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Quantum-chemical properties of Fe-Ile-Trp dimer complex

[1]Sara G. Rahimzade[*], [2]Gulnara A. Akverdieva

[1]Physics faculty, Baku State University, Baku, Azerbaijan
[2]Institute for Physical Problems, Baku State University, Baku, Azerbaijan
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Abstract

Metal complexes of the biologically active Ile-Trp dipeptide are formed by coordinating the Ile-Trp dipeptide with metal ions, most notably iron. These complexes demonstrate potential for medical use because of their immunostimulating and immunomodulating effects, as well as their ability to treat iron and immune deficiencies. We performed DFT/B3LYP calculations, using the 6-31+G(d,p) basis set, on the complex of the dimeric dipeptide Ile-Trp with iron (Fe(II). In this compound, two dipeptides, each consisting of isoleucine (Ile) and tryptophan (Trp), are bound together and chelated by iron. Within the framework of the study, the energies of frontier molecular orbitals, energy gap, chemical reactivity descriptors, atomic charge distribution, and dipole moment were calculated for the Fe-Ile-Trp dimer compound. The data obtained allowed for the accurate characterization of the stable molecular structure of the studied system. The calculations revealed that the nature of the mentioned substituent facilitates the formation of two stable, concave ring-shaped cavities through coordination bonds C16–Fe89, N34–Fe89, C60–Fe89, and N78–Fe89 between iron and side chain atoms of Ile and Trp residues. In addition, the effect of hydrogen bonds on the geometric structure of the complex was also observed. So, N21H22... O44 and N65H66 … O88 hydrogen bonds between the hydrogen atom of the amide group and the oxygen atom of the carboxyl group in the monomers formed the pseudo five-membered rings. To identify the locations of electrophilic and nucleophilic sites, or potential molecular interaction zones, the molecular electrostatic potential (MEP) maps of this complex were analyzed. The results allowed for an identification of the potential reactive sites of this compound and assessment of the Fe substituent's reactivity and the resulting chemical properties, including its catalytic and biochemical activity.

[*]*Corresponding author* – Tel.: (+994) 51 398 04 64
e-mail address: sara.rehimzade@gmail.com; *ORCID ID*: 0009-0000-3397-1899

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1. Introduction

In research paper, the dimer complex formed by the Ile-Trp dipeptide with the Fe atom was studied. Since bioactive peptides have the potential to be used as functional components in the prevention of various diseases, bioactive peptides, especially antihypertensive peptides that inhibit angiotensin-converting enzyme (ACE), are widely studied [1-4]. Recently, interest in combinatorial treatment approaches has increased, and therefore, the antioxidant properties of these peptides have also begun to attract attention [5-6]. Tryptophan-containing dipeptides are often found in the composition of pharmaceutical preparations used in the treatment of a number of diseases [7]. Therefore, the study of Trp-containing peptides is of importance.

Complexes of dipeptides, such as Ile-Trp with metal atoms, can be formed through coordination bonds between metal ions and atoms of the carbonyl, carboxyl, amino groups, and functional groups of side chains of the dipeptide. Studies on similar dimer tryptophan complexes have shown that metal ions can simultaneously interact with the aromatic indole side chain and the peptide skeleton to form stable complexes. Iron-peptide complexes play an important role in the transport and absorption of minerals within the body. Since transition metals such as iron catalyze oxidation reactions, some peptides (especially tryptophan) can "bind" these metals, significantly affecting their biochemical properties (for example, reducing their pro-oxidant effect and thus exhibiting antioxidant properties). This interaction is an important direction in the study of bioactive peptides.

We have shown that the Fe-Ile-Trp dimer complex is formed by coordination bonds between the Ile-Trp dipeptide and iron (Fe(II)). This molecule is a metal-peptide complex in which two dipeptides, each consisting of isoleucine (Ile) and tryptophan (Trp), are linked and chelated by an iron through the side chains of the constituent amino acids. This complex is considered promising in terms of application in medicine; as the Ile–Trp–Fe(II) complex has been studied for its immunostimulatory and immunomodulatory effects, as well as its potential use in the treatment of iron deficiency and immune system disorders [8].

