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Models nanocomplexes based on C_{60} fullerene for creation of biologically active agents for medicine

S. P. Repetsky*,†, I. G. Vyshyvana*, H. M. Kuznietsova* and V. K. Rybalchenko*

*Institute of High Technologies,
Taras Shevchenko National University of Kyiv,
4-g Academician Glushkov Avenue, Kyiv 03022, Ukraine
†National University of Kyiv-Mohyla Academy,
2 Skovorody vul., Kyiv 04070, Ukraine

S. P. Kruchinin

Bogolyubov Institute for Theoretical Physics,
14-6 Metrolohichna Street, Kyiv 03143, Ukraine

O. I. Tykhoniuk, D. S. Milokhov and O. V. Khilya

Department of Chemistry, Taras Shevchenko National University of Kyiv,
12 Lva Tolstoho Street, Kyiv 01033, Ukraine

R. M. Melnyk‡

National University of Kyiv-Mohyla Academy,
2 Skovorody vul., Kyiv 04070, Ukraine
melnykrm@ukma.edu.ua

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Complex drugs based on C_{60} fullerence and pyrrole derivatives are promising for the development of antitumor and anti-inflammatory agents for use in targeted therapy, but have little efficiency in the synthesis of such complexes and have virtually no stable synthesis products with fullerene. The stability of the nanocomplex based on [60] PCBA and the intermediate compound based on "1*H*-pyrrole-2,5-dione" effective for the synthesis of targeted therapeutic agents was investigated by means of numerical calculations. The application of quantum-chemical methods in the Gaussian package establishes the stability of the nanocomplex at human body temperatures, the possibility of using such complexes for further study of the therapeutic properties of the individual components of the decomposition products of the nanocomplex.

Keywords: Modeling of nanocomplexes; quantum-mechanical methods; antitumor and anti-inflammatory agents; fullerene; pyrrole derivative.

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‡Corresponding author.

1. Introduction

Chronic inflammation is the basis of many pathologies, including malignancy genesis. Oxidative stress is one of the basic processes that underlie numerous inflammatory diseases and neoplasms.[1] Numerous studies have demonstrated the antineoplastic effects of natural antioxidants (vitamins, minor amino acids, polyunsaturated fatty acids, plant extracts) *in vitro*, but the effectiveness of these agents *in vivo* systems is highly doubtful.[2] On the other hand, compounds of artificial origin, in particular nanomaterials, have clearly defined properties and are involved in a limited number of cellular processes, which leads to their directional effect and more pronounced therapeutic effect.[3] Biocompatible water-soluble C_{60} fullerenes are able to efficiently capture free radicals and thus act as antioxidants, which causes their antitumor and anti-inflammatory properties,[4,5] in addition, they are nontoxic in *in vitro* and *in vivo* systems at physiological concentrations.[6] In Refs. 7–9, it was suggested that C_{60} fullerene molecules, due to the possibility of simple chemical manipulations with them, can be used for transport of biologically active compounds with other nanoparticles. Complexes of C_{60} fullerene with cytostatics have more potent biological action than cytostatics themselves, and less overall toxicity,[10] such structures are stable.

The pyrrole derivative 3-chloro-1-(4-chlorobenzyl)-4-((3-(trifluoromethyl)phenyl)amino)-1*H*-pyrrole-2,5-dione (MI-1) is a targeted inhibitor of protein kinases and exhibits antitumor and anti-inflammatory properties,[11,12] i.e. it is a potential therapeutic agent. Synthesis of C_{60} fullerene and pyrrole derivatives of structurally similar MI-1 have prospects for the development of antitumor and anti-inflammatory drugs. The coupling of pyrrole derivatives to fullerenes is not effective – low percentage yield, problematic synthesis of intermediate constituents, or low structural similarity to compound MI-1. For the development of the C_{60}-MI complex, attempts have been made to form covalent bonds between the structural fragments of C_{60}-fullerene and 1*H*-pyrrole-2,5-dione using a linker. As the structural fragment "1*H*-pyrrole-2,5-dione" was selected intermediate 8335 KH, Figs. 1(d)–1(e). This compound is structurally similar to MI-1 and is effective in the synthesis of compound 8335 KH and C_{60} fullerene with a "Linker" in the nanocomplex, Figs. 1(a) and 1(b). As the structural fragment "C_{60} fullerene"–"Linker" was selected: [60]PCBA ([6,6]-phenyl-C_{61}-butyric acid, CAS 161196-26-5), Figs. 1(g) and 1(h). In this work, we investigated the stability of the nanocomplex using numerical means. "C_{60}-fullerene"–"Linker" and "1*H*-pyrrole-2,5-dione" are moieties of nanocomplex C_{60}-MI ("C_{60}-fullerene"–"Linker"-"1*H*-pyrrole-2,5-dione").

