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INTERACTION OF MESO-TETRA-(4N-ALLYLPYRIDYL) PORPHYRIN AND ITS Cu-, Co- AND Zn- CONTAINING DERIVATIVES WITH DNA

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The influence of water soluble cationic meso-tetra-(4N-allylpyridyl) porphyrin (H_2TAlPyP4) and its metal complexes with Cu-, Co- and Zn- on hydrodynamic and spectral behaviour of ct-DNA solutions has been studied by viscometry and UV-VIS spectrophotometry methods. The results obtained were compared with the results of previously conducted similar studies on meso-tetra-(3N-allylpyridyl) porphyrin (H_2TAlPyP3). It has been shown that the change in position of peripheral radicals on pyridylic ring has absolutely no effect on rules of interaction of investigated porphyrins with DNA in case of outside binders CoTAlPyP4 and ZnTAlPyP4. Planar porphyrin H_2TAlPyP4 interacts with DNA predominantly by intercalation mode at low relative concentrations of r (r = [*Porphyrin*] / [*DNA*]) and by external binding mode at high values of r. Unusual behaviour shows CuTAlPyP4, which interacts with DNA via non-classical (partial) binding mode. It was shown that H_2TAlPyP3 and its metal complexes bind to DNA much more intensely than H_2TAlPyP4 and its metal complexes.

Porphyrin – ct-DNA – Viscometry – intercalation – outside binding – partial intercalation

Մածուցիկաչափության և սպեկտրոֆոտոմետրիայի մեթոդներով հետազոտվել է ջրալուծ կատիոնային մեզո-տետրա-(4N-ալլիլպիրիդիլ) պորֆիրինի (H2TAlPyP4) և Cu-ի, Co-ի և Zn-ի հետ նրա համալիրների ազդեցությունը ԴՆԹ-ի լուծույթների հիդրոդինամիկական և սպեկտրալ հատկությունների վրա: Ստացված արդյունքները համեմատվել են մեզո-տետրա-(3N-ալլիլպիրիդիլ) պորֆիրինի (H_2TAlPyP4) հետ նախկինում իրականացված նմանատիպ հետազոտությունների արդյունքների հետ: Ցույց է տրվել, որ պիրիդիլային օղակում կողմնային ռադիկալների դիրքի փոփոխությունը բացարձակապես չի ազդում հետազոտվող պորֆիրինների՝ ԴՆԹ-ի հետ փոխազդեցության օրինաչափությունների վրա արտաքինից կապվող CoTAlPyP4-ի և ZnTAlPyP4-ի դեպքում: Հարթ կառուցվածքով H_2TAlPyP4-պորֆիրինը ԴՆԹ-ի հետ առավելապես փոխազդում է ինտերկալման վարքագծով ցածր r (r = [*Porphyrin*] / [*DNA*]) հարաբերական կոնցենտրացիաների և արտաքին կապումով՝ մեծ կոնցենտրացիաների դեպքում: Անսովոր վարքագիծ է դրսևորում CuTAlPyP4-ը, որը ԴՆԹ-ի հետ փոխազդում է ոչ դասական (մասնակի) կապման ռեժիմով: Ցույց է տրվել, որ H_2TAlPyP3-ը և նրա մետաղակոմպլեքսները ԴՆԹ-ի հետ ավելի ինտենսիվ են փոխազդում, քան H_2TAlPyP4-ը և նրա մետաղակոմպլեքսները:

Պորֆիրին – ԴՆԹ, մածուցիկաչափություն – ինտերկալում – արտաքին կապում – մասնակի ինտերկալում

Методами вискозиметрии и спектрофотометрии изучено влияние водорастворимого катионного мезо-тетра-(4N-аллилпиридил) порфирина (H_2TAlPyP4) и его комплексов с Cu-, Co- и Zn- на гидродинамическое и спектральное поведение растворов ДНК. Полученные результаты сравнивались с результатами ранее проведенных аналогичных исследований мезо-тетра-(3N-аллилпиридил) порфирина (H_2TAlPyP3).

