O.O. ZDOREVSKYI, S.N. VOLKOV

Bogolyubov Institute for Theoretical Physics, Nat. Acad. of Sci. of Ukraine
(14b, Metrolohichna Str., Kyiv 03143, Ukraine; e-mail: zdorevskyi@bitp.kiev.ua)

THE POSSIBILITY OF BLOCKING THE PROCESS OF DNA BASE PAIRS OPENING BY HYDROGEN PEROXIDE

UDC 539

One of the most progressive methods of cancer treatment is the ion beam therapy. Simulations of the water radiolysis show that the most long-living species in the cell medium are hydrogen peroxide (H_2O_2) molecules. But up to the present time, the role of H_2O_2 molecules in the deactivation of cancer cells has not been determined yet. To understand the possible role of H_2O_2 in the ion beam therapy, the competitive interaction of H_2O and H_2O_2 molecules with nucleic bases in a pair on the different stages of genetic information transfer is studied in the present work. The method of atom-atomic potential functions is used in the calculations. It is shown that some configurations of $A \cdot T$, and $G \cdot C$ complementary pairs are stabilized much better by an H_2O_2 molecule as compared to a water molecule. The formation of such interaction complexes can terminate the processes of DNA unzipping by enzymes and consequently block the genetic information transfer processes in cancer cells during the ion beam treatment. An experimental method of verification of the interaction of hydrogen peroxide with nucleic base pairs is proposed.

K e y w o r d s: DNA base pairs, hydrogen peroxide, ion therapy.

1. Introduction

The ion beam therapy is one of the most progressive methods of cancer treatment. Nowadays, the corresponding ion facilities, where patients undergo the treatment on special accelerators, are built throughout the Europe. The ion therapy is based on the so-called Bragg effect [1], which means that the maximum amount of energy is transferred by heavy ions to the medium at the end of their track in a certain localized area of space. This effect makes the ion therapy especially effective for the treatment of tumors that are deep enough in the body.

In radiotherapy, it is considered that, to destroy the cancer cells, it is necessary in some way to deactivate their DNA [2]. However, the definite mechanisms of action of high-energy ions on DNA of cancer cells have not been determined yet [3].

It is known that a DNA macromolecule is situated in a cell in the water-ionic solution. This solution stabilizes the double helix, determines its shape, and, accordingly, affects its functioning in a living cell. Due to the water radiolysis, which takes place during the ion beam therapy, this environment changes significantly. A large number of species appear in the solution: free radicals, secondary electrons, ions, as well as molecular products such as H_2O_2 and H_2. Till recently, the most attention in the literature [2, 4] was paid to the DNA strand breaks, which occur due to the action of secondary electrons and free radicals. However, it is known that there are DNA reparation mechanisms, which can eliminate DNA strand breaks [5].

Experimental studies, as well as the Monte Carlo simulation of water radiolysis [6–8], showed that, on the biological time scales, one of the most long-living species are hydrogen peroxide molecules. But their role in the ion beam therapy has not been discussed in the previous works properly.

In our paper [9], the new hypothesis was proposed. According to this hypothesis, a hydrogen peroxide molecule can form stable complexes with active DNA sites, thus blocking the processes of genetic information transfer in living cells. To prove the hypothesis, the interaction of H_2O_2 molecules with nonspecific DNA recognition sites – phosphate groups (PO_4) [9, 10], as well as with specific DNA recognition sites – nucleic bases [11] was investigated in our works. The method of atom-atom potential functions and the density functional theory were used in calculations. The results within both methods revealed that the hydrogen peroxide molecule can form a complex with DNA phosphate groups that is no less stable than the same complex with water molecule. In addition, the definite sites of Adenine (A), Thymine (T), Guanine (G), and Cytosine (C) nucleic bases, where the H_2O_2 molecule can interact much stronger than the water molecule, are determined. These interactions can block the processes of DNA recognition by the enzyme.

