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On a possibility of the blocking of DNA specific recognition sites by hydrogen peroxide molecules during ion beam therapy

Presented by Academician of the NAS of Ukraine A.G. Zagorodny

Ion beam therapy is one of the most effective methods in treatment of cancer diseases. But up to nowadays, the mechanism of action of heavy ions on cancer cells has not been determined yet. Study of water fragmentation processes during ion beam therapy shows that, among different oxygen species, the significant amount of hydrogen peroxide molecules (H_2O_2) occurs in the cell medium. In the present work, the competitive interaction of H_2O_2 and H_2O molecules with specific DNA recognition sites is studied. Interaction energies of complexes consisting of nucleic bases (adenine, thymine, guanine, and cytosine) together with hydrogen peroxide and water molecules are calculated, using the method of atom-atom potential functions and density functional theory. The atomic groups of nucleic bases that are more energetically favorable to be bound by hydrogen peroxide rather than by water molecule are found. Formation of such complexes can block the process of DNA replication on different stages and can be one of the mechanisms of ion beam action on cancer cells.

Keywords: *DNA nucleic bases, hydrogen peroxide, cancer therapy.*

1. Introduction. One of the most important problems of humanity nowadays is the treatment of cancer diseases. Current statistics shows that, over recent decades, the number of new drugs to fight cancer has grown rapidly, while the mortality from oncological diseases is almost unchanged. That is why the different alternatives to pharmacological approaches in the cancer treatment are widely used. One of the most effective methods is radiation therapy. In this approach, the living tissue of the patient is exposed to a certain type of ionizing radiation (X-rays, gamma rays, photons), but the effectiveness of these approaches remains still insufficient. During the recent time, the more and more attention is paid to ion beam therapy. In contrast to other types of ionizing radiation, heavy ions almost do not interact with the molecules of the medium and transfer the most amount of their energy at the end of their track, where the tumor is localized. This effect has been known in nuclear physics for many years (Bragg's peak [1]), but began to be used in medicine only in the last decades. The main advantage of heavy-ions therapy over other types of radiation is the accurate and targeted tumor treatment without significant damage to the rest of the patient's body.

When ionizing radiation passes through the living tissue, different chemical reactions take place. As a result, a variety of species occurs in the water medium. Among them are free radicals, secondary electrons, ions, as well as molecular products (H_2 and H_2O_2). According to the multiscale approach of ion beam therapy [2], the main factor that deactivates cancer cells is the damages to the structure of their DNA called DNA strand breaks. However, due to the DNA reparation mechanisms, the living cell can effectively treat the lesions of its double helix. So, the question about the biological mechanism of deactivation of cancer cells in ion beam therapy still remains open [3].

Simulations of the water radiolysis process [4] shows that, on the scale of biological lifetimes (~1 μsec), the largest concentration among all the products is revealed by hydrogen peroxide molecules (H_2O_2), but their role in the ion therapy of cells remains unexplained yet. In our paper [5], it was proposed a hypothesis that hydrogen peroxide can create stable complexes with DNA active sites and block, in this way, the DNA replication processes. Under physiological conditions, these sites are surrounded by water molecules. But, due to an increase of the concentration of H_2O_2, these molecules should compete with water molecules for the binding with DNA sites. Therefore, it is important to understand whether hydrogen peroxide molecules can interact with active DNA recognition sites stronger than water molecules, thus blocking the processes of genetic information transfer.

In work [5], the interaction of hydrogen peroxide molecules with centers of non-specific protein-nucleic recognition, DNA phosphate groups (PO_4), was studied. It was shown that H_2O_2 molecule can form sufficiently stable complexes with DNA PO_4 groups and counterions, and block the protein-nucleic recognition process. In the present paper, we consider the interaction of H_2O_2 and H_2O molecules with specific DNA recognition sites — atomic groups of adenine, thymine, guanine, and cytosine (A, T, G, and C) nucleic bases — to determine if they can form stable complexes.

