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Density Functional Theory

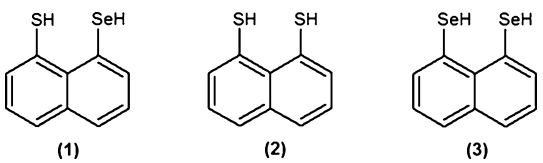
Mechanism of Thyroxine Deiodination by Naphthyl-Based Iodothyronine Deiodinase Mimics and the Halogen Bonding Role: A DFT Investigation

Mariagrazia Fortino,[a] Tiziana Marino,[a] Nino Russo,[a, b] and Emilia Sicilia*[a]

Abstract: This paper deals with a systematic density functional theory (DFT) study aiming to unravel the mechanism of the thyroxine (T4) conversion into 3,3′,5-triiodothyronine (rT3) by using different bio-inspired naphthyl-based models, which are able to reproduce the catalytic functions of the type-3 deiodinase ID-3. Such naphthalenes, having two selenols, two thiols, and a selenol–thiol pair in *peri* positions, which were previously synthesized and tested in their deiodinase activity, are able to remove iodine selectively from the inner ring of T4 to produce rT3. Calculations were performed including also an imidazole ring that, mimicking the role of the His residue, plays an essential role deprotonating the selenol/thiol moiety. For all the used complexes, the calculated potential energy surfaces show that the reaction proceeds via an intermediate, characterized by the presence of a X–I–C (X = Se, S) halogen bond, whose transformation into a subsequent intermediate in which the C–I bond is definitively cleaved and the incipient X–I bond is formed represents the rate-determining step of the whole process. The calculated trend in the barrier heights of the corresponding transition states allows us to rationalize the experimentally observed superior deiodinase activity of the naphthyl-based compound with two selenol groups. The role of the *peri* interactions between chalcogen atoms appears to be less prominent in determining the deiodination activity.

Introduction

The human thyroid prohormone 3,5,3′,5′-tetraiodothyronine (thyroxine, T4) and its corresponding biologically active hormone 3,5,3′-triiodothyronine (T3) represent the main substrates of the type-3 iodothyronine deiodinase (ID-3) enzyme. ID-3 is a member of the iodothyronine deiodinase family, which includes three mammalian selenium-containing enzymes, type-1, -2, and -3, which are isozymes involved in the activation and inactivation of thyroid hormones.[1] In particular, ID-3 catalyzes the conversion of T4 to 3,3′,5′-triiodothyronine (rT3) by a selective inner-ring (5) deiodination.[2,3] Furthermore, ID-3 is implicated in the maintenance of serum T3 concentration by the conversion of T3 into 3,3′-T2, an essential step for the protection of tissues from an excess of thyroid hormone, and also in preventing accumulation of T4 in cells and tissues.[2–4] It was reported that the selenocysteine (Sec) residue in the active site of ID-3 is essential for efficient inner-ring deiodination as it is confirmed by a reduction of the catalytic efficiency due to the substitution of Sec by a cysteine (Cys).[5] Although the deiodinases are involved in basic functions of thyroid hormones,[1] information about their structures and working mechanism is still incomplete. This lack of information can delay the development of more selective and suitable drugs with reduced side effects useful in contrasting the hyper- or hypo- activity of the thyroid gland. For such reasons, in the last decade, several selenium-containing compounds able to mimic the catalytic functions of ID-3[6–9] were extensively investigated to shed light on the chemical mechanism of the type-3 iodothyronine deiodinase, the role played by the selenocysteine (Sec) residue in the catalytic site of the enzyme, and the effects of the substitution of Sec with Cys. In particular, in 2010, Manna and Mugesh[8] proposed a series of *peri*-substituted naphthalenes containing thiol and selenol groups (Scheme 1) as model systems able to catalyze the selective inner-ring deiodination of T4 and T3 by ID-3 under physiological conditions. As no deiodination was observed when pure rT3 was used instead of T4, the high selectivity of these compounds was demonstrated.



Scheme 1.

