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PM3 QUANTUM CHEMICAL CALCULATIONS OF THE BIOACTIVE ALA-TYR DIPEPTIDE

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Abstract. Ala-Tyr (Alanine-Tyrosine) dipeptide is a compound with hypertensive and high antioxidant effect. Here, the structural features of this molecule were studied using the PM3 semi-empirical quantum-chemical method. In order to investigate the research, the initial coordinates of the molecule were obtained by the molecular mechanics method. Geometric and electronic parameters, HOMO and LUMO energies, energy gap, dipole moment and partial charges of atoms were calculated for the stable conformations, belonging to both folded and extended shapes of the dipeptide backbone. The obtained results can be used in the research of the structure-function relationships of the investigated bioactive dipeptide and in the design of new peptidomimetics.

Keywords: *Ala-Tyr dipeptide, spatial structure, electronic parameters, HOMO and LUMO frontier molecular orbitals.*

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1. Introduction

Antioxidants play an important role in the treatment of a number of diseases such as cancer, atherosclerosis, cerebral thrombosis, Alzheimer's, Parkinson's, diabetes and slow down the aging of tissues (Devasagayam *et al.*, 2004). In recent years, peptides as a new source of natural antioxidants have attracted more attention of researchers. Thus, they can scavenge free radicals, prevent chelate transition metal ions or lipid peroxidation. The spatial structure of peptides depends on the amino acid sequence and interatomic interactions. Studying the conformational profiles of peptide molecules and after that investigating molecular modeling based on quantum mechanical calculations, allows obtaining conclusions about their structure-functional properties at the atomic level. Given the importance of peptides and proteins in drug development, it is understandable that such research is important. Note that in Tyr-containing dipeptides, the N-terminal Tyr residue acts as a stronger antioxidant than the C-terminal Tyr residue, and hydrogen bonds and steric, hydrophobic interactions, occur between adjacent residues (Zheng *et al.*, 2016). In this work, structural features, electronic parameters and

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some molecular properties of Ala-Tyr dipeptide were investigated by molecular modeling based on molecular mechanics and PM3 quantum-chemical calculations.

2. Calculation methods

Conformational profiles of Ala-Tyr dipeptide were studied by molecular mechanics method. With the help of this method, it is possible to determine the conformations of peptides and proteins, calculate the potential energy of interactions between the atoms that build the molecules and model the considered systems based on this. The potential energy of the investigated dipeptide was calculated as the sum of non-valent ($E_{n\text{-}v}$), electrostatic (E_{el}), torsional interaction (E_{tors}) energies and hydrogen bond energy (E_h).

The study of the spatial structure of the molecule was carried out using a program written in the FORTRAN algorithmic language (Akverdieva *et al.*, 2017; Godjayev *et al.*, 1983). This program is based on the matrix method principle of Hermans and Ferro (Hermans *et al.*, 1971). The accepted nomenclature and conventions are recommended by IUPAC-IUB (1993).

PM3 quantum-chemical method and HyperChem 8.03 software package (http://www.hyper.com) were used to calculate the electronic parameters of Ala-Tyr dipeptide. The molecule was calculated in the zwitterionic form.

Dewar and his research group suggested semi-empirical quantum chemical methods which are used in the analysis of conformations of molecular structures and the calculation of molecular energies. These methods are combined in the molecular orbitals package, MOPAC. MOPAC (Molecular Orbital PACkage) is a program used in quantum chemistry that allows the calculation of wave functions by the self-consistent field method using the Hartree-Fock formalism. MOPAC contains one Hamiltonian based upon the modified method of intermediate neglect of differential overlap approximation (MINDO/3) and three Hamiltonians based upon the modified neglect of diatomic differential overlap approximation (MNDO, AM1 and PM3) (Jurema & Shields, 1993).

Since ab-initio methods are suitable only for relatively small molecular compounds, semiempirical methods are used for large molecular compounds. The application of the MINDO/3, MNDO and AM1 methods to large molecular compounds is limited because MINDO/3 and MNDO methods cannot model molecular compounds formed by hydrogen bonds, while the AM1 method cannot always analyze hydrogen bonds (Jurema & Shields, 1993). This method is only useful for calculating of intermolecular hydrogen bonds (Ventura *et al.*, 1989; Khalil *et al.*, 1991). Therefore, many authors have shown that the use of the AM1 method for calculating of the intramolecular hydrogen bonds properties is inappropriate.

