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DFT Simulation of Methotrexate Fullerenol Radionuclide Agents of Cancer Therapy

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In order to destroy cancer therapeutic neoplasms commonly used chemotherapy or radiotherapy, and medical isotope injected into the tumor relevant short-lived radionuclides like ^{59}Fe, ^{90}Y, ^{95}Zr, ^{114}In, ^{147}Eu, ^{148}Eu, ^{155}Eu, ^{170}Tm, ^{188}Re, ^{210}Po, ^{222}Rn, ^{230}U, ^{237}Pu, ^{240}Cm, ^{241}Cm, ^{253}Es (below for brevity, the sequence A). Binary (or neutron capture) - a technology developed for the selective effects on malignant tumors and tumors using a tropic preparations containing non-radioactive nuclides (^{10}B, ^{113}Cd, ^{157}Gd at al.). Triadic - sequential administration of a combination of two or more separately inactive and harmless components tropic tumor tissues and can selectively accumulate in them or join each other and a chemical reaction to destroy cancer growths sensitizing under certain external impacts. The aim of this work is the quantum-chemical modeling of the electronic structure and the analysis of the thermodynamic stability of the new methotrexate containing nanoscale fullerenolic radionuclide agents fighter tumor growths. The need for preliminary studies on modeling of such objects is caused by a very labor-intensive, cost and complexity of their practical preparation.

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1. Introduction

Chemotherapy or radiotherapy is usually used for the therapeutic eradication of oncological tumors [1], and in isotope medicine - the corresponding short-lived radionuclides like the sequence A. Binary (or neutron capture) is a technology developed to selectively affect malignant neoplasms and uses drugs that are tropic to tumors containing non-radioactive nuclides (^{10}B, ^{113}Cd, ^{157}Gd, etc.) [2]. Triadic - a sequential introduction into the body of a combination of two or more, individually inactive and harmless components tropic to tumor tissues and capable of selectively accumulating in them or entering into a chemical interaction with one another and destroying tumor growths under the action of certain sensitizing external influences [3].

This report presents the results of quantum-chemical DFT modeling [4–6] of the structure and electronic structure of fullerene cluster systems studied with the aim of developing new radionuclide nanoscale tumor-fighter agents. To improve the effectiveness of these drugs, it is promising to introduce into the composition of their molecules structural fragments of known dosage forms, for example, antimetabolite, an analogue of folic acid - methotrexate [7].

2. MODELS AND METHODS

As endohedral components of inclusion in the inner spheres of methotrexate containing bisfellerolene **1**, ^{210}Po **68** (clusters **2-4**), ^{222}Rn **69** (clusters **5-7**) and alkali metal halides **70-99** (clusters **8-67**) were chosen. The choice of these supramolecular inclusion objects in the internal cavities of bisfellerolene 1 is due to the fact that ^{210}Po **68** and ^{222}Rn **69** radionuclides are convenient sources of therapeutic ionizing α radiation [8, 9]. In particular, polonium ^{210}Po **68** has a half-life of 138.38 days with an energy release of 5.30 MeV [10–12], and radon ^{222}Rn **69** has a half-life of 3.82 days with an energy release of 5.59 MeV [13]. The introduction of alkali metal halides **70-99** (in the form of ions) into the internal cavities of bisfellerolenol 1 leads to a significant increase in the polarity of the resulting endohedral clusters **8-32**, **38-42**,**44-48**, **50-54**,**56-60**, **62-66** (see Table 1), which is the determining factor facilitating their penetration through cell membranes. This transport is carried out with the help of special transport molecules built into the cell membranes. Usually, in the role of carriers of this kind are proteins, which are necessary for the entry into the cell of natural metabolites. This type of transport can tolerate drugs that are close in structure to endogenous molecules - for example, vitamins or methotrexate.

There are two types of transport with the help of carriers: light diffusion - is carried out on a concentration gradient and active transport - is carried out against the concentration gradient [14]. Specialized transport does not obey the Fick diffusion law and does not depend on the presence of a charge in the drug substance. It is a saturated process - i.e. the absorption rate increases only as long as the number of molecules of the drug substance does not equal the number of carriers. Further increase in the rate of absorption, despite the increase in the concentration of the drug, does not occur [15, 16].