It should be noted that, in the DNA double helix, the nucleic bases form complementary pairs – $A \cdot T$ and $G \cdot C$. During the genetic information transfer, the complementary base pairs become to be open for the interaction with the surrounding molecules, i.e., expose their atomic groups to the solvent. The base pair opening can be blocked by H_2O_2 molecules during the ion beam treatment and can serve as an evidence of our proposed mechanism of DNA deactivation. It is sufficient that the opening of base pairs can be investigated now experimentally with the help of the single-molecule manipulation technique [12–14]. Therefore, it can be used for the direct observation of the interaction of H_2O_2 molecules with DNA.

In Sec. 2, the methodology of our calculations is described. In Sec. 3, the stability of the complexes consisting of "preopened" and "stretched" $A \cdot T$ and $G \cdot C$ base pairs together with hydrogen peroxide or a water molecule is studied. The possibility of blocking the process of opening of the nucleic base pairs by H_2O_2 molecules is considered. In Sec. 4, the experimental observation method of the interaction of hydrogen peroxide molecules with DNA nucleic bases is discussed.

2. Calculation Methods

In the present work, we will perform our calculations with the help of the atom-atomic potential function method. This method is now widely used in such force fields as CHARMM and AMBER [15–17] for studying the structure of molecular complexes. Calculations are made using the GNU Octave software package [18]. In the framework of this method, the energy of intermolecular interaction consists of those of the van der Waals interactions, hydrogen bonds, and Coulomb interactions:

$$E(r) = \sum_{i,j} (E_{\mathrm{vdW}}(r_{ij}) + E_{\mathrm{HB}}(r_{ij}) + E_{\mathrm{Coul}}(r_{ij})). \quad (1)$$

In the framework of the present method, we consider all the covalent bonds and angles as rigid.

Van der Waals's interaction is described by the Lennard-Jones "6–12" potential:

$$E_{\mathrm{vdW}}(r_{ij}) = -\frac{A_{ij}}{r_{ij}^6} + \frac{B_{ij}}{r_{ij}^{12}}, \quad (2)$$

where the parameters $A_{ij}^{(10)}$, $B_{ij}^{(10)}$, A_{ij}, and B_{ij} are taken from works [19, 20].

The energy of a hydrogen bond between atoms i and j is modeled by the modified Lennard-Jones "6–12" potential:

$$E_{\mathrm{HB}}(r_{ij}) = \left[-\frac{A_{ij}^{(10)}}{r_{ij}^{10}} + \frac{B_{ij}^{(10)}}{r_{ij}^{12}} \right] \cos\varphi, \quad (3)$$

where r_{ij} – the distance between the atoms i and j, and φ – the angle of the hydrogen bond. For example, when the hydrogen bond is O–H...N, then φ is an angle between the lines of the covalent bond (O–H) and the hydrogen bond (H...N).

The Coulomb interaction is described by the electrostatic potential:

$$E_{\mathrm{Coul}}(r_{ij}) = \frac{1}{4\pi\varepsilon_0 \varepsilon(r_{ij})} \frac{q_i q_j}{r_{ij}}, \quad (4)$$

where q_i and q_j are the charges of the atoms i and j located at a distance r_{ij}, ε_0 is the vacuum permittivity, and $\varepsilon(r)$ is the dielectric permittivity of the medium.

The charges q_i, q_j for nucleic bases were taken from works [19, 20]. The charges of H_2O and H_2O_2 molecules were calculated from the condition that the dipole moment of a water molecule should be equal to $d_{H_2O} = 1.86\ D$ [21], and that of a hydrogen peroxide molecule $d_{H_2O_2} = 2.10\ D$ [22]. Hence, for an H_2O molecule, we obtain the charges $q_H = 0.33e$, $q_O = -0.66e$, and, accordingly, for H_2O_2 $q_H = 0.41e$, $q_O = -0.41e$. The values of charges on the atoms of an H_2O_2 molecule are in good agreement with charges obtained by quantum-chemical calculations in work [23]. The same charge values are used in the recently developed force field for a hydrogen peroxide molecule [24].

Since DNA in a living cell is situated in the water-ion solution, the interacting atoms are screened by water molecules. This leads to a weakening of the Coulomb interaction. Thus, the more effective accounting of Coulomb interactions can be achieved using the dependence of the dielectric permittivity on the distance ($\varepsilon(r)$) developed by Hingerty *et al.* [25] in the explicit form:

$$\epsilon(r) = 78 - 77\,(r_p)^2\,\frac{e^{r_p}}{(e^{r_p}-1)^2}, \qquad (5)$$

where $r_p = r/2.5$.