Показано, что изменение положения периферических радикалов на пиридиловом кольце абсолютно не влияет на закономерности взаимодействия исследованных порфиринов с ДНК в случае внешних связующих CoTAlPyP4 и ZnTAlPyP4. Планарный порфирин H_2TAlPyP4 взаимодействует с ДНК преимущественно интеркаляционным режимом при низких относительных концентрациях *r* (*r* = [*Porphyrin*] / [*DNA*]) и внешним режимом связывания при высоких значениях *r*. Необычное поведение проявляет CuTAlPyP4, который взаимодействует с ДНК по неклассическому (частичному) режиму связывания. Было показано, что H_2TAlPyP3 и его металлокомплексы связываются с ДНК намного интенсивнее, чем H_2TAlPyP4 и его металлокомплексы.

Порфирин – тт-ДНК – вискозиметрия – интеркаляция – внешнее связывание – частичная интеркаляция

Cationic porphyrin macrocycles represent a large class of compounds which are applied in photodynamic therapy of cancer and in biology [30]. The interaction of porphyrins and metalloporphyrins with DNA has a considerable interest due to their medical applications. DNA provides a range of binding sites and binding modes for covalent and non-covalent interactions. The non-covalent interactions include intercalation, partial intercalation, groove binding and electrostatic bonding with metal complexes [1, 11, 12].

Study of cationic DNA interaction with porphyrin in solutions shows that intercalation of porphyrin into DNA requires planar conformation of porphyrin molecule. Groove binding is typical for porphyrins that cannot fit between nucleotides due to steric blockage, i.e. porphyrins having bulky side radicals or axial ligands on the central ion [23-25, 9]. In this case the side of the porphyrin ring fits into the minor groove of the helix or is located in the major groove by electrostatic interaction between the negatively charged phosphate group and the positively charged pyridinium rings.

The strength of binding porphyrin to the DNA is one of important parameters of its efficacy. It is well known, that number of drugs bases their biological activity on intercalation to DNA, so the studies of molecular interactions between drugs and DNA have great importance for studying their biological activity [28, 29].

Under appropriate conditions, intercalation of porphyrins causes a significant increase in viscosity of DNA solutions due to increase in separation of base pairs at intercalation sites and subsequent increase in overall DNA contour length [11]. In contrast, porphyrin molecules that binds exclusively in DNA grooves under same conditions, typically cause less pronounced (positive or negative) or no changes in DNA solution viscosity [18-20, 26].

In this paper, we discuss the factors affecting the character of porphyrin binding to DNA. The research tactics are as follows: the molecular configuration of porphyrins slightly changes, so that the ability of this porphyrin to interact can be correlated with the planarity and effective width of porphyrin molecules. Our basic expectation is to identify the conditions under which the degree of interaction of porphyrins with DNA is maximal. However, the main goal of this series of research is the development and demonstration of viscometry opportunities for similar purposes, as it is one of the most sensitive methods to changes of conformation and configuration of macromolecular compounds.

We already reported the results of investigations of the interaction of water soluble cationic *meso*-tetra-(4N-hidroxyethylpyridyl) porphyrin (H_2THOEtPyP4) and its metal complexes with Ni, Cu, Zn and Co on hydrodynamic and spectral behaviour of ultrapure solutions from *ct-DNA*. It was shown, that presence of planar porphyrins H_2THOEPyP4, NiTHOEPyP4 and CuTHOEPyP4 leads to increase in viscosity at relatively small concentrations, and then decreases to stable values, which was explained

by intercalation of these porphyrins in DNA helical structure. In porphyrins with axial ligands, such as CoTOEPyP4 and ZnTOEPyP4, the hydrodynamic parameters slightly decrease, which is explained by outside binding of these parameters in DNA surface [6-8].

The influence of porphyrin molecules configuration on their ability to affect on the DNA structure – water soluble cationic *meso*-tetra-(3N-hidroxyethylpyridyl) porphyrin (H_2THOEtPyP3) and its metal complexes with Ni, Cu, Co, Zn were also investigated, where we applied the same experimental approach. It was shown, that the change in position of peripheral radicals on pyridylic ring has no effect on laws of interaction of investigated porphyrins with DNA in case of outside binders CoTHOEPyP3 and ZnTHOEPyP3. Planar porphyrins H_2THOEtPyP3 and CuTHOEPyP3 interact with DNA in intercalation mode. It was obtained, that the hidroxyethyl group at 3N-position is favourably located relative to the DNA helix axis than at 4N-position [4].

