

## Quantum chemical calculations of Ile-Trp ACE inhibitor

Sara G. Rahimzade\*<sup>1,2</sup>, Gulnara A. Akverdieva<sup>†2</sup>

<sup>1</sup>Physics Faculty, Baku State University, Baku, Azerbaijan

<sup>2</sup>Division of Biophysics, Institute for Physical Problems, Baku State University, Baku, Azerbaijan

Received 15-Jan-2025; Accepted 20-Feb-2025

DOI: <https://doi.org/10.30546/209501.101.2025.2.300.010>

### Abstract

Ile-Trp (Isoleucine-Tryptophan) dipeptide is a compound with antihypertensive and high antioxidant effects. This is due to its ability to inhibit angiotensin-converting enzyme (ACE), which plays a role in the regulation of blood pressure. In this research, the geometric and electronic parameters of the Ile-Trp molecule, HOMO and LUMO energies, energy gap, dipole moment, and partial charges of atoms were studied by PM3 quantum chemical method. The initial coordinates of the molecule were determined by the molecular mechanics method. The obtained results can be used in the investigation of the structure-function relationships and the study of the pharmacological properties of the Ile-Trp dipeptide.

**Keywords:** Ile-Trp dipeptide; spatial structure; electronic parameters; HOMO and LUMO orbitals; PM3 quantum-chemical method; partial atomic charges.

**PACS:** 87.15.-v, 87.15. A-, 87.15.B-, 87.14.-g, 87.14-ef, 87.15.hp

### 1. Introduction

Cardiovascular diseases and diabetes are among the leading causes of death globally. Therefore, the prevention of these diseases is a focus of pharmaceutical and functional food manufacturers. Bioactive peptides have high potential for use in therapeutic drug and functional food formulations in cardiovascular diseases and diabetes. Such peptides have a positive effect on the body by reducing the risk of certain diseases or certain health-related problems [1, 2].

\*Corresponding author. Tel.: (+994) 51 398 04 64

e-mail: [sara.rehimzade@gmail.com](mailto:sara.rehimzade@gmail.com); ORCID ID: 0009-0000-3397-1899

<sup>†</sup>e-mail: [hagverdiguynara@gmail.com](mailto:hagverdiguynara@gmail.com); ORCID ID: 0000-0003-1851-2234

Nature has a variety of biologically active peptides that are used as the most important sources for drug discovery [3]. More than 7000 natural peptides have been identified and these peptides play important roles in human biological activities (hormones, growth factors, etc.). Peptides are an excellent starting point for the design of new therapeutic drugs due to their pharmacological and intrinsic properties [4]. The increasing interest in peptide-based therapeutics in recent years is due to advances in drug delivery systems.

Dipeptides are short peptide molecules formed by a peptide bond between two amino acids and participate in various biological processes such as protein synthesis, nutrient absorption, cellular signaling, and immune response. Due to their biological compatibility and non-toxicity, dipeptides are widely used in the field of biomedicine [5].

Ile-Trp dipeptide is a natural dipeptide found in various food sources, including milk, eggs, and meat. Ile-Trp has been shown to have a number of health-related activities (angiotensin-converting enzyme (ACE) inhibitory activity - plays a role in regulating blood pressure, antioxidant activity - plays a role in protecting the body from chronic diseases such as cancer and heart disease, and antimicrobial activity - plays a role in protecting against infectious microbes) [6, 7].

In this work, the structural features, electronic parameters, energy contours, and a number of molecular properties of the Ile-Trp dipeptide were investigated using molecular modeling based on molecular mechanics and PM3 quantum mechanical calculations.

## 2. Calculation methods

Quantum chemical calculations are a convenient method for designing new molecules and studying their structural, molecular, and reactivity properties. The conformational structures of the Ile-Trp dipeptide have been studied using molecular mechanics and PM3 quantum-chemical method. The goal of conformational analysis is to elucidate the conformational properties of flexible biomolecules and to understand the relationship between their flexibility and function. Due to the importance of this approach, conformational analysis plays an important role in many calculations, from computer-aided drug design to the analysis of molecular dynamics simulations and protein folding. In quantum chemistry, there are various types of theories such as ab-initio calculations, semi-empirical methods, density functional theory, molecular mechanics, and molecular dynamics methods [8].