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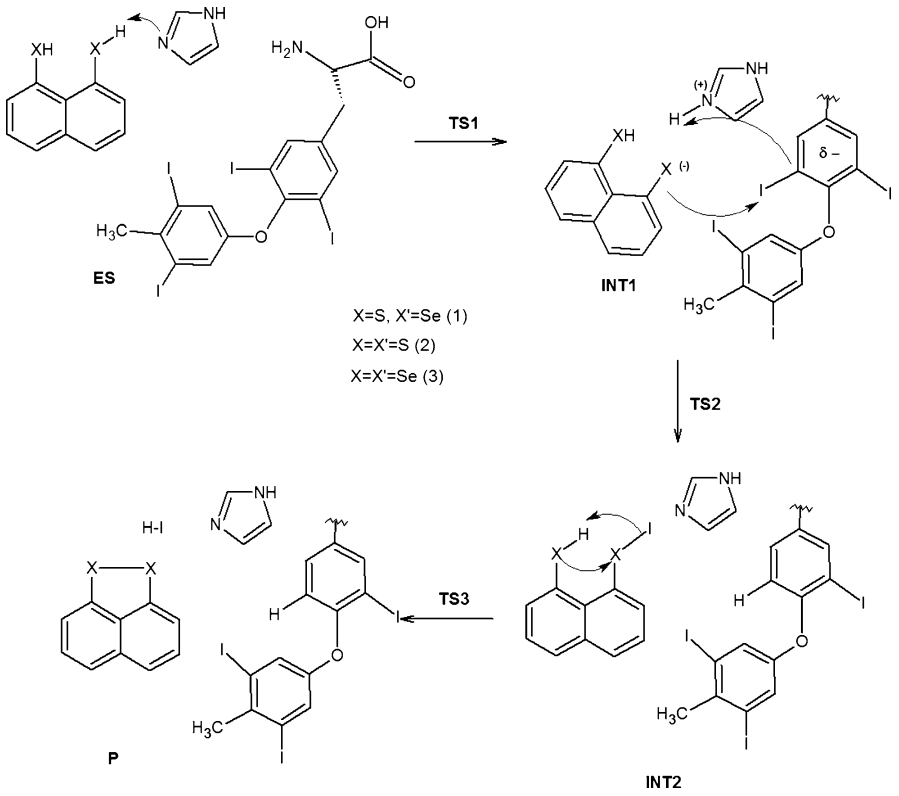
Compound **1** has triggered an extensive research effort through the synthesis of a long series of substituted naphthalene derivatives aimed to satisfy the chemical and geometrical requirements that explain its special selectivity.[9–11] Indeed, the reduced activity in the inner-ring deiodination of the synthesized compound **2**, bearing two thiol moieties on the naphthalene ring, with respect to compound **1** was proved.[8] A further replacement of the –SH group in compound **1** with a selenol, compound **3** in Scheme 1, causes a remarkable increase in the deiodinase activity.[9–11] Moreover, a second substitution with a selenol group should highlight the role that the thiol/selenol cofactor could play, not only in the deiodination process but also in the release of iodide from the involved intermediates. From the studies of the deiodination mechanism of T4 carried out so far by employing these simple models, the formation of a halogen bond between the thiol/selenol group and an iodine atom emerges as a key structural motif, as well as the role played by halogen bonds in the molecular recognition of thyroid hormones.



Scheme 2.

A survey of the recent literature reveals that the theoretical studies dedicated to the characterization of the nature of the S–I and Se–I halogen bonds are limited to the investigation of small systems mimicking Sec in the active site of ID by simple CH_3SeH or CH_3SH models interacting with a truncated model for thyroxine.[12] More recently, a more extended model has been used in which the tyrosine substrate is modeled by a simple iodobenzene group.[10] Detailed theoretical investigations of the whole deiodination process by ID-3 on T4 (and T3), as well as crystallographic data for these enzymes, are still lacking in the literature.

