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Calculation of the energy and geometric parameters for the n-terminal tetrapeptide fragment of LOCMI AST 1

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Abstract

Computer modeling was used to calculate the energy and geometrical parameters of the N-terminal tetrapeptide fragment of the LOCMI AST 1 molecule. For this purpose, two calculation methods were employed: molecular dynamics and theoretical conformational analysis. The calculations were performed both in a vacuum and in a hypothetical rectangular box containing a specific number of water molecules with known boundary conditions. To conduct the calculation, 72 conformations were included, taking into account all possible spatial orientations that the amino acids within the fragment could occupy. It was determined that 40 of these conformations fall within a relative energy interval of (0-4) kcal/mol. The conformation representing the global minimum was selected from the calculated conformations, and the values of its total, non-bonded, electrostatic, and torsional (i.e., rotation around covalent bonds) energies were determined. Subsequently, several parameters of a few low-energy conformations were refined using the molecular dynamics method.

Keywords: conformation, spatial structure, theoretical conformational analysis, theoretical calculation methods
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1. Introduction

LOCMI AST molecules are biologically active neuropeptides that play an important role in regulating the synthesis process, including the inhibition of juvenile hormone synthesis [1-3]. Their conformational properties and three-dimensional

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spatial structures hold a special place in the realization of these functions, and the investigation of these properties is considered one of the essential conditions for understanding the activity mechanisms of neuropeptides at the molecular level. LOCMI AST molecules consist of several neuropeptides, one of which is the LOCMI AST 1 molecule.

The Locmi 1 molecule consists of 13 amino acid residues and has the linear sequence APSGAQRLYGFGL-amide (Figure 1). It was isolated from the brain extract of the locust Locusta migratoria. The characteristic features of the Locmi AST 1 molecule's spatial structure – its geometric and energy parameters, spatial coordinates, and low-energy conformational states – were calculated using the theoretical conformational analysis method [4-6]. For this purpose, the Locmi AT1 molecule was divided into smaller fragments. In this work, the spatial structure of the N-terminal tetrapeptide fragment of the Locmi AST 1 molecule, which has the amino acid sequence Ala1-Pro2-Ser3-Gly4, was investigated.

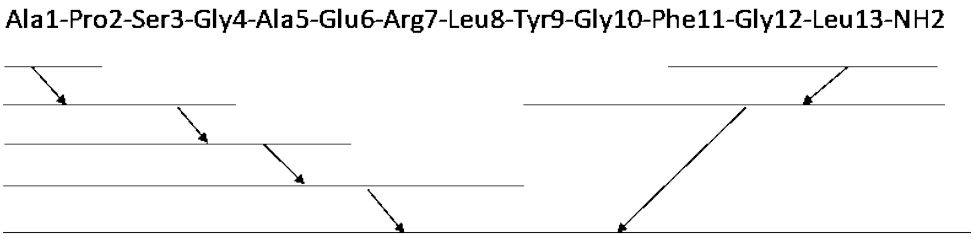

Figure 1. Amino acid sequence and calculation scheme of Locmi AST1 molecules.

2. Calculation methods

Theoretical Conformational Analysis Method. The foundation of the theoretical conformational analysis method was laid in the 1950s. According to this method, any biomolecule is treated as a system of atoms, and its nuclear-electronic structure is not taken into account. In both the theoretical conformational analysis method and the molecular dynamics method, the **total energy** is expressed as the additive sum of the following energies:

$$E_{total}=E_{n.v.}+E_{el.st..}+E_{tor.}+E_{h.b.}$$

The semi-empirical potential functions and their parameters used in the theoretical conformational analysis method were taken from works [4], and the standard system of identifiers [5] was used to interpret the results.

According to this system, the spatial domain is conventionally divided into 4 conformational regions, and each small region is denoted by a single letter (B, R, P, and L). In these regions, the dihedral angles of the amino acids take the following values: R (φ, ψ=-180°÷0°); B (φ =-180°÷0°, ψ= 0°÷180°); L (φ, ψ=0°÷180°) və P(φ =0°÷180°,

ψ=-180°÷0°). These are called forms. These forms, in turn, create two types of structures in space, which are called shapes. Shapes arising from the forms *R-R, R-B, B-L, L-L, B-P, L-R, P-R, P-B* are denoted by the letter f (the first letter of the English word "folding," meaning 'bent' or 'compact'), characterizing the fully folded structure type of the polypeptide chain. Shapes arising from the forms *B-B, B-R, R-L, L-B, R-P, P-L, P-P, L-P* are denoted by the letter e (the first letter of the English word "extended"), characterizing the fully extended structure type of the polypeptide chain.

When performing calculations, the values of the dihedral angles are taken according to the standard nomenclature.

