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Design, Synthesis, and Reaction of π -Extended Coumarin-based New Caged Compounds with Two-photon Absorption Character in the Near-IR Region

Youhei Chitose,¹ Manabu Abe,^{*1} Ko Furukawa,² and Claudine Katan^{*3}

¹Department of Chemistry, Graduate School of Science, Hiroshima University,
1-3-1 Kagamiyama, Higashi-Hiroshima, Hiroshima 739-8526

²Centre for Instrumental Analysis, Niigata University, 8050 Ikarashi 2-no-cho, Nishi-ku, Niigata 950-2181

³Institut des Sciences Chimiques de Rennes, CNRS, Universite Rennes 1, 35042 Rennes, France

(E-mail: mabe@hiroshima-u.ac.jp, claudine.katan@univ-rennes1.fr)

Novel π -extended coumarin-based chromophores were designed with two-photon absorption (TPA) character in the near-IR region. Caged benzoates with a TP-responsive chromophore were synthesized, and their TP-uncaging reactions were conducted under near-IR light. The 6,7-dimethoxy-substituted derivative had a high TPA cross-section of 69 GM at 740 nm. The 7-methoxy-substituted derivative showed a high TPA uncaging efficiency with a TPA efficiency of 3.4 GM at 710 nm.

Keywords: Caged compounds | Two-photon absorption | Donor– π –Acceptor

Caged compounds,¹ the inactive forms of bioactive molecules formed using a photolabile protecting group (PPG),² are now used to elucidate the mechanism of bioactivity of substances in various life processes and phenomena. For instance, caged compounds contribute to the development of new medicines. The PPG is removed photochemically under neutral conditions without chemical reagents, thus rapidly releasing the bioactive compound. This efficient uncaging is biologically useful because the timing, location, and amplitude of photoirradiation can be controlled. Thus, the photoinduced release of bioactive molecules has been utilized in various fields such as neuroscience, cell patterning, or biomedical science.^{3–5}

Coumarin derivatives have been used to study various functions of biomolecules and for cellular imaging.⁶ The advantages of coumarin as a chromophore include its inherent fast response to photolysis, thermal stability, high molar extinction coefficient, and good fluorescent property for monitoring its reactions in vivo.⁷ However, the recent concern for physiological application of coumarin-based compounds is mainly its short absorption wavelength. Coumarin itself possesses an absorption wavelength maximum of 274 nm in methanol.⁸ Due to this short wavelength, cell damages cannot be avoided using one-photon absorption (OPA).⁹ But better penetration to the deeper part of cells¹⁰ can be afforded using chromophores having significant two-photon absorption (TPA) character in the near-IR region.^{11,12}

Chromophores with TPA character have attracted much attention because of their application in physiology. Caged compounds with TPA character enable greater spatial control of the release of bioactive substances.¹³ For practical applications, a higher uncaging efficiency is necessary to conduct biological studies. The uncaging efficiency for OP excitation is defined as the uncaging quantum yield (Φ_u) multiplied by the excitation probability (ϵ : molar extinction coefficient). Similarly, the efficiency δ_u of a TP excitation process is expressed using the TPA cross-section (σ_2): $\delta_u = \Phi_u \sigma_2$. The minimum threshold value of TP efficiency for in vivo studies was reported as 3 GM.¹⁴ In 1999, Furuta et al.

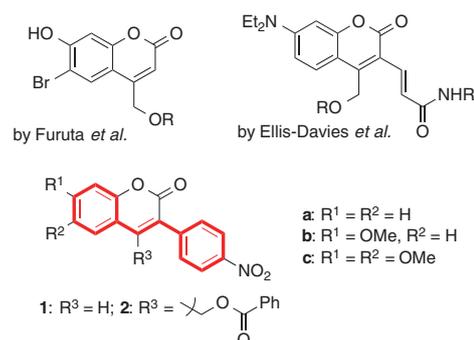


Figure 1. Coumarin derivatives with TPA character.

