JOURNAL OF BAKU ENGINEERING UNIVERSITY - PHYSICS
2025. Volume 9, Number 2 *Pages 82-91*

UDC: 544.18:577.112.3.
DOI: https://doi.org/10.30546/09081.2025.002.1023

DFT STUDY OF THE STRUCTURAL AND ELECTRONIC FEATURES OF THE ALA-TYR DIPEPTIDE

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ARTICLE INFO

Article history:
Received:2025-03-30
Received in revised form:2025-04-20
Accepted:2025-06-05
Available online:2025-12-21

Keywords:
DFT; Ala-Tyr dipeptide; HOMO-LUMO; MEP; hydrogen bonding; reactivity descriptors.

ABSTRACT

In this work, the stable conformations of the Ala -Tyr (alanine-tyrosine) dipeptide were investigated in water environment at the B3LYP/6-31+G(d,p) level of density functional theory (DFT). The geometric parameters (bond lengths, valence angles, dihedral angles), including the intramolecular hydrogen bonds, electron distribution and related properties such as Mulliken atomic charges, Molecular Electrostatic Potential (MEP), and Frontier Molecular Orbitals (HOMO and LUMO) of the dipeptide were analyzed in detail. The results show that significant structural differences exist between the two energetically possible conformations, which are reflected in the specific electron distribution and, accordingly, in the values of the energy gap and the dipole moment. Also, the hydrogen atoms of the α-amino group and the oxygen atoms of the C-terminal carboxyl group play a key role in the reactivity and biological activity of this molecule. The research work contributes to study the structure-activity relationships of the Ala-Tyr dipeptide at the quantum-chemical level, for understanding of its potential applications in drug design.

1. INTRODUCTION

The study of the conformational properties of peptide molecules and the performance of molecular modeling based on quantum mechanical calculations allow us to obtain conclusions about their atomic-level structure and functional properties. Among peptides with biomedical applications, dipeptides and tripeptides are particularly suitable due to their structural simplicity and are widely used in the design of new therapeutic drugs and in the food industry. Dipeptides are short peptide molecules formed by the combination of two amino acids by a peptide bond and play an important role in various biological processes such as protein synthesis, nutrient absorption, cell signaling, and immune response. Dipeptides are widely used in the biomedical field due to their bioavailability and non-toxicity. Such short molecules can also be applied for purposes such as the identification and purification of various substances [1].

Dipeptides containing Tyr and Trp amino acids and protein hydrolysates rich in these dipeptides can be considered as potential functional food components for the protection and improvement of human health [2]. The Ala-Tyr dipeptide, which is used as a biologically active additive, is mainly known as an angiotensin-converting enzyme (ACE) inhibitor [3-4]. It has been shown in [5] that this dipeptide is rapidly hydrolyzed in blood plasma, which indicates its favorable use in the body. Even in hemodialysis patients with chronic renal failure, the breakdown and excretion of Ala-Tyr from the body is normal. That is, even if the kidney function is weakened, Ala-Tyr is effectively metabolized and does not cause problems.

In the presented work, the geometric parameters and electronic properties such as HOMO/LUMO energies, energy gap, dipole moment, partial charges of atoms, electron density distribution, and reactivity descriptors of Ala-Tyr dipeptide were studied using the DFT method.

2. METHODS

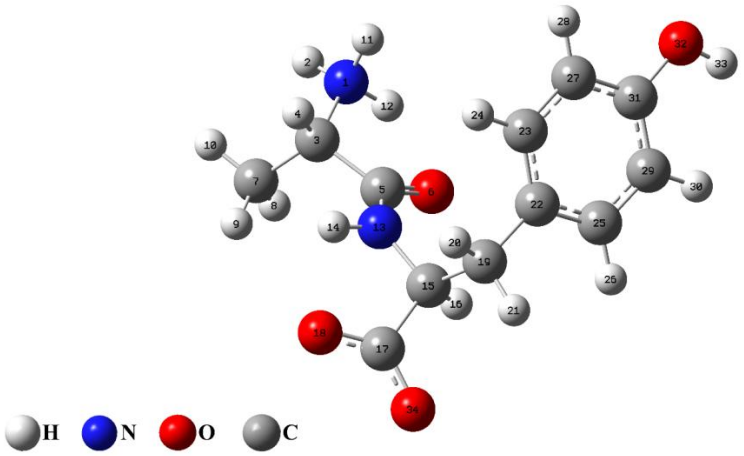
Quantum chemical calculations of polyatomic molecules allow us to determine or predict the geometric structure, energy, dipole moment, ionization potential, charge distribution, and various other physical and chemical properties of molecules. Experimental data show that the results of such calculations are quite reliable. Naturally, since it is impossible to take into account all the factors encountered during the experiment, the accuracy of quantum chemical calculation methods in most cases coincides with experimental results, even if there are certain limitations in the accuracy of the results obtained. The main task of computer modeling is to correctly formulate the goals of the research and provide a detailed analysis of the obtained calculation results.

