

## Research Article

# A Computational Investigation of the Binding of the Selenium Analogues of Ergothioneine and Ovoidiol to Cu(I) and Cu(II) and the Effect of Binding on the Redox Potential of the Cu(II)/Cu(I) Redox Couple

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The complexes formed from the binding of ovoselenol (OSeH) and ergoseloneine (ESeH) to Cu(II) and Cu(I) have been investigated with DFT methods. From the calculated thermodynamics, the binding of OSeH and ESeH to Cu(II) and Cu(I) ions increases the reduction potential for the Cu(II)/Cu(I) redox couple. The calculated reduction potentials for the Cu(II)(OSe)<sub>2</sub>/Cu(I)(OSeH)<sub>3</sub><sup>+</sup> and Cu(II)(ESe)<sub>2</sub>/Cu(I)(ESeH)<sub>3</sub><sup>+</sup> redox couples were found to be 1.15 V and 1.24 V in a dilute aqueous solution. By combining the half reactions for the oxidation of OSeH to the diselenide OSeSeO with the reduction of Cu(II)(OSe)<sub>2</sub> to Cu(I)(OSeH)<sub>3</sub><sup>+</sup>, the calculated EMF was 0.90 V. For the oxidation of ESeH to the diselenide ESeSeE with the concomitant reduction of Cu(II)(ESe)<sub>2</sub> to Cu(I)(ESeH)<sub>3</sub><sup>+</sup>, the calculated EMF was 0.67 V. Thus, for both systems, the reduction of Cu(II) to Cu(I) with concomitant formation of either diselenide is thermodynamically favourable, and it is expected that both OSeH and ESeH are suitable for the protection against copper induced oxidative damage. As a result, the inhibition of the recycling of Cu(I) to Cu(II) is thermodynamically favourable in the presence of OSeH and ESeH.

## 1. Introduction

Reactive oxygen species (ROS) are highly reactive molecules that are naturally produced within living cells [1–3]. While such species are generated in normal physiological conditions, during pathological conditions such as ionizing radiation, UV exposure, inflammation, and the presence of free metal ions (e.g., Cu<sup>II</sup> and Fe<sup>II/III</sup>) these highly reactive species are overproduced [1, 4–9]. The overproduction of ROS leads to oxidative stress which is associated with aging and the pathogenesis of diseases such as cardiovascular disease, cancer, and several neurodegenerative disorders (e.g., Alzheimer's disease, Parkinson's disease, and ALS) [1, 3–10]. To repair or mediate against oxidative stress cells use antioxidants to scavenge free radicals and maintain a healthy redox balance [1, 10, 11]. A key antioxidant in eukaryotes is glutathione (GSH) which is a cysteine-based

tripeptide [9, 10, 12, 13]. However, GSH is not the only naturally produced antioxidant and several organisms produce other thiol containing antioxidants [14]. Such examples include ovoidiol (OSH) and ergothioneine (ESH) which are mercapto-histidine derivatives and are considered the best-known natural antioxidants [6, 13, 15–19]. These mercapto-histidine derivatives are not naturally produced in humans; however, by ingesting foods, we are able to assimilate these antioxidants [13, 20–25].

Under conditions of oxidative stress an increase in the concentration of free metal ions is observed [26]. As noted above, the increase in the concentration of free metal ions leads to the overproduction of ROS. Thus, in addition to reacting with ROS, some antioxidants bind to free metal ions. Notably, OSH and ESH have been found to chelate copper to prevent copper-induced oxidative damage of DNA and proteins [6, 20, 21]. Previously, using a density

functional theory (DFT) approach, the thermodynamics for the reduction of Cu(II) to Cu(I) with concomitant formation of the respective OSH/ESH disulfide (i.e., OSSO/ESSE) was done [6]. From the results, it was concluded that such processes are thermodynamically favourable in the presence of either OSH and ESH [6]. Because of the increased reduction potential of the Cu(II)/Cu(I) redox couple, OSH and ESH limit the oxidative damaging abilities of copper ions in biochemical systems by altering their reduction potentials and inhibiting the recycling of Cu(I) to Cu(II) [6].

