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THE SPECTRAL MANIFISTATION OF THE NEW LUMINESCENT STYRYL DYES PHOTOSTABILITY AND PHOTOTOXIC INFLUENCE ON THE DNA

The spectral investigation methods of the phenomena of luminescent dye probes photostability and phototoxic influence on the DNA were proposed. The optical absorption, fluorescence and phosphorescence spectra of the samples of the newest investigated styryl dyes and the systems DNA +dye were studied. The optical absorption spectra of the samples of these compounds were measured under the irradiation of these samples by visible light. The results of the investigations carried out on a number of dyes were analyzed and discussed. The changes of optical density D value in wavelength regions 250+300 nm (that corresponds to the DNA first electronic transition) and 370+650 nm (that corresponds to a dye electronic transition) of the DNA+dye solutions were fixed. The dynamics ofD(t) was not monotonous. It was shown the Mn-Styr and Di-Styr-30 dyes are photochemically safe for the DNA; these dyes bound to the DNA are more photostable than in free state. The Di-Styr-24 and Dst-MdO dyes show slight phototoxic effect on the DNA. The versions of possible phototoxicity (and photostability) mechanisms are proposed.

Keywords: luminescent dyes, phototoxicity for the DNA, photostability, optical absorption spectrum.

Introduction

It is known the deoxyribonucleic acid (DNA) is a vitally important biopolymer macromolecule and the mainframe object of the transfer, storage and realization of genetic information in every living creature. Thus the detection of the DNA is an important problem in biophysics and medicine. This problem is often solved with the help of the small luminescent molecular probes that can interact with the DNA [1]. Such molecules bind to the DNA by noncovalent interactions being fixed either between the DNA nucleotides (intercalation) or between the sugar-phosphate chains (groove-binding) [2]. The molecule fixation on the DNA for the majority of the small molecules used as the luminescent probes for the DNA detection (often such probes are the organic dyes) results in the strong increase of the dye luminescence intensity [3]. It is important the luminescent probe applied to the study of the living cells (e. g. with the fluorescent microscopy) have not to be toxic or phototoxic. Besides, the probe should be photostable in order that the biomolecule could be studied for enough long period of time without the damage of the probe.

It is known the damage of a biological object can be induced by direct excitation of the luminescent probe that contacts with this object. The phototoxic influence of the dye molecule on the DNA can take place either directly via the excitation energy transfer from the dye to the DNA nucleotide bases or indirectly via the third molecule (e. g. by the triplet excitation energy transfer to the oxygen molecule resulting in the generation of the toxic singlet oxygen [4, 5]). The electronic states of individual nucleotides, the DNA and interaction of the DNA with dyes have been studied since 1960-70s [6-16]. The subjects of these investigations were spectral properties (optical absorption and luminescence) of the DNA and dyes intercalated in the DNA. The absorption bands (connected with the first electronic transition) of the DNA, RNA and nucleotide bases are located in the near UV spectral region with the maxima near 260 nm. At the same time, the corresponding absorption bands of the majority of dyes used as luminescent probes are located in the visual spectral region (more than 400 nm) [1]. The fact that the first excited singlet and triplet energy levels of dyes are situated essentially lower than correspondent levels of any nucleotides (the DNA links) does not allow the excitation energy transfer from the dye to the DNA thus making impossible the direct phototoxic influence of the dye on the

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DNA. Nevertheless, the small molecules (mostly the porphyrynes) that destroy the DNA indirectly by the generating of the singlet oxygen are well known and used in the photodynamic therapy.

Finally the interaction between dyes and the DNA results in the changes of dyes molecules spectral properties. In [16] it was reported the fluorescence intensity of the thiazole orange (TO) dye bound to the DNA was essentially increased in comparison with free dye. Recently it was showed by us [17] the fluorescence intensity of the benzothiazole styryl dyes increase in 2–3 orders of magnitude when bound to the DNA. In this paper the results of investigation of phototoxisity and photostability of several styryl dyes used as the DNA probes will be studied. The influence of irradiation of the dyes bound to the DNA on the absorption spectra of dyes and the DNA could characterize respectively the photostability and phototoxicity of these dyes.