In this paper we present a systematic density functional theory (DFT) study of the mechanistic aspect of the deiodination process. The study was performed considering the entire T4 structure and by using different naphthyl-based models for ID-3, having S–S, S–Se and Se–Se sites, which have been previously synthesized and tested in their deiodinase activity.[9–11] Calculations were performed including also a histidine residue, simulated by an imidazole ring (Im), because its presence appears to be essential for the activation of the –SeH group toward the nucleophilic attack by forming a selenolate–imidazolium zwitterionic species (see Scheme 2). The influence of the two thiols in **2**, the selenol and thiol pair in **1**, and the two selenols in **3** on the catalyzed reaction was rationalized on the basis of the geometrical, electronic, and energetic properties of all stationary points present on the potential energy surfaces (PESs). On the basis of the experimental evidence, a deiodination mechanism was proposed,[10] which involves a direct interaction of one of the selenol (selenolate) moieties with an iodine atom leading to the formation of a halogen bond.[13] Generation of a σ hole or partial positive charge on the selenium atom should facilitate the selenium–selenium interaction, which strengthens the halogen bond, leading to the heterolytic cleavage of the C–I bond. With respect to the proposed mechanism, the outcomes of our calculations, as shown in Scheme 2, support the hypothesis that the process occurs in more steps and underscore the role of proton shuttle of the imidazole ring. Proton transfer from the formed imidazolium ion to the carbon atom causes the heterolytic cleavage of the C–I bond. Formation of the chalcogen–chalcogen (Se–Se, Se–S and S–S) bond, instead, concludes the process with elimination of the iodide as HI. The role the imidazole moiety could play in assisting the proton transfer in the last part of the process leading to the formation of the chalcogen bond was also explored.

Results and Discussion

According to Scheme 2, the mechanism of enzymatic deiodination of thyroxine by iodothyronine deiodinase has been probed by using naphthyl-based models to mimic ID3. Comparison of the calculated energy profile for compound **3**, containing two selenol groups, with those for compounds **1** and

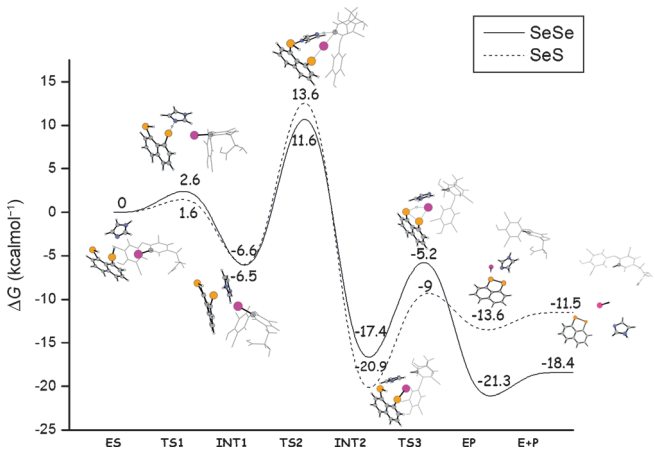


Figure 1. Calculated B3LYP-D3 free energy profile for inner ring **5** deiodination of thyroxine by naphthyl-based compound **3** (——) and **1** (-----). Energies are in kcal mol^{-1} and relative to reactants asymptote.

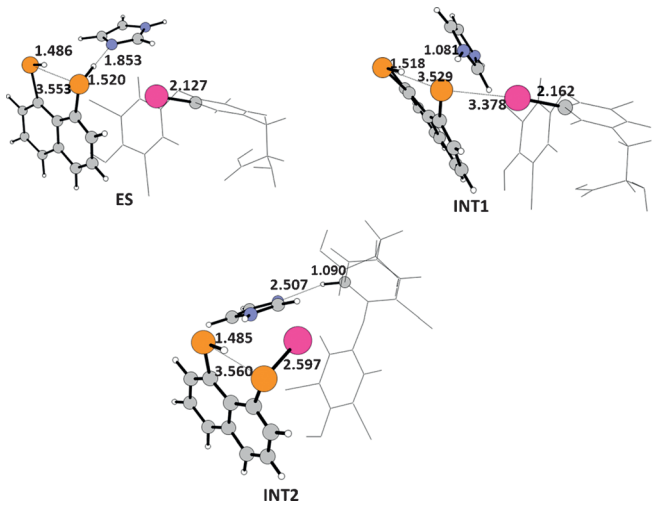


Figure 2. B3LYP-D3-optimized geometrical structure of stationary points intercepted along the pathway for T4 deiodination by compound **3**. Selected bond lengths are in Å and angles in degrees.