Directly below sulfur in the periodic table is selenium. Sulfur and selenium are known to have similar physical and chemical properties [27–29]. Although there are similarities between sulfur and selenium, their antioxidant mechanisms differ in preventing oxidative cellular damage [4, 30]. For instance, selenium has attracted interest due to its stronger reductive ability compared to sulfur [5, 31, 32]. Like sulfur-containing compounds, selenium-containing compounds have shown the ability to inhibit copper-mediated DNA damage metal through the formation of Cu-Se complexes [4, 26, 33–35]. For instance, the binding of methyl-Secysteine and selenomethionine to Cu(I) was looked at, and it was concluded that these selenium-containing compounds prevent the oxidation of Cu(I), thus preventing copper-mediated DNA damage [35, 36]. Moreover, Kimani et al. [36] investigated the binding of N,N'-dimethylimidazole selone and N,N'-dimethylimidazole thione to copper and found that the selone-containing compound reduced Cu(II) to Cu(I) three times faster than thione containing compound. However, it is noted that for N,N'-dimethylimidazole selone and N,N'-dimethylimidazole thione both nitrogens of the imidazole ring are methylated; thus, the possible binding of the nitrogens to the Cu center is not possible.

Herein, the complexes formed upon ligation of the selenium analogues of OSH and ESH (i.e., ovoselenol (OSeH) and ergoseloneine (ESeH)) to Cu(I) and Cu(II) ions was investigated using a DFT approach. To the best of our knowledge, this work represents the first DFT study on the binding of ovoselenol (OSeH) and ergoseloneine (ESeH) to Cu(I) and Cu(II). The reduction potentials of the Cu(II)(OSe)<sub>2</sub>/Cu(I)(OSeH)<sub>3</sub><sup>+</sup>, Cu(II)(ESe)<sub>2</sub>/Cu(I)(ESeH)<sub>3</sub><sup>+</sup>, OSeSeO/OSeH, and ESeSeE/ESeH redox couples were calculated to study the ability of OSeH and ESeH to inhibit the redox cycling of Cu(I)/Cu(II).

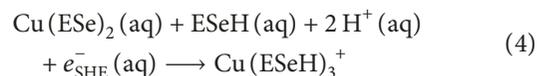
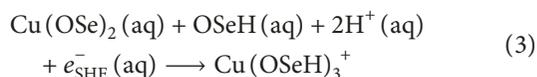
## 2. Computational Methods

All calculations were performed with Gaussian 09 [37]. Optimized geometries and harmonic vibrational frequencies were obtained the BP86/6-311+G(2df,p). Gibbs reaction energies and standard reduction potentials were obtained from single-point energies calculated at the IEFPCM-BP86/6-311+G(2df,p) level of theory and corrected by the addition of the Gibbs energy corrections ( $\Delta G_{\text{corr}}$ ) obtained from the harmonic vibrational frequencies. The solvent used for the calculations was water. The BP86 functional has been shown to provide reliable structural parameters as well as reaction energies for transition metal containing complexes, and it

has been shown to provide reliable geometries of Cu-Se complexes [35, 38, 39]. Lastly, given its past use on the analogous OSH and ESH complexes, it is expected that the BP86 functional is suitable for the present OSeH and ESeH complexes investigated herein.

To simplify the computational models, OSeH and ESeH were modeled as 4-selenol-N<sup>1</sup>-methyl-5-methylimidazole and 2-selenone-4-methylimidazole, respectively. Initial geometries of the Cu-Se complexes were modeled from previous computational studies [6] on ESH and OSH binding to copper where trigonal-planar and square-planar geometries were assumed for the Cu(I) and Cu(II) complexes, respectively. It is noted that experimental work has shown that for Cu(I)-Se containing complexes, a three-coordinate trigonal planar coordination geometry around the Cu center exists [35, 40]. For the Cu(II) complexes, the *cis* and *trans* conformations involving OSeH and ESeH were investigated; moreover, for the ESeH-Cu(II) complexes, the binding of ESeH via either the  $\delta$ - or  $\epsilon$ -nitrogen to the copper was investigated. The Cu-complexes studied herein are shown in Figure 1.

