4,5]. In this case the porphyrin ring fits into the minor groove of the helix or locates in the major groove stabilized by electrostatic interaction between the negatively charged phosphate group and the positively charged pyridinium rings of porphyrin periphery [6,7].

It was shown, that the CuTMPyP4 porphyrin could also bind with DNA by partial intercalation (hemi-intercalation) mode, in which a porphyrin intercalates in one strand of duplex DNA [8]. Additional support for partial intercalation is the preferential binding of porphyrins to melted or partially melted regions of DNA [9].

The binding mode of porphyrins with DNA also depends on the relative concentration of porphyrin and DNA, the nature of DNA and porphyrins (the central metal, type of the peripheral substituents and etc.).

For natural DNA or GC-rich sequences, nonmetal porphyrins or metalloporphyrins, with planar structure, intercalated between DNA base pairs and exhibit a weak negative Circular Dichroism (CD) signal in the Soret absorption band, the co-called induced CD signal (ICD). For AT-rich sequences, porphyrins bind along the groove of DNA and exhibit a clear strong positive CD band in the same region. On the other hand, porphyrins with bulky peripheral substitutes and metalloporphyrins with axial ligands bind with DNA externally, along the groove due to the steric hindrance, and exhibit a positive CD signal [10,11]. With increasing relative porphyrin concentration, the bisignale CD spectra (present and negative and positive signals) become apparent due to stacking at the outside of DNA, regardless of the porphyrin structure or DNA type [12,13]. Porphyrins, depending on their structure, and the presence of the coordinated metal

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including possible axial ligands, display different preferences not only for binding modes, but also for different DNA sequences.

The thermostability of DNA changes upon complex formation with porphyrins, and these changes depend on the binding modes of the porphyrins. Upon intercalation, as in case of planar porphyrins, such as nonmetal and Cu-, Ni-containing porphyrins, changes at GC-rich cites occur, and in the case of Co-, Fe- and Mn-containing porphyrins, which contain axial ligand, the interaction with DNA results in changes which occur at AT-rich cites [7]. The melting temperature (T_m) of DNA is sensitive to its double helix stability; furthermore molecular interactions with DNA change the T_m depending on the strength of interactions. Therefore, the melting temperature can be used as an indicator of binding properties of molecules to DNA and their binding strength. For more details we carry out melting of DNA/porphyrin complexes in the presence of divalent manganese ions, which may be involved in interactions with phosphate groups and with the DNA bases [14–16].

In the current work, utilizing visible absorption spectroscopy, CD spectrophotometry and thermal melting method were used to study the interaction of cationic porphyrins with DNA. As cationic porphyrins, we have chosen copper and cobalt containing CuTBut-PyP4 and CoTButPyP4 water-soluble porphyrins. The structure of these cationic porphyrins is shown in Fig. 1.

2. Materials and methods

Ultra-pure DNA from calf thymus (protein<0.1%, RNA<0.2%, M.w.>30 MDa: GC=42%) was a kind gift from prof. D.Yu. Lando at the Institute of Bioorganic Chemistry (Minsk Belarus).

Porphyrins were synthesized in the Department of Pharmacological Chemistry, Yerevan State Medical University by the method described in Ref. [17].

All spectroscopic measurements were performed in 0.1 BPSE buffer (1BPSE = 6 mM Na_2HPO_4 + 2 mM NaH_2PO_4 + 185 mM NaCl + 1 mM EDTA), pH 7, 0.

The melting experiments were performed in 10^{-3} M NaCl solution, as in 0.1 BPSE buffer (ionic strength $\mu = 0.02$) this complexes are much stabilized and experimentally impossible to finish melting process. The pH of the solutions used throughout the experiments were kept constant at 7.0 ± 0.1.

A stock solution of DNA was prepared in 10^{-3} M NaCl solution at pH 7,0. An extinction coefficient $\varepsilon_{260} = 1.31 \times 10^4\ M^{-1}\ cm^{-1}$ was applied to determine the concentration of DNA in base pairs. Porphyrin concentrations and extinction coefficient of CuTButPyP4 and CoTButPyP4 porphyrins were determined by spectrophotometric method and are respectively equal $\varepsilon_{427} = 1.08 \times 10^5\ M^{-1}\ cm^{-1}$ and $\varepsilon_{437} = 0.74 \times 10^5\ M^{-1}\ cm^{-1}$. The porphyrin solutions were prepared before each experiment and were kept in the dark.

