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# INTERACTION OF NUCLEIC ACIDS WITH MOLECULES OF WATER, PROTEINS, AND INTERCALATORS

(review)

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## Abstract

Modern concepts of intermolecular interactions in the cell are incomplete without understanding how complexes are formed between nucleic acids and the main intracellular components — water and proteins, and what determines the spatial stabilization of such complexes. The same is true for intercalation — intracellular intermolecular interaction of planar structure substances capable of being introduced between adjacent pairs of nitrogenous bases into DNA and RNA molecules, which plays a special role in pharmacology and genetic mutagenesis. In addition, intercalation can have a strong effect on cellular metabolism, slowing down and in some cases stopping the growth of cells, which, under certain conditions, leads to both apoptosis and cancer, or vice versa, to the body's recovery from such diseases (M. Ashrafizadeh et al., 2020). This review is devoted to the consideration of molecular mechanisms and the biological role of these processes. It is known that the DNA double helix can interact with polypeptides through the formation of specific hydrogen bonds between Watson-Crick base pairs and amino acid side chains (C.N. Pace et al., 2004), through intercalation of aromatic amino acid side chains between base pairs, at which some specificity is also manifested (A. Bazzoli et al., 2017), and due to the direct binding of protein α-helices and β-layers in DNA grooves (E. Del Giudice et al., 2009). It is assumed that the latter type of interaction takes place, for example, in DNA complexes with the *cro*-repressor of gene expression and with a protein that activates catabolism, for which two models of the binding of α-helices with the left-sided and right-sided DNA double helix in the B-form have been proposed. It is indicated that if the structure of a nucleic acid molecule is known, then the size of the surface of DNA and RNA available for water molecules or other solvents can be calculated. In the case of DNA folding in solution into a double helix, its molecule becomes polar. With this kind of hydration, two hydration shells are formed around the DNA molecule. The first of them, consisting of ~ 20 water molecules per nucleotide, is impermeable to cations and does not resemble ice in its aggregate structure, while the second shell is indistinguishable from ordinary water. Differences in the structure of hydration shells shed light on the nature of the conformational transition between the B → A forms, which occurs with a decrease in the hydration of the DNA molecule. The interaction of nucleic acids with molecules of medicinal and other planar substances is also described. At the same time, the review considers only intercalation complexes with drugs whose molecules have a planar structure or have planar functional groups. It has been demonstrated that the binding of such substances with a double helix proceeds in two stages: at the first stage, they are attached along the periphery of the helix, at the second, intercalation occurs, that is, the actual insertion of the intercalator in the planar plane between nucleotide pairs. This kind of intercalation is accompanied by unwinding and elongation of the nucleic acid helix, as well as an increase in its rigidity. In accordance with the principle of exclusion of the nearest binding sites, according to which it does not occur at each nearest neighbor along the axis of the DNA double helix due to spatial constraints, which are determined by the stereometry of nucleotides adjacent to intercalators, intercalator molecules fill only half of such places. In general, the interactions of nucleic acids with water molecules, proteins and intercalators described in the work indicate the biological significance of this kind of relationship, since, as is known, the stability and regularity of the processes of replication and expression of genes plays an important role in the genotype—environment interaction and the «implementation» of genetic information at the molecular level.

Keywords: nucleic acids, A-DNA, B-DNA, conformational transitions, water molecules, DNA hydration, proteins, ligands, planar intercalators, intermolecular interactions, replication, gene expression

