Model Study on the Catalytic Cycle of GPx1 and GPx4 by Utilizing Cradled Selenopeptides

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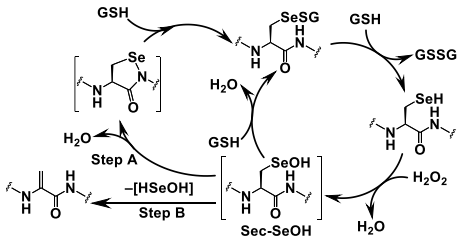
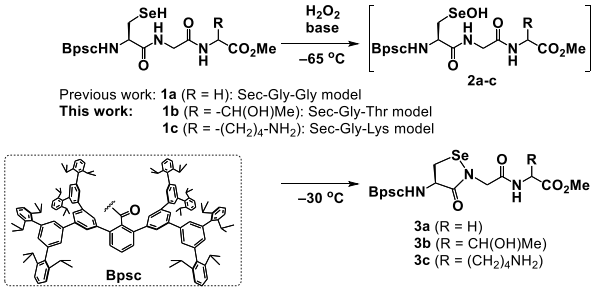
Glutathione peroxidase (GPx) plays crucial roles in redox regulation. GPx1 is a typical isozyme of GPx and catalyzes the reduction of H_2O_2. In contrast, GPx4 is known as a membrane protein that catalyzes the reduction of lipid peroxidase. Selenocysteine selenenic acids (Sec-SeOH) have been accepted as important but elusive intermediates in their catalytic cycle. Recently, we reported the model study on the chemical processes composing the catalytic cycle of GPx (Scheme 1) by the observable Sec-SeOH **2a** of a Sec-Gly-Gly model system, and demonstrated that a Sec-SeOH undergoes the intramolecular cyclization (Step A)[1] more rapidly than the thermal deselenation (Step B).[2] Sec-SeOH **2a** is stabilized by a nano-sized molecular cradle (Bpsc group). Herein, we report the development of tripeptide model systems that mimic the catalytic centers of GPx1 and GPx4. Elucidation of reactivities of Sec-SeOH including the intramolecular cyclization have been examined.

We synthesized selenol **1b** of the Sec-Gly-Thr model for modeling GPx1 and the Sec-Gly-Lys model **1c** for modeling GPx4. Generation of the corresponding Sec-SeOH **2b** and **2c** by oxidation of **1a** and **1b**, respectively, and their conversion to the cyclic *N*-selenoamides **3a** and **3b** were observed (Scheme 2). The intramolecular cyclization of Sec-SeOH was found to proceed more rapidly in the Sec-Gly-Thr and Sec-Gly-Lys models than in the Sec-Gly-Gly model. These results provide chemical corroboration to the proposed protective bypass process of the catalytic cycle of GPx. It is also suggested that the reactivities of Sec-SeOH are modulated by the neighboring amino acid residues.



Scheme 1. Proposed mechanism for GPx function.



Scheme 2. Generation and elucidation of the reactivities of Sec-SeOH.

1) L. Orian, L. Flohé *et al. Free Radic. Biol. Med.* **2015**, *87*, 1.
2) (a) R. Kimura, S. Sase, K. Goto The 97th CSJ Annual Meeting, 3E8-05 (2017). (b) R. Masuda, R. Kimura, T. Karasaki, S. Sase, K. Goto. *in preparation.*