Molecular mechanics is a computational scheme that calculates the structure of a molecule using a force field developed from experimental or ab-initio calculations. Molecular mechanics (MM) is based on classical physics instead of quantum mechanics. It does not use wave functions or electron density. The energy of mol-

ecules can be described by parameters such as bond stretching, bond bending, torsional, Van der Waals forces, electrostatic interactions, and hydrogen bonding [9]. The energies calculated by molecular mechanics are usually conformational energies. This means that the differences between energies calculated for various conformations must be compatible of each other.

Molecular mechanics methods can be parameterized for a specific class of molecules, such as proteins or nucleotides. Depending on the type of molecules, most force fields are needed for parameterization. In general, parameterization is performed based on the results of experimental and ab-initio calculations. Force fields are used to describe the potential energy of a system. Commonly used force fields include Amber, Charmm, Gromos, MMFF, etc. This method is particularly used in conformational analysis and is both faster than other methods and can be applied to very large molecules. Molecular mechanics methods cannot be used to determine new structures and conformations of molecules outside the parameterization range [9]. The main advantage of molecular mechanics methods is that they allow modeling of large molecules, such as proteins and DNA segments.

The study of the spatial structure of the molecule was carried out using the program in [10, 11]. This program is based on the matrix method principle of Hermans and Ferro [12]. The accepted nomenclature and conventions are recommended by IUPAC-IUB [13].

Semi-empirical methods, like ab-initio methods, depend on the solution of the Schrödinger equation [9]. However, semi-empirical methods can be derived from Hartree-Fock or density functional theory by applying systematic approximations, which makes these methods an efficient computational method that is several times faster than ab-initio calculations. Such efficiency, together with modern computational tools and algorithms, allows semi-empirical methods to be applied to very large molecular systems with a large number of conformations. [14]. Semi-empirical methods use approximations that simplify the HFR equations based on the most general empirical regularities. Semi-empirical methods are AM1, PM3, SAM1, INDO, MNDO, MINDO, ZINDO, etc. methods.

The electronic parameters of the Ile-Trp dipeptide (in the zwitterionic form) were calculated using PM3 quantum chemical method with the HyperChem 8.03 software package (<http://www.hyper.com>).

PM3 is a semiempirical method used in quantum chemistry for the quantum calculation of molecular electronic structure, and is based on the method of neglecting the diatomic differential overlap approximation [8].

Parametric method 3 (PM3) uses almost the same equations as AM1, with an improved set of parameters. PM3 is currently one of the most widely used methods for organic systems. It provides more accurate values for hydrogen bond angles than AM1, but AM1 is a more accurate method for calculating hydrogen bond

energies. PM3 and AM1 are more suitable than other semi-empirical methods because of the availability of algorithms to incorporate solvent effects into these calculations. Another advantage of the PM3 method is that it can calculate energies and bond lengths more accurately than the AM1 or MNDO methods [9, 14].

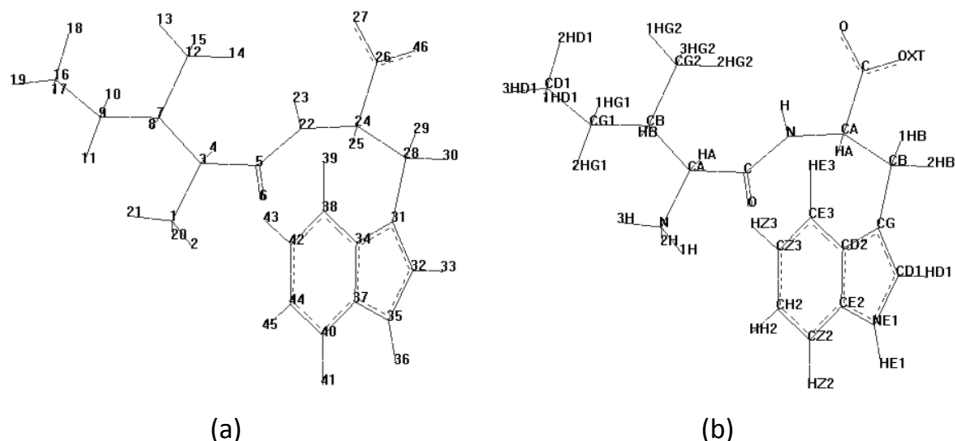
PM3 calculations on the Ile-Trp dipeptide allow us to obtain information about its structure, energy, and other properties. By using PM3 method, we can obtain the values of various electronic properties of this molecule, such as HOMO-LUMO energies, ionization potential, and electron affinity, as well as insights into the reactivity and charge transport of the molecule.