Modern intermolecular interactions at the intracellular level are not complete without considering the creation and stabilization of spatial complexes formed by nucleic acids and such basic intracellular elements as water and proteins. Water is the main element in which all bioorganic components and substances are dissolved inside the cells of a living organism. Water is a highly polar solvent and essential for all living organisms [1-3]. Nucleic acids are very soluble in water [4, 5]. All the main biochemical processes take place in it, due to which the role of water in the chemical structure of living organisms cannot be overestimated. As a reagent, water takes part in many chemical reactions. For example, the hydrolysis of proteins, fats and carbohydrates occurs with the direct participation of water, and during the hydrolysis of ATP energy is released, which is necessary for the implementation of energetically unfavorable enzymatic reactions [6-9]. In a liquid state water is practically not compressed, and as a result, serves as a kind of skeleton for the cell. Water molecules are characterized by cohesion, which, in turn, characterizes the strength of the body ability to withstand external influences. Due to its osmotic properties, water creates excess pressure inside the vacuoles of plant cells [10]. This turgor pressure allows the cell wall to maintain its elasticity and maintain the shape of organs (e.g. leaves). At the same time, water, being an electrically neutral molecule, has a small positive charge in the region of hydrogen atoms, although it is unevenly distributed inside the molecule. However, in the region where the oxygen atom is located, the charge is slightly negative. Due to this structure, water molecules can interact with each other and with other bioorganic molecules inside cells through the so-called hydrogen bonds [11, 12]. All this determines the importance of water as one of the main elements of the cell during its functioning, including the implementation of genetic information at the molecular and cellular level.

Another element that plays a critical role in the cell is proteins [13, 14]. Proteins play not only a building role inside cells, but also allow metadata to be realized, encoded in the main carrier of genetic information - nucleic acids. Proteins are nitrogen-containing high-molecular organic compounds, the monomers of which are amino acids. Proteins are characterized by a complex spatial structure that has primary, secondary, tertiary and quaternary levels of organization. In order to carry out their biological functions, proteins take one or more specific spatial configurations due to such non-covalent interactions as hydrogen, ionic, hydrophobic bonds and other intermolecular interactions [15-18]. The complexity of the structure of protein molecules is associated primarily with the variety of their functions. At the same time, the structure of molecules depends on the properties of the environment and intermolecular interactions. Protein interactions with nucleic acids play a special role in the life cycle of any living organism, since it is they that ensure the constancy and reproducibility of the genetic information encoded in DNA and RNA. However, as practice shows, the spatial stereochemical mechanisms of interaction between proteins and nucleic acids have not been fully elucidated, which is especially important in the light of understanding and the possibility of controlling this kind of intermolecular interactions [19-21].

Another intracellular intermolecular process that attracts some attention, and which plays a special role in pharmacology and genetic mutagenesis, is intercalation [22, 23]. There are several ways in which certain molecules, commonly called ligands, can bind to DNA. Ligands usually either intercalate into the DNA molecule by inserting in the plane between the bases of the double helix, or bind to it electrostatically or covalently. In order for intercalation to occur, the ligand must have the appropriate size and chemical nature. Typically, intercalating ligands are flat and have an aromatic polycyclic structure. In chemotherapy pharmacology, intercalating ligands are used as agents that inhibit DNA replication to

stop the growth of cancer cells. For example, daunorubicin and adriamycin are used to treat Hodgkin's disease [24, 25], for the treatment of Ewing's sarcoma - dactinomycin [26]. The antibiotic actinomycin D, intercalating between adjacent pairs of DNA nitrogenous bases, restricts the binding of RNA polymerase to the DNA matrix and thereby prevents the interaction of the enzyme with the DNA strand [27]. In molecular biological studies, intercalating ligands are used for fluorescent staining of nucleic acid molecules or for mutagenesis. For example, ethidium bromide is typically used in nucleic acid electrophoresis in agarose or polyacrylamide gels [28], and acridine orange or acridine yellow generate cause chromosomal mutations such as deletion, leading to the loss of the middle part of chromosomes, or for in vivo staining of cell nuclei or for the analysis of biological membranes [29, 30].

In this review, we briefly consider the intermolecular mechanisms of interaction of nucleic acids with water, proteins, and intercalating substances. The importance of such interactions, which play a key role in the stability and regularity of the processes of replication and expression of genes in the practical implementation of the "genotype—environment" interaction, as well as the implementation of genetic information at the molecular level, as well as in ensuring the constancy and reproducibility of the genetic information.

