ISSN 1512-1461

УДК 577.3

COMPUTER MODELING IN STUDY OF THE SPATIAL STRUCTURE OF GLYPROLINE MOLECULES

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Abstract. *One of the basic problems for molecular biophysics is investigating of the structure–functional organization of the peptide molecules. Computer modeling helps to solve this problem. This work is devoted to study the spatial organization and conformational possibilities of the glyproline molecules. The calculations were carried out by the method of theoretical conformational analysis and a special computer program. The potential energy of the each molecule was chosen as the sum of the nonvalent, electrostatic and torsional interaction energies and the energy of hydrogen bonds. The low-energy conformations of these molecules, the dihedral angles of the backbone and side chains of the amino acid residues of the di-, tri-, tetra- and pentapeptide molecules, and the energies of intra- and inter-residual interactions were determined.*

Key words: *molecule, peptide, structure, conformation*

1. Introduction

The scientific interest to the structure and function of the small biologically active peptides is very has increased in recent years mainly because of the potential pharmacological use of these molecules. The problem of spatial organization and dynamic conformational properties is very important for our understanding of molecular mechanisms of action and regulation in various biosystems. Peptides regulate all functions of a living organism. Using the regulatory peptides of the human body, you can create new and effective drugs.

It is known, that stress and inflammation lead to disorders in rats mesenteric microcirculatory system. These disorders are connected with mast cells activation. Proline and glysine containing peptides had a protective effect in microcirculatory dysfunction under conditions of inflammation and stress. This effect can be connected with these peptides ability to stabilize mast cells**.** Glyprolines are a new family of biologically active peptide drugs containing Gly (G) and Pro (P) amino asides in their structure [1-3]. Glyprolines are fragments of collagens. These molecules modulate the nervous and immune system, possess antinuclear action, glyprolines affect the blood clotting system and modulate the immunes and nervous systems.

Glyproline peptide family includes the simplest proline-containing linear peptides PG, PGP, PGPGand PGPGP. The biological functions of these peptides in living systems are related with their specific spatial structures. To understand the mechanism by which the glyprolines function, it is necessary to know their spatial structures and the full complement of low-energy conformational states. The aim of this article is to study the structural organization of PG, PGP, PGPG, PGPGP peptide molecules and their analogues with consist of amino acid Arg (R) too.

2. Method

The investigations were carried jut using the theoretical conformational analysis as described in Refs. [4]. The conformational potential energy of peptide molecules is given as the sum of the independent contributions of nonvalent (E_{nv}), electrostatic (E_{el}), torsional (E_{tors}) interactions and hydrogen bonds (E_{hb})

ISSN 1512-1461

$E = E_{nv} + E_{el} + E_{tors} + E_{hb}$

The energy of nonvalent interactions was described by Lennard-Jons potential with parameters proposed by Scott and Sheraga [5]

$f(r) = -Ar^{-6} + Br^{-12}$, where A, B – empiric parameters, r - distance between nonvalence atoms.

The total energy of nonvalent interactions is an additive function of pair interactions where r_{ij} is the distance between a pair of valence disjoint atoms.

The energy of electrostatic interactions was estimated by Coulombs law using partial charges on atoms $E_{el} = k\sum_{j=1}^{n-1}\sum_{j=i+1}^{n}\frac{e_i e_j}{\varepsilon r_{ij}}$ where e_i, e_j - values of partial charges on atoms, r_{ij} - is the distance between atoms, ε - the dielectric permeability of the medium, k - .the proportionality coefficient.

Torsion interactions reflect the phenomenon of braked rotation around single bonds. In peptides, the torsion potentials of the main chain and C-C bonds in the side chains of amino acids are introduced.

Is hydrogen bond-acceptor that is a weak chemical bond. The potential energy of hydrogen bonds was approximated by the Morse potential $E_{hb} = D\left[1 - \exp(-n\Delta r)\right]^2 - D$ where D – the energy of hydrogen bond dissociation, $\Delta r = r - r_0$, r_0 - is the equilibrium distance N-H…O, n – is an empirical parameter.