The effect of the chemical structure (presence of double bond) of a side radical of porphyrins on their ability to affect the DNA structure has also been investigated. Water-soluble cationic *meso*-tetra-(3N-allylpyridyl) porphyrin (H_2TAlPyP3) and its Cu- Co- and Zn-containing derivatives were studied using UV/VIS absorption spectroscopy and viscometry. The change of the chemical structure of side radical of porphyrins has no effect on the regularity of interaction of outside binders CoTAlPyP3 and ZnTAlPyP3. Planar porphyrins H_2TAlPyP3 and CuTAlPyP3 interact with DNA considerably more intensively than H_2THOEtPyP3 and CuTHOEtPyP3. In particular, the maximum value of interaction intensity sharply increases and moves to the high porphyrin content values in DNA solution. The fact of better interactions of H_2TAlPyP3 than H_2THOEtPyP3 with DNA is explained by presence of double bond in side radicals contributes to a more favourable location of porphyrins into DNA groove binding [5].

In this paper we describe the results of UV/VIS absorption spectroscopy and viscometry analysis of the configuration and effective width of the peripheral radicals of cationic *meso*-tetra-(4N-allylpyridyl) porphyrin (H_2TAlPyP4), its Cu-, Co- and Zn-containing derivatives on their ability to affect the DNA structure. The collected data have been compared to our recent results on the influence of H_2TAlPyP3 and its Cu, Co and Zn metal complexes on hydrodynamic and spectral behaviour of DNA solutions, where we applied the same experimental approach [4].

Materials and methods. Ultra-pure DNA from calf thymus (protein < 0.1 %, RNA < 0.2 %, m.m. > 30 MDa: GC = 42 %) was a kind gift from Institute of Bioorganic Chemistry (Minsk, Belarus). Porphyrins were synthesized in the Department of Chemistry of Pharmacy Faculty, Yerevan State Medical University [22]. The structure of cationic *meso*-tetra-(4N-allylpyridyl) porphyrin (H_2TAlPyP4) is shown in fig.1.

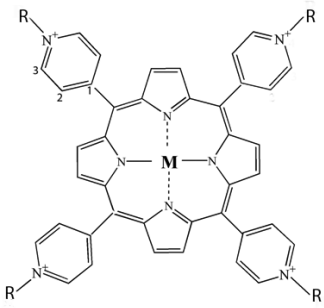

Fig.1. Chemical structure of meso-tetra-(4N-allylpyridyl) porphyrin. M=2H, Cu, Zn, Co, R = – CH_2–CH=CH_2.

The concentrations of investigated porphyrins were determined spectrophotometrically. All conditions for spectral and viscometry measurements are the same as in [4-6].

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

To explore the interaction between the porphyrin to DNA, viscosity measurements were carried out by keeping the DNA concentration as constant and varying the concentration of porphyrin. Viscosity measurements were carried out in a thermo stated bath at a temperature of 22±0.01°C, equipped with an Ubbelohde capillary viscometer (capillary's diameter is 0.56 mm). 6.0 ml of phosphate buffer was transferred to the viscometer to obtain the reading of efflux time. The efflux time of solvent in these conditions was 87.6 sec. The experimental errors were in allowed limits and did not exceed 1%.

Results and Discussion. ***Absorption spectra.*** The spectral features of studied porphyrins at complex formation with DNA and their binding parameters (binding constant K_b and exclusion parameter n) are shown in tab. 1. Details of representation and calculation of spectral data are discussed in [6]. K_b and n were calculated using the titration curves in Soret region. They are not represented in order to reduce the workload.

Table 1. The spectral and binding parameters of complexes H_2TAlPyP4, CuTAlPyP4, CoTAlPyP4 and ZnTAlPyP4 porphyrins with DNA, [Na^+] = 0.02, pH 7.0

Porphyrin	λ_{max} (nm)	$\Delta\lambda$(nm)	H, %	$K_b \times 10^7 (M^{-1})$	n
H_2TAlPyP4	424	13	53	1.02	1.85
CuTAlPyP4	426	3	33	4.08	1.81
CoTAlPyP4	437	-3	31	0.136	0.54
ZnTAlPyP4	440	2	24.5	0.7	1.0

The induced CD spectra of DNA in the presence of CuTAlPyP4 and CoTAlPyP4 porphyrins were shown in fig. 2.

