Рак поджелудочной железы считается одним из наиболее агрессивных видов онкологических заболеваний. Даже при отсутствии биологических предпосылок для быстрого развития злокачественного процесса, локализация этого органа создает трудности в лечении. Даже небольшая опухоль поджелудочной железы вовлекает в патологический процесс важные структуры живота, требуя обширных хирургических операций. Один из единственных способов обеспечить продолжительную жизнь пациента – это операция, которая в некоторых случаях дополняется химиотерапией до или после хирургического вмешательства. Однако необходимость применения химиотерапии возникает практически всегда, за исключением случаев, когда пациент находится в слишком тяжелом состоянии. Если на первом этапе проведение операции невозможно, то пациенту предлагается длительное химиотерапевтическое лечение, успех которого определяет возможность последующей операции. В целом, сравнительный анализ подчеркивает различия в физико-химических свойствах и фармакокинетике у гемцитабина, фторурацила и эрлотиниба, которые могут влиять на их эффективность, безопасность и пригодность для фармацевтических применений.

В зависимости от конкретных требований, таких как целевая активность, биодоступность, токсичность и др., каждое из рассмотренных соединений может быть использовано в клинической практике. Например, эрлотиниб, благодаря своей липофильности и целевой активности, может быть предпочтительным в лечении определенных видов рака, в то время как гемцитабин и фторурацил, с их высокой растворимостью в воде, могут быть предпочтительными для лечения других заболеваний, где важна хорошая растворимость в воде. Препараты обладают высоким поглощением через желудочно-кишечный тракт, и низкой способностью проникновения через гематоэнцефалический барьер. Гемцитабин и фторурацил не влияют на ферменты цитохрома Р450. Кроме того, константы распределения в коже для всех препаратов отрицательны, что может указывать на низкую скорость проникновения через кожу.

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INVESTIGATION OF CHARGE TRANSFER INTERACTION BETWEEN TRIMETHOPRIM WITH PICRIC ACID WITH DENSITY FUNCTIONAL THEORY

ИССЛЕДОВАНИЕ ВЗАИМОДЕЙСТВИЯ ПЕРЕНОСА ЗАРЯДА МЕЖДУ ТРИМЕТОПРИМОМ И ПИКРИНОВОЙ КИСЛОТОЙ МЕТОДОМ ТЕОРИИ ФУНКЦИОНАЛА ПЛОТНОСТИ

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This article presents the ground state structure and CT transition of the complex generated by the reaction of picric acid (PA) with the Trimethoprim (TMP) were theoretically investigated by density functional theory (DFT).

С помощью теории функционала плотности (DFT) была теоретически изучена структура основного состояния и CT-переход комплекса, возникающего в результате реакции пикриновой кислоты (PA) с триметоприм (TMP).

Keywords: PM6, TD-DFT, UV/Vis spectrum.

Ключевые слова: PM6, TD-DFT, УФ спектр.

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With the widespread use of pesticides, the residual problem of pesticides in the environment has been widely concerned by environmental scientists. Trimethoprim (TMP) is widely used in clinical medicine and veterinary animal husbandry, and in agriculture as an effective herbicide [1]. Trimethoprim easily accumulates in ecosystems, adversely affecting aquatic organisms and sometimes even leading to chronic toxicity.

Materials and Equipment. Picric acid, also known as 2,4,6-trinitrophenol, is a yellow crystalline solid compound with the chemical formula $C_6H_3N_3O_7$. It is a powerful and highly explosive compound when in its pure form or in concentrated solutions. Picric acid has been historically used as a yellow dye and as an antiseptic. It has also been employed in the manufacturing of explosives and munitions due to its explosive properties. However, due to its sensitivity and potential hazards, its use has been largely restricted or replaced by safer alternatives in many applications. It's important to handle picric acid with extreme care due to its explosive nature, and proper safety precautions should be taken when working with it. Trimethoprim is an antibiotic medication commonly used to treat various bacterial infections. It works by inhibiting the production of tetrahydrofolic acid, which is essential for the synthesis of DNA and proteins in bacteria. By blocking this process, trimethoprim effectively stops the growth and multiplication of bacteria, helping the body's immune system to fight off the infection.

