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Possible roles of NH···Se hydrogen bond in the catalytic cycle of selenoenzymes

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During the catalytic cycles of selenoenzymes, such as glutathione peroxidase (GPx) and thioredoxin reductase (TrxR), a selenenylsulfide intermediate (E-SeSR) generates as a stable species but is rapidly converted to an active selenol intermediate (E-SeH) by the reaction with a thiol substrate. The selenosulfide (Se-S) bond of E-SeSR is significantly inert compared to selenol (-SeH) and selenenic acid (-SeOH) species that are commonly involved in the catalytic cycles of selenoenzymes. Moreover, the nucleophilic attack of a thiol to the Se-S bond takes place preferentially at the Se atom, resulting in a non-productive thiol exchange reaction.[1] Hence, there should be an ingenious mechanism at the active sites of selenoenzymes to guide a thiol to the less reactive S atom and to convert E-SeSR to E-SeH effectively.

We recently hypothesized that at the active sites, an NH···Se hydrogen bond may play a role in controlling the nucleophilic attack of a thiol to the direction of the intrinsically less electrophilic S atom of the Se-S bond.[2] This hypothesis was supported by the increase in the TrxR-like catalytic activity of Se-S-containing heterocycles conjugated with a basic amino acid histidine (H).[3] In this study, to further investigate the roles of the NH···Se hydrogen bond, a selenopeptide hexamer (CUGHGE, **1**) was synthesized as a TrxR active site model, and its catalytic activity was evaluated.[4]

The reaction of **1** with GSH resulted in a reductive cleavage of the Se-S bond to generate the diselenide (Se-Se) species (**2**). The NMR and MS analyses suggested that in the transiently formed mixed Se-S intermediate (**3**), the NH···Se hydrogen bond between the selenocysteine (U) and histidine (H) residues leads a nucleophilic attack of the second thiol molecule not to the intrinsically more electrophilic Se atom but to the less electrophilic S atom of the Se-S bond (Figure 1). Ab initio calculations for the complex between MeSeSMe and an imidazolium ion demonstrated that NH···Se and NH···S hydrogen bonds are equally favorable. Thus, the relative spatial arrangement of the Se-S bond with respect to the imidazole ring would be important for the activation of the Se-S bond.

The proposed umpolung effect of NH···Se hydrogen bond on the reactivity of a Se-S bond will be a useful tool for developing efficient selenoenzyme models with high redox catalytic activity.

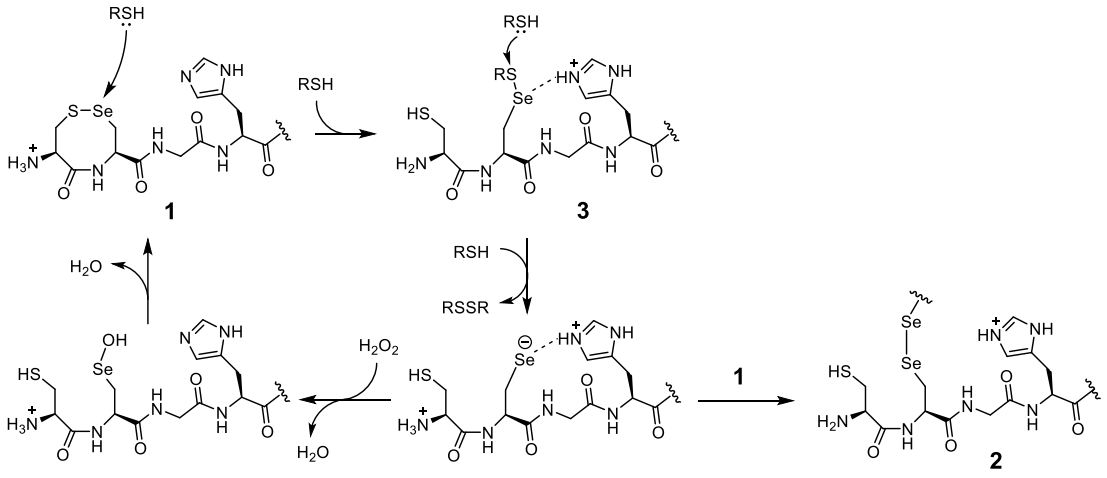

Figure 1: A proposed catalytic cycle of selenopeptide **1**.

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