Water and nucleic acids. Needless to say, how important is the role of the aqueous environment of nucleic acids. Water is not just a medium in which certain molecules are dissolved. Water interacts with dissolved molecules, and it is this water that mainly stabilizes the secondary and tertiary structure of macromolecules [11, 31, 32]. This applies to both proteins and DNA, and DNA, perhaps even more so, since the high dielectric constant of water and hydrated counterions weaken the electrostatic repulsion of phosphates [33-35]. Water molecules also take part in the process of self-assembly of bases into ordered structures, since this process is largely due to hydrophobic interactions. The degree of DNA hydration is of decisive importance for its conformation: at high relative humidity, DNA is in the B-form (fig. 1), a decrease in moisture (or an increase in ionic strength) leads to the transition of DNA from B- to C-, A- or (if the sequence allows) into D- and Z-forms [32, 36].

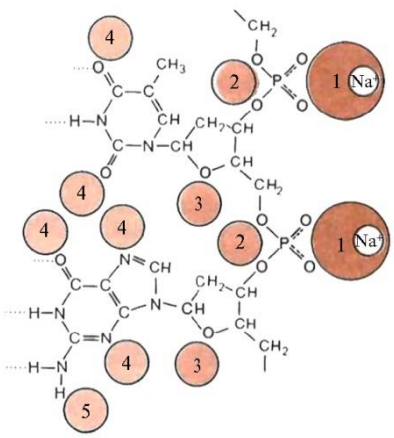


**Fig. 1. Sites of preferred binding of water molecules to B-DNA** (on [42]). The numbers from 1 to 5 indicate the order in which the bond strength decreases. There are about 5 water molecules near the phosphate group.

Hydration of nucleic acids plays an important role in the formation of their structure and is responsible for A ↔ B transitions in DNA [37, 38]. Two hydration shells are formed around the DNA molecule. The first of them, consisting of ~ 20 water molecules per nucleotide, is impermeable to cations and does not resemble crystal water in structure; on the ice. The second shell is indistinguishable from ordinary liquid water. If the structure is known, then the surface of DNA or RNA accessible to solvent molecules can be determined by calculation. The results of such calculations explain some of the features of the behavior of DNA in solution and, in particular, show that when folding into a double helix, the DNA molecule becomes more polar. X-ray diffraction analysis of single crystals of oligonucleotides showed that in the regions consisting of AT-pairs, in the minor

groove of B-DNA, a ridge is formed of water molecules hydrogen-bonded to bases [39]. In A-DNA, water "strands" are formed that cross-link the phosphate groups lying at the edges of the main groove. Such differences in the structure of hydration shells shed light on the nature of the B ↔ A transition that occurs with a decrease in the water content in DNA. In crystals of some cyclodextrins and d(CpG) complex with proflavine, four-, five-, and six-membered cyclic structures are found that form hydrogen-bonded oxygen atoms or O-H groups [40, 41]. It is possible that such structures are included in the hydration shells of macromolecules.

At high water activity, when cations do not violate the primary hydration shell, consisting of 20 water molecules per nucleotide, DNA is in the B-form. As the relative humidity in the fiber or film decreases or as the salt concentration in the solution increases, the degree of hydration also decreases at a certain threshold value G (a parameter that determines the solvation or hydration of a macromolecule, which in the case of DNA is equal to the number of moles of water per mole of nucleotides), corresponding to about 20 water molecules per nucleotide, a structural transition of DNA from the B-form to the C- or A-form is observed, depending on the nature of the counterion present. B → C-transition occurs “continuously” [43, 44], as it should be in the case of two structurally similar forms. As for the transitions B → A and C → A, because of the change in the conformation of the sugar $C_{2\text{-}endo} \rightarrow C_{3\text{-}endo}$, they should occur in a jump, cooperatively.