Molecular Dynamics Method. One of the theoretical methods widely used in modeling the internal mobility of macromolecules is the molecular dynamics method. The basis of this method is the calculation of the classical (Newtonian) motion trajectories of the coordinates and momenta of the atoms constituting the macromolecule in phase space. In the molecular dynamics method, the biomolecule is viewed as a system of small interacting particles, and the classical motion trajectories of the atoms are calculated within the force field of the empirical atom-atom potential. With this method, the macromolecule's internal microscopic thermal motion is modeled over a sub-nanosecond interval. To account for the effects of energy exchange with the environment and to keep the system's temperature constant, a specific algorithm – the Berendsen thermostat is used. Deviations of the temperature from its equilibrium value are corrected using the Landau-Teller equation.

In the molecular dynamics method, the influence of the environment on the conformational mobility of the studied molecule is realized by including water molecules in the system and by setting boundary conditions [6]. With this method, by providing the coordinates and velocities of all particles in the first step, it becomes possible to calculate all the forces acting on the particles, their coordinates, and their velocities in subsequent steps [7, 8].

3. Conclusion

To investigate the spatial structure of the Ala1-Pro2-Ser3-Gly4 tetrapeptide fragment of the Locmi AST 1 molecule and to determine its geometric and energy parameters, 72 initial variants were assembled and subjected to the energy minimization process. It was determined that only 40 of the minimized conformations fall within the relative energy interval of 0-4 kcal/mol (Table 1). Table 2 presents the energy parameters of several low-energy conformations belonging to different shapes.

It is clear from the table that the majority of the calculated low-energy conformations of the Locmi AST 1 molecule's tetrapeptide fragment did not form a fully folded structure type, due to the presence of the rigid Pro amino acid at the 2nd position of the sequence. Furthermore, the calculations determined that the ma-

jority of the low-energy conformations are stabilized not only by non-bonded interactions but also by the formation of hydrogen bonds between the amino acids, specifically Ala(NH)...Ala(CO), Ala(CO)...Gln(NH), Ser(NH)...Ser(CO), Ser(OH)... Gln (NH) and Gln(CO)...Gln(NH).

Table 1. Distribution of low-energy conformational states of the Locmi AST 1 molecule's tetrapeptide fragment by shape.

№	Shape	Relative energy interval, (kcal/mol)					
		0 ÷ 1	1 ÷ 2	2 ÷ 3	3 ÷ 4	4 ÷ 5	> 5
1.	*eee*	2	4	6	-	5	7
2.	*efe*	-	-	1	6	3	2
3.	*eef*	3	2	3	4	6	3
4.	*eff*	-	-	2	7	1	5

Table 2. Energy parameters of low-energy conformations of the Locmi AST 1molecule's tetrapeptide fragment.

Conformations	Shape	Energy parameters, kcal/mol			
		$E_{n.v.}$	$E_{el.st..}$	$E_{tor.}$	E_{total}
BBR₁B	*eef*	-8.31	-0.83	4.33	-4.82
BBR₂B		-7.04	-0.56	3.72	-3.88
BBR₁L	*eee*	-7.77	-0.43	3.87	-4.33
BBR₃P		-6.47	-0.30	3.64	-3.13
BRB₁B	*efe*	-4.90	-0.62	3.61	-1.91
BRR₁R	*eff*	-4.98	-0.64	3.60	-2.01
BRR₁B		-5.00	-0.45	3.56	-1.89

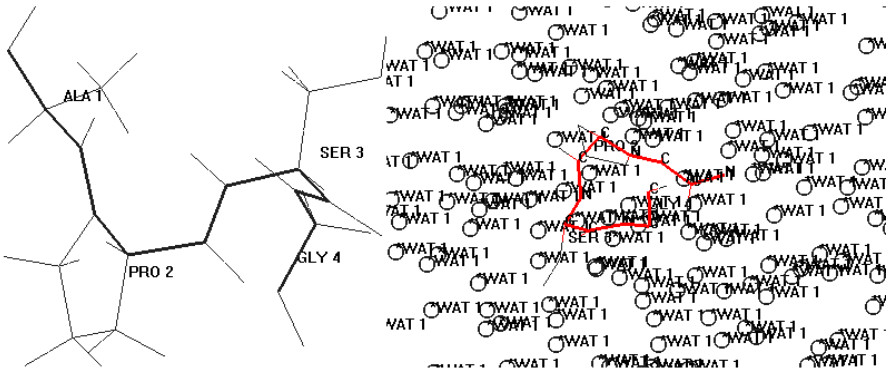

Figure 2. View of the global conformation (shape eef) of Locmi AST 1 molecules in a relaxed (1st) and surrounded by water molecules (2nd).

To examine the mobility of the low-energy conformations obtained for the Locmi AST 1 molecule's tetrapeptide fragment using the theoretical conformational analy-

sis method, the second calculation method – molecular dynamics – was employed. First, these conformations were relaxed for 30 ps and only after that were they placed into a hypothetical cubic box containing approximately 190-230 water molecules. To imitate (visually represent) the aqueous environment, the collision frequency of the atoms with water molecules was set to 50 ps^{-1} (Figure 2).

The results obtained are consistent with those achieved through experimental facts.

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