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THE STUDY OF ANTI-RADICAL ACTIVITY OF ENDOOXIDANT WHEN INTERACTING WITH FREE RADICALS

To decrease the negative effect of free oxygen radicals on a living organism practical medicine widely uses endogenous oxidants since they take part in the system of human organism protection from the aggressive action of free radicals, for example [1-2]. The lack of systematic investigations, especially at the molecular level, of antiradical activity of various antioxidants under their interaction with free radicals in biological systems not only determines availability of contradictory estimates in interpretation of the results of experimental regularities [3-5] but also creates difficulties in development of general ideas concerning the mechanisms of interaction of antioxidants with free radicals and purposeful approach to the control of these processes which are applied to medical practice [6, 7]. The above said actualizes studying the antiradical activity of various antioxidants.

Interaction of antioxidants with free radicals is determined by the influence of the great number of various interrelated kinetic processes which stabilization is rather problematic even in the experiment conditions. Thus, it seem urgent to study efficiency of the influence of endogenous antioxidants by simulating the mechanism of their interaction with free radicals by the methods of quantum chemistry in combination with experimental ones, in particular, with electrochemical method that allows not only obtaining the substantiation of the positive effect of using the antioxidants but also establishing potential significance of these substances as medical remedies.

The work objective was investigation of antiradical properties of endogenous antioxidant glutathione ($C_{10}H_{17}N_3O_6S$) by simulation of the mechanism of its interaction with free radicals (hydroxyl radical (•OH) and superoxide-anion-radical ($•OO^-$).

Materials and methods

Human organism contains a nonenzymatic antioxidant system of cells protection from the influence of free radicals. The compounds with various properties appear as the system components. One of such compounds is glutathione (GSH) [8] synthesized in each organism cell, but antiradical mechanism of its interaction with active oxygen forms at the microscopic level is not completely understood, except for certain results of macroscopic medical [9] and electrochemical [10] investigations which are unfortunately of phenomenological character and do not give a purposeful approach to such processes control.

One of the key active forms of oxygen is $\bullet OO^-$, which is formed when adding one electron to oxygen molecule in the basic state and can be a source of •OH formation in human organism; it may be the strongest oxidizer among free oxygen radicals [11], thus •OH and $\bullet OO^-$ can exist simultaneously and be used for studying their interaction with glutathione for simulation of its antioxidant activity. The above said has determined the choice of investigation objects.

Theoretical study of the mechanism of GSH interaction with $\bullet OO^-$ and •OH is performed with the help of the program module GAMESS (version of March 27, 2007) and program module Firefly 8 by the most modern unempirical quantum chemical method in the basis 6-31G** [12].

Results and Discussion

When GSH molecules interact with one $\bullet OO^-$ at the point of global minimum of full interaction energy there occurs redistribution of the charge of 702e with $\bullet OO^-$ to glutathione molecule through the atom of hydrogen H(23), indicating a possibility of efficient interaction of $\bullet OO^-$ with GSH, with probable formation of stable complexes (Fig. 1). Under analogous interaction with one •OH, on the contrary, there occurs an increase of electron density on oxygen atom of hydroxyl radical by 0.208e, as a result the bond length S(22) - H(23) increases in glutathione molecule from 0.132 to 0.317 nm that points to the possibility of this atom breaking off GSH molecule and its further attachment to •OH with formation of water molecule (Fig. 2).