The next section will describe our calculation methods. In Sec. 3, a comparative analysis of the stability of the complexes consisting of H_2O_2 and H_2O molecules with nucleic base (adenine, thymine, guanine, or cytosine) will be performed. In Sec. 4, it will be discussed how our results can lead to the understanding of the mechanism of blocking of the genetic information transfer processes.

2. Materials and methods. For the analysis of the interaction energy and structure of the investigated molecular complexes, two computational approaches are used — the method of classical atom-atom potential functions (AAPF) and the method of quantum-chemical calculations based on density functional theory with B3LYP functional. In this section, we will briefly describe these two approaches.

2.1. Atom-atom potential function method. The atom-atom potential function method is described in details in work [6]. In addition, when considering the hydrogen bond interaction between atoms i and j situated on a distance r_{ij} between each other,

$$E_{HB}(r_{ij}) = [-\frac{A_{ij}^{(10)}}{r_{ij}^{10}} + \frac{B_{ij}^{(10)}}{r_{ij}^{12}}]\cos\varphi, \qquad (1)$$

we take angle φ into account — 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 covalent bond (O—H) and the

hydrogen bond (H . . . N). In (1), cosφ means that the more the hydrogen bond is bent, the less the interaction energy is.

The Coulomb interaction is described by the electrostatic potential:

$$E_{\text{Coul}}(r_{ij}) = \frac{1}{4\pi\varepsilon_0\varepsilon(r_{ij})}\frac{q_i q_j}{r_{ij}}, \tag{2}$$

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 [7, 8]. 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, and that of a hydrogen peroxide molecule $d_{H_2O_2}$ = 2.10 D [5]. 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 in work [9]. Since DNA in a living cell is situated in a 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 the Coulomb interaction can be achieved using the dependence of the dielectric permittivity upon the distance ($\varepsilon(r)$), developed by Hingerty et al. [10] in the explicit form:

$$\varepsilon(r) = 78 - 77(r_p)^2\frac{e^{r_p}}{(e^{r_p}-1)^2}, \tag{3}$$

where $r_p = r/2.5$. Below, AAPF with the use of expression (3) will be called AAPFh.

2.2. Quantum chemistry approach. In the quantum-chemical calculations, the B3LYP/6-311+G(d,p) method with a supermolecular approach is used. Calculations are made within the Gaussian software [11]. The interaction energy is considered as a difference between the energy of the molecular complex XY and the energies of its components X and Y:

$$\Delta E_{XY} = E_{XY}(XY) - E_X(X) - E_Y(Y). \tag{4}$$

The basis sets of the molecular complex XY (dimer-centered basis set) and of the isolated molecules X and Y (monomer-centered basis sets) are shown in parentheses. The counterpoise correction (CP) is made to avoid the basis set superposition error, as following:

$$\Delta E_{XY}^{CP} = E_{XY}(XY) - E_X(XY) - E_Y(XY). \tag{5}$$

In the framework of this approach, the deformation energies for hydrogen peroxide and water molecules are calculated. It is assumed that nucleic bases are the rigid structures. The deformation energy is calculated to involve the possible differences between the isolated states of the molecules and of those within complexes:

