Chapter 3
Organoselenium in Nature

Abstract Selenium, among the naturally occurring elements, is nowadays considered the most relevant for the redox homeostasis of living systems. In this chapter, its role in plants, bacteria, and humans is scholarly discussed. Some plants have the possibility to accumulate this element, thus becoming a natural source for animals and humans, in which selenium is embedded in selenoproteins, as the 21st amino acid, selenocysteine (L-Sec). The main classes of selenoenzymes (glutathione peroxidase, thioredoxin reductase, and iodothyronine deiodinases) are reported here and the molecular mechanism that characterizes their physiological action is discussed.

3.1 Organoselenium in Plants

Selenium occurs naturally in the sedimentary rocks that were formed during the quaternary period [1]. The average Se concentration in soils is 0.4 mg/kg, even if it exists in areas that can be considered both extremely poorer and richer. In this second case, we refer to seleniferous soils and should be considered that high levels of selenium can emerge because of anthropic activities. From the soil, selenium can be transported into the plants using the normal sulfate transporting systems and, in the plant, it follows the same metabolic pathways of the sulfur derivatives, being assimilated by the incorporation in organic molecules or eliminated by volatilization in the atmosphere as **DMeSe** (dimethyl selenide) and **DMeDSe** (dimethyl diselenide) (Fig. 3.1) [2]. In the soil, and more generally in the environment, selenium is present in four different oxidation states: selenate (SeO_4^{2-}), selenite (SeO_3^{2-}), elemental (Se), and selenide (Se^{2-}). The first two species are the most abundant inorganic forms and are characterized by a good mobility in the soil due to their high solubility in water. As a direct consequence, all the parameters of the soil that affect the oxidation state of selenium can influence its bioavailability. As an example, SeO_4^{2-} is more stable and available in alkaline conditions, whereas SeO_3^{2-} is normally present in all the other conditions. The presence of cations (e.g., Ca^{2+}) promotes its adsorption, whereas the anions (Cl^- or sulfate) result in an inhibition of the process [3, 4].

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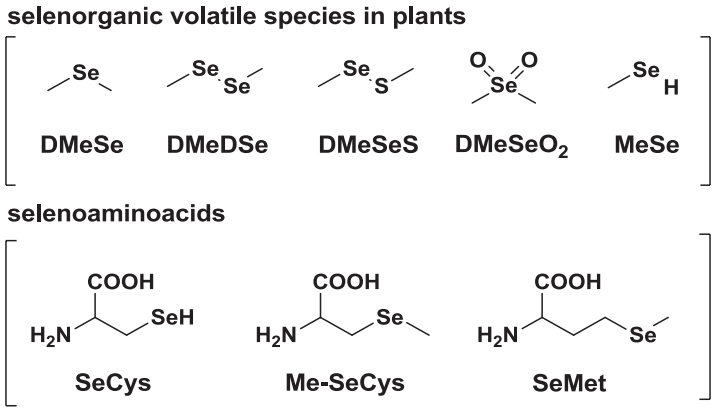

Fig. 3.1 Structures of naturally occurring organoselenium compounds

In addition, the oxidizing or reducing nature of the medium affects the distribution of selenium between the soil and the aqueous phase in a process conceptually close to the chromatography [5]. Zhao et al. reported that exist also a competition for the uptake of selenite and phosphate because they share a common transporter suggesting also a role of the uptake system of silicon in the selenite absorption [6].

Even if several studies reported the beneficial effect of selenium in plants [7–10], it is not considered an essential micronutrient as for humans. Some plants have great affinity for selenium, and for this reason they are currently named Se-accumulators [7]. Specific glutathione peroxidases (GPxs) were identified in these plants incorporating, in their active site, a cysteine in the place of a selenocysteine. These enzymes have reduced substrate specificity if compared to human GpX, thus they can act not only as glutathione peroxidase but also as thyroxine reductase [11, 12].