Visible absorption spectra of the porphyrins in the Soret region in the absence and presence of the DNA duplexes were collected at 20 °C using Perkin Elmer Lambda 800 UV/VIS spectrophotometer.

CD spectra were recorded at 20 °C on Dichrograph Roussel Jouan-II.

Melting curves were recorded on Perkin Elmer Lambda 800 UV/VIS spectrophotometer with heating rate 0.5–1 °C/min.

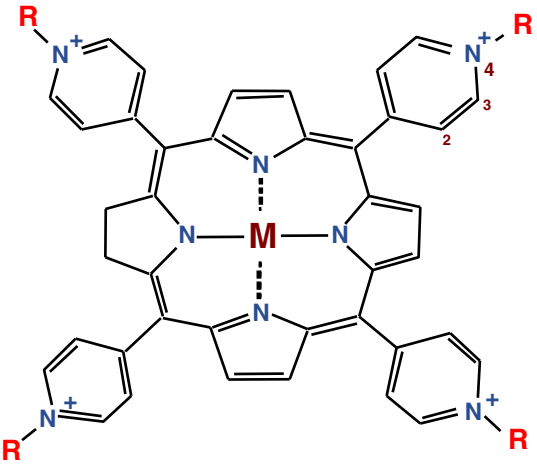

Fig. 1. Chemical structure of meso-tetrakis (4-N-butyl-pyridiniumyl) porphyrin.

3. Results and discussion

3.1. Circular dichroism

To determine the binding modes of the studied porphyrins, the CD spectra of porphyrin/DNA complexes were measured. Variant concentrations of porphyrins were added to a fixed concentration of DNA solution and the CD spectra from 220 nm to 550 nm were recorded.

The planar porphyrins, being symmetric compounds do not posses natures optical activity have zero dichroism throughout the whole spectral region. Consequently, the CD bands observed for porphyrin/DNA complex in the ICD region, where DNA does not have a measurable CD spectra, corresponds to packing of the porphyrin onto the DNA molecule.

The used porphyrins, being planar, symmetric compounds do not possess natural optical activity and actually have zero dichroism in the whole spectral region of their electronic transitions. Consequently, the CD band observed for porphyrin/DNA complexes in the visible region, where DNA does not have a measurable CD spectra, corresponded to packing of porphyrins on the DNA as in a matrix.

The CD spectra of CuTButPyP4(a) and CoTButPyP4(b) in the presence of DNA are presented in Fig. 2. The negative CD signal was observed in the Soret band for CuTButPyP4/DNA complexes at the low relative concentration: 0.05<r<0.24. This is a typical CD signal for the intercalative binding of porphyrin [4,18]. A positive CD signal was observed for CoTButPyP4/DNA complexes in relative concentration of

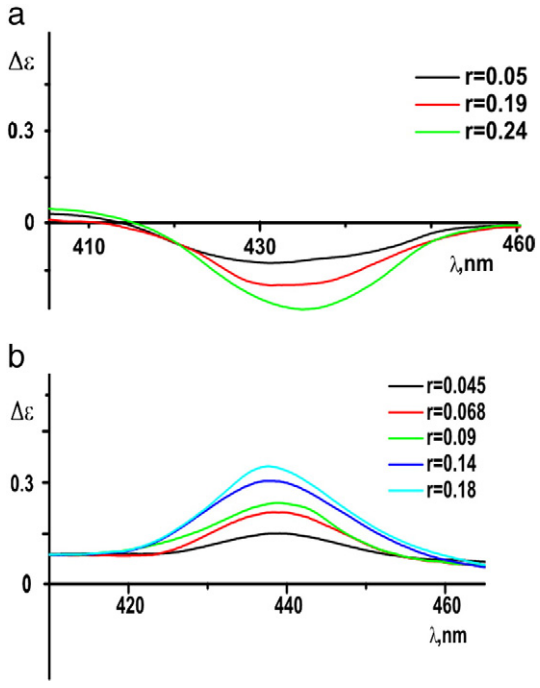

Fig. 2. The induced CD spectra of CuTButPyP4/DNA (a) and CoTButPyP4/DNA (b) complexes at concentration range 0.05<r<0.24 and 0.045<r<0.18 respectively.

