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STRUCTURAL ANALYSIS OF VAL-TRP DIPEPTIDE: MOLECULAR MECHANICS AND DFT CALCULATIONS

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ABSTRACT. The present study of biologically active Val-Trp dipeptide has been performed using computer modeling methods. To search the stable structures the different theoretically possible conformations of this molecule were calculated within molecular mechanics framework. The results showed that two types of conformations, folded and extended, are realized for this compound. Afterwards, the most stable conformations of the Val-Trp dipeptide were optimized using DFT/B3LYP level of theory with 6-31+G(d,p) basis set. The geometry, energy parameters, electronic properties, molecular electrostatic potential (MEP) map, highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) energies, chemical reactivity descriptors, nonlinear optical properties such as the electric dipole moment and polarizability were computed and compared for the optimized extended and folded structures of this molecule. The differences in the electronic structure between two characteristic conformations of title dipeptide were revealed. It was found the redistribution of charges as a result of folding of the peptide chain leads to a decrease in the dipole moment of this molecule. The effects of intramolecular hydrogen bonding on geometry of Val-Trp dipeptide were observed.

KEY WORDS: Val-Trp dipeptide, Molecular Mechanics, DFT calculations

INTRODUCTION

The development of the representations on the interaction mechanism of pharmaceutical substances with the receptor and the understanding of its electoral ability is possible owing to the structure-functional investigations. Many experimental works are devoted to the structure-functional investigations of biologically active molecules. Note that none of these used methods led to sufficient clarity, and even more so to a reasonable quantitative representation of the structure of such molecules. Moreover, developing a new drug, whether it is a new chemical entity or a biological therapeutic, is a very complex process that can take many years and can be very costly. Therefore, the search for new substances with specific biological activity is a problem that requires the use of modern molecular modeling techniques. One of the global challenges facing molecular modeling is to learn how to solve the problem of drug design using the structure of ligands and receptors. At present, the use of various theoretical calculation methods, and the recent achievements of computer technology, including programs with a graphic representation of spatial structures, allow researchers to construct all possible models of the pharmaceutical substance under study and its complex with specific receptors [1-4].

The influence of nutritive compounds on the prevention and treatment of hypertension has taken considerable interest in recent years. It was known that an angiotensin-converting enzyme (ACE) contains two active sites, the C- and N-domain, from which the C-domain is supposed to play a major role in blood pressure regulation and is therefore a promising pharmacological target to reduce blood pressure without side effects. It was found that tryptophan-containing dipeptides such as Ile-Trp or Val-Trp, which were recently found in food protein hydrolysates, are selective and competitive inhibitors for the C-domain with a selectivity factor of 40 and 70, respectively [5, 6]. The results of work [7] demonstrate that the angiotensin I-converting enzyme inhibitory

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peptides Val-Trp-Tyr-His-Thr and Val-Trp, isolated from the izumi shrimp hydrolysate had an antihypertensive effect on rats. It was revealed that the Val-Trp peptide constitutes a substantial portion of the overall ACE inhibitor potential of Antarctic krill (*Euphausia superba*) obtained from the huge biomass in Antarctic waters which is an important food product in Japan [8]. Systolic blood pressure decreased significantly when the hydrolysate of sake lee and peptide fraction of sake were orally administrated to spontaneously hypertensive rats [9]. Tryptophan-containing dipeptides are frequently prescribed for a range of diseases including hypertension, proteinuric chronic kidney disease, and heart failure. It was found that these compounds may have potential as dietary ingredients in the management of type 2 diabetes by virtue of their ability to scavenge reactive oxygen species and to extend the half-life of incretin molecules [10]. The antidiabetic type-2 DM potential of the tryptophan-containing peptides from tilapia skin collagen also was demonstrated in the study [11]. Alternatively, this treatment can be synergistically combined with the available antidiabetic drugs to improve the insulin secretion of type-2 DM patients. Structure-activity studies showed that an N-terminal aliphatic amino acid and a tryptophan moiety in the second position are favorable for C-domain inhibition in dipeptides. To understand the mode of interaction of inhibitors with the active site of the enzyme and subsequently to have lead compounds as possible inhibitors novel peptidomimetics have been designed and synthesized using a combinatorial chemistry approach [12, 13].

In our previous work, the tryptophan-containing immunoactive dipeptide Glu-Trp was investigated by molecular modeling methods and the model of pharmacophore for its interaction with specific receptors was proposed [14]. The object of the present study is the antihypertensive dipeptide Val-Trp (L-Valyl-L-tryptophan, H-Val-Trp-OH). So far, studies of the molecular geometry of this physiologically active dipeptide have not been carried out. Only experimental studies on valine [15] and tryptophan [16] amino acids have been reported in the literature. This study aims to reveal the conformational profiles, structural, electronic, and reactivity properties of the title molecule. At the first stage of the study, this dipeptide was investigated by molecular mechanics followed by DFT calculations. The results of the studies carried out are of great practical importance in medicine and pharmacology since they create prospects for developing peptidomimetics with high stability and efficiency. The received data may be the basis for the development of effective new antihypertensive drugs for medical purposes.