In presenting the results of the calculation of the spatial structure of the molecules we used the classification suggested in the work [5]. According to it all structural versions break down into shapes including certain forms of the main chain and 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 and side chain χ_1, χ_2… dihedral angles. The terms “conformational state” or “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 (R, B, L and P). The conformation of the backbone forms of residue in a given amino acid sequence will specify the backbone form of a fragment. The suggested notations are semi-quantitative characteristics of backbone geometries, which have no direct connection to the actual order of amino acids in a sequence, but merely describe interactions of backbone elements, and also reflect potential side chain interactions with the backbone and with each other. All backbone forms of a dipeptide can be classified into two types, referred to as shapes: folded (f) and extended (e). The f-shape is represented by R-R, R-B and B-L forms, and the e-shape by B-B, B-R, R-L, L-B and L-R forms. Forms belonging to a particular shape have an analogous peptide chain contour and a similar mutual arrangement of backbones and side chains, and thus should exhibit similar medium-range interaction potentialities. Differences may arise from variations in short-range interactions and conformational freedom. A shape is an entirely qualitative category not related to any particular amino acid sequence. A procedure for the minimization fragments global energy was conducted by the method of conjugate gradients using the program described [6]. Designations indications of dihedral angles have been measured up to the generally accepted nomenclature [7].

To designate conformational states of the residues there have been used X (*i, j*) - typed identifiers, where X defines low-energy regions of the conformational map φ-ψ : R (φ, ψ =-180-0^o), B (φ = -180-0^o ,ψ=0-180^o), L (φ, ψ =0-180^o), and P (φ=0-180^o,ψ= -180-0^o), *i, j*…=11…,12…,13…,21…, and etc. conform to the positions of the side chain (χ_1, χ_2…), subscript 1 corresponds to the angle χ = 0-120^o; 2 to χ = 120-(-120 ^{o}), 3 to χ = (-120)-0^o.

ISSN 1512-1461

3. Results and discassion

Regulatory peptides belong to the group of neuromodulators. They are the basis of the mechanism of regulation of the function of the human body. The elucidation of structural and functional properties of these peptides is of great practical importance in medicine and pharmacology. To determine the nature of regulatory peptides and their functions, it is necessary to study the spatial structure of these molecules.

The conformational properties of biologically active glyprolin molecules PG, PGP, PGPG, PGPGP and analogues PGR, RPG, PGPR, RPGP and PRPGP have been investigated by computer modeling method. In order to elucidate the mechanism of action of the peptide the investigation of the native three dimensional structure is necessary, that first of all requaires the infarmation about of the full set of low energy and consequently of these molecules.

The dipeptide PG contains 27 atoms and 6 variable dihedral angles. For this fragment may be 8 forms: extended BB, BR, LB, LR and folded forms RB, RR, PR, PB. The lowest energy conformations PR (E_{rel},=0,0 kcal/mol), RR(0,4 kcal/mol) and RB(1,8 kcal/mol) has folded form of the main chain . Tripeptide molecule PGP contains 39 atoms and 8 variable dihedral angles. For it are possible 32 forms of the main chain. The calculation showed that most low-energy is RRR (0,0 kcal/mol), RPR(1,1 kcal/mol) forms that have folded course of the main chain. For tetrapeptide fragment PGPG , which includes 48 atoms and 11 variable dihedral angles, it was formed more than 200 initial approximations. As a result, only a very restricted set of low-energy conformations was isolated from a great number of analysed combinations of the tetrapeptide fragment. Possible structure of the PGPG under physiological conditions may be described by a set of low-energy folded and half-folded forms of the back bone RRRR, RRRB, RRRB, PRRB. At the final stage of the analysis, a calculation of the N-terminal tetrapeptide PGPGl and the C-terminal dipeptide Gly-Pro enabled us to estimate the conformational properties of the pentapeptide molecule PGPGP. The starting conformations of this molecule were constructed from the low-energy conformations of the tetrapeptide fragment and the stable conformations of the dipeptide fragment. Thus, at the last stage a number of structures of pentapeptide molecule to be analysed amounted to 100. We carried out all of these structures by minimization over all the dihedral angles. The relative energy of the conformations of the pentapeptide varied within the range 0–6 kcal/mol. Table 1 presents the low-energy conformations all of these molecules and their Arg analogues.