The density functional theory (DFT) used in this work replaces the multiparticle electron wave function with the electron density as the main physical quantity in order to eliminate both the inaccuracy of the Hartree-Fock method and the high computational requirements. That is, DFT allows us to calculate all the physical and chemical properties of the system based on the electron density [6].

First, the conformational profiles of the Ala-Tyr dipeptide were investigated by molecular mechanics (MM) and it was shown that this molecule can exist in two stable states corresponding to the extended and folded conformations [7]. Then, using the coordinates obtained from results of MM calculations as initial geometric parameters the most stable extended and folded conformations of the bioactive dipeptide Ala-Tyr were optimized in an water environment by the DFT/B3LYP [8] method using the 6-31+G(d,p) basis set. Here, the Gaussian 16 software package [9] and GaussView 6.0 [10] were used as software.

3. RESULTS AND DISCUSSIONS

Figure 1 shows the optimized extended and folded structures of the Ala-Tyr dipeptide calculated using the DFT/B3LYP/6-31+G(d,p) method.



(a)

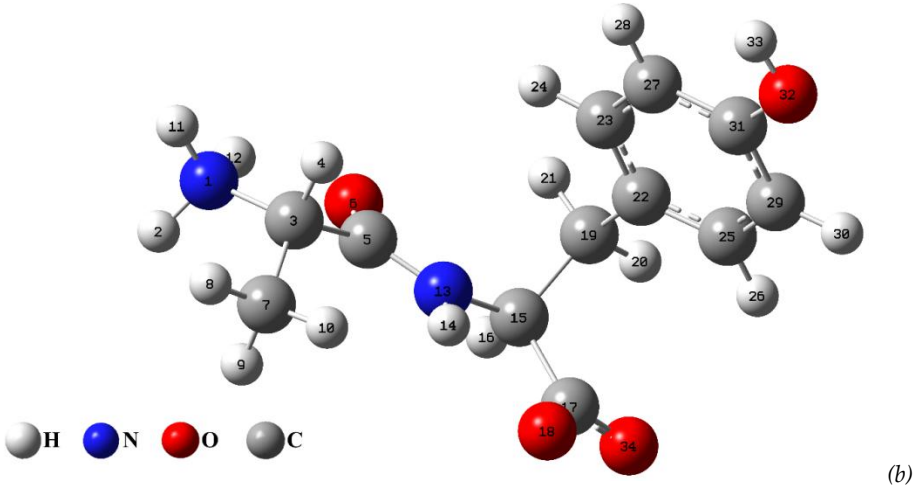


Fig 1. *Optimized extended (a) and folded (b) structures of the Ala-Tyr dipeptide*

Tables 1 and 2 show and compare the calculated values of the geometric parameters (bond lengths and valence angles) of the optimized structures of the dipeptide with the values obtained from experimental studies for the constituent amino acid residues of the dipeptide. As a result of the comparison, it is seen that there are slight differences between the values of the bond angles and bond lengths of both the main and side chains of the Ala-Tyr dipeptide and the experimental values. Table 3 shows the dihedral angles for both stable structures of the dipeptide.