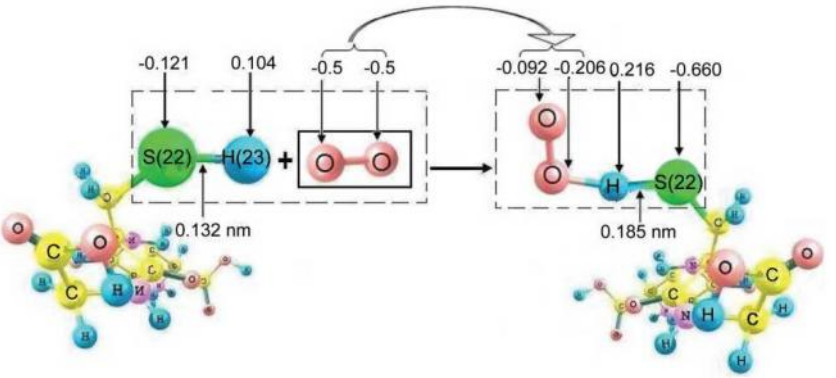

Fig. 1. Scheme of interaction of GSH molecule with $\bullet OO^-$ (arrows point to charges on atoms according to Lyovdin)

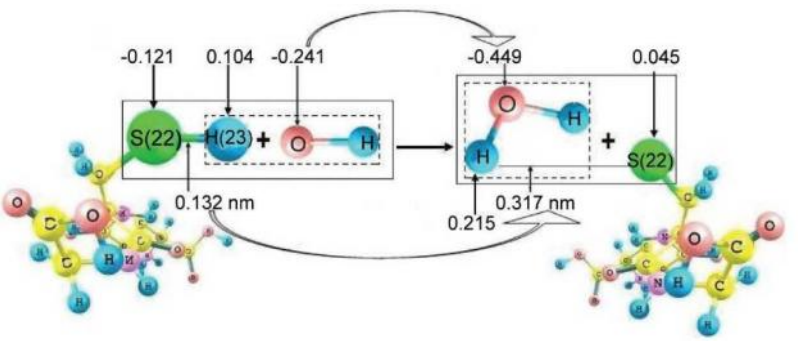

Fig. 2. Scheme of interaction of GSH molecule with •OH (arrows point to charges on atoms according to Lyovdin)

Thus, the interaction of a molecule of studied antioxidant with free oxygen radicals initiates redistribution of electron density in the glutathione molecule in different directions (Fig. 3) [13].

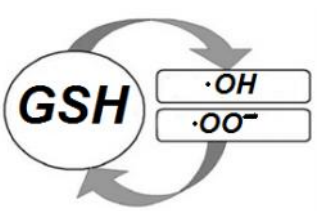

Fig. 3. Scheme of redistribution of electron density of GSH molecule as a result of interaction with radicals

To bring the results of quantum-chemical modeling closer to real conditions of interaction of the antioxidant molecule with •OH and $\bullet OO^-$ in human organism the authors performed simulation of water medium influence on the mechanism of GSH molecule interaction with free oxygen radicals in terms of Firefly 8 program. An analysis of results obtained has shown that the mechanism of electron density

redistribution with allowance for water medium influence with dielectric constant e = 78.355 at T = 298 K within the continual model of the solvent PCM for these interactions remains almost unchanged, that is confirmed by comparison of charges distribution according to Lyovdin, corresponding distances in GSH, •OH, $•OO^-$, as well as the values of activation energy of the reactions of GSH molecule interaction with •OH and $•OO^-$ (Table).

Table

Comparative distribution of charges q according to Lyovdin and activation energies E_a under GSH molecule interaction with free oxygen radicals at a point of global minimum

Interaction			q, a.o.			E_a , kJ/mol
			S(22)	H(23)	O*	
GSH	•OH	Without PCM	0.045	0.215	-0.449	101
		PCM	0.036	0.222	-0.465	100
	$•OO^-$	Without PCM	-0.660	0.216	-0.206	17
		PCM	-0.731	0.211	-0.187	7

*Indicated atom of radical which directly interacts with atom H(23) of GSH molecule.

Thus, the quantum chemical simulation of glutathione molecule interaction with •OH and $•OO^-$ has shown that, allowance for the influence of water medium do not practically influence redistribution of electron density of glutathione molecule and permit concluding that the studied reaction proceeds following the acid-base mechanism, under these conditions GSH appears as acid in respect of •OH in accordance with the set scheme (Fig. 3).

Thus, the mechanism of glutathione molecule interaction with •OH and $•OO^-$ has been investigated.

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