Thesis Summary

Development of a Two-Photon Responsive Chromophore, 2-(*p*-Aminophenyl)-5,6-dimethoxy-1-(hydroxyinden-3-yl)methyl Derivative, as Photoremovable Protecting Group

(2光子応答性に優れた 2-(*p*-Aminophenyl)-5,6-dimethoxy-1-(hydroxyinden-3-yl)methyl 発色団の開発に関する研究)

Nguyen Tuan Phong

Caged compounds are photosensitive molecules that protect bioactive substances by photoremovable protecting groups (PPGs)[1] and can release biologically active substances by irradiation. Important criterions of PPGs are strong absorption at irradiated wavelength, high solubility in target media[3], and less harm for living cells[1,2]. However, normally UV light which damages to living cells is used as a stimulus for uncaging leaving group. For that reason, in our study, we aim to synthesize PPGs with ability of absorbing two-photon (2P) of near IR-light, 650-900 nm which is a biological window Because 2P excitation at near IR region (650-900 nm) can be avoid damage to the living cells. Besides, 2P excitation obtain a deep penetration in living tissues, and the spatiotemporal release of bioactive compounds is possible[3].

In the previous study, a new chromophore, p-aminopheny indene (pAPI), was designed based on the stilbene core[4]. In the previous study: high quantum and chemical yields of the release of benzoic acid were observed in the photoreaction of compound **A**. However, significant two-photon absorption band of **A** could not be observed in the near-infrared region. In this study, we designed a new PPG substituted pAPI (MeOpAPI) chromophore. Two electron-donating groups (OMe groups) are introduced at the stilbene core to shift the 2PA band to longer wavelengths and increase the quadrupolar character that increases 2P response. Caged benzoate **12a** and **12b** were successfully synthesized from the commercially available chemicals. The absorption maximum of **12a** and **12b** were more red shifted than compound **A**. The release of benzoic acid from both substrates was conducted using 365 nm in DMSO (± 20 nm), chemical yields of benzoic acid was observed to be high over 90%. Besides, the high uncasing quantum yield of **12a** and **12b** were found to be $\boldsymbol{\Phi_u}$ = 0.73 and $\boldsymbol{\Phi_u}$ = 0.74, respectively. The products in MeOH were separated and identified to trans-**14** (26%) and cis-**14** (33%). The proposed mechanism of photoreaction of compounds **12a** and **12b** is show in. To detect the generation of cations **B**, the time-resolved UV-vis spectroscopy was performed for the uncaging reaction of **12a** and **12b** using laser flash photolysis (LFP. And the results showed the appearance of **B** when irradiating the compounds in MeOH and DMSO under Air and Ar condition, respectively.

Finally, the 2P absorption cross-section was determind in DMSO (Figure 3) to be 2P cross-section are σ_2 = 49.5 GM at 690 nm and σ_2 = 40.7 GM at the 695 nm for compound **12a** and **12b**, respectively. High 2P uncasing efficiency (**12a**: δ_2 = 36 GM; **12b**: δ_2 = 30 GM)[5] were discoved, suggesting that the new 2P-responsive chromophore can be applied to physiological experiments.

[1] Kaplan J. H., Forbush B. 3rd, Hoffman J. F., Biochemistry, **1978** 17, 1929—1935.

[2] Engels, J.; Schlaeger, E. J. J. Med. Chem. **1977**, 20, 907.

[3] M. Goppert-Mayer, *Ann. Phys.* **1931**, 401, 273 – 294

[4] Miyu Sasaki, Linh Tran Bao Nguyen, Sohshi Yabumoto, Tatsuo Nakagawa, and Manabu Abe , ‘’Structural Transformation of 2-(*p*-Aminophenyl)-1-hydroxyinden-3-ylmethyl Chromophore as a Photoremovable Protecting Group’’, *Chemphotochem, ,* **July 2020**, *5392-5398*.

[5] Tuan Phong Nguyen, Hai Dang Nguyen, and Manabu Abe, ‘’ Development of a Two-Photon Responsive Chromophore, 2-(*p*-Aminophenyl)-5,6- dimethoxy-1-(hydroxyinden-3-yl)methyl Derivative, as a Photoremovable Protecting Group’’, The Journal of Organic Chemistry, **2024**, 89 (7), *4691-4701*.