2, having a selenol–thiol pair and two thiol groups, respectively, allows us to rationalize the observed activity trend.

The B3LYP-D3 free energy profile, calculated by including water-solvent effects, for the deiodination reaction of T4 by compound **3** in presence of an imidazole group (mimicking a histidine residue), is shown in Figure 1. Solvent effects have been accounted for implicitly by using the continuum approximation for the solvent.[14]

Continuum salvation models represent a solvated molecule at an atomic level of detail inside a molecule-shaped electrostatic cavity surrounded by a solvent medium identified by its dielectric constant. The charge distribution of the solute induces polarization in the surrounding dielectric medium and the self-consistently determined interaction between the solute charge distribution and the electric polarization field of the solvent. Continuum models, based on the assumption that the electrostatic interactions of the solute and the surrounding solvent do not depend on the molecular structure of the solvent, reveal their inadequacy when strong, specific interactions between a solute and one or more first-shell solvent molecules are present. In the case under examination, however, the solvent does not play a key role; all the species directly involved in the deiodination process are included in the model system and the effects of the highly anisotropic electrostatic potential of ID-3 is properly considered. Relative free energies are calculated with respect to the first formed adduct (ES) and expressed in kcal mol^{-1}. Fully optimized geometrical structures of ES, INT1, and INT2 stationary points intercepted along the reaction pathway are schematically depicted in Figure 2, whereas complete geometries of all minima and transition states can be found in the Supporting Information. According to the hypothesized mechanism,[9] many unsuccessful attempts to simulate the deiodination process in absence of the imidazole group were performed at the very beginning of the exploration of the deiodination reaction pathway. Indeed, the first step of the whole process is the proton abstraction by the imidazole moiety from one of the Se–H groups of compound **3** to form the selenolate anion. The proton transfer takes place by overcoming an energy barrier of only 2.6 kcal mol^{-1} for the TS1 transition state, and leads to the formation of a selenolate–imidazolium zwitterionic species. The key feature of such intermediate is that a halogen bond is formed between the selenolate group and the iodine atom, which is confirmed by structural and charge analysis of the INT1 intermediate. Even though it was proven that halogen bonds play a crucial role in thyroid hormone recognition,[15] the importance they have in the mechanism of thyroid hormone deiodination was only recently highlighted.[9,12] The increase of the C–I bond length (from 2.127 to 2.162 Å), the almost linear C–I–Se bond angle (173.5°), and the increase in electron density on the I atom (the NBO[16] positive charge 0.227 becomes 0.189) are clear indications that a halogen bond is formed.[13] The reaction is exothermic by 6.6 kcal mol^{-1} with respect to the reference energy of reactants. The proton transfer from the formed imidazolium ion to the carbon atom gives rise to the concerted heterolytic cleavage of the C–I bond and formation of the Se–I halogen bond. The barrier for the corresponding TS2 transition state is 18.2 kcal mol^{-1}, whereas the formed products lie 17.4 kcal mol^{-1} below the entrance channel energy. The chalcogen Se–Se interaction drives the proton transfer from the Se–H group to the I atom with consequent elimination of HI and formation of the Se–Se bond. The energetic cost for the formation of the TS3 transition state is 12.2 kcal mol^{-1}. The whole process is calculated to be exothermic by 21.3 kcal mol^{-1}, and even an additional 2.9 kcal mol^{-1} is required to release the deiodinated product.

As anticipated above, the possibility that imidazole can assist also the final step of the reaction by abstracting the proton from the Se–H group and transferring it to the iodine atom, either in a stepwise or concerted manner, was examined. Results of our computational exploration show that the process can occur in two steps, but it is not competitive with respect to the direct interaction between H and I atoms. Indeed, 11.0 and 9.1 kcal mol^{-1} are required for the proton shift to the