In our work, based on the quantum-chemical method of molecular orbitals implemented in the Gaussian 09W software package,[13–16] we developed a method for modeling nanocomplex C_{60}-MI based on [60]PCBA and 8335 KH. The optimization of clusters was performed and the energy spectrum of electrons was calculated.

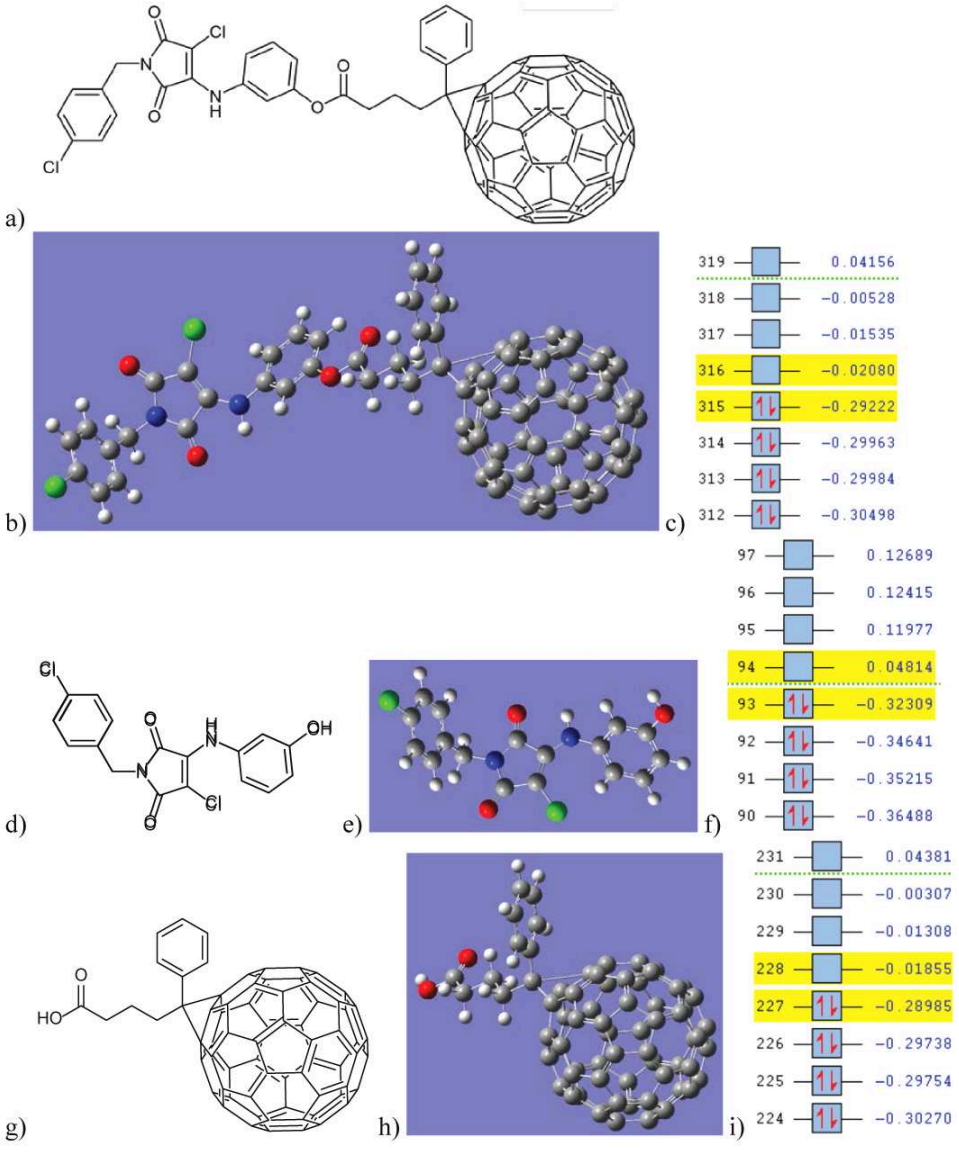

Fig. 1. (Color online) Structural-chemical formula (a) and spatial model (b) of C_{60}-MI nanocomplex based on [60]PCBA and 8335 KH. Gray balls represent carbon atoms, white ones are hydrogen, red ones are oxygen, green ones are chlorine, blue ones are nitrogen. (c) Energy values for the filled and unfilled molecular orbitals of the nanocomplex. Energy values are given in atomic units. (d)–(f) [60] 8335 KH compound, (g)–(i) [60]PCBA compound.

The energy of dissociation of the nanocomplex into possible constituents was calculated and the possibility of such dissociation is ascertaining. The stability of the nanocomplex was investigated.

The width of the energy gap [highest occupied molecular orbital–lowest unoccupied molecular orbital (HOMO–LUMO)] is determined between the energy values for HOMO and LUMO. The energy values of the filled and unfilled molecular orbitals and the width of the HOMO–LUMO gap can be used to determine the degree of dissociation of the nanocomplex by comparing the experimentally and theoretical obtained positions of the long-wave edge of absorption and luminescence.

2. Methods and Modelling Results

Energy values for the filled and unfilled molecular orbitals of the nanocomplex C_{60}-MI, 8335 KH, and [60]PCBA are shown in Figs. 1(c), 1(f), and 1(i) accordingly. Energy values are given in atomic units. The width of the HOMO–LUMO energy gap ΔE are given in Table 1 in atomic units and electron volt units. There are also calculated binding energy $E_{\text{bind.}}$ Appendix A shows the angles between the planes of the nanocomplex parts.

