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Models of Nanocomplexes Based on C_{60} Fullerene for Creation of Anticancer and Anti-Inflammatory Agents

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Based on the quantum-chemical method of molecular orbitals, implemented in the Gaussian 09w software package, a method of modelling nanocomplexes for creation of antitumour and anti-inflammatory medicines is developed. The object of study is a complex of C_{60} fullerene and antitumour agent 1-(4-C1-benzyl)-3-C1-4-(CF_3-phenylamino)-1H-pyrrole-2,5-dione (abbreviated as MI-1). Each detached part, C_{60} and MI-1, has a therapeutic effect. The main antitumour and anti-inflammatory action relies on MI-1 compound. It is found that the nanocomplex of C_{60} fullerene with MI-1 is stable at human-body temperature. The nanocomplex is able to serve as a vehicle of medicines to the tumour tissue and dissociate in the tumour due to its low pH (higher acidity) compared to healthy tissue and exhibit therapeutic properties of individual components.

На основі квантово-хемічної методи молекулярних орбіталей, реалізованої в пакеті програм Gaussian 09w, розвинуто методу моделювання нанокомплексів для створення антипухлинних і протизапальних медичних препаратів. Об'єктом дослідження є комплекс фуллерена C_{60} і протипухлинний засіб 1-(4-C1-бензил)-3-C1-4-(CF_3-феніламіно)-1H-пірол-2,5-діон (інша назва — MI-1). Кожна відокремлена частина, C_{60} і сполука MI-1, мають терапевтичну дію. Основна протипухлинна та протизапальна дія покладається на сполуку MI-1. Було встановлено, що нанокомплекс фуллерена C_{60} зі сполукою MI-1 є стабільним за температури тіла людини. Нанокомплекс здатний слугувати носієм лікарських засобів до ушкодженої тканини та дисоціювати в пухлині завдяки низькому pH (більш високій кислотності) порівняно зі здоровою тканиною, проявляти терапевтичні властивості окремих компонентів.

Key words: modelling of nanocomplexes, quantum-mechanical methods, anticancer and anti-inflammatory agents, fullerene, pyrrole derivative.

Ключові слова: моделювання нанокомплексів, квантово-механічні методи, антипухлинні та протизапальні медичні препарати, фуллерен, похідна піролу.

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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 *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 that cause their antitumour and anti-inflammatory properties [4, 5]. In addition, they are non-toxic 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, could 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 1-(4-Cl-benzyl)-3-Cl-4-(CF_3-fenylamino)-1H-pyrrol-2,5-dione (MI-1) is a targeted inhibitor of protein kinases and exhibits antitumour and anti-inflammatory properties [11, 12], *i.e.*, is a potential therapeutic agent. Therefore, the authors made the assumption regarding the potential prospect of a C_{60} fullerene-based composition and MI-1 compound for the development of antitumour and anti-inflammatory drugs.

In our work, based on the quantum-chemical method of molecular orbitals implemented in the Gaussian 09w software package [13], we developed a method for modelling nanocomplexes based on C_{60} fullerene and pyrrole derivatives on sample 1-(4-Cl-benzyl)-3-Cl-4-(CF_3-fenylamino)-1H-pyrrol-2,5-dione. The calculations are based on density functional theory modelling of electronic structure of mul-

tielectron systems.

RESULTS

The structural formula of C_{60} fullerene with pyrrole derivative MI-1 is shown in Fig., *a*. The geometrical optimization of clusters was performed; the energy spectrum of electrons was calculated, and the binding energy of the cluster was calculated (DFT, STO-3G) [13]. The binding energy of nanocomplex of C_{60} fullerene with MI-1 compound is as follows:

$$E_{bind} = -3922.26 \text{ a.u.}$$

The width of the energy gap (HOMO–LUMO) is determined by difference between the energy values for the upper unoccupied molecular orbit (HOMO) and the lower occupied molecular orbit (LUMO). The energy values given in atomic units for the filled and unfilled molecular orbitals of nanocomplex are shown in Fig., *b*. The width of the HOMO–LUMO energy gap is

$$\Delta E = 0.1867 \text{ a.u.} \approx 5.079 \text{ eV}.$$

The geometrical optimization of C_{60} fullerene was performed and the energy spectrum of electrons was calculated. The binding energy of C_{60} is as follows:

