Interaction of hydrogen peroxide molecules with non-specific DNA recognition sites

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Abstract

Ion beam therapy is one of the most progressive methods in cancer treatment. Studies of water radiolysis process show that under the action of ionizing irradiation in the medium of biological cell different atomic and molecular species occur. The most long-living among them are hydrogen peroxide (H₂O₂) molecules. But the role of hydrogen peroxide molecules in the DNA deactivation of cancer cells in ion beam therapy has not been determined yet. In the present paper competitive interaction of hydrogen peroxide and water molecules with atomic groups of non-specific DNA recognition sites (phosphate groups PO₄) is investigated. Interaction energies and optimized spatial configurations of the considered molecular complexes are calculated with the help of atom-atom potential function method and quantum chemistry approach. It is shown that hydrogen peroxide molecule can form a complex with PO₄ group (with and without sodium counterion) that is more energetically stable than the same complex with water molecule. Formation of such complexes can block genetic information transfer processes in cancer cells and can be a key factor during ion beam therapy treatment.

1 Introduction

Ion beam therapy is one of the most perspective methods of cancer treatment. It uses heavy ion beams produced on special accelerators to treat patients. In the basics of ion beam therapy lies the so-called Bragg’s effect [1], when almost all the energy of the beam is transferred to the medium on some distance from the surface. Due to this effect cancer tumor can be destroyed without any significant damage of healthy tissues.

It is supposed in radiobiology that to destroy cancer cell its DNA must be deactivated. But the certain mechanism of this deactivation has not been determined yet [2]. Some mechanisms of DNA damage during irradiation are already proposed in the literature [3]. Among them are DNA strand breaks caused by secondary electrons and free radicals, heating of the intracellular medium and the shockwave processes [4]. However, in living cell the powerful DNA reparation mechanisms are present that can eliminate single-strand breaks [5]. From the other side, the
probability of the double-strand breaks is relatively low. Consequently, the implementation of this effect as the main mechanism of ion beam therapy remains debatable.

During ion beam therapy the water radiolysis process takes place when different chemical reactions take place due to the energy action from the ion beam. As a result, in the Bragg peak area different species occur, such as secondary electrons, free radicals, ions as well as molecular products ($\text{H}_2\text{O}_2$ and $\text{H}_2\text{O}$ molecules). Monte Carlo simulations $[6–8]$ revealed that on biological time scales ($\sim 1 \mu$s) the highest concentration have hydrogen peroxide ($\text{H}_2\text{O}_2$) molecules. This takes place because free radicals recombine during physico-chemical stage of radiolysis ($10^{-15}$-$10^{-12}$ sec) $[6–8]$ and thus can interact with DNA molecule only in the close proximity. At the same time, as $\text{H}_2\text{O}_2$ molecules are not so chemically active as free radicals, they can live in water medium for longer times and can diffuse on significant distances from the track of incident particle. Therefore, hydrogen peroxide molecules have the higher probability to ‘find’ the DNA molecule in the intracellular water medium.

Up to nowadays, essential attention to the role of hydrogen peroxide in the context of ion beam therapy paid enough. But its participation in other methods of cancer treatment has been already discussed in the literature. In this way, the work $[9]$ emphasized the significant role of hydrogen peroxide in the cancer treatment by ascorbic acid. The paper $[10]$ showed that hydrogen peroxide causes more damage to cancer cells whereas healthy cells are less vulnerable to its action. Due to these facts, it is necessary to study molecular mechanisms of the action of hydrogen peroxide molecules on DNA of cancer cells.

In our work $[11]$ a mechanism of DNA deactivation by hydrogen peroxide was proposed. According to our hypothesis, $\text{H}_2\text{O}_2$ molecule can make some stable complexes with DNA atomic groups and in such way block the processes of DNA recognition by enzyme. As hydrogen peroxide and water molecules have similar structure, they can compete for binding with DNA active sites. Note that the $\text{H}_2\text{O}_2$ molecule has twice as big mass as water molecule, so it can remain in the vicinity to DNA for longer time. DNA sites which are the most probable to interact with solvent molecules are the phosphate groups ($\text{PO}_4^-$) of the DNA backbone. This is due to the geometry of the $\text{PO}_4^-$ group which has two charged oxygen atoms directed to the solvent.