The redox potentials discussed in the present paper were obtained where the electrons and protons were treated as independent ions as shown in equations (1)–(4). Using a first principles quantum and statistical mechanics approach, Llano and Eriksson calculated the chemical potential for a free electron in a dilute aqueous solution with respect to a standard hydrogen electrode (SHE) reference state (i.e.,  $e_{\text{SHE}}^-$ (aq)) to be  $-418.5 \text{ kJ mol}^{-1}$ , whereas for a proton in a dilute aqueous environment (i.e.,  $\text{H}^+$ (aq)), a chemical potential of  $-1124.2 \text{ kJ mol}^{-1}$  was calculated [41]. The standard reduction potentials ( $E^\circ$ ) were then calculated via  $E^\circ = -\Delta_r G^\circ/nF$ , where  $n$  = number of electrons in reaction, and  $F$  is Faraday's constant.



It is noted that the direct measurement of the redox potentials for thiol-disulfide systems is not always feasible due to the possible formation of stable metal-thiolate complexes at electrode surfaces [42, 43]. Moreover, issues with the direct measurement of redox potentials may exist if the redox reactions being investigated are irreversible or if multiple redox couples are present in solution. These problems have been observed in the redox chemistry of OSH [44]. Thus, the scope of this work is to determine the relative differences in reduction potentials between the Cu-Se-containing complexes versus the Cu-S-containing

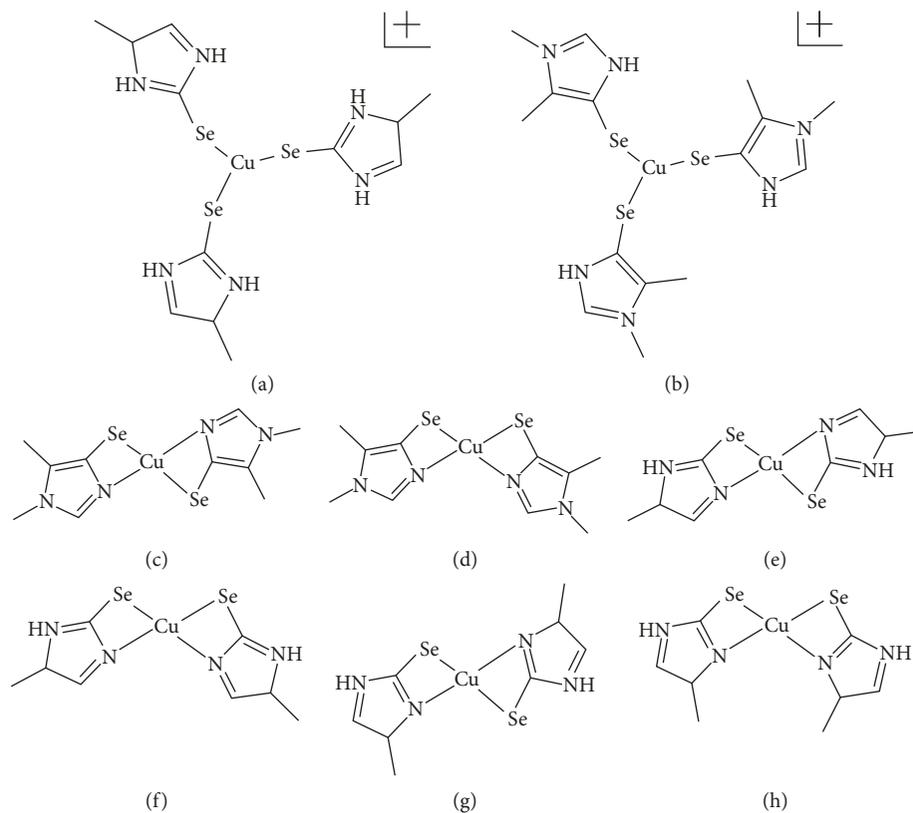


FIGURE 1: Schematic illustration of possible complexes formed by ligation of 4-selenol- $N^1$ -methyl-5-methylimidazole (OSeH) or 2-selenone-4-methylimidazole (ESeH) to Cu(I) and Cu(II).