Table 1. Lowest-energy conformations of glyproline molecules

№	Molecule	The low-energy conformations (forms and sheyps)
1	Pro - Gly	PR, RB, RR, (f)
2.	Pro-Gly-Pro	RRR,BPR (ff), RPR (ef), BLR (fe)
3.	Pro-Gly-Pro-Gly	RRRR, RRRB, PRRB (fff), RRRP, BPBR(ffe), RPRB(eff)
4.	Pro-Gly0Pro-Gly-Pro	RBRRR(feff), RRBPR(ffff),RPRRR(efff), RRRPR(ffef)
5.	Pro-Gly-Arg	RBB_{3222}, RBR_{3222}(fe), BPB, RRB (ff), RPR(ef)
6.	Arg-Pro-Gly	B_{1222}RB, B_{1222} BL(ef)
7.	Pro-Gly-Pro-Arg	$RRBR_{3222}$, $RRRL_{3222}$(ffe), $BPRR_{3122}$, $BPRB_{3222}$(fff)
8.	Arg-Pro-Gly-Pro	B_{2222}RPR, B_{2222} BRR(eef), B_{2222}BRL,B2222RBR(efe)
9.	Pro-Arg-Pro-Gly-Pro	BB_{2222}RPR, RB_{2222}RPR(eeef),BB_{2122}BLB(eefe)

From table 1 is seen that molecules consisting of amino acides Pro and Gly in low-energy conformations have a folded form of the main chain. This form provides the proximity of all parts of the molecules and the possibility of their interaction.

It is known that the amino acid Arg affects the cardio active system of the body. The introduction of this amino acid in the molecule leads to the fact, that low-energy conformations

ISSN 1512-1461

become half-folded shape of the main chain. In this case, the side chain of arginine is usually directed to the solvent and is able to interact with the receptor.

The low-energy conformations of these molecules, the dihedral angles of the backbone and side chains of the amino acid residues of the glyprolines, and the energies of intra- and inter-residual interactions were determined. It is revealed that low energy conformations of this molecule have the folded and half-folded type 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. The low-energy conformations of the natural peptides were used as the initial structural states to explore the conformational possibilities of the artificial analogues.

At last stage many conformational maps for side chains of amino acide residues in the low-energy conformations of the tetrapeptides were investigated on the basis of a semi empirical method of conformational analysis. The investigation of the molecular dynamics of each peptides is of great importance to understanding the mechanism of action these glyproline peptides with their receptors.

The global conformations of these molecules represent schematically the backbone forms and positions of residues in Figures 1,2,3,4 and 5. In these figures show that the C-terminal region is folded forms of the backbone of the glyproline molecules. Comparing the results obtained, we can say that with repeated glyprolines fragments Gly-Pro and Pro-Gly-Pro essential for cytoprotective activity is the C-terminal dipeptide fragment. This C-terminal dipeptide fragment Pro-Gly is present in all of the studed molecules. According to experimental data, the presence of this. fragment is responsible for the protective action meet the following molecules per cell.