To understand complicated molecular mechanisms that take place in living cells, they must be firstly analyzed on a basic elementary level. And then gradually generalize these results and study more complex systems. In our work $[11]$ interactions of hydrogen peroxide molecule with DNA phosphate group was studied. Using atom-atom potential functions method the interaction energy in the considered complexes was calculated. It was shown that hydrogen peroxide can make a complex with $\text{PO}_4^-$ group which is no less stable but more long-living than the same complex with water molecule. Calculations performed in the mentioned works are made in vacuum that leaded to anomalously large interaction energies in atom-atom potential functions method $[11]$. However, it is known that in the cell medium all the molecular structures are screened by water molecules. This results in the weakening of the long-range Coulomb interactions. Therefore, in the present work interaction of $\text{H}_2\text{O}_2$ molecules with DNA $\text{PO}_4^-$ groups will be considered taking into account implicit solvent which simulates interaction with the water medium in living cell.

The goal of the present work is to determine the stable complexes which consist of hydrogen peroxide, water molecules, phosphate group and sodium counterion and analyse the possibility of the blocking the non-specific DNA recognition sites by hydrogen peroxide. In Sec. 2 our calculation methods are described. In Sec. 3 different complexes consisting of $\text{PO}_4^-$ group, sodium counterion, hydrogen peroxide and water molecules are considered. Using atom-atom
potential function method and quantum chemistry approach, interaction energies of the considered complexes are calculated. Additionally, the possibility of blocking of the DNA genetical activity by hydrogen peroxide molecules is discussed.

2 Calculation methods

For the analysis of interaction energy and structure of the investigated molecular complexes two computational approaches are used - the method of classical atom-atomic potential functions (AAPF) and the method of quantum-chemical calculations on different levels of theory.

2.1 Atom-atom potential functions method

The atom-atom potential function method is now widely used in the molecular dynamics in such force fields as CHARMM and AMBER [12–14] for studying the structure of molecular complexes. In the framework of this method, the energy of intermolecular interaction consists of van der Waals interactions, hydrogen bonds and and Coulomb interactions:

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

Van der Waals’s interaction is described by Lennard-Jones’s ‘6-12’ potential:

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

where the parameters \( A_{ij} \) and \( B_{ij} \) are taken from the works [15,16].

The energy of the hydrogen bond between atoms \( i \) and \( j \) is modeled by the modified Lenard-Jones potential ‘10-12’:

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

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

Coulomb interaction is described by the electrostatic potential:

\[ E_{Coul}(r_{ij}) = \frac{1}{4\pi\varepsilon_0\varepsilon(r_{ij})} \frac{q_i q_j}{r_{ij}}, \] (4)

where \( q_i \) and \( q_j \) are the charges of the atoms \( i \) and \( j \) located at a distance \( r_{ij} \), \( \varepsilon_0 \) 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 the works [15,16]. Charges of \( H_2O \) and \( H_2O_2 \) molecules were calculated from the condition that the dipole moment of water molecule should be equal to \( d_{H_2O} = 1.86 \, D \), and of hydrogen peroxide molecule \( d_{H_2O_2} = 2.10 \, D \) [11]. Hence, for the \( H_2O \) 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 \( H_2O_2 \) molecule are in good agreement with charges obtained in the work [17].
The interaction with sodium counterion is modeled by the Born-Mayer potential \[18\] that takes into account the repulsion of atoms on the short distances:

\[ E_{bm}(r_{ij}) = E_{Coul}(r_{ij})[1 - \frac{br_{ij}}{r_0^2} exp(-\frac{r_{ij} - r_0}{b})], \]  

where \( b = 0.3\text{Å} \) is the repulsion constant and \( r_0 = 2.35\text{Å} \) is the equilibrium length. These parameters were taken from works \[19,20\].