In aqueous solutions, B-DNA is slightly untwisted, its spiral rotation angle is less than that of B-DNA in fibers. However, as the salt concentration increases, there is a “continuous” intrafamily structural transition B ↔ C. When the salt concentration reaches a certain value, there is a sharp cooperative interfamily transition C → A or B → A. Such cooperative transitions (B → A or C → A) also occur when the polarity of the medium changes, for example, when ethanol, isopropanol or dioxane are added to the system to concentration ~ 80% [45-47]. When the double helix is formed, the DNA becomes more polar. In other words, if in the unwound elongated DNA, phosphates account for ~ 820% of the surface area, bases for 50% and sugars for 30%, then in double helix phosphates occupy 45% of the surface area, bases 20%, and sugars 35%. Thus, the polarity of the DNA molecule increases during the formation of a double helix. The same picture is observed in proteins during the formation of globular structures: polar groups are located on the surface, and non-polar, hydrophobic ones are inside. In general, we can say that the accessibility of the DNA surface for a solvent determines its properties. Estimates of the accessible surface area of DNA show that the bases of B-DNA are open mainly from the side of the main groove, and the bases of A-DNA are open from the side of the minor. This means that when a protein interacts with an intact double helix, specific contacts between base pairs and side groups of amino acids in the case of the B-form will occur in the main groove, and in the case of the A-form, in the minor. This is consistent with data on the interaction of B-DNA with specific proteins, the *Escherichia coli* RNA polymerase with a *lac*-promoter, a *lac*-repressor with a *lac*-operator, as well as with data on λ- and *cro*-repressors and the interaction of DNA with histones in nucleosomes [48-50].

Interaction between proteins and nucleic acids. The interactions between proteins and nucleic acids occur at all stages of DNA replication and expression, as well as in the course of numerous regulatory processes, and, therefore, their role is extremely important. Nevertheless, our knowledge of the molecular mechanisms of such interactions is still limited. We do not have a clear idea of how restriction endonucleases bind to DNA and cut it at specific locations. There is no complete information about the geometry of recognition of the operator sites by the repressor and how aminoacyl-tRNA synthetases recognize “their”

tRNAs [51]. The main difficulty in studying these complex systems is that it is necessary to simultaneously observe each of the interacting macromolecules. At the same time, spectroscopic methods, with rare exceptions, give inadequate results, and crystallization of complexes of proteins with nucleic acids is associated with many difficulties. Nevertheless, in the early 1980s, publications appeared the authors of which managed to obtain specific complexes of proteins with DNA [52, 53] and tRNA [54] in a form suitable for X-ray structural analysis.

To simplify the process of studying such complex systems, studies of model compounds are carried out using both theoretical and experimental approaches. The main goal of such studies is to establish the specificity of recognition of four types of nucleic acid bases by side groups of twenty amino acids. In this case both monomeric components of both partners and polymers, in some cases synthetic, are used. The binding of nucleotides (inhibitors or coenzymes) in the active centers of enzymes is also studied. Crystals of several proteins that recognize specific DNA sequences were obtained and their spatial structure was determined. This is perhaps the maximum that can be done without crystals of specific DNA-protein complexes. Such structures give an idea of the general principles of nucleic-protein interactions, but the last word ultimately remains with the studies of the complexes themselves [55, 56].

If we carefully analyze the structure of the side groups of amino acids and the polypeptide backbone, we will see that there are four potentially possible types of interactions between proteins and nucleic acids [57-59]: 1) salt bridges between phosphates and positively charged amino acid groups ($N_\xi$-amino group of lysine, guanidine group of arginine and protonated His residue); 2) hydrogen bonds between phosphates, sugars, nucleic acid bases and peptide groups or hydrophilic side chains of amino acid residues; 3) stacking interactions between side groups of aromatic amino acids (Trp, Tyr, Phe, His) and bases; 4) hydrophobic interactions between nucleic acid bases and side groups of non-polar amino acids.

The energy of these four types of interaction generally decreases in the order in which they are listed here. Since the attraction of opposite charges plays the main role, data on the charge distribution in the side chains of amino acids and in the peptide group are extremely important. They need to be compared with similar data for nucleic acid components and then some interactions can be predicted. However, in reality, a more complex situation is observed, since numerous weak interactions can suppress specific interactions of the "charge-charge" type.