Table 1. *Calculated and experimental values of bond lengths (Å) for amino acid residues of the Ala-Tyr dipeptide (Å)*

Bond lengths	Extended structure	Folded structure	[11, 12]
N1-H2	1.023	1.024	1.029
N1-H11	1.024	1.022	1.047
N1-H12	1.036	1.040	1.031
N1-C3	1.509	1.509	1.487
C3-H4	1.091	1.094	1.093
C3-C5	1.546	1.550	1.531
C3-C7	1.531	1.528	1.524
C5-O6	1.243	1.246	1.242
C5-N13	1.334	1.330	-
C7-H8	1.094	1.093	1.082
C7-H9	1.092	1.094	1.081
C7-H10	1.093	1.092	1.081
N13-H14	1.019	1.019	0.850
N13-C15	1.463	1.463	1.493
C15-H16	1.092	1.095	0.960
C15-C17	1.561	1.559	1.531
C15-C19	1.553	1.553	1.535
C17-O18	1.265	1.265	1.257
C17-O34	1.258	1.258	1.243
C19-H20	1.096	1.094	1.030
C19-H21	1.095	1.095	0.960
C19-C22	1.513	1.514	1.516
C22-C23	1.403	1.403	1.393
C22-C25	1.403	1.405	1.395
C23-H24	1.087	1.087	1.020
C23-C27	1.397	1.398	1.393

C25-H26	1.087	1.086	0.940
C25-C29	1.397	1.395	1.386
C27-H28	1.086	1.087	0.960
C27-C31	1.398	1.399	1.390
C29-H30	1.087	1.086	0.930
C29-C31	1.400	1.399	1.384
C31-032	1.375	1.375	1.369
O32-H33	0.968	0.968	0.680

Table 2. *Calculated and experimental values (degrees) of bond angles for amino acid residues of the Ala-Tyr dipeptide*

Bond angles	Extended structure	Folded structure	[11, 12]
H2-N1-H11	107.89	107.97	108.15
H2-N1-H12	110.01	107.78	110.65
H11-N1-H12	107.47	110.37	108.20
H2-N1-C3	112.91	112.05	111.33
H11-N1-C3	112.20	113.00	109.40
H12-N1-C3	106.22	105.56	109.05
N1-C3-H4	107.55	106.08	106.94
N1-C3-C5	104.62	104.45	110.05
N1-C3-C7	110.07	111.11	109.74
H4-C3-C5	111.58	107.24	108.55
H4-C3-C7	111.00	110.36	110.40
C3-C5-O6	118.22	118.18	118.39
C3-C5-N13	115.72	116.95	-
C3-C7-H8	111.06	110.19	110.57
C3-C7-H9	109.47	111.52	110.33
C3-C7-H10	110.66	110.33	110.37
C5-C3-C7	111.75	116.92	111.07
H8-C7-H9	108.38	109.08	108.90
H8-C7-H10	109.31	107.04	108.36
H9-C7-H10	107.87	108.55	108.25
C5-N13-H14	119.88	122.29	-
C5-N13-C15	125.50	124.76	-
O6-C5-N13	126.05	124.83	-
N13-C15-H16	108.30	108.33	-
N13-C15-C17	108.29	107.86	109.6
N13-C15-C19	112.10	112.79	111.0
H14-N13-C15	112.37	112.23	-
C15-C17-O18	116.34	116.68	116.5
C15-C17-O34	115.94	115.70	117.0
O18-C17-O34	127.68	127.62	126.5
C15-C19-H20	108.00	106.34	-
C15-C19-H21	106.44	107.61	-
C15-C19-C22	115.28	115.49	114.4
H16-C15-C19	109.63	107.27	-
H16-C15-C17	109.50	107.94	-
C19-C22-C23	121.41	121.20	121.4
C19-C22-C25	120.92	121.26	120.4
C19-C15-C17	108.99	112.48	111.3
H20-C19-H21	107.16	107.24	-
H20-C19-C22	109.77	110.07	-
H21-C19-C22	109.85	109.74	-
C22-C23-H24	119.49	119.62	-
C22-C23-C27	121.57	121.66	121.2
C22-C25-H26	119.59	119.35	-