2. Methods and Programs

The geometric structure, molecular properties, and reactivity parameters of molecules are studied through quantum-chemical calculations. In the research work, geometric optimization of the dimer complex of the dipeptide with Fe was carried out using the Density Functional Theory (DFT) method. The calculations were performed based on the hybrid B3LYP functional and the 6-31+G(d,p) basis set. The

dimer complex was optimized in a water environment using the Gaussian16 software package [9]. Since the dimer complex of the Ile–Trp dipeptide with Fe has biological activity, DFT calculations were performed in a water environment.

3. Results and Discussions

Initially, the Ile-Trp dipeptide was studied by the MM method, and the stable structures of the molecule were selected [10]. Then, these structures were optimized by DFT/B3LYP, and finally, the dimer complex of the optimal folded structure with Fe was optimized by the 6-31+G(d,p) basis set of the DFT/B3LYP method, and the geometric and energy parameters, chemical reactivity descriptors, dipole moment, and atomic charges were calculated. At the same time, the properties of the hydrogen bonds formed in the compound were also studied. For the optimized structure of the studied compound, the molecular electrostatic potential (MEP) map, HOMO and LUMO contours were visualized using the GaussView 6.0 software [11]. The optimized structure of the Fe-Ile-Trp dimer complex is shown in Figure 1.

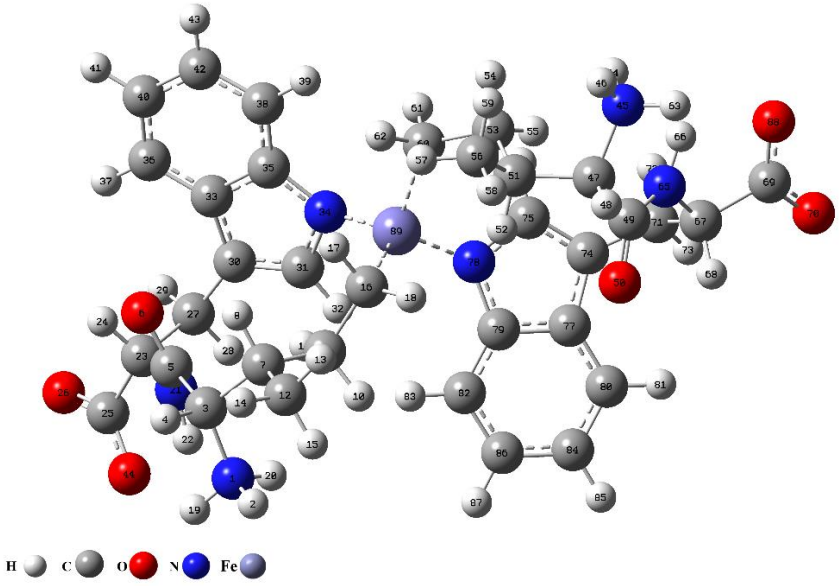

Fig 1. The optimized structure of Fe-Ile-Trp dimer complex

The geometric properties of the optimized structure of this complex formed by the folded structures of two antihypertensive Ile-Trp dipeptides with Fe were analyzed. The Fe-Ile-Trp dimer complex is formed through two concave ring-shaped cavities due to the formation of C16–Fe89, N34–Fe89, C60–Fe89, and N78–Fe89 coordination bonds. The lengths of these bonds were 1.93, 1.84, 1.95, and 1.82 Å, respectively. As can be seen, the lengths of the coordination bonds formed by the

Fe atom with both N and C atoms of the monomers are approximately the same.

The rotation angles of this molecule are given in Table 1. As seen, the torsion angles (ϕ, ψ, ω, and χ) characterizing the main and side chains of the isoleucine and tryptophan residues are not completely identical for both monomers, since they are located in symmetric positions relative to the iron within the complex. The ω angles are in the range of 176–179° in both monomers, indicating that the peptide bond retains almost complete planarity. The rotation angles surrounding the Fe–C and Fe–N bonds given in the table differ sharply between the monomers (for example, N34-Fe89-C60-C53: -160.1° and N78- Fe89-C16-C9: -81.6°, C60-Fe89-N34-C35: -40.5°, and C16-Fe89-N78-C79: 32.7°). As a result, when forming a dimeric complex of two monomers, the Fe atom forms concave, ring-shaped cavities (ensuring the stability of the complex). The dihedral angles surrounding the C16–C9 and C60–C53 bonds, N34-C35 and N78-C79 bonds also contrast significantly between the monomers (such as, Fe89–C16–C9–C7: −139.3° and Fe89–C60–C53–C51: −58.4°, Fe89-N34-C35-C33: −147.9° and Fe89-N78- C79-C82: 18.1°).