3. Calculation Results

It is known that the nucleic bases in the complementary pair have many degrees of freedom, which are defined by the standard nomenclature [26]. Since the base pairs are situated in a double helix, their structure is stabilized by the stacking interaction between adjacent pairs. This essentially limits the degrees of freedom that remove the bases beyond the plane of the pair. Consequently, in this paper, only the degrees of freedom of the bases in the plane of the pair ("stretch", "opening", "shear") are considered. In addition, the degree of freedom called a "propeller twist" was considered (Fig. 1) due to the spatial structure of H_2O_2 molecules.

First, in order to verify the correctness of the parameters chosen for our calculations, the stable Watson–Crick configuration of the complementary pairs of A · T and G · C were calculated (Fig. 2). As is seen from Tabl. 1, the spatial structures of these configurations are close to those obtained from the X-ray structural analysis and the NMR experiments. The main differences occur in the parameter "propeller twist" due to the fact that the experiment measures

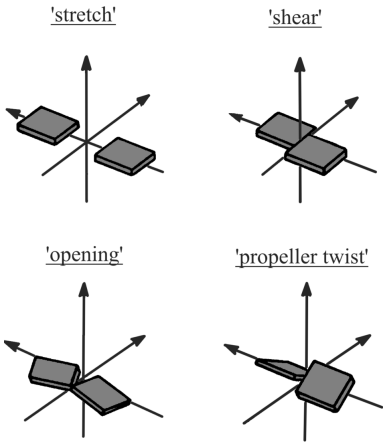

Fig. 1. Degrees of freedom of nucleic bases in a complementary pair, which were taken into account in the calculations of molecular complexes

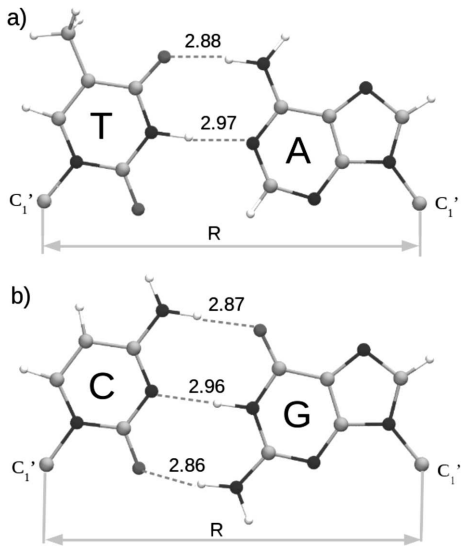

Fig. 2. Watson–Crick configurations of the A · T (*a*) and G · C (*b*) complementary pairs. The numbers indicate the distance (in Å) between the heavy atoms in the corresponding hydrogen bonds. R denotes the distance between the C_1' atoms

pairs which are not isolated, but constitute a structure of a double helix. These parameters are calculated using the 3DNA software package [27]. The visualization is made by VMD [28]. Table 1 shows that the spatial structures of the pairs do not differ significantly from one another, depending on whether the formula (5) is used in the calculations. At the same time, the difference in the interaction energy for G · C pair is significant, which is due to the anoma-

Table 1. **Structural parameters of Watson–Crick A · T and G · C base pairs according to the standard nomenclature (Fig. 1). The parameters "shear", "stretch" are given in Å; "propeller twist", "opening" in degrees**

Parameter	A · T				G · C			
	X-ray [1]	NMR [2]	Our calculations		X-ray [1]	NMR [2]	Our calculations	
			vacuum	using (5)			vacuum	using (5)
"stretch"	-0.16 ± 0.02	-0.15 ± 0.04	-0.02	-0.01	-0.24 ± 0.02	-0.3 ± 0.03	-0.14	-0.14
"shear"	0.12 ± 0.03	0.00 ± 0.04	0.16	0.18	-0.08 ± 0.05	0 ± 0.07	0.16	0.23
"opening"	2.62 ± 0.67	-0.54 ± 0.6	-4.79	-5.01	-2.13 ± 0.4	0.66 ± 0.41	-1.70	-1.70
"propeller twist"	-16.95 ± 0.34	-14.45 ± 2.41	-2.46	3.58	-8.15 ± 1.49	-10.41 ± 1.53	-0.53	-0.44

[1]Calculated from the spatial structures of a Dickerson–Drew dodecamer (files 1bna.pdb, 7bna.pdb, 9bna.pdb, 436d.pdb) obtained by X-ray analysis. The values are averaged separately by the A · T and the G · C base pairs, and the standard errors are calculated.