complexes to examine the antioxidant properties of OSeH and ESeH relative to OSH and ESH.

From Figure 1 to ensure the bidentate coordination to Cu(II) the ligands OSeH and ESeH were modeled as monoanionic (i.e.,  $OSe^-$  and  $ESe^-$ ). For the Cu(I) complexes, because of the monodentate ligation of the ligands, OSeH and ESeH were modeled as neutral. However, the Gibbs energies for the deprotonation of  $Cu(I)(ESeH)_3^+$  and  $Cu(I)(ESeH)_3^+$  in solution were calculated at the IEFPCM-BP86/6-311 +  $G(2df,p)$  +  $\Delta G_{Corr}$  level of theory. For  $Cu(I)(ESeH)_3^+$  and  $Cu(I)(ESeH)_3^+$ , the calculated Gibbs energies were  $+49.8 \text{ kJ mol}^{-1}$  and  $+68.4 \text{ kJ mol}^{-1}$ , respectively. Thus, it is expected that in aqueous solution, the Cu(I) complexes most likely exist as  $Cu(I)(ESeH)_3^+$  and  $Cu(I)(ESeH)_3^+$ .

### 3. Results and Discussion

All optimized Cu-Se-complexes were found to be essentially isostructural to their analogous Cu-OSH and -ESH complexes. Given that the geometries of the Cu-OSH and -ESH analogues are discussed in reference [6], the structures of the Cu-OSeH and Cu-ESeH complexes will only be briefly discussed. However, detailed geometries of the Cu-OSeH and Cu-ESeH complexes are provided in the supporting information (Table S1). Briefly, for  $trans$ - $\epsilon$ -Cu(II)(ESe) $_2$ ,  $cis$ - $\epsilon$ -Cu(II)(ESe) $_2$ ,  $trans$ - $\delta$ -Cu(II)(ESe) $_2$ , and  $trans$ -Cu(II)(OSe) $_2$ , the copper coordination center

was essentially square-planar. For  $cis$ -Cu(II)(OSe) $_2$  and  $cis$ - $\delta$ -Cu(II)(ESe) $_2$ , a slightly twisted, square-planar coordination geometry around the Cu center was observed. Regarding the Cu(I)(ESeH) $_3^+$  and Cu(I)(OSeH) $_3^+$  complexes, a trigonal planar geometry around the Cu(I) coordination center was observed. While the selenium containing complexes are isostructural to their sulfur analogues, the most significant differences in geometries between analogous Se and S complexes are the longer Cu-Se bond lengths; however, this is expected given the larger atomic radius of Se versus S.

Given the  $cis$ - and  $trans$ -binding modes for  $OSe^-$  to Cu(II), the relative Gibbs energies of the  $trans$ -Cu(II)(OSe) $_2$  and  $cis$ -Cu(II)(OSe) $_2$  conformers were calculated and are provided in Table 1. From the relative Gibbs energies, the two conformers are essentially thermoneutral, and as shown in the relative populations in Table 1, both are expected to exist in almost equal amounts in the aqueous solution. From the past work on the Cu(II)(OS) $_2$  complexes, it was found that the  $trans$ -Cu(II)(OS) $_2$  was  $3.5 \text{ kJ mol}^{-1}$  higher in energy [6]. Thus, the substitution of the chalcogen atom seems to have a marginal effect on the relative energies of the two conformers and regardless of choice of chalcogen atoms both the  $cis$  and  $trans$  conformers are expected to contribute to the reaction defined in equation (3).