Table 1. The optimized values of torsion angles (in degrees) of Fe-Ile-Trp dimer complex

Monomer 1		**Monomer2**	
Torsion angles	Values (º)	Torsion angles	Values (º)
H2-N1-C3-C5 (ϕ of Ile)	-177.3	H46-N45-C47-C49 (ϕ of Ile)	-173.1
N1-C3-C7-C12 (χ1 of Ile)	-67.4	N45-C47-C51-C56 (χ1 of Ile)	-70.1
C3-C7-C12-H13 (χ2 of Ile)	-173	C47-C51-C56-H57 (χ2 of Ile)	-174.7
C3-C7-C9-C16 (χ3 of Ile)	155.8	C47-C51-C53-C60 (χ3 of Ile)	155.6
C7-C9-C16-H17 (χ4 of Ile)	-29.8	C51C53C60H61 (χ4 of Ile)	-178.2
N1-C3-C5-N21 (ψ of Ile)	-9.7	N45-C47-C49-N65 (ψ of Ile)	-20.5
C3-C5-N21-C23 (ω of Trp)	176.6	C47-C49-N65-C67 (ω of Trp)	178.8
C5-N21-C23-C25 (ϕ of Trp)	-134.9	C49-N65-C67-C69 (ϕ of Trp)	-141.3
N21-C23-C27-C30 (χ1 of Trp)	-54.9	N65-C67-C71-C74 (χ1 of Trp)	-55.5
C23-C27-C30-C31 (χ2 of Trp)	104.3	C67-C71-C74-C75 (χ2 of Trp)	92.8
N21-C23-C25-O25 (ψ of Trp)	164.3	N65-C67-C69-O70 (ψ of Trp)	164.9
Fe89-C16- C9-C7	-139.3	Fe89- C60- C53-C51	-58.4
Fe89-N34-C31-C30	152.3	Fe89-N78- C75-C74	163.9
Fe89-N34-C35-C33	-147.9	Fe89-N78- C79-C82	18.1
N34- Fe89-C60-C53	-160.1	N78- Fe89-C16-C9	-81.6
C60- Fe89- N34- C35	-40.5	C16 -Fe89-N78-C79	32.7

Since the calculation of atomic charges is important in quantum-chemical calculations, the Milliken atomic charges of the Fe-Ile-Trp dimer complex were calculated in [12] (Table 2). As can be seen from the table, in both monomers of the complex, the N atom of the α-amino group, the C atom of the carbonyl group, the Cδ atoms of the

side chain of the Ile residue, the Cα atom of the main chain of the Trp residue, the O atoms of the carboxyl group and the metal atom have large negative values, while the H atoms of the α-amino group, the Cα atom of the main chain of the Ile residue, and the C atom of the carboxyl group have large positive values.

Table 2. The Mulliken atomic charges (in e) of Fe-Ile-Trp dimer complex

Monomer 1		**Monomer 2**	
1	**2**	**3**	**4**
Atom	Values	Atoms	Values
N1	-0.7669	N45	-0.72638
H2	0.421505	H46	0.423431
C3	1.072044	C47	1.065274
H4	0.214145	H48	0.210109
C5	-0.78026	C49	-0.82977
O6	-0.39952	O50	-0.41192
C7	-0.35499	C51	-0.07792
H8	0.184595	H52	0.167249
C9	-0.35974	C53	-0.71996
H10	0.171259	H54	0.175543
H11	0.154968	H55	0.140391
C12	-0.69014	C56	-0.50109
H13	0.172055	H57	0.170998
H14	0.169601	H58	0.167564
H15	0.149664	H59	0.15674
C16	-0.13616	C60	-0.25725
H17	0.16344	H61	0.165456
H18	0.162718	H62	0.162634
H19	0.432655	H63	0.434687
H20	0.440382	H64	0.429611
N21	0.032006	N65	0.009007
H22	0.331498	H66	0.335593
C23	-0.55916	C67	-0.52666
H24	0.171851	H68	0.170834
C25	0.629331	C69	0.677201
O26	-0.63305	O70	-0.63604
C27	-0.19412	C71	0.069193
H28	0.148134	H72	0.151599
H29	0.168429	H73	0.16608
C30	-0.06097	C74	0.585812
C31	-0.09927	C75	-0.18345
H32	0.149956	H76	0.145218
C33	0.345546	C77	0.00248