[2]Calculated from the spatial structures of a Dickerson–Drew dodecamer (files 1duf.pdb, 1gip.pdb, 1naj.pdb, 2dau.pdb) obtained by the method of nuclear magnetic resonance. The values are averaged separately by the A · T and the G · C base pairs, and the standard errors are calculated.

lous contribution of the Coulomb interaction. More details concerning the necessity to use formula (5) are discussed in [29]. It was shown in [11] that the calculation results of the water-water and peroxide-water complexes with the use of dependence (5) are much closer to the results of quantum-chemical calculations than without this dependence. Therefore, all further calculations will be carried out taking into account formula (5).

The interaction of nucleic bases with water molecules was considered in a series of works [30–32]. In work [33], the hydration shells of A · T and G · C base pairs were calculated; i.e., the simultaneous interaction with a large number of water molecules was considered. However, in the literature, no essential attention was paid to the interaction of nucleic bases with hydrogen peroxide molecules (which, as described in Sec. 1, appears in the cell as a result of the ion beam treatment). We can mention only work [34], where the interaction of hydrogen peroxide molecules with the Adenine base was considered.

In the present paper, the calculations of the interaction energy of complexes consisting of A · T and G · C nucleic base pairs with hydrogen peroxide and water molecules are carried out. In work [35], it was shown that the structures stabilized by water molecules occur on the pathway of the opening of base pairs during the DNA unzipping. For the purposes of the present work, it is important to analyze the possibility of forming the simplest "non-Watson–Crick" configurations of A · T and G · C base pairs stabilized by hydrogen peroxide and water molecules and to establish whether the formation of these complexes can block the genetic information transfer processes. Consequently, the complexes that include only one hydrogen peroxide or water molecule are taken into account.

We now consider three configurations of nucleic base pairs with hydrogen peroxide molecules and water molecules. We denote the complexes consisting of complementary A · T and G · C base pairs and the hydrogen peroxide or water molecule that interacts with the base from the side of the major groove as "closed" pairs (Fig. 3, *a*). The configuration of the pair, where the "opening" pathway dominates, is denote as "preopened" (Fig. 3, *b*), and those, in which the "stretch" pathway dominates, will be denoted as "stretched" pairs (Fig. 3, *c*).

First, let us calculate "closed" configurations. It can be seen that the interaction with these molecules almost does not change the geometry of the Watson–Crick pairs (Tabl. 2, Fig. 4).

In Fig. 5, the stable configurations of the "preopened" A · T and G · C base pairs with water and hydrogen peroxide molecules are shown. For the convenience of the analysis, in Tabl. 2, only structural parameters $\Delta R = R - R_{\mathrm{WC}}$ (difference in $C_1'C_1'$ distances (Fig. 2, *a*) in the corresponding and Watson–

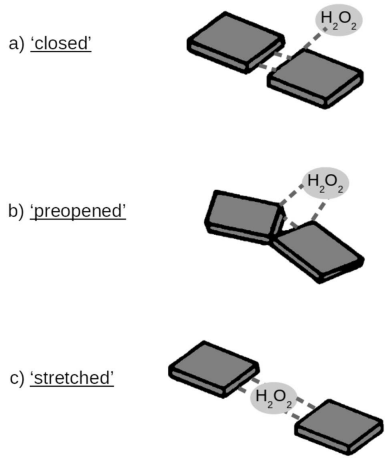

Fig. 3. Complexes of nucleic base pairs with hydrogen peroxide molecules considered in the present work (and should occur on the pathway of the opening of base pairs during the DNA unzipping): "closed" configuration (*a*); "preopened" configuration (*b*); "stretched" configuration (*c*)