### 3. Results and discussion

First, the conformational profiles of the Ile-Trp dipeptide were investigated using molecular mechanics method. Conformational analysis is a key tool used for optimization. Furthermore, this method allows us to obtain information about the structural properties of various drug variants through conformational analysis, even when the 3D structure of the binding site is unknown. Conformational sampling is the process used to generate a list of molecular conformations to be analyzed. Ideally, all locally stable conformations of the molecule should be considered for a complete conformational analysis. However, due to the complexity of proteins and even relatively small peptides, such a list is not feasible. The number of locally stable conformations increases so rapidly with molecular size that a complete list becomes difficult. It becomes rapidly difficult to map all possible  $\{\phi, \psi\}$  conformations of the molecule backbone. Consequently, most conformational studies must rely on sampling methods. The main requirement of such sampling procedures is that the final selected conformational sample will characterize the system as a whole [16].

The computational model of Ile-Trp dipeptide is presented in Figure 1. The conformations of amino acids are characterized by the angles of the main chain ( $\phi, \psi$ ) and the side chain ( $\chi_1, \chi_2, \dots$ ). The main chains of the amino acid residues that make up the molecule can be in the forms  $R(\phi, \psi = -180^\circ - 0^\circ)$ ,  $B(\phi = -180^\circ - 0^\circ, \psi = 0^\circ - 180^\circ)$ ,  $L(\phi, \psi = 0^\circ - 180^\circ)$  according to the Ramachandran maps. BB was considered for the extended conformations of the main chain of the Ile-Trp dipeptide, and RR for the folded conformations. The  $\chi$  angles of the amino acid residues were given values corresponding to the stable states of their side chains. By giving rotational freedom to the torsion angles  $\phi, \psi, \omega, \chi_1, \chi_2, \dots$  of the molecule, the conformations belonging to the extended and folded forms of the main chain were calculated.

The energy parameters of the stable conformations of the Ile-Trp dipeptide were determined and are shown in Table 1. As a result, it was observed that there is a lot of differentiation in the conformations of the RR shape.



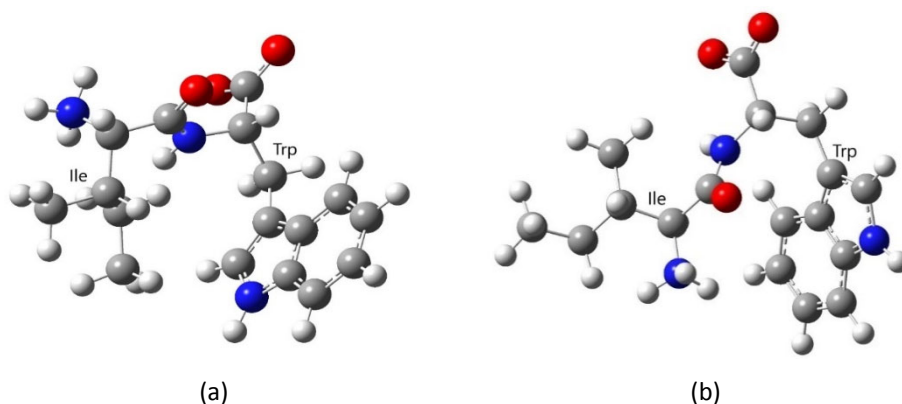
**Fig. 1.** Computational model of molecule atoms with numbering (a) and chemical labeling (b)