More effective accounting of Coulomb interactions can be achieved using the dependence of the dielectric permittivity upon distance \((\varepsilon(r))\), developed by Hingerty \textit{et al.} \[21\] in the form:

\[ \varepsilon(r) = 78 - 77 (r_p)^2 \left( \frac{e^{r_p}}{e^{r_p} - 1} \right)^2, \]  

where \( r_p = r/2.5 \). Further atom-atom potential functions method (AAPF) with the use of expression (6) will be called here as AAPFh.

In the framework of the present method we consider all the covalent bonds and angles as rigid. Particularly, the change of dihedral angle is not considered in the present method because the deformation energy cannot be calculated due to the absence of parameters for atoms of \( \text{H}_2\text{O}_2 \) molecule in modern force fields \[12,13\]. All the geometries of the individual molecules that are considered for calculations in AAPF(AAPFh) method are presented in \[11\].

\subsection*{2.2 Quantum-chemical approach}

In the framework of quantum-chemical approach, the Hartree-Fock method (basis set HF/6-311+G(d,p)), density functional theory (B3LYP/6-311+G(d,p)) and Moller-Plesset perturbation theory (MP2/6-311+G(d,p)) within the Gaussian 03 \[22\] program are used. Calculations are performed for complexes in gas phase and in water solution. To take into account implicit solvent, polarizable continuum model (PCM) of water solution is used. Geometries of \( \text{H}_2\text{O}_2 \) and \( \text{H}_2\text{O} \) molecules as well as of the phosphate group \( \text{PO}_4^- \) are optimized within each of the methods. Interaction energies in the considered molecular complexes are calculated using supermolecular approach. Within this approach, the interaction energy \((\Delta E)\) is defined as the difference between the total energy \((E)\) of the complex and the energies of its constituents \((E_i)\):

\[ \Delta E = E - \sum_i E_i, \]  

(7)

The basis set superposition error (BSSE) is corrected using the counterpoise procedure \[23\]. In the case of the optimized complexes within PCM, the value of counterpoise correction from the same complexes without water solvent is used. Deformation energy defines the change in geometry between the isolated molecule \((E_{i\text{isolated}})\) and molecule within the complex \((E_{i\text{complex}})\):

\[ E_{def} = E_{i\text{complex}} - E_{i\text{isolated}}. \]  

(8)

Consequently, the total interaction energy in the molecular complex can be calculated as

\[ E_{tot} = \Delta E + E_{def}. \]  

(9)
Table 1: Geometries of H$_2$O$_2$ and H$_2$O molecules that are used for the calculations in the framework of AAPF method and that are optimized using the corresponding methods of quantum-chemical approach. Distances are given in Å, angles in degrees.

| Solvent     | Method | O-O | H-O | H$_2$O$_2$ | H$_2$O | H-O | H$_2$O |
|-------------|--------|-----|-----|------------|--------|-----|--------|
| Gas phase   | HF     | 1.39| 0.94| 102.9      | 117.1  | 0.94| 106.2  |
|             | B3LYP  | 1.45| 0.97| 100.5      | 121.1  | 0.96| 105.0  |
|             | MP2    | 1.45| 0.96| 99.6       | 121.0  | 0.96| 103.5  |
| PCM         | HF     | 1.38| 0.95| 103.9      | 101.6  | 0.94| 105.6  |
|             | B3LYP  | 1.45| 0.97| 101.6      | 105.7  | 0.96| 104.5  |
|             | MP2    | 1.44| 0.97| 100.8      | 107.1  | 0.96| 103.1  |
| AAPF(AAPFh) |        | 1.47| 0.96| 94.78      | 111.6  | 0.96| 106.0  |

3 Results and discussion

Let us start with the structural parameters of the individual molecules considered in the present work. These parameters were taken from [24] for AAPF method and were obtained by geometry optimization in the framework of the quantum-chemistry approach. H$_2$O$_2$ molecule is symmetric and can be characterized by the distances between two oxygen atoms, between oxygen and hydrogen atoms, by the angle O-O-H and the dihedral angle H-O-O-H. Tabl. 1 shows that the geometrical parameters which were chosen for the calculations in AAPF(AAPFh) method, as well the values obtained by different methods of quantum-chemical approach, are very similar. Also they are comparable with the values obtained in the work [25]. Note that the dihedral angle H-O-O-H can be very sensitive to the environment. Thus, this value can be considerably different for the isolated molecule and the molecule within a complex. The geometry of H$_2$O$_2$ molecule in the water solution (PCM model) is very similar to its geometry in the gas phase, but with significant differences in their dihedral angles (Tabl. 1). It also should be mentioned that as water molecule has no dihedral angle, its structure is not such sensitive to the environment as the structure of H$_2$O$_2$ molecule.