synthesized brominated 7-hydroxycoumarin-4-ylmethyl (Bhc) esters and carbamates with TPA character in the near-IR region, i.e. 650–1350 nm. Its TP efficiency amounts to ca. 1 GM at 740 nm.¹⁵ In 2012, Zhu et al. reported $\delta_u = 0.25$ GM at 800 nm.¹⁶ In 2013, Ellis-Davies et al. developed a new π -extended caged coumarin molecule that had a TPA maximum at 900 nm.¹⁷

In this study, a coumarin containing a stilbene skeleton (12 GM at 514 nm)¹⁸ with a *p*-nitrophenyl group as the electron-withdrawing group was designed to increase the TPA cross-sections due to its dipolar character (Figure 1).¹⁹ The cyclic structure should prevent *cis*–*trans* isomerization in the excited state. A bathochromically shifted absorption wavelength is also expected because of the donor– π –acceptor conjugated system.

First, the OPA and TPA spectra of coumarin chromophores **1a–1c** were computed at the TD-B3LYP/6-31G*//B3LYP/6-31G* level of theory (Figure 2; see also ESI for more details). The predicted absorption maximum of 6,7-dimethoxy-substituted coumarin **1c** is more red-shifted compared to those of the 7-methoxy-substituted coumarin **1b** and coumarin derivative **1a**. At this level of theory, a TPA cross-section of ca. 50 GM is computed for **1a**. Sizable increase is observed upon substitution with TPA cross-sections of 170 and 179 GM for **1b** and **1c**, respectively, in the 740–780-nm spectral region. The maxima correspond nicely to twice the OPA maxima (370–390 nm). These predictions suggest that TP electronic excitation in the near-IR region is possible for coumarin derivatives. Thus, the photochemical reactions of caged benzoates **2b** and **2c** with π -extended coumarin derivatives²⁰ were investigated experimentally.

Caged benzoates **2b** and **2c** were synthesized using a base-catalyzed Perkin condensation reaction²¹ (Scheme 1). The UV–visible absorption spectrum of 7-methoxy-substituted compound **2b** showed the absorption maximum at 345 nm with $\epsilon = 22726$ M⁻¹ cm⁻¹ in DMSO, whereas 6,7-dimethoxy-substituted

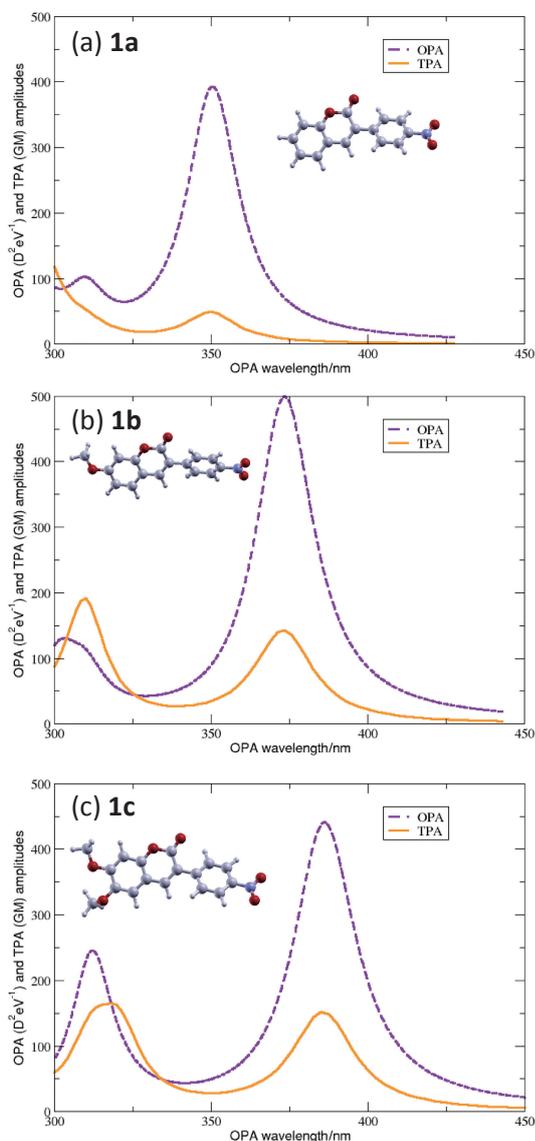
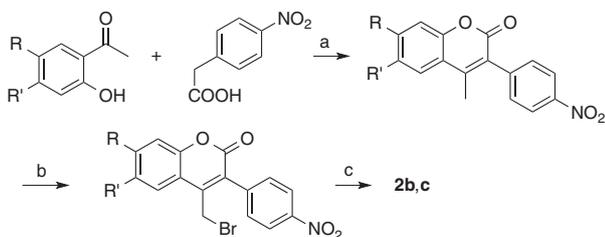