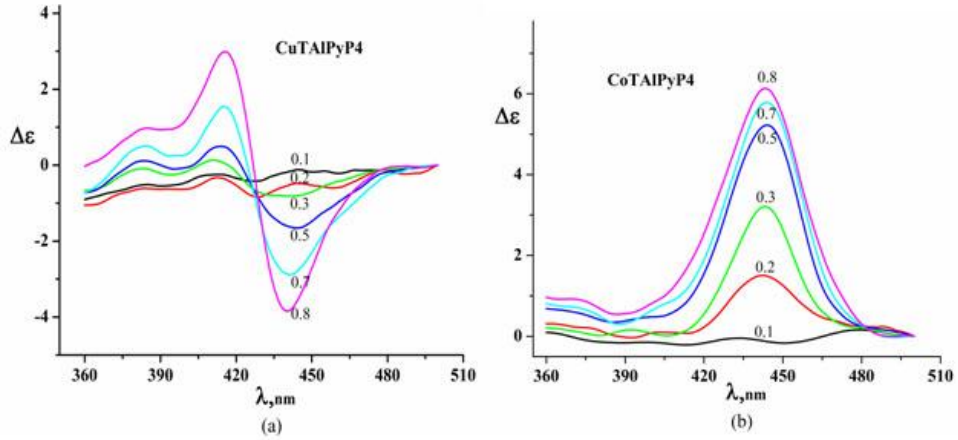

Fig.2. Induced CD spectra of CuTAlPyP4 and CoTAlPyP4 in presence of DNA at different relative concentrations, [Na+] =0.02, pH 7.0.

As seen from tab. 1, the binding of H_2TAlPyP4 to DNA is accompanied by red shift of the Soret maximum ($\Delta\lambda$=13nm) and pronounced hypochromicity (53%), which argue in favour of intercalation binding mode. The forceful evidence for intercalative binding is the

induced CD spectra, which demonstrate both negative (at low r < 0, 01) and conservative (at relatively high r > 0, 01) spectra (fig. 2a). On the basis of obtained data, it was supposed that the observed significant changes in CD spectra were connected to an altered DNA conformation initiated by intercalation of porphyrin H_2TAlPyP4 into DNA.

In case of CuTAlPyP4, the spectral parameters exhibit unusual behaviour for planar molecules contrary to our expectation. It is known, that coordination number is 4 for Cu-porphyrins and they have not axial ligation [22]. However, the spectral characteristics of CuTAlPyP4 in complex with DNA are different from the usual intercalators: small hypochromicity (33 %) and bathochrom shift ($\Delta\lambda$=13*nm*) are observed. At very low relative concentrations, the Soret band is not shifted. It is known, that such behaviour is typical for porphyrins with axial ligands as Co-, Fe-, and Mn-porphyrins. Moreover, the induced CD spectra in the Soret band substantially are positive (at r < 0, 4) and conservative (at r > 0, 4) (fig. 2b). In addition, one cannot exclude the possibility of implementing a partial intercalation binding mode, which is realized when $n < 2$ and is more pronounced in case of Cu-porphyrins [23].

The porphyrins CoTAlPyP4 and ZnTAlPyP4 used in our work are fifth coordinated and have one axial ligand, show the usual behaviour for outside binders [22]. Small hypochromicity (24, 5 %) and small bathochrom shift ($\Delta\lambda$=2*nm*) are observed for ZnTAlPyP4. However, CoTAlPyP4 at complex formation with DNA demonstrates 31% hypochromicity (greater then CoTAlPyP3 [6]) and blue shift ($\Delta\lambda$= –3*nm*) Both porphyrins CoTAlPyP4 and ZnTAlPyP4 exhibit only positively induced CD spectra in Soret band, which confirm outside arrangement of this porphyrin molecules on the surface of DNA helix. The induced CD spectra of fifth coordinated ZnTAlPyP4 and CoTAlPyP4 [22] are a good evidence for external ordered binding mode.