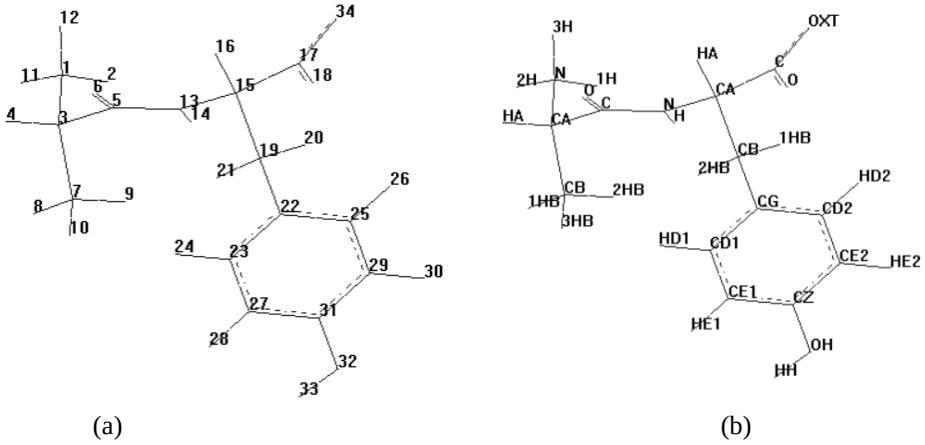
PM3 or Parametric Method 3 is a semi-empirical method used for the quantum-chemical calculation of the electronic structure of a molecule and is based on the method of neglecting the diatomic differential overlap approximation (Stewart & James, 1989).

The PM3 semi-empirical quantum mechanical method is used to systematically describe hydrogen bonding in small polar molecules, modeling hydrogen bonding allows for more accurate quantum-chemical calculations in small molecular compounds. The PM3 method enables the analysis of high-resolution spectroscopy and gas electron diffraction data of geometric parameters of the hydrogen-bonded peptides and complex compounds, as well as high-level ab-initio calculations. For example, both the PM3 method and the experimental results showed that ammonia is a good hydrogen bond

acceptor and a strong hydrogen bond donor (Jurema & Shields, 1993). The PM3 method was also used in the study of OH---N intramolecular hydrogen bonding.

3. Analysis of results

In the first approximation, the conformational profiles of Ala-Tyr dipeptide were investigated by molecular mechanics. The computational model of the molecule by the numbering of atoms (a) and chemical labeling (b) is presented in Figure 1. The conformations of amino acids are characterized by the angles of the main chain (φ, ψ) and the side chain (χ_1, χ_2, …….). According to Ramachandran maps, the main chains of amino acid residues of the molecule can be in R(φ,ψ=-180^0-0^0), B(φ= -180^0-0^0, ψ=0^0-180^0), L(φ,ψ=0^0-180^0) shapes. BB and LB shapes were considered for the extended conformations of main chain of Ala-Tyr dipeptide and RR and LL shapes for the folded conformations. The χ angles of the amino acid residues are assigned the values corresponding to the stable states of their side chains. Thus, 60^0, 180^0 and -60^0 torsion minimas were taken into account for the χ_1 angles of the side chains of both residues. The χ_2 angle of tyrosine is 90^0 and the χ_3 angle is 180^0. Thus, 12 conformations were calculated for the extended and folded structures of the main chain by giving freedom of rotation to the φ, ψ, ω, χ_1, χ_2,… torsion angles.



(a) (b)

Figure 1. Computational model of Ala-Tyr dipeptide atoms by numbering (a) and chemical labeling (b)

Table 1 shows the energy distribution of the conformations for the extended and folded structures of Ala-Tyr dipeptide. As we can see, 67% of the calculated conformations are realized in the relative energy range of 0-3 kcal/mol. The energy parameters of the low-energy conformations of Ala-Tyr dipeptide were determined and presented in Table 2.

