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Helical formation of a 17-residue peptide by molecular dynamics simulations

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ABSTRACT

A molecular dynamics simulation of a 17-residue peptide $AcYKA_4KAGAAKA_4KNH_2$ was carried out using ff03 force field. 1000-ns MD simulations were performed with 2 fs time step. The helical content dynamically fluctuated between 0 and 90 % in all regions of simulation time and it did not converge to any definite value because of the large flexibility of 17-residue peptide. The time-averaged helical contents were calculated by using our simulation data and were in good agreement with the experimental data. Moreover, we proposed the possible pathway of helical formation of the 17-residue peptide.

KEYWORDS

AMBER;
Molecular dynamics;
Secondary structure.

INTRODUCTION

In molecular bio-physical chemistry for protein, one of the most important concerns is the folding and unfolding mechanism. When this elusive problem becomes clear, three dimensional structure of protein can be more easily predictable on a basis of its amino acid sequences. On understanding folding and unfolding mechanism of a protein, molecular dynamics simulation provides a powerful tool to generate detailed information about the interactions between the atoms of a protein and the solvent. However, even with the fastest computer, the simulation of the dynamics of folding process on a whole molecule of protein would take a very long time and to carry out this simulation is un-realistic. For this reason, some kinds of peptides have been often used as a model protein. Chakrabartty *et al.* studied the helical contents of a series of alanine rich 17-residue peptides with a single glycine residue by CD spectroscopy[1]. They systematically demonstrated that changing a position of glycine residue in the peptide brought about a significant change of its helical stability of peptide, showing that the helical contents depends on a distance of glycine residue from the center of the peptides. Their studies give a clue to understanding the effect of amino acid sequence on the secondary structure. However, their results by CD method give just only information on static helicity of peptides, not giving a dynamic aspect of view, such as the pathway of formation of helix structures

In this report, we applied a molecular dynamics simulation method to one of the series of 17-residue

peptides in Chakrabartty's studies ($AcYKA_4KAGAAKA_4KNH_2$ (1)). The helical content obtained by simulation results were compared with Chakrabartty's experimental one to examine whether it was reproduced correctly under a certain molecular dynamics simulation conditions. This means can provide information not only on static secondary structure of peptide, but also a view on dynamics of peptide, such as a pathway of three-dimensional helix formation which occurs with a very fast rate and is hardly observed by a conventional apparatus.

We also report schematically a process of helical formation of the peptide in four consecutive steps by the same method.

SIMULATION PROCEDURE

AMBER10 package[2] was used on DELL Power Edge R610 cluster system. The fully extended conformation of 1 was used as the initial structure. Four chloride anions as counterions of lysine residues were added to adjust for excess charges. To set up the simulation system, peptide 1 was placed in a periodic truncated cube box (8 Å × 8 Å × 8 Å) solvated with explicit water modeled by the TIP3P potential[3]. After the system was energy-minimized using steepest descent method, the molecular dynamics simulation was carried out using *ff03* force field. The simulation was carried with 2 fs time steps and structural data were collected with 2 ps time steps. Initial velocities were taken from a Maxwell distribution at 300 K. SHAKE method[4] was applied. The temperature (300 K) and pressure (1 atm) were kept by Andersen and Berendsen method, respectively. For assessment of secondary structure type and content, the DSSP definition introduced by Kabsh and Sander was used[5].

RESULTS AND DISCUSSIONS

Reproducibility of experimental data

The molecular dynamics simulation was performed on the peptide 1 to evaluate the secondary structural formation for a time span of 1000 ns. Helical content H_C is calculated by the following equation.

$$H_C = \frac{n}{17} \times 100 \quad \textbf{(1)}$$

where *n* is the number of residues satisfying the criteria for helix by DSSP definition and 17 is the number of residues in the peptide 1.

Figure 1 shows the change of the helical content in the course of simulation. The helical' content dynamically fluctuated between 0 and 90 % in all regions of simulation time and it did not converge to any definite value. Chakrabartty *et al.* demonstrated that the helical content of equivalent sequence of 1

