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Modeling of Selenocysteine-Derived Reactive Species Utilizing a Nano-Sized Molecular Cavity as a Protective Cradle

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In the biological functions of selenoproteins, various highly reactive species formed by oxidative modification of selenocysteine residues have been postulated to play crucial roles. Representative examples of such species are selenocysteine selenenic acids (Sec–SeOHs) and selenocysteine selenenyl iodides (Sec–Sels), which have been widely recognized as important intermediates in the catalytic cycle of glutathione peroxidase (GPx) and iodothyronine deiodinase (Dio), respectively. However, examples of even spectroscopic observation of Sec–SeOHs and Sec–Sels in either protein or small-molecule model systems remain elusive so far, most likely due to their notorious instability. For the synthesis of small-molecule model compounds of these reactive species, it is essential to suppress their very facile bimolecular decomposition such as self-condensation and disproportionation. We previously reported the synthesis of non-selenocysteinyl derivatives of selenenic acids and selenenyl iodides by utilizing cavity-shaped steric protection groups. This talk will outline a novel method for the synthesis of stable small-molecule model compounds of the selenocysteine-derived reactive species, in which a nano-sized molecular cavity is used as a protective cradle to accommodate the reactive selenocysteine unit. Stabilization by the molecular cradle led to the successful synthesis of Sec–SeOHs, which are stable in solution at low temperatures, and Sec–Sels, which can be isolated as crystals. The catalytic cycle of GPx was investigated using the NMR-observable Sec–SeOH models, and all the chemical processes proposed for the catalytic cycle of GPx, including the bypass process from Sec–SeOH to the corresponding cyclic selenenyl amide, were experimentally confirmed. Model studies on the reaction pathways involving Sec–Sels proposed for Dio functions will also be delineated.