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Spatial Structure of Octarphin Molecule

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Abstract: *The spatial structure of octarphin molecule appropriate to the fragment 12-19 of β- endorphin has been investigated using the method of theoretical conformational analysis. It is shown that the spatial structure of octarphin molecule can be presented by fifteen low-energy forms of the main chain. Low–energy conformations of the molecule, values of dihedral angles of main and side chains of amino acid residues are found out, the energy of intra- and interresidual interactions are evaluated.*
Keywords: *β- endorphin, octarphin, theoretical conformational analysis, spatial structure, conformation*

I. Introduction

Amino acid sequence of octarphin conforms to the fragment 12-19 of β- endorphin. It is established that octarphin is related to macrophages of high affinity and specificity. Inhibition activity of octarphin analogues is 100 and more times as low as β- endorphin. It is shown that octarphin stimulates the activity of immunocompetent cells of the mouse in vitro and in vivo at the concentration 1-10 nM. It increases the adhesion and spreading of peritoneal macrophages, also their ability to digest the bacteria of virulent culture Salmonella typhiniurium 415 in vitro: intraperitoneal incorporation of peptide results in inereasing peritoneal macrophage activity, T- B- lymphocytes of spleen as well [1].

Spatial structure of octarphin molecule Thr1-Pro2-Leu3-Val4-Thr5-Leu6-Phe7-Lys8-NH2 has been investigated by method of theoretical conformational analysis. Calculations of conformational states of octarphin molecule are carried out regarding nonvalent, electrostatic and torsional interactions, hydrogen bonds as well. Nonvalent interactions are estimated by Lennard-Jones potential with Momany and Scheraga parameters [2]. Valence angles of amid groups as well as bond lengths and valence angles of side chains are in agreement with the values given in work [2] earlier. Electrostatic interactions have been calculated in the monopole approximation by Coulombs law using partial charges on the atoms suggested in work [2] earlier. Conformational possibilities of fragments and entire molecule of octarphin are calculated in conformity with the conditions of aqueous surroundings, in this connection the value of permittivity is taken to be 10 [3]. Hydrogen bonds are evaluated by Morze potential [4] are suggested to be weakened (bond energy in aqueous medium by optimal distance NH…OC 1,8Å is taken to be (-1,1) kcal/mol [4], torsional potentials and values of rotation barriers around the bonds Cα – N (φ), Cα – C (ψ), C – N (ω), Cα - Cβ (χ) and other bonds of side chains are taken from work by Momany and coauthors [2].

Classification used for peptide structures has been plotted on the "tree" principle according to which all structural versions of peptide first fall within comparatively limited amount of types (shapes0. each shape involves several certain forms of the main chain but each form is presented by a number of conformations having exact qualitative characteristics of amino acid residue geometry. The number of shapes for sequence of n residues is generally equal to 2 n -1, the number of forms in shape is defined by the number of combinations R, B, L, P of residue forms, but the number of conformational states of one form is defines by the number of one form is defined by the number of rotational degree of freedom of the side chains of the residues.

To designate conformational states of the residues there has been used X_{ij}^{N} - typed identifiers, where X determines low-energy regions of conformational map φ-ψ : R (φ, ψ =-180-0o), B (φ = -180-0o ,ψ=0-180o), L (φ, ψ =0-180o), and P (φ=0-180o,ψ= -180-0o); N – the number of residue in sequence; i, j…=11…,12…,13…,21…, and etc. conform to the positions of the side chain (χ1, χ2…), in this case subscript 1 corresponds to the angle χ = 0-120o; 2 to χ = 120-(-120 o), 3 to χ = (-120)-0o.

Designation indications of dihedral angles have been measured up to the generally accepted nomenclature [5]. Given work is the extension of our investigations on structural and functional organization of peptide molecules [6-12].

