論文 / 著書情報
Article / Book Information

題目(和文)	安定なセレノペプチド由来高反応性化学種を用いたセレン含有酵素の触媒サイクルのモデル研究
Title(English)	Modeling the Catalytic Cycle of Selenocysteine-Containing Enzymes by Stable Selenopeptide-Derived Highly Reactive Species
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出典(和文)	学位:博士(理学), 学位授与機関:東京工業大学, 報告番号:甲第11700号, 授与年月日:2022年3月26日, 学位の種別:課程博士, 審査員:後藤 敬,岩澤 伸治,江口 正,豊田 真司,小野 公輔
Citation(English)	Degree:Doctor (Science), Conferring organization: Tokyo Institute of Technology, Report number:甲第11700号, Conferred date:2022/3/26, Degree Type:Course doctor, Examiner:,,,,
学位種別(和文)	博士論文
Category(English)	Doctoral Thesis
種別(和文)	論文要旨
Type(English)	Summary

（博士課程）
Doctoral Program

論 文 要 旨

THESIS SUMMARY

系・コース： 化学 系
Department of, Graduate major in 化学 コース

申請学位（専攻分野）： 博士 （ 理学 ）
Academic Degree Requested Doctor of

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要旨（英文 800 語程度）
Thesis Summary（approx.800 English Words ）

Selenium is one of the trace essential elements for humans and is contained as the form of selenocysteines. Selenocysteine-derived highly reactive species play crucial roles in various biological functions. For example, selenocysteine selenenic acids (Sec–SeOHs) in glutathione peroxidase (GPx), which is one of the most widely studied antioxidant enzymes, have been proposed as key intermediates in the catalytic cycle of GPx. It has been also postulated that selenocysteine selenenyl iodides (Sec–SeIs) or *Se*–nitrososelenocysteines (Sec–SeNOs) were formed by the iodination of the selenocysteine residue in iodothyronine deiodinases (Dios) or the nitrosation of selenocysteine residue in various selenoproteins, respectively. However, even direct observation of these selenocysteine-derived highly reactive species in either proteins or small-molecule systems has remained elusive so far, which is mainly due to their instability. The observation and isolation of nonselenocysteinyl-derivatives, i.e., selenenic acids (R–SeOHs), selenenyl iodides (R–SeIs), and *Se*–nitrososelenols (R–SeNOs), were achieved by use of either kinetic or thermodynamic stabilization techniques. However, these nonselenocysteinyl derivatives do not adequately reproduce the characteristic reactivity of selenocysteine-derived reactive species in proteins, e.g., the deselenation to dehydroalanines and the intramolecular cyclization to cyclic selenenyl amides. In his doctoral thesis, the author has worked on the modeling the catalytic cycles of selenoproteins by utilizing the cradled selenopeptides, which are protected in the molecular cradle to prevent the bimolecular reactions of R–SeOHs and R–SeIs. The author has also studied the development of an efficient method for the late-stage functionalization of oligophenylene dendrimers and the first isolation of a *Se*–nitrososelenocysteine (Sec–SeNO) by taking advantage of a novel expanded molecular cradle. After introduction and discussion regarding the purpose and significance of this doctoral study in Chapter 1, the author reports the direct spectroscopic evidence for the formation of Sec-SeOHs in small-molecule selenocysteine and Sec-Gly-Gly selenopeptide model systems with the cradle-type protective group in Chapter 2. The catalytic cycle of GPx was investigated using NMR-observable Sec-SeOH models in detail. All the hitherto proposed chemical processes, i.e., not only those of the canonical catalytic cycle but also those involved in the bypass mechanism, including the intramolecular cyclization of Sec-SeOH to the corresponding five-membered ring selenenyl amide, were examined in a stepwise manner. Furthermore, the author reports the X-ray crystallographic analysis and reactivities of the cyclic selenenyl amides. In Chapter 3, the author reports the development of the novel Sec-Gly-Thr model and Sec-Gly-Lys model, which mimic the catalytic center of GPx1 and GPx4, respectively, and their application to modeling the catalytic cycle of GPx. The author designed these model systems to elucidate the process of cyclization of Sec-SeOHs in more detail. In comparison with the Sec-Gly-Gly model, significant acceleration of the formation of the cyclic selenenyl amides from the Sec-SeOHs was revealed in both model systems. In Chapter 4, the author reports modeling the second half-reaction in the catalytic cycle of Dios by utilizing the stable Sec-SeIs. From the results obtained in Chapter 2, the author has postulated that the cyclic selenenyl amides, which have been proposed only as protective intermediates in the catalytic cycle of GPx, would serve as highly reactive species with highly electrophilic character in the catalytic center of Dios. In contrast to GPx, there are -Sec-Pro- sequences, which do not have -Sec-NH- protons in Dios. The author postulated that the formation of an eight-membered cyclic selenenyl amide by the cyclization of a Sec-SeI could proceed in Dio1. Therefore, the synthesis, crystallographic analysis, and elucidation of the reactivities of Sec-SeIs of the Sec-Gly-Gly model, Sec-Pro-Ser model for Dio1, and Sec-Pro-Pro model for Dio2 and Dio3 were investigated. It was concluded that the cyclization of Sec-SeI of the Sec-Pro-Ser model to the corresponding eight-membered cyclic selenenyl amide was disfavored. However, these results obtained in this Chapter provided an opportunity to formulate new hypotheses on the second- half reaction and the inhibition mechanism in the catalytic cycle of Dios. In Chapter 5, the author reports development of the late-stage functionalization of the periphery of oligophenylene dendrimers via site-selective C-H activation of a preconstructed, readily accessible dendron. By fourfold iridium-catalyzed C-H borylation followed by Suzuki-Miyaura cross-coupling, various arene units were introduced into the end points of the 1,3,5-phenylene-based hydrocarbon dendron. Coupling of the modified dendrons with a core unit, such as 2,6-dibromobenzoic acid derivatives, afforded the periphery-functionalized dendrimers that also have an endohedral functionality at the core position. In Chapter 6, the author reports the first isolation of Sec-SeNO in small-molecule selenocysteine model systems by taking advantage of a novel expanded molecular cradle along with its spectroscopic (^{1}H and ^{77}Se NMR) properties. Sec-SeNO with the expanded molecular cradle, which was prepared via the methods developed in Chapter 5, exhibited the higher stability both in solution and solid state. The reactivities of the Sec-SeNO were also elucidated.