$$E_{\text{def}} = E_{\text{complex}} - E_{\text{isolated}} \tag{6}$$

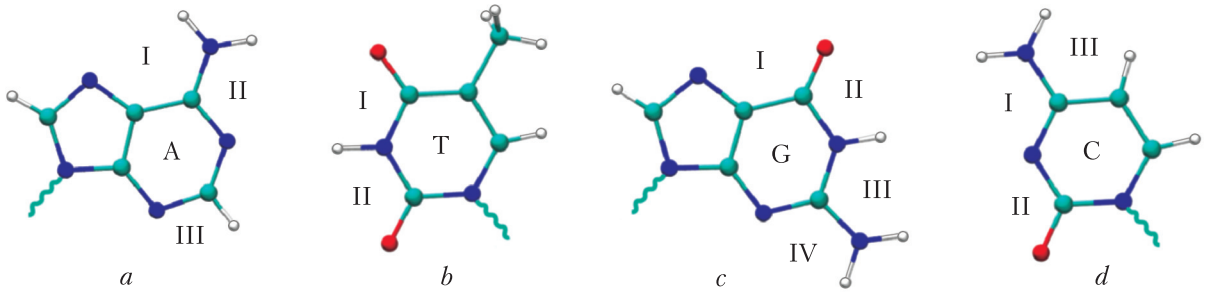

Fig. 1. The scheme of the sites of adenine (*a*), thymine (*b*), guanine (*c*) and cytosine (*d*), where the solvent molecule (H_2O or H_2O_2) can form a complex with a corresponding nucleic base with two hydrogen bonds. Roman numerals denote the number of the site

Thus, the complete interaction energy in a complex is presented by the formula

$$E_{\text{complete}} = \Delta E^{CP} + E_{\text{def}}. \qquad (7)$$

In addition, in the framework of the present method, to get an electrostatically neutral structure, the atoms C_1' that form glycosidic bonds of the nucleic base with the DNA backbone are changed to H atoms for adenine and thymine and to CH_3 group for guanine and cytosine.

3. Calculation results. The interaction of nucleic bases with water molecules has been considered in the set of works [12, 13], but the interaction with hydrogen peroxide molecules has not been studied sufficiently yet. Up to now, only the work [14] is known. In the present work, the stable complexes of hydrogen peroxide molecules with nucleic bases A, T, G, and C are found and compared to the same complexes with the water molecule.

It is clear that hydrogen peroxide, as well as water, can form hydrogen bonds with nucleic bases. As known [15], for the recognition of specific DNA sites by an enzyme, it is necessary to interact through at least two hydrogen bonds. Moreover, due to the structures of a hydrogen peroxide molecule and a nucleic base, it is much more favorable for peroxide to form two hydrogen bonds with base atomic groups, where two different oxygen atoms of the H_2O_2 molecule are involved in the formation of hydrogen bonds. Unlike a complex with one hydrogen bond, in a complex with two hydrogen bonds, the peroxide molecule should be more stable. It has no possibility to rotate around hydrogen bonds. Therefore, in accordance with all the mentioned facts, we consider only the complexes with two hydrogen bonds, not taking complexes with one hydrogen bond into account. It also should be mentioned that the tautomeric forms of nucleic bases have not been considered in the present work.

For each nucleic base, a few binding sites for the interaction with hydrogen peroxide exist. These binding sites are schematically shown in Fig. 1. For each site, the length of the hydrogen bond and the energy minima are calculated. Binding sites from the backbone side are not considered.

The results of our calculations are presented in Fig. 2 and Table. One can see that, for the adenine base at sites A-I and A-II, a hydrogen peroxide molecule interacts with this nucleic base stronger than water molecule (see Table). For sites A-I and A-II, interaction energies are close to the values obtained in work [14]. The AAPFh method shows that, at site A-III, there is a weak

