Studies on the Synthesis and Optical Properties of BODIPY-based Functional Dyes

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論　文　内　容　の　要　旨

In the modern life sciences, as the development of treatments for diseases such as cancer has remarkably progressed, bioimaging techniques have been essential for understanding biological phenomena and elucidating their causes. Super-resolution microscopy (SRM) has recently been actively developed as a high-resolution imaging technique. This technique enables observation of specific structures and intracellular events on live imaging. On the other hand, the non-invasive deep visualization technique of living cells and organs can also be applied to detect cancer and other malignant tumors without damaging normal tissues. However, in the development of functional dyes suitable for deep bioimaging and SRM, several issues render their synthesis challenging.

Boron dipyrromethene (BODIPY) is a representative fluorescent dye and exhibits intriguing properties such as sharp absorption arising from the π-π* transition and intense fluorescence emission with high fluorescence quantum yields in the visible region. Therefore, BODIPY and its analogues have found their wide applications in bioimaging, photocatalyst, organic solar cells (OSC), and so on. To develop suitable BODIPY-based dyes for deep bioimaging and SRM, as an alternative strategy to the conventional π-expansion method, two functionalization strategies using triisopropylsilyl (TIPS)-ethynyl-substituted BODIPYs were investigated in this thesis.

In Chapter 2, to introduce ethynyl groups to the BODIPY core, the direct C-H alkynylation reaction was investigated using a gold catalyst and TIPS-ethynylbenzoiodoxolone as an ethynyl reagent. The developed synthetic method was also applied to dipyrromethene, a precursor of BODIPY, resulting in the regioselective synthesis of α- and β-ethynyl substituted BODIPY derivatives. These compounds showed distinct optical properties depending on the position of the ethynyl substitution. α-Ethynyl BODIPY exhibited optical properties similar to conventional BODIPY, while those of β-ethynyl BODIPY were influenced by the charge transfer effect from the ethynyl group to the BODIPY core.

In Chapter 3, two D-π-A-π-D BODIPYs with diethylaminophenyl donor groups and ethynyl groups at other positions were synthesized, and their properties as two-photon excitation-induced photoacoustic (TPPA) contrast agents for deep imaging were estimated using the near-infrared second (NIR-II) light. They exhibited intense absorption in the NIR region, and the fluorescence emission was virtually quenched. Moreover, both compounds successfully showed photoacoustic signals upon two-photon excitation in the NIR-II region (1000–1200 nm). Image pictures using nanoparticles of these dyes were acquired at depths on the millimeter scale with higher intensity than that of Rhodamine B. D-π-A-π-D BODIPY bearing donors at the α-positions exhibited more clear photoacoustic signals than that with donors at the β-positions upon excitation at 1064

nm due to the high two-photon absorption cross-section. These results indicate the potential application of these BODIPY dyes for *in vivo* TPPA imaging in deep tissue.

In Chapter 4, the author described the design of a novel β,β'-butadiyne bridged cyclic BODIPY oligomers and their synthesis via *cis*-platinum coordination inspired by the synthesis of cycloparaphenylenes. The target tetramer was successfully isolated albeit with a low yield. Although its structure could not be fully characterized, the optical properties supported the formation of the cyclic structure. The tetramer displayed a broad absorption spectrum and fluorescence bands with a large apparent Stokes shift of 2736 cm^{-1}. In the future study, structural determination by single crystal X-ray diffraction analysis, optimization of the reaction conditions to improve the yields, and the synthesis of larger cyclic BODIPY oligomers will be performed.

In Chapter 5, the author investigated machine learning (ML) to predict the optical properties of BODIPY dyes as a member of university fellowships towards the creation of a science technology innovation. The author built a supervised learning classification ML model with compound images of BODIPYs for predicting their optical properties. Using the model, the fluorescence properties of the BODIPY derivatives have successfully been predicted. Further expansion of the amount of data and a search for the best algorithm will be conducted to improve performance.

In this thesis, the author focused on the molecular design of BODIPY dyes to achieve unique optical properties, which cannot be attained with conventional π-expanded BODIPYs. The guidelines for structural design will be of great help for developing novel imaging contrast agents, such as D-π-A-π-D BODIPYs for TPPA and cyclic BODIPY oligomers for SRM. This thesis also describes the possibility of predicting optical properties by ML methods instead of theoretical calculations. ML in chemistry is expected to revolutionize the new approach and support efficient research in the future.