The optimized structure of phosphate group obtained in the quantum-chemical approach is more complicated. In this regard, we present only the distance between the two oxygen atoms, which contain the negative charge (Fig. 1). The total charge on phosphate group is $-e$ (e - elementary electronic charge). In the framework of the quantum-chemical approach, the phosphate group PO$_4^-$ is considered as a part of DNA backbone with two hydrogen atoms placed instead of the backbone atoms (C$'$$_3$ and C$'$$_5$). Firstly the geometry optimization of the PO$_4^-$ group was made, and then this geometry was fixed. In the calculations of molecular complexes PO$_4^-$ group is considered as the rigid structure. In the framework of AAPF(AAPFh) method the interaction of H$_2$O$_2$ and H$_2$O molecules only with the two oxygen atoms that are open to the solvent is considered, not taking into account other atoms of PO$_4^-$ group. The charge on each of these oxygen atoms is considered to be equal to $-0.5e$. 
3.1 Complexes consisting of H$_2$O$_2$ and H$_2$O molecules with phosphate group

Firstly, let us calculate the complexes of hydrogen peroxide and water molecules with the phosphate group. Their optimized geometries are shown in Fig. 2. It should be mentioned that, as PO$_4^-$ group is considered as a part of DNA backbone, we take into account only those complexes, where H$_2$O$_2$ and H$_2$O molecules are situated near two oxygen atoms which are open into solution (on the right side of PO$_4^-$ on Fig. 2).

Fig. 2 shows that hydrogen peroxide and water molecules are situated almost symmetrically near oxygen atoms of PO$_4^-$. In the case of hydrogen peroxide there are two hydrogen bonds. In the framework of quantum-chemistry approach, in all the used methods hydrogen peroxide molecule is compressed - its dihedral angle is close to 55° which is lower than the corresponding value in the isolated molecule (Tabl. 1). Such a change in the dihedral angle makes a contribution into the deformation energy (about 3-4 kcal/mol for different methods). At the same time, in the complex with water molecule, due to its smaller size (absence of O-O bond) the corresponding hydrogen bonds are significantly bent (angles O-H-O are near 145°), that results in the weakening of the interaction energy (Fig. 2). Moreover, the energy difference be-
Table 2: Interaction energies of complexes of H₂O₂ and H₂O molecules with PO₄⁻ group. Energy values are given in kcal/mol.

| Solvent   | Method | H₂O₂-PO₄⁻ | H₂O-PO₄⁻ |
|-----------|--------|------------|----------|
| HF        | -20.1  | -14.2      |          |
| Gas phase | B3LYP  | -21.4      | -14.8    |
|           | MP2    | -19.9      | -14.3    |
| HF        | -7.0   | -3.3       |          |
| PCM       | B3LYP  | -9.8       | -4.8     |
|           | MP2    | -8.1       | -4.0     |
| AAPF      | -11.0  | -12.0      |          |
| AAPFh     | -5.6   | -4.9       |          |

¹ calculated in [11]
² AAPF method with the use of expression [6]

between the complexes with H₂O₂ and H₂O molecules is large enough (≈6 kcal/mol in gas phase and ≈4-5 kcal/mol within PCM). In AAPF(AAPFh) method the energy difference between the corresponding complexes is much lower because the dihedral angle of H₂O₂ molecule in the framework of these method is rigid. Note, that in our previous work [11] such significant energy difference was not obtained due to the rigidity of the dihedral angle of H₂O₂ molecule.

