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SPATIAL STRUCTURES OF THE N-TERMINAL ANALOGUES OF NOCICEPTIN MOLECULE

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ABSTRACT

This scientific work is devoted to study the spatial structure and conformational possibilities of the tripeptide Phe1-Gly2-Gly3 and tetrapeptide Phe1-Gly2-Gly3-Phe4 molecules. The knowledge of the structural and functional properties of these peptide molecules is of great practical importance for medicine and pharmacology. This neuropeptide molecules are stable analogues of the nociceptin molecule. The calculations were carried out by the method of theoretical conformational analysis with regard to nonvalent, electrostatic and torsional interactions, energy of the hydrogen bonds and a special computer program. The low-energy conformations of these molecules and the values of the dihedral angles of the main chains and side chains are found and the energy of the intra- and inter-residue interactions were estimated. 15 low-energy conformations were found for tripeptide for four spatial structures and 12 low-energy conformations were found for tetrapeptide for six spatial structures. It is revealed that low energy conformations of these molecules have the half-folded and folded type of backbone. The side chains of the Phe1 and Phe4 amino acids in low-energy conformations carry out effective interactions and are conformationally labile amino acids. They bring together sections of the main chain and side chains of amino acids that are part of the tri- and tetrapeptide, which leads to important interactions.

1. Introduction

It I s known, that new families of the regulatory peptides are being discovered and their properties are being studied. One of these families is nociceptins. For medicine and pharmacology, knowledge of the structure-functional properties of these peptide molecules is of great practical importance. Nociceptin is an opioid-related peptide with strong anti-analgetic properties. It is widely present in the central nervous system, affecting motor, anxiety and pain sensitivity. It is important to note that the original synthetic analogues of the N-terminal fragment of nociceptin, the tripeptide Phe1-Gly2-Gly3 (FGG) and tetrapeptide Phe1-Gly2-Gly3-Phe4 (FGGF). It causes the binding of natural nociceptin to a specific ORL1 receptor [1, 2].

More recently, new nociceptin analogues FGGF-GP, FGGF-PGP and FGGF-VGP have been synthesized. It has been shown that the FGGF-VGP peptide, like natural nociceptin, significantly reduces the level of locomotor activity of animals [3, 4]. The most pronounced effect of FGGF-GP was the anxiolytic effect. Our scientific work is devoted to study the spatial structure and

conformational possibilities of the tripeptide Phe1-Gly2-Gly3 and tetrapeptide Phe1-Gly2-Gly3-Phe4 molecules. It was found that the N-terminal tripeptide and tetrapeptide of this molecule are active [5, 6].

The short linear regulatory peptides in solutions do not have a fixed spatial structure. Usually, the amino acid sequence and physicochemical properties of the solvent determine the set of low-energy conformations of the peptide molecule. The biologically active conformation of this peptide molecule, which is realized upon interaction with the receptor molecule, is included in the set of low-energy structures. Therefore, the study of the spatial structure and conformational capabilities of peptide molecules is of great interest. The peptide molecules and thear biological functions in living systems are related with their specific spatial structures. Therefore, to understand the mechanism by which the peptides function it is necessary to know their three-dimensional structures. It is important to know the full complement of low-energy conformational states.

The calculations were carried out by the method of theoretical conformational analysis with regard to nonvalent, electrostatic and torsional interactions, energy of the hydrogen bonds and a special computer program [7]. The low-energy conformations of this molecule and the values of the dihedral angles of the main chain and side chains are found and the energy of the intra- and inter-residue interactions was estimated. The present paper is an extension of our previous investigations of structural and functional organization of peptide molecules [8-19].

2. Materials and methods

Neuropeptides play an important role in all nervous systems and structure-functional studies of these peptides is one approach to understanding this role. The objects of our scientific research are the analogues of noceciptin molecule tripeptide Phe1-Gly2-Gly3 and tetrapeptide Phe1-Gly2-Gly3-Phe4. These molecules have the amino acid Gly, which has no side chain and amino acid Phe with large and labile side chain. Our calculations were carried out by the method of theoretical conformational analysis. The potential energy of these molecules were chosen as the sum of the nonvalent, electrostatic and torsional interaction energies and the energy of hydrogen bonds. Non-valent interactions were assessed using the Lennard-Jones potential. Electrostatic interactions were calculated in the monopole approximation according to Coulomb's law using partial charges on atoms. The conformational properties of these molecules were studied in an aqueous environment, and therefore the dielectric constant was taken to be 10. The energy of hydrogen bonds was estimated using the Morse potential.