0.045<r<0.18, and this is typical CD signal for external binding mode [4,18].

3.2. Absorbance

The interaction of these porphyrins with DNA duplexes were also studied by monitoring the changes of absorbance spectra in Soret region. Porphyrin solutions were titrated with stock solution of calf thymus DNA at 20 °C. The results are presented in Fig. 3. The absorption maxima of CuTButPyP4 (a) and CoTButPyP4 (b) are 427 nm and 437 nm respectively. Upon binding with DNA the CuTButPyP4 spectrum exhibits 44% hypochromism and 5 nm red-shift whereas CoTButPyP4 spectrum exhibits 29.3% hypochromism and 1 nm red-shift. It is worth noting that when the total base-pair concentration was 15–20 times greater than the porphyrin concentration, no further changes in the Soret band occurred indicating absence of free porphyrin in solution. One set of isosbestic points was observed in each case thus the binding is said to proceed in a single step.

3.3. Melting curves

To investigate the effects of Cu- and Co-porphyrins on DNA thermostability, DNA–porphyrin thermal melting experiments were performed. It is known, that the melting temperature (T_m) of DNA is sensitive to double helix stability and the binding of compounds with DNA result in change of T_m, depending on the strength of interactions [19]. Therefore, it can be used as an indicator of binding properties of molecules to DNA and their binding strength.

To study the changes of thermostability upon interaction of CuTButPyP4 and CoTButPyP4 with DNA, T_m was measured in the range of relative porphyrin concentrations of 0.001<r<0.1. It appeared that at ionic strength μ=0.02 the melting process of DNA/porphyrin complexes finished above 98 °C, which made it impossible to record the entire melting process. Consequently, it is not possible to accurately determine melting curve parameters under these conditions. Therefore the melting curves of CuTButPyP4/DNA and CoTButPyP4/DNA complexes were carried out at relatively low ionic strength (μ=0.001) in 10^{-3} M NaCl solution.

The melting parameters of DNA in presence of investigated porphyrins at ionic strength μ=0.001 are summarized in Table 1.

The analysis of data shows that both porphyrins strongly stabilize the DNA double helix (the melting temperature increases). In our previous work [6] it was shown that both types of porphyrins—planar and nonplanar with axial ligands—increased the thermal stability of DNA. The similar effect observed for DNA/Fe-porphyrin complexes, with two axial ligands [20]. Besides the shift of melting curve to high-temperature region, the overall shape of the melting curve also changes (data not shown). The end of melting region, corresponding to the melting of GC-rich sites of DNA, exhibits a strong shift towards the high-temperature area. The melting interval is also increases. On the basis of these data it is possible to ascertain, that the investigated Cu/Co-porphyrins may selectively stabilize the GC-pairs of DNA. As a result it may be safe to assume that predominant interactions stabilizing the double helix occur within the GC-rich area of DNA.

The planar CuTButPyP4 and nonplanar CoTButPyP4 porphyrins investigated in this study interacted with DNA via two distinct binding modes, intercalation and outside binding respectively. Such selective binding characteristics of intercalation into the GC-rich areas and external biding at the AT-rich regions have previously been characterized for different porphyrins [21].

It is known, that Mn^{2+} ions, like many other transition metals, stabilizes the DNA secondary structure at low concentration, and destabilizes it at high concentration [22,23]. In order to modulate demonstrated effects of these porphyrins and to extrapolate the selective interactions with AT and GC base pairs, the melting profile of DNA/porphyrins complex was obtained in the presence of manganese ions. Manganese ions were selected because Mn^{2+} has been proposed to interact with phosphate groups and with the bases of DNA [24]. In Fig. 4 the melting curves of CuTButPyP4/DNA (a) and CoTButPyP4/DNA (b) complexes in the presence of Mn^{2+} ions in 10^{-3} M NaCl are shown, when the concentration of manganese ions per phosphate groups of DNA varied between 0 and 1 ([Mn^{2+}]/[P]). It was shown, that binding of Mn^{2+} ions with DNA depend on the manganese/DNA phosphates molar ratio [Mn^{2+}]/[P]. At the concentrations of