Regarding the Cu(II)(ESe) $_2$  complexes, the energy differences between the four conformers are provided in Table 2. For the  $trans$ - $\epsilon$ -Cu(II)(ESe) $_2$ ,  $cis$ - $\epsilon$ -Cu(II)(ESe) $_2$ ,

TABLE 1: The relative energies and populations of the Cu(II)(OSe)<sub>2</sub> complexes investigated.

Conformer ( <i>j</i> )	Relative energy in kJ mol <sup>-1</sup>	$N_j/N^a$
<i>trans</i> -Cu(OSe) <sub>2</sub>	0.0	52%
<i>cis</i> -Cu(OSe) <sub>2</sub>	0.2	48%

<sup>a</sup>The relative population of conformer *j* calculated using Boltzmann statistics. See supporting information for more details.

TABLE 2: The relative energies and populations of the Cu(II)(ESe)<sub>2</sub> complexes investigated.

Conformer ( <i>j</i> )	Relative energy in kJ mol <sup>-1</sup>	$N_j/N^a$
<i>trans-ε</i> -Cu(ESe) <sub>2</sub>	0.0	52%
<i>cis-ε</i> -Cu(ESe) <sub>2</sub>	2.0	23%
<i>trans-δ</i> -Cu(ESe) <sub>2</sub>	1.9	24%
<i>cis-δ</i> -Cu(ESe) <sub>2</sub>	10.5	1%

<sup>a</sup>The relative population of conformer *j* calculated using Boltzmann statistics. See supporting information for more details.

and *trans-δ*-Cu(II)(ESe)<sub>2</sub> conformers, very similar energies are observed, and therefore, each is expected to exist in large amounts in solution as indicated by the calculated relative populations (Table 2). In the case of *cis-δ*-Cu(II)(ESe)<sub>2</sub>, its relative energy is considerably higher than the other three conformers and is therefore not expected to exist in large amounts in solution. If we consider the structures in Figure 1, the *cis-δ*-Cu(ESe)<sub>2</sub> complex has the methyl groups sterically clashing with the ligating Se atoms, whereas for *cis-ε*-Cu(ESe)<sub>2</sub>, while the imidazole rings are *cis* to each other, the methyl groups are pointing away and do not sterically clash with the ligating Se atoms. For the sulfur analogues, the relative ordering of the Cu-complexes is significantly different where the calculated relative energies for *trans-δ*-Cu(II)(ES)<sub>2</sub>, *cis-ε*-Cu(II)(ES)<sub>2</sub>, *cis-δ*-Cu(II)(ES)<sub>2</sub>, and *trans-ε*-Cu(II)(ES)<sub>2</sub> are 0.0 kJ mol<sup>-1</sup>, 1.8 kJ mol<sup>-1</sup>, 6.7 kJ mol<sup>-1</sup>, and 10.1 kJ mol<sup>-1</sup>, respectively [6]. Thus, the substitution of the chalcogen atoms, while resulting in isostructural complexes, causes a reordering of the complexes in terms of energies that affect the relative contributions of the conformers to the reaction defined in equation (4).

Previously, the energy difference between the thiol and tautomer form of OSH was determined, where it was found that the imidazolium-thiolate form is preferred in solution lying 13.3 kJ mol<sup>-1</sup> lower in energy at the IEFPCM-BP86/6-311 +  $G(2df,p)$  +  $\Delta G_{\text{corr}}$  level of theory [6]. Given the possible tautomeric form of OSeH, the energy difference between the selenol (OSeH) and its imidazolium-selenolate tautomer (OSeH<sub>t</sub>) was calculated. At the IEFPCM-BP86/6-311 +  $G(2df,p)$  +  $\Delta G_{\text{corr}}$  level of theory, the imidazolium-selenolate form lies 20.0 kJ mol<sup>-1</sup> lower in energy in solution. Thus, like OSH, it is expected that OSeH exists as OSeH<sub>t</sub> in solution. Thus, the energies discussed below involving OSeH are relative to OSeH<sub>t</sub>.