C22-C25-C29	121.59	121.62	121.2
C23-C27-H28	120.90	120.18	-
C23-C27-C31	119.67	119.61	119.4
H24-C23-C27	118.94	118.72	-
C25-C29-H30	120.16	120.89	-
C25-C29-C31	119.63	119.71	119.8
C25-C22-C23	117.67	117.54	118.2
H26-C25-C29	118.82	119.03	-
C27-C31-C29	119.87	119.86	120.3
C27-C31-O32	117.51	122.67	122.2
H28-C27-C31	119.43	120.21	-
C29-C31-O32	122.62	117.47	117.6
H30-C29-C31	120.21	119.40	-
C31-O32-H33	110.22	110.20	-

Table 3. *Calculated values of dihedral angles of the Ala-Tyr dipeptide (in degrees)*

Dihedral angles	Extended structure	Folded structure
H11-N1-C3-C5 (φ - Ala)	-87.44	-139.80
N1-C3-C7-H8 (χ1 - Ala)	58.51	-55.86
N1-C3-C5-N13 (ψ - Ala)	155.54	-167.87
C3-C5-N13-C15 (ω - Tyr)	169.16	178.87
C5-N13-C15-C17 (φ - Tyr)	-135.34	-157.80
N13-C15-C19-C22 (χ1 - Tyr)	-64.62	60.48
C15-C19-C22-C23 (χ2 - Tyr)	96.17	-92.35
C15-C19-C22-C25 (χ3 - Tyr)	-83.80	87.78
N13-C15-C17-O34 (ψ - Tyr)	162.06	171.10

The values for the interatomic distances of the oppositely charged groups of the molecule (reflecting the distances between the atoms of the functional group) were calculated. The interatomic distances between the functional groups for the extended and folded structures were determined as 5.96 and 5.98 Å for N1-O18, 7.03 and 7.10 Å for N1-O34, 6.63 and 6.23 Å for H2-O18, 7.81 and 7.35 Å for H2-O34, 6.35 and 6.76 Å for H11-O18, 7.46 and 7.98 Å for H11-O34, 6.10 and 6.10 Å for H12-O18, 6.85 and 6.90 Å for H12-O34, respectively. These values indicate that both structures have favorable interactions.

One of the factors that affects the geometry of the molecule are the hydrogen bonds. Therefore, the intramolecular hydrogen bonds were studied for the Ala-Tyr dipeptide by DFT calculations. Possible intramolecular hydrogen bonds for the optimized conformations were revealed. The geometric parameters of the identified intramolecular hydrogen bonds were calculated to evaluate the stability of the Ala-Tyr conformers in water environment (Table 4). It was established that in the optimized structures of the dipeptide, the following hydrogen bonds were formed: between the hydrogen atom of the α-amino group and the oxygen atom of the carbonyl group of the alanine backbone; hydrogen bonds between the hydrogen atom of the amide group of the tyrosine backbone and the neighboring oxygen atom of the C-terminal carboxyl group. Weak hydrogen bonds are formed between the hydrogen atoms of the methyl qroup of the Ala residue side chain and the oxygen atoms of the backbone carbonyl group and the the C-terminal carboxyl group in both the extended (H8 …O6 (3.11 Å), H9 …O6 (3.71 Å), H9…O18 (3.79 Å)) and folded structure (H9 …O6 (3.74 Å), H10…O18 (3.72 Å)).

Table 4. *Parameters of strong hydrogen bonds in the optimized structures of the Ala-Tyr dipeptide*

DH…A	DH (Å)		H…A (Å)		D…A (Å)		∠DHA (degrees)	
	Extended structure	Folded structure	Extended structure	Folded structure	Extended structure	Folded structure	Extended structure	Folded structure
N1H12 … O6 (I)	1.04	1.03973	2.00	1.90	2.60	2.56158	114.00	118.38
N13H14 … O18 III)	1.02	1.01872	2.14	2.04	2.63	2.59694	107.69	111.78

Due to resonance interactions, all atoms in the peptide bond should be located in the amide plane. However, due to the formation of hydrogen bonds between the α-amino group of the molecule and the hydrogens of the amide group and the oxygen atom of the C-terminal carboxyl group, the planarity of the amide plane structure is not disturbed for both conformations. To explain the planarity, the dihedral angles and geometric parameters of the molecule were analysed. It was found that the calculated value of the C3-C5-N13-C15 rotation angle is 169.160 for the extended structure, and 178.870 for the folded structure, respectively. Due to stereochemical factors, planarity in the peptide bond is possible only when the dihedral angle ω is close to 180° (trans) since this angle ensures that the atoms of the amide group are located in the same plane.