II. Results And Discussions

Spatial structure of octarphin molecule has been studied in fragments. All the first stage conformational possibilities of N-terminal pentapeptide fragment Thr1-Pro2-Leu3-Val4-Thr5 and C- terminal tetrapeptide fragment Thr5-Leu6-Phe7-Lys8-NH_2 on the basis of low energy conformations of appropriate monopeptides have been investigated. On the base of these penta- and tetrapeptide fragments the three-dimensional structure

of octarphin molecule is examined. Energy distribution of conformations of N-terminal pentapeptide fragment Thr1- Thr5 is shown in Table 1 and C- terminal tetrapeptide fragment is shown in Table 2.

Table 1. Energetic distribution of the conformations of N-terminal pentapeptide fragment Thr1-Thr5 of octarphin molecule

№	Form of the main chain	Energy interval, kcal/mol					
		0-1	1-2	2-3	3-4	4-5	>5
1	B B B B B	-	2	1	2	1	22
2	B B B R R	1	2	3	1	-	21
3	B B R R R	-	1	1	-	1	25
4	B R R R R	-	-	-	2	1	25
5	B R B R R	-	-	-	1	2	25
6	B B R B B	-	-	2	2	2	22
7	B R B B B	-	1	1	-	1	25
8	B R R B B	-	-	1	1	3	23

Table 2. Energetic distribution of the conformations of C-terminal tetrapeptide fragment Thr5-Lys8-NH_2 of octarphin molecule

№	Form of the main chain	Energy interval, kcal/mol					
		0-1	1-2	2-3	3-4	4-5	>5
1	B B B B	-	-	1	-	7	14
2	R R R R	1	1	2	3	4	7
3	B B R R	-	-	1	-	1	13
4	B R R R	-	2	4	-	2	8
5	B R B B	-	-	1	3	3	8
6	R R B B	2	1	4	1	1	7
7	R B B B	-	1	3	2	3	7
8	R B R R	-	-	-	1	1	14

It is shown that for any amino acid residue except glysine being ahead of praline all R – form conformations are high energy. Therefore such state for Thr1 is not taken account. Calculation results of penta- and tetrapeptide fragments show that energy differentiation between conformations has been taken place. Conformations of all forms under the consideration of the main chain of penta- and tetrapeptide fragments fall within the energy interval 0-5 kcal/mol. Thus to calculate the spatial structure of octarphin molecule there have been chosen conformational states of eight forms of the main chain of N-terminal pentapeptide and C- terminal tetrapeptide fragments.

Initial structural versions of octarphin for energy minimization have been formed of eight forms of the main chain of N-terminal pentapeptide fragment (Thr1- Thr5) and eight forms of the main chain of C-terminal tetrapeptide fragment (Thr5- Lys8-NH_2) fragments. Among the structural versions of octarphin under the examination some of them turned out to be steric forbidden, some of them turned to be high-energy.

In Table 3 there have been presented the best optimal conformations of the molecule which energy do not exceed 7,0 kcal/mol. They have 15 various forms of the main chain. There have been given energy contributions from nonvalent, electrostatic and torsional interactions for each conformation; energy of hydrogen bonds is included in value U_{nv}. Concerning geometry of N-terminal tetrapeptide fragment Thr1-Val4 given in Table 3 the low-energy conformations of octarphin fall into four groups (A-D). States of group A have the least free energy preferential both in internal energy and entropy. However sets of conformations B and C are at disadvantage a little in relation to both factors.

Table 3. Relative energy (U_{rel}) and contributions of nonvalent (U_{nv}), electrostatic (U_{el}), torsional (U_{tors}) interactions of optimal conformations of octarphin molecule

