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Models of Nanostructures Based on Titanium Dioxide TiO_2 for Transport of Biologically Active Compounds

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Using the density functional theory to quantum-mechanical calculations in the Gaussian 09w software package, antitumor drug of target action on the basis of titanium dioxide and pyrrole derivative 1-(4-Cl-benzyl)-3-Cl-4-(CF_3-fenylamino)-1H-pyrrol-2.5-dione (chemical compound MI-1) is simulated. MI-1 compound has high therapeutic potential as an antitumor agent. Titanium dioxide is insoluble in the stomach and used as a filler and sheath of medicines. There is reason to use TiO_2 to transport MI-1 to the site of the affected tissue for targeted effect on colorectal tumours. Computational tools of the software package reveal that titanium dioxide TiO_2 together with MI-1 forms a stable nanocomplex. Upon penetration into the tumour tissue, due to the low pH in comparison with healthy tissue, a significant proportion of these nanocomplexes will be dissociate with the separation titanium dioxide and MI-1 compound that will be have a therapeutic effect on damage tissue.

Застосуванням теорії функціоналу густини до квантово-механічних обчислень у пакеті програм Gaussian 09w виконано моделювання нанокомплексу антипухлинного препарату тарґетної дії на основі діоксиду титану та похідної піролу 1-(4-Cl-бензил)-3-Cl-4-(CF_3-феніламін)-1H-пірол-2,5-діон (хемічна сполука MI-1). Сполука MI-1 має високий терапевтичний потенціял як протипухлинний засіб. Діоксид титану TiO_2 не розчиняється у шлунку, застосовується в якості наповнювачів і оболонок медичних препаратів. Є підстави використати TiO_2 для транспорту MI-1 до місця ураженої тканини для цільового впливу на колоректальні пухлини. Обчислювальними засобами програмного пакету встановлено, що діоксид титану TiO_2 разом з MI-1 утворює стабільний нанокомплекс. При проникненні у тканину пухлини, завдяки пониженому pH у порівнянні зі здоровою

тканиною, значна частина нанокомплексів буде дисоціювати з відокремленням від діоксиду титану похідної піролу MI-1, яка і буде спричиняти терапевтичну дію на уражену ділянку тканини.

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

Ключові слова: моделювання нанокомплексів, квантово-механічні методи, антипухлинні протизапальні медичні препарати, діоксид титану, пірол.

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Targeted therapy is an undoubted achievement of medical oncology in recent years. The use of means of directed action can selectively inhibit the growth of tumours with minimal damage to healthy body tissues. The most common targeting agents are antibodies against basic proteins of signalling pathways (usually protein kinases) that are overexpressed in a malignant cell, or low molecular weight compounds that are inhibitors of these proteins [1]. The former are highly specific, while the latter cover a wider range of targets, are easier to use and less expensive to manufacture [2]. However, since action of these agents also have an effect on healthy cells and the use of these antitumor agents is systemic, the side effects of therapy cannot be avoided, although they are certainly weaker and less critical than traditional chemotherapy [3]. One of the advantages of low molecular weight protein kinase inhibitors is the possibility of their oral administration. This method allows targeted delivery of the agent to the tumour in the digestive tract that reduces the burden of drug loading on other organs and systems. However, the development of targeted delivery systems to a specific section of the digestive tube with the possibility of local and prolonged release of the therapeutic agent is extremely small [4].

The pyrrole derivative 1-(4-Cl-benzyl)-3-Cl-4-(CF_3-fenylamino)-1H-pyrrol-2,5-dione (named MI-1) has a high therapeutic potential for the correction of colon cancer [5, 6]. Titanium dioxide TiO_2 in its properties is insoluble in the stomach that gives grounds for its use for the transport of therapeutic compounds, in particular, of MI-1 compounds, to the colon to correct its pathologies, including malignant ones.

Nanoparticles of metals and their oxides smaller than 10 nm in size are systems with excess energy and high chemical activity. Particles of about 1 nm with virtually no activation energy enter the aggregation processes leading to the formation of metal nanoparticles, and in reactions with other chemical compounds, cause the formation of substances with new properties. The conserved energy of such objects is noted, first of all, by the uncompensated bonds between surface and near-surface atoms. The latter can cause new unusual surface phenom-

ena and reactions.

Among the well-known metal oxide nanoparticles are titanium dioxide (chemical formula TiO_2) based complexes that can be used to transport the agent to a particular area of damage. Titanium dioxide is widely used as a component in the shell of medicines, heterogeneous catalyst, photocatalyst [7], and is used as a food colouring. It has E number E171.

