



## DFT modeling of the prevention of Fe(II)-mediated redox damage by imidazole-based thiones and selones

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### ABSTRACT

Peroxide reduction involving Fe(II) (i.e., Fenton chemistry) forms hydroxyl radicals which cause oxidative damage to DNA *in vivo*. Sulfur and selenium compounds have been investigated for their antioxidant properties in preventing this metal-mediated oxidative damage. The effect of the coordination of sulfur/selenium derivatives of imidazolidinone (thiones/selones) on the electronic structure and reduction potential of Fe(II) ions solvated or coordinated to guanine are examined using density functional theory (DFT). The zwitterionic character of the thione/selone ligands increases with substitution of electron donating methyl groups and results in more stable complexes with Fe(II). The highest occupied molecular orbital (HOMO) for the Fe(II)-aqua complex is metal centered, but the HOMO of the Fe(II)-guanine complex is localized on the nucleobase. Complexation of the thione/selone shifts the HOMO to the sulfur/selenium center suggesting a mechanism for protection of DNA by sacrificial oxidation of the sulfur/selenium ligand in preference to Fe(II) or DNA.

### 1. Introduction

Reactive oxygen species (ROS) are byproducts of cellular respiration and act as messengers at low concentration [1–4]. If not controlled, these species damage cellular components including proteins, lipids, and nucleic acids [2,5–11]. Lipids and proteins are rapidly replaced during cellular maintenance, but recovery of lost information stored in DNA is difficult which makes it a critical biological issue. Despite numerous cellular DNA repair mechanisms, cumulative DNA damage contributes to aging, Alzheimer's disease, cardiovascular disease, and various forms of cancer [12–19]. Accordingly, the behavior of free radicals in biological systems has been a recent area of significant interest [20–22]. The most damaging ROS is the hydroxyl radical ( $\cdot\text{OH}$ ) [23] produced by Fenton and Fenton-like chemistry between hydrogen peroxide and transition metal ions such as Fe(II) and Cu(I) [24,25]. Density functional theory (DFT) studies have examined several pathways for Fe(II)-mediated generation of hydroxyl radicals [26–29].



Metal-mediated  $\cdot\text{OH}$  generation is proposed as a major cause of the DNA damage and cell death through apoptosis [30–33]. Single-strand break and nucleobase oxidation are commonly studied types of Fe(II)-mediated DNA damage [34]. Fe(II) is believed to travel along the phosphate backbone to coordinate to DNA at N7 of a guanine, [35] the most easily oxidized nucleobase [36]. The intermediate product 8-oxo-deoxyguanine is commonly used as an oxidative damage marker because it can be detected in the femtomolar range [34]. Fe(II)-mediated

DNA damage occurs preferentially at certain sequences (i.e. RGGG or RTGR) [35,37,38]. Lee et al. have shown that GTGR is also a sensitive sequence for oxidative damage [39]. Radical scavengers such as ethanol and dimethyl sulfoxide inhibit Fe(II)-mediated DNA damage *in vitro*, by preventing hydroxyl radical-induced nicking of the phosphate backbone or oxidation of guanine [40]. Enzymatic radical scavenging has limited effectiveness in combating hydroxyl radicals formed in locations too hindered for effective access by scavenging systems [25,41]. As a result, prevention of metal-mediated radical formation may be a superior approach to protecting against oxidative damage [42].

*In vitro* studies have shown that sulfur and selenium compounds protect DNA from metal-mediated damage [42–48]. Seven of nine selenium compounds tested prevented Cu(I)-mediated oxidative DNA damage, while only five inhibited Fe(II)-mediated damage [49–51]. Interestingly, only *N,N'*-dimethylimidazole selone ( $3_{\text{se}}$ ) prevented significant Fe(II)-mediated DNA damage within selenium's biological range (3.2  $\mu\text{M}$ ) [42]. In contrast, eight of eleven sulfur compounds tested inhibited Cu(I)-mediated DNA damage with  $\text{IC}_{50}$  values from 3.34 to 1550  $\mu\text{M}$ , but only three compounds prevented Fe(II)-mediated DNA damage, among which glutathione inhibited only 23% of damage [42]. *N,N'*-dimethylimidazole thione ( $3_{\text{s}}$ ) inhibited Cu(I)-mediated damage at a substantially higher concentration than  $3_{\text{se}}$  ( $\text{IC}_{50}$ : 1550  $\mu\text{M}$  vs. 240  $\mu\text{M}$ ) [42]. Ergothioneine has shown significant free radical scavenging capacity, but has not been tested for prevention of metal-mediated DNA damage [52]. Overall, sulfur and selenium-containing compounds have shown greater inhibition of Cu(I) over Fe(II)-mediated DNA damage. Thione and selone derivatives are a notable exception

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with  $3_S$  and  $3_{Se}$  about 17.3 and 75 times more effective, respectively, against inhibition of Fe(II)-mediated DNA damage [42].