Double helix DNA can interact with polypeptides in several ways: (a) through the formation of specific hydrogen bonds between Watson-Crick base pairs and amino acid side chains; (b) by intercalation of side chains of aromatic amino acids between base pairs ("bookmark" model), which also exhibits some specificity, (c) by direct binding of protein α-helices and β-sheets in DNA grooves. It is assumed that the latter type of interaction (it is more correct to say "two types of interaction") takes place in DNA complexes with a *cro*-repressor (in the model of the complex, the α-helix and β-sheet fall into the major and minor grooves of the double helix, respectively) and with a protein that activates catabolism, for which two models of binding of α-helices have been proposed, i.e., with the left and right double helix of B-DNA [60]. Based on the data on the crystal structure of prealbumin, a hypothetical complex of prealbumin with DNA was proposed [61]. However, in reality, such a complex, apparently, does not form [62]. Both polylysine and polyarginine bind irreversibly to DNA; in both cases, the process of joining is cooperative, but the structure of the corresponding complexes is different.

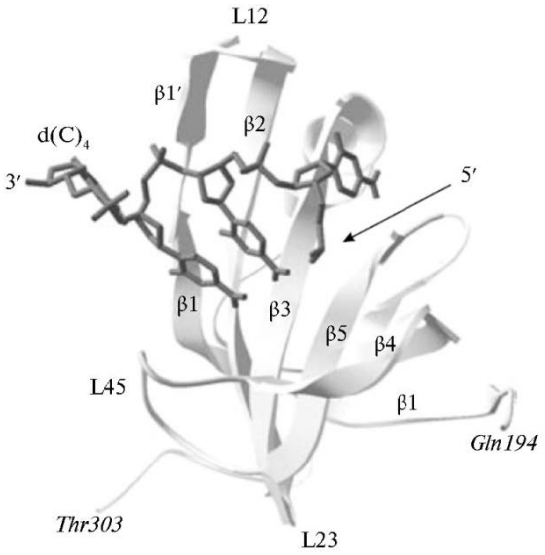


**Fig. 2. An example of "straight polarity" binding of nucleic acids in the tertiary structure of the complex of the OB-domain p70A** (a.b. 194-303) **hsRPA with the oligonucleotide residue d(C)4** (highlighted in dark gray) (on [63]).

Another example of "straight polarity" binding of nucleic acids in the tertiary structure of the OB-domain complex (the domain that binds oligosaccharides and oligonucleotides) p70A hsRPA with the oligonucleotide residue d(C)4 (Fig. 2). The resulting β-sheets are arranged orthogonal to each other and form a β-cylinder with the chain topology β1-β2-β3-β5-β4-β1. Usually, the canonical surface of interaction of the OB-packing with ligands is located in the region of chains β2 and β3. Additionally, the interaction can involve loops between β1 and β2 (loop L12), β3 and α (loop L3a), α and β4 (loop La4) and, finally, between β4 and β5 (loop L45). These loops form a trough that runs along the domain surface perpendicular to the axis of the topological β-cylinder [63].

Nucleotides and single-stranded RNA and DNA, when bound to proteins, usually take on an elongated shape, i.e., the torsion angle γ for them lies in the region *-ck* or *an*. Such a change in the γ angle occurs when NAD+ binds to dehydrogenases, when dinucleotide phosphates bind to ribonucleases A and S, and when RNA binds to the tobacco mosaic virus protein [64]. Interactions in the complex can represent contacts of any type and affect any part of the molecule of each partner. For example, in the case of a specific complex of ribonuclease T1 with guanylic acid, guanine is recognized through the formation of a hydrogen bond with the peptide backbone and stacking with the tyrosine side group. It turned out that interactions between nucleotides and atoms of the protein backbone are generally more common and more specific than interactions with side groups of amino acids [65].

Binding of DNA to the phage fd gene 5 protein promotes the divergence of the strands of the double helix. If (single-stranded) DNA and protein form a complex, i.e., if DNA is attached to the "active center" of the protein, which consists exclusively of β-structure elements, the formation of protein aggregates begins. In this case, the protein molecules line up one after the other, forming a spiral onto which single-stranded DNA sections are wound [66].