Energy of dissociation of nanocomplex into fragments is calculated by the formula

$$E_{\text{dis}} = E_{\text{bind}} - E_{\text{bind},1} - E_{\text{bind},2}\,,$$

where E_{bind}, $E_{\text{bind},1}$, E_{bind} are the binding energy nanocomplex and fragments, respectively.

Table 1. The width of the HOMO–LUMO energy gap ΔE and binding energy E_{bind}.

Compound	ΔE (a.u.)	ΔE (eV)	E_{bind} (a.u.)
C_{60}-MI	0.2714	7.39	−4646.894
8335 KH	0.3712	10.10	−2829.137
[60]PCBA	0.2713	7.38	−1893.352

The binding energy of nanocomplex (Table 1)

$$E_{\text{bind}} = E_{\text{bind,C60-MI}} = -4646.894 \text{ a.u.}$$

The spatial models of "C_{60}-fullerene"–"Linker" and "1H-pyrrole-2,5-dione" is shown in Fig. 2. The binding energy of "C_{60}-fullerene"–"Linker" is $E_{\text{bind},1} = -2754.039$ a.u. The binding energy of "1H-pyrrole-2,5-dione" is $E_{\text{bind},2} = -1892.760$ a.u. Energy of dissociation of nanocomplex into fragments is $E_{\text{dis}} = -0.095$ a.u. $= 2.58$ eV.

As shown by calculations using the Gaussian program, "C_{60}-fullerene"–"Linker" is unstable and attaches a hydroxide, the [60]PCBA molecule is formed, Fig. 1(h). The results of the calculation of such compound is binding energy $E_{\text{bind,[60]PCBA}}$ (Table 1). "1H-pyrrole-2,5-dione" is unstable and attaches a hydrogen atom, the 8335 KH compound is formed, Fig. 1(e). The result of the calculation of such

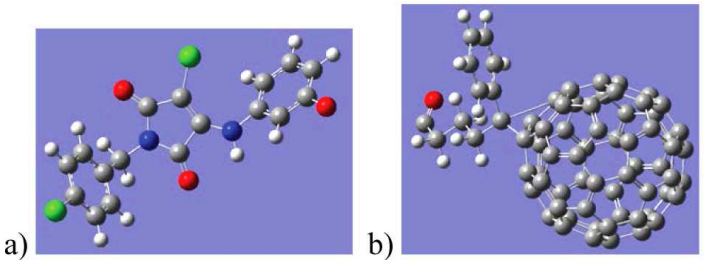

Fig. 2. (Color online) Spatial model: (a) "1H-pyrrole-2,5-dione"; (b) "C60-fullerene"–"Linker". Gray balls represent carbon atoms, white ones are hydrogen, red ones are oxygen.

