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Spatial Structure of the Acth-(6-9)-PGP Molecule

Namiq Akhmedov, Leyla Agayeva, Gulnara Akverdieva, Rena Abbasli and Larisa Ismailova
Baku State University, Institute for Physical Problems Z.Khalilov 23 Str., Baku, AZ-1148, Azerbaijan.
Namig.49@bk.ru*

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Summary. The spatial structure of ACTH-(6-9)-PGP molecule has been investigated using theoretical conformational analysis method. Amino acid sequence of the N-terminal pentapeptide fragment of His-Phe-Arg-Trp-Pro of this molecule conforms to the fragment 6-9 of ACTH hormone. Calculations of conformational states of this molecule are carried out regarding nonvalent, electrostatic and torsional interactions and the energy of hydrogen bonds. The spatial structure of the His-Phe-Arg-Trp-Pro-Gly-Pro molecule was estimated on the low–energy conformations of the N-terminal tetrapeptide fragment His-Phe-Arg-Trp and C-terminal tripeptide fragment Pro-Gly-Pro of this molecule. It is shown that the spatial structure of heptapeptide molecule can be presented by 11 low-energy forms of the main chain. The low–energy conformations of this molecule, the values of dihedral angles of the backbone and side chains of the amino acid residues were founded and the energies of intra- and inter-residual interactions were determined.

Keywords: ACTH-(6-9)-PGP, Conformational analysis, Spatial structure, Conformation, Intramolecular interactions.

Introduction

As peptides, which by their nootropic and neuroprotective activity would not be inferior to Semax, various fragments of ACTH were tested: ACTH- (7-10) -PGP, ACTH- (4-10) -PGP, ACTH- (6-10) -PGP and ACTH- (5-7) -PGP. Animal experiments have shown that ACTH- (6-9) -PGP has proven to be particularly successful in terms of biological properties. This peptide not only showed nootropic and anxiolytic activity, but also increased the viability of cultured glial cells obtained from the cerebral cortex of rats with ischemic brain damage. When studying the effect of ACTH- (4-10) -PGP on the size of the necrotic focus in rats, it turned out that this peptide, like Semax, reduces the size of necrosis during the development of ischemic stroke in rats by approximately 50%. All these drugs are planned to be used as medicines. With different routes of administration, a different set of hydrolysis products is formed from the initial peptides, and it is known that the resulting shorter peptides often have their own biological activity [1].

The development of the ideas about the mechanism of action of the peptide molecules is possible due to the structural studies on the molecular level that can not be achieved solely on the basis of the experimental methods. Molecular modelling can fundamentally advance our ability to gain insights and detailed information on biomolecules. Currently, using the different theoretical calculation methods, the recent advances in computer technology allow researchers to construct the various models of the peptide molecules [2-12].

This paper is devoted to the theoretical investigation of the spatial structure of the ACTH- (6-9) -PGP molecule - His6-Phe7-Arg8-Trp9-Pro10-Gly11-Pro12. To find the conformational profiles of the peptide molecule, we used the method of theoretical conformational analysis, which allows us to calculate the three-dimensional structure of biomolecules on the basis of a known amino acid sequence. Specially introduced classification (conformation, form of the main chain, shape) made it possible to navigate in a huge number of structures under consideration, suggesting that the low-energy structure of a biomolecule is formed from separate structural blocks of smaller length, which then fit into the spatial structure of the entire molecule. The forms of residues were determined by the low-energy regions B, R, L, P of the dihedral angles of the main chain φ-ψ. The conformational state of each amino acid residue is designated by the symbol Xij, where X means one of the possible forms of the main chain B, R, L, P, and the indices jj = 11 ..., 12 ..., 13 ..., 21 ..., etc. denote the positions of the angles of the side chain χ1, χ2, χ3. Index 1 corresponds to the angle χ in the range (0–120 °), 2– (120–120 °), 3– (-120–0 °). The dihedral angles of rotation were calculated according to the standard IUPAC-IUB nomenclature [13].

The calculation was carried out within the framework of the mechanical model of molecules, taking into account non-valent, electrostatic, torsion interactions and the energy of hydrogen bonds. Non-valent interactions were assessed by Lennard-Jones potential. Electrostatic interactions were calculated in a

*To whom all correspondence should be addressed.

monopole approximation according to the Coulomb's law using partial charges on atoms. The conformational capabilities of the molecule are studied under the conditions of the water environment, in connection with which the value of the dielectric constant is assumed to be 10. The energy of hydrogen bonds was estimated using the Morse potential.