Table 2. **Values of the distances $\Delta R = R - R_{\mathrm{WC}}$ (R – distance (in Å) between C_1' atoms in the corresponding pair (Fig. 2), R_{WC} – the same distance in a WC pair); parameters "opening" and "propeller twist" (in degrees), as well as the interaction energies E (in kcal/mol) for "closed", "preopened", "opened" and "stretched" configurations of base pairs with H_2O_2 and H_2O molecules***

State	Pairs	Molecules	ΔR	"Opening"	"Propeller twist"	E
"closed"	A · T	H_2O	0.1	−5.6	−2.6	−14.7
		H_2O_2	0.1	−5.6	−2.7	−16.0
	G · C	H_2O	0.0	−1.7	−0.5	−21.2
		H_2O_2	0.0	−1.7	0.0	−22.1
"preopened"	A · T	H_2O	−1.7	36.0	3.7	−15.8
		H_2O_2	−1.6	35.0	12.9	−16.6
	G · C	H_2O	−0.3	23.3	−0.8	−16.9
		H_2O_2	−0.5	17.2	42.9	−18.6
"opened"	G · C	H_2O_2	−0.1	47.0	7.3	−19.0
"stretched"	A · T	H_2O	3.4	−35.9	1.8	−10.9
		H_2O_2	3.1	−11.7	−69.1	−17.6
	G · C	H_2O	3.1	−31.5	0.0	−13.0
		H_2O_2	2.9	−7.0	−72.4	−20.9

*All the values are rounded to the first decimal due to the accuracy of the parameters that are used for the calculations of the corresponding structures.

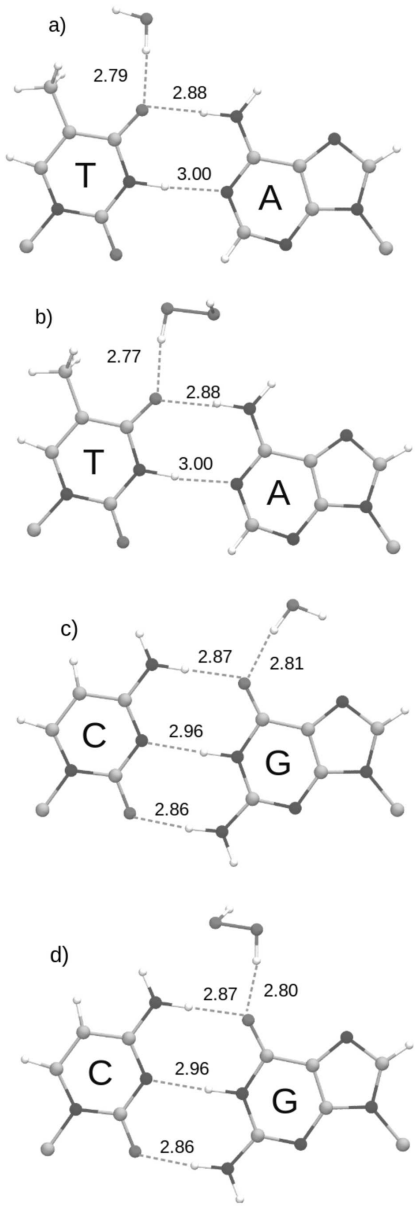

Fig. 4. Complexes of complementary pairs of A · T and G · C with water and hydrogen peroxide molecules, bound from the major groove ("closed" pair): A · T with H_2O molecule (*a*); A · T with H_2O_2 (*b*); G · C with H_2O (*c*) G · C with H_2O_2 (*d*)

Crick pair), "opening" and "propeller", as well as the interaction energies are shown. From Tabl. 2, it can be seen that the configurations of "preopened" A · T pairs with water and hydrogen peroxide molecules have almost identical parameters. The "opening" parameter has the maximum value, the rest of the