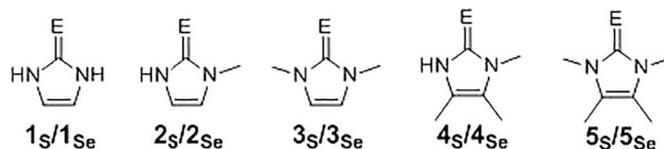
Since scavenging of the short-lived hydroxyl radical by sulfur and selenium compounds seems unlikely [53,54], metal coordination has been proposed as the primary mechanism by which these antioxidants prevent DNA damage [24,49–51]. Protection would occur through sacrificial oxidation of the coordinated thione/selone [55,56] rather than through the direct ROS scavenging observed for a broad range of sulfur and selenium compounds [48,57,58]. Thiones and selones prefer to coordinate through the zwitterionic resonance form [48,56,59–61] which allows these ligands to be classified as potential  $\pi$ -donors similar to other anionic chalcogen ligands such as thiolates and selenolates [56,62]. The zwitterionic resonance structures suggest that thiones/selones will have longer C–E bonds than “true” chalcogenones, E will carry a partial negative charge, and the heterocyclic ring will be partially positive. Thione/selone coordination to Fe(II) results in higher ligand-based oxidation potentials and significantly more negative Fe(III/II)-derived reduction potentials indicating that thiones/selones would more easily undergo oxidation [56].

The effect of thione/selone coordination on the prevention of DNA damage by Fe(II) was investigated through DFT studies of the free ligands and their complexes with Fe(II) coordinated to water and guanine. The contribution of the zwitterionic character of the thiones/selones to the stability of the complexes was analyzed through changes in the C–E bond distances and the relative energies of ligand substitution. The highest occupied molecular orbital (HOMO) character of Fe(II) complexes indicates that localization of the electron density on the ligands rather than the metal provides a potential antioxidant mechanism through sacrificial oxidation of the coordinated thiones/selones.

## 2. Theoretical methods

Density functional theory (DFT) optimized geometries were calculated using Gaussian 09 [63] and the mPW1PW91 [64,65] exchange correlation functional. Iron was represented by the Wachters-Hay all-electron basis set [66]. The Wadt-Hay relativistic effective core potential basis set [67,68] augmented with diffuse and polarization functions was used for sulfur and selenium. Carbon, nitrogen, oxygen, and hydrogen basis sets were triple- $\zeta$  quality augmented with diffuse and polarization functions. All structures were confirmed as minima on the potential energy surface through inspection of their vibrational frequencies. Wiberg bond indices (WBIs) [69] and Natural Population Analysis (NPA) charges were calculated using Natural Bond Orbital (NBO) version 3.1 [70].

## 3. Results and discussion



Scheme 1. Chalcogenone resonance structures (E = S/Se).