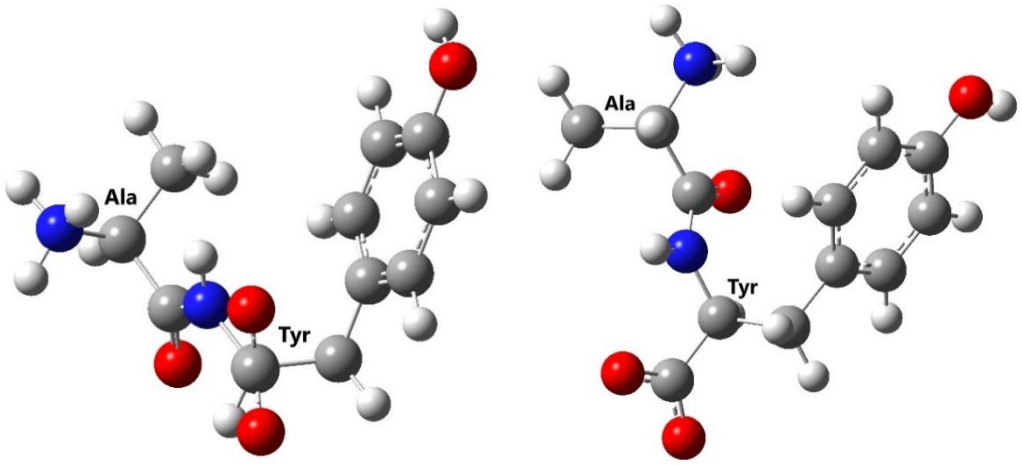
Table 1. Energy distribution of calculated conformations for Ala-Tyr dipeptide

Shape	Energy interval (kcal/mol)					
	0-1	1-2	2-3	3-4	4-5	>5
e	-	-	4	2	-	-
f	1	2	1	2	-	-

Table 2. Energy parameters (kcal/mol) of conformations of Ala-Tyr dipeptide in the energy range of 0-3 kcal/mol

Shape	Conformation	$E_{rel.}$	Ala-Tyr interaction energy	E_{n-v}	E_{el}	E_{tors}
f	RR_1	0	-7.99	-4.64	-0.34	1.02
	RR_2	1.96	-6.38	-2.30	-0.44	0.74
	RR_3	1.16	-7.56	-3.21	-0.18	0.60
	LL_3	2.35	-7.82	-2.57	-0.43	1.38
e	BB_1	2.74	-4.92	-3.08	0.99	0.88
	LB_1	2.74	-5.85	-3.61	1.43	0.96
	BB_3	2.46	-6.02	-3.76	0.91	0.93
	LB_3	2.46	-6.30	-3.57	1.36	0.71

It was determined that the global conformation of the dipeptide RR_1 (E_{rel}=0.0 kcal/mol) has folded structure of the main chain. The most stable state of the molecule with the extended structure of the backbone is the BB_1 conformation (E_{rel}=2.74 kcal/mol). The electrostatic interaction energy of this structure is 1.33 kcal/mol lower than folded conformation and the torsional interaction energy is 0.14 kcal/mol more. The optimized folded and extended conformations are shown in Figure 2. Table 3 represents the dihedral angles of these structures.



(a) (b)

Figure 2. Optimized folded (a) and extended (b) conformations of Ala-Tyr dipeptide

Table 3. The geometrical parameters of Ala-Tyr dipeptide (in deg.)

Amino acids	Torsion angles	Conformations	
		Folded	Extended
Ala	φ	-51	-70
	ψ	-61	150
	χ_1	180	59
	ω	179	181
Tyr	φ	-152	-144
	ψ	-33	162
	χ_1	56	-58
	χ_2	94	89
	χ_3	180	180

It was revealed the formation of intramolecular hydrogen bonds as a result of calculations. So, the hydrogen bonds between the hydrogen atom of the amide group of Tyr backbone and the oxygen atoms of the C-terminal carboxyl group are formed in the extended structure (E_h=-0.11 kcal/mol, bond length= 2.88 Å); the folded structure is stabilized by hydrogen bonds between the H atoms of the α-amino group and the oxygen atoms of the C-terminal carboxyl group of this dipeptide (E_h=-0.58 kcal/mol, bond length= 2.31 Å).

Because each conformation has its special electron density distribution and electronic parameters, studying the electronic structure of Ala-Tyr dipeptide is important. For this purpose, some electronic parameters, HOMO (highest occupied molecular orbital) and LUMO (lowest unoccupied molecular orbital) energies, energy gap, electric dipole moment, polarizability and partial charges of atoms were calculated for two characteristic optimized conformations of the molecule by PM3 semi-empirical quantum-chemical method (Tables 4 and 5).