At present, many studies are devoted to the study of the effect of TiO_2 on human and laboratory animals. Nanoparticles based on titanium dioxide are capable of forming agglomerations with proteins, which also gives grounds to consider it a good candidate for transport to the affected area [8].

In our work, on the basis of the quantum-chemical method of molecular orbitals, implemented in the Gaussian 09w software package [9], a method for modelling nanocomplexes for the transport of antitumor and anti-inflammatory agents is developed. The geometrical optimization of clusters was performed and the energy spectrum of electrons was calculated. The binding energy of the clusters was calculated [9]. The width of the energy gap (HOMO–LUMO) is determined between the energy values for highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO).

Simulations were performed for nanocomplexes based on anatase, one of the mineral forms of titanium dioxide. Anatase is a metastable mineral form at all temperatures and pressures; it is stable near room temperature. Nevertheless, anatase is often the first titanium dioxide phase to form in many processes due to its lower surface energy. The (101) plane of anatase is the most thermodynamically stable surface and, thus, is the most widely exposed facet in natural and synthetic anatase [10].

The structural formula of anatase and MI-1 compound are shown in Fig. 1, *a*. The energy values are given in atomic units for filled and unfilled molecular orbitals of nanocomplex are shown in Fig. 1, *b*. The width of the HOMO–LUMO energy gap (Fig. 1, *b*):

$$\Delta E = 0.00457 \text{ a.u.} \approx 0.1243 \text{ eV}.$$

The binding energy of nanocomplex TiO_2 with MI-1:

$$E_{bind} = -12549.13 \text{ a.u.}$$

The anatase nanocluster, mineral form of titanium dioxide, is shown in Fig. 2, *a*. The nanocluster consists of 33 atoms: 11 atoms of titanium and 22 atoms of oxygen. The width of the HOMO–LUMO energy gap:

$$\Delta E = 0.05479 \text{ a.u.} \approx 1.4903 \text{ eV}.$$

The binding energy of the TiO_2 nanocluster is equal:

$$E_{bind}^{(1)} = -10864.14 \text{ a.u.}$$

The structural formula of pyrrole derivative MI-1 is shown in Fig. 2, *b*. The width of the HOMO–LUMO energy gap:

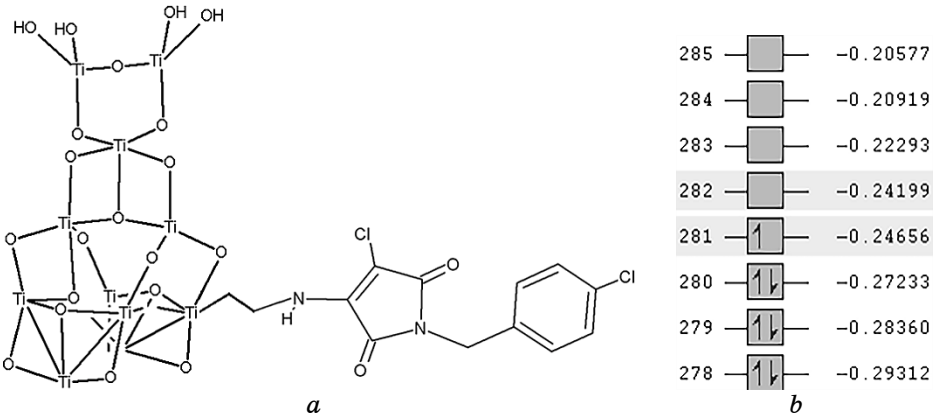

Fig. 1. (*a*) The structural formula of TiO_2 (anatase) with 1-(4-Cl-benzyl)-3-Cl-4-(CF_3-fenylamino)-1H-pyrrol-2,5-dione; (*b*) energy values for filled and unfilled molecular orbitals of nanocomplex; the energy values are given in atomic units.