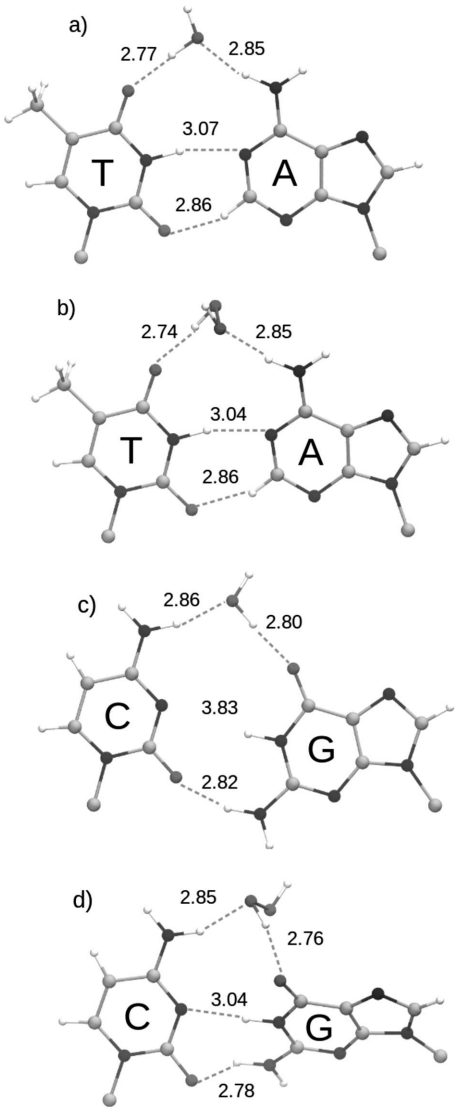

Fig. 5. Stable configurations of the "preopened" base pairs calculated in the present work: A · T with water (*a*) and hydrogen peroxide (*b*) molecules; G · C with water (*c*) and hydrogen peroxide (*d*) molecules. The numbers indicate the distance (in Å) between heavy atoms in the corresponding hydrogen bonds

parameters are not changed significantly. It should be noted that the "propeller twist" parameter almost does not take the bases out of the plane of the pair. Moreover, the configurations of "preopened" G · C pairs with H_2O_2 and H_2O molecules are significantly different, since the spatial structure of hydrogen peroxide increases the parameter "propeller twist", taking the bases out of the plane of the pair.

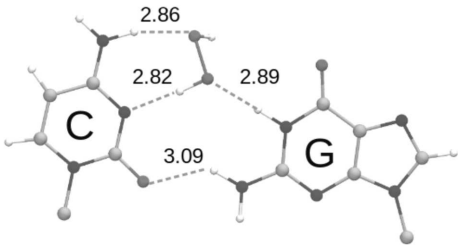

Fig. 6. "Opened" configuration of G · C pair with an H_2O_2 molecule calculated in the present work. The numbers indicate the distance (in Å) between heavy atoms in the corresponding hydrogen bonds

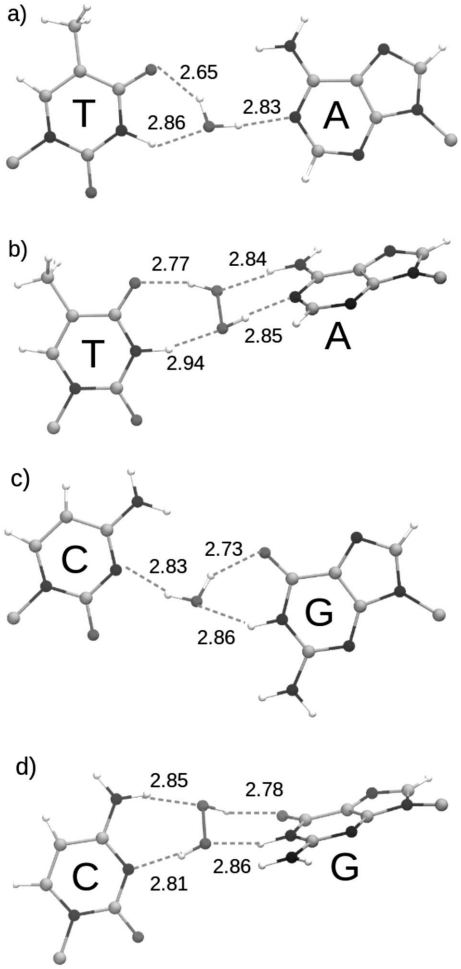

Fig. 7. Stable configurations of "stretched" base pairs calculated in the present work: A · T with water (*a*) and hydrogen peroxide (*b*) molecules; G · C with water (*c*) and hydrogen peroxide (*d*) molecules. The numbers indicate the distance (in Å) between heavy atoms in the corresponding hydrogen bonds

