A Principal Approach to the Detection of Radiation-Induced DNA Damage by Circular Dichroism Spectroscopy and Its Dosimetric Application

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Abstract: Using cholesteric liquid-crystalline dispersion (CLCD) of DNA, we demonstrate that the molecularly organized systems may be used both for qualitative assessment of the degree of radiation-induced DNA damage, as well as for detection of radiation doses in a very wide range. The doses up to 500 Gy do not cause any significant changes in optical signals of DNA in solution. However, when irradiated molecules are used to prepare the CLCD by addition of crowding polymer, a clear correlation of its optical signals with an absorbed dose is observed. For example, at a dose of 500 Gy, a maximum drop in the circular dichroism (CD) signal for DNA solution and for CLCD formed from preliminary irradiated molecules is ≈20% and ≈700%, respectively. This approach can also be used to expand the dosimetric capabilities of DNA CLCD. Compared to the case of irradiation of ready-made DNA CLCD, formation of the dispersed system from irradiated DNA allows to increase its sensitivity by more than 2 orders of magnitude. A similar decrease in the CD signal (≈1.45-fold) is observed in these systems at the doses of 100 kGy and 200 Gy, respectively. This principal approach seems to be relevant for other biomolecules and molecularly organized systems.

Keywords: liquid-crystalline DNA; DNA damage; ionizing radiation; radiation detection; radiation dosimetry; circular dichroism

1. Introduction

Chemical dosimeters are one of the most widely used measuring systems in the current economic use of ionizing radiation. The operation principle of the detectors of this class is based on radiation-chemical transformations of a sensitive substance and concomitant changes in its properties. For example, the absorbed dose can be related to the intensity of gas evolution from polymer targets [1], degree of gels polymerization [2], electrical conductivity of solutions [3], etc. The dosimetric systems with an optical response are also of great interest, e.g., radiochromic films [4], Fricke dosimeter and its modifications [5], as well as various systems based on organic dyes [6–10]. Moreover, due to the progress in supramolecular chemistry and nanotechnology, a considerable interest is associated with more complex optical dosimetric systems: plasmonic nanoparticles [11], semiconductor quantum dots [12], as well as various nanoclusters and supramolecular frameworks [13–15].

At the same time, the field of supramolecular construction often involves biomolecules as “building blocks”, for instance, molecules of nucleic acids [16]. Quite a lot of works are known, where various nanodevices and sensor systems were built from DNA molecules [17–19]. Among other things, the DNA-based constructions and supramolecular assemblies can be used to create sensitive elements for optical detectors of ionizing radiation. For instance, several works in this direction have been performed with optically
active DNA mesophases. De Groot et al. have shown the change in the cholesteric pitch of the DNA liquid crystal under Co-60 irradiation [20]. In addition, in the recent works, we have shown the possibility of registration of high-energy bremsstrahlung by the change in the amplitude of circular dichroism (CD) signal of cholesteric liquid-crystalline dispersion (CLCD) of low-molecular-weight DNA [21,22]. However, the doses of ionizing radiation, leading to a noticeable response of these systems, turned out to be of the order of thousands and tens of thousands of Gy. Although such doses are widely used in radiation processing and sterilization [23], it is obvious that the development of dosimetric systems based on optically active DNA mesophases requires an expansion of the recorded dose range downward.

DNA is the main target of radiation exposure [24]. Therefore, investigation of radiation-induced damage of DNA both in situ and in various model systems is a very important task of radiation biology. In addition to a variety of traditional techniques [25,26], several spectroscopic approaches may also be used for such investigation [27]. For instance, a number of works demonstrate a possibility to detect DNA lesions using Raman and IR-spectroscopy [28–30]. Despite a huge amount of the research devoted to the radiation biology of DNA, there is a very limited information on the application of optical (UV-vis) spectroscopy methods for studying its radiation-induced damage (e.g., [31–35]). In these works, the assessment of integrity of DNA molecules was performed in dilute solutions via absorption and CD spectroscopy. The latter is widely used for studying of DNA secondary structure and conformation. However, judging by the published data, a quite significant optical response allowing to make a clear correlation between the magnitude of radiation exposure and state of the system is usually observed at the doses of the order of hundreds and thousands of Gy (this is especially true for the CD data). This fact also raises a question of the need to adapt this method to registration of radiation-induced DNA lesions at the much lower doses.