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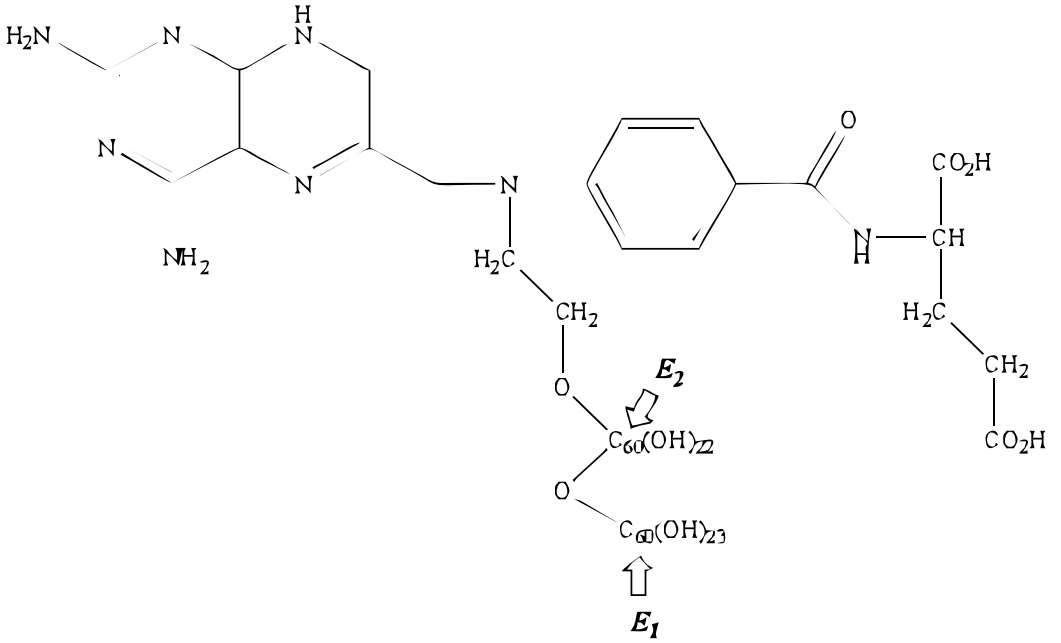

FIG. 1. Transport scheme: E_1 and E_2 are absent **1**;E_1 = Po, E_2 is absent **2**; E_1 is absent, E_2 = Po **3**; $E_1 = E_2$ = Po **4**; E_1 = Rn, E_2 is absent **5**; E_1 is absent, E_2 = Rn **6**; E1 = E_2 = Rn **7**; E1 = Li, E_2 = F **8**, Cl **9**, Br **10**, I **11**, At **12**; E_1 = Na, E_2 = F **13**, Cl **14**, Br **15**, I **16**, At **17**; E_1 = K, E_2 = F **18**, Cl **19**, Br **20**, I **21**, At **22**; E_1 = Rb, E_2 = F **23**, Cl **24**, Br **25**, I **26**, At **27**; E_1 = Cs, E_2 = F **28**, Cl **29**, Br **30**, I **31**, At **32**; E_1 = Fr, E_2 = F **33**, Cl **34**, Br **35**, I **36**, At **37**; E_1 = F, E_2 = Li **38**, Na **39**, K **40**, Rb **41**, Cs **42**, Fr **43**; E_1 = Cl, E_2 = Li **44**, Na **45**, K **46**, Rb **47**, Cs **48**, Fr **49**; E_1 = Br, E_2 = Li **50**, Na **51**, K **52**, Rb **53**, Cs **54**, Fr **56**; E_1 = I, E_2 = Li **56**, Na **57**, K **58**, Rb **59**, Cs **60**, Fr **61**; E_1 = At, E_2 = Li **62**, Na **63**, K **64**, Rb **65**, Cs **66**, Fr **67**; Po **68**; Rn **69**; LiF **70**, LiCl **71**, LiBr **72**, LiI **73**, LiAt **74**; NaF **75**, NaCl **76**, NaBr **77**, NaI **78**, NaAt **79**; KF **80**, KCl **81**, KBr **82**, KI **83**, KAt **84**; RbF **85**, RbCl **86**, RbBr **87**, RbI **88**, RbAt **89**; CsF **90**, CsCl **91**, CsBr **92**, CsI **93**, CsAt **94**; FrF **95**, FrCl **96**, FrBr **97**, FrI **98**, FrAt **99**.

