

Quantum chemical designing of cholesterol containing radionuclide anticancer agents

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Received December 18, 2015

In this work DFT simulation of the electron structure of cholesterol containing radionuclide agents (cluster systems of carborane (*ortho-1*, *meta-2*, *para-3*) and fullerene derivatives) for oncological diseases therapy was carried out. Cluster systems of endohedral backminsterfullerene C₆₀ derivatives have a promise perspectives in medical application as radionuclide (Fe **10a**, Y **10b**, Re **10c**, Po **10d**, Rn **10e** isotope contained) nanosized anticancer agents. According to the cluster stability data obtained by the DFT calculation there is a possibility of their real practical obtainment.

Keywords: cholesterol, radionuclide agent, backminsterfullerene cancer-fighting agent.

Проведено DFT-моделирование электронных структур содержащих холестерин радионуклидных агентов (кластерных карборановых систем (*орто-1*, *мета-2*, *пара-3*) и производных фуллеренола), перспективных для применения в терапии онкологических заболеваний. Кластерные системы эндодральных производных бакминстерфуллеренолов C₆₀ имеют многообещающие перспективы для применения в медицине в качестве радионуклидных наноразмерных изотопсодержащих (Fe **10a**, Y **10b**, Re **10c**, Po **10d**, Rn **10e**) противораковых агентов. В соответствии с данными стабильности кластеров, полученными с использованием DFT вычислений, оценена возможность их реальной практической реализации.

Квантово-хімічне моделювання електронних структур, які містять холестерин радіонуклідних агентів. *Е.А. Дікусар, В.М. Зеленовський, А.Л. Пушкарчук, Д.А. Рудаков, В.І. Поткін, С.Ю. Кілін, А.Г. Солдатов, С.А. Кутень.*

Проведено DFT-моделирование электронных структур які містять холестерин радіонуклідних агентів (кластерних карборанових систем (*орто-1*, *мета-2*, *пара-3*) і похідних фуллеренола), перспективних для застосування у терапії онкологічних захворювань. Кластерні системи ендоедральних похідних бакмінстерфуллеренолов C₆₀ мають багатообіцяючі перспективи для застосування в медицині як радіонуклідні нанорозмірні ізотоповміщуючі (Fe **10a**, Y **10b**, Re **10c**, Po **10d**, Rn **10e**) протираківі агенти. Відповідно до даних стабільності кластерів, отриманих з використанням DFT обчислень, оцінена можливість їх реальної практичної реалізації.

1. Introduction

One of the commonly used cancer therapy method consists in the tumor cells irradiation by high energy proton or neutron dose to a well-defined target with little or no fractionation [1]. Nowadays the new modern technologies of tumor treatments are intensively introduced in clinical practice of radiation oncology: radiological destroying tumors by introducing the relevant short-lived radionuclides (Y^{90} , Zr^{95} , Fe^{59} , In^{114*} , Eu^{147} , Eu^{148} , Eu^{155} , Tm^{170} , Re^{188} , Po^{210} , Rn^{222} , U^{230} , Pu^{237} , Cm^{240} , Cm^{241} , Es^{253}), which are used in the isotopic medicine. The binary (or neutron capture) therapy is a technology that was designed for the selective action on malignant neoplasm. It uses the tumor-tropic drugs that contain nonradioactive nuclides (B^{10} , Cd^{113} , Gd^{157} , etc.) [2]. The triadic therapy is consistent placement in a body the combination of two or more tumor-tropic tissue components that are individually inactive and harmless. These components are able to be selectively accumulated in tumors. They join each other in chemical interaction and destroy the tumor neoplasm under certain sensitizing external influences [3].

The designing and synthesis of the new boron-organic compounds [4] that can be used in the binary oncological diseases therapy [2] is very perspective. In order to

avoid the biological incompatibility these compounds should contain some natural fragments, for example cholesterol [5].

This work presents the results of quantum-chemical DFT simulation [6] of the electron structure and construction of cholesterol containing cluster systems of carborane and fullerene derivatives with aim to develop the new radionuclide nanosized anticancer agents [7–12].

