



## Molecular Docking and Energies Studies of 4-(Trifluoromethyl) pyridine-2-carboxylic acid

Hatice Vural

Amasya University, Faculty of Engineering, Electrical and Electronics Engineering, Amasya, Turkey

Accepted 25 November 2022

### Abstract

The density functional theory (DFT) calculations were used to estimate the highest occupied molecular orbital (HOMO) – the lowest unoccupied molecular orbital (LUMO) energies, energy gap, and the global chemical reactivity descriptors of 4-(trifluoromethyl)pyridine-2-carboxylic acid (4TPCA). The ionization potential, electron affinity, electronegativity, chemical hardness, softness, chemical potential, and electrophilic index were calculated by using the DFT/B3LYP/6-311++G (d, p) level. The B-DNA interaction of 4TPCA was analyzed by molecular docking simulations. AutoDock4 program was used to generate the binding energy of 4TPCA. Out of twenty docked conformations obtained for 4TPCA one which has the lowest binding energy was selected.

Keywords: *Energy, DFT, Molecular Docking*

### 1. Introduction

DNA has become one of the main biological targets for antitumor compounds since the development of cisplatin, the most important cancer drug [1, 2]. Therefore, the experimental and computational study of the interaction of appropriate molecules with DNA is of great importance in drug design. Pyridine and its derivatives are preferred in the synthesis of different compounds because they have many pharmacological properties such as antimicrobial [3], antifungal [4, 5], and antitubercular [6].

Preferring computational methods to investigate many new properties while working on a molecule provides a great advantage in terms of time and cost. DFT has been increasingly used for calculating a wide variety of molecular properties that includes stability structure, charge transfer interactions, transition states, etc. In the previous study, the 4-(trifluoromethyl)pyridine-2-carboxylic acid was characterized with FTIR and NMR techniques by Vural [7]. The nonlinear optical (NLO) parameters were calculated at the B3LYP, PBEPBE, CAMB3LYP levels of the DFT method.

In this study, the global chemical reactivity descriptors and the B-DNA interaction of 4TPCA have been investigated by using the DFT method

B3LYP functional with the 6-311++G (d, p) basis set. Therefore, the ionization potential ( $I$ ), electron affinity ( $A$ ), electronegativity ( $\chi$ ), chemical hardness ( $\eta$ ), softness ( $s$ ), and electrophilic index ( $w$ ) have been investigated for 4TPCA. The indicator used in the computational bio-activity study of the molecule is the electrophilic index. In addition, the toxic potential of substances can be estimated by calculating the electrophilic index [8]. The second part of study has been devoted to non-covalent interactions between 4TPCA and the B-DNA. The investigation has been carried out by using molecular docking method (Autodock 4 programme).

### 2. Theoretical Method

#### 2.1. Computational details

The ground state geometry optimization of 4TPCA is implemented by DFT method at GAUSSIAN 09W program packages [9]. The Gauss View 5.0 program was used to generate visual presentation [10]. The geometry of 4TPCA was optimized by using the B3LYP [11] (Lee et al., 1988) level of DFT. The ionization potential ( $I$ ), electron affinity ( $A$ ), electronegativity ( $\chi$ ), chemical hardness ( $\eta$ ), softness ( $s$ ), and electrophilic index ( $w$ ) of 4-(Trifluoromethyl)pyridine-2-carboxylic acid were investigated by using DFT/B3LYP method with the 6-311++G (d, p) basis set.

By considering frontier molecular orbital (FMO) energies obtained at the DFT/B3LYP/ 6-311++G, the molecular parameters defined as global chemical reactivity descriptors were computed by using eq. (1)-(5) [12].

$$\text{Chemical hardness } (\eta) = (I-A)/2 \quad (2.1)$$

$$\text{Elektronegativity } (\chi) = (I+A)/2 \quad (2.2)$$

$$\text{Chemical potential } (\mu) = -(I+A)/2 \quad (2.3)$$

$$\text{Electrophilicity index } (w) = \mu^2/2\eta \quad (2.4)$$

$$\text{Softness } (s) = 1/2\eta \quad (2.5)$$

## 2.2. Docking procedure

Molecular docking study was performed using the AutoDock4 program [13]. The crystal structure of the B-DNA dodecamer d(CGCGATATCGCG)<sub>2</sub> (PDB ID: 1BNA) was taken from the RCS Protein Data Bank (<http://www.rcsb.org/pdb>). In the docking simulations, the grid box size of the dimensions (50x50x60 Å) was created along the x, y, and z axes, with a grid spacing of 0.375 Å. After the generation of the grid box, the Lamarckian Genetic Algorithm (LGA) was employed to search for the energy

minimized docked poses of 4TPCA in combination with B-DNA.

