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Feasibility of the C_{60} Fullerene Antioxidant Properties: Study with Density Functional Theory Computer Modeling

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Fullerene C_{60} compound was recently found to be a potent anti-oxidant, which may be envisioned as a result of alteration of the inner mitohondria membrane electric potential with protons transport boosted by fullerenes. Here we briefly report on the theoretical test of the very possibility of protons to pass through the surface of C_{60} fullerene to become confined within latter thus possibly decreasing the transmembrane electric field gradient when fullerene crosses the mitochondria membrane. Quantum-chemical calculations within Density Functional Theory are employed as a means of checking described scenario.

fullerene; C_{60}; Sculachev ions; mitochondria membrane potential; antioxidant activity; Density Functional Theory; DFT

I. Introduction

Fullerene C_{60} may be a powerful antioxidant demonstrating anti-aging activity. Recently Baati et al. showed that fullerene prolonged rat's life span approximately twice [1]. Besides, rats treated with fullerene C_{60} demonstrated high resistance to carbon tetrachloride capable of triggering generation of huge amounts of harmful reactive oxygen species. Consequently, fullerene C_{60} was proposed to have high antioxidant activity *in vivo*. Geroprotective activity of C_{60} fullerene found experimentally in [1] is much higher than those of the most powerful reactive oxygen species scavengers.

Reactive oxygen species may cause oxidative damage to DNA, lipids and proteins leading to malfunctioning of cell components and eventually its death. Such mechanism is considered to be the main cause of organisms' aging, and currently free-radical theory plays a pivotal role in modern biological concepts of aging [2].

As of today, it is still unknown how fullerene exactly acts as an antioxidant. Fullerene C_{60} is known to be able to inactivate hydroxyl radicals by attaching to the double bonds [3]. However, this mechanism cannot explain substantial (near two-times!) increase in the lifespan of rats. We propose there is an additional mechanism determining fullerene anti-aging activity. This mechanism is based on mild uncoupling of respiration and phosphorylation processes in a cell related to the proton gradient alteration on the mitochondrial membrane. The majority of reactive oxygen species is generated in mitochondrial respiratory chain; the latter is the source of superoxide anion that triggers a reaction chain resulting in formation of other radicals. That is why most effective antioxidants are mitochondrial-targeted. Among such compounds are alipophilic cations (so-called Skulachev ions) with antioxidant load [4].

Because of electron transport chain activity, transmembrane potential drop is generated by creating the difference in concentrations of protons inside and outside of the inner membrane. The outer side of the internal mitochondria membrane has positive charge, while the inner side is negatively charged. This difference in electric potentials makes accumulation of Skulachev ions in the mitochondria possible. Therefore, lipophilic cations concentrate in mitochondria via electric field forces [4].

Fullerene C_{60} is also a lipophilic compound [5]. Theoretical simulations with molecular dynamics indicated that C_{60} may penetrate into membrane and accumulate there [6]. Although such simulations do not account for the charge of the mitochondrial membrane one can suppose that fullerene is indeed able to cross the inner mitochondrial membrane.

Let us assume that fullerene can absorb protons and obtain a positive charge, which allows it to cross the membrane. Next, fullerene could enclose protons within and transfer them through the inner mitochondrial membrane, which leads to the decrease in transmembrane electric potential. Korshunov et al. demonstrated [7] that even small (about 10%) decrease in transmembrane potential leads to the tremendous ten-fold decline in superoxide anion-radical generation. Therefore, such so-called mild uncouplers of oxidative phosphorylation can facilitate proton movement inside the mitochondria and thereby possess an excellent oxygen radicals-protective effect, although they are not antioxidants in terms of chemistry [5].

In order to prove outlined mechanism theoretically, we performed theoretical analysis of the fullerene C_{60} ability to acquire positive charge and absorb protons using Density Functional Theory (DFT). We found that the proposed mechanism indeed might take place.