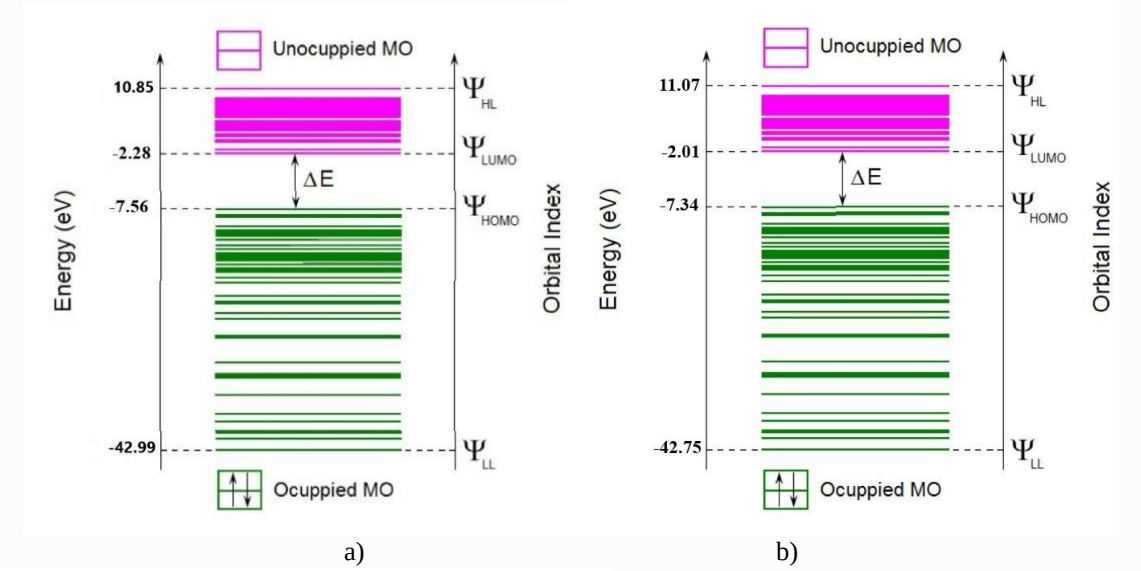
Table 4. The electronic parameters of the optimized structures of Ala-Tyr dipeptide

Parameters	Folded structure	Extended structure
Total energy, kcal/mol	-72985.21	-72992.67
Binding energy, kcal/mol	-3421.15	-3428.61
Isolated atomic energy, kcal/mol	-69564.06	-69564.06
Electronic energy, kcal/mol	-491074.29	-488555.6
Core-Core interaction energy, kcal/mol	418089.08	415562.92
Heat of formation, kcal/mol	-72.60	-80.06
Dipole moment, debyes (D)	21.49	23.92
E_{HOMO} (eV)	-7.56	-7.34
E_{LUMO} (eV)	-2.28	-2.01
Energy gap, ΔE (eV)	5.28	5.33
Polarizability (Å)	24.56	3.73

As can be seen from Table 4, the total energy, binding energy and heat of formation for the folded and extended optimized structures differ only slightly by the value of 7.46 kcal/mol, but electronic energy and the core-core interaction energy differ significantly by the value of 2518.69 kcal/mol and 2526.16 kcal/mol, correspondingly.

HOMO and LUMO energies are used to obtain information about the chemical reactivity and kinetic stability of a molecule, these parameters are important in quantum chemical calculations (Rocha *et al.,* 2015). The frontier molecular orbitals HOMO and LUMO are associated with the abilities to donate and accept electrons, respectively. Using the values of HOMO and LUMO energies, parameters such as chemical potential, chemical hardness, softness and electrophilic index are calculated to understand aspects related to chemical reactivity in drug design (Gil *et al.,* 2015). Ionization potential and electron affinity are related to the HOMO and LUMO energies, while chemical hardness and softness are related to the HOMO-LUMO energy gap (ΔE). A small energy gap is associated with high chemical softness and a high energy gap is one of the important parameters for predicting chemical stability (Jordaan *et al.,* 2021). The HOMO-LUMO energy gap is also a necessary characteristic of a molecule's conductivity. The smaller the energy gap, more conductive the molecule and conversely, the larger the energy gap, more insulating and stable it is (Ramachandran *et al.,* 2008). The electrophilic index is an important parameter that provides information about chemical potential, chemical hardness and chemical reactivity.