imidazole and the subsequent proton transfer from the imidazolium ion to I, respectively. Details are given in the Supporting Information (Figure S33). It is worth underlining that, additionally, in analogy with the model previously proposed,[12] which involves two imidazole moieties acting as proton donor/acceptors, the influence of the contemporary presence of two Im molecules was examined. Nevertheless, any attempt to model the concerted protonation and deprotonation steps assisted by two Im molecules, one acting as proton acceptor and a second, protonated, to serve as the proton donor failed. The computational description of the deiodination process does not involve, as previously assumed, formation of an initial halogen-bonded adduct between T4 and the diselenol compound **3**. Instead, proton transfer occurs, thanks to the assistance of a basic imidazole group, and the rate-determining step of the whole process (requiring 18.2 kcal mol^{-1} to occur) appears to be the concerted proton transfer from the formed imidazolium ion to the carbon atom, definitive C–I bond cleavage, and formation of the Se–I bond. To demonstrate that proton transfer and C–I bond cleavage occur simultaneously, Figure S34 in the Supporting Information shows intercepted structures along the reaction coordinate from the transition state to the products.

To check the influence that the polarity of the solvent might have on the described energy profile, additional calculations in a much less polar solvent (see the Supporting Information for more details, Figure S35) have been carried out. The calculated relative free energies along the reaction pathway show only small changes with respect to analogous values in water.

Deiodination of T4 was experimentally investigated by using compounds **1**–**3**, which are all able to mediate deiodination to form the corresponding chalcogenides.[8–11] However, it has been shown that compound **3**, having two selenol moieties, is about 75-fold more active than compound **2**, whereas only a 13-fold enhancement in the activity was observed when only one of the thiols in compound **2** was replaced by a selenol (compound **1**).

To rationalize the observed behaviors, analogous calculations to generate the free energy profiles for **1** and **2** compounds were performed. The calculated B3LYP-D3 free energy profile for compound **2** is sketched in Figure 3 along with a schematic view of the structures of the intercepted stationary points. For compound **1**, instead, two alternatives pathways were explored. Indeed, initial proton transfer can occur from either the selenol SeH or thiol SH groups. The free energy profile calculated for the former and the latter are reported in Figures 1 and 3, respectively. Schematic views of all the intercepted stationary points are sketched in the same Figures, whereas the Supporting Information gives the geometries of all the optimized structures shown here. For the sake of clarity, from now on, compound **3** will be indicated as **SeSe**, compound **2** as **SS** and the two alternatives of compound **1** will be indicated as **SeS** and **SSe** when the first deprotonation occurs on Se and S, respectively.

Deiodination by compound **2** begins by surmounting an energy barrier of only 1.3 kcal mol^{-1}; the imidazole molecule abstracts the proton from one of the thiol groups and forms

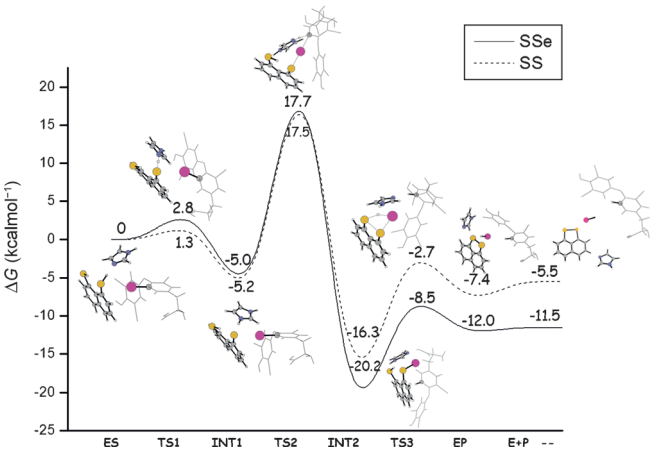


Figure 3. Calculated B3LYP-D3 free energy profile for inner ring **5** deiodination of thyroxine by naphthyl-based compounds **1** (——) and **2** (-----). Energies are in kcal mol^{-1} and relative to reactants asymptote.

the imidazolium thiolate complex, which is stabilized by 5.2 kcal mol^{-1} with respect to the ES energy. Once again it is confirmed that a halogen-bonded adduct is formed. The **TS2** transition state lies 22.7 kcal mol^{-1} higher in energy than the minimum leading to it, whereas the next connected minimum is stabilized by 16.3 kcal mol^{-1} with respect to the entrance channel energy. The last barrier relative to the **TS3** transition state that allows for the elimination of a HI unit and formation of the S–S bond is 13.6 kcal mol^{-1}. The last step of the process is calculated to be exothermic by 7.4 kcal mol^{-1}, whereas the release of the deiodinated product costs 1.9 kcal mol^{-1}. The alternative stepwise proton transfer from the S atom to I assisted by the Im molecule entails two energy barriers of 13.2 and 12.1 kcal mol^{-1}, respectively, as reported in Figure S33 of the Supporting Information.