3.2 Complexes consisting of H₂O₂ and H₂O molecules with phosphate group in the presence of sodium counterion

It is well known that the DNA macromolecule in the cell nucleus is situated in water-ionic solution [24]. This means that the DNA phosphate groups are neutralized by alkali metal ions (Na⁺, K⁺, Li⁺). Consequently, the interaction of the solvent molecules with DNA atomic groups can take place in the presence of counterions. Since sodium ion is one of the most spread one in a living cell, in the present work the interaction only with the sodium (Na⁺) counterion is taken into account. Firstly we will consider the complex of Na⁺ with PO₄⁻ group and then determine how the presence of the counterion can influence the interaction of water and hydrogen peroxide molecules with the phosphate group.

The optimized geometries of complexes Na⁺-PO₄⁻ are shown in Fig. 3. Geometry (a) can be obtained by both methods (AAPF(AAPFh) and quantum chemistry) as in gas phase as well as in water solution, and geometry (b) is only given by the quantum-chemistry approach within the PCM model. Fig. 3 shows the distances between Na⁺ counterion and oxygen atoms of the phosphate group. Due to the certain values of the parameters for the Born-Mayer potential [5], these distances are quite different for AAPF(AAPFh) and for the quantum chemistry approach. Interaction energies of Na⁺-PO₄⁻ complex presented in Tabl. 3 show that taking into account implicit solvent reduces the interaction energies by ~5 times within AAPFh and by ~20 times within PCM.

Let us consider molecular complexes consisting of three components Na⁺-H₂O₂-PO₄⁻ and Na⁺-H₂O-PO₄⁻. Figs. [4] and [5] show that AAPF(AAPFh) method and quantum-chemistry approach give different spatial structures. The optimized geometry where H₂O₂ or H₂O molecule is situated symmetrically to two oxygen atoms of PO₄⁻ group with Na⁺ counterion between
Figure 3: Interaction complexes consisting of PO$_4^-$ group with sodium (Na$^+$) counterion. Distances are obtained from the different calculation methods in the following order (from top to bottom): AAPF, HF, B3LYP, MP2. Values taking into account implicit solvent (AAPFh and PCM model for the corresponding methods) are shown in parenthesis. Distance values are given in Å.

Figure 4: Spatial structures of complexes consisting of hydrogen peroxide (a) and water molecules (b) with PO$_4^-$ group in the presence of sodium (Na$^+$) counterion obtained by AAPF method. Distances are given in Å. Values taking into account implicit solvent (AAPFh) are shown in parenthesis.

Quantum chemistry approach gives an optimized structure where sodium counterion and hydrogen peroxide or water molecule are each situated near different oxygen atoms of PO$_4^-$ that are open into solution (Fig. 5a,c). In other words, addition of sodium counterion into two-molecule complexes H$_2$O$_2$-PO$_4^-$ and H$_2$O-PO$_4^-$ leads to the displacement of peroxide or water molecule with comparison to the complexes without counterion (Fig. 2 a,b). These structures are almost similar for the calculations in gas phase and in water solution (PCM model). In both cases H$_2$O$_2$ or H$_2$O molecule forms one hydrogen bond with phosphate group. Additionaly, PCM model gives a structure of the complex with hydrogen peroxide where the O-O distance from H$_2$O$_2$ molecule is situated almost parallel to the O-P-O plane of the phosphate group (Fig. 5 b). As can be seen from the Tabl. 4 this structure is $\approx$1 kcal/mol more stable than those shown in Fig. 5a.
Table 3: Interaction energies of complexes of sodium counterion (Na\(^+\)) with PO\(_4^−\) group. Energy values are given in kcal/mol.

| Solvent Method       | Energy Values (kcal/mol) |
|----------------------|--------------------------|
| Gas phase (Fig. 3a)  |                          |
| HF                   | -127.5                   |
| B3LYP                | -127.4                   |
| MP2                  | -124.2                   |
| PCM (Fig. 3a)        |                          |
| HF                   | -5.5                     |
| B3LYP                | -5.7                     |
| MP2                  | -4.2                     |
| PCM (Fig. 3b)        |                          |
| HF                   | -7.8                     |
| B3LYP                | -7.6                     |
| MP2                  | -5.9                     |
| AAPF\(^1\)           | -122.0                   |
| AAPFh\(^2\)          | -21.8                    |