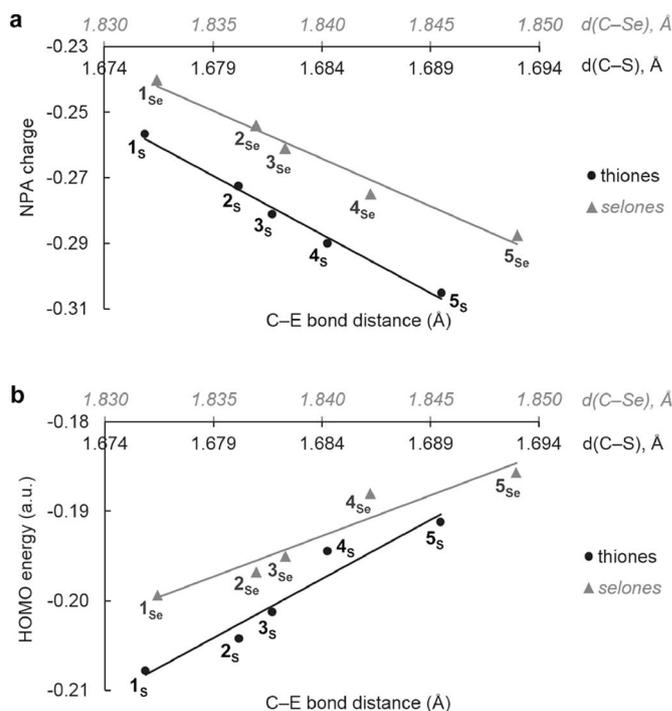


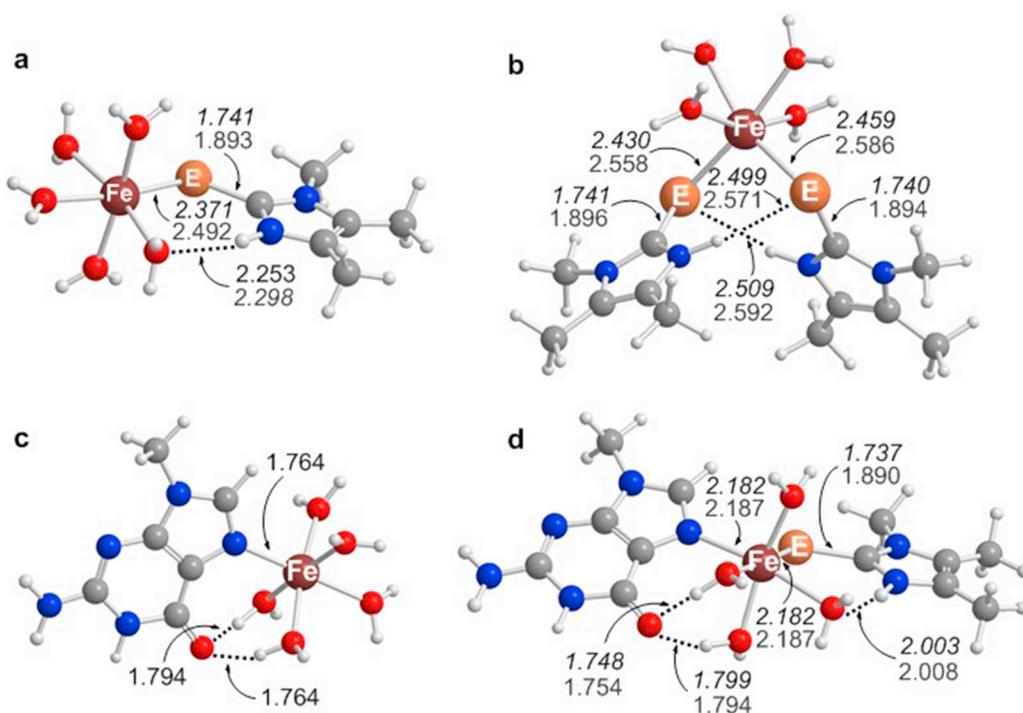
Fig. 1. C–E bond distance vs (a) NPA charge on E of free ligands and (b) HOMO energy of free ligands.

0.009–0.016e and 0.007–0.014e with addition of each methyl group to the thione and selone compounds, respectively. In general, the sulfur of thione derivatives are more partially negative than the selenium centers of their selone counterparts ( $q_S(3_S) = -0.281e$ ;  $q_{Se}(3_{Se}) = -0.261e$ ). However, the Wiberg bond indices of the selones ( $3_{Se}$ :  $WBI_{C=Se} = 1.338$ ) are smaller than the thiones ( $3_S$ :  $WBI_{C=S} = 1.433$ ) indicating that the selenium compounds have more zwitterionic character in agreement with previous studies [59,71,72]. The HOMOs of methylated thiones/selones are also destabilized (i.e.,  $1_{Se}$  vs

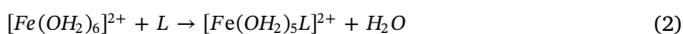
$5_{Se} = -0.19934$  a.u. vs  $-0.18564$  a.u.) (Fig. 1a), consistent with increased Lewis basicity and stronger metal coordination.

Inhibition of DNA damage may result from the effect of thione/selone coordination on the electronic structure and reduction potential of Fe(II) either as aquated ions or coordinated to guanine. The relative energy of substitution of a water ligand of  $[Fe(OH_2)_6]^{2+}$  by a thione/selone according to reaction (2) was calculated to determine trends in the effect of electron donating methyl groups on the affinity of L for the Fe(II) center.