Intercalation. DNA, as a carrier of genetic information, interacts with many drugs, carcinogens and mutagenic substances, as well as with dyes, a characteristic feature of which is the presence of elongated (hetero)cyclic aromatic chromophores. Such substances include: acridines (yellow and orange), proflavine, ethidium, ellipticine, 3,5,6,8-tetramethyl-N-methylphenanthroline, 2-hydroxyethanethiolate-2,2',2''-terpyridine-platinum (III), daunomycin, actinomycin and a number of others (Fig. 3). Since DNA plays a key role in the processes of replication and protein biosynthesis, its modification when interacting with these compounds has a strong effect on cellular metabolism, slowing down and in some cases stopping cell growth. All these properties of the compounds mentioned above

aroused great interest in them, especially increased over the past decades. The possibility of their use in medicine was discovered; they also found wide use in laboratories in the study of the structure and function of DNA [67, 68]. One of the categories of such compounds is formed by substances that lead to chemical modification of DNA (and the target is primarily guanine), the other is those that bind to the double helix. Binding occurs either at the periphery of the molecule, or, as, for example, in the case of drugs such as daunomycin and actinomycin, by intercalation (i.e., by incorporation) between adjacent base pairs without breaking Watson-Crick pairing (Fig. 4). The interaction of DNA with medicines is of great importance for pharmacology [69]. If we consider only intercalation complexes with drugs with planar groups, then the binding of such drugs with a double helix occurs in two stages: at the first, they are attached along the periphery of the helix, at the second, intercalation occurs, which is accompanied by unwinding and lengthening of the helix, as well as an increase in its rigidity. In accordance with the principle of exclusion of the nearest binding sites, intercalator molecules fill only half of such sites.

In all known crystalline complexes, intercalators are located between two Watson-Crick pairs formed (in the case of ribo- and deoxyriboside) by self-complementary dinucleoside monophosphates, in which the nucleoside at the 5′-end is always pyrimidine, and at the 3′-end-purine. If the bases are reversed, then either crystals are not formed, or the complex will have a non-helical structure. This specific sequence dependence of intercalation was also found for aqueous solutions. It also received a theoretical basis. It was shown that for both DNA and RNA upon intercalation into the pyrimidine-3',5'-purine sequence, much stronger base overlap with the intercalator occurs than upon intercalation into the purine-3',5'-pyrimidine sequence [70]. Therefore, in the first case, intercalation turns out to be 7-13 kcal $mol^{-1}$ more favorable than in the second [71]. This intermolecular interaction is stabilized by intramolecular electrostatic forces, which also provide preferential insertion into the pyrimidine-3′,5′-purine sequence. In addition, in the case of an inverted sequence, sterically unfavorable contacts may occur, which complicate the integration.

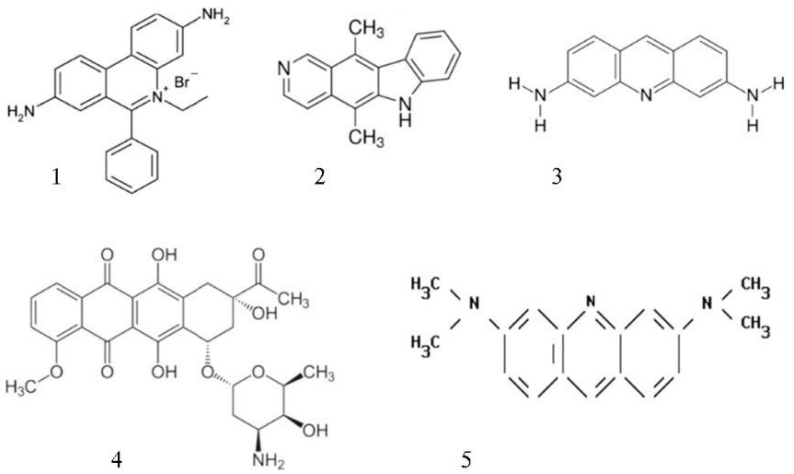


**Fig. 3. Examples of some medicines and dyes that form complexes with nucleic acids by the type of intercalation:** 1 — ethidium bromide, 2 — ellipticine, 3 − proflavine, 4 — daunomycin, 5 — acridine orange.