During the bioaccumulation, the inorganic forms of selenium are transformed into amino acids like selenomethionine (**SeMet**), selenocystine (**SeCys**), and methyl selenocystine (**MeSeCys**), or they can be methylated, leading to the formation of **DMeSe**, **DMeDSe**, dimethyl selenone (**$DMeSeO_2$**), methylselenol (**MeSeH**), and dimethyl selenyl-sulfide (**DMeSeS**) [13, 14], sometimes with the assistance of some microorganisms, such as *Alternaria* and *Penicillium corynebacterium* [15]. Selenate and selenite ions, after the uptake from the soil, are metabolized in the chloroplasts, where the first one is transformed into the second by the action of an ATP sulfurylase that affords the intermediate formation of the adenosine 5′-phosphoselenate (**APSe**), which is subsequently reduced to selenite by a specific reductase (Fig. 3.2). Even if in vitro the conversion of selenate in selenite can be easily and directly obtained by the treatment with glutathione (GSH), in vivo, the same process needs to be activated by a molecule of ATP. Once formed, selenite is reduced by GSH to selenide, which acts as co-substrate of the *O*-Acetyl-Serine (**OAcSer**) in the synthesis of the **SeCys**, that occurs still in the chloroplast. At this point, **SeCys** pass into the cytoplasm as it is, or after a series of enzymatic reactions to lead to the formation of the second main seleno-amino acid: the selenomethionine (**SeMet**) (Fig. 3.2).