Figure 2. Calculated OPA (magenta dashed line) and TPA (orange solid line) spectra at the TD-B3LYP/6-31G*//B3LYP/6-31G* level of theory for (a) **1a**, (b) **1b**, and (c) **1c**.



Scheme 1. Synthesis of **2b** and **2c**. a) Acetic anhydride, triethyl amine, 65 °C to RT, overnight, 51% yield. b) NBS, benzoyl peroxide, CCl₄, 90 °C, 15 h, 40% yield. c) benzoic acid, K₂CO₃, KI, DMF, 50 °C, 6 h, 20% yield.

compound **2c** showed an absorption peak at 369 nm with $\epsilon = 16902 \text{ M}^{-1} \text{ cm}^{-1}$. As predicted by TD-DFT calculations (Figure 2), the absorption maximum of **2c** exhibited bathochromic and

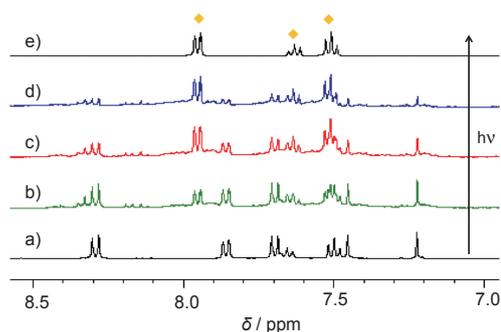


Figure 3. ¹H NMR spectra of compound **2c** in DMSO-*d*₆ (a) before and after (b) 48, (c) 72, and (d) 96 h of irradiation at 360 nm; (e) ¹H NMR spectrum of benzoic acid in DMSO-*d*₆.

hypochromic shifts as compared to **2b**. The OP photolysis of **2b** and **2c** was investigated using a Xe lamp at $360 \pm 10 \text{ nm}$ in DMSO-*d*₆ (Figures 3 and S1). The quantitative uncaging of benzoic acid from **2b** and **2c** was confirmed by comparing the ¹H NMR signals of benzoic acid with those of the photolysate (Figures 3 and S1). The uncaging quantum yields Φ_u were determined in DMSO using the photochemical actinometer ferrioxalate coupled with HPLC analyses. Approximately three-times higher quantum yield for the uncaging reaction of **2b** ($\Phi_u = 0.09$) than **2c** ($\Phi_u = 0.03$) was obtained. The OP uncaging efficiencies ($\epsilon_{360} \times \Phi_u$) of **2b** ($\epsilon_{360} = 18718$) and **2c** ($\epsilon_{360} = 16102$) were 1684 and 483, respectively. The lower uncaging efficiency of **2c** may be attributed to the increased electronic stability of the excited state of **2b**.²²

The TP-uncaging reactions of **2b** and **2c** were also investigated in DMSO using 700-nm, 710-nm, 720-nm, 730-nm, 740-nm, 750-nm, and 760-nm lights obtained from a Ti:sapphire laser (pulse width 100 fs, 80 MHz) at an average power of 700 mW. To determine the TPA cross-section and efficiency of **2b** and **2c**, the rate constants of the TP-uncaging reactions were compared with that of a caged benzoate NPBF-BA (Figure 4c).^{23,24} The consumption of **2b** and **2c** upon TP photolysis was monitored by HPLC (Figure 4).

As shown in Figure 4, the TP-uncaging reaction rates depend on the excitation wavelength. The photolysis of **2b** proceeded the fastest at 710 nm ($k_{710} = 6.5 \times 10^{-6} \text{ s}^{-1}$), whereas the fastest photolysis rate for **2c** was observed at 740 nm ($k_{740} = 3.9 \times 10^{-6} \text{ s}^{-1}$). The values of TPA cross-sections at each wavelength were extrapolated from the rate constant of TP uncaging of NPBF-BA, 18 GM at 720 nm.²³ This allowed extrapolation of the TPA cross-section of **2b** to ca. 38 GM at 710 nm, and that of **2c** to ca. 69 GM at 740 nm.