In presenting the results of the calculation of the spatial structure of these molecules we used the classification suggested in the work [20]. All structural versions according to it break down into shapes including certain forms of the main chain, each form is represented by a set of conformations. The conformations are determined by the number of rotational degrees of freedom of the side chains of the residues being included in the molecule. The conformational state of each amino residue is conveniently described by the backbone φ, ψ, ω and side chain χ_1, χ_2… dihedral angles. The terms "conformation" used in the following analysis will always imply exact quantitative characteristics of residue or fragment geometry. For a stable conformation, the φ and ψ dihedral angles are located in low-energy region R, B, L and P of the conformational map. We introduce the notion "form of a residue" to denote the region of its backbone dihedral angle. The conformation of the backbone forms of residue in a given amino acid sequence will

specify the backbone form of a fragment. Forms belonging to a particular shape have an analogous peptide chain contour and a similar mutual arrangement of backbones and side chains. Designations indications of dihedral angles have been measured up to the generally accepted nomenclature [21].

3. Results and Discussion

The three-dimensional structure and conformational possibilities of the tripeptide Phe1-Gly2-Gly3 and tetrapeptide Phe1-Gly2-Gly3-Phe4 molecules were determined based on the stable conformations of the monopeptides. It is known that the active site of the noceciptin molecule that activates the receptor is the N-terminal tetrapeptide Phe1-Gly2-Gly3-Phe4 [5, 6].

The conformational properties of the tripeptide Phe1-Gly2-Gly3 were studied based on the stable conformations of the monopeptides N-acetyl-L-phenylalanine and N-acetyl-L-glycine. For a given tripeptide containing 37 atoms and 10 variable dihedral angles, 4 shapes are possible (ee, ef, fe and ff), represented by 16 forms of the main chain. In total, about 100 conformations were calculated, all of them were minimized in energy, and their geometric and energy parameters were estimated. The calculation results are presented in Table 1. The geometric parameters of the four low-energy conformations of the tripeptide molecule are presented in Table 2.

The calculation revealed the presence of a sharp energy differentiation in the forms of the main chain and shapes. Just as in the experimental work [2], these conformations can represent four structures. The $B_{21}BL$ conformation has the lowest energy (U_{total} = -2.6 kcal/mol), which belongs to the ef shape. This semi-folded shape is represented by the largest number of low-energy conformations - 12. In the global conformation of $B_{21}BL$ (ΔU_{rel}=0 kcal/mol), the energy of nonvalent interactions is -6.4 kcal/mol, electrostatic 2.3 kcal/mol and torsional 1.5 kcal/mol. The fully unfolded form of the main chain $B_{21}BR$ (U_{total}

Table 1. The energy parameters: monopeptide (U_1, U_2, U_3), dipeptide (U_{12}, U_{23}), tripeptide (U_{13}) energies, relative energy (U_{rel}) and energy of nonvalent (U_{nv}), electrostatic (U_{el}) and torsion (U_{tors}) interactions of optimal conformations of tripeptide molecule