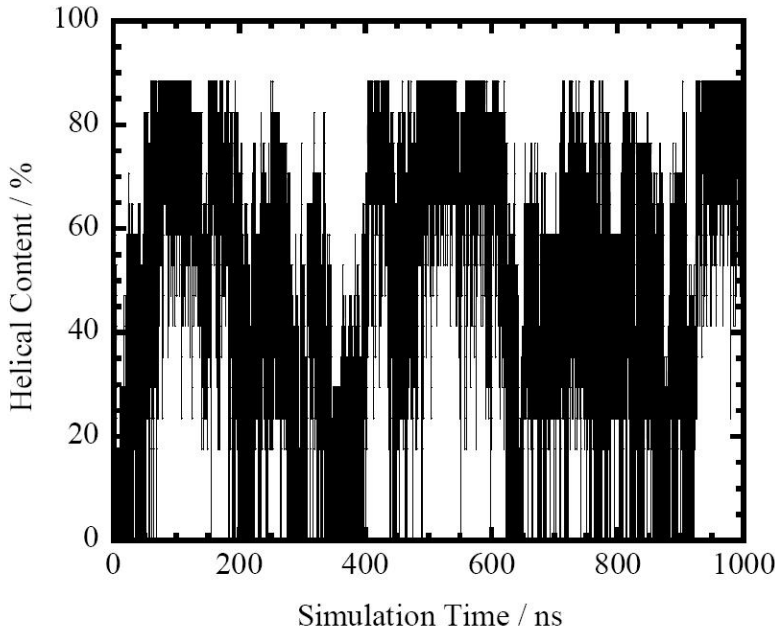

Figure 1 : The change of helical content against simulation time

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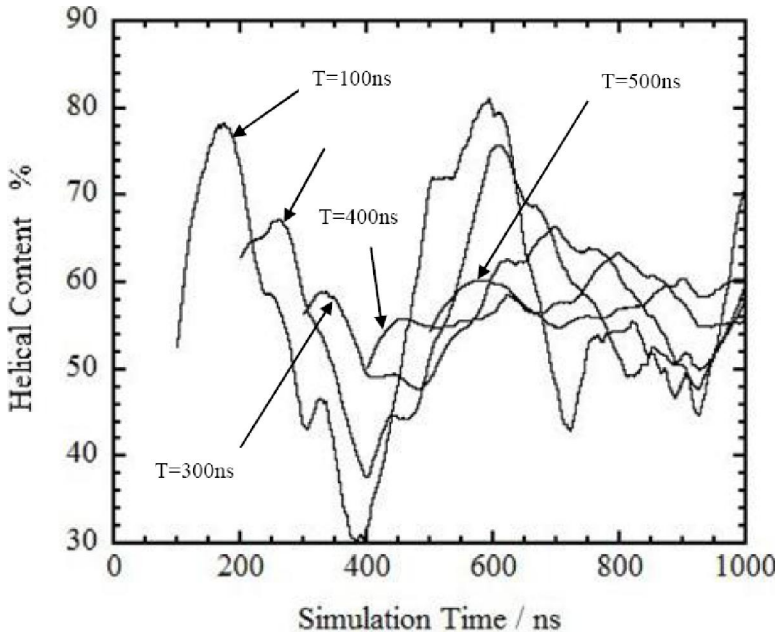

Figure 2 : The change of *H*(*t*) against simulation time

was 55 ± 5 % by CD experiments[1]. However, the value of 55 % cannot be determined in Figure 1. The peptide 1 is a flexible molecule, interacting with the environmental water molecules and atoms within the peptide, the conformation of peptide 1 continuously changes, therefore, the helical content fluctuates at each 2 ps time step.

In comparison of the helical content by CD results with one by simulation method, we notice that it is impossible to observe spectroscopically the motions of the atoms of a very single peptide chain at such a small time scale (2 ps). However, the helical content by CD results can only be a conformational averaged one and is essentially equivalent with a time averaged one of the single peptide chain. A later type of helical content *H*(*t*) at time *t* can be calculated by the following equation.

$$H(t) = \sum_{i=t-T}^{T} h(i) \quad (2)$$

where *T* is the time width to perform a time averaging and *h*(*i*) is helical content at time of *i*.

Figure 2 shows the change of *H*(*t*) in the course of simulation at different averaging time period of *T*. It is clear that in all the cases of *T*, the dynamic range of *H*(*t*) becomes smaller and more distinctive, compared with *H(t)* without averaging proceduce in Figure 1. As *T* becomes longer, the magnitude of change of helical content becomes smaller; 37 – 75% at *T* = 200 ns, 48 – 65 % at *T* = 300 ns, 50 – 63 % at *T* = 400 ns. When *T* is 500 ns, *H*(*t*) converged to 55 ± 5 % in all time regions. This converged value is in good agreement with Chakrabartty's experimental results[1]. Thus, under this condition (at least *T*=500ns), we could correctly reproduce the experimental CD results by using the time-averaged method. The results of this report also indicate that the flexible molecule like 1 does not converge to any particular helical structures without time-averaged process and subsequently this kind of time-average approach successfully allowed us to predict the helical content for other conformers with the different length of amino acids under this condition.

Folding pathway

The folding of the peptide 1 proceeds at the very early simulation period (~100 ns) as observed in Figure 1. From the trajectory of molecular dynamics simulation, we proposed the folding pathway. Figure 3 represents a folding pathway for the peptide 1 in which representative conformations of the occurring temporarily-stable structures. As a representative folding pathway displayed in Figure 3, the peptide 1 was found in a collapsed, random coil state at 20 ns. At 35 ns, the molecule contained two helical segments perpendicular to each other, then, their axes got into one plane at 50 ns. At 60 ns, the peptide folded into a single rod-like helix. After 70 ns, the molecule stayed in the cluster to the end of MD simulation, showing a fluctuation around the

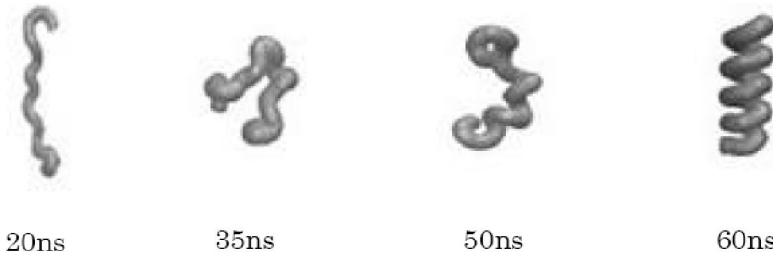

Figure 3 : Folding pathway for the peptide 1

helical conformation, in the course of which unfolding and refolding could be observed for both N- and C- terminal parts of the peptide.

CONCLUDING REMARKS

The molecular dynamics simulation of 17-residue peptides 1 was carried out. The helical contents by simulation data almost correctly reproduced Chakrabartty's experimental results under a certain molecular dynamics conditions. Moreover, the folding pathway of peptide 1 can be clarified in a nanosecond order of time scale and roughly shown in consecutive four stages; from coil state to a single rod-like helix molecule through a terminally stabile combination of two partially helix structures.

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