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Conformational stability of the tetrameric *de novo* designed hexcoil-Ala helical bundle

Kadir Demir[a,*], Hakan Alıcı[a], Fatih Yaşar[b]

[a] Bülent Ecevit University, Department of Physics, Zonguldak 67100, Turkey
[b] Hacettepe University, Department of Physics Engineering, Ankara 06800, Turkey

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ABSTRACT

We have performed molecular dynamics method to investigate the conformational stability of the homotetramer form of HexCoil-Ala (PDB Code 3S0R). The previous experiments showed that the chains tend to form tetramer structures. The system was simulated in explicit water model at several temperatures by using isobaric-isothermal ensemble to better understand the behaviour of each monomer and its tetramer form. It was observed that central residues of each monomer have highly helical percentages in comparison with the termini residues. As the temperature increased, these percentages decreased, and bend-like configurations came into being due to the fact that the C-and N-terminals of the monomer were getting closer. When free energy landscapes of HexCoil-Ala were calculated by using the distance between Leu-Zipper and Ala-Coil interface, it was seen that the assemblies of monomers were very strong. What's more, the average values obtained from them were very close to the native case between 300 K and 350 K. It was also observed that the direct salt bridge forming between the residues E8 with R25 in the other chains plays a significant role for keeping tetramer structure. Consequently, our results are in better agreement with the results of experimental observations.

1. Introduction

In cells and living organisms, proteins are responsible for stability, mobility, catalysis, recognition, pathogen clearing, signalling, ordering and shaping. These biological functions of proteins depend on their conformational shapes and folding mechanisms. There is, therefore, a growing interest in the design of protein to find out novel functionalities unavailable in nature [1,2]. These designed structures bring a lot of advantages in comparison with native proteins; for instance, conformational stability, well-folded secondary structure and self-assembly [3,4]. The ability to manipulate these functions of the proteins has particularly led to a possible design of new proteins bearing a biological value [5,6]. In recent years, thanks to computationally designed proteins, such impressive fields of application as biotechnology and drug discovery (cancer [7–10], Alzheimer's [11,12] and human immunodeficiency virus drugs [13–15], antibody therapeutics [16–20], novel biocatalyst [21–29] and self-assembling nanomaterials [30–32]) have been demonstrated.

The functional proteins can be either developed from scratch, known as *de novo* design technique or by modification of structural motifs pre-existing in the repertoire of nature. Symmetry is one of the commonly used procedures and facilitates the design process during the design of *de novo* and modified structures. The importance of the symmetries, like screw symmetry in β-strands and α-helices and quasi-symmetrical arrangements occurring in proteins assemblies, is disputable for protein structures. In addition, such

* Corresponding author.
E-mail address: kadirdemir@beun.edu.tr (K. Demir).

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macromolecular structures as tetrameric, hexameric etc. which include parallel or anti-parallel oligomer states were designed with symmetry formed through *de novo* helical sub-units.

Grigoryan et al. developed a *de novo* peptide, known as HexCoil-Ala which has alanine-rich sequence (11 Alanine per monomer). This peptide was originally designed to form hexameric antiparallel coiled-coil bundle around the single-walled carbon nanotube (SWCNT) [33] and its anti-parallel dimeric sub-unit was revealed by X-ray crystallography (PDB accession code: 3S0R). This peptide has 30 amino acids with an one letter code of AEAESALEYAQQALEKAQLALQAARQALKA in each monomer and has 90% α-helix secondary structure. Owing to their potential capacity for drug design, transporting, biocompatibility, targeting, delivery and adsorption treatments in membrane, there has been an increasing interest in these type structures recently [34–38]. Further, HexCoil-Ala has a significant influence on design engineering and can also be used for developing highly ordered macromolecular assemblies. As HexCoil-Ala is an alanine-based polypeptide, it has also drawn great attention for the investigation of helix-folding processes [39–41].

The computational molecular modelling of proteins from their amino acid sequences is a suitable technique for the evaluation of the conformational ensemble of any peptide showing a variety of conformations. As it is difficult to trace some of the specific interactions by experiments, simulations of molecular modelling may be used for revealing them. In this context, molecular dynamic (MD) simulation is one of the most preferred simulation techniques to understand the details of protein conformation and stability [42–49]. MD simulation is also considered as an up-and-coming tool to design drugs and complex structures based on the structure stability and hydrophobicity information.