Results and Discussion

The spatial structure of the ACTH- (6-9) -PGP molecule is studied in fragments. At the first stage, the conformational properties of the N-terminal tetrapeptide fragment His6-Phe7-Arg8-Trp9 and the C-terminal tripeptide fragment Pro10-Gly11-Pro12 were studied. The results of the calculation of the tetrapeptide and tripeptide fragments are shown in Tables 1-2. The three-dimensional structure of the His6-Phe7-Arg8-Trp9 fragment was calculated based on the stable conformations of the corresponding amino acid residues. This fragment consists of polyatomic amino acid residues; therefore, there is a strong energy differentiation between the shapes, the main chain forms and the conformations. Many tetrapeptide conformations were spatially impossible, only some conformations of this fragment were spatially possible.

Table-1: Energetic contributions of nonvalent (U_{nv}), electrostatic (U_{el}), torsional (U_{tors}) interactions and relative energy (U_{rel}) of optimal conformations His6-Phe7-Arg8-Trp9 molecule

№	Shape	Conformation	U_{nv}	$U_{el.}$	$U_{tors.}$	$U_{tot.}$	$U_{rel.}$
1	eee	$B_{21}B_1\,B_{3322}B_{11}$	-22.3	3.4	1.4	-17.5	0
2	fee	$R_{13}B_1\,B_{3122}B_{11}$	-21.9	2.1	2.3	-17.5	0
3	efe	$B_{21}R_3\,B_{3322}B_{11}$	-20.7	3.3	4.4	-12.9	4.6
4	fff	$R_{11}R_3\,R_{3222}R_{11}$	-16.7	3.4	9.3	-3.9	13.6

Table-1 shows the lowest energy conformations of shapes eee, fee, efe, and fff, the contributions of non-valent, electrostatic, torsion interactions and relative energy. As can be seen from the table 1, the relative energy of the conformations of shapes eee, fee, efe and fff falls in the energy interval of 0-5.0 kcal / mol. In this case, the conformations of the fully folded shape fff have a relative energy above 13.6 kcal / mol.

Table-2: The energy distribution of the conformations of the C-terminal tripeptide fragment Pro10-Gly11-Pro12

Shape	Energy intervals (kcal / mol)					
	0-1	1-2	2-3	3-4	4-5	>5
ee	-	2	-	1	-	1
ff	2	1	-	1	-	-
ef	1	2	1	-	-	-
fe	-	1	1	1	1	-

The conformational abilities of the tripeptide fragment Pro10-Gly11-Pro12 are studied on the basis of the stable conformations of the corresponding amino acid residues. Table 2 shows *the energy distribution of the calculated conformations. The calculation results show that energy differentiation occurs according to conformations and forms of the main chain.*

Low-energy forms of the main chains of the tetra- and tripeptide fragments were used as initial approximations to study the three-dimensional structure of the heptapeptide molecule His6-Phe7-Arg8-Trp9-Pro10-Gly11-Pro12. The spatial structure of this molecule (ACTH- (6-9) -PGP) is calculated on the basis of the low-energy conformations of the N-terminal tetrapeptide and C-terminal tripeptide fragments, which are shown in Tables 1, 2.

The results of the calculation of the heptapeptide molecule ACTH- (6-9) -PGP showed that there is a strong energy differentiation between the shapes, the forms of the main chain and the conformations. The conformations of eleven shapes fall into the energy range of 0–5.0 kcal/mol. These conformations, contributions of non-valent, electrostatic and torsion energy and their relative energy are given in Table 3. The N-terminal tetrapeptide fragment has a fairly rigid structure, it is represented by three structural types fee, eee and efe. The C-terminal tripeptide fragment has a labile structure, it is represented by four shapes ff, fe, ef, and ee.

Table-3: Energy contributions of non-valent ($U_{nv.}$), electrostatic ($U_{el.}$), torsion ($U_{torc.}$) interactions and the relative energy of the optimal conformations of the ACTH- (6-9) -PGP molecule.