Experimental

The total DNA from chicken erythrocytes was purchased from Sigma. The dyes Mn-Styr and Dst-MdO (Fig. 1) were obtained by the boiling of quaternary salt and *p*-dimethylaminobenzaldehyde in acetic anhydride similarly as described in [18]. Dyes Di-Styr-24 and Di-Styr-30 (Fig. 1) were obtained similarly to the TOTO dye [19] by the reaction of iodalkyl derivative of dimethylaminostyrylbenzothiazolium with corresponding diamines by long-term heating in DMF at 90 °C. The structure of the dyes was confirmed with H^1 NMR and element analysis.

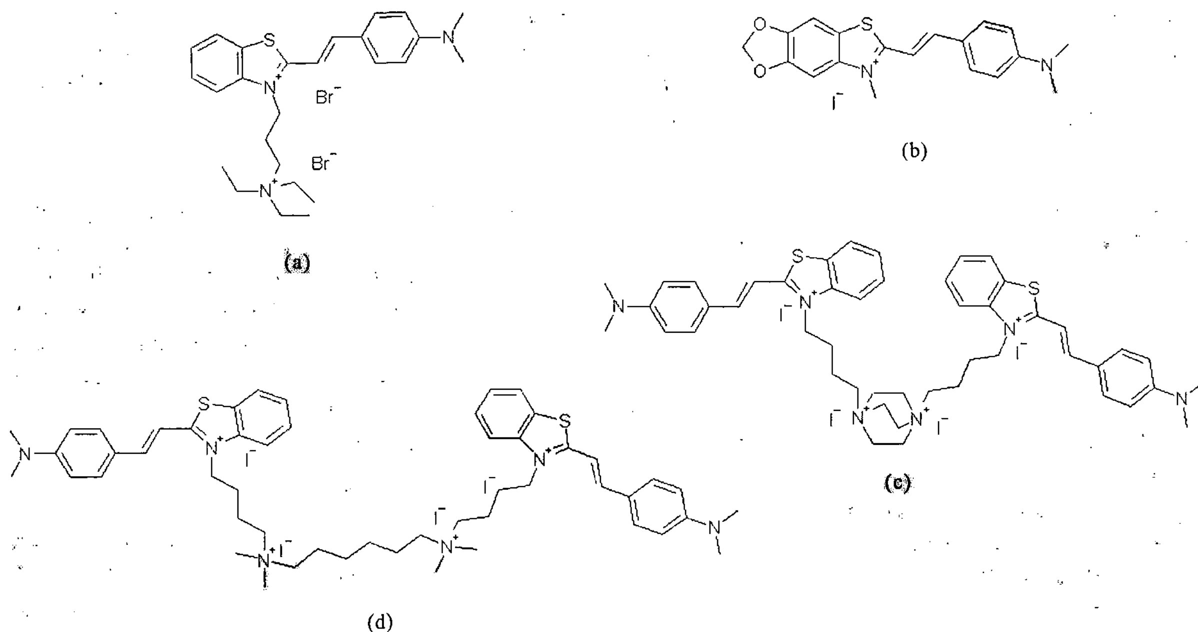


Fig. 1. The structure chemical formulae of the styryl monomer dyes Mn-Styr (a) and Dst-MdO (b), and dimer dyes Di-Styr-24 (c) and Di-Styr-30 (d)

The samples were prepared in distilled water and 0.05 M TRIS-HCl buffer, pH 7.5. The concentrations of dye and DNA were respectively 10^{-5} M and 6Ч10^{-5} M b. p. (base pairs) for the absorption measurements and photodamage experiment, and 10^{-4} M and 6Ч10^{-4} M b. p. for the luminescence measurements. For the low-temperature measurements, the prepared solutions were poured out into the special cell so that the upper surface is open, and then frozen. The excitation beam was directed to the open surface, and from the same surface the luminescence was registered.