**Table 1.** Energy parameters of the conformations of Ile-Trp dipeptide in the energy range of 0-3 kcal/mol (kcal/mol)

Shape	Conformation	$E_{rel}$	Ile-Trp interaction energy	$E_{n-v}$	$E_{el}$	$E_{tors}$
f	R <sub>2222</sub> R <sub>11</sub>	0.49	-10.06	-6.74	-0.51	1.08
	R <sub>2222</sub> R <sub>31</sub>	0.42	-10.17	-7.21	-0.15	1.12
	R <sub>2222</sub> R <sub>12</sub>	0.92	-8.25	-6.66	-0.23	1.15
	R <sub>2222</sub> R <sub>32</sub>	2.75	-11.13	-4.6	-0.31	1.00
e	B <sub>1111</sub> B <sub>11</sub>	0.98	-7.02	-7.83	0.68	1.46
	B <sub>1111</sub> B <sub>21</sub>	2.75	-5.27	-6.42	0.90	1.61
	B <sub>1111</sub> B <sub>31</sub>	1.73	-6.88	-7.23	0.82	1.49
	B <sub>1111</sub> B <sub>12</sub>	2.08	-5.81	-6.95	0.85	1.53
	B <sub>1111</sub> B <sub>22</sub>	2.77	-5.42	-6.22	0.88	1.45
	B <sub>1111</sub> B <sub>32</sub>	0.0	-8.18	-8.64	0.68	1.29
	B <sub>3333</sub> B <sub>11</sub>	1.64	-6.90	-7.33	0.62	1.69
	B <sub>3333</sub> B <sub>31</sub>	2.4	-6.40	-6.47	0.72	1.50
	B <sub>3333</sub> B <sub>12</sub>	2.71	-5.41	-6.22	0.76	1.51
	B <sub>3333</sub> B <sub>32</sub>	0.96	-7.92	-7.93	0.64	1.59

It was determined that the global conformation of the dipeptide B<sub>1111</sub>B<sub>32</sub> ( $E_{nis}=0.0$  kcal/mol) has an extended structure of the main chain. The most stable state of the main chain of the molecule in the folded structure is the R<sub>2222</sub>R<sub>31</sub> conformation ( $E_{nis}=0.42$  kcal/mol). Compared to the extended conformation, the electrostatic interaction energy of the folded structure is 0.83 kcal/mol, and the torsional interaction energy is 0.17 kcal/mol smaller. The optimal conformations of the main chain in the folded and extended forms are shown in Figure 2. Table 2 gives the dihedral angles of these structures.

As a result of calculations, the formation of intramolecular hydrogen bonds was determined. Thus, in the extended structure, hydrogen bonds were found between the hydrogen atom of the amino group of the main chain of Trp peptide and the oxygen atom of the C-terminal carbonyl group (energy -0.76 kcal/mol, length 2.21 Å), and in the folded structure, hydrogen bonds were found between the oxygen atoms of the C-terminal carboxyl group of this dipeptide and the hydrogen atom of the amide group (energy -0.14 kcal/mol, length 2.80 Å).



**Fig. 2.** Optimal folded (a) and extended (b) structures of the Ile-Trp dipeptide

**Table 2.** Geometric parameters of the optimal folded and extended structures of Ile-Trp dipeptide

Amino acids	Torsion angles (degrees)	Conformations	
		Folded	Extended
Ile	$\phi$	-155	-198
	$\psi$	-67	149
	$\chi_1$	-60	185
	$\chi_2$	-175	184
	$\chi_3$	173	170
	$\chi_4$	-171	188
	$\omega$	-176	180
Trp	$\phi$	-102	-136
	$\psi$	-51	162
	$\chi_1$	-52	-56
	$\chi_2$	108	-101

Since each conformation has its own unique electron density distribution and electronic parameters, it is important to study the electronic structure of the Ile-Trp dipeptide. For this purpose, a number of electronic parameters, HOMO and

LUMO energies, energy gap, electric dipole moment, polarization, and partial charges of atoms were calculated for two characteristic optimal conformations of the Ile-Trp molecule using PM3 semiempirical method (Tables 3 and 4).