№	Shape	Conformation	Energy contributions			
			U_{nv}	$U_{el.}$	$U_{tors.}$	$U_{rel.}$
1	feeeff	$R_{13}B_1B_{3122}B_{11}$BPR	-28.4	-1.3	3.9	0
2	feeefe	$R_{13}B_1B_{3122}B_{11}$BLR	-27.9	-0.9	3.3	0.2
3	feeeef	$R_{13}B_1B_{3122}B_{11}$RPR	-26.9	-1.1	2.9	0.6
4	feeeee	$R_{13}B_1B_{3122}B_{11}$RLR	-26.6	-0.7	3.0	1.4
5	eeeeef	$B_{21}B_1B_{3322}B_{11}$RPR	-27.6	0.4	2.6	1.1
6	eeeefe	$B_{21}B_1B_{3322}B_{11}$BLR	-28.1	0.8	3.6	2.0
7	eeeeee	$B_{21}B_1B_{3322}B_{11}$RLR	-26.7	0.6	2.7	2.3
8	eeeeff	$B_{21}B_1B_{3322}B_{11}$BPR	-26.0	0.1	4.3	4.1
9	efeefe	$B_{21}R_3B_{3322}B_{11}$BLR	-27.9	0.5	4.6	2.9
10	efeeef	$B_{21}R_3B_{3322}B_{11}$RPR	-25.7	0.2	4.4	4.6
11	efeeff	$B_{21}R_3B_{3322}B_{11}$BPR	-25.1	-0.1	4.5	5.0

Table-4: Energy of intra-and inter-residual interactions (kcal / mol) in conformations of the molecule ACTH-(6-9) –PGP.

$R_{13}B_1B_{3122}B_{11}$BPR (U rel.=0 kcal/mol, upper line), $B_{21}B_1B_{3322}B_{11}$RPR (U rel.=1,1 kcal/mol, middle line), $B_{21}R_3B_{3322}B_{11}$BLR (U rel.=2,9 kcal/mol, lower line)

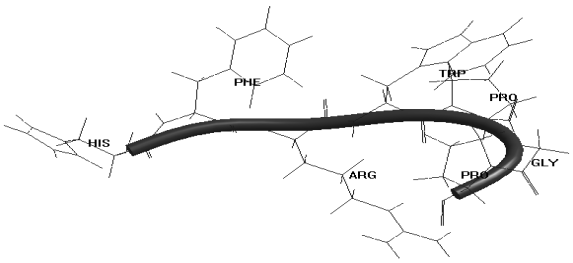
His6	Phe7	Arg8	Trp9	Pro10	Gly11	Pro12	
0.3	-5.6	-3.3	-0.4	0	0	0	His6
0.5	-3.4	-2.9	-1.3	0	0	0	
0.5	-3.8	-2.5	-2.7	-0.1	0	0	
	0.6	-3.4	-3.3	0	0	0	Phe7
	0.2	-2.9	-4.0	0	0	0	
	0.1	-2.5	-1.5	0	0	0	
		0.2	-2.7	-0.4	0.1	-0.8	Arg8
		0.6	-2.8	-0.5	0	0.3	
		0	-2.2	-0.3	0.1	-0.4	
			-0.7	-3.3	-0.9	-4.3	Trp9
			-1.0	-3.3	-2.2	-0.2	
			-1.1	-3.7	-2.0	-4.1	
				0.2	0.9	-1.5	Pro10
				0.3	-0.2	-2.6	
				0.3	0.4	-0.9	
					1.3	-4.3	Gly11
					1.4	-4.2	
					1.4	-3.6	
						1.5	Pro12
						1.5	
						1.4	

Table-4 shows the energy of intra- and inter-residual interactions in the best conformations of each structural type, and the numerical values of the geometric parameters of these conformations are shown in Table 5. Fig 1 shows the spatial arrangement of amino acids in low-energy conformations $R_{13}B_1B_{3122}B_{11}$BPR, $B_{21}B_1B_{3322}B_{11}$RPR and $B_{21}R_3B_{3322}B_{11}$BLR of the heptapeptide molecule His6-Phe7-Arg8-Trp9-Pro10-Gly11-Pro12.

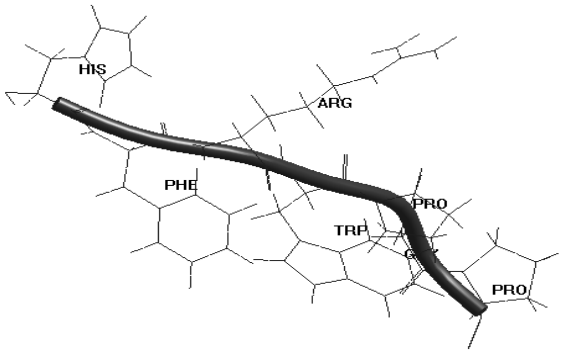
Table-5: Geometric parameters (degree) of the optimal conformations of the molecule ACTH- (6-9) –PGP (the values of the dihedral angles are given in the sequence φ, ψ, w, χ1, χ2 …...)