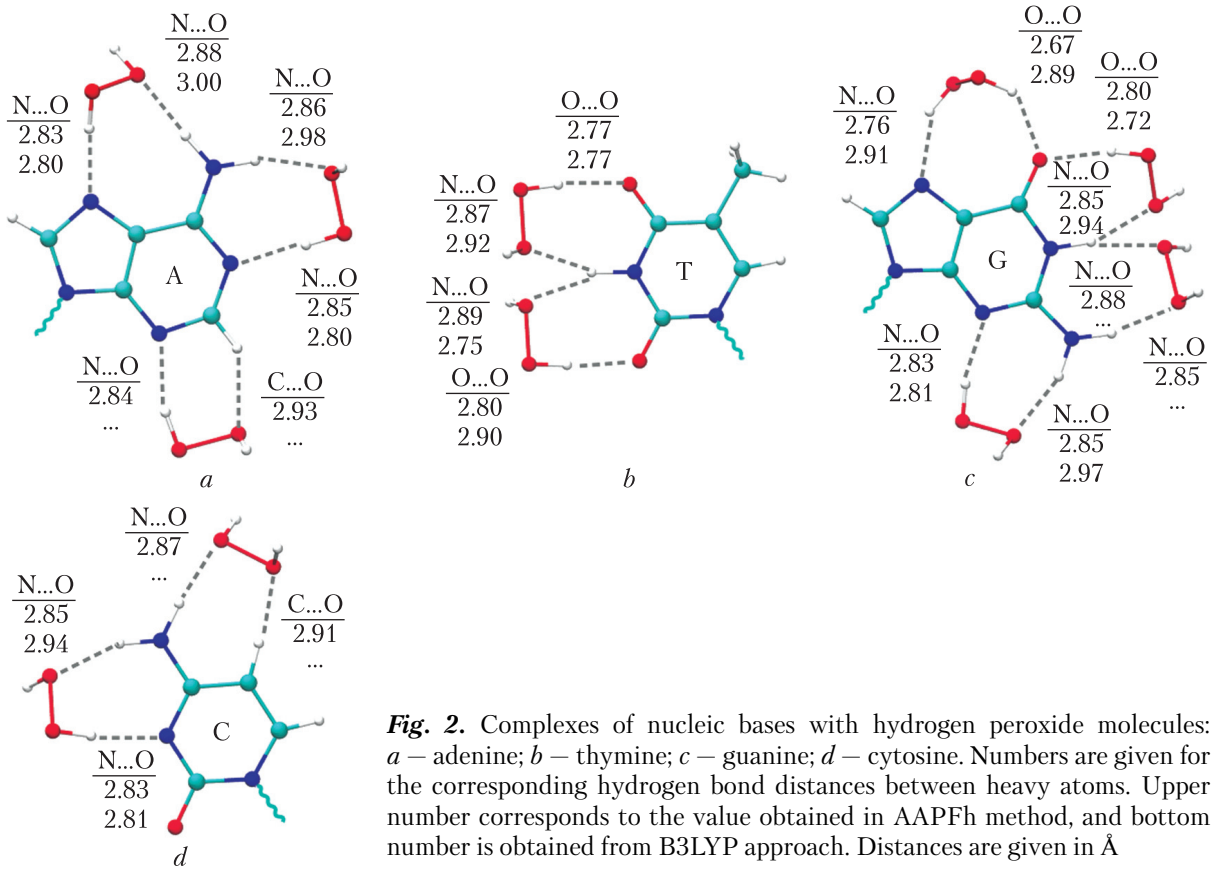

Fig. 2. Complexes of nucleic bases with hydrogen peroxide molecules: *a* — adenine; *b* — thymine; *c* — guanine; *d* — cytosine. Numbers are given for the corresponding hydrogen bond distances between heavy atoms. Upper number corresponds to the value obtained in AAPFh method, and bottom number is obtained from B3LYP approach. Distances are given in Å

Interaction energies of complexes of adenine, thymine, guanine, and cytosine with solvent molecules (H_2O or H_2O_2), as well as the differences between these energies ($\Delta E = |E_{H_2O_2}| - |E_{H_2O}|$) calculated by AAPFh and B3LYP methods. Energies are given in kcal/mol. "—" means that there is no minimum with two hydrogen bonds in this site

