Density functional study of local and nonlocal molecular interactions in secondary structures

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The three-dimensional structure of a protein determines its functions and chemical properties. The second structures such as α-helices and β-sheets are important components for the protein architecture. The local and nonlocal molecular interactions, in particular hydrogen bonding, play significant roles in the formation of the secondary structures. Quantitative estimate of these interactions is required to understand the principle of the formation of the three-dimensional protein structure. In the present study, to improve the force field for accurate description of protein behavior, we have investigated the local and nonlocal molecular interactions in the α-helices and β-sheets composed of alanine residues, using quantum chemical (QC) methods (B97D/6-31+G(d)) and molecular mechanics (MM) (AMBER99-SB) . The characteristic interactions essential for forming the secondary structures are discussed quantitatively.

In the formation of antiparallel β-sheets, odd- and even-number residues contribute to the stability in a significantly different fashion, because the odd-numbered sheets form small H-bond ring structures and cause lower stability, while the even-numbered sheets form large H-bond ring structures providing higher stability. Compared to the QC calculations, the MM force field overestimates the interaction energies in the odd-numbered antiparallel β-sheets. This difference in the electrostatic repulsions causes the large discrepancy of the interaction energies, indicating the requirement of improvement of the electrostatic interaction.

Computational results using both the MM force field and quantum chemical calculations showed that almost linear relationship is found between the interaction energies and the number of peptide bonds in the formation of parallel β-sheets. This is due to the formation of almost same size of H-bond ring structures. The MM force field also overestimates the interaction energies in the parallel sheets.

The increment of the interaction energies increases together with the number of the peptide bonds in α-helices, indicating the cooperativity in the formation of α-helix due to the long-range electrostatic interactions such as dipole interactions. The MM force field stabilizes the α-helix much more than the QC method. In addition, the MM force field overestimates the interaction energies of the α-helix, compared to those of the β-sheet, implying that the improvement of the electrostatic interaction is required.