It is promising to study the possibility of nanocapsulating radionuclides (^{8}Li, ^{21}Na, ^{22}Na, ^{24}Na, ^{25}Na, ^{37}K, ^{40}K, ^{47}K, ^{79}Rb, ^{81}Rb, ^{87}Rb, ^{97}Rb, ^{112}Cs, ^{133}Cs, ^{135}Cs, ^{137}Cs, ^{151}Cs, ^{223}Fr) by the method of quantum- (^{18}F, ^{36}Cl, ^{38}Cl, ^{80m}Br, ^{80}Br, ^{81}Br, ^{125}I, ^{128}I, ^{131}I, ^{211}At, ^{218}At, ^{219}At) [11, 17] into the internal cavities of bis-fullerenol **1**. An example of the relevance of these studies is the fact that ^{211}At excels radioactive iodine in its destructive effect on the thyroid gland, which is due to the localized effect of 5.9 MeV α -particles emitted at a distance of about 70 μ in living tissues, while the least active β -radiation of radioactive iodine - acts at a distance of up to 2000 μ [18].

3. Simulation and results

Interest in similar endohedral compounds of inclusion of various atoms and molecules in the internal cavities of fullerenes is constantly growing [19-21]. The need for preliminary studies on the modeling of such objects is due to the very high labor intensity and complexity of their production.

Stability of above-mentioned endohedral clusters is determined by their interaction energy ΔE_{int}. This quantity can be determined by the equation:

$$\Delta E_{int(\mathbf{2,3,...,32})} = E_{(\mathbf{2,3,...,32})} - (E_{(\mathbf{1})} + E_{(\mathbf{68,69,...,94})}) \quad (1)$$

where $\Delta E_{int(\mathbf{2},\mathbf{3},...,\mathbf{32})}$ is the interaction energy of endohedral clusters **2-32** . The results quantum chemical calculations of energy characteristics of the clusters of interest are presented in Tables 1-2. Data in these Tables denote on stability of clusters under consideration and a decrease or increase in the total energy of the systems by hypothetically "dissolving" 1 or 2 grams of Po or Rn atoms, or 1 gram-mol of the E_1E_2 salt in the internal cavities of bis-fulllerenol (**1**) (Fig.1).

The total energies of the systems (E, amu) and dipole moments (D, D) of compounds **1-32, 68-94** are presented in Table 1, while Table 2 contains the interaction energy.

Table 1. The total energies of the systems E, amu and dipole moments D, D of compounds **1-32, 68-94**.

N	*E*	*D*	N	*E*	*D*	N	*E*	*D*
1	−9707.8160079	5.46	**21**	−17203.7386185	33.40	**76**	−619.3761608	9.13
2	−30332.7895515	4.26	**22**	−31519.2494339	33.08	**77**	−2725.3373191	10.37
3	−30332.7945994	3.83	**23**	−12735.8509083	28.50	**78**	−7060.0925727	10.80
4	−50957.7653731	3.85	**24**	−13094.6064768	31.99	**79**	−21375.6214854	10.86
5	−31520.8152247	4.55	**25**	−15200.5682962	33.78	**80**	−696.3995963	7.68
6	−31520.8144673	4.55	**26**	−19535.3069898	33.72	**81**	−1055.2543501	11.20
7	−53333.8104697	4.28	**27**	−33850.8178066	33.37	**82**	−3161.2207349	12.94
8	−9814.5295171	25.41	**28**	−17340.2965462	28.60	**83**	−7495.9785289	13.66
9	−10173.2845731	28.63	**29**	−17699.0520758	32.03	**84**	−21811.5088909	14.02
10	−12279.2461539	30.60	**30**	−19805.0138740	33.87	**85**	−3027.9638343	8.08
11	−16613.9849323	30.55	**31**	−24139.7526601	33.74	**86**	−3386.8216551	11.92
12	−30929.4959644	30.33	**32**	−38455.2634416	33.43	**87**	−5492.7898598	13.84
13	−9968.3955632	25.36	**68**	−20624.9882378	0.0	**88**	−9827.5483478	14.67
14	−10327.1501067	29.42	**69**	−21813.0447589	0.0	**89**	−24143.0791829	15.12
15	−12433.1119628	30.74	**70**	−106.7003851	0.32	**90**	−7632.4087303	8.78
16	−16767.8506796	30.70	**71**	−465.5302923	8.42	**91**	−7991.2718587	13.08
17	−31083.3615844	30.44	**72**	−2571.4873906	9.53	**92**	−10097.2437532	15.06
18	−10404.2827000	28.13	**73**	−6906.2411696	9.90	**93**	−14432.0028264	16.06
19	−10763.0381383	31.71	**74**	−21221.7700714	9.90	**94**	−28747.5341337	16.72
20	−12868.9998739	33.45	**75**	−260.5353049	6.52	-	-	-

Table 2. Estimating the interaction energy of endohedral clusters **2-32** (ΔE_{int}).

