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QUANTUM CHEMICAL STUDY OF THE REDUCTIVE ACTIVATION OF QUINONES BY ENZYME NQO1

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ABSTRACT

A quantum chemical modeling of the interaction of the NQO1 enzyme with a several quinones was carried out. The calculation of the geometric and energy parameters of the studied substrates was done. The potential energy surface of reduction of heterocyclic quinones by the enzyme was drawn. Relationships between structure of substrates and their binding strength with NQO1 were pointed out.

АННОТАЦИЯ

Проведено квантово-химическое моделирование процесса взаимодействия фермента NQO1 с рядом хинонов. Осуществлен расчет геометрических и энергетических параметров изучаемых субстратов. Проведено построение поверхности потенциальной энергии процесса восстановления гетероциклических хинонов ферментом. Установлены закономерности взаимосвязи между строением субстратов и силой их связывания с молекулой NQO1.

Keywords: Quantum chemical calculations, semi-empirical methods, PM7, heterocyclic quinones.

Ключевые слова: Квантово-химические расчеты, полуэмпирические методы, PM7, гетероциклические хиноны.

Background.

Among the many potential therapeutic targets for cancer treatment, the NQO1 NAD(P)H enzyme: quinone oxidoreductase is an enzyme that is overexpressed in a number of tumors, including lung, colon, breast, liver cancer, 2-50 times more than in surrounding normal tissues [1-4]. NQO1 can specifically catalyze the two-electron reduction of various quinones directly to hydroquinones. Therefore, prodrugs containing a quinone fragment that are activated by NQO1 must exhibit specific anti-tumor activity.

The aim of this work was to study the process of enzymatic reduction of several heterocyclic quinones using semi-empirical quantum-chemical calculation methods.

Methods.

The construction of structures, the initial configuration of the simulated systems and the subsequent quantum-chemical modeling were carried out according to the following scheme:

The construction of simulated systems and the creation of source files containing z-matrices with the coordinates of the structure for calculation were performed using the CambridgeSoft ChemOffice 2010 software package.

Quantum chemical calculations were performed using the MOPAC 2012 software package (Molecular Orbital PACkage), using the semi-empirical PM7 method. Visualization of the calculation results was performed using the JMol 12.0.3 program.

Results.

The structures of quinones - substrates for the human enzyme NQO1 are presented in Figure 1.

In the process of quinone reduction, coenzyme flavin adenine dinucleotide (FAD), which is part of NQO1, is directly involved.

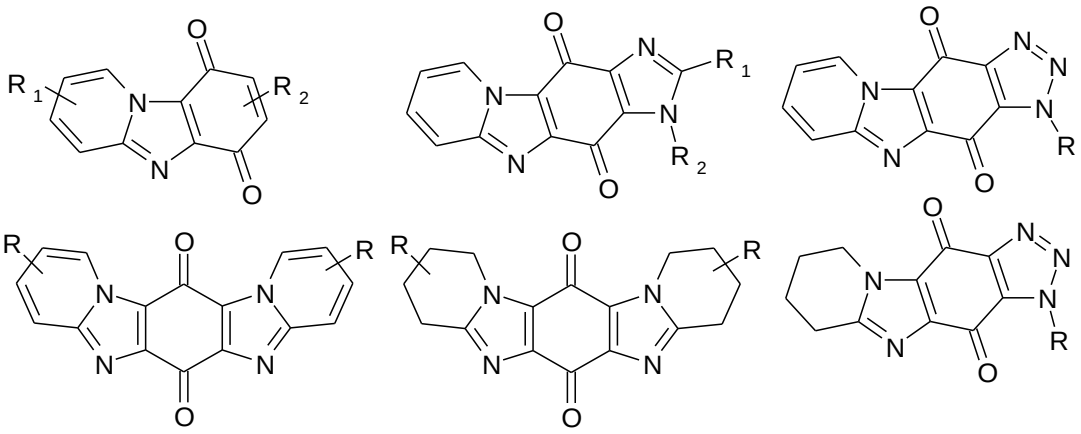

Figure 1. Molecular structures of the studied quinones

Figures 2–3 show the optimized spatial configurations of one of the simulated compounds for the initial molecular systems A (FADH2 + quinone), systems B (intermediates formed after the transfer of the first hydrogen atom from FADH2 to dione, i.e., FADN + QH, where Q - denotes quinone) (Figure 2) and C (intermediates formed after the transfer of the second hydrogen atom from FADH2 to quinone, i.e., FADH + QH2) and the final systems D (FAD + hydrobenzimidazoledione) (Figure 3).

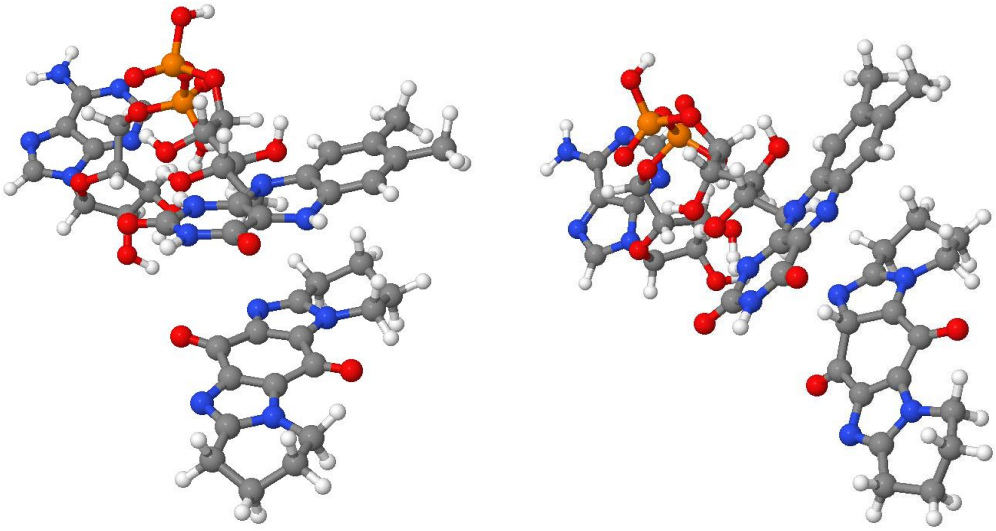

Figure 2. The spatial structure of system A (left) and B (right)