COMPUTATIONAL METHODS

The conformational profiles of Val-Trp dipeptide were investigated within molecular mechanics (MM) framework as described in [17]. MM force fields are the methods of choice for peptide and protein simulations, which are essential in the study of conformational flexibility. Given the importance of protein flexibility in drug binding, MM is involved in most if not all computational structure-based drug discovery (CSBDD) projects. The conformational potential energy of the dipeptide is given as the sum of the independent contributions of nonvalent, electrostatic, torsion interactions and hydrogen bond energies. The force field parameters for calculation are taken from the following works. The energy of nonvalent interactions was described by the Lennard-Jones 6-12 potential with the parameters proposed by Scott and Sheraga [18]. The contribution of electrostatic interactions was taken into account in a monopole approximation corresponding to Coulomb's law with partial charges of atoms as suggested by Scott and Sheraga. The effective dielectric constant was taken to be equal to ten, as described by Lipkind *et al.* [19]. The torsion energy was calculated using the value of internal rotation barriers given by Momany *et al.* [20]. A rigid valence scheme of the molecule was assumed, namely, the searches were made only on torsion angles. The molecule was calculated in zwitterionic form with the water environment. Hydrogen bonding energy was calculated based on Morse potential and the dissociation energy of the hydrogen bond was taken to be 1.5 kcal/mol. The investigations were carried out using a program for calculating molecular conformations [21, 22]. This program was developed from the

matrix method principle of Hermans and Ferro [23]. The nomenclature and conventions adopted are those recommended by IUPAC-IUB [24].

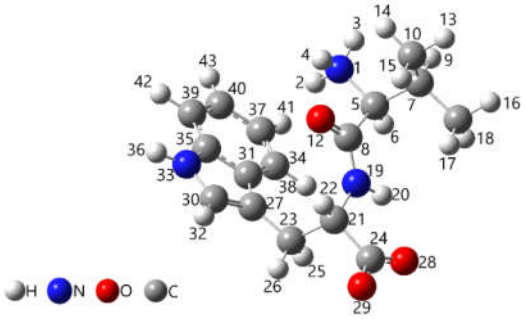
The geometry optimization of this dipeptide was computed within the framework of density functional theory (DFT) [25] using Gaussian 09 software package [26] and GaussView 6.0 [27]. The DFT method is adequate for calculating structures and energies for medium-sized systems of biological, pharmaceutical, and medicinal interest. The huge importance of DFT in physics and chemistry is evidenced by the 1998 award of the Nobel Prize to Walter Kohn for his development of the density-functional theory. DFT is now by far the most widely used electronic structure method. In this method of calculating the electronic structure, as in the Hartree-Fock method, the stationary Schrodinger equation is solved in the Born-Oppenheimer approximation, but the ground state energy of the system of interacting particles is represented as a unique function that depends only on the particle density. The replacement of the multi-electron wave function with the electron density leads to a substantial simplification of the problem, since the electron density is a function of only three spatial coordinates, and the multi-electron wave function depends on 3N variables. DFT methods that include the non-local Hartree-Fock exchange potential are called hybrid methods. The three-parameter functional B3LYP is the most widely used. The DFT/B3LYP method is fairly reliable and is widely used in the study of biological molecules. For a more reliable description of the atomic orbitals, the polarization functions can be added to the basis set, which helps to better describe the interatomic interactions and chemical bonds, and diffuse functions, which are important for the correct description of anions and weak bonds (for example, hydrogen bonds), for calculating the dipole moment, polarizability, etc. In our calculations, the hybrid density functional B3LYP with an extended basis set for the polarization and diffuse functions 6-31+G(d,p) was used [28]. Taking into account the correlation of electrons on a wide basis, the methods of the density functional theory provide accuracy comparable to non-empirical calculations.