Group	№	Shape	Conformation	$U_{nv.}$	$U_{el.}$	$U_{tors.}$	$U_{rel.}$
A	1	efeffee	$B_{12}RB_{21}R_1R_{12}B_{31}B_1B_{3222}$	-40.6	10.2	4.3	0
	2	efeeffe	$B_{12}RB_{23}B_1R_{12}R_{22}B_1B_{3122}$	-38.4	7.4	7.1	2.2
	3	efeefee	$B_{12}RB_{23}B_1R_{12}B_{31}B_1B_{3122}$	-38.0	9.0	5.8	3.0
	4	efeefff	$B_{12}RB_{23}B_1R_{12}R_{21}R_2R_{2122}$	-38.1	9.0	6.0	3.0
	5	efeefef	$B_{12}RB_{23}B_1R_{12}B_{21}R_1R_{2122}$	-35.6	9.3	5.5	5.3
	6	efeeeff	$B_{12}RB_{23}B_1B_{12}R_{32}R_1R_{3222}$	-38.3	10.3	7.4	5.6
B	7	eefffff	$B_{12}BR_{22}R_1R_{12}R_{21}R_2R_{2122}$	-40.5	8.5	7.0	1.1
	8	eefffee	$B_{12}BR_{22}R_1R_{12}B_{21}B_1B_{2122}$	-40.9	9.1	8.1	2.4
	9	eefffef	$B_{12}BR_{22}R_1R_{12}B_{21}R_1R_{2122}$	-36.2	10.4	6.6	6.9
C	10	effefee	$B_{12}RR_{21}B_1R_{12}B_{31}B_1B_{3122}$	-38.0	9.0	6.2	3.3
	11	effeffe	$B_{12}RR_{21}B_1R_{12}R_{22}B_1B_{3122}$	-37.4	8.3	7.8	4.7
	12	effefef	$B_{12}RR_{21}B_1R_{12}B_{21}R_1R_{2122}$	-35.8	9.4	4.5	4.2
	13	effefff	$B_{12}RR_{21}B_1R_{12}R_{21}R_2R_{2122}$	-37.4	10.4	5.6	4.7
	14	effeeee	$B_{12}RR_{21}B_1B_{12}B_{21}B_3B_{1222}$	-33.9	9.8	3.8	5.8

D	15	eeeffee	$B_{12}BB_{21}R_1R_{12}B_{31}B_1B_{3122}$	-39.4	11.0	6.6	4.4

In Table 4 these has been shown the energy of intra- and interresidual interactions in three low-energy structures. Values of dihedral angles φ, ψ, ω of the main chain and angles χ of the side chains in these three conformations of the molecule are illustrated in Table 5. Atomic arrangement in stable conformations is shown in Figure.1.

Table 4. Energy of the intra- and inter-residue interactions (kcal/mol) in conformations of octarphin molecule $B_{12}RB_{21}R_1R_{12}B_{31}B_1B_{32}$ ($U_{rel.}$=0 kcal/mol, upper line), $B_{12}BR_{22}R_1R_{12}R_{21}R_2R_{21}$ ($U_{rel.}$= 1,1 kcal/mol, middle line), and $B_{12}RR_{21}B_1R_{12}B_{31}B_1B_{31}$ ($U_{rel.}$ = 3,3 kcal/mol, lower line)

Thr1	Pro2	Leu3	Val4	Thr5	Leu6	Phe7	Lys8	
5.5	-0.3	0	-3.6	-2.3	-1.8	-0.5	1.5	Thr1
3.0	-0.1	-3.8	-2.0	0.1	-0.9	-2.7	1.2	
4.8	0	0	-4.4	0.9	-2.3	0	1.6	
	0.2	0.3	0	-0.8	1.0	-1.8	-0.9	Pro2
	0.1	0.3	-2.3	-1.1	1.0	-1.2	-0.1	
	0.4	0.3	0	-1.8	1.6	0	1.6	
		-3.8	-0.4	0	0	0.4	-4.4	Leu3
		-4.5	-1.0	0	-1.3	0.7	-2.3	
		-4.0	-0.3	0	-3.7	-1.6	0	
			-3.4	-1.3	-0.7	-0.1	-1.5	Val4
			-0.7	-0.2	-0.3	0	-1.5	
			-2.8	-1.3	-1.2	-0.1	-1.2	
				-0.3	-1.3	0.4	-0.2	
				-0.3	-1.1	-0.1	-0.1	
				-0.6	-1.2	0.3	0	
					-0.7	-2.9	-2.1	Leu6
					-1.9	-1.3	-2.8	
					-3.8	-0.3	-3.5	
						-1.2	-0.9	Phe7
						-2.4	0	
						-3.0	-2.1	
							-1.4	Lys8
							-2.3	
							0	

