MOLECULAR DYNAMICS INVESTIGATION OF FOLDING AND NANOMECHANICAL CHARACTERIZATION OF AN α-HELICAL PEPTIDE KR1

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ABSTRACT

The scientific knowledge that mankind has at its disposal enables us to study the interactions that occur in biological molecules in the nanoscale. Nevertheless, what about the entire dynamic process of conformational changes? Is it possible to characterize the short peptide folding process by the fluctuation of nanomechanical parameters? In this work, a short sytnthetic peptide has been used and its folding and unfolding events have been simulated. All this attempt have been made to obtain nanomechanical constants of the peptide in its folded and unfolded confgurations.

SYSTEM PREPARATION

The simulated KR1 peptide is described by sequence of 13 amino acids and blocking C-terminus amidated group, what can be denoted in three letter symbols:

Gly-Asn-Ala-Ala-Gln-Ala-Ala-Ala-Ala-Gln-Ala-Ala-Gly-NH_2

In the project, two simulations of folding trajectory of the α-helical KR1 peptide were carried out. In both cases simulations were performed in the CHARMM36 force field in an aqueous environment (TIP3P water model) by using GROMACS software. The main difference between the two cases was the conformation of the initial structure from which the simulation started – in the first case it was an unnaturally extended structure (see Fig. 1.), and in the second case, the trajectory was started by an artificially generated, ideal α-helix (see Fig. 2.). In both trajectories, the time course was 10μs. The whole process of preparing the system was presented in Fig 3. In the case of trajectory starting from the extended structure, the system preparation process was performed twice in order to minimize unnatural stresses in the conformation (see Fig. 1.).

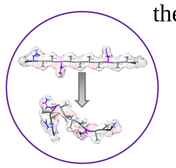


Fig. 1. The KR1 peptide extended conformation with the structure minimize with unnatural stresses in the conformation.

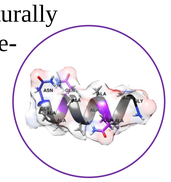


Fig. 2. The KR1 peptide ideal α-helix conformation.

Fig. 3. GROMACS molecular dynamics simulation workflow with a brief description of the function of each step.

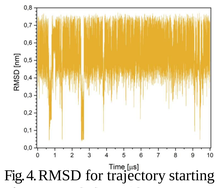


Fig. 4. RMSD for trajectory starting from extended peptide structure.

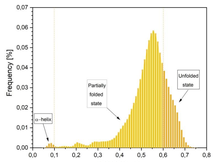


Fig. 5. Histogram of RMSD for trajectory starting from extended peptide structure – represents average states population.

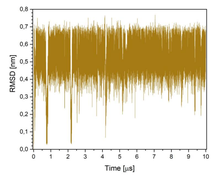


Fig. 6. RMSD for trajectory starting from α-helical peptide structure.

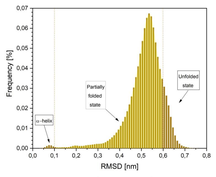
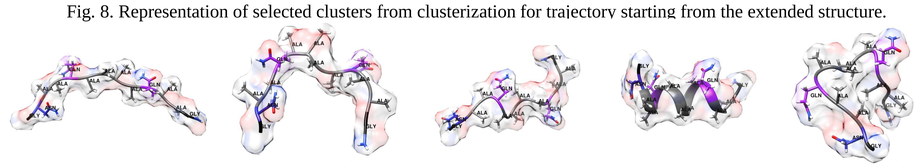


Fig. 7. Histogram of RMSD for trajectory starting from α-helical peptide structure – represents average states population.

CHARACTERIZATION

Fig. 8. Representation of selected clusters from clusterization for trajectory starting from the extended structure.



a) 1st representation of clustering with no hydrogen bonds. b) 2nd representation of clustering with no hydrogen bonds. c) 3rd representation of clustering with 1 hydrogen bond. d) 6th representation of clustering with 5 hydrogen bonds. e) 9th representation of clustering with 2 hydrogen bonds

Tab. 1. Calculated parameters for the trajectory starting from extended peptide structure with the given formulas.