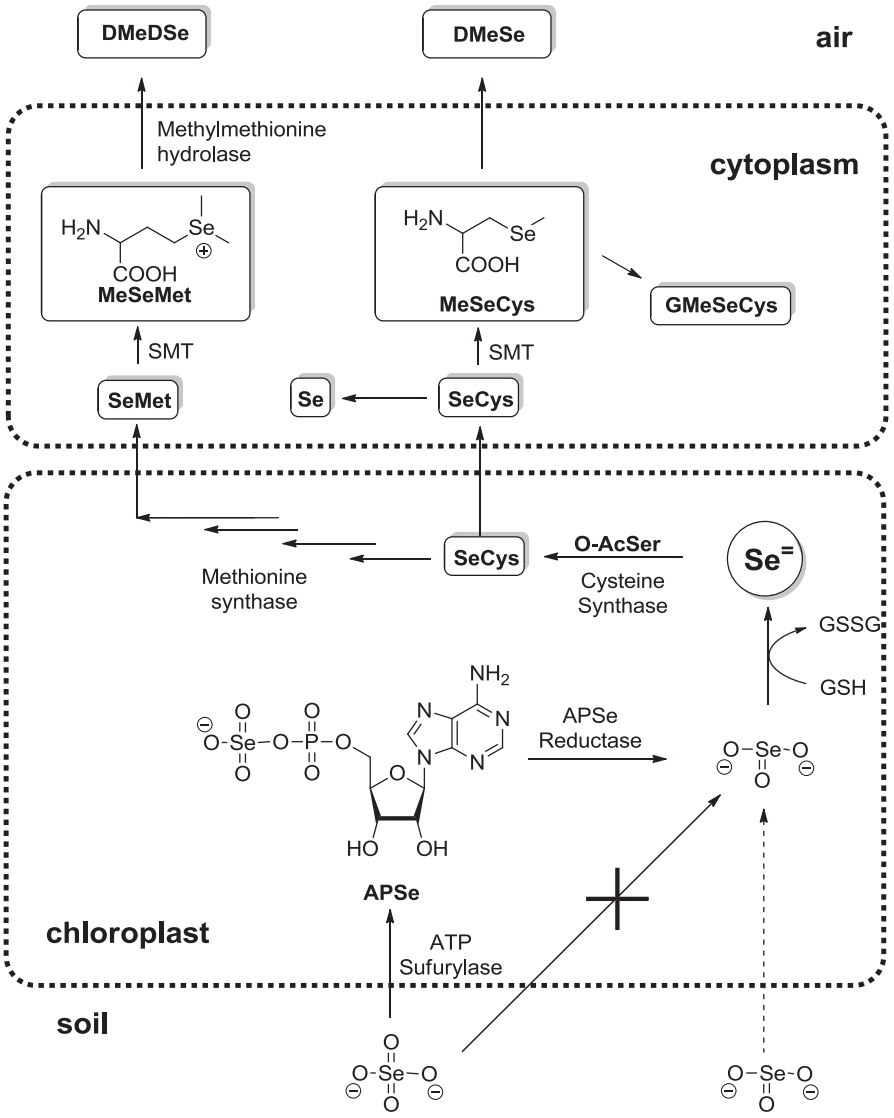

Fig. 3.2 Biosynthesis of seleno-amino acids

SeCys and **SeMet** cannot be safely stored in the plant due to the risk of their misincorporation in the proteins. In some plants, **SeCys**, by the action of a lyase, is transformed into elemental selenium. More frequently, **SeCys** and **SeMet** are methylated to obtain intermediates that, because of the impossibility to be incorporated into the proteins, can be stored in the plant, or can be hydrolyzed to the volatile form of organic selenium, that are normally released on air. In more details, **SeMet** is subjected to a methylation catalyzed by L-methionine-*S*-methyltransferase, affording

methylselenomethionine (**MeSeMet**). The *S*-methyltransferase (SMT), using *S*-methylmethionine as a source of a methyl group, promotes the conversion of selenocysteine into the corresponding methylselenocysteine (**MeSeCys**). Both the methylated form **MeSeMet** and **MeSec** can be degraded to afford **DMeDSe** and **DMeSe**, respectively. In some cases, the volatilization from **MeSeMet** has been demonstrated to involve dimethyl selenopropionate as an intermediate and when it occurs, normally both mechanisms can be present at the same time. Furthermore, **MeSeCys** can be accumulated as it is or conjugated in the form of gamma-glutamyl-methylselenocysteine (**GMSeC**) [16]. Quite recently, it has been reported that some plants have the capacity to absorb organic forms of Se such as **SeCys** and **SeMet**, but not insoluble elemental Se (Se^0) or metal selenide compounds [17].

Considering the ability to accumulate selenium from the natural habitat, plants can be classified as non-Se-accumulators (<100 mg Se/kg DW), secondary-Se-accumulators (100–1000 mg Se/kg DW), and hyper-Se-accumulators (>1000 mg Se/kg DW). The latter species are normally characterized by high concentrations of selenium stored as organic **MeSec**, preferentially in young leaves and in pollen, ovules, and seeds among reproductive organs. Based on a recent theory, the ability on hyperaccumulation is a defense mechanism rapidly developed by some vegetal species that affects its interaction with herbivores, pollinators, and other plants in the neighboring area. Of course, such higher selenium content, negatively affects those partners that are selenium sensitive while facilitating the selection of the more adapted species able to survive in a seleniferous ecosystem [18].

In consideration that selenium-contaminated soils represent a potential health hazard for animals and humans (because this element rapidly enter in the food chain), the use of hyper-Se-accumulators as phytoremediators represents an eco-friendly and cost-effective strategy. The remediation occurs mainly through three mechanisms: phytoextraction, phytovolatilization, and rhizofiltration, affording Se-enriched biomass, which requires to be properly handled in terms of storage and disposal. One of the most promising uses of this biomass is the Se-biofortification of agricultural products [19]. For this purpose, it is in general necessary to select plant tissues that are edible or easily convertible into food, and that can accumulate higher and safe concentrations of Se, but not other toxic compounds [20]. Furthermore, biomass as natural selenium source could be interestingly used in the preparation of products for alimental integration in the regions with low concentration of selenium in the soil.

3.2 Selenoproteins from Bacteria to Mammals

Selenium is incorporated into selenoproteins in the form of **SeCys**, which is considered as the 21st amino acid because it is currently the unique known proteogenic *Se*-amino acid. The GPx1 was the first selenoprotein to be discovered in the rat liver, in 1978 [21]. Studies involving this enzyme have shown that the insertion of **SeCys** is codified by the codon UGA [22], which usually serves as one of the three termination codons for non-Se-protein genes.