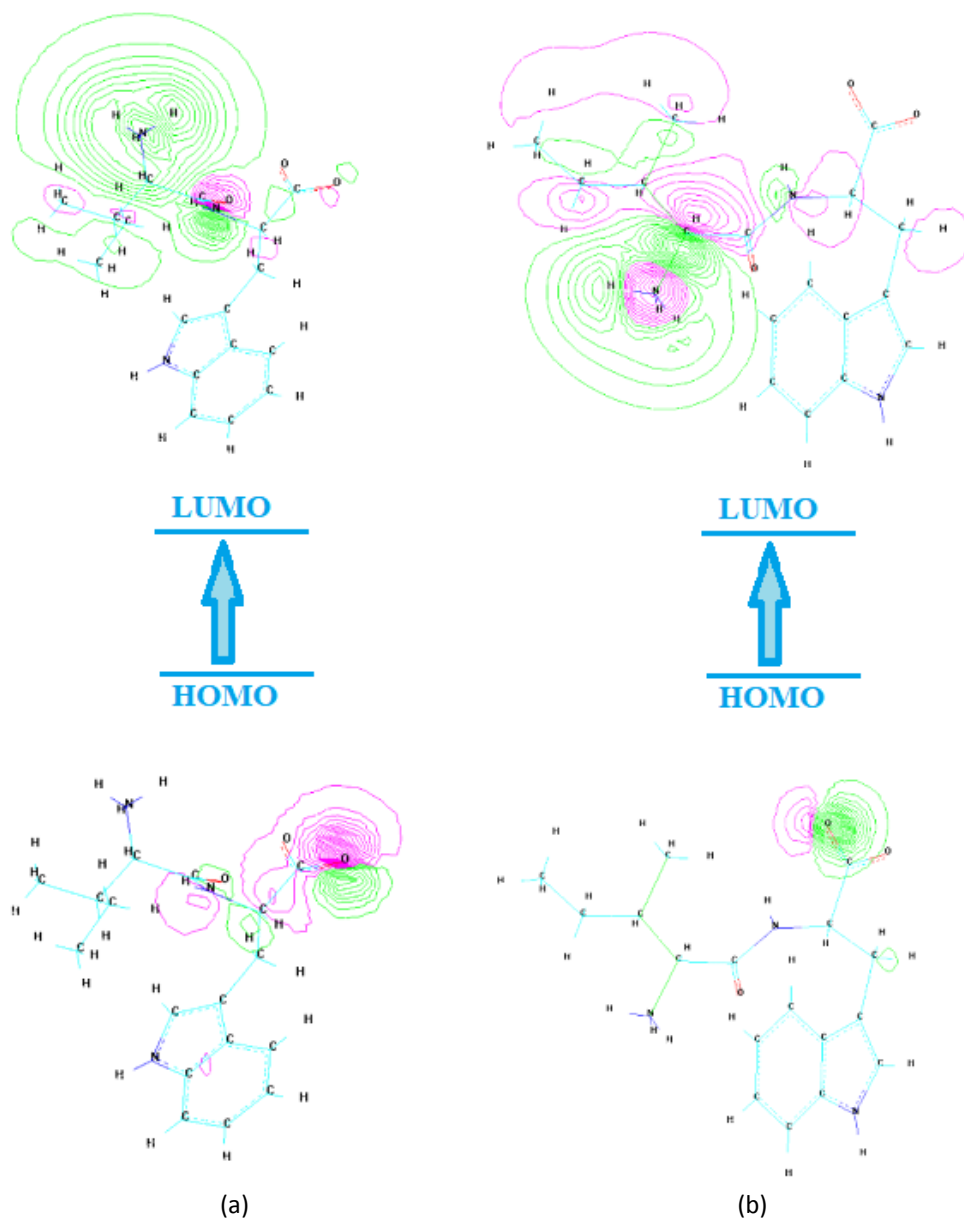
**Table 3.** Electronic parameters of the optimal folded and extended structures of Ile-Trp dipeptide

Parameters	Folded structure	Extended structure
Total energy (kcal/mol)	-86050.99	-86089.30
Binding energy (kcal/mol)	-4588.90	-4627.31
Isolated atomic energy (kcal/mol)	-81461.99	-81461.99
Electronic energy (kcal/mol)	-714467.96	-707289.87
Core-Core interaction energy (kcal/mol)	628416.97	621200.57
Heat of formation (kcal/mol)	32.16	-6.16
Dipole moment (D)	22.48	24.14
$E_{\text{HOMO}}$ (eV)	-7.34	-7.28
$E_{\text{LUMO}}$ (eV)	-1.98	-1.68
Energy gap, $\Delta E$ (eV)	5.36	5.60
Polarizability ( $\text{\AA}$ )	34.70	3.18

As can be seen from Table 3, the total energy and bond energy for folded and extended optimal structures differ by 38.41 kcal/mol, and the heat of formation by 38.41 kcal/mol. The electronic energy differs sharply by 7178.09 kcal/mol, and the internuclear interaction energy by 7159.97 kcal/mol.