The steady state fluorescence and phosphorescence measurements were performed using laboratory-designed equipment; absorption spectra were recorded with the help of a Specord UV-VIS spectrophotometer. The photodamage of dyes and the DNA+dye systems was performed by exposition of the corresponding solution (in quartz cell) to the visible spectrum irradiation of the 1 kW Hg-lamp. The measurements were carried out at 77 K and ambient temperatures.

Results and Discussion

1. The first excited singlet and triplet levels of luminescent dye probes

In order to use dyes as luminescent probes for the DNA (or RNA) detection and imaging in the study of the living objects the phototoxic influence of these dyes realized directly via the excitation energy transfer from the dye to the DNA has to be absent. For realization of this situation the first excited singlet and

triplet levels of dyes must be situated lower than correspondent levels of any nucleotide. The optical absorption, fluorescence and phosphorescence spectra of the investigated dyes Mn-Styr, Di-Styr-24 and Di-Styr-30 as well as correspondent the DNA+dye systems are given in fig. 2.

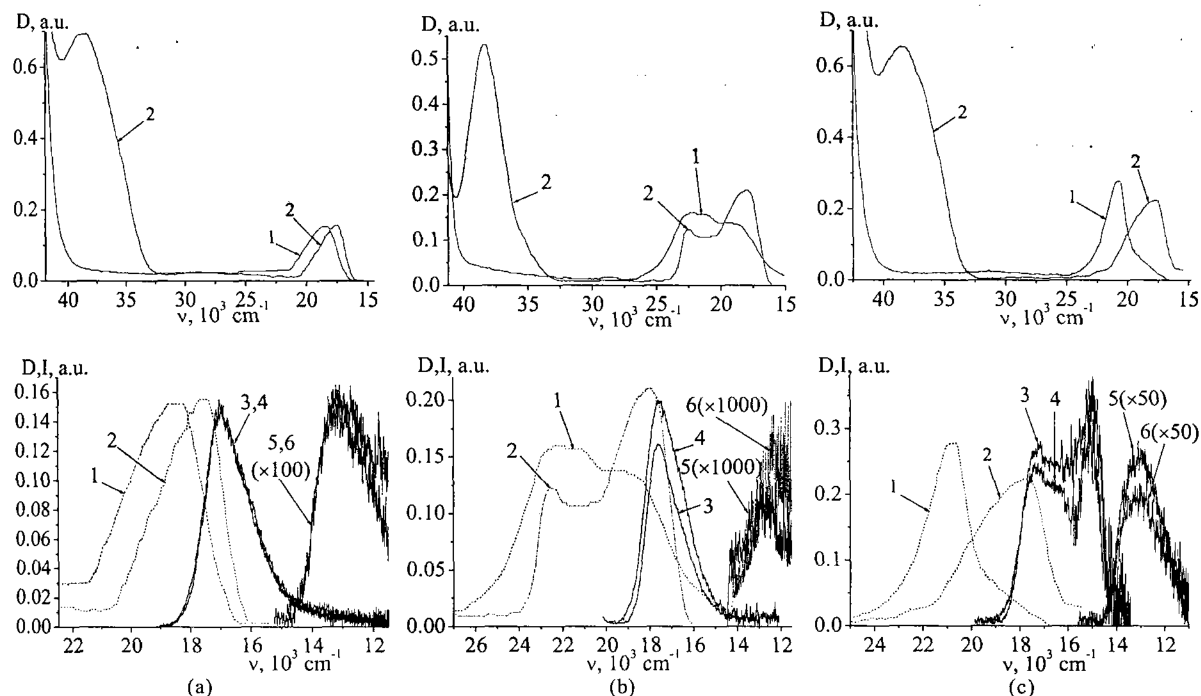


Fig. 2. The absorption (1, 2), fluorescence (3, 4) and phosphorescence (5, 6) spectra (3–6 at T = 77 K) of free styryl dyes (1, 3, 5) and correspondent systems DNA+dye (2, 4, 6) of: (a) styryl monomer Mn-Styr, (b) dimer Di-Styr-24 and (c) dimer Di-Styr-30