2. Experimental

Synthesis of B^{10} -riched cholesterol esters of *o*-, *m*-, and *p*-carborane-C-carboxylic acids **1–3** [11] is intensive labor and high cost task. Recently we synthesized cholesterol esters of *o*-carborane-C-carboxylic acid **1**, m.p. = 101–102°C [13], and *m*-carborane-C-carboxylic acid **2**, m.p. = 162–163°C [14], which have native relation of boron isotopes. Corresponding derivative of *p*-carborane-C-carboxylic acid **3** (Fig. 1–4) has not been synthesized yet caused by high cost of precursors. Characteristics of their electronic structure and relative stability are very important parameters that determinate these compound behaviors in biological media.

In order to estimate stability of isomeric cholesterol ester of *o*-, *m*-, and *p*-carborane-C-carboxylic acids **1–3** and to study their electronic structure and construction the non-empiric quantum chemical calculations of these compounds were carried out by

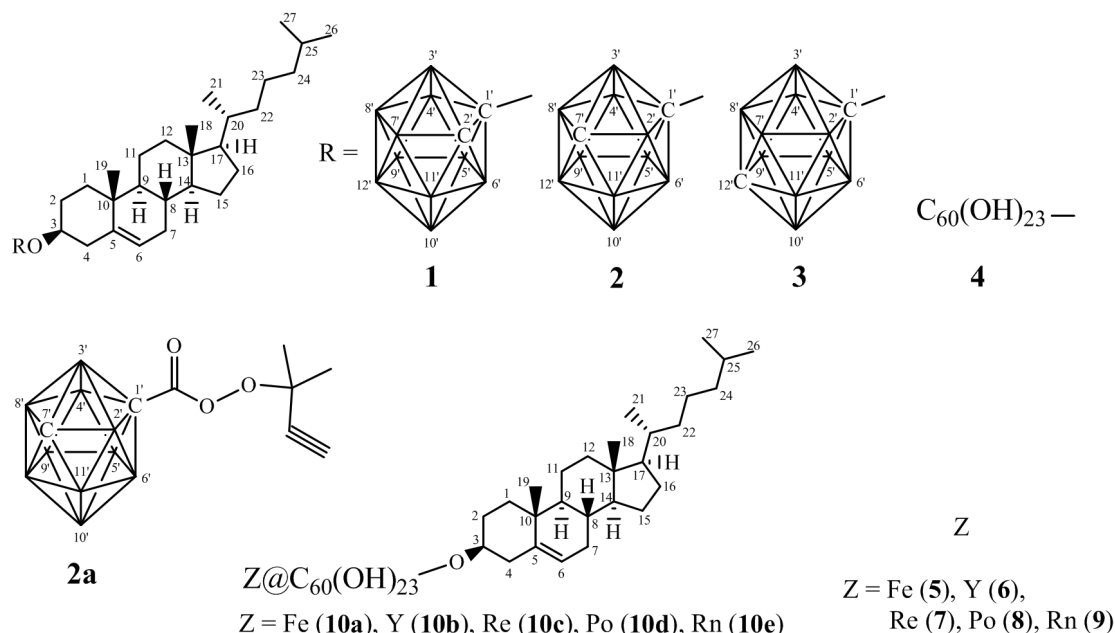


Fig. 1. Synthesized cholesterol esters of carborane-C-carboxylic acids **1–3**, peroxide **2a**, fullereneol **4** and DFT simulated backminsterfullerenol derivatives $Z@C_{60}(OH)_{23}O$ -cholesterol [$Z = Fe$ (**10a**), Y (**10b**), Re (**10c**), Po (**10d**), Rn (**10e**)].