Viscosity measurement

As a means for further exploring the binding of the porphyrins to DNA, viscosity measurements were carried out with a fixed concentration of DNA by varying the concentration of the added porphyrins. The viscosity values were calculated from the observed flow time of DNA containing solutions with porphyrin (t) duly corrected for that of the DNA solution alone (t_0). The changes in the viscosity of DNA in the presence of H_2TAlPyP4, CuTAlPyP4, CoTAlPyP4 and ZnTAlPyP4 porphyrins were shown in fig. 3.

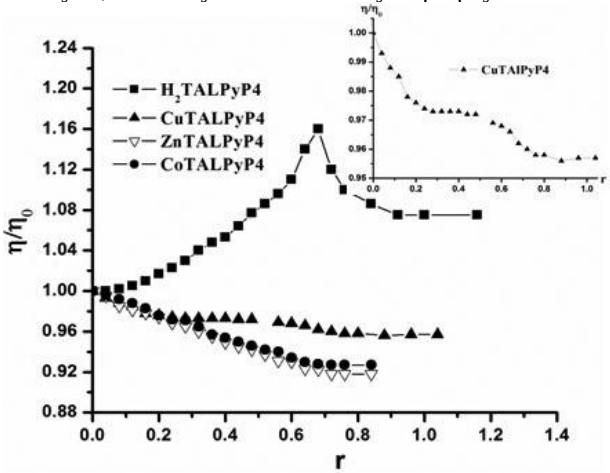

Fig.3. Plots of the relative viscosity of DNA vs. r values of H2TAlPyP4, CuTAlPyP4, ZnTAlPyP4 and CoTAlPyP4 porphyrins in phosphate buffer. The inserted graph present the enlarged plot of the relative viscosity of DNA versus r values of CuTAlPyP4.

We characterize the viscosity behaviour of DNA-porphyrin solution through the relative viscosity, defined as the ratio (η/η_0) where η_0 and η are the specific viscosity contributions of DNA in the absence and in the presence of the porphyrin, respectively. Obtained data were presented as (η/η_0) versus r (r= [Porphyrin]/[DNA]).

As it seen from fig. 3 the relative viscosity decreases with the addition of ZnTAlPyP4 and CoTAlPyP4 to the buffer solution of DNA. This decrease corresponds to the external binding mode and the type of central metal in porphyrin cavity is not important. Such behaviour was also observed in case of ZnTAlPyP3 and CoTAlPyP3 at complexation with DNA at same conditions [5].

The relative viscosity of DNA shows small growth with increase in concentration of the H_2TAlPyP4 up to concentration range r ≈ 0,7 and decreases thereafter. Of course, the processes of intercalation and external binding of porphyrin preceede simultaneously, but apparently, at initial dozes, porphyrin intercalation process prevails. As a result, by intercalation of porphyrins into the double helix of DNA, the distance between base pairs is increased, due to which an increase in viscosity is observed. Furthermore, in concentration range r > 0,7 due to saturation of intercalation sites, added amounts porphyrin molecules are located predominately on the surface of the DNA helix. As a result, the relative viscosity of H_2TAlPyP4 decreases monotonically in high concentration range up to constant values. That is why we can prove it by presence of two types of binding porphyrins to DNA.

On the basis of obtained data, it was supposed that the observed dependence of viscosity on r is connected to an altered DNA conformation initiated by intercalation of porphyrin H_2TAlPyP4 into base pairs of DNA. These results are in good agreement with optical absorption experiments.

The unusual behaviour displays the CuTAlPyP4 porphyrin at complexation with DNA. The relative viscosity decreases even at low concentrations of CuTAlPyP4, which means that this porphyrin shows the behaviour typical of outside binder such as externally binding porphyrins ZnTAlPyP4 and CoTAlPyP4. However, the decrease is not monotonic (fig.3, enlarged plot of the relative viscosity of DNA versus r values of CuTAlPyP4). At first, the relative viscosity decreases up to $r < 0,2$, afterwards it remains constant in concentration range $0,2 < r < 0,5$ and thereafter decreases again. Coordination number for Cu is four [22] hence the CuTAlPyP4 molecule is flat, which means that this molecule must act as an intercalators. However, as seen in fig.3 the behaviour of CuTAlPyP4 does not correspond to classical view of traditional intercalators. In comparison with the above spectral studies, which suggest that this porphyrin interacts with DNA via non-classical or partial intercalation, we can assume that predominantly partial intercalation takes place in concentration range 0,2 < r < 0,5. The induced CD spectra confirm this assumption: only positive spectra are observed up to r < 0,2 and the conservative spectra are observed starting from values of r < 0,3. These results certainly reflect the substantial difference between binding modes of H_2TAlPy4 and CuTAlPyP4 porphyrins.

