Model Study on the Mechanism and Inhibition of Thyroid Hormone Activating Enzyme by Taking Advantage of a Cradled Selenopeptide

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Although selenocysteine selenenyl iodides (Sec–SeIs) have been proposed as important reaction intermediates in the catalytic cycle of iodothyronine deiodinases (Dios), even their trapping has never been reported due to their instability (Figure 1). Recently, we have succeeded in the first isolation of Sec–SeIs by utilizing selenocysteine and selenopeptide models bearing a cradled-type molecular framework.[1] Herein, we report the model study on the chemical processes in the catalytic cycle of Dios by taking advantage of these stable Sec–SeIs.

Sec–SeI **1** derived from a Sec-Gly-Gly tripeptide incorporated in the molecular cradle was successfully isolated as reddish-purple crystals. Its structure was established by X-ray diffraction analysis (Figure 2). As widely accepted mechanism shown in Figure 1, treatment of Sec–SeI **1** with a cysteine thiol afforded the corresponding selenenyl sulfide (Step B in Figure 1). The formation of a selenocysteine selenenic acid (Sec–SeOH) by the hydrolysis of a Sec–SeI was confirmed by the reaction of **1** with aqueous NaOH (Step D in Figure 1). The model study on the inhibition of Dios by propylthiouracil (PTU) was also examined by utilizing **1**.

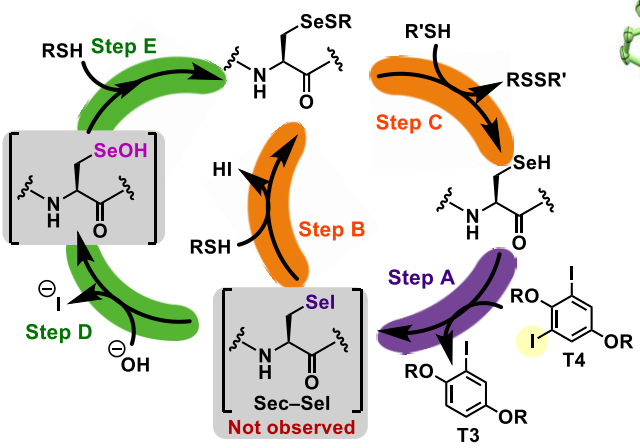

Figure 1. Proposed catalytic mechanism of Dios.

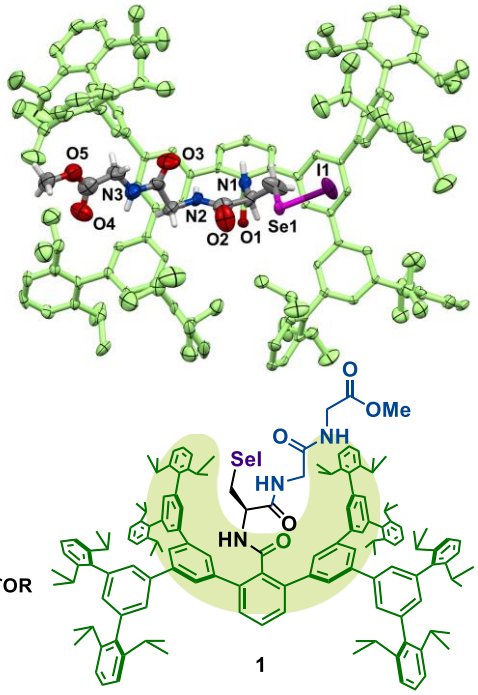

Figure 2. Molecular structure of Sec–Sel 1.

1) R. Masuda, R. Kimura, T. Karasaki, S. Sase, K. Goto, *J. Am. Chem. Soc.*, **2021**, *143*, 6345.