Results for trajectory starting from extended peptide structure										
	Other properties							Nanomechanical properties		
	Propability p [a.u.]	Correlation time of hydrogen bond decay τ_1[ns]	Correlation time of peptide folding τ_2[ns]	The equilibrium constant K [a.u.] [1]	The rate constans [2] unfolding state $\frac{k_{-1}}{k_1}$ folding state		The diffusion coefficient D [cm²/s] [3][7]	Mechanical energy dissipation constant ζ [kg/s] [4][5]		Elastic spring constant κ [pN/nm] [5][6]	
					k_{-1} [1/ns]	k_1 [1/ns]					
1st method	See Fig.5.			$K = \frac{p}{1-p}$	$k_{-1} = \frac{1}{\tau \times (K+1)}$ τ - correlation time of peptide folding τ_2[ns]	$k_1 = K \times k_{-1}$	$D = \frac{\delta^2}{2 \times \tau_1}$ δ - distancealong the helical axis between residues	$\zeta = \frac{k_B T}{D}$ k_B-the Boltzmann constant; T – temperature	$\zeta = \frac{k_B T}{(\Delta x_{1,\varepsilon=\varepsilon_2})^2}(\frac{1}{k_1} + \frac{1}{k_{-1}})$ Δx - the distance to the transition state	$\kappa = \frac{k_B T}{(\Delta x)^2 p(1-p)}$ Δx - the distance to the transition state	$\kappa = 2\frac{-k_B T \times ln(\frac{k_{-1}}{k_1})}{(\Delta x_a)^2}$ Δx - the distance to the transition state k_A - Arrhenius frequency factor
	0.007	2.42	60.10	0.007	0.017	0.437	4.65 ×10⁻⁸	0.891 ×10⁻⁹	2.332 ×10⁻⁹	5212.15	566.27
	0.788			3.715	0.004	1052.546			-	-	-
	0.205			0.258	0.013	19.491			2.809 ×10⁻⁹	337.84	4523.56
2nd method	Average hydrogen bond population			0.051	0.016	3.234			2.357 ×10⁻⁹	801.43	572.17
	0.0487										

Tab. 2. Calculated parameters for the trajectory starting from α-helical peptide structure.

Results for trajectory starting from α-helical peptide structure										
	Other properties							Nanomechanical properties		
	Propability p [a.u.]	Correlation time of hydrogen bond decay τ_1[ns]	Correlation time of peptide folding τ_2[ns]	The equilibrium constant K [a.u.] [1]	The rate constans [2]		The diffusion coefficient D [cm²/s] [3]	Mechanical energy dissipation constant ζ [kg/s] [4][5]		Elastic spring constant κ [pN/nm] [5][6]	
					k_{-1} [1/ns]	k_1 [1/ns]					
1st method	0.006	1.69	39.36	0.006	0.025	0.227	6.66 ×10⁻⁸	0.622 ×10⁻⁹	1.747 ×10⁻⁹	7011.10	524.65
	0.889			8.040	0.003	2860.444			-	-	-
	0.105			0.117	0.023	5.155			1.754 ×10⁻⁹	422.71	4661.36
2nd method	Average hydrogen bond population			0.040	0.024	1.635			1.649 ×10⁻⁹	1075.16	529.42
	0.0384										

SUMMARY

- The two 10 μs peptide folding trajectories were successfully obtained. It is possible to describe the system by the nanomechanical constants – elastic spring constant, mechanical and energy dissipation constant.
- The KR1 peptide occurs most of the time in the unfolded state. These conformations constituting a global minimum.
- The constants obtained for the KR1 peptide differ depending on the trajectory. Longer simulations should be performed to obtain better estimates of the constants.
- It is necessary to verify the obtained results experimentally.

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