STUDY OF SPACE STRUCTURE OF DIPPU- AST5 MOLECULE

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The space structure of Dippu-AST5 molecule belonging to allatostatin family is established in work by theoretic conformation analysis method. The stability quantitative estimation of possible molecule conformation states in conditions of dipolar medium is carried out on the base of calculation of intramolecular conformation energy.

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INTRODUCTION

The investigations of structure and conformation dynamics of Dippu-AST5 [1-4] allatostatin molecule are carried out in the given work by molecular mechanics method on the base of step-by-step approach described in works [5-9]. The molecule primary structure is the linear sequence of eight amino-acid residues H-Asp1-Arg2-Leu3-Tyr4-Ser5-Phe6-Gly7-Leu8-NH_2 (DRLYSFGL**)** and consists in the residues with aromatic rings in positions 4 and 6 of peptide chain. The molecule also consists in the two residues with charged functional groups on ends of its side chains. This are negatively charged carboxyl group of asparaginic acid residue (Asp1) and positively charged guanidine group of arginine (Arg2). The presence of volume side chain with branching atC^{γ}-atom in (Leu3, Leu8) lysine residues can significantly influence on interconnection of conformation states of main and side chains of Dippu-AST5 allatostatin molecule.

CALCULATION RESULTS AND DISCUSSION

The molecular model and graph of step-by-step calculation of separate fragments of Dippu-AST5 allatostatin molecule is given in Fig.1. The molecule space structure is studied on the base of stable metal-amid conformations of N-acetyl-α-amino-acids taking under consideration the different orientations of their side chains. The step-by-step calculation of Dippu-AST5 allatostatin molecule space structure consists in the study of conformation states of sequentially extensible fragments according to graph given in Fig.1,b.

The forms of main chain R and B are considered at calculation of Asp1-Arg2-Leu3 tripeptide fragment for asparaginic acid as these forms are isoenergetic ones for molecule first residue. The forms of its main chain R,B and L are considered for lysine residue in position 3 of peptide chain and values of side chain dihedral angles(χ_1, χ_2) are equal to 60, 180 and -60^0 before procedure of conformation energy minimization. The values of χ_2 angle in side chain of Tyr4 and Phe6 residues are equal 90^0. The general number of low-energy conformation states calculated for fragments Asp1-Arg2-Leu3, Leu3-Tyr4-Ser5-Phe6 and Phe6-Gly7-Leu8 is 171, 1215 and 324 correspondingly. The values of fragment conformation relative energy chosen for further calculation of overlapping parts of Dippu-AST5 allatostatin molecule in dependence on peptide chain length vary in limits 0÷5 kcal/mol.

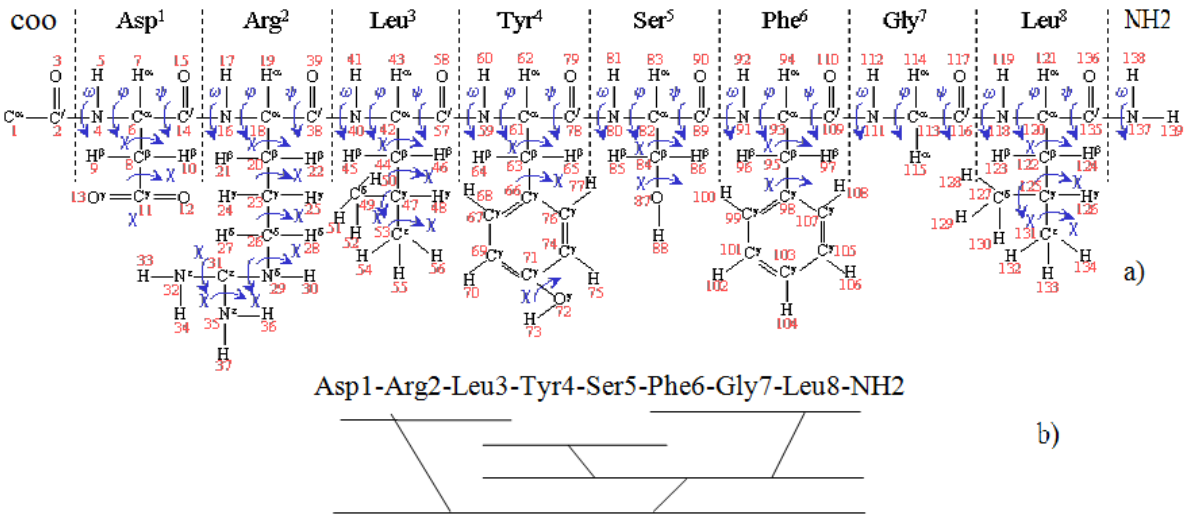

Fig.1. Molecular model, alternatives of dihedral angles (a) and calculation scheme (b) of stable Dippu-AST5 molecule conformations.