The absorption spectrum of the dye Mn-Styr both in presence and in absence of the DNA in visible spectral region consists of the single band with the maximum near 17540 and 18470 cm^{-1} respectively (Fig. 2, a, c. 1,2). Since this band is the most long-wave band in the visible spectral region and the corresponding fluorescence spectrum (Fig. 2, a, c. 3, 4) obeys the mirror symmetry rule respectively to this absorption band, it should be attributed to the absorption transition to the first excited singlet level of the dye molecule. The shift between the maxima of the free dye and the DNA+dye system spectra points to the dye interaction with the DNA. In the absorption spectra of the dimer dyes Di-Styr-24 and Di-Styr-30 in presence of the DNA the same band with the maximum near 18000 cm^{-1} (Fig. 2b, c. 2) and 17750 cm^{-1} (Fig. 2, c, c. 2) respectively could be observed. At the same time, the spectrum of Di-Styr-24 in the DNA presence contains one more band with the maximum at 22500 cm^{-1} shifted to the short-wavelength region relatively to the main band. This short-wavelength band with the maxima at 22200 and 20800 cm^{-1} respectively dominates in absorption spectra of both Di-Styr-24 and Di-Styr-30 in absence of the DNA (Fig. 2, b, c. 1 and Fig. 2, c, c. 1). Taking into account all the abovementioned results, the short-wavelength band could be attributed to the aggregates of the styryl chromophore. Since for the dimer dyes the tendency to form aggregates is much higher than for corresponding monomers [20], the short-wavelength band is present in the spectra of Di-Styr-24 and Di-Styr-30 in free state, but is absent in the spectrum of Mn-Styr containing the same chromophore. At the same time, interaction of dimer dyes with the DNA at low dye to the DNA concentrations ratio generally leads to the fixation of separate chromophores on the DNA molecule, thus resulting in decrease in the aggregates concentration in solution [21]. This explains the decrease in the short-wavelength band contribution to the absorption spectrum of Di-Styr-24 in presence of the DNA, as well as the disappearing of this band in the same spectrum of Di-Styr-30.

Since in the absorption spectra of Mn-Styr no aggregate bands were observed, we could suppose that both fluorescence and phosphorescence spectra of this dye also belong to the non-aggregated dye. As the spectra of the dyes Mn-Styr, Di-Styr-24 and Di-Styr-30 contain the fluorescence and phosphorescence bands with the maxima near 17000 cm^{-1} and 13000 cm^{-1} respectively, we could suppose these bands correspond to the non-aggregated chromophore for all these dyes. This is supported by the fluorescence excitation measurements (data not presented).

The positions of the first excited singlet (obtained by intersection of the absorption and fluorescence spectra curves) and triplet (obtained by phosphorescence blue edge) levels of the investigated dyes in non-aggregated form in the presence of the DNA were calculated using these spectra and given in table 1.

Table 1. **Positions of singlet (S_1) and triplet (T_1) levels of the dyes in presence of the DNA, cm^{-1}**

Compound	Mn-Styr	Di-Styr-24	Di-Styr-30
S_1	19100	18550	19100
T_1	14800	14450	14900

Table 2. **Positions of singlet (S_1) and triplet (T_1) levels of the nucleotides, cm^{-1}**

Compound	dCMP	dGMP	dTMP	dAMP
S_1	33090	33030	33530	34490
T_1	26630	26320	26160	25950

The values of singlet and triplet energy levels of the nucleotides obtained by us in [22, 23] are presented in table 2. The comparison of these data with data given in table 1 removes all doubts that even the triplet level of any nucleotide is situated much upper than the singlet level of any investigated dye. That is why the irradiation of the dye in the visual spectral region exciting the first singlet electronic level of the dye can not be resulted in the excitation energy transfer from the dye to the DNA.