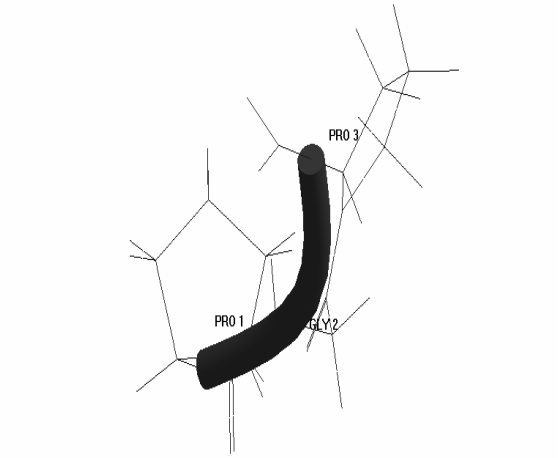

Fig. 1. Atomic model of spatial structure of Pro-Gly-Pro molecule.

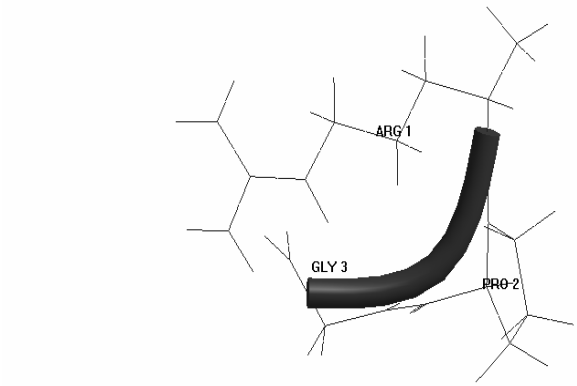

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Fig.2 Atomic model of spatial structure of Arg-Pro-Gly molecule.

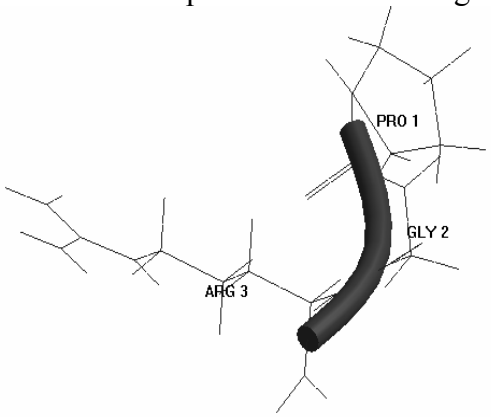

Fig.3 Atomic model of spatial structure of Pro-Gly-Arg molecule.

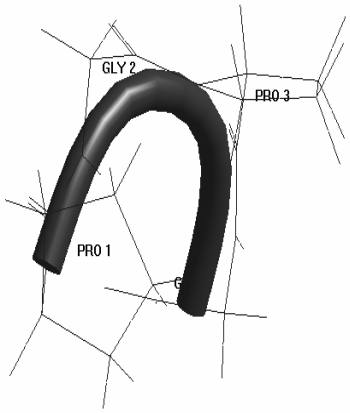

Fig. 4. Atomic model of spatial structure of Pro-Gly-Pro-Gly molecule.

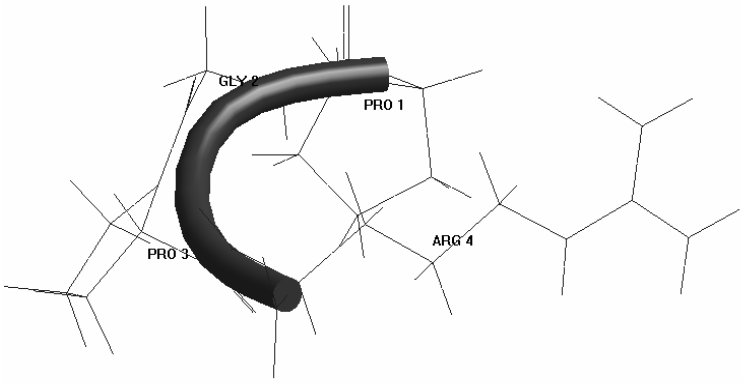

Fig. 5. Atomic model of spatial structure of Pro-Gly-Pro-Arg molecule.

ISSN 1512-1461

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There are one table and five figures in our article.

Article received: 2018-10-09