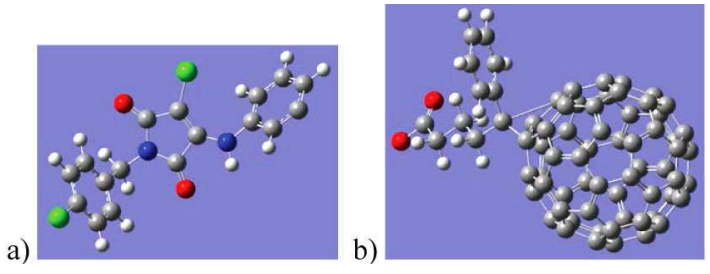

Fig. 3. (Color online) Spatial model: (a) "1H-pyrrole-2,5-dione" without oxygen; (b) "C60-fullerene"–"Linker" with oxygen. Gray balls represent carbon atoms, white ones are hydrogen, red ones are oxygen.

compound is binding energy $E_{\text{bind,8335 KH}}$ (Table 1). As can be seen from the above results, the dissociation energy of the nanocomplex into fragments "C_{60}-fullerene"–"Linker" and "1*H*-pyrrole-2,5-dione" is

$$E_{\text{dis}} = -0.0943 \text{ a.u.} = -2.57 \text{ eV}.$$

The average energy of thermal motion per atom at a temperature $T = 300$ K is $k_{\text{B}}T = 0.026$ eV. The results show that the $|E_{\text{dis}}| \gg k_{\text{B}}$ T module. This indicates that the nanocomplex is stable. Upon penetration into the tumor tissue, due to the low pH compared to the healthy tissue,[17] it is likely that a significant proportion of these complexes will dissociate and act in the tumor as two independent components, this is [60]PCBA and 8335 KH.

Another scheme of the dissociation process can be assumed. The spatial models of "C_{60}-fullerene"–"Linker" without oxygen atom and "1*H*-pyrrole-2,5-dione" with oxygen atom is shown in Fig. 3. In this case, calculated binding energies is

$$E_{\text{bind,1a}} = -2828.510 \text{ a.u. and } E_{\text{bind,2a}} = -1818.254 \text{ a.u.}$$

The dissociation energy of the nanocomplex into fragments "C_{60}-fullerene"–"Linker" without oxygen and "1*H*-pyrrole-2,5-dione" with oxygen is

$$E_{\text{dis,a}} = E_{\text{bind}} - E_{\text{bind,1a}} - E_{\text{bind,2a}} = -0.129 \text{ a.u.} = -3.51 \text{ eV}.$$

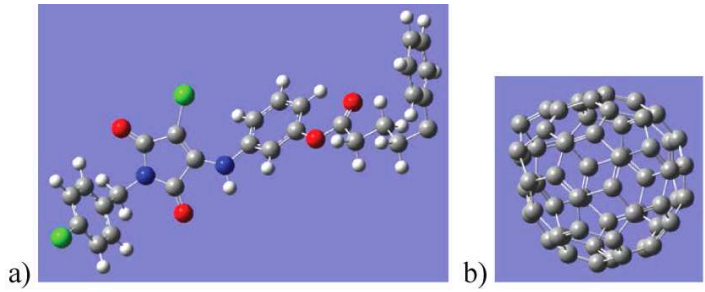

Fig. 4. (Color online) Spatial model: (a) "Linker"–"1H-pyrrole-2,5-dione"; (b) "C60-fullerene". Gray balls represent carbon atoms, white ones are hydrogen, red ones are oxygen.