Since the optical response of the aforementioned dosimetric systems is based on the radiation damage of DNA molecules, in our opinion, both problems may have the same solution. In the present work, by the example of DNA CLCD, we demonstrate a principal approach that may help to detect DNA lesions at relatively low radiation doses and increase the sensitivity of the optically active DNA mesophase detectors of ionizing radiation.

2. Materials and Methods

Two ways of radiation exposure of the experimental samples were compared: preliminarily irradiation of isotropic DNA solutions subsequent formation of DNA CLCD particles (way I), and irradiation of ready-made DNA CLCD samples (way II). Both approaches are schematically shown in Figure 1.

The aqueous saline solution of DNA was prepared using a phosphate (NaH₂PO₄) buffer (10⁻² M) containing 0.3 M NaCl (pH ≈ 7.4). The commercial ultrasonically depolymerized purified DNA preparation from salmon sperm (Derinat®, (0.25–0.5) × 10⁶ Da (≈400–800 bp); Technomedservice, Moscow, Russia) was used. The samples of 2 mL volume containing 1.7 × 10⁻⁴ M of DNA (it was determined spectrophotometrically using the extinction coefficient ε₂₆₀ ≈ 6600 M⁻¹ cm⁻¹) were irradiated using LNK-268 X-ray machine (Diagnostika-M, Moscow, Russia). The samples were filled in 35 mm plastic Petri dishes (GenFollower, Shaoxing, China) to ensure a conformal dose coverage. The voltage on the X-ray tube was 80 kVp, and the dose rate was 250 Gy/min. The determination of the dose rate was performed using Fricke dosimeter in accordance with [36].

The DNA CLCD samples were prepared by mixing (1:1 v/v) the aqueous saline solution of DNA with 40% solution of 4000 Da polyethylene glycol (PEG; Sigma, St. Louis, MO, USA), made using the same buffer solution, according to [37]. After mixing, the samples were intensively shaken and kept at room temperature for 90 min. Irradiation of the ready-made DNA CLCD samples was performed using industrial linear electron accelerator ILU-14 (Budker Institute of Nuclear Physics, Novosibirsk, Russia) in the bremsstrahlung generation mode. Whereinto the maximum energy of electrons in the beam was 7.6 MeV.
The samples of 2 mL volume each ([C_{DNA}] = 1.7 \times 10^{-4} M) were placed in 5 mL glass tubes (MiniMed, Bryansk, Russia). The procedure for irradiation and dosimetric control is described in detail in [21].

**Figure 1.** Schematic representation of the studied ways of radiation exposure: (A) preliminarily irradiation of aqueous-saline solutions of DNA and subsequent formation of DNA CLCD particles (way I), (B) irradiation of ready-made DNA CLCD samples (way II).

Preparation of the DNA CLCDs from preliminarily irradiated DNA molecules was performed in a similar way: at the end of the exposure, 750 µL were taken from each irradiated DNA-containing solution and mixed with the same volume of 40% PEG.

Absorption spectra were recorded using UV-3101 PC spectrophotometer (Shimadzu, Kyoto, Japan) in 1.0 × 0.4 cm quartz cells. The CD spectra of the samples were recorded using SKD-2 dichrometer manufactured at Laser Spectral Instrumentation Department of Institute of Spectroscopy of Russian Academy of Sciences (Troitsk, Russia). The measurements were performed in 1.0 × 1.0 cm quartz cells. The CD spectra were presented as dependence of the difference in the absorption intensity of left- and right-polarized light (ΔA = A_L – A_R) on the wavelength.

Visualization of the DNA CLCD particles was performed using a Leica TCS SP5 confocal laser-scanning microscope with LAS AF software (Leica Microsystems GmbH, Wetzlar, Germany). A DNA-specific fluorescent dye SYBR Green I (SG; Lumiprobe, Hunt Valley, MD, USA) was used as a fluorescent probe. Staining of the samples was performed after formation of the dispersion particles. The procedure is also described in detail in [21].