The deiodinase activity of compound **1** was explored by considering the possibility that both thiol and selenol groups can first act as proton donors to the Im group. As shown in Figure 1, when the SeH group transfers the proton to the imidazole, the corresponding transition state barrier is only 1.6 kcal mol^{-1}, whereas the formed product is stabilized by 6.5 kcal mol^{-1} with respect to the reference energy. The height of the barrier that is necessary to overcome to simultaneously transfer the H atom from the imidazolium ion to the C atom and the I atom from C to Se is 20.1 kcal mol^{-1}. Once again, formation of the Se–I bond driven by the proton transfer to carbon atom results to be the rate-determining step of the whole process. Indeed, the subsequent intermediate INT2, in which the iodine is bonded to the Se atom, resides in a well 20.9 kcal mol^{-1} deep and the transition state leading to the elimination of a HI molecule lies at 9.0 kcal mol^{-1} below the energy of the entrance channel. Then, 11.9 kcal mol^{-1} is the height of barrier for such TS, which leads to the formation of rT3, HI, the corresponding selenenyl sulfide, and the regenerated Im unit. The adduct formed by such species is stabilized by 13.6 kcal mol^{-1}, and 2.1 kcal mol^{-1} is required to yield the separated products. Alternatively, to eliminate HI in the presence of an imidazole molecule, the heights of the barriers to overcome

are 14.4 kcal mol^{-1} for the release of the H atom from the SH group and 11.7 kcal mol^{-1} for the release of the I atom from Se. The free energy profile can be found in the Supporting Information, Figure S33.

The effect of the inversion of the role of the S and Se atoms in compound **1** is illustrated by the energy profile reported in Figure 3. To transfer the proton to the Im unit, a low barrier of 2.8 kcal mol^{-1} has to be overcome to form the INT1 intermediate, which lies 5.0 kcal mol^{-1} below the reference energy of the reactant. From this intermediate, following the C–I and N–H bond-breaking and Se–I and C–H bond-forming coordinate, the concerted transition state TS2 is intercepted, which lies 17.7 kcal mol^{-1} above the reactant complex; that is, the corresponding activation energy barrier is 22.7 kcal mol^{-1}, and, in analogy with the energy profiles described above, represents the highest barrier along the deiodination pathway. Formation of the next intermediate INT2 is exothermic by 20.2 kcal mol^{-1}, whereas the elimination of a HI molecule from it and the concomitant formation of a new S–Se bond requires 11.7 kcal mol^{-1} to occur. The final adduct formation and, therefore the whole process, is exothermic by 12.0 kcal mol^{-1}, although 0.5 kcal mol^{-1} are needed to liberate the final deiodinated product. The calculated energy barriers along the alternative two-step pathway involving an imidazole molecule as acceptor–donor of an H atom are 14.0 and 11.6 kcal mol^{-1}, respectively (see Figure S33 of the Supporting Information). In analogy with **SeSe** compound, the influence of the polarity of the solvent on the energy profile has been checked also for **SS**. As the PES reported in the Supporting Information (Figure S35) clearly shows, the described behavior does not change appreciably when a much less polar solvent is considered.