2. Irradiation of Mn-Styr and Di-Styr-30 dyes and the DNA+dye correspondent systems. Dyes photostability

One of the spectral manifestations of luminescent dye probe phototoxicity for the DNA (the damage of the DNA) is the changes of optical density in the DNA absorption band (260 nm) corresponding to the $S_0 \rightarrow S_1$ electronic transition in the system the DNA+dye under direct excitation of this dye. Moreover, the measurement of the dye photostability is the change of the optical density of the dye absorption band corresponding to its $S_0 \rightarrow S_1$ electronic transition under the dye excitation at the wavelength of the same band. With the aim to study both the dye photostability and its phototoxicity influence on the DNA, the absorption spectra of Mn-Styr, Di-Styr-24, Di-Styr-30 dyes and the DNA+dye correspondent systems during the irradiation of the investigated compounds solutions by visible light of 1 kW Hg-lamp were recorded. It is worth to note the DNA absorption band connected with the first electronic transition (at 260 nm) is located far from the same band of majority of dyes used in this study (400–500 nm). This fact and the fact that the value of optical density of the dyes absorption band connected with the second electronic transition (located at ~260 nm) is much less than correspondent value of the DNA band give the possibility to study the behavior dynamics of the absorption bands optical density almost independently for a dye and for the DNA.

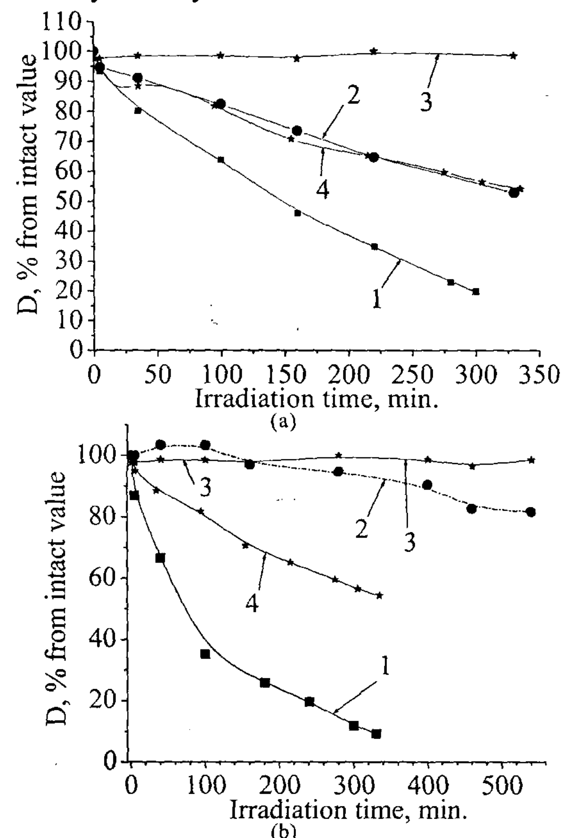


Fig. 3. The dependence of optical density of (a) styryl monomer Mn-Styr and (b) dimer Di-Styr-30 (1 – free dye, 2 – dye with the DNA, 3 – the DNA maximum 260 nm, 4 – TO with the DNA) on irradiation time

The dependencies of the investigated compounds optical density *D* (obtained from optical absorption spectra) on irradiation time are given in Fig. 3. It is obvious the gradual decreasing of *D* of free dyes absorption spectra bands is observed under the increasing of time of dyes irradiation (Fig. 3; c. 1). This is the evidence the damage of dyes π-electron systems takes place. It means that free dyes are not photostable (*D* of free dyes decreased at 80–90% after approximately 300 min. of irradiation). The gradual decreasing of *D* of the dyes absorption spectra bands (in the DNA+dye systems) takes place too but essentially slower than for free dyes. As it is shown on fig.3 the decreasing rate of *D* of the system DNA+Di-Styr-30 (Fig. 3, b; curve 2) is lower than of the system DNA+Mn-Styr (Fig. 3, a; curve 2). It means that dimer Di-Styr-30 bound to the DNA is more photostable than monomer Mn-Styr bound to the DNA. The comparing of the curves of optical density