Inoptimal conformations of octarphin the contribution of nonvalent interactions varies within energy (-40,9) – (-33,9) kcal/mol, electrostatic interactions (7,4-11,0) kcal/mol, torsional interactions (4,3 – 8,1) kcal/mol (Table 3). The most stable conformation of octarphin molecule is $B_{12}RB_{21}R_1R_{12}B_{31}B_1B_{3222}$ of shape efeffee. In given conformation amino acid residues are in space in such a way that Val4, Thr5, Leu6 have effective interactions with N-terminal molecule, Leu3, Val4, Leu6 have effective interactions with C-terminal residue Lys8 (Table4). The conformation $B_{12}BR_{22}R_1R_{12}R_{21}R_2R_{2122}$ of shape eeffff has a relative energy 1,1 kcal/mol. As it is seen N-terminal dipeptide is in expanded form of the main chain, the rest of amino acid residues are rolled up the spiral-like ones and form the compact structure of octarphin molecule. In this conformation Thr1 (total contribution with the rest of amino acid is (-9,4 kcal/mol, Table4), Pro2 (total contribution is (-4,7) kcal/mol), Leu3 (total contribution is (-6,0) kcal/mol) have effective interactions with the rest of amino acid residues and stabilize this structure. Group C is presented by five conformations, low-energy conformation of the group is $B_{12}RR_{21}B_1R_{12}B_{31}B_1B_{3122}$ of the shape effefee. Given conformation is different from the global conformation by the form of the main chain Leu3-Val4.

Table 5. Geometric parameters (degree) of the optimal conformations of octarphin molecule

	Shape		
Residue	e f e f f e e	e e f f f f	e f f e f e e
Thr1	-111 149 179 56 180 180	-68 150 175 47 -176 179	-110 147 173 50 -179 180
Pro2	-60 -64 176	-60 130 -175	-60 -66 -174
Leu3	-125 138 -172 -173 65 178 175	-113 -67 -172 -173 159 -169 180	-106 -69 -165 175 63 179 176
Val4	-62 -40 178 70 179 -173	-72 -34 -179 73 179 -175	-138 151 174 54 176 177
Thr5	-73 -67 179 58 -177 174	-76 -39 174 58 -177 178	-105 -57 178 -47 -176 174
Leu6	-89 83 180 -74 66 180 171	-60 -46 -179 176 62 180 176	-86 78 177 -74 66 180 172

Phe7	-98 148 -177 66 85	-63 -41 180 178 88	-100 149 -174 66 83
Lys8	-98 84 180 -60 180 180 180 180	-62 -51 179 176 63 174 178 180	-98 80 179 -74 67 167 180 -178
U_{rel}	0	1.1	3.3

Note: The values of dihedral angles are given in the sequence φ, ψ, ω, χ_1, $\chi_{2,\ldots}$

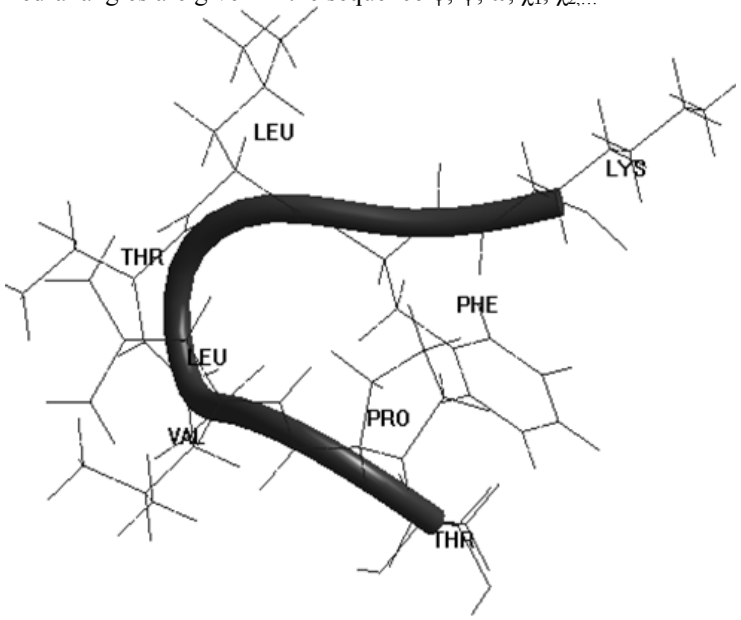

Fig. 1 a) Spatial structure of conformation $B_{12}RB_{21}R_1R_{12}B_{31}B_1B_{32}$