Trimethoprim is often used in combination with sulfamethoxazole in a fixed ratio (co-trimoxazole or TMP-SMX) to create a synergistic effect that enhances their antibacterial activity. This combination is frequently prescribed for treating urinary tract infections, respiratory tract infections, and other bacterial infections. As with any antibiotic, it's important to take trimethoprim exactly as prescribed by a healthcare provider and to complete the full course of treatment to ensure the infection is completely eradicated. It's also essential to be aware of any potential side effects and to consult a doctor if any adverse reactions occur during treatment.

Picric acid (PA; $C_6H_3N_3O_7$; 229.10; purity ≥99%) was obtained by Sigma-Aldrich Chemical Co. Ciprofloxacin; chemical name: 5-((3,4,5-Trimethoxyphenyl) Methyl)-2,4-Pyrimidinediamine; (TMP; $C_{14}H_{18}N4O_3$; 290.32). All chemical used in this study were of analytical reagent grade. Experimental UV/Vis spectrum of the compound was recorded on UV-Visible Spectrophotometer Cary 300 (Varian, USA). Experimental IR-spectrum of the synthesized compound was recorded in the frequency region 400-4000 cm^{-1} on a Spectrophotometer of Protégé 460 (Nicolet, US). Trans-cis (E→Z) isomerization of structures was studied using unfiltered radiation of high-pressure Hg-lamp DRSH-1000 (Belarus). The intensity of light falling perpendicular to the surface of the sample was 0.009 W/cm2. At exposure temperature of sample was 20-22 °C.

Computational Details. All computational studies were carried out on personal computers using density functional theory (DFT) DFT/B3LYP was used to calculate the structure and vibration assignment of the TMP-PA complex in the ground state. A Pentium IV personal computer (CPU at 4.80 GHz) with the Windows 10 operating system was used. The initial geometry optimization of title compounds was performed with HyperChem (Version 8.0 Hypercube, Inc., Alberta, Canada). For all the ab initio calculations, Gaussian 16 was employed. The molecular properties of the compounds were calculated by TDB3LYP/6-31G method [1]. Lowest energy structures of the species were computed by conformational analysis. Geometry optimization was performed at the M052X density functional theory with the same basis set. For the geometry optimization of parent molecules restricted approach was applied, while for the free radicals the unrestricted was used. The IEFPCM (Integral Equation Formalism Polarized Continuum Model) [2] was used for calculations of the solvent effect. It employs a molecule shaped cavity composed of spheres centered on the nuclei, while the reaction field is modeled by placing charges on the cavity surface.

Results and discussion

Geometric parameters and spectral characteristics. In addition, the optimal bond length of the complex was obtained by DFT/B3LYP method in the gas phase. The corresponding atoms were O59 and H27, and the bond size was 2.55Å. The theoretical absorption spectra of the complex were calculated by TDB3LYP/6-31G method. In the electronic spectrum, the scale factor was calculated as 0.96. The precise absorption wavelength of the complex was detected in a relatively small computational time using the TDDFT method, as shown in Table 2. Electron transitions, vibrator intensities and their energies at specific wavelengths calculated from the ground state geometry.

The results showed that the excited state at 290.10 nm corresponds to seven single electron excitation configurations 138→ 143,138 → 144,138 → 145,139 → 143,139 →145, and 142→145. The formation of the absorption band at 290.10 nm was attributed to the excitation of electrons from 138 MO to 143 MO. The excited state at 260.05nm corresponded to seven single-electron excitation configurations 128→ 144,131 → 144,132 → 143, 133 → 143,135 →143, and 138→143. The formation of the absorption band at 260.05 nm was attributed to the excitation of electrons from 135 MO to 144 MO.

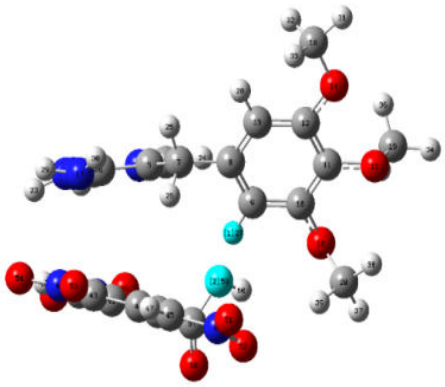

Figure 1 – Optimized ground state geometric structure of the TMP-PA complex in the gas phase

Energy calculation. LUMO-HOMO analysis is a method in quantum chemistry used to study the energy levels of molecules. HOMO (Highest Occupied Molecular Orbital) represents the highest energy level occupied by electrons in a molecule, while LUMO (Lowest Unoccupied Molecular Orbital) is the lowest energy level available for electrons.