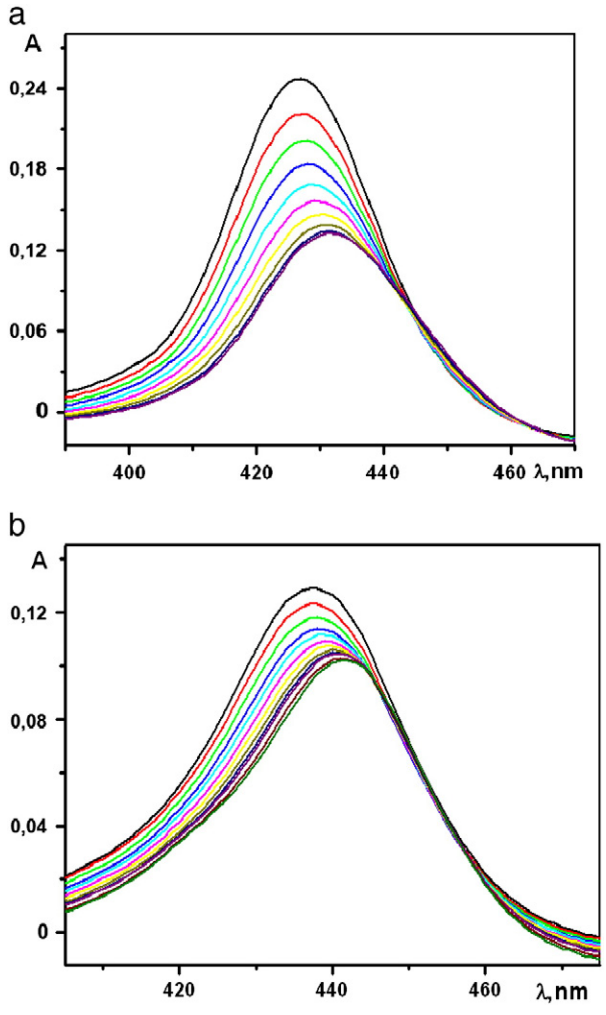

Fig. 3. Visible absorption spectra of CuTButPyP4 (a) and CoTButPyP4 (b) in the presence of DNA at 20 °C.

Table 1
The melting temperature (T^*_m) and melting interval (ΔT^{**}) at λ=260 nm of DNA complexes with different concentrations of Cu/Co-porphyrins in 10^{-3} M NaCl (μ=0.001). (All obtaining data are averaged over three experiments and the error is 0.1–0.22).

r=[P]/[DNA]	CuButPyP4/DNA		CoButPyP4/DNA	
	T_m	ΔT	T_m	ΔT
0	54.6	13.2	54.6	13.2
0.001	53.8	13.01	54.53	13.38
0.01	55.9	13.0	56.06	14.5
0.03	59.6	15.34	58.86	17.58
0.05	70.4	16.85	61.68	18.85
0.1	62.65	12.65	68.35	21.9

* T_m—melting temperature is midpoint of melting curve.
** ΔT—melting interval: $\Delta T = \frac{1}{(\delta\theta / \delta T_{max})}$.