RESULTS AND DISCUSSION

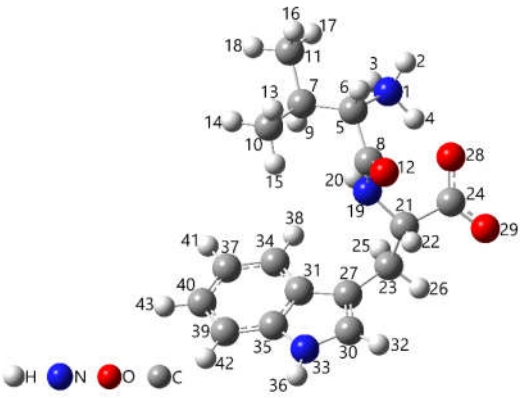
Conformational and structural analysis

The conformational profiles of Val-Trp dipeptide have been investigated on the basis of the low-energy states of Val and Trp monopeptides by molecular mechanics method. The conformational state of each amino acid residue is characterized by backbone (φ,ψ) and side chain (χ_1, χ_2, …….) torsion angles. The backbone chains of amino acid residues that construct this molecule can be in R(φ,ψ = -180º-0º), B(φ = -180º-0º, ψ = 0º-180º), L(φ,ψ = 0º-180º) forms according to low energy regions of Ramachandran maps. Since the dihedral angle ψ characterizes the spatial arrangement of two C-terminal oxygen atoms of this molecule, the B and R forms of Trp, which differ in angle ψ, can be assumed to be identical. For the above reasons, the extended shape of dipeptide backbone was represented by the BB, LB and RL forms, and the folded shape - by the RR, BL and LL forms. For the dihedral angles χ_1 of the side chain of Val and χ_1 of the side chain of Trp all three values of torsion minima 60º, 180º, -60º were considered. The value 180º for χ_2 and χ_3 of Val and the values 90º and -90º for χ_2 of Trp, which correspond to stable states of side chains of these residues, were taken. Thus, 108 conformations, belonging to the folded and extended shapes were calculated by variation of the torsion angles φ, ψ, ω of the main chain and χ_1, χ_2,…of the side chain. The geometry parameters and stabilizing interaction energies in the preferred conformations of this molecule have been determined. Calculation results reveal that 11% of the examined conformations have the relative energy up to 3 kcal/mol and both backbone shapes are equiprobable for this dipeptide. It was revealed, that the energy of dipeptide is very sensitive to the positions of the side chains of the aminoacid residues. The observed differentiation of the calculated conformations in energy is mainly determined by the nonvalent interactions. There are also insignificant stabilizing effects because of electrostatic interactions of the charged atom groups of the N-and C-terminals of the molecule. It was revealed that the conformations of the

folded shape that have the LL form and the conformations of the extended shape that have the LB and RL forms of the backbone proved to have high energy. The most stable folded conformation of this dipeptide with relative energy 0.0 kcal/mol has RR form of backbone, in this structure the dispersion, electrostatic and torsion interactions are the best balanced. The most stable extended conformation of this molecule has BB form of backbone, its relative energy is 1.79 kcal/mol. The electrostatic and torsion interactions energies of this structure are higher by 1.66 and 1.97 kcal/mol, respectively, than in the most folded conformation. Though the extended shape of this dipeptide is the best from the point of view of monopeptide energy, in the conformations of folded backbone the side chains are more close to each other and form effective contacts. Note that in the optimal folded conformation of dipeptide the side chains of the valine and tryptophan amino acid residues are coplanar and thus interact more efficiently, by 3.85 kcal/mol, than in the optimal extended structure.



(a)



(b)

Figure 1. The optimized extended (a) and folded (b) structures of Val-Trp dipeptide calculated by DFT/B3LYP/6-31+G(d,p).

Afterwards, these most stable extended and folded conformations of the Val-Trp dipeptide were optimized using DFT/ B3LYP level of theory with 6-31+G(d,p) basis set. The geometry, obtained from MM calculations was used for starting to initiate DFT calculations of Val-Trp. The optimized extended and folded structures are shown in Figure 1.

Since the amino acid residues of the title molecule have massive side chains, the dispersion interactions are an important factor for the stabilization of the spatial structure. The existence of charged atom groups at the N-and C-terminals is also essential for formation of the stabilizing electrostatic forces and hydrogen bonds. Therefore, the dipeptide energy is very sensitive to the positions of both the side chains of amino acid residues and ionogenic groups.

We assessed and compared the geometry of the optimized characteristic structures of the title molecule. Tables 1 and 2 show the calculated values of bond lengths and valence angles, as well as, for comparison, their experimental values for the constituent amino acid residues**.** As can be seen from the represented data, the insignificant deformations of some bond angles of the backbone and side chains of this molecule relative to their experimental values are occurred, but the changes in bond lengths are not observed. The torsion angles that define the stable characteristic states of title molecule are given in Table 3**.**

Table 1. The calculated and experimental values of the bond lengths (in Å) for the constituent amino acid residues of Val-Trp dipeptide.