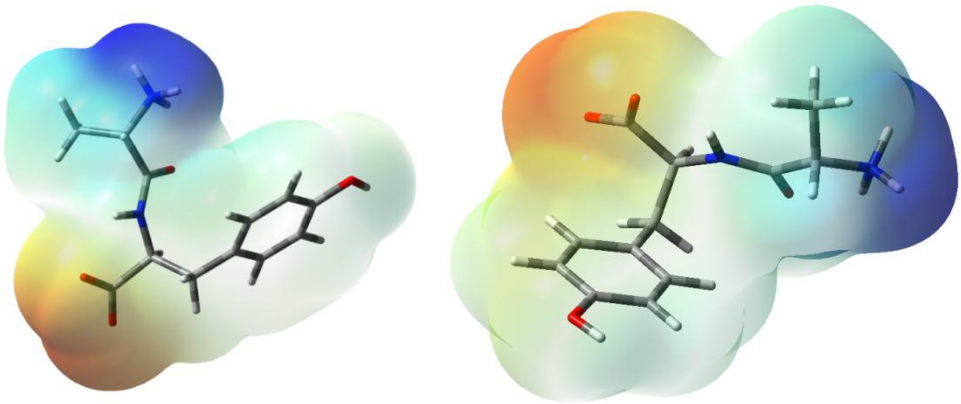
Since the calculation of atomic charges is an important aspect of quantum mechanical calculations, the Milliken atomic charges of the Ala-Tyr dipeptide [13] are also calculated in this work (Table 5). According to these results, in both the extended and folded structures, the N1 atom of the α-amine group of the molecule, the O6 atom of the carbonyl group, the C7 atom of the methyl group of the side chain of the Ala residue, the C15 atom of the main chain of the Tyr residue, the C19 of the side chain of the Tyr residue and the C23, C25 and O32 atoms of the phenol ring, and the O18 and O34 atoms of the carboxyl group of the molecule carry a large negative charge. As a result of dipeptide folding, N1 (0.017458 e), H2 (0.003758 e), H4 (0.017416 e), C5 (0.040790 e), O6 (0.022502 e), C7 (0.025101 e), H8 (0.003190 e), N13 (0.070043 e), O18 (0.025461 e), C19 (0.353327 e), H20 (0.011422 e), C23 (0.072390 e), H24 (0.004646 e), C25 (0.293917 e), H26 (0.000639 e), C27 (0.046784 e), C29 (0.014925 e), H30 (0.003329 e), H33 (0.000471 e), O34 (0.014397 e) atoms' charges have increased, while the charges of C3 (0.118247 e), H9 (0.003619 e), H10 (0.004692 e), H11 (0.006066 e), H12 (0.001811 e), H14 (0.015084 e), C15 (0.047648 e), H16 (0.005286 e), C17 (0.042414 e), H21 (0.008776 e), C22 (0.729206 e), H28 (0.004338 e), C31 (0.009744 e) atoms have decreased. The largest charge shift in terms of value occurred at the C22 atom of the phenol ring of the Tyr residue. Since the identified moieties can act as both donors and acceptors when interacting with receptor residues, these data provide insights into charge transfer processes.

Table 5. *Milliken atomic charges (e) for optimized structures of the Ala-Tyr dipeptide*

Atoms	Extended structure	Folded structure
N1	-0.559525	-0.542067
H2	0.406978	0.410736
C3	0.249169	0.130922
H4	0.213496	0.230912
C5	0.015014	0.055804
O6	-0.534900	-0.557402
C7	-0.569213	-0.544112
H8	0.185948	0.189138
H9	0.193558	0.189939
H10	0.186923	0.182231
H11	0.416794	0.410728