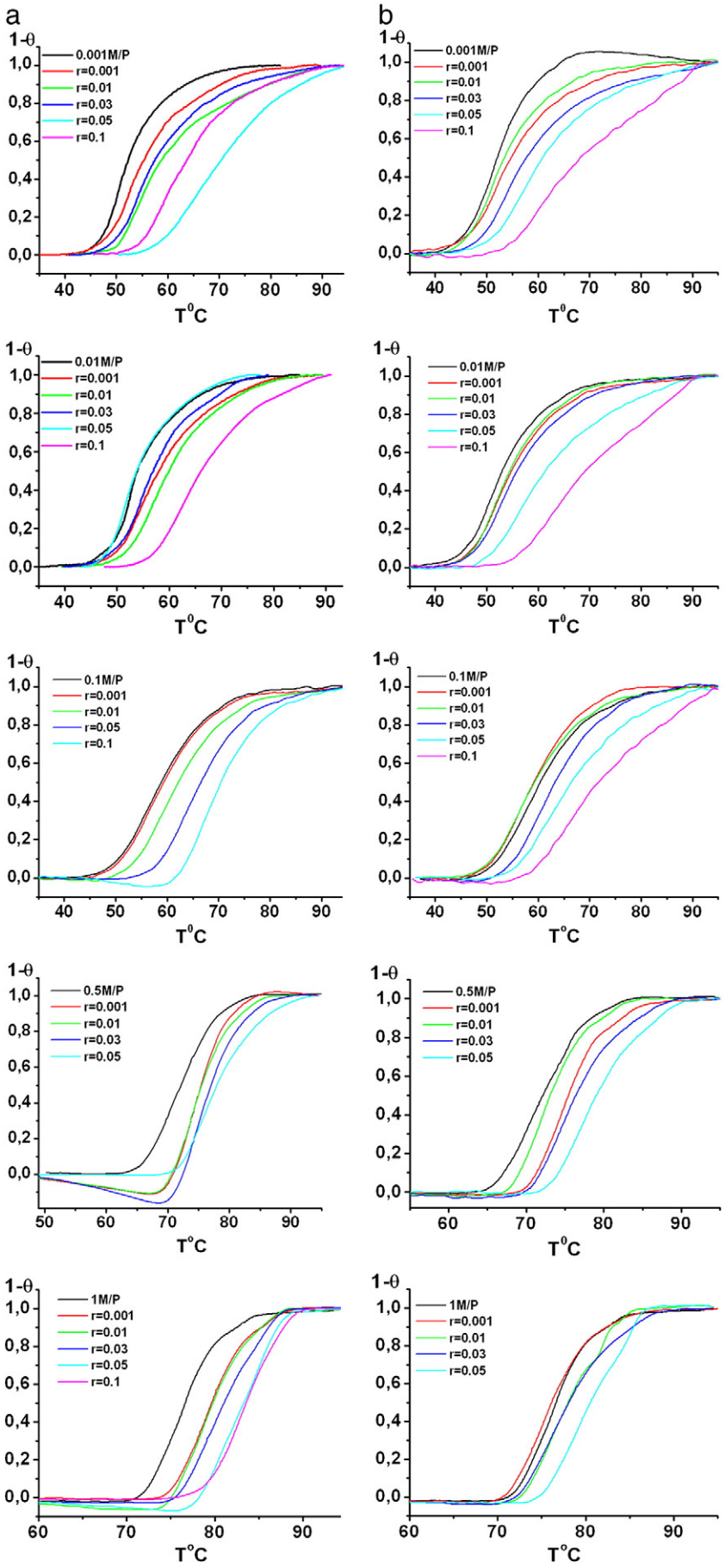

Fig. 4. The normalized melting curves of CuTButPyP4/DNA (a) and CoTButPyP4/DNA (b) complexes in the presence of Mn^{2+} in 10^{-3} M NaCl.

Table 2
The thermodynamic parameters of CuButPyP4/DNA and CoButPyP4/DNA complexes in presence of manganese ions: $[Mn^{2+}]/[P]=0.5$.

CuButPyP4/DNA					CoButPyP4/DNA			
r = [P]/[DNA]	T_m	ΔT	ΔH kcal/mol	ΔS	T_m	ΔT	ΔH kcal/mol	ΔS
0	72.2	8.2	–	–	72.2	8.2	–	–
0.001	75.45	6.3	−0.94 ± 0.02	−0.01 ± 0.001	75.4	8.0	−0.11 ± 0.02	−0.001 ± 0.0005
0.01	75.5	7.4	−3.83 ± 0.15	−0.05 ± 0.002	73.2	7.4	−20.97 ± 0.3	−0.29 ± 0.03
0.03	77.1	7.5	−4.56 ± 0.10	−0.06 ± 0.002	76.4	9.4	5.35 ± 0.4	0.074 ± 0.01
0.05	78	10.2	15.49 ± 0.20	0.21 ± 0.01	79.1	9.8	4.41 ± 0.3	0.061 ± 0.015
0.1	81.3	11	17.62 ± 0.30	0.24 ± 0.02	81.4	9.6	4.34 ± 0.3	0.06 ± 0.015

manganese ions $0.001<[Mn^{2+}]/[P]<1$ an additional screening of DNA phosphates negative charge occurs and stabilize the double helix. The optimal concentration of divalent manganese ions equal 0.5 $[Mn^{2+}]/[P]$, when all phosphate groups are screening and realize the best conditions for intercalation of planar CuTButPyP4 porphyrin or for peripheral rings of nonplanar CoTButPyP4. The results of the UV melting experiments of this complexes in presence of manganese ions at molar ratio $[Mn^{2+}]/[P]=0.5$ are summarized in Table 2.