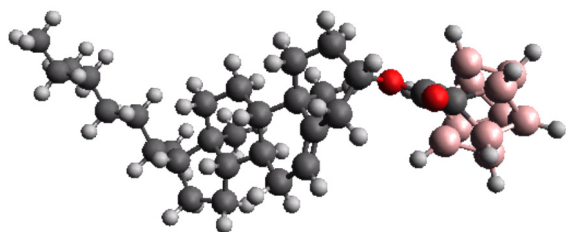


Fig. 2. DFT B3LYP1/6-31G(d) model of cholesterol ester of *o*-carborane-C-carboxylic acid **1**.

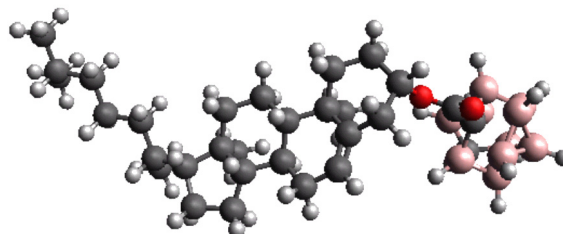


Fig. 3. DFT B3LYP1/6-31G(d) model of cholesterol ester of *m*-carborane-C-carboxylic acid **2**.

DFT method on the level of B3LYP/MIDI theory following the GAMESS software [15]. Full energy of the systems, energy of HOMO, LUMO and dipole moments computed by the DFT method for compounds **1–3** are presented in Table.

3. Results and discussion

Computed unit cell parameters of the *m*-carborane-C-carboxylic fragment of cholesterol ester **2** (Fig. 3) are in well agreement with the X-ray data of 3-methyl-3-[1,7-dicarba-*closo*-dodecaboran(12)-1-oilperoxy] but-1-ine **2a**, which has the same fragment [16]. In particular, the bridge C–C bond length in the *m*-carborane-C-carboxylic fragment calculated by the DFT located between *m*-carborane-C- and -C=O groups is 0.1525 nm for compound **2**. According to the X-ray data the same bridge C–C bond length in peroxide **2a** is 0.1518(6) nm [16].

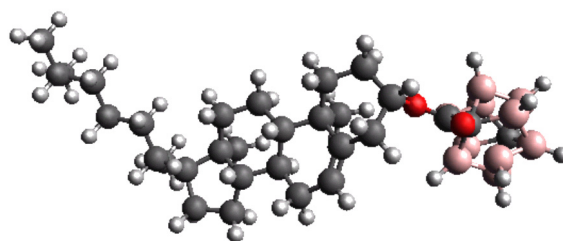


Fig. 4. DFT B3LYP1/6-31G(d) model of cholesterol ester of *p*-carborane-C-carboxylic acid **3**.

Comparison of the calculated full energy values of the compounds **1–3** (see Table) shows that among the cholesterol esters of *o*-, *m*-, and *p*-carborane-C-carboxylic acids **1–3** the compounds **3** is the most energetically favorable.

Dipole moments, which characterize distribution asymmetry of positive and nega-

Table. Total energies (E_{tot}) of systems (I–XIV), energies HOMO (E_{HOMO}) and LUMO (E_{LUMO}), and dipole moments. Interaction estimation (ΔE_{int}) calculated by DFT method

No.	E_{tot} , a.u.	E_{HOMO} , a.u.	E_{LUMO} , a.u.	Dipole moments, D	ΔE_{int} , kJ/mole
1	-1576.049067	-0.2371	0.0183	7.00	–
2	-1576.072327	-0.2311	0.0734	5.07	–
3	-1576.077013	-0.2274	0.0268	2.39	–
4	-5130.939156	-0.0915	-0.0236	3.89	–
5	-1258.130847	-0.1078	0.0493	0	–
6	-3321.291999	-0.1598	-0.1205	0	–
7	-15743.255420	-0.0948	-0.0526	0	–
8	-20624.988237	-0.2134	0.0463	0	–
9	-21813.044758	-0.3204	0.1530	0	–
10a	-6389.137488	-0.1040	-0.0306	8.87	-177.2
10b	-8452.284126	-0.1005	-0.0561	5.08	-139.1
10c	-20874.306882	-0.0749	-0.0281	4.02	-294.9
10d	-25755.848398	-0.0816	-0.0294	8.57	207.4
10e	-26943.936066	-0.0888	-0.0250	3.90	125.6