1	2	3	4
N34	0.255791	N78	0.481362
C35	-0.09518	C79	-0.51263
C36	-0.13406	C80	-0.05622
H37	0.134734	H81	0.137598
C38	0.151129	C82	-0.12871
H39	0.125757	H83	0.110281
C40	-0.2768	C84	-0.31564
H41	0.13776	H85	0.138637
C42	-0.32237	C86	-0.24611
H43	0.138478	H87	0.138447
O44	-0.6418	O88	-0.63849
		Fe89	-0.74576

The quantum-chemical parameters and reactivity descriptors of the Fe-Ile-Trp dimer complex are given in Table 3. These parameters provide information about the electronic structure, chemical behavior, and reactivity of the complex. The values obtained for the total electronic energy, energy gap, and ionization potential of the complex indicate that this system is stable and at the same time chemically active. The low hardness and high softness values calculated for the complex indicate that it is favorable for chemical interactions. This is especially important for metal-ligand interactions and biomolecular binding. The high electrophilicity of the Fe-Ile-Trp dimer complex may allow it to interact with nucleophilic biological targets (proteins, DNA, enzyme active centers). The molecule has a strong polarity due to its 36.663 Debye dipole moment, which allows it to be well soluble in aqueous and biological environment and to have strong electrostatic interactions with proteins and enzymes.

Table 3. The reactivity descriptors of Fe-Ile-Trp dimer complex

Physical quantities	Values
Electronic energy (eV)	-91554.649
EHOMO (eV)	-5.683
ELUMO (eV)	-2.957
Energy gap ΔE=2.726 eV	2.726
Electron affinity A=[-ELUMO] (eV)	2.957
Ionization potential I=[-EHOMO] (eV)	5.683
Global hardness η=(I-A)/2 (eV)	1.363
Softness S=1/2η (1/eV)	0.367
Electronegativity χ=(I+A)/2	4.320
Chemical potential μ= -(I+A)/2	-4.320
Electrophilicity index ω=μ 2 /2η	6.846
Dipole moment (Debye)	36.663

Visualizations of the HOMO and LUMO molecular orbitals of the Fe-Ile-Trp dimer complex are given in Figure 2. As can be seen from the figure, the HOMO orbitals are localized on the Fe atom, the carboxyl group atoms, the Cα and Hα of the main chain of the Trp residue, the Cβ of the side chain, and the C atom of the indole ring of both monomers, while the LUMO orbitals are localized on the Fe atom, the phenol ring atoms of the Trp residue of both monomers, the C_1^{δ}, H_1^{δ}, H_2^{δ} atoms of the side chain of the Ile residue of monomer 1, and the C atoms of the indole ring of monomer 2.

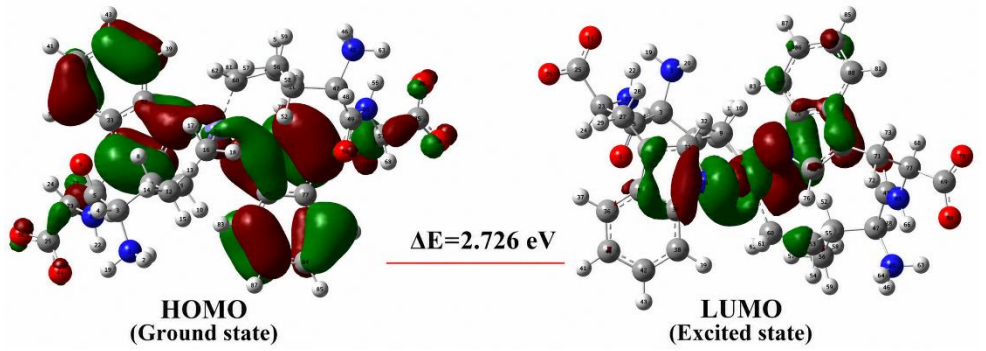

Fig. 2. The frontier molecular orbitals for Fe-Ile-Trp dimer complex

The charge distributions were visualized by molecular electrostatic potential maps (MEP). The positive, negative, and neutral electrostatic potential parts for the optimal structure of the molecule are shown in Figure 3. As can be seen from the MEP, the negative potential part (-0.184e - the most nucleophilic part) is localized on the oxygen atoms of the C-terminal carboxyl group of the molecule, and the positive potential part (0.184e - the most electrophilic part) is on the hydrogen atoms of the α-amino group of the molecule. This means that the O atoms of the COO- group exhibit a strong repulsion, and the H atoms of the NH_3^+ group exhibit a strong attraction, and these areas are of great importance in the biological activity of the molecule.