The hexameric form of HexCoil-Ala which is coiled around the single-walled carbon nanotube, has also been studied through experimentation and simulation techniques. In the work, it was reported that the hexameric form kept its stability and was situated in anti-parallel configuration over the surface of SWCNT as well as keeping α-helical arrangements [50]. In present work, our aim is to investigate the temperature dependency of the association and folding of HexCoil-Ala that tends to form tetrameric structure according to experimental observations which showed this peptide associated into tetrameric forms by analytical ultracentrifugation method [33]. For this purpose, the effect of temperature on conformational stability, hydrophobicity and self-assembly properties of tetrameric HexCoil-Ala in explicit solvent was systematically examined through MD simulations. Thus, the results obtained from our molecular dynamics simulation can explain the reason why HexCoil-Ala tends to mostly form tetrameric structure in the light of experimental observations. Moreover, thanks to MD simulation technique, we can get insight into the chain dependency of the interactions of oligomer forms comparing with the larger number of chains which lead to oligomers.

2. Material and methods

2.1. Construction of the tetrameric structure of hexcoil-Ala

The *de novo* anti-parallel tetrameric structure of HexCoil-Ala was prepared with PyMOL (Delano 2002 [51]) by using atomic structures derived from the X-ray of the anti-parallel dimer unit (PDB Code 3S0R). In Fig. 1(a) and (b), visulations of dimer and tetramer units are shown respectively. In here, each anti-parallel monomer chains of HexCoil-Ala are illustrated in green for chain A, cyan for chain B, magenta for chain C and yellow for chain D. The designed *de novo* tetrameric structure of HexCoil-Ala has geometrically a tubular shape as seen in Fig. 1(b).

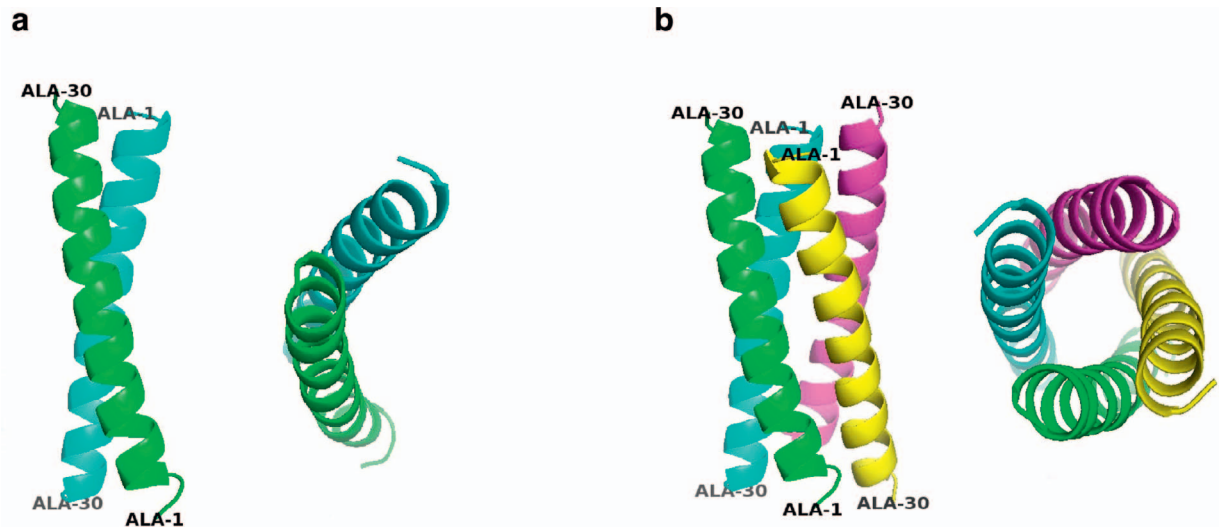

Fig. 1. Side and top view of (a) dimer unit (3SOR) (b) *de novo* anti-parallel tetrameric structure. Colour: green, chain A; blue, chain B; magenta, chain C; yellow, chain D. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)