II. Method of Calculation

Density Functional Theory (DFT) is a powerful and widely used method for quantum-chemistry calculations [8]. DFT enables one to accurately compute electronic and structural properties of a variety of molecular systems. In the present work, DFT implemented in ADF 2012 program suite [9] was used to simulate the interaction between the single fullerene and surrounding proton(s) by searching for the most probable

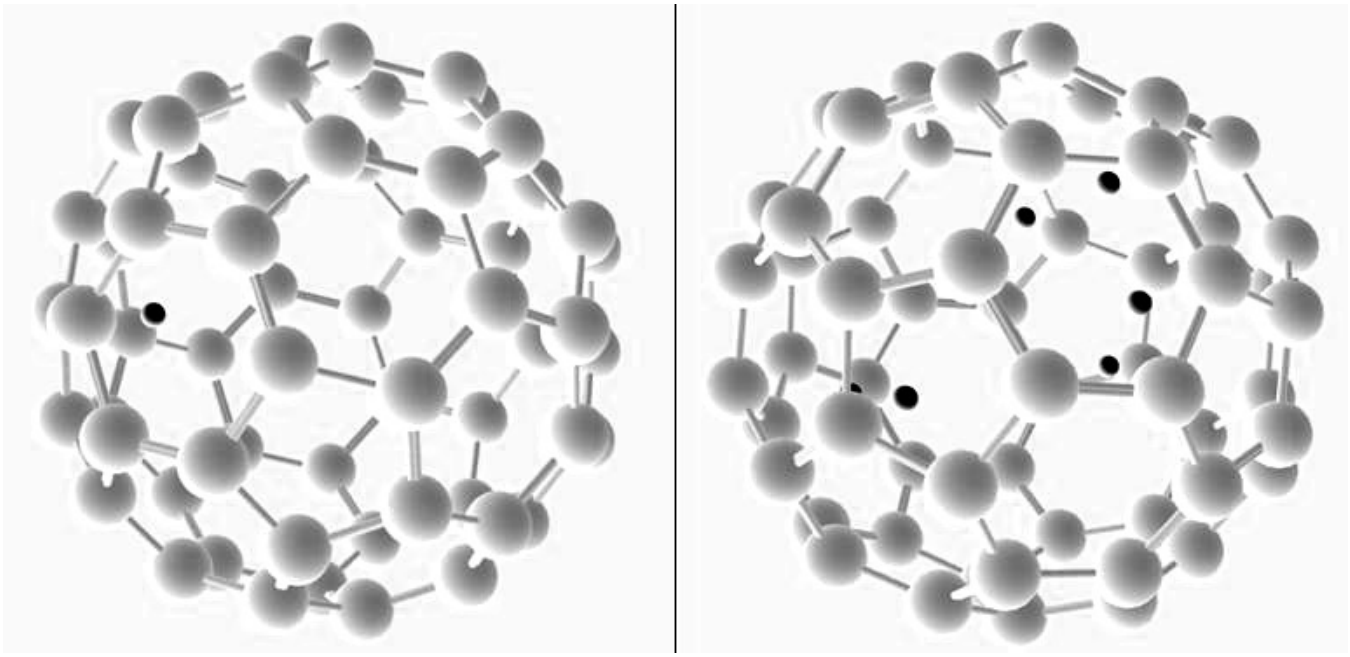

Figure 1. The results of DFT geometry optimization for one (left) and six (right) protons and fullerene.

atomic configuration of the whole system. Such configuration is found by minimizing the total energy of the system during the so-called process of the geometry optimization, which means evaluation of the system stable configuration corresponding to the minimum on the total energy hypersurface among multitude of close structures.

We applied General Gradient Approximation (GGA) for the exchange-correlation part of potential in two forms: GGA-BLYP [10] and GGA-BLYP-D3 [11]. Slater-type basis sets called double-zeta and triple-zeta with polarization function were used; frozen core approximation was employed to shorten computation time.

III. Results and Discussion

Initially, interaction between single proton and fullerene was simulated. The proton was placed outside of the C_{60} above one of the carbon pentagons at the distance about 1Å from the pentagon plane. Calculation resulted in the proton passing through the fullerene and finally appearing inside C_{60} (Fig. 1, left panel). Next, more and more protons were consecutively added by allocation them above both carbon pentagons and hexagons in the initial configuration before the geometrical optimization. In all cases when there were from one to six protons present, they penetrated into the fullerene. However, the seventh proton added to the system failed to enter space inside the fullerene. One may conclude then that maximum amount of protons fullerene can accommodate is equal to six (Fig. 1, right panel).