HOMO (highest occupied molecular orbital) and LUMO (lowest unoccupied molecular orbital) energies are used to obtain information about the chemical reactivity and kinetic stability of a molecule, which play an important role in the quantum chemical calculations [17]. Using the values of HOMO and LUMO energies, parameters such as chemical potential, chemical hardness, softness, and electrophilic index are calculated to explain aspects related to chemical reactivity in drug design studies [18]. Data on the number of occupied molecular orbitals and virtual molecular orbitals for Ile-Trp dipeptide were obtained using PM3 method, and the results are summarized in Table 4. Green lines - represent the energies of the occupied molecular orbitals, which are the orbitals where electrons are currently present in the molecule. Pink lines - represent the energies of the unoccupied molecular orbitals, which are the orbitals where electrons could potentially be excited to. Energy gap ( $\Delta E$ ) is the difference in energy between the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO). This gap is crucial for understanding the molecule's reactivity and its ability to absorb light [19, 20].

The energy contours of the ground-state molecular orbitals (MOs) were calculated using PM3 method. Figure 3 depicts the HOMO and LUMO energy contours for the optimally folded and extended structures of Ile-Trp dipeptide, respectively.



**Fig. 3.** The frontier molecular orbitals of the optimal folded (a) and extended (b) structures of Ile-Trp dipeptide



**Table 4.** Partial atomic charges for optimized folded and extended conformations of Ile-Trp dipeptide

No of atoms	Atoms	Atomic charges (e) in folded structure	Atomic charges (e) in extended structure
1	N (NH <sub>3</sub> <sup>+</sup> )	0.823473	0.820610
2	1H (NH <sub>3</sub> <sup>+</sup> )	0.009033	0.022460
3	CA Ile	-0.323774	-0.322830
4	HA Ile	0.143108	0.130168
5	C Ile	0.166557	0.162195
6	O Ile	-0.345184	-0.447091
7	CB Ile	-0.099764	-0.099958
8	HB Ile	0.127744	0.099330
9	CG1 Ile	-0.227870	-0.119615
10	1HG1 Ile	0.045105	0.072977
11	2HG1 Ile	0.160476	0.016996
12	CG2 Ile	-0.134512	-0.138304
13	1HG2 Ile	0.084890	0.072535
14	2HG2 Ile	0.056460	0.104472
15	3HG2 Ile	0.022546	0.055926
16	CD1 Ile	-0.114497	-0.110169
17	1HD1 Ile	0.066071	0.049472
18	2HD1 Ile	0.062324	0.067463
19	3HD1 Ile	0.043000	0.050300
20	2H (NH <sub>3</sub> <sup>+</sup> )	0.040809	0.041610
21	3H (NH <sub>3</sub> <sup>+</sup> )	0.035172	0.023749
22	N Trp	0.060880	0.187467
23	H Trp	0.122392	0.100395
24	CA Trp	-0.167107	-0.185346
25	HA Trp	0.113282	0.109429
26	C (COO <sup>-</sup> )	0.406460	0.415187
27	O (COO <sup>-</sup> )	-0.556768	0.621805
28	CB Trp	-0.029871	-0.022080
29	1HB Trp	0.076476	0.073908
30	2HB Trp	0.089131	0.088755

No of atoms	Atoms	Atomic charges (e) in folded structure	Atomic charges (e) in extended structure
31	CG Trp	-0.105521	-0.111708
32	CD1 Trp	-0.317106	-0.229743
33	HD1 Trp	0.154468	0.157969
34	CD2 Trp	-0.131945	-0.127895
35	NE1 Trp	0.297187	0.312145
36	HE1 Trp	0.064436	0.069917
37	CE2 Trp	-0.134135	-0.144087
38	CE3 Trp	-0.003914	-0.055099
39	HE3 Trp	0.124429	0.115723
40	CZ2 Trp	-0.164173	-0.144229
41	HZ2 Trp	0.108526	0.113958
42	CZ3 Trp	-0.160701	-0.197520
43	HZ3 Trp	0.104837	0.098036
44	CH2 Trp	-0.054829	-0.089605
45	HH2 Trp	0.095551	0.097697
46	OXT (COO <sup>-</sup> )	-0.633153	-0.563767

\* Note: the atomic numbers and chemical symbols are given according to Fig. 1.