It should be noted that, in the case of G · C pair, there is still a configuration with the H_2O_2 molecule (Fig. 6), which, on the one hand, is similar to the "preopened" state, because the parameter R is almost unchanged, and the "opening" parameter is significantly larger than in the Watson–Crick ones, but since the hydrogen peroxide molecule is "embedded" to the internal ($N_3 \ldots N_1$) hydrogen bond in this case, we call this state "opened". Note that, due to the geometry of the molecules, the "opened" state occurs only for G · C pair and only with H_2O_2 molecules.

Configurations of "stretched" pairs with water and hydrogen peroxide differ significantly by their parameters (Fig. 7). It should be noted that, for both the A · T and the G · C base pairs, the interaction energy of the "stretched" pair for the complex with a water molecule is lower than the corresponding value for the "preopened" configuration. For complexes with a hydrogen peroxide molecule, on the contrary, it is substantially higher (Tabl. 2).

4. About the Possibility of an Experimental Observation of the Formation of Complexes of Hydrogen Peroxide Molecules with the DNA Base Pairs

During the last decades, the technique that allows one to study features of single molecules was improved significantly. With the help of single-molecule micromanipulation methods, important properties of a DNA macromolecule such as the stretching, bending, twisting [12], and the consequent opening of nucleic base pairs under the action of an external force (unzipping) [13, 14] can be investigated. The experiment is carried out at a constant opening velocity, and the dependence of the opening force on the displacement is measured. At the beginning, the force is not enough to open a double helix, so it sharply increases and then reaches the plateau, which corresponds to the beginning of the opening of base pairs.

In work [29], it has been shown that, during the unzipping of a double helix, depending on the opening velocity, base pairs can be opened along the "stretch" pathway, as well as along the "opening" pathway. In work [35], it was shown that, during the unzipping, the configurations of base pairs that are stabilized by water bridges occur. In this regard, if a certain concentration of hydrogen peroxide is added to the solution, "preopened", and "stretched" pairs stabilized by H_2O_2 molecules can appear under the conditions of this experiment. As follows from our calculations, the binding energy of these complexes is significantly higher than the energy of the same complexes with the water molecule. Therefore, the opening force of a double helix in the experiment carried out in the presence of a certain concentration of H_2O_2 molecules should be higher, as a result of the interaction of the base pairs with H_2O_2 molecules. The observation of an increase in this force in the unzipping experiment can serve as the proof of our hypothesis about the blocking of the DNA base pairs by hydrogen peroxide molecules.

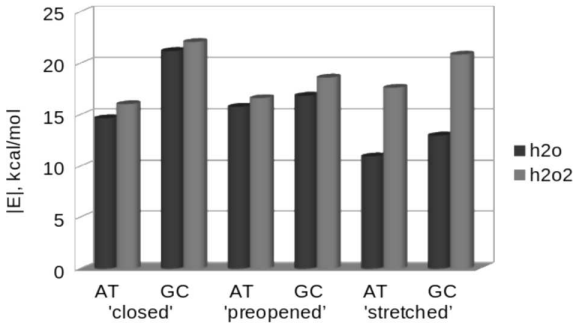

Fig. 8. Diagram of the interaction energy for complexes consisting of hydrogen peroxide and water molecules with "closed", "preopened" and "stretched" configurations of A · T and G · C base pairs

The complexes of hydrogen peroxide with DNA base pairs can be observed by the methods of Raman spectroscopy. It is known that all DNA atomic groups have their own vibrational frequencies. As is known, the vibration frequencies of atomic groups of DNA nucleic bases are in the range of $\sim$1500 cm^{-1} [36]. The interaction of base pairs with water molecules can slightly lower the frequency and amplitude of vibrations [37]. Therefore, the interaction of hydrogen peroxide molecules with DNA base pairs must manifest itself as a shift of the absorption peak to the low-frequency range and as a decrease in its height with comparison to the same complexes with water molecules.