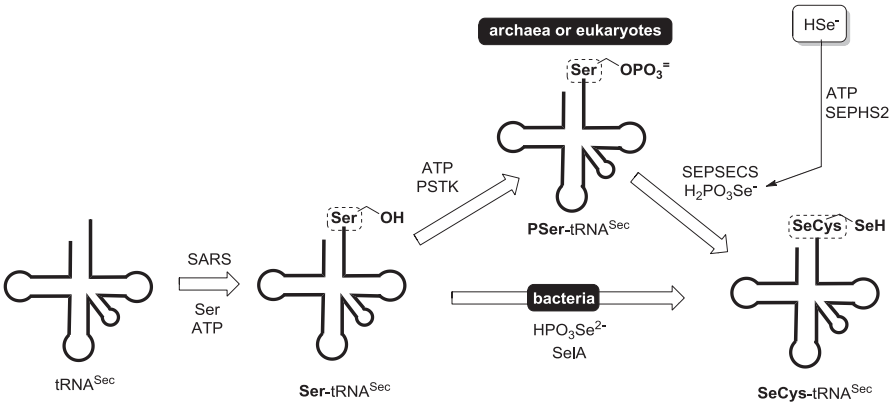

Fig. 3.3 Selenoproteins from bacteria

SeCys does not exist in cells as a free amino acid, but it is synthetized on its tRNA, with initial attachment of serine to $tRNA^{Sec}$ by seryl-tRNA synthetase (SARS), to afford the Sec-specific transfer RNA (**Ser**-$tRNA^{Sec}$). At this point, in the bacteria, **SeCys**-$tRNA^{Sec}$ is formed by the direct conversion of the OH group of serine to a selenol (SeH) group, by the action of the bacterial homodecameric enzyme selenocysteine synthase (SelA), which uses selenophosphate (HPO_3Se^{2-}) as a selenium donor [23]. In Archaea and Eukaryota, the serine residue is phosphorylated by a phosphoseryl-tRNA kinase (PSTK). Subsequently, the resulting phosphoserine (PSer), is transformed into an intermediate by Sep-tRNA:Sec-tRNA synthase (SEPSECS), and selenylated by selenophosphate to generate SeCys-$tRNA^{Sec}$ [24]. Selenophosphate derives from the reaction of selenide and ATP, catalyzed by selenophosphate synthetase 2 (SEPHS2) [25]. A multiprotein complex containing SeCys-$tRNA^{Sec}$ is bound to the selenocysteine-insertion sequence (SECIS) stem-loop in the mammalian selenoprotein mRNAs, decoding UGA SeCys codons at the ribosomal acceptor and mediating the incorporation of **SeCys** into the growing polypeptide in a process subjected to a multifactorial control (Fig. 3.3) [26].

In the human genome, 25 genes for selenoproteins have been identified even if new computational analysis were recently developed to search the SECIS sequence overcoming the complication due to the dual meaning of the UGA codon as stop and selenocysteine [27]. All the selenoproteins have a function closely correlated to the presence of the selenium atom and are generally involved in redox reactions having biological functions in redox processes, redox signaling, antioxidant defense, thyroid functionality, immune response, and their malfunctions are correlated to a series of human and animal diseases. Among all the known selenoproteins, three main classes were studied in terms of reaction mechanisms in different physiologically relevant redox processes: GPxs, thioredoxin reductases (TRxRs), and iodothyronine deiodinases (DIOs). As stated, the lack of correct functionality of these enzymes is correlated to several human diseases, such as cancer, Keshan disease, virus infections, male infertility, and abnormalities in immune responses and thyroid hormone function [28].

Table 3.1 Classification of selenoenzymes

Name	Description	Ref
GPx1	Ubiquitous cytosolic Gpx	[29]
GPx2	Gastrointestinal Gpx	[29]
GPx3	Plasma Gpx	[29]
GPx4	Ubiquitous phospholipid hydroperoxide Gpx	[29]
GPx6	Olfactory epithelium- and embryonic tissue-specific Gpx	[29]