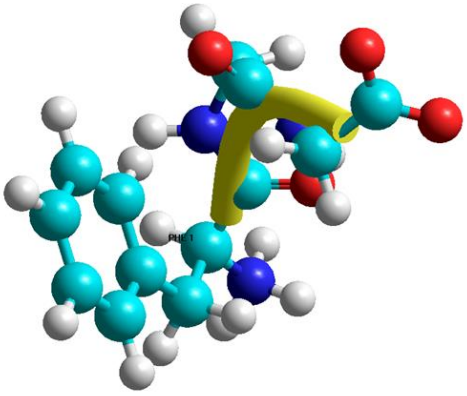
№	Shapes, conformations	U_1 monopep	U_2 tide	U_3 energy	U_{12} dipeptide	U_{23} energy	U_{13} tripeptide	U_{nv}	U_{el}	U_{tors}	U_{rel}
1	ee $B_{11}BB$	0.6	1.3	1.6	-1.4	-0.4	-4.3	-5.5	2.6	1.6	1.3
2	$B_{11}BR$	0.6	1.3	1.6	-1.4	-0.4	-4.3	-5.6	2.6	1.6	1.2
3	$B_{21}BB$	0.8	1.3	1.6	-2.4	-0.3	-4.2	-6.0	2.7	1.5	0.9
4	$B_{21}BR$	0.7	1.3	1.6	-2.4	-0.3	-4.3	-6.2	2.7	1.5	0.6
5	$B_{21}RL$	0.6	1.3	1.5	-2.2	-0.5	-3.7	-5.6	2.8	1.4	1.3
6	$R_{21}LB$	1.3	1.2	1.5	-1.9	-0.3	-3.6	-6.1	3.3	1.7	1.1
7	ef $B_{21}BL$	0.7	1.3	1.6	-2.5	-0.2	-4.9	-6.4	2.3	1.5	0.0
8	$B_{21}BP$	0.8	1.3	1.6	-2.5	-0.3	-4.9	-6.3	2.3	1.7	0.3
9	$B_{11}RB$	0.6	1.3	1.6	-2.2	-0.6	-3.1	-5.2	2.5	1.4	1.4
10	$B_{11}RR$	0.6	1.3	1.7	-1.7	-0.7	-4.1	-5.3	2.4	1.4	1.1
11	$R_{21}PR$	1.2	1.3	1.6	-1.8	-0.4	-0.5	-6.1	3.2	2.1	1.7
12	fe $B_{21}PL$	0.6	1.2	1.6	-1.7	-0.4	-2.8	-4.0	2.6	1.5	2.8
13	ff $B_{21}PB$	0.6	1.2	1.5	-1.8	-0.3	-3.8	-4.4	2.0	1.5	1.7
14	$B_{21}PR$	0.7	1.3	1.6	-1.8	-0.3	-3.8	-4.4	2.0	1.6	1.8
15	$R_{21}PL$	1.3	1.3	1.6	-1.9	-0.3	-4.7	-6.1	3.3	1.7	1.5

Table 2. Geometric parameters (degree) of the optimal conformations of Phe-Gly-Gly tripeptide molecule

Residues	Shape (conformation)			
	ee (B_{21} B R)	ef (B_{21} B L)	fe (B_{21} P L)	ff (R_{21} P L)
Phe 1	-61 149 178 174 80	-59 153 180 180 86	-59 150 179 180 86	-56 -69 -177 170 73
Gly2	-83 69 180	-78 78 177	82 - 70 180	81 -69 180
Gly3	-93 -84 180	94 71 176	88 92 180	93 85 178
U_{rel} (kcal/mol)	0.6	0.0	2.8	1.5

Note: The values of dihedral angles are given in the sequence φ, ψ, ω, χ^1, χ^2, ...

= -2.0 kcal/mol) of the ee shape is inferior to it by only 0.6 kcal/mol. The conformations of the completely folded shape ff B_{21}PR (U_{total}= -0.6 kcal/mol) are low-energy. More than 3 kcal/mol is inferior to the conformation of another half-folded shape fe B_{11}PL (U_{total} = 0.4 kcal/mol). It should be noted that the main contribution to the energy of low-energy conformations is made by dipeptide and tripeptide interactions. The main energy contribution comes from nonvalent interactions. This contribution varies in the range from -1.1 to -7.0 kcal/mol. Figures 1(a, b, c, d) represent schematically the backbone forms and positions of residues in four low-energy conformations B_{21}BR (0.6 kcal/mol), B_{21}BL (0.0 kcal/mol), B_{21}PL (2.8 kcal/mol) and R_{21}PL(1.5 kcal/mol) of the tripeptide molecule Phe1-Gly2-Gly3 (table 2).



Figures 1a. Spatial structure of the low energy conformation B_{21}BR (0.6 kcal/mol) of the tripeptide molecule

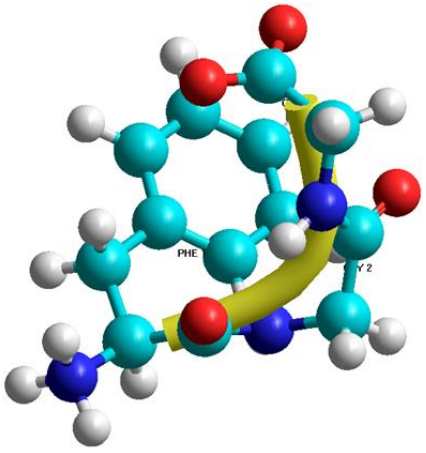


Figure 1b. Spatial structure of the low energy conformation B21BL (0.0 kcal/mol) of the tripeptide molecule