## 3. Results and Discussion

### 3.1. Electronic Properties

The optimized geometry of 4TPCA was performed by the B3LYP method with the 6-311++G (d, p) basis set (Fig. 1). Global reactivity descriptors for the gas phase and solvent (water) of 4TPCA were estimated using the DFT/ B3LYP/6-311++G (d, p) method.

The HOMO (Highest Occupied Molecular Orbital) and the LUMO (Lowest Unoccupied Molecular Orbital) are called frontier molecular orbitals (FMOs). Figure 2 displays the frontier molecular orbitals (FMOs) and energies for 4TPCA [14, 15]. The energy gap between FMOs is a critical parameter in determining chemical reactivity of the molecule such as hardness, softness, chemical potential and electronegativity (Table 1) [16, 17]. The ionization potential (I) and electron affinity (A) are given by  $I = -E_{\text{HOMO}}$  and  $A = -E_{\text{LUMO}}$ .

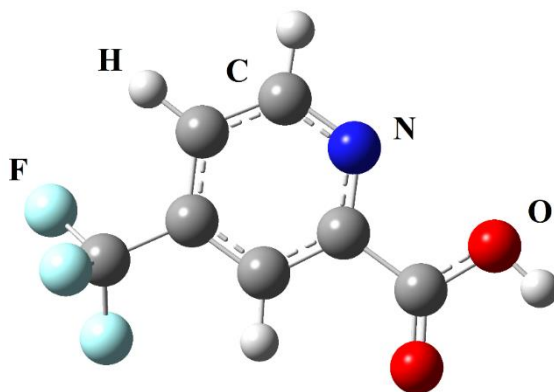


Figure 1. The optimized (with B3LYP/6-311++G (d, p) level) geometric structure of 4TPCA

As given in Table 1, the I and A parameters of 4TPCA are calculated by the DFT/B3LYP method are 7.96 eV and 2.50 eV in water. The corresponding parameters are computed as 7.95 eV and 2.56 eV in the gas phase. The  $\Delta E$  values of 4TPCA are computed as 5.39 eV and 5.46 eV in the gas phase and water. It can be said that the energy gap increases in the solvent. The  $\eta$  value of 4TPCA is calculated as 2.69 eV in the gas phase and 2.73 eV in water. Hard materials have a large energy gap and soft materials have a small energy gap.

The  $\chi$  value of 4TPCA is calculated as 5.25 eV in the

gas phase and 5.23 eV in water. Large  $\chi$  values mean that the investigated system is acidic while small  $\chi$  values indicate that the system is basic [18]. Additionally, for any two molecules, electrons will be partially transferred from the region of low  $\chi$  to that of high  $\chi$ . Calculated large  $\chi$  values demonstrated that 4TPCA is acidic.

The  $w$  values are computed as 5.12 eV in the gas phase and 5.00 eV in water. The low chemical softness value ( $s = 0.18$  eV) of the title molecule indicates that it is theoretically non-toxic [8].

Table 1. The FMO energies and related properties obtained by the DFT method.

Parameters (eV)	DFT/B3LYP/6-311++G (d, p)	
	Gas phase	Water
$E_{\text{HOMO}}$	-7.95	-7.96
$E_{\text{LUMO}}$	-2.56	-2.50
$\Delta E$	5.39	5.46
I	7.95	7.96
A	2.56	2.50
$\chi$	5.25	5.23
$\mu$	-5.25	-5.23
$\eta$	2.69	2.73
S	0.18	0.18
$w$	5.12	5.00