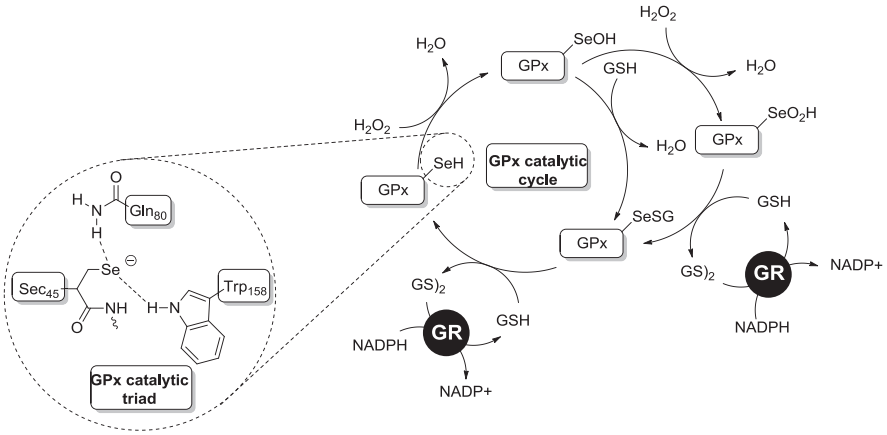

Fig. 3.4 Reaction mechanism of GPx

3.2.1 Glutathione Peroxidases (GPxs)

The family of GPx is the most important component of the antioxidant defense in mammalians. Among the eight known forms, five are demonstrated to be selenoenzymes in which the selenium of a **SeCys** is the catalytic center in the reduction of reactive species of oxygen (ROS). They are mainly classified based on the location as summarized in Table 3.1.

GPx1, GPx2, and GPx3 are homotetrameric proteins with a subunit molecular mass of 22–25 kDa and catalyze the reduction of peroxides (hydrogen peroxide and organic hydroperoxides). GPx4 is a 20–22 kDa monomeric enzyme specific for the reduction of phospholipid and cholesterol hydroperoxides, with an importance in the sperm maturation and, consequently, a role in the male fertility [30].

In the catalytic cycle of GPx (Fig. 3.4), one molecule of peroxide is reduced to water (or alcohol) consuming two molecules of glutathione (GSH), which is oxidized into the corresponding disulfide [$(GS)_2$]. The first intermediate is a selenenic acid that can be rapidly reduced by GSH affording a selenenyl sulfide, which reacts with a second molecule of cofactor GSH, regenerating the catalytic selenolate. The reducing ambient is maintained thanks to the action of the glutathione reductase and

using NADPH as a cofactor. Selenium, compared to sulfur, has two main advantages: (1) being stabilized by the catalytic triad, it exists as selenol that, at physiological pH, is deprotonated; (2) it is more resistant to overoxidation. Even when it occurs, it is still possible to recover the catalytic cycle by the reduction of the possibly formed seleninic acid with glutathione [31]. In the case of sulfur, when it is subjected to overoxidation to sulfinic or sulfonic derivatives, they cannot be easily reduced back to thiols. Indeed, while sulfonic acid formation is irreversible [32], sulfinic acid was demonstrated to be reduced only in few cases by sulfiredoxin [33]. Several attempts to reproduce a GPx-like activity have been reported over the last ten years contributing to a deeper elucidation of the reaction mechanism reported in Fig. 3.4. These studies are not reported in this chapter because they are detailed in Chap. 2, besides being recently reported in several review articles [34] and book chapters [35].

3.2.2 Thioredoxin Reductases (TrxRs)

TrxRs are classified in the family of pyridine nucleotide-disulfide oxidoreductase. Nowadays, three different enzymes of this class are identified in mammals: TrxR1 in the cytosol/nucleus [36, 37], TrxR2 in mitochondria [38, 39], and TrxR3 in testis, having also glutathione and glutaredoxin reductase activity (Table 3.2) [40].

The TrxR contains a FAD-binding domain and a NADPH-binding domain and is constituted by two subunits: the *N*-terminal subunit contains a redox-active dithiol and the *C*-terminal subunit a selenothiol, representing the redox active center of the enzyme. The mechanism proposed for the catalytic activity of TrxR starts with the reduction of the *Se-S* bond on selenenylsulfide subunit, affording a selenolate that, at physiological conditions, due to the pKa of the selenol, exists as a selenium-centered anion. The reduction occurs with the consumption of a NADPH and involves the intermediate action of a molecule of FAD. At this stage, a second electron-transfer from a molecule of NADPH reduces also the disulfide subunit, generating a thiol and a free cysteine, which is stabilized by the interaction with FAD. The anionic selenium reduces the disulfide of a molecule of Trx and the reduction is completed by the attack of the neighboring thiolate. Finally, the catalytic center is regenerated by the oxidation and the formation of a disulfide in the second subunit (Fig. 3.5) [41].