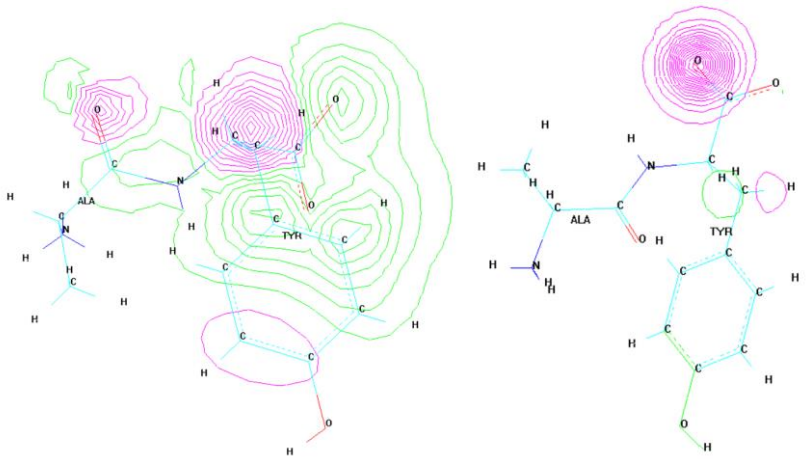
Results on the number of doubly occupied molecular orbitals and virtual molecular orbitals were obtained for the Ala-Tyr dipeptide by the PM3 method and they are summarized in Table 4. Figure 3 shows the energy spectrum of MOs calculated for the Ala-Tyr dipeptide in the ground state (S_0). As can be seen, the corresponding energy value (ϵ_j-eigenvalue) and eigenfunction (Ψ_j) are obtained for each molecular orbital. The green lines show the eigenvalues of the occupied molecular orbitals (OMO), and the pink lines show the energy levels of the empty (virtual) orbitals (UMO). Such spectra provide important information about energy values and energy gap (ΔE) of frontier molecular orbitals (Cojocaru *et al.*, 2013; Grimme, 2004).



a) b)

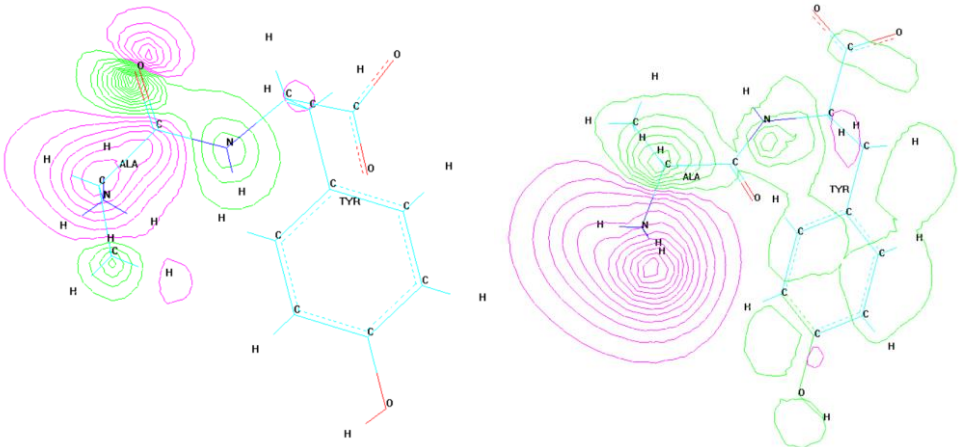
Figure 3. Energy spectra of molecular orbitals calculated by the PM3 method for the optimized folded (a) and extended (b) structures of Ala-Tyr dipeptide (ground state (S_0))

The energy contours of ground-state molecular orbitals (MOs) were calculated using the PM3 method. The HOMO and LUMO energy contours for the optimized folded (a) and extended (b) structures of the Ala-Tyr dipeptide are demonstrated in Figures 4 and 5. As can be seen from the presented images, in the folded structure the HOMO contours are localized on the peptide and C-terminal carboxyl groups of the Tyr residue, while the LUMO contours are localized on the α-amino group of the molecule, the Ala residue and the CA-CB bond of the Tyr residue and as a result, the HOMO-LUMO transition of the molecule implies the transfer of electron density from the Tyr residue, peptide and C-terminal carboxyl groups to the Ala residue and the CA-CB bond of the Tyr residue. In the extended structure, the HOMO contours are localized on the C-terminal carboxyl group, HA and HB atoms of the Tyr residue and the LUMO contours are localized with greater density on the almost entire molecule, excluding the oxygen atoms of the carbonyl and carboxyl groups, mainly on the α-amino group, the Ala residue, and amide group of the Tyr residue. Therefore the HOMO-LUMO transition involves the transfer of electron density from the carboxyl group, HA and HB atoms of the Tyr residue to the rest part of the molecule. As can be seen from Table 4, the calculated values of the HOMO-LUMO energy gaps are 5.28 and 5.33 eV for the folded and extended structures, respectively. The large value of the energy gap for both structures again indicates that the molecule is stable in these states.