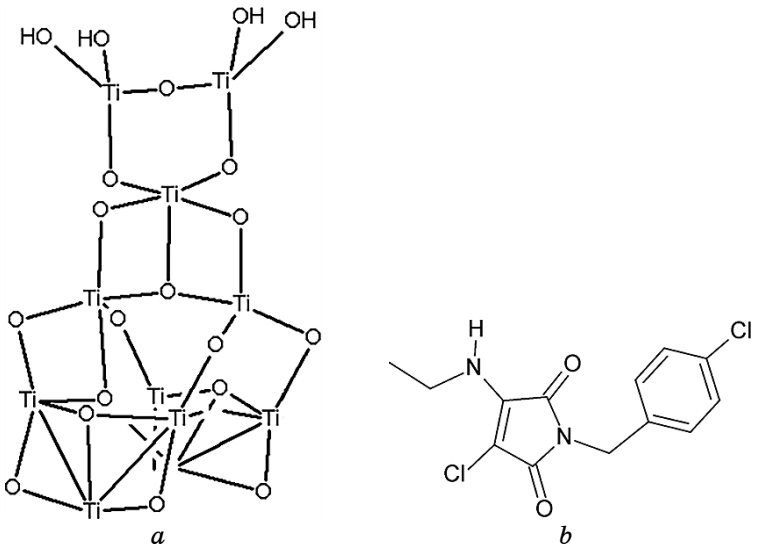

Fig. 2. (*a*) The structural formula of anatase; (*b*) the structural formula of 1-(4-Cl-benzyl)-3-Cl-4-(CF_3-fenylamino)-1H-pyrrol-2,5-dione.

$$\Delta E = 0.0171 \text{ a.u.} \approx 0.4651 \text{ eV}.$$

The binding energy of compound MI-1:

$$E_{bind}^{(2)} = -1681.06 \text{ a.u.}$$

The dissociation energy of the anatase nanocomplex TiO_2 with the pyrrole derivative MI-1 is 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 a nanocomplex with TiO_2 separation from MI-1 is

$$E_{dis} = -3.93 \text{ a.u.} \approx -106.9 \text{ eV}.$$

The average energy of thermal motion per atom at a temperature $T = 300$ K is $k_B T = 0.026$ eV, magnitude of the dissociation energy $|E_{dis}| >> k_B T$. This indicates that the nanocomplex is stable. Upon penetration into the tumour tissue, due to the low pH compared to the healthy tissue [12], it is likely that a significant proportion of these nanocomplexes will dissociate with the separation of titanium dioxide TiO_2 from compound MI-1. In this case, the latter will cause a therapeutic effect on the tumour.

The energy values of filled and unfilled molecular orbitals and HOMO–LUMO slit width can be used to determine the degree of dissociation of titanium dioxide nanocomplex TiO_2 with compound MI-1 by comparing experimentally obtained positions of the longwave edge of absorption and luminescence values HOMO–LUMO.

REFERENCES

1. D. E. Gerber, *Am. Fam. Physician*, **77**, No. 3: 311 (2008).
2. F. Broekman, E. Giovannetti, and G. J. Peters, *World J. Clin. Oncol.*, **2**, No. 2: 80 (2011); https://dx.doi.org/10.5306/wjco.v2.i2.80
3. E. Elez, T. Macarulla, and J. Tabernero, *Annals of Oncology*, **19**, No. 7: vii146 (2008); https://doi.org/10.1093/annonc/mdn476
4. A. Bose, A. Elyagoby, and T. W. Wong, *Int. J. Pharm.*, **468**, Nos. 1–2: 178 (2014); https://doi.org/10.1016/j.ijpharm.2014.04.006
5. L. V. Garmanchuk, E. O. Denis, V. V. Nikulina, O. I. Dzhus, O. V. Skachkova, V. K. Ribalchenko, and L. I. Ostapchenko, *Biopolym Cell*, **29**, No. 1: 70 (2013); http://dx.doi.org/10.7124/bc.000808
6. 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
7. U. Diebold, *Surface Science Reports*, **48**, Nos. 5–8: 53 (2003);

https://doi.org/10.1016/S0167-5729(02)00100-0
8. N. S. Aliakhnovich and D. K. Novikov, *Immunopathology, Allergology, Iinfectology*, **1**: 37 (2016); doi: 10.14427/jipai.2016.1.37
9. J. Foresman and A. Frisch, *Exploring Chemistry with Electronic Structure Methods (3rd ed.)* (Wallingford, CT: Gaussian, Inc.: 2015).
10. M. Hussein N. Assadi and Dorian A. H. Hanaor, *Applied Surface Science*, **387**: 682 (2016); https://doi.org/10.1016/j.apsusc.2016.06.178
11. S.-D. Mo and W. Ching, *Physical Review B*, **51**, No. 19: 13023 (1995); https://doi.org/10.1103/PhysRevB.51.13023
12. 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