tive charges of electrically neutral molecules of the cholesterol esters of *o*-, *m*-, and *p*-carborane-C-carboxylic acids **1–3**, gradually decreases from *o*-isomer to the *p*-one (see Tabl. 1). So we can conclude that among the cholesterol esters **1–3** the compound **1** is more polar than compound **2** and compound **3** is less polar than others. In biological media all "guest" molecules undergo fermentative attack by polar peptides (hydrolysis, alcoholysis, ammonolysis etc.). We guess that the ester **1** will be more stable in biological liquids than the others and the ester **3** will be the most unstable.

Modelling of the electronic structure and construction of endohedral buckminsterfullerenol clusters $Z@C_{60}(OH)_{23}O$ -cholesterol **10a–e** was performed for $Z = Fe$ (**10a**), Y (**10b**), Re (**10c**), Po (**10d**), Rn (**10e**) (Fig. 5), "empty" fullerolenol cluster is the monoester of fullerolenol and cholesterol $C_{60}(OH)_{23}O$ -cholesterol **4**, and isolated atoms are incorporated components: Fe (**5**), Y (**6**), Gd (**7**), Po (**8**), Rn (**9**). The necessity of preliminary investigations by computer modelling is caused by the intensive labor and high cost [17]. The non-empirical quantum chemical calculations of the compounds (**4**, **10a–e**) were carried out by the DFT method on the level of B3LYP/MIDI theory following the GAMESS software [15, 18]. Total energy of systems, computed by the DFT method for compounds (**4–10e**), the energy of the HOMO, LUMO and dipole moments are presented in Table.

The quantum-chemical simulation allows making conclusions about the stability and the possible existence of endohedral fullerene clusters $Z@C_{60}(OH)_{23}O$ -cholesterol **10a–e**, which electron density distribution is shown in Fig. 5 for $Z = Rn$. According to the quantum chemical calculation data (see Table) the interaction energy of endohedral clusters **10a–e**, which can be calculated by the following formula (1):

$$\Delta E \int (\mathbf{10a-e}) = \quad (1)$$

$$= E_{tot}(\mathbf{10a-e}) - [E_{tot}(\mathbf{4}) + E_{tot}(\mathbf{5-9})]$$

shows that thermodynamic stability [19, 20] of the endohedral fullerolenol cluster systems C_{60} **10a–e** differs by $\pm 126–295$ kJ/mole from the total energy sum of "empty" fullerolenol cluster (IV) and isolated molecules Z **5–9**.

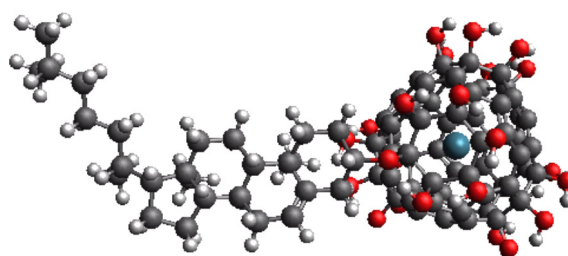


Fig. 5. DFT B3LYP/MIDI model of $Rn@C_{60}(OH)_{23}O$ -cholesterol **10e**.

4. Conclusions

Cluster systems of endohedral buckminsterfullerenol C_{60} derivatives (**10a–e**) have the promise perspectives in medical application as radionuclide (Fe , Y , Re , Po , Rn isotope contained) nanosized anticancer agents. According to the cluster (**10a–e**) stability data obtained by DFT calculation there is a possibility of their real practical embodiment.

Acknowledgments. Support by the "Convergence" and "Nanotech" national scientific programs, Belarus, is gratefully acknowledged. This work was performed using computational facilities of joint computational cluster of SSI "Institute for Single Crystals" and Institute for Scintillation Materials of National Academy of Sciences of Ukraine incorporated into Ukrainian National Grid.

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