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As it is followed from calculation results, the more than half of acceptable conformations on tripeptide fragments Asp1-Arg2-Leu3 (58,9%) belong to *fe* shape with semi-folded form of peptide chain. The preference of these structures is caused by effective interactions of side chains of oppositely charged side chains of arginine and asparaginic acid residues.

As a whole the sum contribution from energy of non-valence and electrostatic interactions of these residues in low-energy conformations vary in limits 5,1÷-7,8 kcal/mol. The general number of low-energy conformations of tripeptide chosen for further step of calculations is 39.

The shape conformations *eef* and *eff* are the energy profitable ones for Leu3-Tyr4-Ser5-Phe6 tetrapeptide fragment. The stable structures with energy local minimums of this fragment are mainly stabilized by non-valence interactions of residues with aromatic side chains Tyr4 and Phe6 (5,0 kcal/mol order). β-bend on Leu3-Phe6 section at which the distance between C^{α}-atoms of Tyr4 and Phe6 residues are equal to 5,4 Å. Such bend corresponds to approximation and almost parallel disposition of residue aromatic rings so that the distance between ring centers of gravity varies in limits 4,2÷4,5Å. The presence of serine residue consisting in the hydroxyl group in side chain defines the specifics of spatial structure of Dippu-AST5 allatostatin molecule given part. It is known that Ser has the strongly expressed tendency to take part in formation of β-structures because of electrostatic interactions between its side and main chains. The hydrogen bond between OH group of side chain and NH group of main one of serine the length of which varies in very narrow interval of 2,48÷2,51Å values forms in all calculated fragment conformations. Thus, the tetrapeptide fragments densely packed in space and mainly stabilized by non-valence interactions is presented in following calculations by shape conformations *eef, fee* and *eff.*

The number of calculated conformations on Phe6-Gly7-Leu8 tripeptide fragment belonging to 4 shapes and 16 forms of peptide chain is 324. The effective inter-residue interactions between Phe6 and Leu8 form in low-energy fragment conformations because of glycine residues playing the role of hinge in fragment structure. That's why the states with unfolded and semi-folded form of main chain realize with equal probability. This fact is affirmed by both the minimization results and analysis of contributions in fragment low-energy conformation states. The hydrogen bond between atoms of main chain of Phe6 and Leu8 residues the length of which varies in dependence on conformation state of main chain from 2,03 up to 2,07Å forms in fragment global conformation.

Table 1. Energy distribution of allatostatin conformations Dippu-AST5

№	Shape	Relative energy interval, kcal/mol						Conformation percentage (%)
		0÷1	1÷2	2÷3	3÷4	4÷5	>5	
1	*feeefef*	1	6	3	7	6	26	28.1
2	*feeefee*	-	1	-	2	1	22	15.3
3	*feeefff*	-	-	-	3	4	16	13.2
4	*feefff*	-	-	1	-	3	17	12.7
5	*feeeffe*	-	-	1	-	1	16	10.4
6	*fffefff*	-	-	-	1	-	10	6.2
7	*eeeefef*	-	1	2	1	-	2	3.4
8	*effefff*	-	-	-	-	1	4	2.8
9	*eeefff*	-	-	1	1	-	2	2.3
10	*eefeeee*	-	-	-	-	1	3	2.3
11	*eeeeffe*	-	-	-	-	1	2	1.7
12	*fefeeee*	-	-	1	1	-	1	1.6

Table 2. Energy parameters of low-energy conformations of allatostatin Dippu-AST5