The reduction potential for the OSeSeO/OSeH<sub>t</sub> redox couple at the IEFPCM-BP86/6-311 +  $G(2df,p)$  +  $\Delta G_{\text{corr}}$  level of theory was calculated to be 0.25 V (equation (1)), whereas for the ESeSeE/ESeH redox couple, the calculated reduction potential is 0.57 V (equation (2)). For the analogous OSSO/

OSH and ESSE/ESH redox couples, the reduction potentials were calculated to be 0.31 V and 0.70 V, respectively [6]. Thus, the substitution of the chalcogen atom results in OSeH and ESeH being more reducing than OSH and ESH, respectively. Past work has shown that ovothiols and imidazole disulphides are readily reduced by glutathione; moreover, the diselenide derivatives of ovothiols are also readily reduced by glutathione [15, 45, 46]. As a model for the redox chemistry of GSH, the reduction potential for the reaction  $\text{MeSSMe} + 2e_{\text{SHE}}^-(\text{aq}) + 2\text{H}^+(\text{aq}) \longrightarrow 2\text{MeSH}$  at the IEFPCM-BP86/6-311 +  $G(2df,p)$  +  $\Delta G_{\text{corr}}$  level of theory has been calculated to be 0.25 V [6]. From the differences in calculated reduction potentials, it appears that GSH is indeed able to reduce the OSeSeO and ESeSeE diselenides in agreement with experiment.

Regarding the Cu-complexes, the average calculated reduction potentials for the Cu(II)(OSe)<sub>2</sub>/Cu(I)(OSeH)<sub>3</sub><sup>+</sup> redox couple is 1.15 V, whereas for the Cu(II)(ESe)<sub>2</sub>/Cu(I)(ESeH)<sub>3</sub><sup>+</sup> redox couple is 1.24 V (Table 3). Given that the standard reduction potential for the Cu(II)(aq)/Cu(I)(aq) redox couple is 0.16 V, the greater positive reduction potentials for Cu(II)(OSe)<sub>2</sub>/Cu(I)(OSeH)<sub>3</sub><sup>+</sup> and Cu(II)(ESe)<sub>2</sub>/Cu(I)(ESeH)<sub>3</sub><sup>+</sup> suggest that the reversible cycling between the two ions is less likely to happen [47].

Previously, for the Cu(II)(OS)<sub>2</sub>/Cu(I)(OSH)<sub>3</sub><sup>+</sup> redox couple, a reduction potential of 1.32 V was calculated, whereas for the Cu(II)(ES)<sub>2</sub>/Cu(I)(ESH)<sub>3</sub><sup>+</sup> redox couple, a reduction potential of 1.39 V was calculated [6]. Thus, the Cu(II)(OSe)<sub>2</sub>/Cu(I)(OSeH)<sub>3</sub><sup>+</sup> and Cu(II)(ESe)<sub>2</sub>/Cu(I)(ESeH)<sub>3</sub><sup>+</sup> redox couples are 0.17 V and 0.15 V more reducing than their respective sulfur analogues. While the sulfur compounds have the more positive potential and therefore suggests a greater protection from the recycling of Cu(I) to Cu(II) from past experiments into the binding of N,N'-dimethylimidazole selone and N,N'-dimethylimidazole thione to Cu, similar differences in reduction potentials were observed [36, 40]. In particular, the reduction potentials for the Cu(II)-selone complexes were more negative than the Cu(II)-thione analogues by an average of 0.11 V [36, 40]. While both the thione and selone prevented copper redox cycling and copper-mediated DNA damage, it was found that the selone did so where the reduction of Cu(II) to Cu(I) occurred 3x faster than in the presence of the thione [36]. Moreover, other experimental work has shown that the introduction of the selenium atom in ovothiol-derived 4-mercaptoimidazoles resulted in antioxidants that were approximately 8x more effective at a 5x lower dosage [24, 45, 46].

