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Theoretical elucidation of the antioxidant mechanism of 1,3-dihydro-1-methyl-2*H*-imidazole-2-selenol (MSeI)

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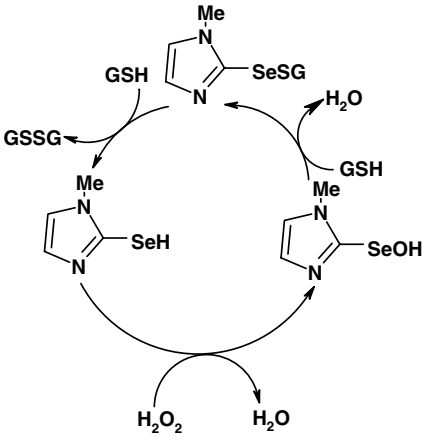
Abstract—Theoretical calculations by means of density functional theory (DFT) at the B3LYP/6-31G(d) level have been performed to elucidate the antioxidant mechanism of 1,3-dihydro-1-methyl-2*H*-imidazole-2-selenol (MSeI) at the molecular level. The present detailed computational study of individual steps of the mechanism provides energetics and structures of all the intermediates and transition states. DFT results suggest a highly synchronous stepwise mechanism wherein the nucleophilic attack of thiol at the sulfur atom in selenyl sulfide (TS **VII**–**VIII**) is found to be the rate-determining step, which initiates the catalytic regeneration of selenol. The current computational studies are in excellent agreement with the mechanism proposed earlier.

Currently the most commonly employed drugs in the treatment of hyperthyroidism are methimazole (MMI), 6-*n*-propyl-2-thiouracil (PTU) and 6-methyl-2-thiouracil (MTU),[1] all of which reduce the conversion of T4 to T3 by reacting with the selenenyl iodide intermediate (E–SeI) of iodothyronine deiodinase (ID-1)[2] to form a selenenyl sulfide as a dead-end product.[3–5] Interestingly, the selenium analogues are found to be insensitive to ID-1 due to their inability to form a stable Se–Se bond. However, recent experimental studies have revealed that the selenium analogues directly participate in the catalytic reduction of hydrogen peroxidase and thereby exhibit high glutathione peroxidase (GPx)-like activity.[6] Since the proposed mechanism of the overall catalytic cycle (Scheme 1) is solely based on inhibition experiments of lactoperoxidase (LPO), the catalytic mechanism of the anti-thyroid drug, 1,3-dihydro-1-methyl-2*H*-imidazole-2-selenol (MSeI) and the factors controlling its activity are not yet unambiguously established. The redox chemistry of selenoprotein, glutathione peroxidase, and small molecule GPx mimics have been investigated earlier with ab initio and density functional theoretical methods.[7,8] Understanding the structure and catalytic mechanism of the active site structure will provide a solid basis for the rational design of more potent antioxidants. The present computational study attempts



Scheme 1.

to explore the plausibility of the reaction mechanism by careful scrutiny of all the intermediate structures and the transition states. All the intermediates and transition structures were located and characterized, which provide a good quantitative estimate of the energetics of the various steps involved in the catalytic cycle.

DFT calculations were carried out using the B3LYP exchange-correlation functional, together with the 6-31G(d) basis set. Earlier reports have demonstrated the excellent ability of the B3LYP/6-31G(d) method in computing reliable geometrical parameters for reactants, products and transition structures in similar cases.[7]

Keywords: DFT; Glutathione peroxidase; Anti-thyroid; Selenium.
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The potential energy surface (PES) for the entire reaction mechanism was scanned systematically for all possible intermediates and transition state structures (TS). Geometry optimizations were carried out without any symmetry constraints. Vibrational frequencies were evaluated at the optimized geometries to verify the nature of the stationary points. The transition structures were characterized by one imaginary frequency and all the intermediates, reactants and products all have real frequencies. Intrinsic reaction coordinate (IRC) calculations were performed in forward and backward directions, by following the eigenvector associated with the unique negative eigenvalue of the Hessian matrix to unambiguously establish the TS connectivity. B3LYP energy calculations were performed at a more adequate 6-311+G(d,p) basis set, and the zero-point vibrational and thermal corrections were made based on the vibrational analysis performed at the B3LYP/6-31G(d) level. Based on the stabilities of various tautomers of MSeI we chose selenol as the initial structure for our calculations.[6] The overall charge of the model was chosen to be zero. The substrate GSH (γ-glutamylcysteinylglycine, γ-GluCysGly) has been modeled by ethanethiol, C_2H_5SH. All calculations were performed using the GAUSSIAN 03 suite of programs.[9]