Residue	Conformations		
	$R_{13}B_1B_{3122}B_{11}$BPR	$B_{21}B_1B_{3322}B_{11}$RPR	$B_{21}R_3B_{3322}B_{11}$BLR
His6	-64 -38 175 65 -95	-120 139 179 180 89	-119 138 -165 -173 89
Phe7	-91 152 -178 75 87	-113 161 180 69 90	-80 -62 -173 -62 93
Arg8	-114 146 178 -53 -63 -178 -177	-119 137 -176 -74 -73 -177 -170	-125 122 177 -58 -65 -177 180
Trp9	-125 154 -179 56 102	-138 149 -179 67 106	-140 151 -179 67 98
Pro10	-60 123 -179	-60 -55 -175	-60 127 -175
Gly11	134 -78 165	135 -73 172	64 70 179
Pro12	-60 -51 179	-60 -51 179	-60 -54 179
U rel.	0	1.1	2.9

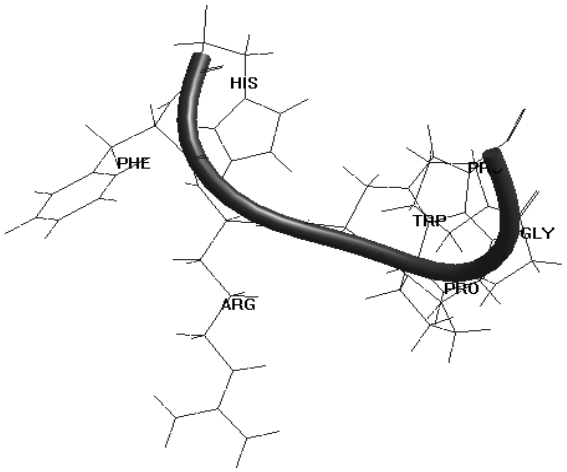
The contribution of non-valent interactions to the total energy in low-energy conformations varies in the range (-25.1) - (-28.4) kcal / mol, the electrostatic interactions in the interval (-1.3) - (0.8) kcal / mol, torsion interactions in the interval (2.6) - (4.6) kcal / mol (table 3). The lowest-energy conformations are the feee shape conformations of the N-terminal pentapeptide fragment (Table-3). The lowest-energy conformation of the ACTH- (6-9) - PGP molecule is $R_{13}B_1B_{3122}B_{11}$BPR. In this conformation, effective energy interactions of the His6 residue with the Phe7 and Arg8 residues arise, whose contribution is (-8.9) kcal / mol; Phe7 residue with Arg8 and Trp9 residues whose contribution is (-6.7) kcal / mol; Arg8 residue with Trp9 residue, the contribution of which is (-2.7) kcal / mol; Trp9 residue with Pro10 and Pro12 residues, the contribution of which is (-7.6) kcal / mol; Gly11 residue with Pro12, the contribution of which is (-4.3) kcal / mol (table 4).



a)



b)



c)

Fig. 1: Spatial structure of amino acids in low-energy conformations: a) R $_{13}$B $_{1}$B $_{3122}$B $_{11}$BPR,
b) B $_{21}$B $_{1}$B $_{3322}$B $_{11}$RPR, c) B $_{21}$R $_{3}$B $_{3322}$B $_{11}$BLR.

Three more conformations of the feee N-terminal pentapeptide structural type are low-energy, they have a relative energy of 0.2 kcal / mol, 0.6 kcal / mol and 1.4 kcal / mol (table 3). The conformation of $B_{21}B_1B_{3322}B_{11}RPR$ from the global conformation differs in the shape of the main chain of His6 and in the C-terminal tripeptide fragment Pro10-Gly11-Pro12, and has a relative energy of 1.1 kcal / mol. In this conformation, efficient interactions occur between His6 residues with Phe7, Arg8, Trp9; Phe7 with Arg8, Trp9; Arg8 with Trp9; Trp9 with Pro10, Gly11; Pro10 with Pro12 and Gly11 with Pro12 (table 4).