In summary, the outcomes of the DFT computational analysis carried out in the present paper suggest that the inner-ring deiodination of thyroxine (T4) by ID-3 takes place in four steps. The importance of the presence of histidine residue, simulated by an imidazole ring, was demonstrated. The first step of the whole process is the proton abstraction by the imidazole moiety from one of the Se/S–H groups to form the corresponding selenolate/thiolate anion. The proton transfer from the formed imidazolium ion to the carbon atom gives rise to the consequent heterolytic cleavage of the C–I bond and formation of a Se/S–I bond. The chalcogen interaction forces the proton transfer from the remaining Se/S–H group to I with consequent elimination of HI and formation of a chalcogen–chalcogen bond. The role of proton acceptor/donor of the imidazole/imidazolium ion appears to be crucial for the process to occur. The rate-determining step of the entire process is calculated to be the simultaneous proton transfer from the imidazolium ion to the C atom of the ring, the heterolytic cleavage of the C–I bond, and the formation of a chalcogen–iodine bond. The described behaviors can be rationalized invoking several kinds of noncovalent interactions: Hydrogen, halogen, and chalcogen bonds. Common features of all these interactions are the directionality of the bond, bond lengths smaller than the corresponding sum of van der Waals radii, and anisotropy in electron density distribution, which causes the generation of an electropositive region of the electrostatic potential,

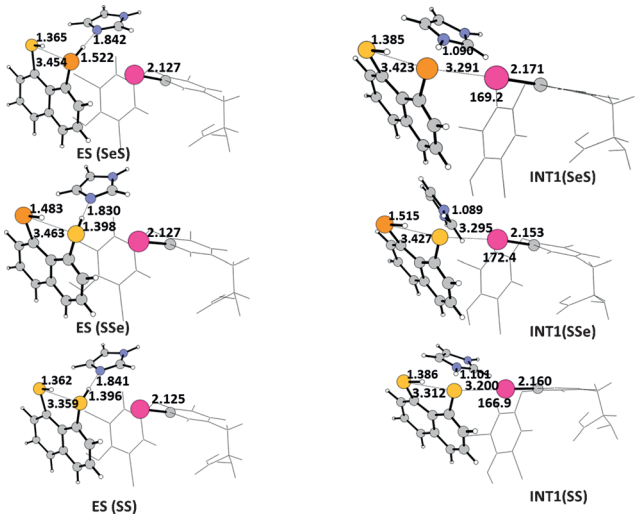


Figure 4. B3LYP-D3-optimized geometrical structure of stationary points intercepted along the pathway for T4 deiodination by both alternatives (**SeS** and **SSe**) of compounds **1** and **2**. Selected bond lengths are in Å and angles in degrees.

called σ-hole. The step that determines the rate of the whole process involves the transformation of the halogen-bonded adduct, INT1, into the corresponding intermediate, INT2, in which the C–I bond has been definitively broken and a new chalcogen–iodine bond has been formed.

In Figures 2 and 4 the most relevant geometrical parameters for the INT1 intermediates are reported, whereas Figure 5 shows the maps of the molecular electrostatic potential (MEP) for both ES and INT1 species formed by reaction of compounds **1**, **2**, and **3** with T4. The colors have been chosen such

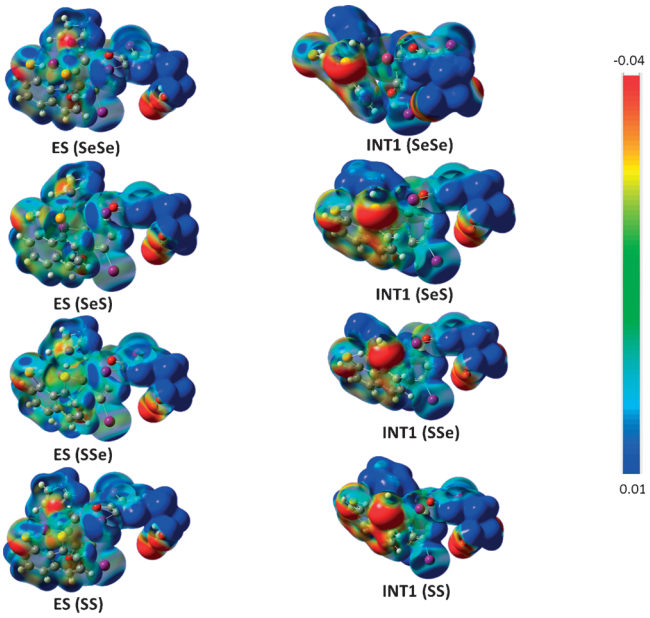


Figure 5. Maps of the molecular electrostatic potential (MEP) for both ES and INT1 species formed by reaction of compounds **1**, **2**, and **3** with T4. The electrostatic potential is represented with a color scale going from red (−0.04 au) to blue (0.01 au).