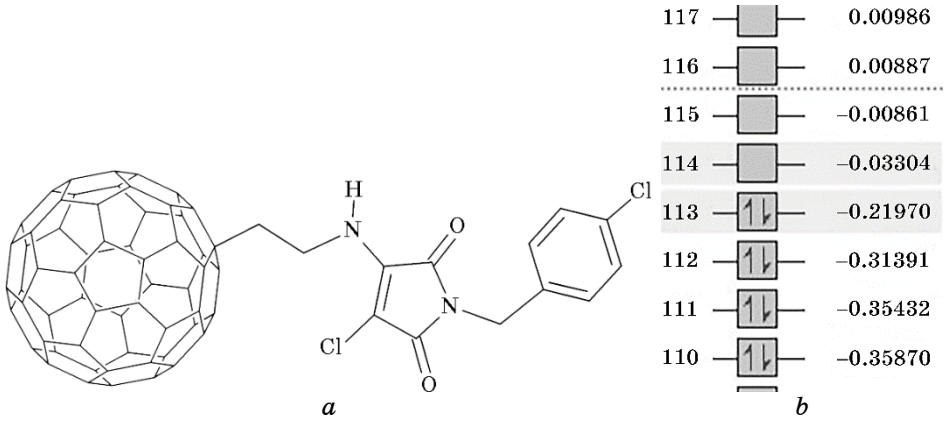

Fig. (*a*) Structural formula of C_{60} fullerene with pyrrole derivative MI-1; (*b*) energy values for the filled and unfilled molecular orbitals of nanocomplex; the energy values are given in atomic units.

$$E_{bind}^{(1)} = -2259.03 \text{ a.u.}$$

The energy values for filled and unfilled molecular orbitals of C_{60} determined, the width of the HOMO–LUMO energy gap is

$$\Delta E = 0.28288 \text{ a.u.} \approx 7.6974 \text{ eV}.$$

The geometrical optimization of MI-1 compound was performed and the energy spectrum of electrons was calculated. The binding energy of MI-1 compound is as follows:

$$E_{bind}^{(2)} = -1663.29 \text{ a.u.}$$

The energy values for the filled and unfilled molecular orbitals of MI-1 compound was determined, and the width of the HOMO–LUMO energy gap is

$$\Delta E = 0.0450 \text{ a.u.} \approx 1.225 \text{ eV}.$$

The dissociation energy of the C_{60} fullerene nanocomplex with MI-1 compound was calculated by the formula

$$E_{dis} = E_{bind} - E_{bind}^{(1)} - E_{bind}^{(2)}.$$

From the above results, it follows that the dissociation energy of the nanocomplex with the separation of C_{60} from compound MI-1 is

$$E_{dis} = -0.00662 \text{ a.u.} \approx -0.18 \text{ eV}.$$

DISCUSSION

The average energy of thermal motion per atom at a temperature $T = 300$ K is $k_B T = 0.026$ eV. The results show that modulo $|E_{dis}| >> k_B T$. This indicates that the nanocomplex C_{60} with MI-1 is stable. Based on the above results, it can be argued when nanocomplexes penetrate the tumour tissue through a low pH (higher acidity) compared to healthy tissue [14]; a significant part of these complexes will dissociate. In the tumour, two independent components C_{60} and MI-1 will be act. Nanocomplex is transport means, but each separated part, fullerene and MI-1 compound, has therapeutic effect. The main anticancer and anti-inflammatory action relies on MI-1 compound.