a) b)

Figure 4. HOMO energy contours for the optimized folded (a) and extended (b) conformations of Ala-Tyr dipeptide



a) b)

Figure 5. LUMO energy contours for the optimized folded (a) and extended (b) conformations of Ala-Tyr dipeptide

The distribution of atomic charge in a molecule is of great importance and has a significant effect on the electrostatic potential, dipole moment and theoretically determined absorption spectra. Table 5 lists the atomic charges for the optimized folded and extended structures of the Ala-Tyr dipeptide calculated by the PM3 method. As can be seen from Table 5, the N atom of the α-amino group of the molecule and the C atom of the terminal carboxyl group, the NA atom of the main chain of the alanine residue, the C atom of the carbonyl group, the N atom of the amide group of the tyrosine residue, the HE2 and HD2 atoms of the indole ring have a large value positive charge. The CA atoms of the main chain of the alanine and tyrosine residues, the O atom of the carbonyl group, the O atoms of the terminal carboxyl group and the CE1 atom of the side chain of the tyrosine residue carry a large negative charge. The charge distribution in the optimized extended and folded conformations of the Ala-Tyr dipeptide was compared. It was determined that as a result of the folding of the peptide chain, the groups of oppositely charged atoms of the molecule come closer in space and the charge distribution changes in the atoms at the N-end of the molecule, in the aliphatic chain of the Ala residue and in

the indole ring of the Tyr residue. Therefore, in these structures, there are noticeable differences in the charges of H atoms of the α-amino group, HB atoms of the side chain of the alanine residue, HB, CE2, CD2, CE2 and H atoms of the side chain of the tyrosine residue. Such a change in charge distribution causes a shift of the positive charge and as a result, a decrease in the electric dipole moment by 2.43 D.

Table 5. Partial atomic charges for the optimized folded (a) and extended (b) conformations of the Ala-Tyr dipeptide

Atom №	Atom	Folded structure	Extended structure
1	N (NH_3^+)	0.845715	0.857136
2	1H (NH_3^+)	0.029536	0.001003
3	CA Ala	-0.331696	-0.327362
4	HA Ala	0.136486	0.120295
5	C Ala	0.145544	0.151505
6	O Ala	-0.371955	-0.441689
7	CB Ala	-0.129313	-0.112603
8	1HB Ala	0.050222	0.074249
9	2HB Ala	0.085246	0.112601
10	3HB Ala	0.109608	0.047580
11	2H (NH_3^+)	0.006153	0.022821
12	3H (NH_3^+)	0.029979	0.039538
13	N Tyr	0.126350	0.194431
14	H Tyr	0.091697	0.098886
15	CA Tyr	-0.168939	-0.186937
16	HA Tyr	0.102193	0.108041
17	C (COO^-)	0.406432	0.414902
18	O (COO^-)	-0.621719	-0.617652
19	CB Tyr	-0.042854	-0.046936
20	1HB Tyr	0.089867	0.066193
21	2HB Tyr	0.047316	0.097795
22	CG Tyr	-0.106822	-0.102405
23	CD1 Tyr	-0.105726	-0.101723
24	HD1 Tyr	0.084821	0.096992
25	CD2 Tyr	0.006326	-0.018783
26	HD2 Tyr	0.130590	0.120141
27	CE1 Tyr	-0.231638	-0.183646
28	HE1 Tyr	0.094019	0.101093
29	CE2 Tyr	-0.128095	-0.192865
30	HE2 Tyr	0.118963	0.110765
31	CZ Tyr	0.105841	0.099642
32	OH Tyr	-0.238122	-0.250276
33	HH Tyr	0.195556	0.209654
34	OXT (COO^-)	-0.561581	-0.562386

*Note: numbers and chemical symbols of atoms are given according to Figure 1

4. Conclusion

As a result of the calculations, the similar and different features of the spatial and electronic structures of the Ala-Tyr dipeptide were determined. The obtained results are the basis for understanding the physiological action mechanism of the molecule at the molecular level and can be used in the design of new peptidomimetics.

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