Bond lengths	Extended structure	Folded structure	From [15, 16]	Bond lengths	Extended structure	Folded structure	From [15, 16]
N1-H2	1.03	1.021	1.03	C21-C24	1.558	1.567	1.54
N1-H3	1.023	1.022	1.05	C23-H25	1.097	1.098	1.05
N1-H4	1.030	1.100	1.04	C23-H26	1.095	1.093	1.04
N1-C5	1.511	1.526	1.49	C23-C27	1.503	1.506	1.53
C5-H6	1.091	1.091	1.11	C24-O28	1.265	1.282	1.26
C5-C7	1.550	1.543	1.53	C24-O29	1.259	1.248	1.24
C5-C8	1.544	1.541	1.54	C27-C30	1.377	1.378	1.34
C7-H9	1.099	1.099	1.10	C27-C31	1.445	1.444	1.45
C7-C10	1.537	1.538	1.52	C30-H32	1.081	1.082	1.03
C7-C11	1.537	1.538	1.52	C30-N33	1.382	1.382	1.38
C10-H13	1.094	1.096	1.09	C31-C34	1.410	1.41	1.38
C10-H14	1.095	1.098	1.08	C31-C35	1.427	1.426	1.41
C10-H15	1.097	1.094	1.08	N33-C35	1.377	1.378	1.39
C11-H16	1.094	1.096	1.09	N33-H36	1.009	1.009	1.09
C11-H17	1.095	1.095	1.09	C34-C37	1.395	1.392	1.40
C11-H18	1.095	1.094	1.08	C34-H38	1.086	1.087	1.07
C8-O12	1.242	1.232	1.20	C35-C39	1.402	1.401	1.40
C8-N19	1.336	1.360	1.32	C37-C40	1.416	1.414	1.40
N19-H20	1.017	1.014	1.00	C37-H41	1.087	1.086	1.06
N19-C21	1.462	1.464	1.45	C39-C40	1.392	1.393	1.39
C21-H22	1.092	1.092	1.00	C39-H42	1.086	1.086	1.00
C21-C23	1.558	1.544	1.54	C40-H43	1.086	1.086	1.13

The interatomic distances characterizing the contacts between the atoms of the functional groups were assessed. It was found N1-O28 is 6.0 and 2.6 Å, N1-O29 is 7.1 and 4.8 Å, H2-O28 is 6.1 and 3.1 Å, H2-O29 is 7.2 and 5.3 Å, H3-O28 is 6.8 and 3.1 Å, H3-O29 is 8.0 and 5.3 Å, H4-O28 is 6.3 and 1.5 Å, H4-O29 is 7.0 and 3.7 Å for extended and folded structures, respectively. These values represent the distances between the atoms of oppositely charged end groups of the molecule. The above data demonstrates that the mentioned distances in the optimal folded structure are shorter than those in the optimal extended structure and, thus, favour efficient interactions. As seen the values of distance between the nitrogen atom of an α-amino group and neighboring oxygen atom of deprotonated carboxyl group in the folded structure is shorter by 3 Å, which confirms the formation of the salt bridge in it. It was revealed that in the folded structure the atoms of indole ring of tryptophan residue and isopropyl group of valine residue do not approach at distances less than 5 Å, although in this structure the side chains of the constituent

residues are closer in space than in the extended. Note that the extended form of backbone makes the molecule ensures the proximity between the atoms of the side chains of valine and tryptophan acid residues to N- and C-terminal groups, respectively, so the interactions between these parts of the molecule are realized more efficiently.

The effects of intramolecular hydrogen bonding on the geometry of dipeptide molecule were observed. The DFT calculations yielded a strong intra-molecular hydrogen bonds. The possible intra-H-bonding interactions for the most stable conformations were predicted (Table 4**)**. Depending on the arrangement of the functional groups the following types of hydrogen bonds are forming in the optimized structures of Val-Trp : I - the hydrogen bonds between the hydrogens of the α-amino group and the oxygen atom of the carbonyl group of Val backbone; II - the hydrogen bonds between the hydrogen atom of amide group of Trp backbone and neighboring oxygen atom of the C-terminal carboxyl group; III - the hydrogen bonds between hydrogens of an α-amino group and neighboring oxygen atom of the C-terminal carboxyl group.

Table 2. The calculated and experimental values of the bond angles (in deg.) for the constituent amino acid residues of Val-Trp dipeptide.