3. Results and Discussion

Figure 2 shows the absorption and CD spectra of aqueous-saline solutions of low-molecular-weight DNA irradiated with 80 kVp X-rays in the range of 0–500 Gy, as well as the normalized dependences of the peak intensity of corresponding signals on the exposure dose. Under the conditions studied, irradiation lead only to a slight change in the spectral characteristics of the samples. For example, the radiation hyperchromicity, which may be associated with partial denaturation of DNA molecules, is expressed as an increase in the optical density by a mere 5% (its decrease, on the contrary, may indicate the destruction of base chromophores). A similar effect in the same dose range was shown in [34,38]. In addition, irradiation results a decrease in the amplitude of both negative (≈241 nm) and positive (≈271 nm) CD-bands characteristic of an isotropic B-DNA solution by ≈20%
and ≈8%, respectively. Such a change is much less significant compared to the data by Tankovskaia et al.: they showed an up to twofold drop in the amplitude of the CD-bands when DNA solutions in the presence of 0.15 M NaCl were irradiated with 0–500 Gy [34]. This discrepancy may be due to a difference in the salt concentration or another molecular weight of DNA. In addition, a different dose rate was used in this work. Nevertheless, it is obvious that the picture observed does not allow to assess veraciously the integrity of the system after the irradiation.

The situation turned out to be completely different when the preliminarily irradiated aqueous-saline solutions of DNA were used to prepare DNA CLCD samples (way I; the fundamentals of condensation of low-molecular-weight DNA in the presence of PEG and salt, which is a special case of psi-condensation, are described in detail in [39,40]). It is clearly seen that the behavior of both absorption and CD spectra demonstrates the apparent correlation with the magnitude of the exposure dose (Figure 3). For example, if a dispersed system with a characteristically broadened and bathochromically shifted absorption band was formed by the addition of PEG in the absence of preliminary irradiation of DNA, then at a dose of 500 Gy the spectrum of the obtained DNA CLCD was close to the original spectrum of an isotropic DNA solution (comparison of the spectra is shown in Figure 3A). The corresponding dependences of the maximum amplitude of the absorption band, its...
full width at half maximum (FWHM), and position of the peak on the exposure dose are presented in Figure 3B. There is no significant change in the signal intensity up to 150 Gy, however, a further increase in the dose leads to an increase in the amplitude of the band up to \( \approx 1.32 \)-fold. This effect is accompanied by a gradual shift of the peak position from \( \approx 266.2 \) to \( \approx 259.5 \) nm. In addition, the absorption band noticeably narrows: the FWHM in the non-irradiated control is \( \approx 63.3 \) nm, while at a dose of 500 Gy its value is \( \approx 47.4 \) nm.

Figure 3C shows the CD spectra of the DNA CLCD samples prepared from preliminarily irradiated aqueous-saline solutions of DNA (way I). As is known, DNA molecules within the CLCD particles are arranged in parallel layers rotated at a certain angle relative to each other, thereby forming a helical (cholesteric) twist, which is responsible for the characteristic CD signal (also called anomalous [41]). The amplitude of the CD signal in the non-irradiated control is \( \approx 39 \)-fold greater than the value of the negative CD-band in case of isotropic DNA solution. Starting from 50 Gy, a distinct decrease in the amplitude of the CD-band is observed, and at a dose of 500 Gy, its intensity was only \( \approx 14\% \) of the initial value. The corresponding curve in Figure 3D, which describes the dependence of the
CD-band peak intensity on the exposure dose, has slight bends, but in general the deviation from the linear trend does not exceed 11% ($R^2 = 0.995$).

The demonstrated behavior of the absorption and CD spectra indicates that assembling of CLCD particles is highly sensitive to the integrity of DNA molecules. Their modification/damage because of both direct ionization and action of radiolysis products may impede “mutual recognition” of DNA molecules and formation of the dispersion particles. This is clearly confirmed by the confocal microscopy data. In the absence of radiation exposure (Figure 4A), the common “deep starry sky” picture is observed: the dispersion particles have well-defined boundaries, spherical shape, and sizes from ≈0.5 to ≈3.5 µm. A noticeably fewer number of particles is observed in the sample irradiated with 500 Gy (Figure 4B). In this case, large particles are practically absent in the system. The same consistent pattern was found in our recent work [21], where the radiation-induced degradation of ready-made DNA CLCD (way II) particles was investigated.