As can be seen, in the folded structure the HOMO contours are localized on all atoms of the peptide group, on the CA - CB bond of the Trp residue, and on the C-terminal carboxyl group, but the LUMO contours, in addition to the indicated areas, with the exception of the oxygen atoms of the C-terminal carboxyl group, are also localized on the  $\alpha$ -amino group and Ile residue. Therefore, it can be stated in the folded structure the HOMO-LUMO transition is possible on the CA – CB side chain bond of Trp residue, CA – C(COO<sup>-</sup>), and C(COO<sup>-</sup>)- OXT (COO<sup>-</sup>) bonds. In the extended structure HOMO contours are localized only on the C-terminal carboxyl group of the molecule and CB – 2HB side chain bond of Trp residue, but the LUMO contours are localized on other parts of the molecule, except the C-terminal carboxyl group and indole ring of tryptophan. We can conclude that the HOMO-LUMO transition in the extended structure is possible only on the CB – 2HB bond of tryptophane side chain. The calculated values of the HOMO-LUMO energy gaps for folded and extended structures are 5.36 and 5.60 eV, respectively (Table 3). The large values of the energy gap indicate that the molecule is stable in these structures.

Partial charges are created due to the asymmetric distribution of electrons in chemical bonds. The distribution of atomic charges in a molecule has a significant

effect on parameters such as electrostatic potential and dipole moment. Table 4 shows the atomic charges for optimal structures of Ile-Trp dipeptide calculated by PM3 method. As can be seen from Table 4, N atom of the  $\alpha$ -amino group of the molecule and the C atom of the carboxyl group, 2HG1 atom of the side chain of Ile residue, C atom of the carbonyl group, NE1 and HD1 atoms of the indole ring of Trp residue have a large positive charge. CA atoms of the main chain of Ile and Trp residues, O atom of the carbonyl group, O atoms of the carboxyl group, CG1, CG2 atoms of the side chain of Ile residue, and CD1, CZ2, CZ3 atoms of the side chain of Trp residue have a large negative charge. When comparing the charge distribution in the optimal extended and folded conformations of Ile-Trp dipeptide, it was found that as a result of the folding of the peptide chain, the oppositely charged atomic groups of the molecule come closer in space and a change in the charge distribution occurs at the atoms at the N-terminus of the molecule, in the aliphatic chain of the Ile residue, and in the indole ring of the Trp residue. Therefore, in these structures there are noticeable differences in the charges of H atoms of the  $\alpha$ -amino group, HA, HG1 atoms of the side chain of Ile residue, H atom of the amide group of the molecule, and CE3 and HZ3 atoms of the side chain of Trp residue. Such redistribution of electron density leads to a decrease in the electric dipole moment by 1.66 D.

#### 4. Conclusions

Molecular modeling of Ile-Trp having hypertensive and high antioxidant effects was carried out. At the first stage of the study the conformational profiles of compound were investigated within molecular mechanics framework. It was found that this dipeptide can exist in two stable states corresponding to the optimal folded and extended conformations. Then by the PM3 semiempirical method of quantum chemistry the electronic structure of the stable conformations of Ile-Trp was investigated. It was revealed that each of these characteristic dipeptide structures has the specific distribution of electron density, which reflects on the values of effective atomic charges of the functional groups. It was established that the folded structure of this molecule has smaller dipole moment, due to the uniformity of distribution of electron density, of the negative and positive charges.

#### References

- [1] Admassu H, Zhao W, Yang R, Gasmalla MAA, Alsir E. Development of functional foods: sea weeds (algae) untouched potential and alternative resource. *Intl J Sci Technol Res.*, 2015, 4:108–15.
- [2] Agyei D, Danquah MK. Rethinking food-derived bioactive peptides for antimicrobial and immunomodulatory activities. *Trends Food Sci Technol.*, 2012, 23:62–9
- [3] Uhlig, T., Kyprianou, T., Martinelli, F. G., Oppici, C. A., Heiligers, D., Hills, D., Verhaert, P.

The emergence of peptides in the pharmaceutical business: From exploration to exploitation. *EuPA Open Proteomics*, 2014, 4, 58–69.