Nucleic bases		H_2O_2		H_2O		ΔE	
		AAPFh	(B3LYP)	AAPFh	(B3LYP)	AAPFh	(B3LYP)
Adenine	I	10.71	(−10.81)	−7.95	(−9.65)	2.76	(1.16)
	II	−9.22	(−11.19)	−5.65	(−9.00)	3.57	(2.19)
	III	−6.76	(—)	—	(—)	—	(—)
Thymine	I	−9.26	(−10.39)	−5.54	(−8.64)	3.72	(1.75)
	II	−8.63	(−11.17)	−5.26	(−9.29)	3.37	(1.88)
Guanine	I	−9.67	(−10.98)	−9.06	(−8.45)	0.61	(2.53)
	II	−9.56	(−13.43)	−5.99	(−11.62)	3.57	(1.81)
	III	−10.36	(—)	−6.35	(—)	4.01	(—)
	IV	−9.02	(−9.83)	—	(−7.83)	—	(2.00)
Cytosine	I	−11.22	(−12.92)	−6.82	(−11.11)	4.40	(1.81)
	II	—	(−10.39)	−7.40	(—)	—	(—)
	III	−7.62	(—)	—	(—)	—	(—)

binding of the H_2O_2 molecule with bent hydrogen bonds. At the same time, B3LYP method shows no binding at this site. It should also be mentioned that, in the case of B3LYP method, water and hydrogen peroxide molecules change their shape insignificantly — deformation energies do not exceed 0.5 kcal/mol.

Our calculations show that, in the case of thymine, there are two binding sites T-I and T-II (see Fig. 1, *b*). The corresponding complexes with a hydrogen peroxide molecule are shown in Fig. 2, *b*. For water molecules and hydrogen peroxide, the binding takes place at the same sites of thymine, but with a significant difference in the interaction energy (see Table). Both our approaches (AAPFh and B3LYP) give dominance in the interaction energy to a complex with peroxide as compared with the same complex with a water molecule. In the case of B3LYP method, the deformation energy of peroxide and water molecules plays an insignificant role (< 0.3 kcal/mol).

Complexes with the binding of hydrogen peroxide molecules to guanine (G-I, G-II, G-III, G-IV) are also shown in Fig. 1, *c*. Differences in the interaction energies are given in Table. Studying these complexes by B3LYP method shows that, in position I, a hydrogen peroxide molecule is significantly deformed (2.5 kcal/mol), what is the reason for the differences between hydrogen bond distances in AAPFh and B3LYP methods (see Fig. 2, *c*).

Cytosine has two binding sites (see Fig. 2, *d*). At site C-I, there is the binding of both of the water and hydrogen peroxide molecules. In addition, hydrogen peroxide is more energetically favorable to bind (see Table). At site C-III, there is the binding only of hydrogen peroxide. For site C-II, there is no binding of hydrogen peroxide in the framework of AAPFh method due to the geometric features of an H_2O_2 molecule, which is rigid. As it can be seen from the structure of the complex, for B3LYP method in position II, hydrogen peroxide dramatically changes its dihedral angle (deformation energy is 4.2 kcal/mol) to form two hydrogen bonds with cytosine. This allows an H_2O_2 molecule to make a stable complex with cytosine at this cite.

Summarizing the results of our calculations by both methods used in the present work, it can be seen that, for adenine, thymine, guanine, and cytosine nucleic bases, there are places which are more favorable for the binding by a hydrogen peroxide molecule rather than by a water molecule.

4. Conclusions. In the present work, we have obtained the stable configurations of hydrogen peroxide with DNA specific recognition sites by two methods: the method of atom-atom potential functions and density functional theory. Both methods show similar results. It can be seen (see Fig. 2) that it is most probable for hydrogen peroxide to bind to thymine from the side of atomic groups responsible for the formation of complementary hydrogen bonds. To adenine and guanine — from the side of major and minor grooves, as well as complementary hydrogen bonds. To cytosine — from the side of the major groove and the complementary hydrogen bonds.