Partial intercalations of small molecules and DNA were discussed in many works [2, 10, 14, 17, 21, 23, 27].

A classical intercalation model demands, that the DNA helix lengthens as base pairs are separated to accommodate the bound ligands, leading to the increase of DNA viscosity. In contrast, a partial, non-classical intercalation of ligands could bend the DNA helix, reducing its length and, respectively, its viscosity. In addition, complexes that binds exclusively in the DNA grooves by partial (non-classical) intercalation, under the same conditions, typically cause less pronounced (positive or negative) or no change in DNA solution viscosity [18, 20, 26].

Partial intercalators also reduce the axial length observed as a reduction in relative viscosity, whereas the classical organic intercalators such as ethidium bromide increase the axial length of the DNA and make it more rigid [10, 17, 21, 27] resulting in increase in relative viscosity.

We have developed two possible interpretations for reasons of partial intercalation mode of CuTAlPyP4 with DNA. Binding of CuTAlPyP4 with DNA by partial intercalation mod can be the result of the bulkiness/rigidness of the side radicals of CuTAlPyP4 (steric blockage). Second interpretation implies, that it is possible to expand the coordination number of Cu during the synthesis/processing in manner described in [3, 15] about the extending of coordination numbers of some metal ions by cation interaction with H_2O or other molecules. If this happens with Cu, the presence of axial ligands will not facilitate the intercalation of CuTAlPyP4 into base pairs of the nucleic acid. This may explain the partial intercalating properties of CuTAlPyP4. A similar explanation was applied to explain the binding mode of AgTAlPyP4 with poly (rA) poly (rU) and poly (rI) poly (rC) homopolymer RNA duplexes [16].

We prefer the first version of the interpretation, since earlier we conducted similar studies with CuTAlPyP3. The only difference between CuTAlPyP4 and the CuTAlPyP3 is the position of the side radical. Our studies showed that CuTAlPyP3 possesses the most pronounced properties of classical intercalation among all studied porphyrins, whereas, in case of validity of our second interpretation, CuTAlPyP3 also had to bind to DNA by a partial intercalation mode.

Data collected have been compared with the previously conducted results of similar studies for H_2TAlPyP3 and its metal complexes with Cu, Co and Zn [5]. A comparative plot of the relative viscosity of DNA versus *r* -values: a–H_2TAlPyP3 and H_2TAlPyP4; b–CuTAlPyP3 and CuTAlPyP4; c –ZnTAlPyP3 and ZnTAlPyP4; d–CoTAlPyP3 and CoTAlPyP4 are shown in fig. 4.