№	Shape	Residue conformation								Energy contributions, kcal/mol				
		Asp	Arg	Leu	Tyr	Ser	Phe	Gly	Leu	$E_{нев}$	$E_{эл}$	$E_{торс}$	$E_{полн}$	$E_{отн}$
1	*feeefef*	R_1	B_3	B_3	B_3	R_1	R_1	P	R_3	-44,3	3,0	4,3	-36,9	0,0
2	*eeeefef*	R_1	L_3	B_3	B_3	R_1	R_1	P	R_3	-44,9	4,5	5,1	-35,4	1,6
3	*feeefee*	R_1	B_3	B_3	B_3	R_1	R_1	P	L_3	-42,4	2,3	4,9	-35,2	1,8
4	*feeeffe*	R_1	B_1	B_3	B_3	R_1	R_1	B	B_3	-42,9	3,1	4,9	-34,9	2,1
5	*fefeeee*	R_1	B_1	R_2	B_3	B_2	B_3	B	R_3	-41,7	2,8	4,2	-34,6	2,4
6	*eeefffff*	R_1	L_3	B_3	R_3	R_1	B_3	P	R_3	-42,4	3,9	4,1	-34,3	2,6
7	*feeefff*	B_2	L_3	B_3	B_3	R_2	B_3	P	R_3	-40,0	2,5	3,8	-33,7	3,3
8	*fffefff*	R_1	R_3	R_3	B_3	R_1	B_3	P	R_3	-40,0	3,2	3,4	-33,4	3,5
9	*feefffff*	R_1	B_1	B_3	R_3	R_1	B_3	P	R_3	-40,1	2,6	5,8	-32,8	4,1
10	*eeeefff*	R_1	L_3	B_3	B_3	R_2	B_3	P	R_3	-40,3	4,0	3,9	-32,4	4,6
11	*effefff*	B_1	R_3	R_3	B_3	R_1	B_3	P	R_3	-40,9	5,3	2,6	-32,2	4,8
12	*eefeeee*	R_1	L_3	R_2	B_3	B_1	B_3	P	R_3	-41,4	3,8	5,8	-31,8	5,1

Table 3. Energy contributions (kcal/mol) of interresidue interactions and distances between **C**$^{\alpha}$-atoms of peptide chain in low-energy conformations of allatostastin Dippu-AST5

Amino-acid residues	Shape conformation *feeefef* with E_{rel} = 0,0 ккал/mol		Shape conformation *eeeefef* with E_{rel} = 1,6 kcal/mol	
	Distance between C^{α} atoms (Å)	$\sum_{i,j}^{8} E_{i,j}$	Distance between C^{α} atoms (Å)	$\sum_{i,j}^{8} E_{i,j}$
Asp1-Arg2	3.8	-7.5	3.8	-5.1
Arg2-Leu3	3.8	-1.6	3.8	-1.6
Leu3-Tyr4	3.8	-2.1	3.8	-2.1
Tyr4-Ser5	3.8	-1.9	3.8	-1.9
Ser5-Phe6	3.8	-2.2	3.8	-2.3
Phe6-Gly7	3.8	0.8	3.8	-0.8
Gly7-Leu8	3.8	-1.5	3.8	-1.5
Asp1-Leu3	6.4	-0.7	5.6	-4.8
Arg2-Tyr4	6.0	-3.3	5.9	-2.8
Leu3-Ser5	7.2	-0.2	7.2	-0.2
Tyr4-Phe6	5.4	-5.0	5.4	-5.1
Ser5-Gly7	5.0	-1.0	5.0	-1.0
Phe6-Leu8	5.7	-3.3	5.7	-3.3
Asp1-Tyr4	9.5	0.5	8.9	0.5
Arg2-Ser5	9.3	-0.1	9.3	-0.1
Leu3-Phe6	8.7	-0.1	8.6	-0.1
Tyr4-Gly7	4.3	-2.5	4.2	-2.6
Ser5-Leu8	8.4	-0.0	8.3	-0.0
Asp1-Ser5	12.9	-0.1	12.4	0.1
Arg2-Phe6	9.3	-0.3	9.2	-0.2
Leu3-Gly7	6.1	-0.2	5.9	-0.2
Tyr4-Leu8	7.4	-0.2	7.3	-0.2
Asp1-Phe6	13.0	0.1	12.9	0.1
Arg2-Gly7	6.1	-1.3	6.0	-1.1
Leu3-Leu8	8.6	-0.0	8.4	0.0
Asp1-Gly7	9.5	-0.1	9.5	-0.1
Arg2-Leu8	6.8	-3.3	6.6	-2.3
Asp1-Leu8	9.8	-0.0	10.0	0.1