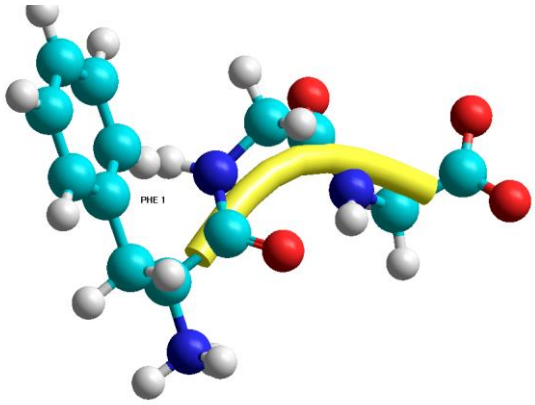


Figure 1c. Spatial structure of the low energy conformation B21PL (2.8 kcal/mol) of the tripeptide molecule

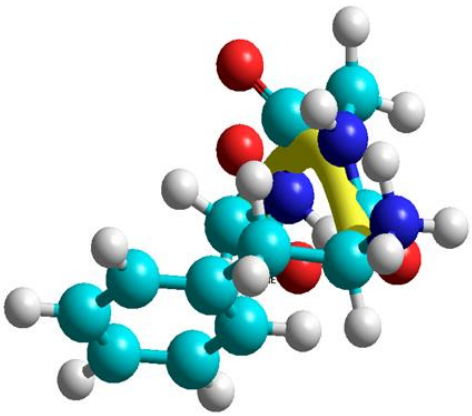


Figure 1d. Spatial structure of the low energy conformation R21PL (1.5 kcal/mol) of the tripeptide molecule

Figure 1b shows that in the global conformation $B_{21}BL$ (0.0 kcal/mol) of the tripeptide molecule, the phenylalanine side chain hangs over the backbone of the two glycines. This promotes efficient di- and tripeptide interactions. In the case of a fully folded structure $R_{21}PL$ (1.5 kcal/mol), the phenylalanine side chain is folded into the solvent and can interact with the receptor. All low-energy conformations of the tripeptide molecule were taken into account when calculating the structure of the tetrapeptide molecule Phe1-Gly2-Gly3-Phe4.

The amino acid sequence of the tetrapeptide molecule included two amino acids each phenylalanine and glycine. Tetrapeptide Phe1-Gly2-Gly3-Phe4 contains 57 atoms and 15 variable dihedral angles. The specificity of the amino acid side chains of the tetrapeptide molecule determined the number of initial approximations. In total, over 150 conformations were calculated, belonging to 64 forms of the main chain and 8 possible shapes for this molecule. All of them were minimized in energy, and their geometric and energy parameters were estimated. The calculation showed the presence of a sharp energy differentiation of conformations. Representatives of 22 forms of the main chain fall into the energy range 0 – 4 kcal/mol. The relative energy of the conformations of the tetrapeptide molecule varied within the range 0– 8 kcal/mol. There are the energy differentiation both in respect of the conformations, and forms of the main chain and shapes.

The low-energy conformations of the tetrapeptide molecule are presented in Table 3.

The global conformation of this molecule (U_{rel}=0 kcal/mol) is $B_{11}RRR_{11}$. The contribution of the stabilizing nonvalent to this conformation is (–14.6) kcal/mol, where as electrostatic interactions account for 2.6 kcal/mol and torsion for 1.9 kcal/mol. The main contributions of the interresidual interactions in this conformation were dipeptide contributions (–4.8) kcal/mol, tripeptide (–2.8) kcal/mol, tetrapeptide (–6.6) kcal/mol. In this conformation, amino acid residues Phe1-Gly2-Gly3-Phe4 form folded structure. The geometric parameters of this conformation of the tetrapeptide molecule are presented in Table 4. It is revealed that low energy conformations of this molecule have the folded and half folded types of backbone. These folded forms bring parts of the backbone and the side chains of the amino acids together, and they result in convenient interactions.

Table 3. The energy parameters: contributions of monopeptide (U_1, U_2, U_3, U_4), dipeptide (U_{12}, U_{23}, U_{34}), tripeptide (U_{13}, U_{24}), tetrapeptide (U_{14}) energies, relative energy (U_{rel}) and energy contributions of nonvalent (U_{nv}), electrostatic (U_{el}), torsion (U_{tors}) interactions of optimal conformations of the tetrapeptide molecule