Bond angles	Ext. struc.	Fold. struc.	From [15,16]	Bond angles	Ext. struc.	Fold. Struc.	From [15,16]	Bond angles	Ext. struc.	Fold. Struc.	From [15,16]
H2-N1-H3	108.1	106.6	107.3	H14-C10-H15	108.0	107.7	105.0	C23-C27-C31	127.9	127.5	126.5
H2-N1-H4	107.1	108.3	106.9	C7-C11-H16	109.5	110.8	110.9	C30-C27-C31	106.0	106.1	105.5
H2-N1-C5	110.8	111.1	110.8	C7-C11-H17	111.7	113.1	111.2	C27-C30-C32	129.4	129.6	124.3
H3-N1-H4	110.0	107.9	110.2	C7-C11-H18	111.8	109.7	112.1	C27-C30-N33	110.3	110.2	111.5
H3-N1-C5	112.8	112.1	112.3	H16-C11-H17	107.7	108.0	107.2	C32-C30-N33	120.3	120.2	-
H4-N1-C5	108.0	110.7	110.1	H16-C11-H18	107.8	108.0	107.3	C27-C31-C34	134.2	134.3	131.2
N1-C5-H6	106.3	107.0	106.7	H17-C11-H18	108.4	107.1	107.9	C27-C31-C35	107.3	107.2	107.7
N1-C5-C7	110.8	112.4	110.9	C8-N19-H20	120.9	116.5	124.0	C34-C31-C35	118.5	118.6	115.0
N1-C5-C8	103.7	105.2	109.3	C8-N19-C21	125.7	120.3	121.0	C30-N33-C35	109.2	109.3	107.4
H6-C5-C7	109.0	109.5	108.8	H20-N19-C21	113.0	114.0	115.0	C30-N33-H36	125.0	125.1	123.2
H6-C5-C8	111.3	106.2	109.0.	N19-C21-H22	108.5	107.4	110.0	C35-N33-H36	125.7	125.6	-
C7-C5-C8	115.4	116.0	111.8	N19-C21-H23	111.6	111.4	109.7	C31-C34-C37	119.3	119.2	114.6
C5-C7-H9	105.2	108.6	108.0	N19-C21-C24	108.6	110.4	107.0	C31-C34-H38	120.6	120.7	-
C5-C7-C10	114.4	109.8	114.3	H22-C21-C23	109.4	108.8	-	C37-C34-H38	120.2	120.1	122.5
C5-C7-C11	110.1	111.7	116.1	H22-C21-C24	109.8	106.8	-	C31-C35-N33	107.2	107.2	107.8
H9-C7-C10	108.4	108.0	109.0	C23-C21-C24	109.0	111.8	-	C31-C35-C39	122.5	122.5	123.2
H9-C7-C11	107.2	108.4	108.8	C21-C23-H25	107.9	109.1	109.6	N33-C35-C39	130.3	130.3	129.2
C10-C7-C11	111.1	110.7	111.8	C21-C23-H26	106.6	106.4	109.6	C34-C37-C40	121.0	121.1	124.5
C5-C8-O12	118.1	120.5	120.5	C21-C23-C27	115.7	114.5	114.2	C34-C37-H41	119.6	119.6	-
C5-C8-N19	116.1	115.5	115.0	H25-C23-H26	106.9	106.2	-	C40-C37-H41	119.3	119.3	117.7
O12-C8-N19	125.8	123.8	124.5	H25-C23-C27	110.1	109.8	-	C35-C39-C40	117.7	117.5	116.4
C7-C10-H13	109.0	111.0	110.8	H26-C23-C27	109.6	110.5	-	C35-C39-H42	121.2	121.2	121.7
C7-C10-H14	113.0	109.8	113.7	C21-C24-O28	116.3	118.1	118.3	C40-C39-H42	121.2	121.3	-
C7-C10-H15	111.5	112.1	111.3	C21-C24-O29	116.0	116.4	115.6	C37-C40-C39	121.1	121.1	119.7
H13-C10-H14	107.1	107.9	107.7	O28-C24-O29	127.7	125.5	127.5	C37-C40-H43	119.4	119.5	-
H13-C10-H15	108.1	108.3	107.8	C23-C27-C30	126.1	126.4	128.0	C39-C40-H43	119.5	119.5	120.5

Ext. struc. = Extended structure, Fold. struc. = Folded structure.

Table 3. The calculated values of torsion angles (in deg.) of Val-Trp dipeptide.

Torsion angles	Extended structure		Folded structure	
	Initial	Optimized	İnitial	Optimized
H2-N1-C5-C8 (φ of Val)	-74.9	-74.9	- 42.3	-120.6
N1-C5-C7-C10 (χ_1 of Val)	65.2	63.6	177.5	175.4
C5-C7-C10-H13 (χ_2 of Val)	176.3	-175.8	61.6	60.5
C5-C7-C11-H16 (χ_3 of Val)	179.2	173.7	-61.4	-61.6
N1-C5-C8-N19 (ψ of Val)	148.8	140.4	-64.9	-61.7
C5-C8-N19-C21 (ω of Trp)	180.0	-178.5	178.8	140.9
C8-N19-C21-C24 (φ of Trp)	-138.1	-145.2	-99.6	-72.8
N19-C21-C23-C27 (χ_1 of Trp)	-56.4	-61.4	-56.4	-63.4
C21-C23-C27-C30 (χ_2 of Trp)	-102.3	-94.4	-89.8	-78.1
N19-C21-C24-O29 (ψ of Trp)	161.7	160.8	133.9	179.4

Table 4. The hydrogen bonds (in Å) in the optimized structures of Val-Trp dipeptide.