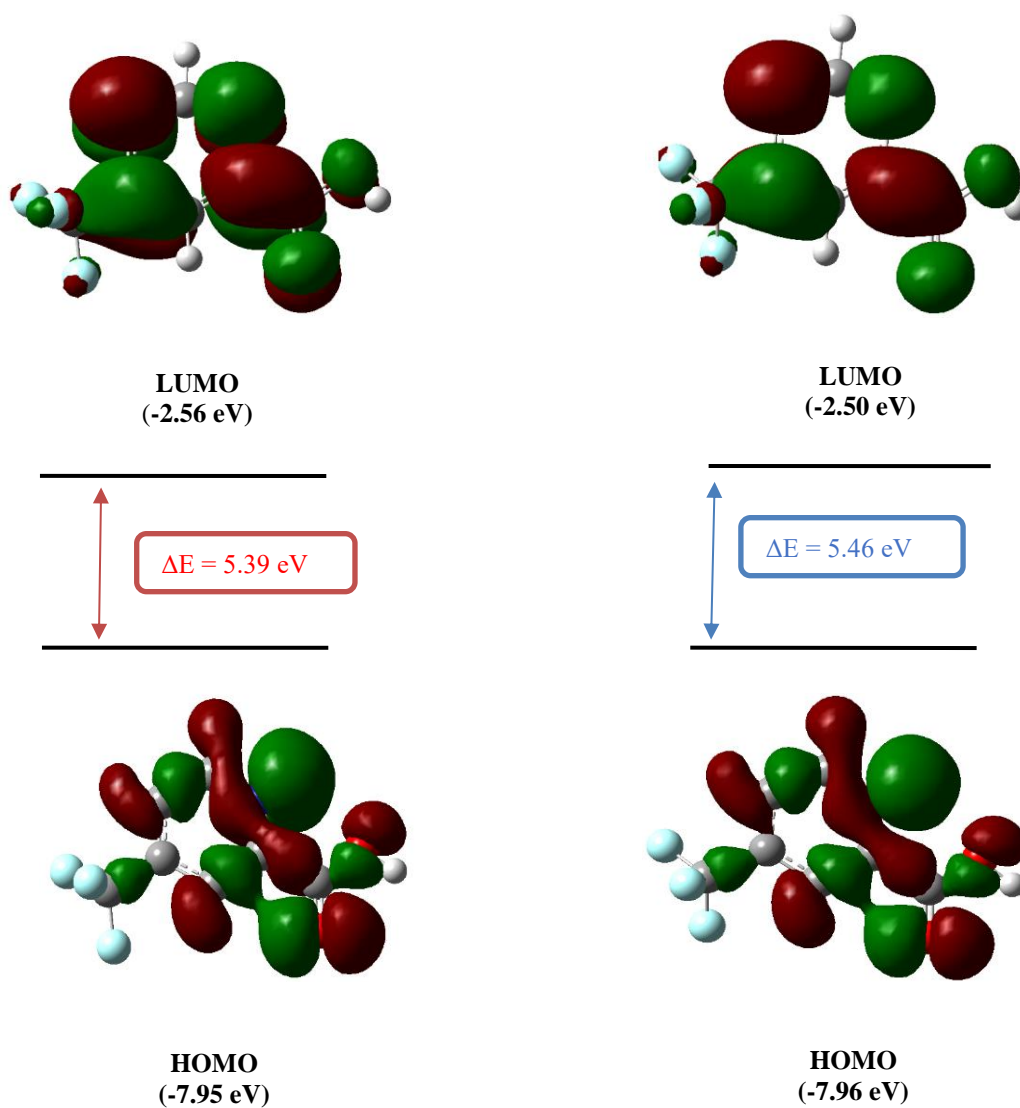


Figure 2. The FMOs of 4TPCA by using DFT/B3LYP/6-311++G (d, p) level in the gas phase and water.

### 3.2 Molecular Docking

The B-DNA interaction of 4TPCA has been analyzed molecular docking simulations using AutoDockTools graphical user interface [13]. AutoDock4 program was used to generate the binding energies of the compound. Out of twenty docked confirmations obtained for 4TPCA, one which has lowest binding energy was selected.

In order to understand comprehensively the docking results, the energy minimized docked pose of 4TPCA is presented in Fig. 3, and the binding free energy is

tabulated in Table 2. The binding free energy of 4TPCA is calculated as -4.35 Kcal/mol. Tamer et al. performed the molecular docking simulation on 4Clpic, 4Mpic, and pic. In this work, the binding free energy of the interaction of the 4Clpic, 4Mpic, and pic with B-DNA were calculated as -4.84 Kcal/mol, -5.12 Kcal/mol and -4.45 Kcal/mol, respectively [18]. According to the docking results, the binding free energy of 4TPCA is in a good agreement with 4Clpic, 4Mpic, and pic.

Table 2. DNA docking results of 4TPCA.