that regions of attractive potential appear in red and those of repulsive potential appear in blue. As anticipated above, the chalcogen–I–C bond angle in INT1 intermediates is almost linear (see Figures 2 and 4) indicating donation of the Se/S lone pair into the σ* orbital of the C–I bond. For both INT1 intermediates, the C–I bond lengths are elongated by about 0.035 Å. The maps of the MEP clearly show a region of positive potential, that is, a σ-hole, located on the iodine atom in ES. A region of negative electrostatic potential, instead, corresponding to a dark-red area is located on the chalcogen atom in INT1, whereas the electrostatic potential becomes significantly less positive on I, which confirms the lone pair donation to the iodine σ hole and formation of a halogen bond. The strength of the halogen-bonding interaction was estimated by performing NBO second order energy analysis.[16] The halogen bond energy, which is confirmed to be due to the donation of a S/Se lone pair into the σ* C–I orbital, is calculated to be 13.5 kcal mol^{-1} for **SeSe**, 11.1 kcal mol^{-1} for **SeS**, 7.8 kcal mol^{-1} for **SSe**, and 7.4 kcal mol^{-1} for **SS**. The stronger Se–I interaction corresponds to a lower barrier (18.2 kcal mol^{-1} for **SeSe** and 20.1 kcal mol^{-1} for **SeS**), which is necessary to overcome for the definitive cleavage of the C–I bond and formation of a covalent Se–I bond with respect to the analogous barriers of 22.7 kcal mol^{-1}, for both **SSe** and **SS**, for the formation of a S–I bond. Contrary to the proposed mechanism,[9] which assumes that the S/Se–I bond formation is facilitated by the interaction between the halogen-bonded S/Se atom with the adjacent thiol/selenol (thiolate/selenolate) moiety, elimination of a HI unit and formation of a chalcogen–chalcogen bond occurs in the next steps. As a consequence, *peri* interactions do not play the central role in the rate-determining step that was previously hypothesized, even if the proximity of a selenol or thiol in their protonated forms causes a weakening of the halogen bond, due to electron density donation to the selenium or sulfur atom of the SeH or SH groups. Electron density donation from lone pairs on S/Se atom to the antibonding σ S–H/Se–H orbital is confirmed by both the presence of a region of positive potential on the SH/SeH groups and NBO second order analysis.

Conclusion

A systematic DFT study of the mechanistic details of the inner-ring deiodination process of thyroxine T4 by ID-3 to 3,3′,5′-triiodothyronine (rT3) was carried out by considering different *peri*-substituted naphthalenes mimicking the catalytic activity of type-3 deiodinase ID-3. The superior catalytic activity of the naphthyl compound having two selenol groups in the *peri* positions with respect to the ones having two thiol groups or a thiol–selenol pair was investigated and rationalized. The importance of the presence of a histidine residue, simulated by an imidazole ring, was demonstrated. The computational analysis presented here reveals that the mechanism encompasses four steps. The first step is the proton abstraction by the imidazole moiety from one of the Se/S–H groups to form the corresponding selenolate/thiolate anion. The subsequent heterolytic cleavage of the C–I bond and formation of a Se/S–I bond occur simultaneously to the proton transfer from the formed imidazolium ion to the carbon atom. The interaction between the two chalcogens forces the proton transfer from the remaining Se/S–H group to the iodine atom followed by the elimination of a HI unit and formation of a chalcogen–chalcogen bond. The rate-determining step of the whole process is the transformation of the intermediate characterized by the presence of a S/Se–I–C halogen bond into the intermediate in which the C–I bond is definitively broken and the chalcogen–I bond formed. The strongest Se–I interaction for the naphthyl compound having two selenol groups corresponds to a barrier lower than those calculated for the other examined compounds and, as a consequence, deiodination is faster. The presence of an adjacent selonol or thiol group influences the strength of the chalcogen–iodine bond due to electron density donation from lone pairs on the S/Se atom to S–H/Se–H antibonding σ orbital.

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