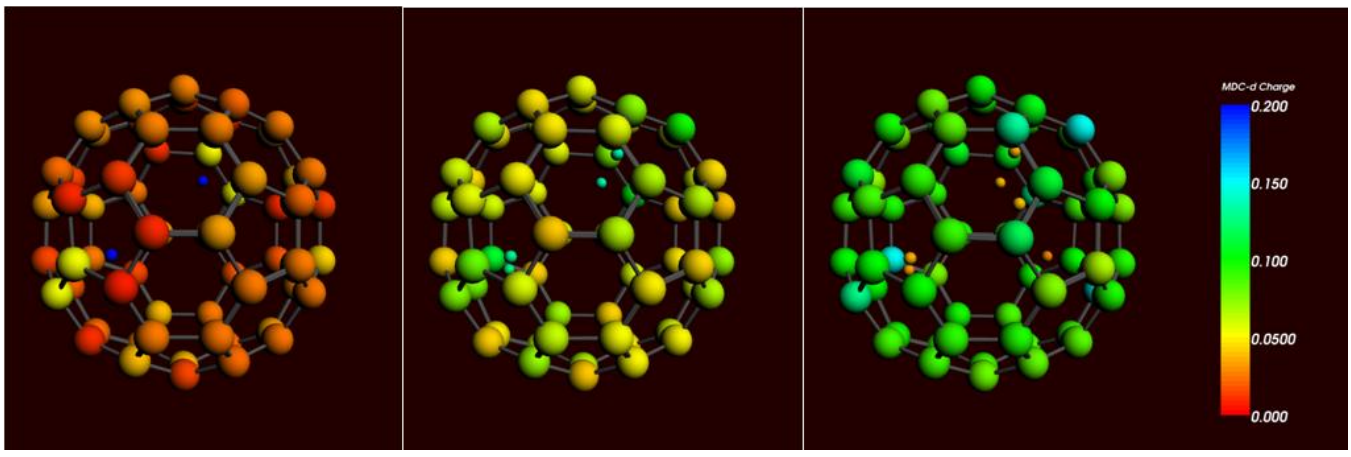

Figure 2. The distribution of charge for two, four and six protons inside the fullerene, from the left to the right, respectively.

To be able to penetrate into the mitochondrial membrane according to the mechanism described in the Introduction the fullerene must have positive charge distributed on its surface. Thus it is crucial to confirm the positive charge distribution over C_{60} surface for each tested configuration of protons. Fig. 2 illustrates charge distribution obtained with DFT within Mulliken scheme for two, four, and six protons caught inside the fullerene. One can note that when amount of protons stuck inside fullerene increases, its surface accumulates more positive charge.

As the next step, the presence of water molecules in real cell was taken into account by surrounding fullerene with water molecules. The simulation was carried out for a fullerene with single proton placed above a pentagon and 47 water molecules randomly distributed around the fullerene. We found water molecules do not influence the fullerene's capability of absorbing protons.

To sum up, DFT simulations allowed us to propose the following mechanism. C_{60} fullerene molecules enter the space between inner and outer membranes of mitochondria, where there is excess of protons due to diffusion. In this compartment fullerenes are loaded with protons and acquire positive charge distributed over their surface. Such "charge-loaded" particles can be pushed through the inner membrane of the mitochondria due to the potential difference generated by the inner membrane, using electrochemical mechanism described in detail by Skulachev et al. [4, 12]. In this case, the transmembrane potential reduces, that, in turn, significantly lowers the intensity of superoxide anion radical production. The key role of mitochondria in the cellular regulation makes such "charge-loaded" fullerenes of great scientific interest not to say about prospective route for development of novel anti-aging drugs. There are number of issues to be addresses further including fullerenes' toxicity and consideration of the more realistic theoretical models. Simulations of the fullerenes' anti-oxidant activity are under way and to be published elsewhere.

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