LUMO-HOMO analysis helps to determine various properties of a molecule, such as its stability, reactivity, and optical properties. This method is also used to predict chemical reactions and molecular interactions. Studying LUMO-HOMO transitions can aid in understanding how different chemical processes occur, such as addition reactions, photochemical reactions, and others. This analysis is an important tool in the study of organic chemistry compounds and other molecules. HOMO-LUMO analysis of the TMP-PA complex was performed at the B3 LYP/6-31 G theoretical level (Figure 2). Wave function analysis indicated that LUMO-HOMO value was calculated as HOMO energy =-5.90 eV, LUMO energy =-3.48 eV, LUMO-HOMO gap = 2.442eV. Using HOMO and LUMO energies, the energies of different orbitals of the TMP-PA complex frontier molecular orbitals were also calculated and shown in Table 2.

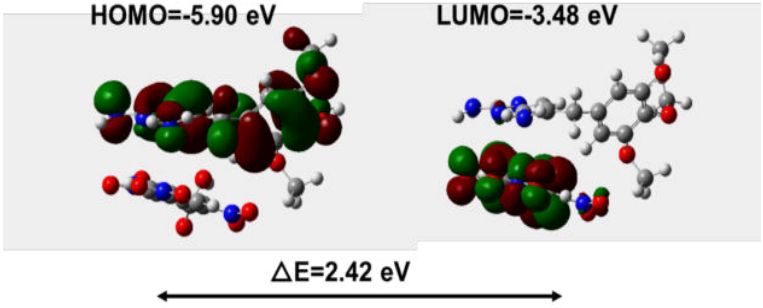

Figure 2 – HOMO LUMO plot of the TMP-PA CT complex

Table 2

LUMO–HOMO energy, total energy and dipole moment of Cip-PA CT complex by DFT/B3LYP/6-31G method*

Energies	DFT/B3LYP/6-31G*
E_{HOMO} (eV)	-5.90
E_{LUMO} (eV)	-3.48
E_{HOM}–E_{LUMO} (eV)	2.42
Total energy (au)	-2022.32
Dipole moment (debyes)	X=-1.157 Y=-5.046 Z=1.494

In summary, the molecular orbitals showed that the electron density in HOMO was mainly concentrated on the benzene ring (the hydroxyl group and the two nitro groups), while the electron density in LUMO was mainly concentrated on the entire benzene ring.

Mulliken Analysis. Mulliken Analysis is a method in quantum chemistry used to analyze the electron distribution in molecules. It was developed by Robert S. Mulliken and is based on the concept of molecular orbitals. In Mulliken Analysis, the electron density of a molecule is partitioned into atomic contributions, allowing for the calculation of atomic charges and population analysis. By performing Mulliken Analysis, researchers can gain insights into the distribution of electrons within a molecule, identify the electron density around specific atoms, and understand the nature of chemical bonding. This method provides valuable information about the reactivity and properties of molecules, helping to predict

their behavior in various chemical reactions. Mulliken Analysis is widely used in computational chemistry to study molecular structures, reactivity, and electronic properties. It is a fundamental tool for understanding the electronic structure of molecules and plays a crucial role in theoretical chemistry and quantum mechanics. Mulliken analysis provided an effective method for studying interbond interaction and intramolecular and intermolecular bonding [3]. Mulliken atomic charge calculation results of TMP-PA complex are shown in Figure 3. The charge in the complex studied changes from -0.766 in N17 to 0.576 in C2. The delocalization of electron densities between non-Lewis NBO orbitals and occupied Lewis NBO orbitals corresponds to stable donor-acceptor interactions. This method provides a convenient basis for studying conjugate interactions or charge transfer interactions in molecular systems.

Figure 3 – Mulliken's atomic charges of TMP-PA CT complex

Conclusions. In this work, the geometric structures of TMP-PA complexes have been studied by means of computational methods. Theoretical studies have revealed the existence of charge transfer transitions in the complex. The electron spectra of the compounds were determined and the important molecular orbitals of the compounds were determined by TD-DFT method. The electron density in HOMO was mainly concentrated on the benzene ring (the hydroxyl group and the two nitro groups), while the electron density in LUMO was mainly concentrated on the entire benzene ring. The calculated LUMO-HOMO orbital energy can be used to estimate molecular hardness, ionization energy, and other physical parameters.

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