Since hydrogen bonds are one of the factors that affect the geometric structure of the molecule, the hydrogen bonds of the Fe-Ile-Trp dimer complex were also studied. Possible non-covalent interactions and their parameters are given in Table 4. As can be seen, strong hydrogen bonds are formed between the hydrogen atom of the amide group and the oxygen atom of the carboxyl group in both monomers of the Fe-Ile-Trp dimer complex. It is also formed salt bridges between oppositely charged terminal groups in each monomer unit, accompanied by the hydrogen bonding between hydrogen and oxygen atoms of these moieties of the complex.

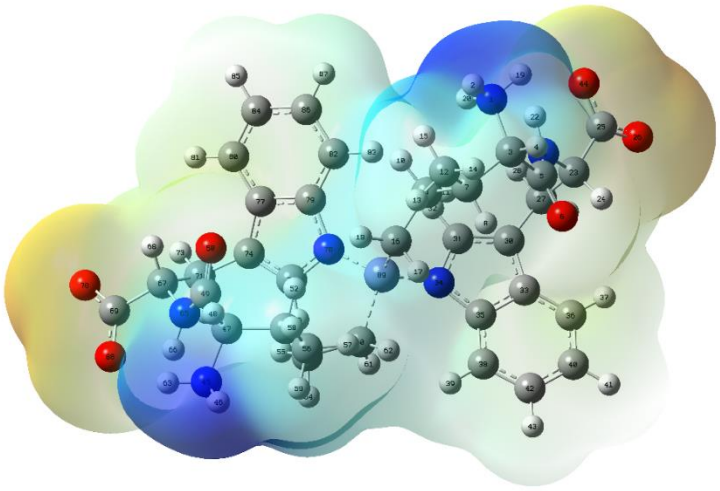

Fig. 3. The MEP maps for Fe-Ile-Trp dimer complex

Table 4. Non-covalent interactions in Fe-Ile-Trp dimer complex

DH…A	DH (Å)	H…A (Å)	D…A (Å)	∠DHA (degree)
N1H19…O6	1.025	3.946	3.677	67.458
N1H19…O44	1.025	3.739	4.315	117.892
N21H22…O44	1.018	2.074	2.618	111.050
N21H22…O26	1.018	3.667	3.584	77.320
N45H63…O50	1.025	3.863	3.661	71.043
N45H63…O88	1.025	3.836	4.312	111.116
N65H66…O70	1.019	3.661	3.583	77.595
N65H66…O88	1.019	2.063	2.613	111.398

Conclusions

The biological activity of Ile-Trp (Isoleucine-Tryptophan) complexes with Iron (Fe) is a focal point in nutritional science and pharmacology. While Ile-Trp is a power-house antihypertensive dipeptide on its own, its interaction with iron transforms it into a functional vehicle for health.

This study characterizes the electronic and structural properties of the Fe-Ile-Trp dimer complex through a comprehensive computational DFT/B3LYP/6-31+G(d,p) framework. A suite of electronic parameters: HOMO-LUMO energies and their resulting energy gap, ionization potential, electron affinity, global hardness/softness, electronegativity, chemical potential, electrophilicity index, and dipole moment were calculated to evaluate the compounds' stability and reactivity. To map the internal electronic environment, Mulliken charges were calculated to reveal charge distribution patterns. Furthermore, Molecular Electrostatic Potential (MEP) surfa-

ces were visualized to pinpoint specific sites susceptible to electrophilic or nucleophilic attack. The study examined how non-covalent interactions, specifically hydrogen bonds, influence the geometry of this complex. The results confirm that these interactions facilitate the formation of a stable complex between the isoleucine-tryptophan dimer and the iron ion.

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