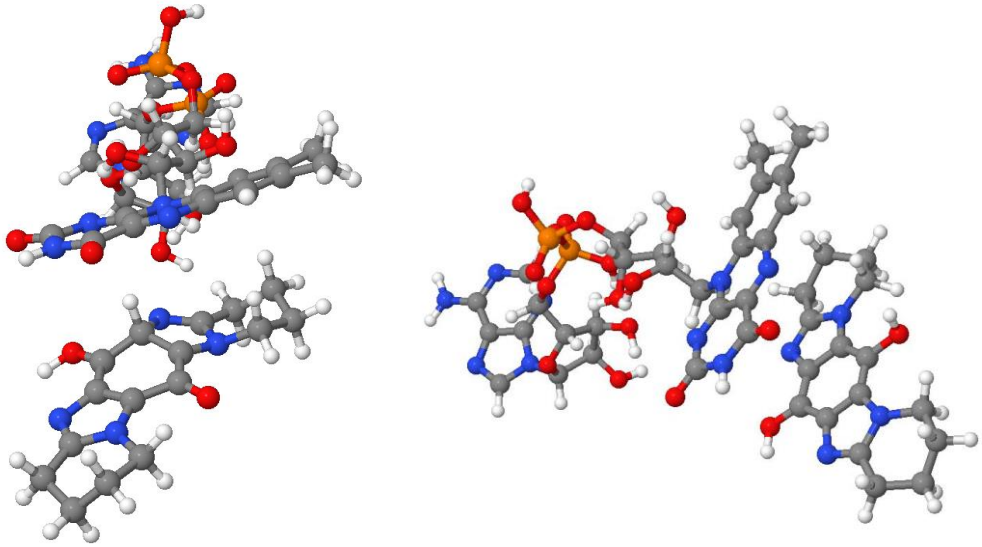

Figure 3. The spatial structure of system C (left) and D (right)

Conclusions.

Quantum chemical modeling of the reduction of heterocyclic quinones by the NQO1 enzyme was carried out; optimal configurations of quinone-FADH2 systems were established taking into account the results of docking of the corresponding ligands with NQO1 and taking into account the necessary distance between the reaction centers.

The process of reduction of quinones by the FADH2 molecule was studied, accompanied by the transfer of two hydrogen atoms from the flavin ring of the FADH2 molecule to the carbonyl groups of quinones, followed by the oxidation of FADH2 to FAD and the reduction of quinone to hydroquinone. The geometric and energy parameters of the starting compounds, intermediates, and reaction products were studied.

Surface of potential energy of reduction processes are built. It is shown that the maximum energy on the PES corresponds to the stage of attachment of the second hydrogen atom to heterocyclic quinones.

The nature of the charge redistribution on the flavin ring of the FAD molecule as a result of the reaction was established: the most significant changes occur on the carbon atoms of the benzene ring of the flavin ring, and nitrogen atoms bonded to the leaving hydrogen atoms.

The nature of charge redistribution on heterocyclic quinones has been established: the most significant changes occur on the carbon atoms of the middle link of the polycyclic quinone system, as well as on the nitrogen atoms directly associated with them.

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ИССЛЕДОВАНИЕ ОРГАНОЛЕПТИЧЕСКИХ И ФИЗИКО-ХИМИЧЕСКИХ СВОЙСТВ БЕЗАЛКОГОЛЬНЫХ НАПИТКОВ ДЛЯ СНЯТИЯ ПОХМЕЛЬНОГО СИНДРОМА "КЛЮКВА-ОБЛЕПИХА" И "КЛЮКВА-ЧЕРНИКА".

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АННОТАЦИЯ

В работе представлено исследование органолептических и физико-химических свойств безалкогольных напитков для снятия похмельного синдрома "Клюква-облепиха" и "Клюква-черника".

ANNOTATION

The paper presents a study of the organoleptic and physico-chemical properties of soft drinks to relieve the hangover Cranberry-sea-buckthorn and Cranberry-blueberry.

Ключевые слова: безалкогольный напиток, похмельный синдром, натуральное сырье, органолептические свойства, антиоксиданты.

Key words: soft drink, hangover, natural raw materials, organoleptic properties, antioxidants.

Похмелье — это состояние, которое наступает в результате интоксикации организма алкогольными напитками. Оно сопровождается целым рядом неприятных эффектов как физического, так и психологического свойства: одутловатостью лица, головной болью, повышенной раздражительностью и так далее. Основная причина возникновения похмелья — это избыток продуктов распада алкоголя, которые отравляют организм. Под действием ферментов этанол распадается на составляющие, что влечет за собой постепенное отрезвление. Однако кроме этанола алкогольные напитки часто содержат и многие другие примеси — например метанол, который распадается на формальдегид и муравьиную