Next, we compared the obtained data with the case of irradiation of the ready-made DNA CLCD samples (way II), containing 20% of PEG, with high-energy bremsstrahlung at doses from 0 to 100 kGy. Figure 5A shows the absorption spectra of the samples. The corresponding dependences of the maximum amplitude of the absorption band and position of the peak on the exposure dose are presented in Figure 5B. The super intense growth of the band in the wavelength region below 240 nm corresponds to the well-known reaction of PEG to high-dose irradiation. A slight (up to ≈9%) increase in the absorption occurs also in the wavelength region of ≈260–280 nm when the DNA CLCD samples are irradiated up to 30 kGy. A subsequent increase in the radiation dose leads to a decrease in the band amplitude. However, the maximum drop in the absorption does not exceed ≈24% relative to the non-irradiated control. Irradiation also leads to a shift in the position of the peak: a sharp jump from 266.9 to 271.4 nm is observed at the initial section of the curve, followed by a gradual shift in the opposite direction to 268.8 nm. Due to the highly-amplitude absorption band of PEG, it is not possible to determine the FWHM values for all the samples; nevertheless, it can be seen that the spectrum is narrowed noticeably with increasing dose (the FWHM value changes from ≈53 nm in the non-irradiated control to ≈39 nm at a dose of 100 kGy). This behavior generally corresponds to our assumption about the degradation of DNA CLCD particles as a result of the action of the radiolytic products [21,22].
The behavior of the CD spectra generally repeats the picture described above: an increase in the amplitude of CD-band is observed up to 20 kGy, but a further increase in the radiation dose leads to a gradual decrease in the signal. The maximum signal drop for the studied system containing 20% of PEG does not exceed 30% relative to the non-irradiated control. It is significantly less than one showed in our recent work: for the system with PEG content of 17% the drop in the CD-band was more than 70% at a dose of 100 kGy [21]. Thus, we can conclude that change in the PEG concentration may significantly vary the sensitivity of DNA CLCDs to irradiation.

A comparison of the sensitivity of DNA CLCDs to ionizing radiation for the two studied approaches to radiation exposure (ways I and II) is shown in Figure 6. The data are presented as a ratio $\Delta A_0 / \Delta A$ (where $\Delta A_0$ and $\Delta A$ are the peak intensity of the CD signals corresponding to non-irradiated control and to irradiated samples, respectively). In the case of preliminary irradiation of aqueous-saline solutions of DNA with 500 Gy (way I), the CD-band of the resulting dispersed system decreases by more than 7-fold, while in the case of irradiation of the ready-made DNA CLCD with 20% content of PEG (way II) a twofold drop cannot be achieved even at a dose of 100 kGy. A similar decrease in the CD signal by a factor of $\approx 1.45$ is observed in these systems at the doses of 200 Gy and 100 kGy,
respectively. Thus, the sensitivity of these DNA systems to irradiation differs by more than 2 orders of magnitude.

![Diagram](https://example.com/diagram.png)

**Figure 6.** Comparison of dose dependences of optical responses of: (A) DNA CLCDs prepared from preliminarily irradiated DNA solutions (way I), (B) ready-made DNA CLCDs (way II). Error bars indicate the standard deviations calculated from three repetitive measurements.

Thus, the use of DNA CLCDs as sensitive elements for detectors of ionizing radiation makes it possible to cover a very wide range of radiation doses: from hundreds of Gy to tens of kGy. This dose range is widely used in modern radiation technology (e.g., in radiation processing and sterilization). However, it is important to note that, in our opinion, the most actual is the area of significantly lower doses, relevant for the present practices of external beam radiotherapy (usually from ≈1 to ≈50 Gy per fraction [42,43]) and radionuclide therapy (focal dose per course can exceed 100 Gy [44]). Therefore, in future works, we will adapt the DNA CLCDs to detect the radiation doses of this order.

### 4. Conclusions

The present work is pointed at two goals: (1) development of the approach to registering of radiation-induced DNA damage using UV-vis spectroscopy methods and (2) expansion of the range of doses of ionizing radiation detecting by the optical response of DNA CLCDs. We mainly focused on the CD spectroscopy. To do this, we have compared two different ways of radiation exposure of the experimental samples: preliminarily irradiation of isotropic DNA solutions subsequent formation of DNA CLCD particles (way I), and irradiation of ready-made DNA CLCD samples (way II). We have shown that assembling of the DNA CLCD particles from irradiated molecules (way I) may improve the accuracy and quality of assessment the integrity of the nucleic acid for relatively low doses of ionization radiation that do not cause significant changes in optical signals of DNA in dilute solutions. In the future, we will try to collate the observed optical response with specific types of DNA damage. The assembling of CLCD particles from preliminary irradiated DNA molecules (way I) makes it possible to detect significantly lower doses of ionizing radiation via this system than we demonstrated earlier by using ready-made DNA CLCD (way II). In this way, the sensitivity of DNA CLCD to irradiation may be increased by more than 2 orders of magnitude. We believe that the principal approach presented may also be used for other biomolecules and molecularly organized systems.

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