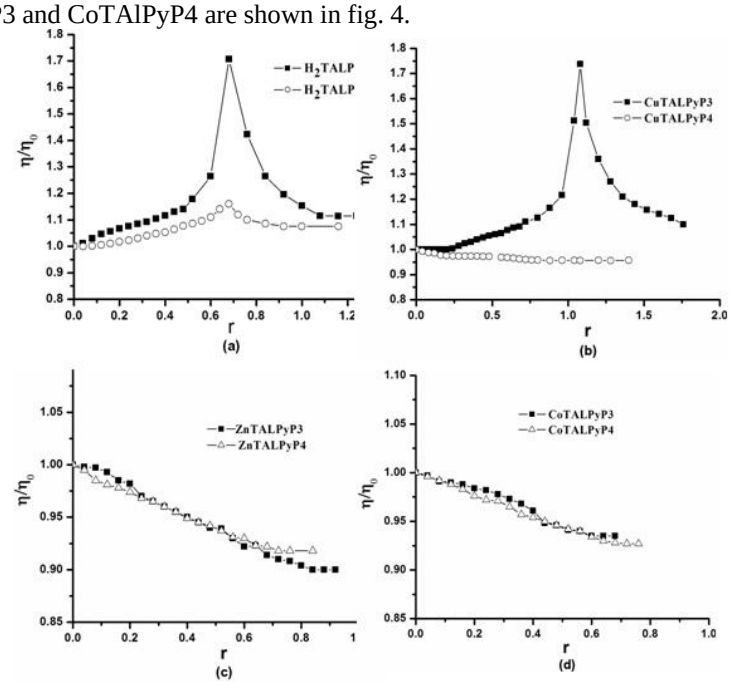

Fig.4. A comparative plots of the relative viscosity of DNA in phosphate buffer in presence of porphyrins: a–H2TAlPyP3 and H2TalPyP4; b–CuTAlPyP3 and CuTAlPyP4; c–ZnTAlPyP3 and ZnTAlPyP4; d–CoTAlPyP3 and CoTAlPyP4. On (b) the inserted graph present the enlarged plot of the relative viscosity of DNA versus r values of CuTAlPyP4.

The results reflected in fig. 4 clearly show, that the change of the configuration of porphyrins has no effect on the regularity of interaction of investigated porphyrins with DNA in case of outside binders CoTAlPyP4 and ZnTAlPyP4. This result is consistent with the binding parameters (see tab. 1) and, in our opinion, is quite logical. Such results were also obtained when similar investigations were conducted with porphyrins H_2THOEtPyP4, H_2THOEtPyP3 and H_2TAlPyP3 [4-6].

Planar porphyrins H_2TAlPyP4 and CuTAlPyP4 interact with DNA considerably less intensively than H_2TAlPyP3 and CuTAlPyP3 (fig. 4, a, b). This fact may be explained by presence of double bond in side radicals, as increase in rigidness and effective width of side radicals contributes to a less favourable location of porphyrins into DNA groove binding as it follows from CD spectra also (fig. 2).

Thus in this work, we employed the spectrophotometry and viscometry measurements to study the binding of novel water-soluble porphyrins *meso*-tetra-(4N-allylpyridyl) porphyrin (H_2TAlPyP4), and its Cu-, Co- and Zn-containing derivatives to the ct-DNA. Taken together, the spectroscopic and hydrodynamic data provided strong evidence that CoTAlPyP4 and ZnTAlPyP4 porphyrins bind to DNA by outside binding mode; H_2TAlPyP4 is bound with DNA predominately by intercalative mode. For the interaction of CuTAlPyP4 with DNA the partial or non-classical intercalative mode was attributed that may be realized via hydrophobic interaction between the porphyrin and DNA. Data collected have been compared with the previously conducted results of similar studies for H_2TAlPyP3 and its metal complexes with Cu, Co and Zn. The greater increase in viscosity is observed for H_2TAlPyP3 compared to the H_2TAlPyP4 likely due to the lower binding constant of the latter to DNA ($2.2\times10^{-7}M^{-1}$ against $1.02\times10^{-7}M^{-1}$). The fact of better interactions of H_2TAlPyP3 than H_2TAlPyP4 with DNA was explained by suggesting that presence of double bond in side radicals, increasing the rigidness and effective width of side radicals contributes to a less favourable location of porphyrins into DNA groove binding as it also follows from CD spectra. Comparison of different locations of peripheral radicals on pyridylic rings leads to the conclusion that H_2TALPyP3 and its metal complexes bind to DNA much more intense than H_2TALPyP4 and its metal complexes.

The above research demonstrates, that viscometry is an effective tool to investigate the binding mode of small molecules and DNA and provides assertive results for intercalative DNA-binding mode.

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List of abbreviations: (ct-DNA) calf thymus Deoxyribonucleic acid, (H_2TAlPyP4) *meso*-tetra-(4N-allylpyridyl) porphyrin, (H_2TAlPyP3) *meso*-tetra-(3N-allylpyridyl) porphyrin, (H_2THOEtPyP4) *meso*-tetra-(4N-hidroxyethylpyridyl) porphyrin, (H_2THOEtPyP3) *meso*-tetra-(3N-hidroxyethylpyridyl) porphyrin, (UV/VIS spectrophotometry) ultraviolet-visible spectrophotometry, (CD spectroscopy) circular dichroism spectroscopy.

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