Energy values of the filled and unfilled molecular orbitals and HOMO–LUMO gap width can be used to determine the degree of dissociation of the nanocomplex C_{60} molecule with the MI-1 com-

pound by comparing experimentally obtained positions of the long-wave edge of absorption and luminescence of cells with the width of the gap HOMO–LUMO.

REFERENCES

1. S. Reuter, S. C. Gupta, M. M. Chaturvedi, and B. B. Aggarwal, *Free Radic. Biol. Med.*, **49**, No. 11: 1603 (2010); https://doi.org/10.1016/j.freeradbiomed.2010.09.006
2. Zh. Wang, Zh. Li, Ya. Ye, L. Xie, and W. Li, *Oxid. Med. Cell Longev.*, **2016**: 7891574 (2016); http://dx.doi.org/10.1155/2016/7891574
3. A. Medhat, S. Mansour, S. El-Sonbaty, E. Kandil, and M. Mahmoud, *Tumour Biol.*, **39**, No. 7: 1010428317717259 (2017); https://doi.org/10.1177/1010428317717259
4. I. V. Byelinska, H. M. Kuznietsova, N. V. Dziubenko, O. V. Lynchak, Yu. I. Prylutskyy, O. A. Kyzyma, O. Ivankov, V. K. Rybalchenko, and U. Ritter, *Mat. Sci. Eng. C*, **93**: 505 (2018); https://doi.org/10.1016/j.msec.2018.08.033
5. O. V. Lynchak, Yu. I. Prylutskyy, V. K. Rybalchenko, O. A. Kyzyma, D. Soloviov, V. V. Kostjukov, M. P. Evstigneev, U. Ritter, and P. Scharff, *Nanoscale Res. Lett.*, **12**, No. 8: 1 (2017); https://doi.org/10.1186/s11671-016-1775-0
6. S. V. Prylutska, O. P. Matyshevska, I. I. Grynyuk, Yu. I. Prylutskyy, U. Ritter, and P. Scharff, *Mol. Cryst. Liq. Cryst.*, **468**, No. 1: 265 (2007); https://doi.org/10.1080/15421400701230105
7. A. Montellano, T. Da Ros, A. Bianco, and M. Prato, *Nanoscale*, **3**: 4035 (2011); doi:10.1039/c1nr10783f
8. C.-M. Lin, and T.-Y. Lu, *Recent Patents on Nanotechnology*, **6**: 105 (2012); doi:10.2174/187221012800270135
9. M. M. Mędrek, F. Pluciński, and A. P. Mazurek, *Acta Poloniae Pharmaceutica – Drug Research*, **70**, No. 4: 659 (2013); https://www.ptfarm.pl/download/?file=File%2FActa_Poloniae%2F2013%2F4%2F659.pdf
10. R. R. Panchuk, S. V. Prylutska, V. V. Chumak, N. R. Skorokhyd, L. V. Lehka, M. P. Evstigneev, Yu. I. Prylutskyy, W. Berger, P. Heffeter, P. Scharff, U. Ritter, and R. S. Stoika, *J. Biomed. Nanotechnol.*, **11**, No. 7: 1139 (2015); https://doi.org/10.1166/jbn.2015.2058
11. H. M. Kuznietsova, O. V. Lynchak, M. O. Danylov, I. P. Kotliar, and V. K. Rybal'chenko, *Ukr. Biochem. J.*, **85**, No. 3: 74 (2013); http://dx.doi.org/10.15407/ubj85.03.074
12. H. M. Kuznietsova, M. S. Yena, I. P. Kotlyar, O. V. Ogloblya, and V. K. Rybalchenko, *The Scientific World Journal*, **2016**: 2145753 (2016); http://dx.doi.org/10.1155/2016/2145753
13. J. Foresman and A. Frisch, *Exploring Chemistry with Electronic Structure Methods* (Wallingford, CT: Gaussian Inc.: 2015).
14. J. L. Wike-Hooley, J. Haverman, and H. S. Reinhold, *Radiother. Oncol.*, **2**: 343 (1997); https://doi.org/10.1016/S0167-8140(84)80077-8