The efee structural type of the N-terminal pentapeptide fragment have a relative energy above 2.9 kcal / mol.

Theoretical conformational analysis of the heptapeptide molecule His6-Phe7-Arg8-Trp9-Pro10-Gly11-Pro12 led to such a structural organization of the molecule, which does not preclude the implementation of the molecule of a number of functions that require strictly specific interactions with different receptors.

Conclusion

Low-energy conformations of the ACTH-(6-9) –PGP heptopeptide molecule were found. The energy parameters of intramolecular interactions are determined and the contributions of non-valent, electrostatic and torsion interactions, as well as the energy of hydrogen bonds are estimated. Geometric parameters of the conformations of the molecule were obtained, and the conformational mobility of the side chains of amino acid residues entering the molecule was estimated.

References

1. K.V.Shevchenko, S.A.Dulov, L.A.Andreeva, I.Yu.Nagaev, V.P.Shevchenko, A.S.Radilov, N.F.Myasoedov Stability of His-Phe-Arg-Trp-Pro-Gly-Pro to Leucine Aminopeptidase, Carboxypeptidase Y, and Rat Nasal Mucus, Blood, and Plasma of Rats, *Russ. J. Bioorg. Chem.*+, **42**, 171 (2016).
2. G.A. Akverdieva., N.M. Godjaev, S. Akyuz. A. Molecular Mechanics Conformational Study of Peptide T, *J. Mol. Struct.*, **403**, 95 (1997).
3. G.A. Akverdieva., N.M. Godjaev, S. Akyuz. Conformational dynamics of peptide T molecule, *J. Mol. Struct.*, **609**,115 (2002).
4. G.A. Akverdieva., N.M. Godjaev, S. Akyuz. Comparative conformational analysis of peptide T analogs. *J. Mol. Struct.*, **917**, 21 (2009).
5. W. Qin, X.Li, W.-W. Bian, X.-J. Fan, J.-Y.Qi. Density functional theory calculations and molecular dynamics simulations of the adsorption of biomolecules on graphene surfaces, *Biomaterials*, **31**, 1007 (2010).
6. S.Kecel-Gunduz, B.Bicak, S.Celik, S.Akyuz, A.E.Ozel, Structural and spectroscopic investigation on antioxidant dipeptide, L-Methionyl-L-Serine: A combined experimental and DFT study, *J. Mol. Struct.*, **1137,** 756 (2017).
7. S. Celik, S. Kecel-Gunduz, S.Akyuz & A. E. Ozel. Structural analysis, spectroscopic characterization and molecular docking studies of the cyclic heptapeptide, *J. Biomol. Struct. Dyn.*, **36**, 2407 (2018).
8. H.Geng, F.Chen, J. Ye, F. Jiang, Applications of Molecular Dynamics Simulation in Structure Prediction of Peptides and Proteins, *C.S.B.J.*, **17,** 1162 (2019).
9. S. Celik, A.E. Ozel,V. Durak &S.Akyuz Vibrational spectroscopic characterization, quantum chemical and molecular docking studies of Valyl-Methionine dipeptide, *Int. J. Rap. Commun., Spectrosc. Lett.*, **1,** 1 (2020).
10. S. V. Efimov, M. V. Dubinin, P. P. Kobchikova. Yu. O. Zgadzay, I. A. Khodov, K. N. Belosludtsev, V. V. Klochkov. Comparison of cyclosporin variants B–E based on their structural properties and activity in mitochondrial membranes, *Biochem. Bioph. Res.Co.*, **526**, 1054 (2020).

11. V. P. Barannikov, M. S. Kurbatova, D. L. Gurina, N. Giricheva, Quantum chemical and molecular dynamics modeling of interaction of isomolecular dipeptides of α-L-alanyl-α-L-alanine and β-alanyl-β-alanine with sodium dodecyl sulfate micelles, *Comput. Theor. Chem.*, **1182**, 112844 (2020),
12. A.V.Gurbanov., M. L. Kuznetsov, S. D. Demukhamedova, I. N. Alieva, N.M. Godjaev, F. I. Zubkov, K.T. Mahmudov and A. J. L. Pombeiro. Role of substituents on resonance assisted hydrogen bonding vs. intermolecular hydrogen bonding, *Cryst. Eng. Comm.,* **22**, 628 (2020).
13. IUPAC-IUB. Quantities, Units and Symbols in Physical Chemistry, *Blackwell Scientific, Oxford* (1993)