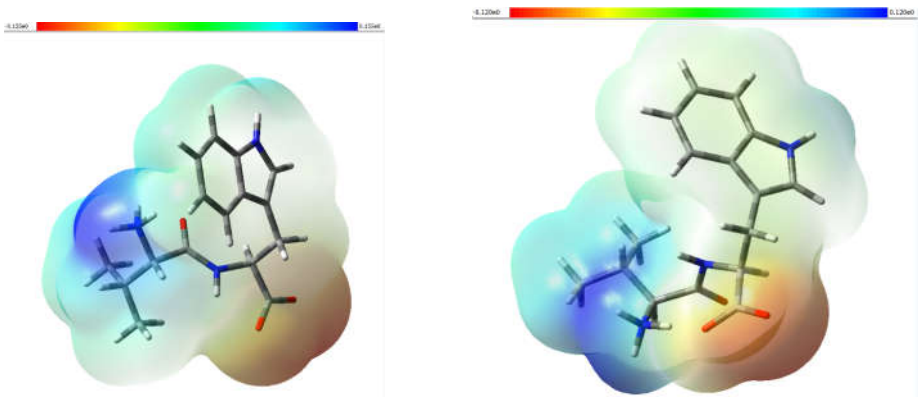
H- bond	Extended structure	Folded structure
H2 … O12 (I)	3.00	-
H3 … O12 (I)	3.57	-
H4 … O12 (I)	2.15	3.19
H20 … O28 (II)	2.16	2.81
H2 … O28 (III)	-	3.10
H3 … O28 (III)	-	3.12
H4 … O28 (III)	-	1.53

As seen, in the extended structure of the hydrogen bonds of I and II types are formed for this molecule. Since the folded structure is characterized by close positions of H_3N^+ and COO^- groups in the space, therefore there all three types of hydrogen bonds are forming in it. In the folded structure also weak hydrogen bonds are forming between the hydrogens connected with C^β atom of Trp residue and oxygens of the C-terminal carboxyl group (H25 …O28, H25… O29, H26 … O28, H26 … O29: 3.6, 3.3, 3.9, 2.6 Å). It is known that resonance interactions give the peptide bond a partial double character and therefore the atoms in the peptide bond all must lie in the amide plane. But due to H-bonding between hydrogens of the amide group, the α-amino group and the neighboring oxygen atom of the C-terminal carboxyl group (H20 … O28, H2 …O28, H3… O28, H4 … O28: 2.8, 3.0, 3.1, 1.5 Å) the structure of the amide plane is non-planar for folded structure. We investigated the dihedral angles and the geometry around the amide plane to explain its deviations from planarity. It was found that the calculated values of torsion angles C5-C8-N19-C21 and C5-C8-N19-H20 are 140.87º and -3.97º, respectively. Due to the stereochemical factors, these angles should be around values 180º and 0º respectively, for planarity. We examined also, the valence angles and the bond lengths of the amide plane of dipeptide. Due to deformation of the amide plane the value of C8-N19-H20 angle decreased by 7.5º from value 124º and the value N19-C21-C24 angle increased by 1.8º from value 111º. The mentioned deviations are related also to the interactions between electropositive and electronegative regions of the molecule.

MEP and atomic charges

The molecular electrostatic potential (MEP) maps are very useful to visualize the charged distributions. These surfaces show positive, negative and neutral electrostatic potential regions for each investigated structure of the molecule (Figure 2). These regions may be the reactive sites of molecule. The different values of the electrostatic potential at the surface are represented by different colors. Red as the most nucleophilic region and blue as the most electrophilic region

correspond to the lowest and highest electrostatic potential, respectively. As seen from the map, the negative potential region (lowest values -0.155e. and -0.120e. for the extended and folded structures, respectively) are over the oxygen atoms of the C-terminal carboxyl group of the molecule, and positive potential regions (highest values 0.155e. and 0.120e. for the extended and folded structures, respectively) are over the hydrogen atoms of the N-terminal amino group and slightly on the NH group of Trp indole ring. So, O atoms of COO^- group indicate the strongest repulsion and H atoms of NH_3^+ group indicate the strongest attraction. The mentioned active sites may be important for biological activity of the title molecule.



(a) (b)

Figure 2. Molecular electrostatic potential for the optimized extended (a) and folded (b) structures of Val-Trp dipeptide.

In [29] it is shown that the Hirshfeld method provided an excellent correlation for H atomic charge with the H–C–H bond angle, giving hydrogen charges in an agreement with an experimental study. Therefore, we chose this method for charge calculations. The calculated atomic charges of the dipeptide molecule are tabulated in Table 5. It was revealed that the distribution of electron density affects the charges of the dipeptide atoms. H-atoms of the α-amino group, C8 atom of the carbonyl group of the Val residue backbone, H20 atom of the amide group of the Trp residue backbone, C24 atom of the C-terminal carboxyl group, H36, connected with N atom of the indole ring of the side chain of Trp residue have a large positive charge, but C10 and C11 atoms of isopropyl group of Val residue, N19 atom of the amide group of the Trp residue backbone, C23 atom of Trp side chain, O28 and O29 atoms of the C-terminal carboxyl group, N33 and C34 atoms of the indole ring of Trp residue have a large negative charge; revealed sites may be donors and acceptors for possible interactions with active residues of a specific receptor.