The CuTButPyP4 porphyrin have planar structure with the central metal is in plane of porphyrin core, and its intercalation is natural. The hindrances for intercalation may create only the bulky peripheral radical.

It is known that the CuTMPyP4 porphyrin can bind to DNA by partial intercalation (hemi-intercalation) [8], in which a porphyrin intercalates in one strand of duplex DNA. Additional support for partial intercalation is the preferential binding of porphyrins to melted or partially melted regions of DNA [9]. The porphyrin binds by normal intercalation between the C and G of 5″TCG3″ and by extruding the C of 5″CGA3″. The DNA forms a distorted right-handed helix with only four normal Watson–Crick base pairs. Two pyridyl rings are located in each groove of the DNA. The complex appears to be extensively stabilized by electrostatic interactions between positively charged nitrogen atoms of the pyridyl rings and negatively charged phosphate oxygen atoms of the DNA. Favorable electrostatic interactions appear to draw the porphyrin into the duplex, offsetting unfavorable sterical hindrances between the pyridyl rings and the DNA backbone. These pyridyl-backbone hindrances extend the DNA along its axis and preclude formation of van der Waals stacking contacts in the complex. Stacking contacts are the primary contributor to stability of DNA. The unusual lack of van der Waals stacking contacts in the porphyrin complex destabilizes the DNA duplex and decreases the energetic cost of local melting [8]. According to this work we conclude, that CuTButPyP4 porphyrin bind with DNA by two binding modes: partial intercalation at small relative concentrations and outside binding at high relative concentrations of porphyrin. Furthermore Mn^{2+} ions make this effect more significant.

The CoTButPyP4 porphyrins have one axial ligand (nonplanar structure) and respectively prefer outside binding mode. Outside binders interact preferably in AT-rich regions of DNA. For relatively rigid porphyrins, this preference could reasonably be attributed to distortion of AT regions; this distortion may maximize electrostatic interactions [25–27]. As seen in Fig. 4 the melting curves of CoTButPyP4/DNA complexes change strongly in high-temperature area, according to the melting of GC-rich sites of DNA. Hence we conclude that intercalation binding mode take place. It is clear, that CoTButPyP4 porphyrin with axial ligand cannot intercalate. The spacing between adjacent base pairs to intercalated ligands is ~6.8 Å, cationic metalloporphyrin possessing even one axial group is thick for intercalation into DNA [28]. At other hand, it has been reported, that 5 coordinately ZnTMPyP and CoTMPyP porphyrins have approximate "thickness" of 5 Å [29]. Co-porphyrins, having one axial ligand, exclude the intercalation into DNA duplex independent of type of peripheral radicals. We assume that the observed effects at GC-rich regions on melting curves are the result of the so-called semi-intercalation binding mode of porphyrins during which one of the peripheral rings intercalates into the DNA helix, but the center of porphyrin core stays out near the phosphate groups of DNA. It has been reported [18,28], that the angle of Co-porphyrins independent of peripheral substitutes (methyl, butyl) with the helix axis of DNA is ~45°. The presence of axial ligands on the metal ion of the Co-porphyrin excludes porphyrin intercalation; however hemi-intercalation is possible.

Increasing of T_m for both metalloporphyrins/DNA complexes is the general evidence for stabilization. The resulting complex is stabilized by favorable electrostatic interactions between the alkylated pyridine nitrogen atoms and the negatively charged phosphate groups of DNA. As a result, the double helical structure of DNA at binding sites is disrupted. The role of water in stabilizing the complex is also important since intercalation effectively "hides" the hydrophobic core of the porphyrin from solvent. At concentrations of manganese ions, when all phosphate groups pair wise are occupied and the best conditions for intercalation take place ($[Mn^{2+}]/[P]\geq 0.5$ M), the effect of stabilization is more pronounced (T_m increased).