N	ΔE_{int} kJ/mol	N	ΔE_{int} kJ/mol	N	ΔE_{int} kJ/mol
2	38.58	**13**	−116.18	**24**	81.88
3	25.33	**14**	110.43	**25**	98.64
4	71.18	**15**	108.60	**26**	150.61
5	119.57	**16**	152.02	**27**	203.17
6	121.56	**17**	199.30	**28**	−188.53
7	249.57	**18**	−176.16	**29**	93.97
8	−34.46	**19**	84.59	**30**	120.48
9	162.06	**20**	96.80	**31**	173.74
10	150.30	**21**	146.81	**32**	227.63
11	189.68	**22**	198.13	-	-
12	236.60	**23**	−186.58	-	-

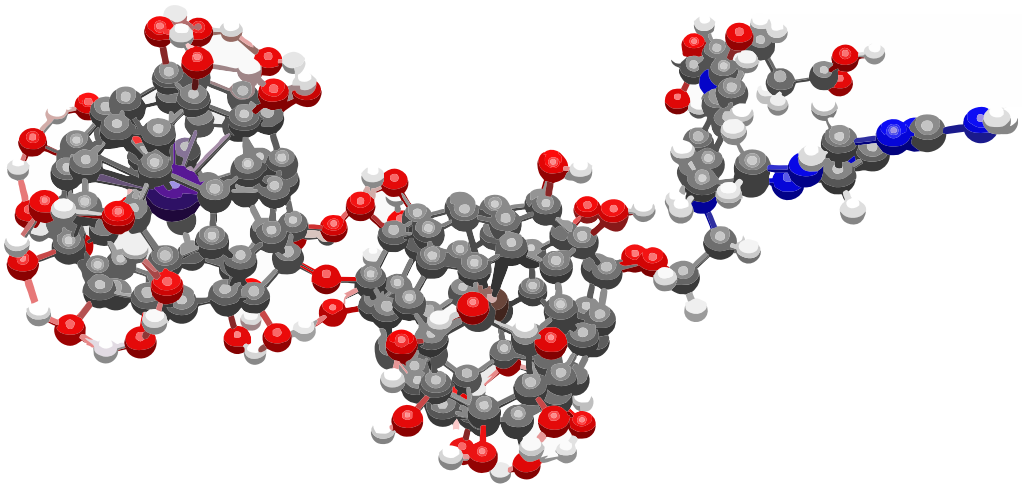

FIG. 2. The model of the methotrexate-containing bis-fullerenol cluster **32**, with Cs^+At^- ions encapsulated in its internal cavities

The calculations carried out in accordance with the additive formula (1) show that the thermodynamic stability of endohedral Po- and Rn-containing Baxminsterfullerol cluster systems C_{60} **2-7** is 25-250 kJ/mol lower than that of systems consisting of an "empty" Baxminsterfullerol cluster **1** and components of their isolated components **68** and **69**. The stability of the F-containing systems **8**, **13**, **18**, **23** and **28** was higher by 34-189 kJ/mol than the stability of their constituent components **1**, **70**, **75**, **80**, **85** and **90**. This is caused by the gain in the energy due to the formation of covalent C-F bonds within the fullerene spheres of these compounds. The stability of the remaining clusters: **9-12**, **14-17**, **19-22**, and **24-17** decreases by about 82-228 kJ / mol lower than that of the constituent initial components. Changes in the stability of endohedral clusters are relatively small (especially in terms of one atom of the fullerene C_{60} cluster).

4. Conclusion

DFT simulations of endohedral clusters **2-32** show their energy stability. We also have carried out non-empirical quantum chemical calculations of a number of potential agents for diagnosis and therapy of oncological diseases - fullerenol C_{60} derivatives (using the DFT method using the B3LYP / MIDI theory level) under the GAMESS program. Based on the calculations obtained (Tables 1 and 2), conclusions were drawn about their stability and the feasibility of their practical implementation.

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