	Shapes, conformations	U_1	U_2	U_3	U_4	U_{12}	U_{23}	U_{34}	U_{13}	U_{24}	U_{14}	U_{nv}	U_{el}	U_{tors}	U_{rel}
1	eee $B_{11}BBB_{11}$	-0.2	1.3	1.2	-0.3	-1.7	-0.2	-2.3	-3.0	-3.2	-1.5	-13.1	3.4	2.1	2.4
2	$R_{21}PLB_{21}$	1.3	1.3	1.3	-0.3	-1.8	0.3	-2.8	-3.5	-1.6	-2.3	-12.3	4.0	2.2	4.1
3	efe $B_{21}BLB_{11}$	-1.0	1.2	1.3	-0.3	-2.3	-0.3	-1.9	-2.6	-0.7	-6.1	-13.5	3.2	2.1	1.8
4	$B_{21}BLR_{11}$	1.2	1.2	1.3	-0.2	-2.3	-0.3	-1.9	-2.6	-0.7	-6.0	-13.2	3.2	2.0	2.1
5	eff $B_{11}RRB_{11}$	0.3	1.3	1.3	-0.4	-1.8	-0.4	-2.1	-1.8	-0.7	-6.6	-13.4	2.7	2.0	1.3
6	$B_{11}RRR_{11}$	0.1	1.3	1.3	-0.5	-2.0	-0.3	-2.5	-2.1	-0.7	-6.6	-14.6	2.6	1.9	0.0
7	fee $B_{11}PLB_{11}$	-0.2	1.3	1.3	-0.3	-1.4	0.2	-2.8	-1.2	-1.6	-4.4	-12.0	3.2	2.2	3.4
8	ffe $B_{11}PBR_{21}$	-0.1	1.3	1.3	-0.1	-1.4	0.1	-1.4	-1.0	-1.2	-3.2	-10.2	2.9	2.5	5.3
9	fff $B_{11}PRB_{11}$	0.3	1.3	1.3	-0.4	-1.4	-0.2	-2.0	-1.2	-0.6	-6.8	-11.0	0.9	2.0	2.1
10	$B_{11}LPB_{11}$	-0.1	1.3	1.3	-0.4	-1.6	0.3	-1.6	-0.4	-1.6	-7.0	-10.9	0.8	2.0	2.0
11	$B_{11}LPR_{11}$	-0.1	1.3	1.3	-0.2	-1.6	0.1	-1.6	-0.4	-1.6	-7.4	-10.8	0.8	2.0	2.0
12	$B_{11}PRR_{11}$	0.2	1.3	1.3	-0.3	-1.4	-0.3	-1.7	-1.2	-0.8	-7.3	-11.3	1.0	1.9	1.7

Table 4. Geometric parameters (degree) of the optimal conformations of Phe-Gly-Gly-Phe tetrapeptide molecule

Residues	Shape (conformation)			
	eff (B_{11} R R R_{11})	efe (B_{21} B L B_{11})	fff (B_{11} L P B_{11})	fee (B_{11} P L B_{11})
Phe 1	-67 161 176	-71 156 179	-80 166 179	-85 163 179
Gly2	-90 -69 180	-84 84 175	79 -74 176	79 -73 176
Gly3	-81 -62 -179	90 93 -179	-77 -51 -179	81 83 175
Phe 4	-150 -37 180	-147 151 180	-143 -43 180	-140 151 180
U_{rel} (kcal/mol)	0.0	1.8	1.7	3.4

Note: The values of dihedral angles are given in the sequence φ, ψ, ω, χ^1, χ^2, ...

The results can be used to study the spatial structure of tetrapeptide molecule as well as to study the conformational capabilities of side chains of the Phe1 and Phe4 when interacting with receptor molecules. The side chains of these residues have conformational freedom in the low-energy structures of the tetrapeptide molecule. Thus, the theoretical conformational analysis of this peptide molecule led to such structural organizations of molecules that do not exclude the realization by the molecule of a number of various functions that require strictly specific interactions with various receptors.

Figures 2 (a, b, c, d) represent schematically the backbone forms and positions of residues in low-energy conformations $B_{11}RRR_{11}$, $B_{21}BLB_{11}$, $B_{11}LPRB_{11}$ and $B_{11}PLB_{11}$ of the tetrapeptide molecule. The figures show that this molecule has folded N-terminal fragment of the molecule. Conformational possibilities of side chains of Phe1 and Phe4 in the best low energy conformations of peptide molecule have been investigated by plotting conformational maps. The conformational maps show that side chains of this residues have conformational freedom.