	Binding free energy ( $\Delta G_{\text{binding}}^*$ ) (Kkal/mol)	vdW_hb_desolv energy ( $\Delta G_{\text{vdW+hb+desolv}}$ ) (Kkal/mol)	Electrostatic energy ( $\Delta G_{\text{elec}}$ ) (Kkal/mol)	Total internal energy ( $\Delta G_{\text{total}}$ ) (Kkal/mol)	Torsional free energy ( $\Delta G_{\text{tor}}$ ) (Kkal/mol)	Unbound system's energy ( $\Delta G_{\text{unb}}$ ) (Kkal/mol)
<b>4TPCA</b>	-4.35	-4.61	-0.63	-0.35	0.89	-0.35

$$^a \Delta G_{\text{binding}} = \Delta G_{\text{vdw+hb+desolv}} + \Delta G_{\text{elec}} + \Delta G_{\text{total}} + \Delta G_{\text{tor}} - \Delta G_{\text{unb}}$$

The Van der Waals desolvation energy relates to the formation of hydrogen bonds between the synthesized complex and the DNA. The docking result of 4TPCA revealed that the carboxyl group

oxygen atoms of 4TPCA linked by the hydrogen bonds involving the hydrogen atoms of the G10 and G16 (H bond distances = 1.784 Å and 1.879 Å).

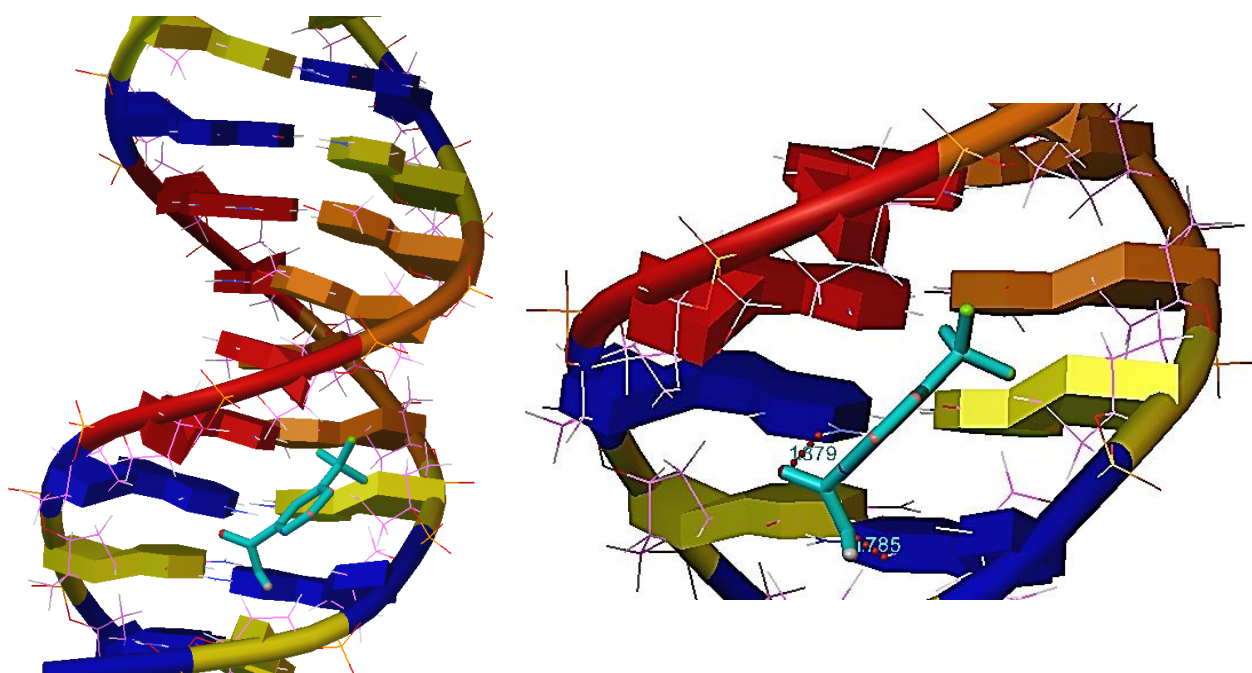


Figure 3. Lowest energy docked pose and hydrogen bond interactions of 4TPCA with B-DNA.

#### 4. Conclusions

In this study, the energy gap and global reactivity descriptors of 4TPCA have been evaluated by using the DFT/B3LYP method with 6-311++G (d, p) basis set. The influence of the solvent on the energy gap of 4TPCA is estimated using two different media (the gas phase and water). The calculated energy gap of 4TPCA in water is higher in the energy gap calculated in the gas phase. The comparatively low energy

gap between FMOs suggests that the charge transfer may occur within 4TPCA. The binding free energy of 4TPCA-BDNA docked structure is calculated as -4.35 Kcal/mol. 4TPCA may be used as reagents or precursors in many fields such as physics, chemistry, pharmacology, and materials science.

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