As shown in Scheme 1, the selenol (EnzSeH) is first oxidized by peroxide to the corresponding selenenic acid (EnzSeOH), which reacts with GSH to afford a selenenyl sulfide intermediate (EnzSeSG). The latter undergoes further reaction with GSH, thereby regenerating the original selenol and producing oxidized glutathione (GSSG) as a by-product.

The principle geometrical parameters of all the stationary points optimized at the B3LYP/6-31G(d) level are depicted in Figure 1. The energy values of all the reactants, transition states and products involved in the studied reaction are collected in Table 1. The energy diagram of the studied reaction is,

$$[\text{E–Se–H}] + \text{HOOH} + 2\text{RSH} \rightarrow [\text{E–Se–H}](\text{H}_2\text{O})_2 + \text{RS–SR}$$

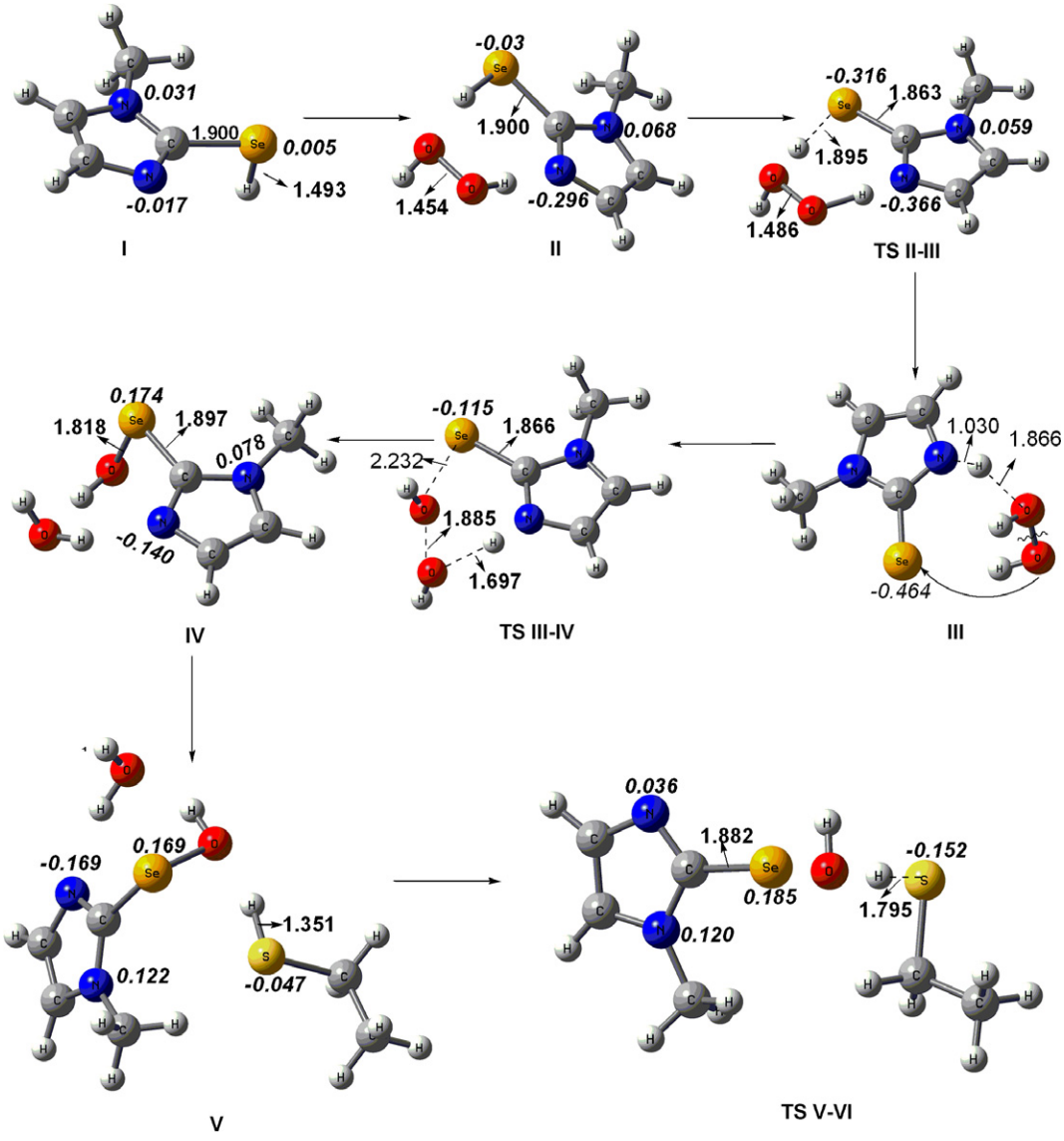

Figure 1.

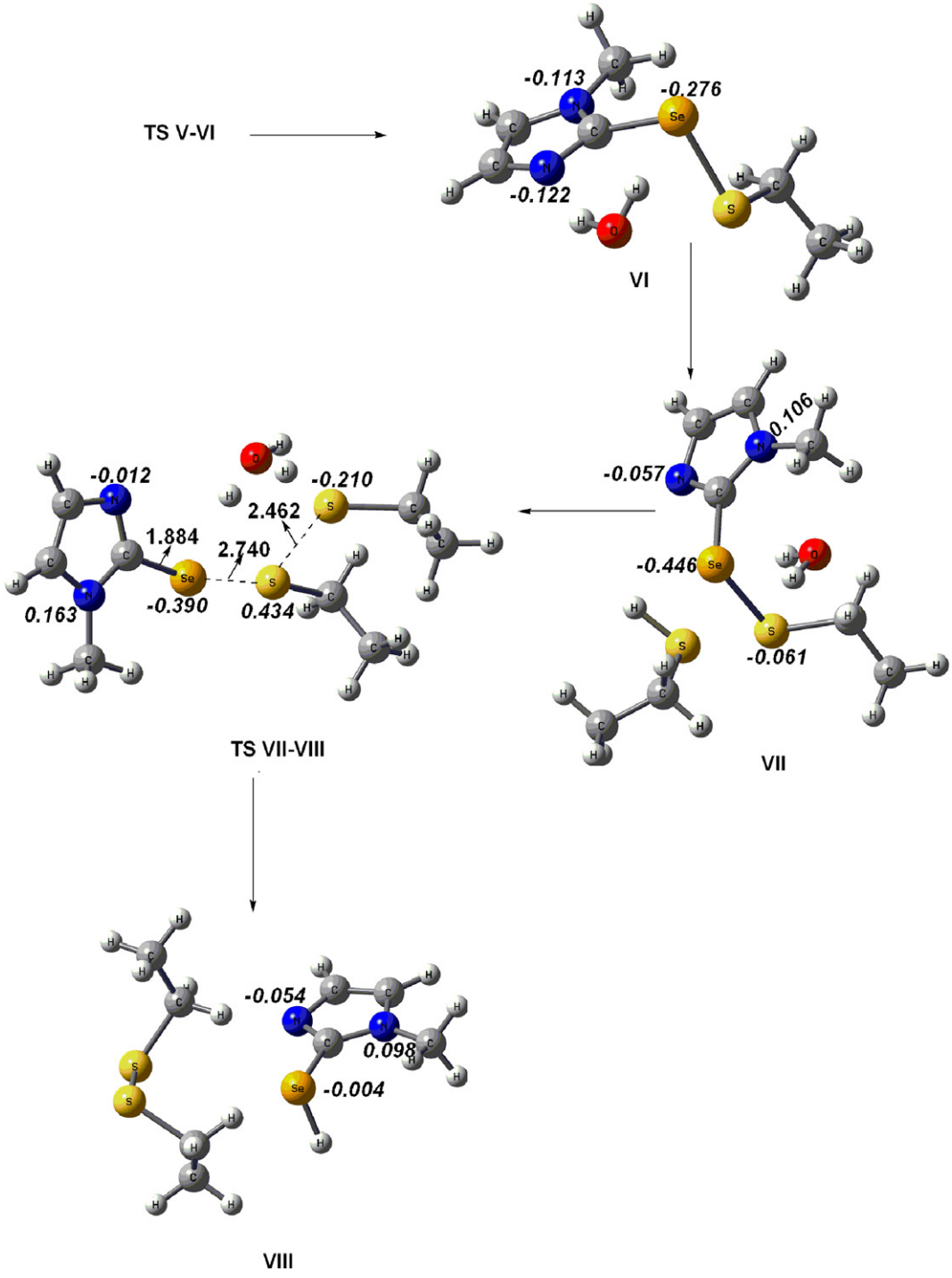

Figure 1. (*continued*)