Similar to past work [6] by combining the half reactions defined in equations (1) and (2) with those of equations (3) and (4), respectively, the overall abilities of OSeH and ESeH to inhibit the recycling of Cu(I) to Cu(II) was investigated. At the IEFPCM-BP86/6-311 +  $G(2df,p)$  +  $\Delta G_{\text{corr}}$  level of theory, the EMF for the reduction of Cu(II)(OSe)<sub>2</sub> to Cu(I)(OSeH)<sub>3</sub><sup>+</sup> with concomitant oxidation of OSeH<sub>t</sub> to OSeSeO is calculated to be 0.90 V, whereas the EMF for the reduction of Cu(II)(ESe)<sub>2</sub> to Cu(I)(ESeH)<sub>3</sub><sup>+</sup> with concomitant oxidation of ESeH to ESeSeE is calculated to be 0.67 V. Hence, the reduction of Cu(II) to Cu(I) with concomitant

TABLE 3: Standard reduction potentials ( $E^\circ$ ) for the  $\text{Cu(II)(OSe)}_2/\text{Cu(I)(OSeH)}_3^+$  and  $\text{Cu(II)(ESe)}_2/\text{Cu(I)(ESeH)}_3^+$  redox couples at the IEFPCM-BP86/6-311 +  $G(2df,p)$  +  $\Delta G_{\text{corr}}$  level of theory.

Cu(II)(OSe) <sub>2</sub> / Cu(I)(OSeH) <sub>3</sub> <sup>+</sup>			Cu(II)(ESe) <sub>2</sub> /Cu(I)(ESeH) <sub>3</sub> <sup>+</sup>				
trans-	cis-	Avg. <sup>a</sup>	trans-ε-	cis-ε-	trans-δ-	cis-δ-	Avg. <sup>a</sup>
1.15	1.15	1.15	1.23	1.25	1.25	1.34	1.24

<sup>a</sup>Calculated using a weighted average according to Boltzmann statistics.

formation of either diselenide is thermodynamically favourable. However, the reduction of Cu(II) in the presence of OSeH is thermodynamically more favourable. Previously at the IEFPCM-BP86/6-311 +  $G(2df,p)$  +  $\Delta G_{\text{corr}}$  level of theory, the EMF for the reduction of  $\text{Cu(II)(OS)}_2$  to  $\text{Cu(I)(OSH)}_3^+$  with concomitant oxidation of  $\text{OSH}_t$  to  $\text{OSSO}$  was calculated to be 1.02 V, whereas the EMF for the reduction of  $\text{Cu(II)(ES)}_2$  to  $\text{Cu(I)(ESH)}_3^+$  with concomitant oxidation of  $\text{ESH}$  to  $\text{ESSE}$  was calculated to be 0.69 V [6].

While, the overall process for the reduction of Cu(II) to Cu(I) is thermodynamically more favourable for the OSH and ESH systems, it has been previously been stated [14] that S-containing compounds can undergo rapid oxidation in the presence of  $\text{O}_2$  when bound to a heavy metal. This is not the case for Se-containing ligands [14]. Moreover, in the case of biochemical systems, Se-containing catalyst has been found to have enhanced durability over their S-analogues [48, 49]. Specifically, it has been found that the substitution of the S-atom with a Se-atom confers resistance to irreversible oxidation and inactivation due to the difference in redox chemistry between selenium and sulfur where sulfur has a greater tendency to be oxidized to sulfoxides and sulfones [50, 51]. Lastly, it has been stated that almost all chemical reactions involving Se are faster than the analogous reactions involving S [36]. Thus, the results presented herein provide evidence for the possible inhibition of Cu(I) to Cu(II) recycling by OSeH and ESeH.