DFT geometry optimizations were performed on a series of imidazole-based thiones and selones with increasing methyl substitution. The electron-donating effect of the methyl groups stabilizes the zwitterionic resonance structure (Scheme 1) [48,56,60], resulting in longer C–E bonds and more negative NPA charges on E for the series of five thione/selone derivatives (Fig. 1a). The average C–E bond increases by 0.014 Å (thiones) and 0.017 Å (selones) in tetra-substituted compounds compared to  $1_S$  and  $1_{Se}$ , respectively. The NPA charge on E decreases by



**Fig. 2.** Representative intramolecular bonds lengths (Å) in (a)  $[\text{Fe}(\text{OH}_2)_5\text{L}]^{2+}$ , (b)  $[\text{Fe}(\text{OH}_2)_4\text{L}_2]^{2+}$ , (c)  $[\text{Fe}(\text{OH}_2)_5\text{G}]^{2+}$ , and (d)  $[\text{Fe}(\text{OH}_2)_4\text{GL}]^{2+}$  complexes (L =  $4_s/4_{se}$ ; G = guanine).



The DFT structures of the  $[\text{Fe}(\text{OH}_2)_5\text{L}]^{2+}$  (L = thione/selone) complexes were optimized assuming octahedral coordination and a high-spin Fe(II) center. Previously synthesized Fe(II)-thione/selone complexes adopted a distorted tetrahedral coordination geometries, preferred by the two or more weak-field thione/selone ligands (i.e.  $[\text{Fe}(\text{3Se})_2\text{Cl}_2]$ ) [56]. For thiones/selones interacting with free Fe(II) at low concentrations, we expect that water, as a small  $\sigma$ -donor ligand, will fill the coordination sphere at low L substitution and favor 6-coordination. However, there is some experimental indication of tetrahedrally coordinated disubstituted Fe(II) ions (i.e.,  $[\text{Fe}(\text{OH}_2)_2\text{L}_2]^{2+}$ ) (J.L. Brumaghim, personal communication). The optimized structures are roughly octahedral with E–Fe–O<sub>eq</sub> bond angles ranging from 83.4° to 107.3° (thiones) and from 88.2° to 109.1° (selones).  $[\text{Fe}(\text{OH}_2)_5\text{L}]^{2+}$  complexes

**Table 1**

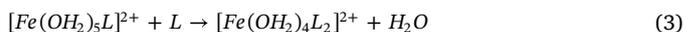
Relative energies for substitution of water ligands at the Fe(II) center by thione/selone (L) and guanine (G) calculated from the reactions in Eqs. (2), (3), (5) and (6).<sup>a</sup>

Ligand	$\Delta E + \text{ZPE}$ , kcal/mol			
	$[\text{Fe}(\text{H}_2\text{O})_5\text{L}]^{2+}$	$[\text{Fe}(\text{H}_2\text{O})_4\text{L}_2]^{2+}$	$[\text{Fe}(\text{H}_2\text{O})_4\text{GL}]^{2+}$	
	Eq. (2)	Eq. (3)	Eq. (5)	Eq. (6)
<b>Thiones</b>				
1 <sub>s</sub>	−26.05	−26.24	−20.69	−46.70
2 <sub>s</sub>	−27.14	−29.21	−22.25	−47.17
3 <sub>s</sub>	−27.70	−22.85	−18.65	−43.01
4 <sub>s</sub>	−33.70	−31.72	−26.37	−44.73
5 <sub>s</sub>	−33.53	−25.95	−23.56	−42.08
<b>Selones</b>				
1 <sub>se</sub>	−27.38	−27.21	−21.95	−46.63
2 <sub>se</sub>	−27.85	−30.27	−23.45	−47.66
3 <sub>se</sub>	−29.33	−23.58	−21.24	−43.98
4 <sub>se</sub>	−34.75	−32.34	−27.51	−44.82
5 <sub>se</sub>	−34.51	−27.30	−25.79	−43.34

<sup>a</sup> Eq. (4):  $\Delta E + \text{ZPE} = -52.06$  kcal/mol.

with L containing an NH group (i.e. 2<sub>s</sub>), are stabilized by intramolecular hydrogen bonding with the oxygen of a water ligand ( $\text{N}_L\text{---H}_L\cdots\text{O}_{\text{aq}}$ ) (Fig. 2a). The longer C–E bonds in  $[\text{Fe}(\text{OH}_2)_5\text{L}]^{2+}$  (i.e. for 3<sub>se</sub>:  $d(\text{C}=\text{Se}) = 1.893$  Å) vs the free ligand ( $d(\text{C}=\text{Se}) = 1.838$  Å) are consistent with stabilization of the zwitterionic resonance form of the thione/selone through coordination to Fe(II).