H12	0.413417	0.411606
N13	-0.176211	-0.106168
H14	0.351833	0.336749
C15	-0.361248	-0.408896
H16	0.167002	0.161716
C17	0.448305	0.405891
O18	-0.667206	-0.641745
C19	-0.428830	-0.075503
H20	0.152796	0.164218
H21	0.168487	0.159711
C22	0.874414	0.145208
C23	-0.390493	-0.318103
H24	0.127506	0.132152
C25	-0.648227	-0.354310
H26	0.137664	0.138303
C27	0.124641	0.171425
H28	0.142648	0.138310
C29	0.227369	0.242294
H30	0.139932	0.143261
C31	-0.178726	-0.188470
O32	-0.568238	-0.568269
H33	0.383940	0.384411
O34	-0.645018	-0.630621

The charge distributions are visualized by molecular electrostatic potential (MEP) maps [14, 15]. The positive, negative and neutral electrostatic potential parts for the optimized structures of the molecule are shown in Figure 2. As can be seen from the MEP, the negative potential parts (the lowest values for the extended and folded structures are -0.165e. and -0.170e, respectively) are the most nucleophilic moieties localized on the oxygen atoms of the C-terminal carboxyl group of the molecule, while the positive potential parts (the highest values for the extended and folded structures are 0.165e. and 0.170e, respectively) are the most electrophilic moieties localized on the hydrogen atoms of the α-amino group of the molecule and the atoms of the methyl group of the alanine side chain. As a result, the O atoms of the COO- group exhibit a strong repulsion, while the H atoms of the NH_3^+ group and the methyl group of Ala exhibit a strong attraction, and these sites are of great importance in the biological activity of the molecule.



(a) *(b)*

Fig 2. *Molecular electrostatic potential for the optimized extended (a) and folded (b) structures of the Ala-Tyr dipeptide*

The electronic parameters of the Ala-Tyr molecule obtained from DFT calculations are given in Table 6.

Table 6. *Electronic parameters and molecular properties of the Ala-Tyr dipeptide*

Physical quantities	Extended structure	Folded structure
Electronic energy (eV)	-23876.079	-23876.082
EHOMO (eV)	-6.156	-6.219
ELUMO (eV)	-0.573	-0.662
Energy gap ΔE (eV)	5.583	5.557
Electron affinity A=[-ELUMO] (eV)	0.573	0.662
Ionization potential I=[-EHOMO] (eV)	6.156	6.219
Global hardness η=(I-A)/2 (eV)	2.792	2.779
Softness S=1/2η (1/eV)	0.179	0.180
Electronegativity χ=(I+A)/2	3.365	3.441
Chemical potential μ= -(I+A)/2	−3.365	−3.441
Electrophilicity index ω=μ 2 /2η	2.03	2.13
Dipole moment (Debye)	28.242	25.217

The values of HOMO and LUMO energies are used to obtain information about the chemical reactivity and kinetic stability of the molecule, and these indicators are considered important parameters in quantum-chemical calculations [19-19]. As can be seen from Figure 3, in the folded structure, the HOMO orbitals are localized over the entire molecule except for the α-amino group of the molecule and the side chain of the Ala residue, and the LUMO orbitals are localized over the entire molecule except for the atoms of the carboxyl group of the molecule and the O and H atoms in the phenol ring of the Tyr residue (red color characterizes the negative charge for the molecule, and green color characterizes the positive charge for the molecule). In the extended structure, the HOMO orbitals are localized over the entire molecule except for the α-amino group of the molecule and the side chain of the Ala residue, and the LUMO orbitals are localized over the N atom of the amide group and the side chain of the Tyr residue. Therefore, while the HOMO-LUMO transition is observed in the folded structure at the α-amino group of the molecule, the side chain of the Ala residue, the carboxyl group atoms, and the O and H atoms of the hydroxyl group of the Tyr residue side chain (this type of transition decreases the polarization of the molecule and causes an decrease in the dipole moment during electronic excitation), in the extended structure it is observed on the C^{α} of the main chain of the Tyr residue, the atoms of the carbonyl and carboxyl groups of the dipeptide. Thus, the HOMO-LUMO transition is characterized as an electron transition directed from a broadly delocalized donor site to a more specific, local acceptor center in the extended structure.