## 4. Conclusions

The complexes formed from the binding of ovoselenol (OSeH) and ergoseloneine (ESeH) to Cu(II) and Cu(I) have been investigated using DFT methods. From the results, the complexes are isostructural to the analogous sulfur containing ovothiol and ergothioneine complexes. In particular, a square-planar copper coordination center was observed for the *trans-ε*-Cu(II)(ESe)<sub>2</sub>, *cis-ε*-Cu(II)(ESe)<sub>2</sub>, *trans-δ*-Cu(II)(ESe)<sub>2</sub>, and *trans*-Cu(II)(OSe)<sub>2</sub> complexes, whereas a slightly twisted, square-planar coordination geometry around the Cu-center was observed for *cis*-Cu(II)(OSe)<sub>2</sub>, and *cis-δ*-Cu(II)(ESe)<sub>2</sub>. For both the  $\text{Cu(I)(ESeH)}_3^+$  and  $\text{Cu(I)(OSeH)}_3^+$  complexes, a trigonal planar coordination geometry around the Cu(I) center was observed.

The calculated reduction potentials for the  $\text{Cu(II)(OSe)}_2/\text{Cu(I)(OSeH)}_3^+$  and  $\text{Cu(II)(ESe)}_2/\text{Cu(I)(ESeH)}_3^+$  redox couples were found to be 1.15 V and 1.24 V in aqueous solution, respectively. Given the large positive reduction potentials for the  $\text{Cu(II)(OSe)}_2/\text{Cu(I)(OSeH)}_3^+$  and  $\text{Cu(II)(ESe)}_2/\text{Cu(I)(ESeH)}_3^+$

redox couples, it is likely that the presence of OSeH and ESeH in solution inhibits the recycling of Cu(I) to Cu(II).

By combining the half reactions for the oxidation of ESeH and OSeH to the diselenides ESeSeE and OSeSeO with the reduction of the  $\text{Cu(II)(OSe)}_2$  and  $\text{Cu(II)(ESe)}_2$  to  $\text{Cu(I)(ESeH)}_3^+$  and  $\text{Cu(I)(OSeH)}_3^+$ , respectively, the likelihood of ESeH and OSeH to protect against Cu-induced oxidative damage was studied. Overall, the EMF for the reduction of  $\text{Cu(II)(OSe)}_2$  to  $\text{Cu(I)(OSeH)}_3^+$  with concomitant oxidation of  $\text{OSeH}_t$  to  $\text{OSeSeO}$  was calculated to be 0.90 V, whereas the EMF for the reduction of  $\text{Cu(II)(ESe)}_2$  to  $\text{Cu(I)(ESeH)}_3^+$  with concomitant oxidation of ESeH to ESeSeE was calculated to be 0.67 V. Thus, for both systems, the reduction of Cu(II) to Cu(I) with concomitant formation of either diselenide is thermodynamically favourable, and it is expected that both OSeH and ESeH are suitable for the protection against copper-induced oxidative damage.

## Data Availability

The optimized geometries at the BP86/6-311 +  $G(2df,p)$  level of theory data used to support the findings of this study are included within the supplementary information file. The Boltzmann equation used in calculating the relative populations of  $\text{Cu(II)(OS)}_2$  and  $\text{Cu(II)(ES)}_2$  is also provided.

## Conflicts of Interest

The authors declare that they have no conflicts of interest.

## Authors' Contributions

Jacqueline Wiebe and Vasyl Zaliskyy contributed equally to this article.

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## Supplementary Materials

Table S1: the Boltzmann equation used for the calculation of the relative populations of the Cu-OSeH and Cu-ESeH complexes.  $N_i/N$  is the relative population of species  $i$ ,  $\mu_i$  is the relative chemical potential in solution for species  $i$ ,  $g_i$  is the degeneracy, and  $\sum g_i e^{\mu_i/RT}$  is the partition function. Table S2: all  $xyz$ -coordinates of the selenium containing compounds optimized at the BP86/6-311 +  $G(2df,p)$  level of theory. (*Supplementary Materials*)

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