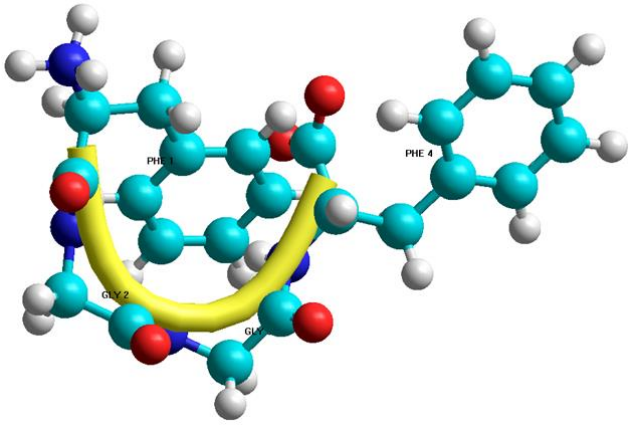
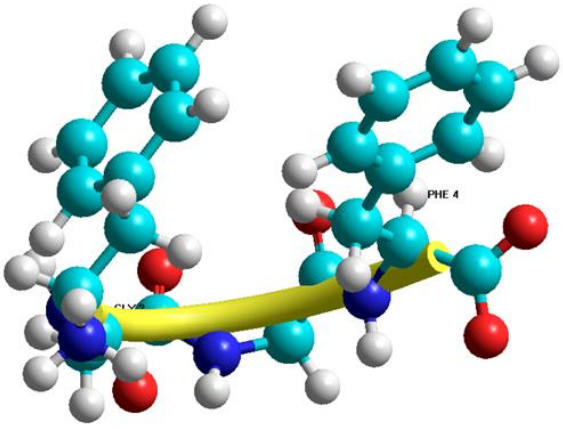


Figure 2a. Spatial structure of the low energy conformation B_{11} R R R_{11} of the tetrapeptide molecule



Figures 2b. Spatial structure of the low energy conformation B_{21} B L B_{11} of thetetrapeptide molecule

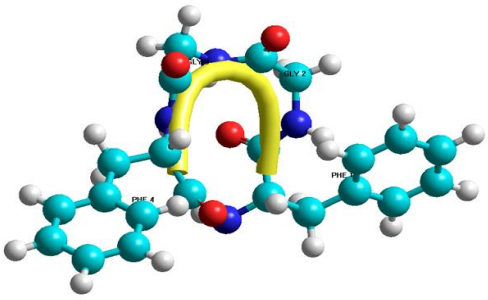


Figure 1c. Spatial structure of the low energy conformation B_{11} L P B_{11} of the tetrapeptide molecule

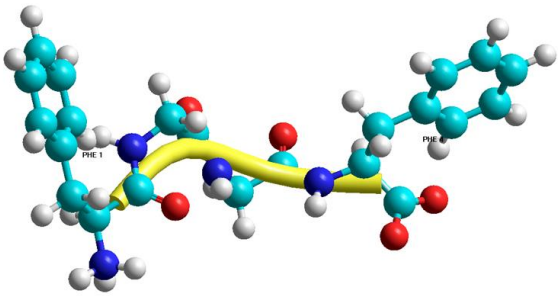


Figure 2d. Spatial structure of the low energy conformation B_{11} P L B_{11} of the tetrapeptide molecule

4. Conclusion

We have studied in detail the spatial structure and conformational properties of tri- and tetrapeptide molecules Phe1-Gly2-Gly3 and Phe1-Gly2-Gly3-Phe4. The conformational possibilities of these molecules were studied by the method of theoretical conformational analysis. The potential function of the system is chosen as the sum of non-valence, electrostatic and torsion interactions and the energy of hydrogen bonds. The low-energy conformations of these molecules, the values of the dihedral angles of the main and side chains of amino acid residues were found, the energy of intra- and inter-residual interactions was estimated. The spatial structure of the tripeptide and tetrapeptide molecules were calculated based on the low-energy conformations of the corresponding amino acid residues. It has been shown that the spatial structure of the tripeptide molecule can be represented by 15 low-energy conformations for four spatial structures and the spatial organization of the tetrapeptide can be represented by 12 low-energy conformations.

Conformational maps were constructed around the dihedral angles of the Phe1 and Phe4 side chains. The conformational maps show that almost complete conformational freedom is possible around the dihedral angles $\chi 1$ of the Phe1 and Phe4 residues. The positions of the Phe1 and Phe4 side chains found by us are energetically the most favorable. It is revealed that low energy conformations of these molecules have the half-folded and folded type of backbone.

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