In the initial step, the Se–H bond of the selenol is broken to form a selenolate anion (R–Se$^-$) and simultaneously the proton is transferred to the oxygen atom of hydrogen peroxide giving an intermediate **III** through the transition state TS **II**–**III**. The transition state is stabilized by a hydrogen-bond network created from nitrogen to selenium atoms. The computed barrier for this step is 21 kcal/mol. In the second step, the formation of selenic acid is triggered by an increase in the bond length of the O–O bond and consequently by its cleavage. All the bond distances change smoothly from intermediate **III** to product **IV**. In the third step, the weakly bonded selenic acid + C_2H_5SH complex (3.6 kcal/mol of binding energy) produces seleno-sulfide adduct **VI** and a water molecule via transition state TS **V**–**VI** with a barrier of 18 kcal/mol. Finally, the Se–S bond in **VII** can be cleaved typically by nucleophilic attack either at the sulfur or selenium. Experimental evidence points to the fact that any substituent capable of enhancing nucleophilic attack of a thiol at the sulfur in a selenyl sulfide would enhance the antioxidant potency of organoselenium compounds.[10] Inversely, addition of thiol at selenium

Table 1. Total (Hartrees) and relative (kcal/mol) energies evaluated at the B3LYP/6-311+(d,p) level, sum of zero-point vibrational energy and thermal correction to energy (TCH) in Hartrees for all of the reactants, transition states and products involved in the studied reactions

Species	B3LYP/6-311+G(d,p)	Sum of ZPE[a] and TCH[b]	Relative energy
I	−2818.747457	0.137082	0
II	−2818.765278	0.137259	−11
II–III	−2818.744505	0.132965	10
III	−2818.784661	0.141632	−20
III–IV	−2818.761598	0.137407	11
IV	−2818.853358	0.14050	−55
V	−3296.925562	0.223692	−0.2
V–VI	−3220.405979	0.192191	18
VI	−3220.488245	0.197712	−48
VII	−3698.556197	0.280995	3
VII–VIII	−3698.493216	0.279181	38
VIII	−3622.084990	0.252721	−56

[a] Evaluated at the B3LYP/6-31g(d) level.
[b] Evaluated at 298.15 K and 1 atm.

leads to undesirable thiol exchange reactions which are found to inactivate the catalytic activity of many organoselenium compounds.[10–13] However, for methimazole the calculated Mulliken charges on selenium (−0.390) and sulfur (0.434) atoms in the transition state (TS **VII–VIII**) indicate that nucleophilic attack is preferred at the sulfur atom, thus regenerating selenol and oxidized C_2H_5S–SC_2H_5. This might be the reason for the high GPx activity experimentally found for MSeI than for other anti-thyroid drugs. The calculated barrier for the last step is found to be slightly higher than the energy barrier calculated for a selenocysteine residue.[7] The higher barrier might be a result of the small model system that is used in the calculations. However, proton-water mediated proton transfer as a general step has been observed in biological systems.[14] Therefore we believe that the incorporation of additional general acid and general base sites mimicking the Gln83 and Gly50 residues in a selenoprotein might assist the proton transfer arrangements and brings down the high energy barrier calculated in the present model. While this manuscript was in preparation a paper on modeling the reduction of hydrogen peroxide by ebselen model compounds was published.[15] A comparison of the energy barriers for the reduction of hydrogen peroxide of these model compounds (56.7, 53.4 and 35.3 kcal/mol) with that of MSeI demonstrates that MSeI is the most active antioxidant in the GPx redox pathway.

In conclusion, the theoretical calculations performed in the present study have provided invaluable insights into the catalytic mechanism of MSeI wherein MSeI constitutes a redox cycle involving catalytic reduction of H_2O_2 and thereby exhibits GPx-like antioxidant activity.

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Supplementary data

The Cartesian coordinates of all the optimized stationary point structures (in Å) at the B3LYP/6-31G(d) are provided. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.01.131.

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