The action spectra of TPA cross-section for **2b** and **2c** are shown in Figure 5. The TP efficiency δ_u was determined to be 3.4 GM for **2b** at 710 nm, higher than the minimum threshold value of 3 GM. Compound **2c** has a lower efficiency of ca. 2.1 GM at 740 nm due to the lower quantum yield of the uncaging reaction, despite the higher TPA cross-section than **2b**. Compared to the previously reported NPBF-BA chromophore ($\sigma_2 = 54 \text{ GM}$ and $\delta_u = 5 \text{ GM}$ at 740 nm), 6,7-dimethoxy-substituted coumarin **2c** is superior in terms of TPA cross-section but inferior in terms of TP efficiency. This is due to its higher dipolar character afforded by the methoxy group substitution, enhancing the TPA character, but at the expense of a reduced uncaging quantum yield.

In conclusion, novel coumarin chromophores were designed and synthesized, which exhibited efficient reactivity for TP-

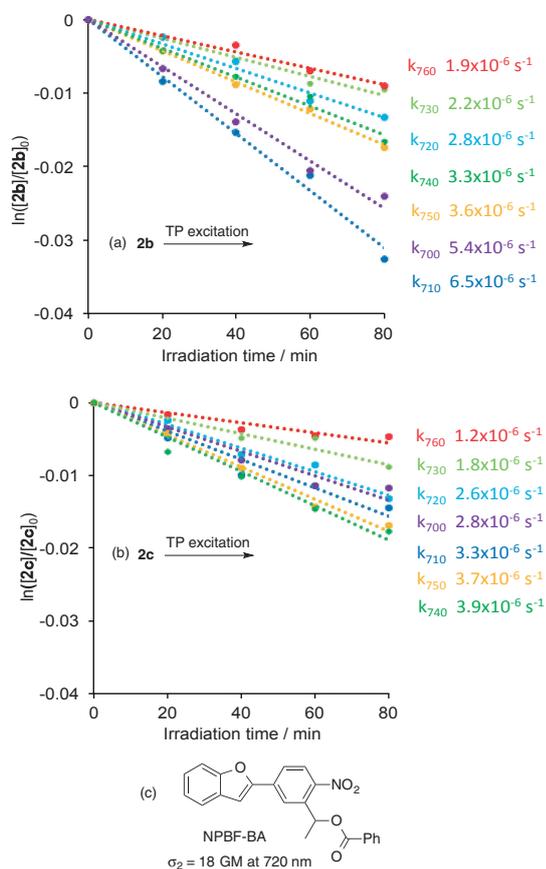


Figure 4. Time profile of the TP uncaging of (a) **2b** and (b) **2c**, $\ln([\text{sub}]/[\text{sub}]_0)$ vs. irradiation time at wavelengths of 700, 710, 720, 730, 740, 750, and 760 nm at 700 mW. (c) TP reaction of NPBF-BA at 720 nm, $\sigma_2 = 18$ GM at 720 nm.

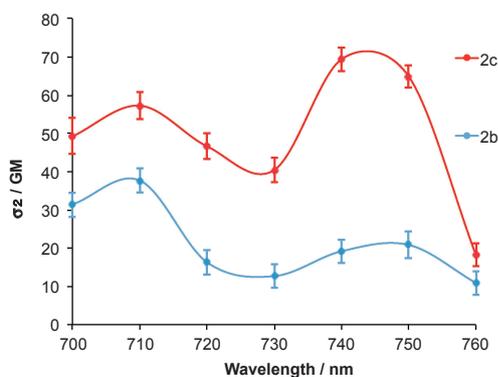


Figure 5. Extrapolated experimental TPA spectra of **2b** (red) and **2c** (blue).

uncaging reactions. Compound **2b** showed a relatively high TP efficiency (3.4 GM). The TPA cross-section (69 GM) of compound **2c** was approximately twice as large as that of **2b** (38 GM). These new TP chromophores have great potential for application in physiological studies.

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