\(^1\) calculated in [11]
\(^2\) AAPF method with the use of expression [6]

Figure 5: Spatial structures of complexes consisting of hydrogen peroxide (a,b) and water (c) molecules with PO\(_4^−\) group in the presence of sodium (Na\(^+\)) counterion obtained by quantum-chemical approach. Distances (in Å) obtained from the different levels of theory are listed in the following order (from top to bottom): HF, B3LYP, MP2. Values taking into account implicit solvent (PCM) are shown in parenthesis.
All the interaction energies for the considered complexes are presented in Tabl. 4. Taking PCM model into account significantly lowers interaction energy but complex with H$_2$O$_2$ remains to be more energetically favorable than the same complex with water molecule. It also should be noted, that complexes presented on Fig. 5 c are more probable to be found in crystal structures experimentally [26].

To sum up this part of our study, the addition of sodium counterion to the complexes H$_2$O$_2$-PO$_4^-$ and H$_2$O-PO$_4^-$ significantly influences the interaction of hydrogen peroxide and water molecules with phosphate group. Herewith, the interaction energy in gas phase increases up to ~100 kcal/mol that is very close to the energy of the covalent bond formation. Taking implicit solvent into account makes the obtained values more realistic and comparable with the energy barriers of the intramolecular interactions that take place in living cell [27].

Table 4: Interaction energies of complexes of H$_2$O$_2$ and H$_2$O molecules with PO$_4^-$ group in the presence of Na$^+$ ion. Energy values are given in kcal/mol.

| Solvent      | Method | Na-H$_2$O$_2$-PO$_4^-$ | Na-H$_2$O-PO$_4^-$ |
|--------------|--------|------------------------|-------------------|
| Gas phase    | HF     | -148.8                 | -148.2            |
| (Fig. 5 a,c) | B3LYP  | -150.4                 | -149.3            |
|              | MP2    | -145.1                 | -144.1            |
| PCM (Fig. 5 a,c) | HF | -13.4                 | -13.2             |
|              | B3LYP  | -15.0                  | -14.9             |
|              | MP2    | -11.8 (-18.6)$^1$     | -11.7             |
| PCM (Fig. 5 b) | HF | -14.5                 | —                 |
|              | B3LYP  | -16.4                  | —                 |
|              | MP2    | -13.2                  | —                 |
| AAPF$^1$     | -130.3 | -129.2                |
| AAPFh$^2$    | -27.4  | -26.5                 |

$^1$ calculated in [11]
$^2$ AAPF method with the use of expression [6]

Calculations performed by AAPFh method as well as by quantum chemistry approach reveal that hydrogen peroxide molecule can form a complex with PO$_4^-$ group that has approximately the same interaction energy as the same complex with water molecule. These results are in accordance with our previous calculations performed by AAPF method in vacuum [11]. In that paper we also showed that, as H$_2$O$_2$ molecule has approximately twice larger mass than H$_2$O molecule, hydrogen peroxide can stay near the phosphate group. This means that hydrogen peroxide can accumulate near the DNA macromolecule in solution and influence its activity. Consequently, such processes as blocking of DNA specific recognition sites [28] and blocking of DNA base pair opening [29] are much more probable to take place in living cell.

4 Conclusions

In the present work complexes consisting of hydrogen peroxide or water molecule, phosphate group and sodium counterion are considered. Interaction energies of the considered complexes are calculated using atom-atom potential functions method and quantum-chemistry approach. Calculations are performed in gas phase as well as taking into account implicit solvent. Both
methods show that hydrogen peroxide molecule can form a stable complex with phosphate group which is more energetically favorable than the water molecule (Fig. 2). This energetical advantage takes place due to the flexibility of the dihedral angle of hydrogen peroxide molecule. Addition of the sodium counterion to these complexes makes these interactions much more stable. Moreover, complex with H$_2$O$_2$ molecule will be more long-living than the same complex with H$_2$O molecule. As hydrogen peroxide molecules occur in high concentrations in the vicinity of Bragg peak under ionizing irradiation, the formation of such complexes can block the genetical activity of DNA macromolecule of cancer cells and can be a key factor during ion beam therapy treatment.

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