At the concentrations manganese ions $1<[Mn^{2+}]/[P]<4$ (the corresponding melting curves are not presented here), the manganese ions interact with both the phosphates and the bases of DNA. At a higher $[Mn^{2+}]/[P]$ ratio, the destabilization of the double helix is observed and partial breakage of the hydrogen bonds between the nitrogen bases occurs. Correspondingly the destabilization of DNA in the presence of both porphyrins takes place.

The complex formation of porphyrins with DNA leads to changes of stability of DNA. The thermodynamic parameters of CuTButPyP4/DNA and CoTButPyP4/DNA complexes, such as T_m and ΔT, the enthalpy of helix–coil transition (ΔH) are determined from the melting curves by means of general formula (1), which contain values directly obtained from the experiments [30] with the combination of the "area" method [31].

$$\Delta H=\frac{\delta(\Delta T)}{(\delta T_m)^2}\cdot T_0^2\cdot r,\quad \Delta S=\frac{\Delta H}{T_0}$$
$$\delta(\Delta T)=\Delta T_m-\Delta T_0,\quad \delta T_m=T_m-T_0. \tag{1}$$

where r = [porphyrin]/[DNA] and $r\ll 1$, T_m and ΔT are the melting temperature and width of the melting range for the ligand/DNA complex, T_0 and ΔT_0 are the same quantities for DNA without ligand.

The changes of enthalpy and entropy can give important information on binding of porphyrins to DNA. The data presented in Table 2 show, that at low ionic strength the binding of both porphyrins to DNA is accompanied by "unfavorable" enthalpy change and "favorable" entropy change. It has also been indicated (Table 2) that the binding of CuButPyP4 to DNA is an exothermic interaction at relative concentrations r = 0.001; 0.01 and 0.03, and in case of CoButPyP4—at relative concentrations r = 0.001 and 0.01 respectively. Upon interaction of the CuButPyP4 with DNA the enthalpy changes (ΔH) are less exothermic (ΔH = −4.56 kcal/mol) than in case of CoButPyP4 metalloporphyrin (ΔH = −20 kcal/mol). Data from Table 2 show that binding of metalloporphyrins to DNA is accompanied by small negative entropy

changes at relative concentrations r = 0.001; 0.01 and 0.03 and positive entropy changes at r = 0.03; 0.05 and 0.1. It is known that the Columbic interaction between cation and anion is driven by positive entropy changes [32]. Therefore, the positive entropy change upon the binding of the cationic metalloporphyrin to DNA probably arises from the electrostatic interaction between positively charged meso-substituents and negatively charged phosphate groups. Upon closer contact or interaction between these charged groups, the water molecules bound to these ionic groups are released and the positive translational entropy would lead to positive entropy changes in the overall thermodynamics of interactions. In the case of the binding of these porphyrins with DNA at comparably high concentrations, desolvation which occurs due to the ionic interaction is observed as shown by the positive enthalpy changes. In addition, interaction of the metalloporphyrin with DNA gives rise to a large distortion in the DNA structure [8,33]. Such a distortion results in a change in the local charge density, which undergoes a condensed counter-ion release from the interacting surface. Both distortions of DNA and condensed counter-ion release lead to large positive entropy changes [34].

The interaction of DNA with a drug involves proceeding from an initial (free) state where water molecules are bound to the surfaces of both interacting species to the final (bound) state where these water molecules would be removed or expelled from the binding interface. So that, during this process there is a resultant gain in entropy from the release of bound water into bulk phase. However, this favorable entropy is accompanied by enthalpically unfavorable effects resulting from disruption of water–DNA hydrogen bonding or disruption of other ordered solvent molecules on the binding interface. Therefore DNA–porphyrin interactions are essentially entropically driven. On the basis of these results it can be concluded that the nature of interaction forces is predominately hydrophobic.

4. Conclusions

The visible spectrophotometer methods as well as the melting temperature determination were applied to evaluate the affinity and thermodynamic parameters of binding cationic porphyrin to DNA. The DNA-binding processes for both investigated porphyrins changed from exothermic for low molar ratio to endothermic for high molar ratio and similar changes for entropy were observed. The transition entropy of DNA/CoTButPyP4 complexes (outside binder) is apparently larger than transition entropy for DNA/CuTButPyP4 complexes (intercalator). Thus the binding of metalloporphyrins with DNA duplexes depend on the type of central metal.

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