<https://doi.org/10.1016/j.euprot.2014.05.003>

- [4] Fosgerau, K., & Hoffmann, T. Peptide therapeutics: current status and future directions. *Drug Discovery Today*, 2015, 20(1), 122–128. doi:10.1016/j.drudis.2014.10.
- [5] Panda, J. J., & Chauhan, V. S. Short peptide based self-assembled nanostructures: implications in drug delivery and tissue engineering. *Polym. Chem.*, 2014, 5(15), 4431–4449. doi:10.1039/c4py00173g
- [6] Huettner, C., Hagemann, D., Troschke, E., Hippauf, F., Borchardt, L., Oswald, S., ... Kaskel, S. Tailoring the Adsorption of ACE-inhibiting Peptides by Nitrogen Functionalization of Porous Carbons. *Langmuir*, 2019. doi:10.1021/acs.langmuir.9b00996
- [7] Zheng, L., Zhao, Y., Dong, H., Su, G., & Zhao, M. Structure–activity relationship of antioxidant dipeptides: Dominant role of Tyr, Trp, Cys and Met residues. *Journal of Functional Foods*, 2016, 21, 485–496. doi:10.1016/j.jff.2015.12.003
- [8] Stewart, James J. P. "Optimization of parameters for semiempirical methods I. Method". *J. Comput. Chem.* 1989, 10 (2): 209–220. doi:10.1002/jcc.540100208. S2CID 36907984
- [9] Young, D., *Computational Chemistry: A Practical Guide for Applying Techniques to Apply World Problems*. Wiley, 2004,
- [10] Akverdieva, G.A.; Godjayevev, N.M. Improvement of program of calculation of molecular conformation. *J. Modern Technol. Eng.* 2017, 2, 140-145.,
- [11] Godjayevev, N.M.; Maksumov, I.S.; Ismailova, L.I. Program of semiempirical calculations of conformations of molecular complexes. *J. Struct. Chem.* 1983, 4, 147-148. ]
- [12] Hermans, J.; Ferro D. Representation of a protein molecule as a tree and application to modular computer programs which calculate and modify atomic coordinates. *Biopolymers* 1971, 10, 1121-1129.
- [13] IUPAC-IUB, *Quantities, Units and Symbols in Physical Chemistry*, Blackwell Scientific: Oxford; 1993.
- [14] Christensen, A. S., Kubař, T., Cui, Q., & Elstner, M. (2016). Semiempirical Quantum Mechanical Methods for Noncovalent Interactions for Chemical and Biochemical Applications. *Chemical Reviews*, 116(9), 5301–5337. doi:10.1021/acs.chemrev.5b00584
- [15] Jurema, M. W., & Shields, G. C. Ability of the PM3 quantum-mechanical method to model intermolecular hydrogen bonding between neutral molecules. *Journal of Computational Chemistry*, 1993, 14(1), 89–104. doi:10.1002/jcc.540140113
- [16] Oren M. Becker, Alexander D. MacKerell Jr., Benoit Roux, Masakatsu Watanabe. *Computational Biochemistry and Biophysics*. Boca Raton, 2001, ISBN9780429207501, <https://doi.org/10.1201/9780203903827>
- [17] Rocha, M., Di Santo, A., Arias, J. M., Gil, D. M., & Altabef, A. B. Ab-initio and DFT calculations on molecular structure, NBO, HOMO–LUMO study and a new vibrational analysis of 4-(Dimethylamino) Benzaldehyde. *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy*, 2015, 136, 635–643. doi:10.1016/j.saa.2014.09.077

- [18] Jordaan, M. A., Ebenezer, O., Mthiyane, K., Damoyi, N., & Shapi, M. Amide imidic prototropic tautomerization of efavirenz, NBO analysis, hyperpolarizability, polarizability and HOMO–LUMO calculations using density functional theory. *Computational and Theoretical Chemistry*, 2021, 1201, 113273. <https://doi.org/10.1016/j.comptc>.
- [19] Cojocaru, C., Airinei, A., & Fifere, N. Molecular structure and modeling studies of azobenzene derivatives containing maleimide groups. *SpringerPlus*, 2013, 2(1). doi:10.1186/2193-1801-2-586
- [20] Grimme, S. Calculation of the electronic spectra of large molecules. *Reviews in Computational Chemistry*, 2004, 20, 153-218. <https://doi.org/10.1002/0471678856.ch3>