博士論文概要

論文題目
A Study of the Molecular Conformations and the Electronic Structures of Peptide Nanorings and Nanotubes

ベプチドナノリング及びナノチューブの分子構造並びに電子構造に関する研究

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Chapter 1: Introduction

Progress in modern nano-technology has been able to lead the physical components of machines and devices to dramatic miniaturization. Researchers in this field have continued to devise nano-scale materials and discover new chemical and physical properties. Fullerenes and carbon nanotubes are of especial interest and their applications in molecular electronics are continuously researched. Attention to the nano-constructs has not been limited to these carbon-based molecules but has also been expanded into biomolecules. Since the 1980s, several new types of biomolecules have been synthesized. Of immediate concern is a nano-tubular structure of protein termed “peptide nanotube”. The peptide nanotube (PNT) is formed by the spontaneous stacking of cyclic peptides (or peptide nanorings; PNRs) consisting of an alternate sequence of D- and L-amino acid residues (D,L-peptide). Because of its peculiar periodic structure with an open-ended hollow core, PNT has attracted the interest of many scientists. PNT also has an excellent advantage into molecular modeling. Since the number and kind of component amino acids are artificially adjusted, both the internal diameter and surface property can be controlled. Therefore, the PNT is expected to have a wide range of potential applications in medicine, biology, chemistry, physics, materials science, and so on.

An aim of the present thesis is to provide the guiding principle of molecular modeling in peptide nanorings (PNRs) and peptide nanotubes (PNTs). For this purpose, possible molecular conformations of PNRs and PNTs were mathematically investigated and novel types of backbone structures were explored by the numerical conformation analysis (Chapter 2).

The energetically stable backbone forms of the PNRs and PNTs were also investigated and the electronic structures were discussed based on \textit{ab initio} molecular orbital calculations (Chapter 3). The effects of the amino acid substitution were studied and the electronic characteristics of the individual side chains were systematically understood.

Not only the theoretical studies, but also the synthesis and atomic force microscopy were carried out for the D,L-peptide nanotubes (Chapter 4). PNTs having six and eight amino acid residues were synthesized and their self-assembling morphologies were compared in terms of the difference in the number of component amino acid residues.

In addition to the D,L-peptide nanotubes, an unusual peptide nanotube consisting of all the L-amino acid residues was newly synthesized (Chapter 5). Following the theoretical prediction and synthesis, an atomic force microscopy study of the homo-L-pentapeptide nanotube was carried out and the self-assembling morphology was investigated.
The results of the present studies are summarized below.

**Chapter 2: Conformation analysis of regular periodic polymers**

The mathematical conformation analysis in this study has indicated that the alternate sequence of D- and L-amino acid residues (D.L.-peptide) basically forms a peptide nanoring having an even number of residues. Moreover, even with the same number of residues, two types of the nanoring backbone are shown, i.e., the Extended-type (E-type) nanoring with the larger diameter and the Bound-type (B-type) nanoring with the smaller diameter. While the former is the conventional backbone type, the latter B-type backbone is a novel ring conformation first predicted in this thesis.

On the other hand, the homo L-amino acid sequence basically forms the right-handed or left-handed helix. However, the present conformation analysis has indicated that the homo-L-peptide can form an unexpected peptide nanoring at the boundary between the right-handed and the left-handed helices. Interestingly, the number of residues is limited to five in order to close the peptide backbone of the homo-L-amino acid sequence. This result suggests the possibility of an all-new peptide nanotube (nanoring) having an odd number of residues.

**Chapter 3: Ab initio studies on the electronic and molecular structures of D,L-peptide nanorings and nanotubes**

*Ab initio* calculations have revealed that the energetically preferable backbone of the D,L-peptide nanorings changes in accordance with the ring size, i.e., the smaller rings \((n \leq 8)\) prefer the B-type backbone, while the larger rings \((n \geq 10)\) prefer the E-type backbone. The energy calculations for the amino acid substitution have indicated that all 20 encoded residues can form both E-type and B-type peptide nanorings as local minimum structures, while either type is provided as the energetically stabler form in accordance with the kind of replaced side chains.

Electronically, both the highest occupied molecular orbital and the lowest unoccupied molecular orbital of the nanoring backbones are formed by the in-plane \(\pi\) states. The replacement by the appropriate residues has provided additional energy levels in the energy gap and formed the frontier orbitals localized at the side chains.

The total energy calculations for the self-assembling peptide nanotubes have revealed that both the E-type and B-type nanorings can stack to form the straight peptide nanotubes. Because the resulting total energies become comparable, both the E-type nanotube having the larger diameter and the B-type nanotube having the smaller diameter have been theoretically predicted. *Ab initio* calculations have also indicated that the parallel stacking of the peptide nanorings provides a monotonous
stacking form, while the antiparallel stacking causes a twisted stacking.

Chapter 4: The synthesis and the atomic force microscopy of the D,L-peptide nanotubes

The \( \text{cyclo}[-(\text{D-Ala-L-Gln})_3] \) and \( \text{cyclo}[-(\text{D-Ala-L-Gln})_4] \) nanotubes were synthesized by the solid-phase method and identified by mass spectrometry. The morphology of the synthesized peptides was investigated by atomic force microscopy, and the direct observation of the single peptide nanotubes was first reported in this thesis. The observed D,L-peptide nanotubes have a straight form and this characteristic is well understood by \textit{ab initio} calculations.

The microscopic study has revealed that the synthesized peptides form not only single nanotubes but also self-assembling bundles. The observed bundle forms are quite different between hexapeptide and octapeptide nanotubes. While the hexapeptide nanotubes show thinner nano-bundles and also micro-bundles, the octapeptide nanotubes produce larger aggregated-bundles, which are formed by the assembly of several micro-bundles. \textit{Ab initio} calculations indicate that the formation of these bundles is mainly caused by the inter-tube hydrogen bonding and the different assembled forms are derived from the difference in the space filling manner between the hexapeptide and the octapeptide nanotubes.

Chapter 5: Theoretical prediction and atomic force microscopy observations of the peptide nanotube consisting of homo-L-amino acid pentapeptide nanorings

In this thesis, the first synthesis of an unusual pentapeptide nanotube was reported. This new peptide nanotube consists of five L-amino acid residues in the component nanoring \( \text{cyclo}[-(\text{L-Gln})_5] \), being different from the already-known D,L-peptide nanotubes having an even number of residues. The morphology of the synthesized nanotube was investigated by atomic force microscopy and the meandering tubular structures were observed on the substrate. This meandering characteristic is in stark contrast to the straight nature of the D,L-peptide nanotubes. However, this result is consistent with \textit{ab initio} calculations which show that the homo-L-pentapeptide nanorings stabilize by breaking the \textit{C}_5 symmetry and therefore stack themselves to form a meandering nanotube through the inter-ring hydrogen bonds.

Chapter 6: Summary

A summary of the above studies is given in Chapter 6.
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