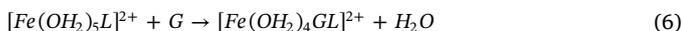
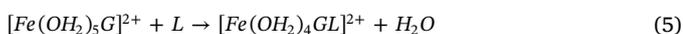
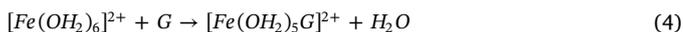
Substitution of an aqua ligand by L (Eq. (2)) is more energetically favorable with increasing methylation and for selone derivatives relative to the thiones (Table 1), consistent with the trends in the zwitterionic properties of the free ligand. Intramolecular H-bonding ( $\text{N}_L\text{---H}\cdots\text{O}_{\text{aq}}$ ) stabilizes the complexes more than N-methylation (i.e. compare 1<sub>s</sub>/1<sub>se</sub> and 2<sub>s</sub>/2<sub>se</sub> in Table 1). Methylation at C-positions while preserving the  $\text{N}_L\text{---H}\cdots\text{O}_{\text{aq}}$  bond offers a greater stability of ~3 kcal/mol per methyl group (i.e. 4<sub>s</sub>/4<sub>se</sub> vs 2<sub>s</sub>/2<sub>se</sub>, Table 1). Due to this combination of the effects of hydrogen bonding and methylation, the most stable  $[\text{Fe}(\text{OH}_2)_5\text{L}]^{2+}$  complexes are those of 4<sub>s</sub>/4<sub>se</sub> rather than 5<sub>s</sub>/5<sub>se</sub>, the most zwitterionic free ligands. 4<sub>s</sub>/4<sub>se</sub> have the shortest Fe–E bonds, while 3<sub>s</sub>/3<sub>se</sub> and 5<sub>s</sub>/5<sub>se</sub> have the longest due to the steric bulk of the ligand.



The IC<sub>50</sub> values reported by Brumaghim [42] suggest that thiones and selones coordinate to Fe(II) in varying ratios. The optimized structures of bis-thione/selone  $[\text{Fe}(\text{OH}_2)_4\text{L}_2]^{2+}$  complexes preserve the distorted octahedral geometry of the Fe(II) center. Complexes with L containing NH groups are stabilized by intramolecular hydrogen bonds between N–H of one L and the S/Se atom of the other (Fig. 2b) instead of intramolecular hydrogen bonds to water ligands found in  $[\text{Fe}(\text{OH}_2)_5\text{L}]^{2+}$ . This interaction is the major factor that stabilizes the bis-thione Fe(II) complexes followed by degree of methylation, such that the order of complex stability (Eq. (3)) is: 3<sub>s</sub>/3<sub>se</sub> < 5<sub>s</sub>/5<sub>se</sub> ~ 1<sub>s</sub>/1<sub>se</sub> < 2<sub>s</sub>/2<sub>se</sub> < 4<sub>s</sub>/4<sub>se</sub>. Overall, substitution of a second L is generally less energetically favorable than the first due to steric interactions between the ligands.

The replacement of an aqua ligand of  $[\text{Fe}(\text{OH}_2)_6]^{2+}$  by guanine (G) (Eq. (4)) was modeled to mimic the proposed biological interaction of Fe(II) and DNA [35,38,73,74]. The substitution by G is more favorable

than substitution by L in Eq. (2) by  $-17$  to  $-26$  kcal/mol (Table 1), due to the preference of the borderline acid Fe(II) for the borderline nitrogenic base. The optimized  $[\text{Fe}(\text{OH}_2)_5\text{G}]^{2+}$  complex has a distorted octahedral coordination and is stabilized by two internal hydrogen bonds between water ligands and the guanine carbonyl oxygen (Fig. 2c). The energetic favorability of substitution of G over L (Eqs. (2) vs (4)) could suggest that the mechanism by which thiones/selones protect against Fe(II)-mediated damage may occur after initial metal coordination to DNA. However, kinetics studies of the relative rates of substitution would be required to confirm these conclusions.