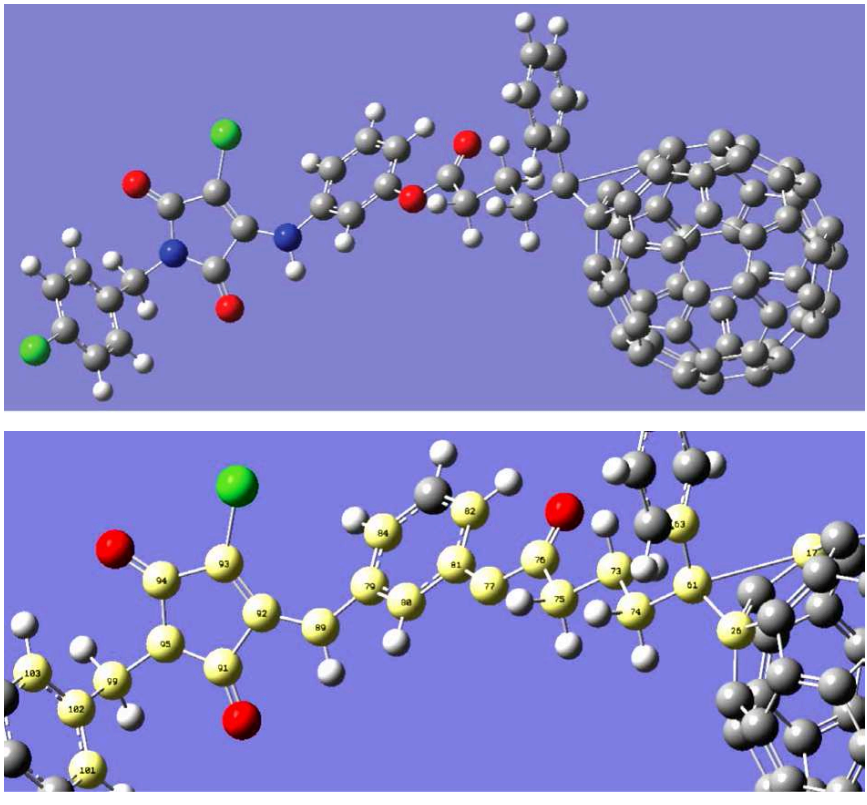

Fig. 5. (Color online) Angle_80_81_77 = 113.92, Angle_82_81_77 = 125.14, Angle_81_77_76 = 128.16, Angle_77_76_75 = 109.43; Angle_26_61_17 = 70.37, Angle_63_61_17 = 92.31, Angle_74_61_26 = 117.52, Angle_63_61_26 = 117.15, Angle_74_61_17 = 139.77, Angle_63_61_26 = 117.15.

Dissociation energy $|E_{\mathrm{dis,a}}|$ by absolute value is significantly greater than $|E_{\mathrm{dis}}|$. Another case is dissociation nanocomplex C_{60}-MI on moieties "C_{60}-fullerene" and "Linker"–"1*H*-pyrrole-2,5-dione" shown in Fig. 4.

Received values binding energy of "C_{60}-fullerene", binding energy of "Linker"–"1*H*-pyrrole-2,5-dione," and dissociation energy accordingly are

$$E_{\text{bind,1b}} = -2258.998 \text{ a.u. and } E_{\text{bind,2b}} = -2387.717 \text{ a.u.}$$

$$E_{\text{dis,b}} = -4.87 \text{ a.u.} = -15.6 \text{ eV}.$$

Dissociation energy $|E_{\text{dis,b}}|$ by absolute value is much greater than $|E_{\text{dis,a}}|$ or $|E_{\text{dis}}|$. Decomposition into "C60-fullerene"–"Linker" and "1*H*-pyrrole-2,5-dione" to form [60]PCBA and 8335 KH compounds is more likely than decomposition into "C60-fullerene" and "Linker"–"1*H*-pyrrole-2,5-dione".

3. Conclusions

Based on the above results, it can be argued when nanocomplexes penetrate the tumor tissue through a low pH (higher acidity) compared to healthy tissue a significant part of these complexes will dissociate. In the tumor will be act two independent components PCBA (C_{60} fullerence) and 8335 KH compounds. Nanocomplex is transport means but each separated part, fullerene and piroll derivative, has therapeutic effect. The main anticancer and anti-inflammatory action relies on 8335 KH compound.

Acknowledgments

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Appendix A

Angles between the planes of the nanocomplex parts (Fig. 5). Angle between the planes 80-81-82 and 81-77-76 is 0.72° (0.0125 rad), angle between the planes 63-61-74 and 17-61-25 is 67.51° (1.1783 rad).

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