Table 4. The dihedral angles of main and side chains of amino-acid residues in low-energy conformations of allatostatin Dippu-AST5

Amino-acid residue	Dihderal angles, grad		
Asp1	φ= -89,ψ= -44,ω=178, χ_1=54, χ_2=105	φ= -73,ψ= -43,ω=178, χ_1=61, χ_2=112	φ= -89,ψ= -44,ω=180, χ_1=54, χ_2=105
Arg2	φ= -134,ψ=97,ω=179, χ_1= -67,χ_2=174, χ_3=161	φ=53,ψ=57,ω=175, χ_1=57,χ_2=179,χ_3=181	φ= -133,ψ=98,ω=183, χ_1= -67, χ_2=174, χ_3=182
Leu3	φ= -99,ψ=94,ω=183, χ_1=54, χ_2=177, χ_3=182	φ= -100,ψ=94,ω=183, χ_1= -56, χ_2=174, χ_3=187	φ= -99,ψ=96,ω=182, χ_1= -54,χ_2=177,χ_3=187
Tyr4	φ=-150,ψ=165,ω=177, χ_1= -67, χ_2=95, χ_3=180	φ= -148,ψ=165,ω=178, χ_1= -65, χ_2=96, χ_3=179	φ= -148,ψ=164,ω=178, χ_1= -61, χ_2=95, χ_3=180
Ser5	φ= -71,ψ= -52,ω=171, χ_1=56, χ_2=177	φ= -69,ψ= -52,ω=171, χ_1=57, χ_2=179	φ= -71,ψ=-53,ω=170, χ_1=57, χ_2=180
Phe6	φ= -60,ψ= -29,ω=178, χ_1=62, χ_2=81	φ= -60,ψ= -29,ω=178, χ_1=62, χ_2=81	φ= -61,ψ= -35,ω=179, χ_1=57, χ_2=80
Gly7	φ=80,ψ= -77,ω=182	φ=80,ψ= -77,ω=182	φ=72,ψ=-89,ω=181
Leu8	φ= -104,ψ= -60,ω=179, χ_1=53,χ_2=176,χ_3=186	φ= -104,ψ= -60,ω=179, χ_1=-53,χ_2=176,χ_3=186	φ=50,ψ=59,ω=180, χ_1= -58,χ_2=174,χ_3=186
E_{rel}	0.0 kcal/mol	1.6 kcal/mol	1.8 kcal/mol

The general number of 458 initial variants written for minimization procedure of whole molecule conformation energy is equal o 90 forms and 41 shapes of peptide chain. They are combinations of low-energy conformation states of Arg1-Leu3, Leu3-Phe6, Phe6-Leu8 fragments and their overlapping parts the relative energy of which doesn't exceed 5kcal/mol. The conformation analysis of sequentially expansion and overlapping fragments of Dippu-AST5 allatostatin molecule reveals the significant succession of results with length increase of considered peptide chain (table 1). The low-energy conformations of Dippu-AST5 allotastatin molecule are found in the result of energy minimization of written structural variants (table 2).

The conformations of octapeptide 12 structural types are included in relative energy interval 0÷10 kcal/mol. As a whole, 53% of calculated structures have the unfolded form of Arg2-Tyr4 section and differ only by conformation states of C-end fragment Ser5-Leu8 (i.e. NH2). The distances between $\mathbf{C^{\alpha}}$ -atoms of peptide chain are given in table 3; the values of dihedral angles in molecule conformation state with global minimum of intramolecular conformation energy are given in table 4.

β-turn of peptide chain that evidences the distance between C^{α}-atoms of Tyr4 and Gly7 residues (4,3 Å; table 3) and hydrogen bonds between main chain atoms Tyr4 and Gly7 forms in molecule global conformation.

CONCLUSION

Generalizing the investigation results one can suppose that Dippu-AST5 allotastotin molecule can realize the series of low-energy conformation states differing mainly by conformation states of C-end fragment. The obtained results can serve as the base for purposeful modification of Dippu-AST5 allatostatin with the aim of analogue formation of more selective and prolonged action.

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