It should be noted that the protein recognition of a DNA macromolecule can take place as from the major and minor grooves, depending on the type of an enzyme and on the form of a double helix. Therefore, the formation of a complex of a nucleic acid with a hydrogen peroxide molecule, which binds to the bases from the major (see Fig. 1, A-I, C-III, G-I) or minor groove (see Fig. 1, A-III, G-IV), can prevent the recognition of this base by the enzyme and to block the DNA replication. On the final stage of the DNA replication, when the double-stranded DNA is already unzipped up to two single strands, the formation of the complexes of H_2O_2 molecules with nucleic bases from the side of complementary hydrogen bonds (TI, T-II, A-II, CI, C-II, G-II,

G-III) can take place. It should lead to the mistakes in the copying of the genetic information during the synthesis of complementary strands.

To sum up, there are definite sites of nucleic bases, where the binding by hydrogen peroxide is much more advantageous than that by a water molecule. As can be seen from our calculations (see Table), the energy of the blocking of nucleic bases by a hydrogen peroxide molecule at these sites is comparable to the energy of the formation of complementary pairs [6]. Consequently, the formation of such complexes is sufficiently probable in cells during the ion beam treatment. In this way, the processes of genetic information transfer should be blocked in cancer cells.

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ПРО МОЖЛИВІСТЬ БЛОКУВАННЯ ЦЕНТРІВ СПЕЦИФІЧНОГО ВПІЗНАВАННЯ ДНК МОЛЕКУЛАМИ ПЕРОКСИДУ ВОДНЮ ПІД ЧАС ІОННОЇ ТЕРАПІЇ

Іонна терапія є одним з найефективніших методів лікування ракових захворювань. Але до цього часу механізм дії важких іонів на ракові клітини не визначений. Вивчення процесів фрагментації води під час іонної терапії показує, що серед великої кількості різних фрагментів у середовищі клітини утворюється значна концентрація молекул пероксиду водню (H_2O_2). У роботі наведено результати дослідження конкурентної взаємодії молекул H_2O_2 та H_2O із центрами специфічного розпізнавання ДНК. Енергії взаємодії комплексів, що складаються з нуклеїнових основ (аденін, тимін, гуанін і цитозин) разом з молекулами пероксиду водню і води, обчислені із застосуванням методу атом-атомних потенціальних функцій і теорії функціонала густини. Знайдено атомні групи нуклеїнових основ, які є більш енергетично вигідними для зв'язування з молекулами пероксиду водню, ніж з молекулами води. Утворення таких комплексів може блокувати процес реплікації ДНК на різних етапах і може бути одним з механізмів дії високоенергетичних іонів на ракові клітини.

***Ключові слова**: нуклеїнові основи ДНК, пероксид водню, ракова терапія.*

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О ВОЗМОЖНОСТИ БЛОКИРОВАНИЯ ЦЕНТРОВ СПЕЦИФИЧЕСКОГО УЗНАВАНИЯ ДНК МОЛЕКУЛАМИ ПЕРОКСИДА ВОДОРОДА В ХОДЕ ИОННОЙ ТЕРАПИИ

Ионная терапия является одним из наиболее эффективных методов лечения раковых заболеваний. Но до настоящего времени механизм действия тяжелых ионов на раковые клетки не установлен. Изучение процессов фрагментации воды при ионной терапии показывает, что среди большого количества различных фрагментов в клеточной среде образуется значительная концентрация молекул пероксида водорода (H_2O_2). В работе приведены результаты изучения конкурентного взаимодействия молекул H_2O_2 и H_2O с центрами специфического узнавания ДНК. Энергии взаимодействия комплексов, состоящих из нуклеиновых оснований (аденин, тимин, гуанин и цитозин) вместе с молекулами пероксида водорода и воды, рассчитаны с использованием метода атом-атомных потенциальных функций и теории функционала плотности. Найдены атомные группы нуклеиновых оснований, с которыми молекула пероксида водорода связывается значительно энергетически выгоднее, чем молекула воды. Образование таких комплексов может блокировать процесс репликации ДНК на разных стадиях и может быть одним из механизмов воздействия высокоэнергетических ионов на раковые клетки.

***Ключевые слова**: нуклеиновые основания ДНК, пероксид водорода, терапия рака.*