During intercalation, the physical properties of double helices change. For the first time, the assumption about the possible incorporation of planar aromatic

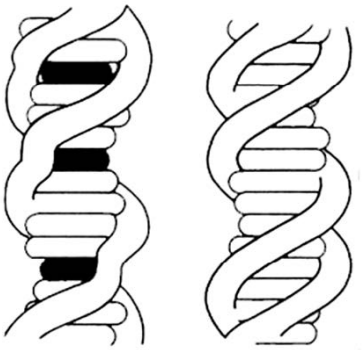

**Fig. 4. Intercalation of planar molecules of intercalating substances** (black plates) **into the DNA double helix.** The regular course of the sugar-phosphate backbone (right) in the intercalation sites is disrupted (left).

molecules between neighboring base pairs was made on the basis of the results of hydrodynamic and X-ray structural studies of DNA in the presence of acridine dyes [72]. If you add an acridine dye to the DNA solution, and then prepare the fiber and irradiate it with X-rays, you will get an X-ray diffraction pattern in which the reflections due to the presence of a regular helical structure blur and disappear. Only equatorial reflections remain, indicating a regular packing of molecules along the fiber, and a strong meridional reflex (0.34 nm), which corresponds to the interplanar distance between pairs [72, 73]. Generally speaking, when the aromatic molecules are embedded with a thickness of 0.34 nm, the overall stacking scheme may not be violated. However, for intercalation to occur, the pairs must move apart, and this will lead to a change in the geometry of the sugar-phosphate backbone and the destruction of the regular helical structure (see Fig. 4). In accordance with this concept, a DNA molecule should elongate as a dye is added to the system. This is precisely what the experimental data prove that the viscosity increases and the sedimentation coefficient decreases [72]. Both of these effects also suggest an increase in the rigidity of the DNA double helix.

Intercalation leads to unwinding of the DNA molecule. The base pairs must move apart to make room for the intercalator. This is carried out due to the simultaneous stretching of the B-DNA double helix along the axis of its untwisting, which is necessary so that the sugar-phosphate backbone does not break during stretching [73]. The fact that unwinding actually occurs is evidenced by the results of experiments on the intercalation of a number of compounds into plasmid DNA, a circular closed double helix that forms a right supercoil [67, 74]. During intercalation, unwinding of the double helix is observed (10-20° for each intercalated molecule), at which the number of right-handed supercoils decreases until equilibrium is reached, i.e., until DNA becomes a simple ring without supercoils. Upon further intercalation, the double helix continues to unwind, and as a result, a left super helix is formed. The process is easy to observe by the change in the sedimentation coefficient [75].

In our experiments, the effect of intercalator dyes and laser radiation was observed both for unwinding double helices of native phage and high molecular weight plant DNA, and for directed formation of single- and double-stranded breaks to increase the frequency and spectrum of recombination in order to release selectable genotypic variability in various plant species [76-79]. As a result, it was found that dyes-intercalators form a stable complex, which, when irradiated with laser light, transfers energy from the donor-intercalator to the DNA acceptor, which leads not only to unwinding of double DNA strands, but also to the formation of single- and double-stranded DNA breaks. At the same time, the DNA structure in places other than intercalation does not change and retains the ability to replicate, and intercalating dyes are able to inhibit nuclease activity. Thus, not only a mutagenic, but also a recombinogenic effect is achieved, which leads to the induction of genotypic variability in plants and can be used in practical genetic selection studies.

It is noteworthy that during intercalation into A-type double helices, all sugar residues can remain in the $C_{3\text{-}endo}$-conformation. The divergence of pairs is mainly due to a change in the conformational angles of the framework $\zeta$ and $\gamma$,

the values of which are shifted to the region an; in this case, the process proceeds without untwisting and the complexes of proflavine with CpG and with 5-iodine-CpG are apparently acceptable [80, 81]. Since the conformation and orientation of sugars do not essentially change, it can be assumed that the principle of exclusion of the nearest binding sites is not fulfilled during intercalation in A-DNA and A-RNA.