TrxRs are involved in the control of cellular proliferation, viability, and apoptosis through the control of the Trx activity and redox state. TrxR is the only enzyme able to reduce oxidized Trx, providing electrons to ribonucleotide reductase, which is essential for DNA synthesis [41].

Table 3.2 Thioredoxin reductases

Name	Description	Ref
TRxR1	Cytosol/nucleus Trx	[36, 37]
TRxR2	Mitochondrial Trx	[38, 39]
TRxR3	Testis Trx	[40]

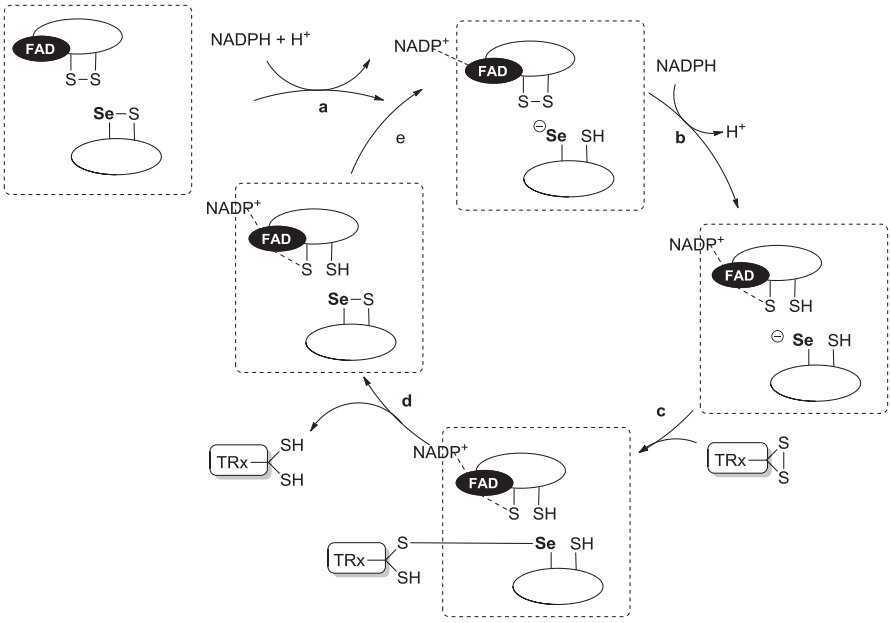

Fig. 3.5 Proposed mechanism for TrxR

Table 3.3 Iodothyronine deiodinases

Name	Description	Ref
ID-I	Inner and outer ring deiodination	[42, 43]
ID-II	Outer ring deiodination	[43]
ID-III	Inner ring deiodination	[43]

3.2.3 Iodothyronine Deiodinases (IDs)

The selenoenzymes classified as deiodinase are essential to control thyroid activity by the activation and deactivation of thyroid hormones. Three main classes of ID's are currently known and, besides their presence in different tissues, they have a selective interaction with the hormone, promoting a selective and reductive deiodination (Table 3.3). ID-I and ID-II are mainly involved in the activation of thyroxine (T4) into triiodothyronine (T3), increasing the thyroid activity by 5′-deiodination in the outer ring of the T4 molecule. ID-III reduces the thyroid activity by the conversion of T4 into reverse T3 (iT3) and it is also responsible for the deiodination that transforms iT3 into T2 (Fig. 3.6) [44].

