Thesis Summary

Sulfur Atom Effect on Photo-uncaging Reaction of (Coumarin-4-yl)methyl Derivatives
((クマリン-4-イル)メチル誘導体の光脱ケージング反応に対する硫黄原子の影響)

Name: NGUYEN HAI DANG

Photolabile protecting groups (PPGs)[1] have been widely used as a powerful tool to protect (= cage) various types of useful compounds such as bioactive molecules, precursors for organic synthesis, fluorophores, and gasotransmitters such as H_2S, CO, and NO. The key idea behind this strategy is that the function such as bioactivity and fluorescence of target molecules can be temporally masked by attaching PPGs, which are subsequently removed under light irradiation to revive (= uncage) the original function of molecules. The temporally masked compounds are called caged compounds. The use of light as a sole reagent renders the uniqueness of caged compounds, which is a mild, non-invasive technique.

The 7-diethylamino(coumarin-4-yl)methyl (DEACM) is among the most studied PPGs because of its attractive features such as fast release rates of leaving groups under light with wavelengths above 400 nm, large extinction coefficients and stabilities under dark condition. In 2018, Rivera-Fuentes and coworkers examined the photochemistry of a series of DEACM-based caged compounds, including different leaving groups.[2] It was observed that the lower the pK_a of the leaving groups, the higher the photochemical quantum yield of caged compounds. In other words, the leaving ability of the leaving group has a profound influence on the photochemistry of DEACM-based caged compounds. On the other hand, it was reported that pK_a values of thiobenzoic acid and thioacetamide are higher than that of benzoic acid and acetamide, respectively, suggesting that the sulfur atom could have a large influence on the photo-uncaging reactions of DEACM-based caged compounds. To clarify the sulfur atom effect, in this study, we synthesized and examined the photochemical properties of DEACM-based caged carboxylic acids **1a-c** and DEACM-based caged amines **2a-b** (Figure 1).

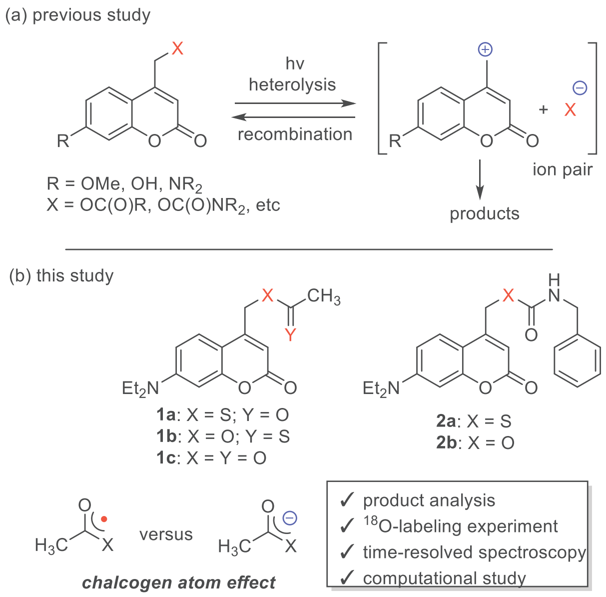
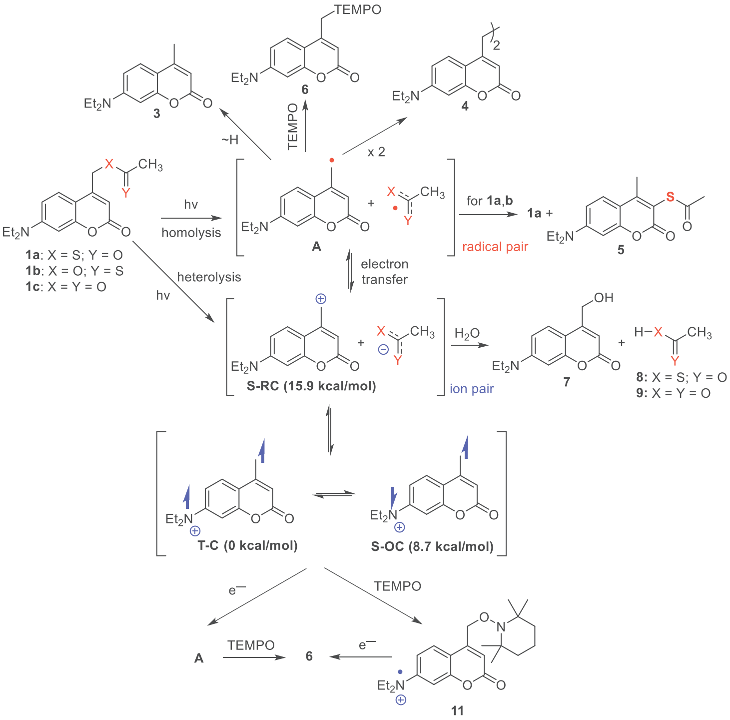


Figure 1. This study

The photoreaction of **1a** in Ar-saturated DMSO resulted in the formation of compound **4** as the main product (24%) (Figure 2), which was strong evidence of the existence of radical **A**, originating from the homolytic bond dissociation. In the presence of TEMPO, the TEMPO-adduct product **6** was observed, which supported the formation of **A**. Based on these observations, the mechanism of the photoreaction of **1a** was proposed as described in Scheme 1. The photoreactions of **1b** were conducted in the same manner with **1a**. Interestingly, an effective photoinduced isomerization from **1b** to **1a** was observed, which has not been reported so far. The photoreaction of **1b** in the presence of TEMPO generated compound **6**, revealing the formation of **A** during irradiation. The photoreaction of **1c** in DMSO in the presence of TEMPO yielded compound **6** as the main product (58%), which may be originated from the homolysis of C-O bond. However, compound **7** was observed as the main product (39%) after photoreaction of **1c** in DMSO/H_2O (3:2), indicating the existence of **S-RC** generated from the heterolysis of C-O bond. In addition, the DFT calculation and ^{18}O-labeling experiment suggest the existence of **T-C** (Scheme 1).



Scheme 1. Proposed mechanism

Photochemical properties of compound **2a** and **2b** were examined to clarify the sulfur effect on the release of amine (Figure 1). The photoreactions of **2a** and **2b** in DMSO generated benzyl amine **14** with the yields of 36% and 29%, respectively. These low chemical yields are due to the side reaction of free amine **14** with the starting material and photoproducts. Therefore, a reagent which can trap amine **14** is necessary to improve the chemical yield of **14**. To this end, pyridinium hydrochloride was added as a trapping reagent for **14**. The photoreactions of **2a** and **2b** in the presence of pyridinium hydrochloride released compound **14** with the yield of 70% and 89%, respectively. The photochemical quantum yield of **2a** and **2b** were measured using Ferrioxalate complex as an actinometer. It was observed that the photochemical quantum yield of **2a** was 0.024, which was 20 times higher than that of **2b** (0.0012). This significantly higher photochemical quantum yield reveals a profound influence of sulfur atom on the release of amine leaving group, making thiocarbamate linkage a promising substitution for the conventional carbamate linkage.

1. Barltrop, J. A.; Schofield, P. Q. *Tetrahedron Lett* **1962**, *3* (16), 697–699.
2. Bassolino, G.; Nançoz, C.; Thiel, Z.; Bois, E.; Vauthey, E.; Rivera-Fuentes, P. *Chem Sci* **2018**, *9* (2), 387–391