In the case of B-DNA, the main natural form in which, upon intercalation, the angles α and γ shift to the *an* region, a different picture is observed. In the best model from the point of view of intercalation [82] the conformation of the sugar located on the 5'-side of the intercalation site changes from $C_{2'\text{-}endo}$ to $C_{3'\text{-}endo}$ in accordance with what was observed for complexes of dinucleotide monophosphates with intercalators. Conformational changes are not limited to the violation of the position of two pairs adjacent to the intercalator, but extend to other, distant pairs. The 18° unwinding associated with the incorporation of each molecule of the intercalator affects at least three pairs before and after the intercalation site.

This "long-range action" can be clearly seen, for example, in the complex of daunomycin with hexadeoxynucleotide [83] and is consistent with the principle of excluding closest binding sites. Experiments on dichroism have shown that the plane of the intercalator is not perpendicular to the axis of the spiral, but is inclined to it at an angle of about 20°. This affects the location of both the closest pair and the pair following it, i.e., in this case, there is a cooperative effect [84].

Therefore, the presented data allow for the conclusion that the interactions between proteins and nucleic acids are very diverse: these can be salt bridges, hydrogen bonds, stacking and hydrophobic interactions. Any part of both molecules can be involved in them. Molecules of nucleotides, single-stranded DNA and RNA usually elongate when bound to proteins.

Water is not just a medium in which certain molecules are dissolved. Water stabilizes the secondary and tertiary structure of macromolecules. This applies to both proteins and DNA, and to DNA, perhaps even more so [85, 86]. Nucleic acid hydration, as mentioned above, plays an important role in the formation of their structure and is responsible for the A ↔ B conformational transitions. It should be noted that the B-form is the main natural form in which DNA is in the cell and interacts with intracellular proteins, ensuring the activity and replication of encoded genetic information.

When folding into a double helix, the DNA molecule becomes more polar, and this can determine intercalation of flat substances into a double strand of nucleic acids. Intercalation of planar medicinal and other chemical substances or their planar groups is of great importance not only for pharmacology [77, 78]. It also affects replication, including inhibition of nuclease activity, and can also be used for directed mutagenesis and recombinogenesis [76, 79]. Intercalation has a key effect in the modification of DNA during replication and protein biosynthesis [87, 88]. Structural modifications due to DNA interaction with intercalators strongly affect cell metabolism leading to slowing down and even stopping cell growth which can result in apoptosis and malignancy or, conversely, in recovery from cancer diseases [89, 90]. Understanding the mechanisms of such interactions elucidates the role of each intercalator in order to solve practical problems of genetics, physiology, and pharmacology. For example, preparations with a planar structure, containing a Pt chelate complex with bipyridine, strongly change the DNA structure, which takes the form of a "rope ladder" [91]. Moreover, in each Watson-Crick pair, one nucleotide is in *syn*-form and the other in *anti*-form, like in Z-DNA.

So, intracellular interactions of nucleic acids with water and protein molecules are extremely important, since this fixes and stabilizes the spatial structure of DNA and RNA at the molecular level, which, in turn, ensures the stability and regularity of replication processes and gene expression, especially under genotype-environment interactions. Water stabilizes the secondary and tertiary structure of the macromolecules dissolved in it. This is extremely important for DNA, since the conformational changes of its molecule and, ultimately, the functional activity of DNA as a carrier of genetic information depend on the degree of hydration. The interaction of DNA with intercalator drugs is also of great importance. Intercalation, influencing replication and protein biosynthesis, affects cell metabolism, which under certain conditions can have a therapeutic effect. It is reasonable to hope that the study of the interactions of nucleic acids with water and with proteins at the intracellular level will soon disclose mechanisms of nucleic acid-protein recognition and thereby allow us to come close to managing such interactions. The study of the complexes themselves that are formed by nucleic acids with water, proteins, and intercalating agents are also highly informative.

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