Doctoral Dissertation Evaluation Review

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Title of Doctoral Dissertation

Exploration of Biomolecularly Transparent IR Region for Structural Identification of Biomolecules Using VCD
（生体分子の構造同定を目指した生体分子非吸収スペクトル領域における VCD 研究）

Results of Evaluation of the Doctoral Dissertation (Report)

Biomolecules such as amino acid, sugars, lipids, and nucleic acid make up the fundamental building block of biological system. The structure of these biomolecule influences their function in biological system. Amino acid for instance can polymerize to form complex peptides system and act as primary building blocks in conducting essential cell functions. They form complex 3D structure and perform all the specific bioprocesses such as photosynthesis in the plant cell and gaseous exchange in the red blood cell. However, peptide chain can also form aggregate structure that leads to disease such as Alzheimer. These examples of complex biological phenomena are closely related to the structural characteristic of the biomolecules. Thus, a comprehensive information of biomolecules structural properties is the key to fully understand and regulate their biological functions. However, stereostructural elucidation of biomolecules is rather challenging because of the limitation of conventional analytical methods. To characterize the structure of biomolecules and their synthetic derivatives, one of the major bottlenecks is that they possess multiple chiral centers. Although conventional characterization methods that includes mass spectrometry and NMR spectroscopy are primarily used for structural characterization for biomolecules, they are generally blind to chirality. This makes conformational and stereostructural study of biomolecule far more challenging. Whereas, solving 3D structure using X-rays crystallography method is only limited to solid state samples. Therefore, in some cases, solving 3D structure in solution can still be very challenging. Hence, the development of techniques and methods used for conformational characterization and stereostructural identification of biomolecules is an urgent necessity.

In this study, the author uses VCD as a tool for the conformational and stereostructural elucidation of biomolecules. (VCD) is defined as the differential absorbance of left versus right circularly polarized IR, in vibrational transitions of a chiral non-racemic molecules. This method has deemed to be useful in assigning absolute configuration of biomolecules including natural product. VCD works in the region of IR in the electromagnetic spectrum typically over the range of 4000 to 400 cm^{-1}. It is useful to show vibrational absorption for common functional group in biomolecules especially in the alcohol, amine, and carbonyl region. However, for large biomacromolecules those regions contain complex VCD signals or spectral overlapping so it can be very difficult to analyze. In this work, the author focused on functional group that shows vibration in the biomolecularly transparent IR region where these functional groups do not commonly exist in biomolecules. This region lies between 2300 to 1900 cm^{-1}. Chromophores such as azido, alkyne, isonitrile, nitrile, and carbon-deuterium bond exhibit characteristic IR absorptions in this region. Therefore, in this study the author conducted the installation of these chromophores to model chiral molecules and glycosides. Subsequently, the author investigated which of these chromophores that can yields the best and

strong VCD signals which can be advantageous for extracting stereochemical and conformational information the biomolecules with less structural overlapping.

In conclusion, the author has new findings related to the VCD chromophore in the 2300–1900 cm^{-1} region yields VCD signals that reflect molecular structures. Alkynes VCD signals was negligible as it was too small due to the non-polar nature of the alkyne groups. While nitrile and isonitrile groups exhibited moderate, but complex anharmonic VCD signals that can be difficult and computationally demanding to analyze. The azido group shows the best and strong VCD couplet whose pattern is easily predicted by computational calculation and was suitable when applied to sugar molecules. The VCD studies on a series of C-1 deuterated glycosides, demonstrated that the introduction of one VCD chromophore can extract the local stereochemical information of the chiral center of interest. With the combination of other characterization techniques, VCD spectroscopy using these chromophores group should facilitate future structural studies of biomolecules which aid in understanding their role in bioprocesses and drug development. Further studies on this fundamental concept will also contribute to the development of more advance methods useful for the conformational and stereostructural elucidation of other types of more complex molecules such as oligosaccharides, peptide aggregates and other glycosylated biomolecules. Therefore, we acknowledge that the author is qualified to be granted a Doctorate of Life Science from Hokkaido University.