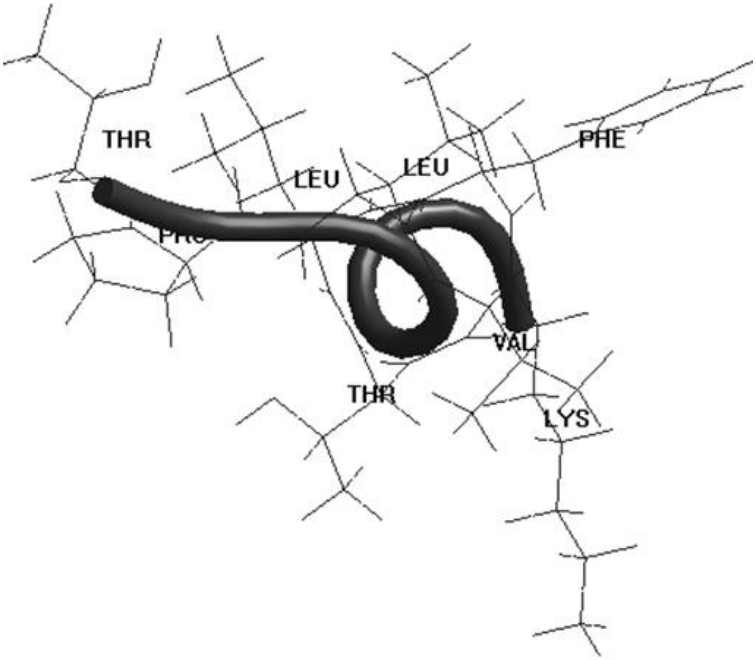

Fig. 1 b) Spatial structure of conformation $B_{12}BR_{22}R_1R_{12}R_{21}R_2R_{21}$

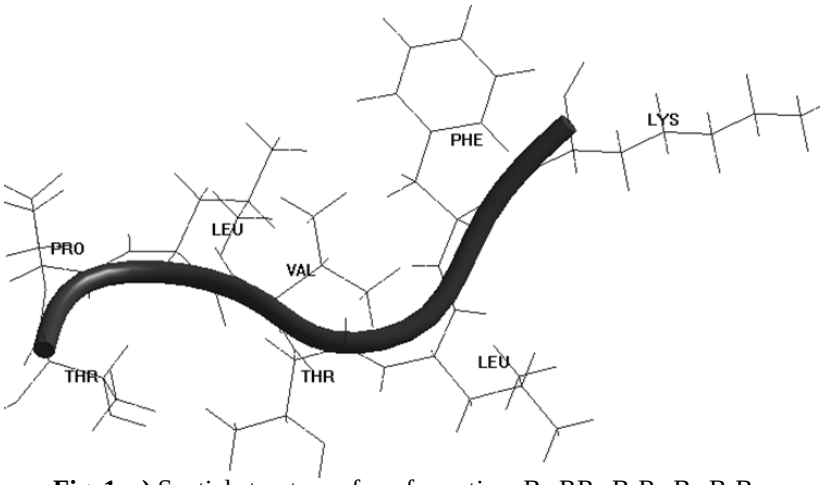

Fig. 1 c) Spatial structure of conformation $B_{12}RR_{21}B_1R_{12}B_{31}B_1B_{31}$

III. Conclusion

The calculation shows that side chains Thr1, Pro2, Leu3, Val4 and Leu6 are oriented within the molecule, but the side chains Phe7 and Lys8 are oriented to the medium of the most low-energy spatial structures of octarphin molecule. Otherwise they take the positions which are the most suitable regarding intermolecular interactions. Theoretical conformational analysis of octarphin results in such structural organization of the molecule that do not exclude the hormone realization of the entire group of the most various functions requiring strictly specific interactions with the different receptors.

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