dependence on irradiation time for investigated styryl dyes and well-known thiazole orange (TO) dye (Fig. 3, c. 4) demonstrates that both Mn-Styr and Di-Styr-30 dyes (bound to the DNA) are more photostable even than TO dye (bound to the DNA). The fact that the dye bound to the DNA is more photostable than free dye can be explained by the formation of the tough spatial fixation of a dye molecule after the intercalation of this dye in the DNA macromolecule. This causes the screening of the dye molecule against external influences and the decreasing of contacts between the dye molecules and surrounding molecules of oxygen. The last is transferred in the singlet excited state under excitation of the dye and becomes an active oxidant [24, 25]. Moreover, the dye molecule spatial fixation causes the increase of the fluorescence emission quantum yield. This entails the decrease of the probabilities of other excitation deactivation pathways (including pathways to the dye photoreaction). Our results are in agreement with the results of the investigations of the cyanine dyes in polymeric matrices obtained in [20]. The difference in Mn-Styr and Di-Styr-30 photostability in the DNA presence can be explained in the following way. It is known [19, 26] the constant of binding to the DNA is often much higher for the dimer than for the monomer with the same chromophore group. That is why the number of bonds with the DNA is much higher for the dimer Di-Styr-30 than for the monomer Mn-Styr. Thus the dimer molecules can be screened by the DNA rather than the monomer molecules.

To study phototoxic influence of the investigated dyes on the DNA the dependence of the DNA band maximum optical density *D* on time of irradiation (Fig. 3; c. 3) was investigated. Fig.3 shows that *D* changes within 3% out of its intact value. Our experiments show the optical density value of the dyes absorption band connected with the second electronic transition is not changed practically during time of irradiation. The changes of *D* within 3% at 260 nm may be connected with these negligible changes of the dyes absorption band and experimental errors. It is known the DNA destruction is either the double strand untwisting or the strand cutting that is reverse to the hypochromic effect (the value of hypochromic effect for the DNA is 20–50% out of intact value [8]). Even if the 3%-changes mentioned above are connected with the DNA destruction then this destruction cannot be significant (because it do not reach 20–50%) and can be included in experimental errors.

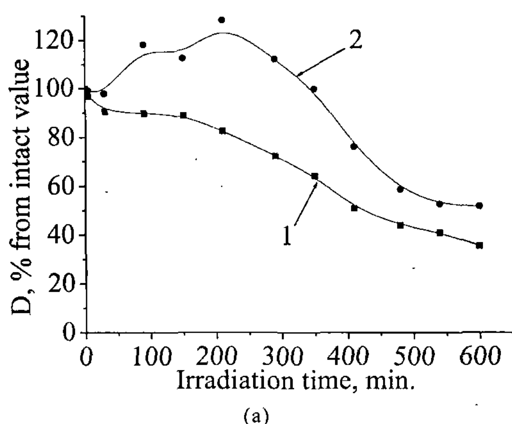
So, Mn-Styr and Di-Styr-30 dyes can be considered as non-phototoxic for the DNA. On the other hand, the DNA protects the investigated dyes against the photodamage.

3. Irradiation of Di-Styr-24 and Dst-MdO dyes and the DNA+dye correspondent systems. Phototoxicity for the DNA

The dependencies of the optical density *D* of Di-Styr-24 dye and the DNA+Di-Styr-24 system on irradiation time are obtained from optical absorption spectra and given in fig. 4. This figure shows the dye absorption band consists of two bands. Comparing fig. 2, a and fig. 2, b it can be seen the long-wave band (18500 cm^{-1}) is located close to the monomer Mn-Styr band and corresponds to non-aggregated state. The short-wave band (23100 cm^{-1}), in our opinion, is connected with aggregates (the similar case was observed for cyanine dyes [27, 28]). During the irradiation of the free dye the band of aggregates decreased gradually while the band of non-aggregated dyes showed some increase at first. In our opinion, it is connected with that aggregates are damaged and turn into non-aggregated state. The dye Di-Styr-24 is more photostable than Mn-Styr and Di-Styr-30, its *D* decreases by 40–50% after 600 min. of irradiation.