5. Discussion and Conclusions

In the present paper, the spatial configurations of complexes consisting of nucleic base pairs with hydrogen peroxide and water molecules are investiga-

ted. The comparison of the interaction energies is schematically shown in Fig. 8. As can be seen from the results, there are configurations of A · T and G · C base pairs ("preopened" and "stretched"), which are stabilized by hydrogen peroxide molecules much better than by water molecules.

The interaction of hydrogen peroxide molecules with DNA base pairs can manifest itself in living cells, namely, in the process of DNA replication, when two DNA macromolecules are formed from one double helix. At the initial stage of this process, an enzyme passes along a double helix [38] and consequently opens its base pairs one after another. DNA bases interact with water molecules all the time. But, as was mentioned above, a significant amount of H_2O_2 molecules are introduced to the medium during the ion beam therapy. If the interaction energy of nucleic bases of the pair with a hydrogen peroxide molecule is large enough compared to the same interaction energy with a water molecule, the DNA unzipping by the enzyme can be terminated.

As can be seen from the obtained results, the most significant difference in the interaction energies is for "stretched" configurations of the pairs. Therefore, the possibility of blocking the "stretched" pairs by hydrogen peroxide molecules is significantly more probable. In this case, the difference between the opening energies is $\approx 7 - 8$ kcal/mol (Tabl. 2). This is due to the fact that a hydrogen peroxide molecule, because of its spatial structure, forms four hydrogen bonds with nucleic bases (Fig. 7, *b, d*). At the same time, a water molecule forms three hydrogen bonds, and two of them are substantially curved, that is, their energy is weakened (Fig. 7, *a, c*). It should be noted that the "propeller twist" parameter is significant. Therefore, the formation of such configurations is possible only in the unzipping fork, where there is no stacking interaction from one side of the pair.

We note that the energy values obtained in the present work are only the enthalpy values, the entropy is not taken into account. However, due to the similar structures of H_2O_2 and H_2O molecules, the entropy contributions to the interaction of these molecules with nucleic bases should also be similar. Therefore, our approach allows us to obtain a qualitative picture of the formation of complexes of hydrogen peroxide molecules with base pairs and to see a essential energy advantage compared to the same complexes with a water molecule.

The formation of complexes of H_2O_2 molecules with DNA can completely block the DNA transcription in cancer cells and can be a key factor of the action of high-energy ions on cancerous tumors in the process of ion beam therapy.

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О.О. Здоревський, С.Н. Волков

МОЖЛИВІСТЬ БЛОКУВАННЯ ПРОЦЕСУ РОЗКРИТТЯ ПАР ОСНОВ МАКРОМОЛЕКУЛИ ДНК МОЛЕКУЛАМИ ПЕРОКСИДУ ВОДНЮ

Р е з ю м е

Променева терапія важкими іонами є одним з найбільш прогресивних методів лікування ракових захворювань. Результати моделювання процесу радіолізу води показали, що в середовищі живої клітини найбільший час життя мають молекули пероксиду водню (H_2O_2). Проте, на сьогоднішній день не встановлено, яку участь беруть молекули H_2O_2 у деактивації ракових клітин. Для того, щоб встановити роль молекул пероксиду водню в іонній терапії, в даній роботі досліджено конкурентну взаємодію молекул H_2O та H_2O_2 з парами нуклеїнових основ на різних стадіях процесу передачі генетичної інформації. Для розрахунків використано метод атом-атомних потенціальних функцій. Показано, що існують конфігурації пар $A \cdot T$ та $G \cdot C$, які стабілізовані молекулою H_2O_2 суттєво краще, ніж молекулою води. Утворення таких комплексів може зупинити процес розкриття пар основ макромолекули ДНК ферментом, і, відповідно, заблокувати процес передачі генетичної інформації в ракових клітинах під час іонної терапії. Запропоновано метод експериментального підтвердження взаємодії молекул пероксиду водню з нуклеїновими основами ДНК.