The understanding of the selective deiodination mechanism is still a matter of debate and for this reason some research groups, during the last decades, proposed small-sized selenium containing derivatives as mimetics of the three isoforms of deiodinase. Mugesh and coworkers investigated a series of naphthyl-derivatives

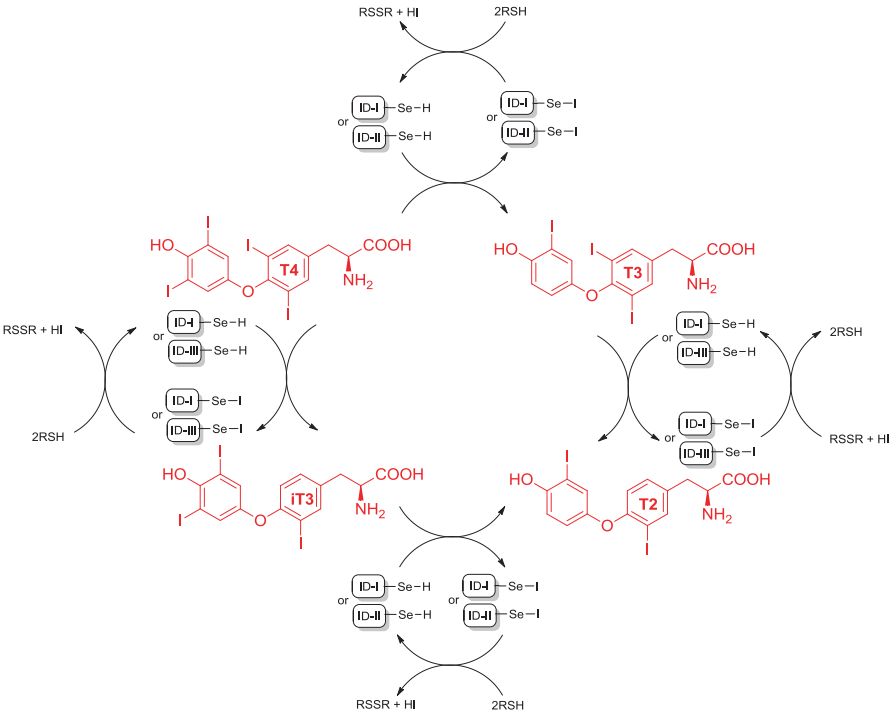

Fig. 3.6 Selective deiodination by ID-I, ID-II and ID-III

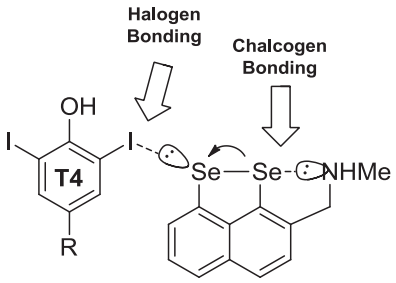

Fig. 3.7 Diselenide with deiodinase mimetic properties

functionalized as dithiol, thiol-selenol or diselenol, demonstrating the superiority of the latter based on the simultaneous presence of an intermolecular halogen bonding and an intramolecular selenium bonding (Fig. 3.7) [45–48]. The regioselectivity of these derivatives is in favor of the inner ring deioidination and, consequently, directed to reduce the thyroid function by the transformation of T4 into iT3 (mimicking the isoform III of the deiodinase).

Recently, a steric-based approach was attempted through the synthesis of hindered selenols in which the hydrophobic bulky cavity stabilizes the selenol group,

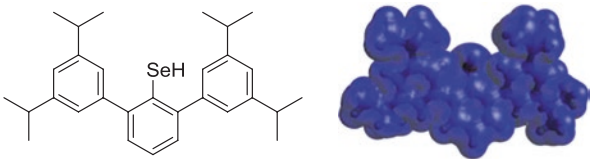

Fig. 3.8 Structure of 3,3″,5,5″-tetraisopropyl-[1,1′:3′,1″-terphenyl]-2′-selenol

as depicted in Fig. 3.8, even if it is reasonable to consider this condition still far from a real mimetic reproduction of the enzymatic cavity [49, 50].

As observed for the diselenides of Mugesh and coworkers (Fig. 3.7), in this case also an inner ring selective deiodination was observed. In consideration of the potential use as therapeutic agents in the treatment of the hypothyroidism, the synthesis of new molecules having the ability to promote the outer ring deiodination and the understanding of the different mechanisms involved in the two different deiodinations are currently highly attractive targets.

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