The obtained results point out that the noticeable differences between the extended and folded favorable structures are in the charges of N1, H2, H3, and H4 atoms of the α-amino group and C10 atom of Val residue, N19 and H20 atoms of peptide group, H22 atom of Trp residue, C-terminal O28 and O29 atoms. Thus, the redistribution of charges as a result of the folding of the peptide chain is observed both for the atoms of the backbone and side chains of valine and tryptophan residues. Significant charge shift occurs both in magnitude and in sign of N1 atom of an α-amino group. In general, the molecule in both forms of backbone is negatively charged, although the charge of the extended structure is lower than the charge of the folded by 0.000062 e.

Table 5. The Hirshfeld atomic charges (in e) for the optimized structures of Val-Trp dipeptide.

Atoms	Extended structure	Folded structure
N1	0.029859	-0.008481
H2	0.167458	0.196011
H3	0.205748	0.182185
H4	0.170748	0.112774
C5	0.060220	0.055567
H6	0.072701	0.067359
C7	-0.009497	-0.013874
C8	0.181423	0.182674
H9	0.052657	0.046507
C10	-0.101579	-0.095624
C11	-0.095280	-0.093895
O12	-0.335620	-0.347320
H13	0.048244	0.043536
H14	0.040774	0.048264
H15	0.036634	0.037666
H16	0.049541	0.045023
H17	0.037087	0.043227
H18	0.044720	0.049608
N19	-0.094157	-0.120940
H20	0.121433	0.134851
C21	0.021919	0.024331
H22	0.037823	0.043388
C23	-0.058427	-0.056978
C24	0.130462	0.151989
H25	0.037929	0.042622
H26	0.039423	0.038124
C27	-0.045629	-0.048300
O28	-0.459840	-0.369707
O29	-0.486419	-0.442278
C30	-0.004226	-0.006776
C31	-0.035397	-0.038790
H32	0.069171	0.068644
N33	-0.085784	-0.088192
C34	-0.059486	-0.062804
C35	0.035998	0.031904
H36	0.167686	0.166595
C37	-0.068661	-0.074809
H38	0.048807	0.048099
C39	-0.061950	-0.068065
C40	-0.062767	-0.068875
H41	0.049481	0.044488
H42	0.056562	0.053622
H43	0.049985	0.046478
Total	-0.000231	-0.000169

The electronic parameters and molecular properties

The computed electronic parameters and physical quantities, characterized the molecular properties of Val-Trp molecule were derived from DFT calculations and they are represented in Table 6.

Table 6. The electronic parameters and molecular properties of the optimized structures of Val-Trp dipeptide.

Physical quantities	Extended structure	Folded structure
Electronic energy (eV)	-27549.147	-27549.147
E_{HOMO} (eV)	-5.755	-5.714
E_{LUMO} (eV)	-0.875	-0.762
ΔE (eV)	4.88	4.95
Dipole moment (D)	26.026	14.394
Polarizability (eV)	8225.373	8185.719

It is known that frontier molecular orbitals are involved in chemical reactivity [30, 31], as they are most accessible to electrophiles and nucleophiles. HOMO represents the ability to donate an electron, and LUMO acts as an electron acceptor. The energies of HOMO and LUMO orbitals correlate to the energies of ionization potential and electron affinity of the molecule. As can be seen from Figure 3, the frontier molecular orbital density of both structures is distributed approximately identical, only in the folded structure LUMO is also located above the α-amino group, C^{β} atom and one H^{β} atom of the valine residue of the molecule.

Therefore the HOMO-LUMO transition implies an electron density transfer to the C-terminal carboxyl group, H^{α}, C^{β} and H^{β} atoms of the tryptophan residue in the extended structure, and to the α-amino group, peptide group, C^{α} atom of the valine side chain, C^{β} and H^{β} atoms of the tryptophan residue, O atoms of the C-terminal carboxyl group in the folded structure. The calculated values of the ionization potential $I = -E_{HOMO}$ and electron affinity $A = -E_{LUMO}$ are 5.755, 0.875 eV and 5.714, 0.762 eV for the extended and folded structures, respectively. For the title molecule the values of other chemical reactivity descriptors such as electronegativity $\chi = (I+ A)/2$ (3.315 eV and 3.238 eV for extended and folded structures, respectively), hardness $\eta=(I-A)/2$ (2.440 eV and 2.475 eV for extended and folded structures, respectively), softness $S= 1/2\eta$ (0.205 eV and 0.202 eV for extended and folded structures, respectively), chemical potential $\mu= -(I+A)/2$ (-3.315 eV and -3.238 eV for extended and folded structures, respectively), electrophilicity index $\omega=\mu^{2}/2\eta$ (2.252 eV and 2.118 eV for extended and folded structures, respectively) are also calculated according theory [32-40]. The HOMO–LUMO energy gap (ΔE) is an important stability index and also it reflects the chemical activity of a molecule. As seen from the results, both structures have a large energy gap (HOMO-LUMO), high hardness, low chemical potential and softness that indicate this dipeptide is a stable and hard molecule. The calculated value of the electrophilicity index, which is a measure of the electrophilic power of the molecule, describes the biological activity of this molecule. The calculated values of total dipole moment and polarizability (α) which characterize the nonlinear optical (NLO) properties of this molecule also point out that these physical quantities are at the ground state geometry. It was revealed that the redistribution of charges on the atoms as a result of folding of the peptide chain leads to the displacement of the positive charge and decrease of the dipole moment of the molecule on 11.632 D.