Fig. 4, b indicates that in presence of the DNA the optical density of aggregate band was decreasing gradually with the irradiation time increasing while *D* of non-aggregated dyes remained constant. It can be explained by assumption that non-aggregated dyes intercalate into the DNA and aggregates bind outside the DNA chain. Therefore, generated singlet oxygen damages the aggregated dyes. Non-aggregated dyes are protected from the influence of singlet oxygen and, therefore, are not damaged.

The dependencies of the optical density *D* of the DNA band obtained from the absorption spectra of the DNA+Di-Styr-24 system (Fig. 5) is shown on (Fig. 4, b). This figure shows that optical density of the DNA absorption band increase by 30% during time of irradiation. In our opinion, this fact is connected with cutting or untwisting of the strands of the DNA macromolecule that interacts with the Di-Styr-24 dye molecules (this effect is reverse to the hypochromic effect). Our results is in agreement with 20–50% obtained in [8]. Thus it can be supposed the DNA destruction by Di-Styr-24 takes place. So, Di-Styr-24 showed phototoxic influence on the DNA. On the other hand, phototoxicity of dyes is manifested not only in cutting or untwisting of the strands. Fig. 6 shows that optical density of the DNA absorption band in the DNA+Dst-MdO system decrease by 10%. In our opinion, it is connected with the fact that Dst-MdO molecules favor to the DNA p-electron systems destruction.



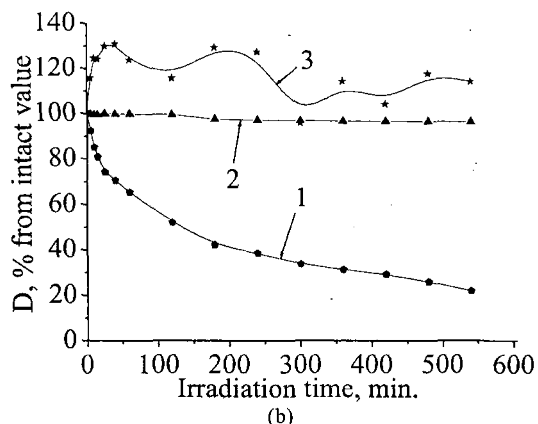


Fig. 4. The dependence of optical density of dimer Di-Styr-24 on irradiation time: (a) free dye, (b) bond to the DNA (1 – at 23100 cm^{-1}, 2 – at 18500 cm^{-1}, 3 – the DNA maximum at 38460 cm^{-1}(260 nm))

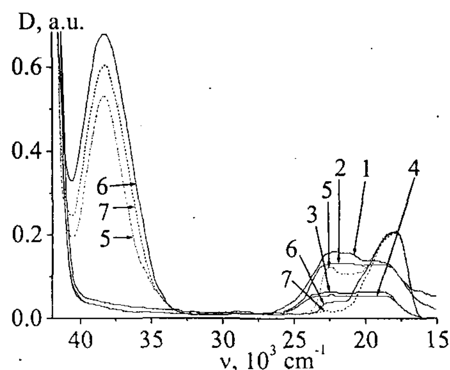


Fig. 5. The absorption spectra of dimer Di-Styr-24 during irradiation (free dye: 1 – intact, 2 – 210 min, 3 – 540 min, 4 – 600 min; dye with DNA: 5 – intact, 6 – 240 min, 7 – 540 min)

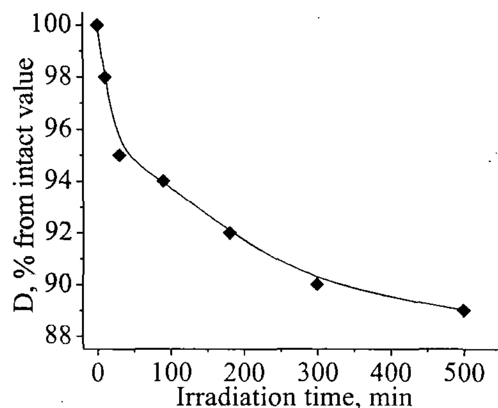


Fig. 6. The dependence of optical density of the DNA maximum in the DNA+Dst-MdO system

So, Di-Styr-24 and Dst-MdO dyes can be used for the DNA destruction in photodynamic therapy.