Table 6 shows the values of other chemical reactivity descriptors such as ionization potential, electron affinity, chemical hardness and softness, electronegativity, chemical potential, and electrophilic index for the molecule. Looking at the energy gap value, we see that both structures are insulating and rigid molecules (stable), but the folded structure is more reactive than the extended structure. The higher ionization potential and electron affinity in the folded structure is explained by the fact that this structure is somewhat less able to donate electrons than the extended structure, and its tendency to accept electrons (acceptor property) is stronger. The extended structure is more likely to be a donor. The electrophilicity index (ω) is larger in the folded structure, meaning that the molecule behaves as a stronger electrophile in this conformation. In the folded structure of the dipeptide, the electronegativity has increased and the chemical potential has decreased, which means that the tendency of the molecule to attract electron density has increased. The calculated values of the dipole moment, which characterizes

the nonlinear optical properties, show that the dipole moment has decreased by 3.025 Debye as a result of the folding of the dipeptide.

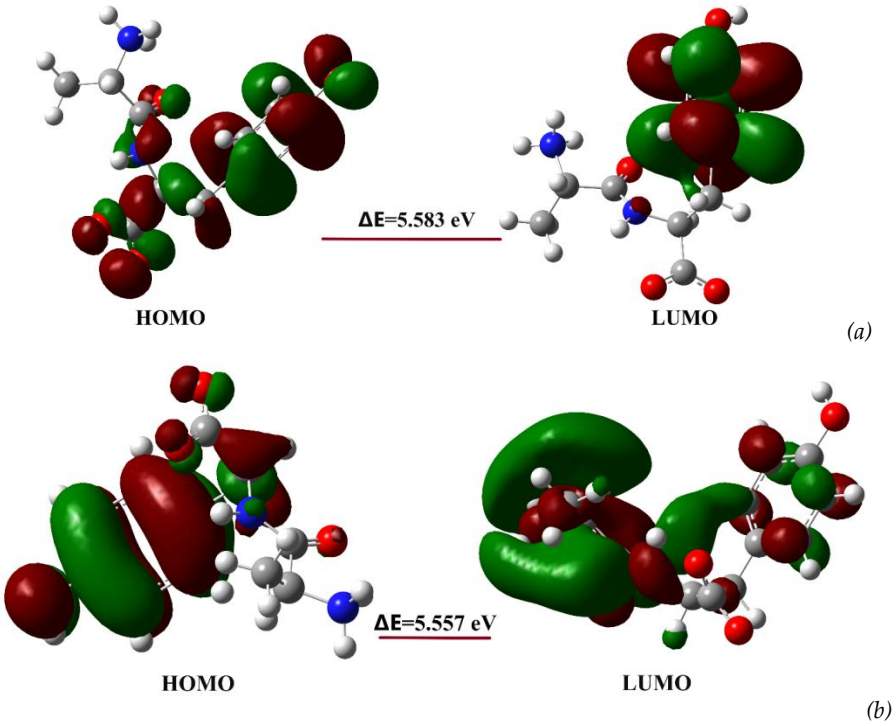


Fig 3. *HOMO and LUMO molecular orbitals for the optimized extended (a) and folded (b) structures of the Ala-Tyr dipeptide*

4. CONCLUSION

In the research work, the geometric and electronic properties of the extended and folded conformations of the Ala–Tyr dipeptide were studied using DFT/B3LYP/6-31+G(d,p) calculations. The results showed that this molecule is stabilized by both non-valent and electrostatic interactions, as well as intramolecular hydrogen bonds. During peptide chain folding, a redistribution of electron density is observed within the molecule. Analysis of the HOMO and LUMO orbitals revealed that the mechanisms of electron transition between the extended and folded structures are different in nature, and it was established that the dipole moment of the molecule decreases upon charge shifts by the folding of peptide chain. A significant decrease in the dipole moment upon folding indicates that the interaction of the Ala–Tyr dipeptide with the environment is strictly conformation-dependent. Overall, the obtained results provide a deeper understanding of the structure-activity relationship of the Ala-Tyr dipeptide, as well as an explanation of its biological activity and behavior as an ACE inhibitor at the atomic and electronic levels. These results can be used as a theoretical basis for the future development of similar bioactive peptides and functional food additives.

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