Thus, the calculations identified the different features of the electronic structure of two characteristic favorable conformations of Val-Trp dipeptide. It can be concluded that the used DFT method is sensitive to the changes in the charge distribution on atoms and as result to the changes in the dipole moments, depending on the conformational rearrangements of the peptide chain of this molecule.

The received results provide an improved description of the molecular structure of Val-Trp dipeptide and may be used for structure-function relationship investigations and search for new antihypertensive drugs.

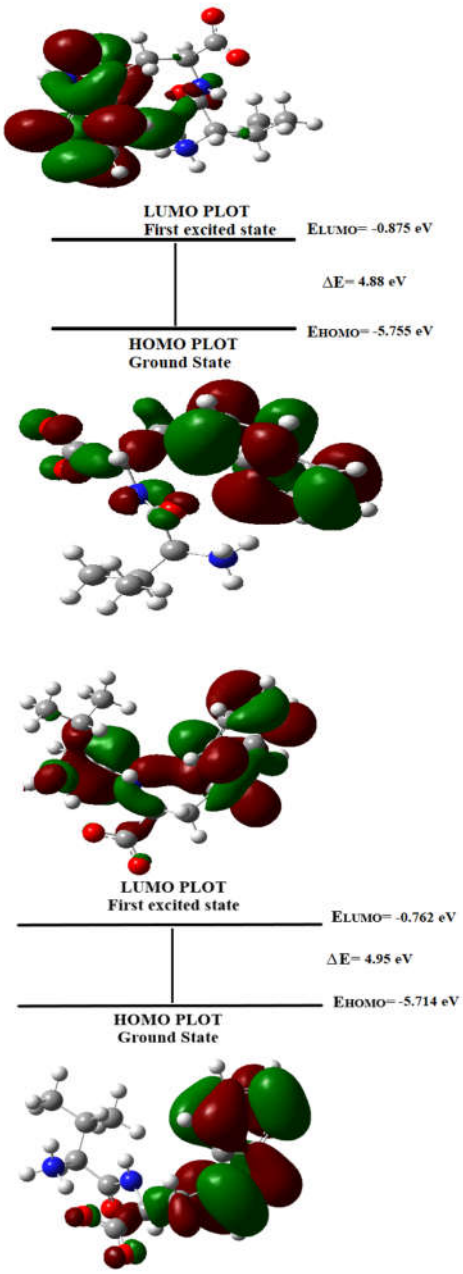


Figure 3. The HOMO and LUMO molecular orbitals for the optimized extended (upper) and folded (lower) structures of Val-Trp dipeptide (the red color indicates the negative charge and green color indicates the positive charge for the molecule).

CONCLUSION

The Val-Trp dipeptide molecule was investigated by molecular mechanics followed by DFT calculations with the B3LYP/6-31+G(d,p) basis set. It was found the stable states of this dipeptide are characterized by the extended and folded backbone shapes, the relative energies of most stable representatives of which are 0.0 and 1.79 kcal/mol, respectively. As seen from the obtained results, both structures have a large energy gap (HOMO-LUMO), high hardness, low chemical potential, and softness, which indicate this dipeptide is a stable and hard molecule in these states. The qualitative and quantitative estimates of their differences were revealed. The charge transitions due to conformational rearrangement of title dipeptide are found according to HOMO-LUMO and MEP maps analysis results. It was revealed that the redistribution of charges on the atoms as a result of folding of the peptide chain leads to the displacement of the positive charge and decrease of the dipole moment of the molecule on 11.632 D. The effects of intramolecular hydrogen bonding on the geometry of the title molecule were observed. It was found due to the interactions between electropositive and electronegative regions of the molecule and H-bonding between hydrogens of both the amide and α-amino groups with the neighboring oxygen atom of the C-terminal carboxyl group the structure of the amide plane is non-planar for folded structure.

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