Conclusions

A number of the newest luminescent styryl dyes (monomers and dimers) was synthesized and investigated. The spectral investigations of these dyes photostability and phototoxic influence on the DNA were carried out. All investigated dyes are rather photostable when bound to the DNA while the photostability of the free dyes is much lower. This phenomenon is connected, in our opinion, with the fact the DNA macromolecule is screening a dye molecule against external influences and decreasing the contacts between the dye molecule and surrounding molecules of oxygen that is transferred in the singlet excited state under excitation of the dye and, as the result, becomes an active oxidant. The Di-Styr-24 dye is the most photostable (from investigated dyes). The dyes Mn-Styr and Di-Styr-30 are worse photostable. because the values of D of free dyes have decreased by 80–90% already after 300 min. of irradiation and by 20–50% for the DNA+dye systems. All investigated styryl dyes (bound to the DNA) are more photostable than well-known thiazole orange (TO) dye.

The Mn-Styr and Di-Styr-30 dyes are photochemically safe for the DNA. This conclusion is confirmed by the fact the values of D of the DNA absorption band for the DNA+dye systems are practically without changes during the time of irradiation. In contrast to them the Di-Styr-24 dye showed the phototoxic influence on the DNA (optical density of the DNA band increase by 30% during time of irradiation). In our opinion, this fact is connected with cutting or untwisting of the DNA macromolecule that interacts with the Di-Styr-24 dye molecules (this effect is reverse to the hypochromic effect). But phototoxicity of dyes is manifested not only in such effect. It was shown optical density of the DNA band in the DNA+Dst-MdO system decreased by 10%. In our opinion, this phenomenon is connected with the fact that Dst-MdO molecules favor to the DNA p-electron systems destruction.

All styryl dyes investigated in this paper could be used in biology and medicine: Mn-Styr and Di-Styr-30 as luminescent probes, Di-Styr-24 and Dst-MdO – in the photodynamic therapy.

Acknowledgement

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СПЕКТРАЛЬНИЙ ПРОЯВ ФОТОСТАБІЛЬНОСТІ ТА ФОТОТОКСИЧНОГО ВПЛИВУ НА ДНК НОВИХ ЛЮМІНЕСЦЕНТНИХ СТИРИЛОВИХ БАРВНИКІВ

У роботі запропоновано методи спектральних досліджень фотостабільності та фото-токсичного впливу люмінесціюючих зондів-барвників на ДНК. Досліджено спектри оптичного поглинання, флюоресценції та фосфоресценції нових стирилових барвників та систем ДНК+барвник. Спектри оптичного поглинання досліджуваних сполук реєструвалися під час опромінювання зразків цих речовин видимим світлом. У роботі аналізуються результати цих експериментів, проведені на низці барвників. Зафіксовано зміни оптичної густини D розчинів систем ДНК+барвник на ділянці спектра 250+300 нм (що відповідає першому електронному переходу в ДНК) та 370+650 нм (що відповідає першому електронному переходу в молекулах барвників). Динаміка D(t) не є монотонною. Показано, що бавники Mn-Styr та Di-Styr-30 є фотохімічно безпечними для ДНК; ці барвники є більш фотостабільними у зв 'язаному з ДНК стані, ніж: у вільному. Барвники Di-Styr-24 та Dst-MdO, на відміну від попередніх, проявляють невеликий фототоксичний вплив на ДНК. Пропонуються версії щодо можливих механізмів фотогтокичності (та фотостабільності).