The formation of the tetraaquairon(II) guanine thione/selone complex  $[\text{Fe}(\text{OH}_2)_4\text{GL}]^{2+}$  was modeled along two possible pathways of initial G or L coordination. Coordination of L to  $[\text{Fe}(\text{OH}_2)_5\text{G}]^{2+}$  (Eq. (5)) may be more biologically relevant, since sterics may prevent Fe(II)-thione/selone complexes from effectively approaching DNA (modeled by Eq. (6)). The  $\Delta E + \text{ZPE}$  of  $[\text{Fe}(\text{OH}_2)_4\text{GL}]^{2+}$  complexes by these two pathways follows the trend in the  $[\text{Fe}(\text{OH}_2)_4\text{L}_2]^{2+}$  series. In both disubstituted series, trends are reported for the *cis* complexes only, which are more stable than the *trans* (Table 1 and Fig. 2d). The relative energy of substitution by G on  $[\text{Fe}(\text{OH}_2)_5\text{L}]^{2+}$  is almost independent of the nature of L, but less favorable than initial coordination of G in  $[\text{Fe}(\text{OH}_2)_5\text{G}]^{2+}$  due to steric interactions with L. Fe(II)-guanine thione/selone complexes are stabilized by two hydrogen bonds from water ligands to the guanine carbonyl oxygen and, if applicable, one hydrogen bond from water ligand to N–H of thione/selone. These results may explain the different outcomes of the experimental studies examining the ability of inorganic selenium compounds to prevent Fe(II)-mediated DNA damage [75]. The lesser protection by inorganic selenium compounds added after incubation of Fe(II) and DNA may be due to reduced accessibility of the selenium species to the DNA-bound Fe(II). In

contrast, addition of Fe(II) and selenium species prior to addition of DNA was more successful in preventing DNA damage.

Thiones and selones are proposed to prevent oxidative DNA damage by coordinating to the metal and undergoing oxidation more easily than the metal center [55,76]. In this targeted ROS scavenging [42], the thione/selone ligands sacrifice their electrons to prevent Fe(II) oxidation and DNA damage. Assuming that electrons will be lost from the HOMO in an oxidative process, we examined the character of the frontier orbitals of the Fe(II) complexes to understand how thiones/selones protect against DNA damage. The HOMO of  $[\text{Fe}(\text{OH}_2)_6]^{2+}$  is the metal-centered  $e_g^*$  orbital with antibonding character between the metal and water ligands (Fig. 3). From these results, we can conclude that aquated (i.e., “free”) Fe(II) ions undergo oxidation at the metal center consistent with Fenton-type chemistry. In contrast, the HOMO of  $[\text{Fe}(\text{OH}_2)_5\text{G}]^{2+}$  is localized on the nucleobase (Fig. 3). Therefore, when Fe(II) coordinates to DNA through the N7 of guanine, damage may occur by direct oxidation of the metallated nucleobase. Likewise, the HOMOs of  $[\text{Fe}(\text{OH}_2)_5\text{L}]^{2+}$  are similarly ligand-based and localized on an E-type lone pair of the thione/selone (Fig. 3). Therefore, in agreement with previous modeling of Cu(I) complexes of thiones/selones [42,55], the ligands would be preferentially oxidized to protect the iron center.  $[\text{Fe}(\text{OH}_2)_4\text{L}_2]^{2+}$  complexes maintain the same HOMO character as the mono-complexes, being predominately composed of delocalized p orbitals of the two L ligands (Fig. 3). So, bis-thione/selone Fe(II) complexes are similarly predicted to oxidize at L in preference to the Fe(II) center. In the model of the L-protected Fe(II)-guanine complex  $[\text{Fe}(\text{OH}_2)_4\text{GL}]^{2+}$ , the HOMO is also L based with similar to the  $[\text{Fe}(\text{OH}_2)_5\text{L}]^{2+}$  complexes (Fig. 3). As a result, protection of DNA from Fe(II)-mediated oxidative damage is consistent with a mechanism of secondary coordination of a thione/selone ligand which is preferentially and sacrificially oxidized over Fe(II) or the nucleobase. The hydroxyl radical scavenging capacity of ergothioneine [52], a thione similar to the ligands in this study, may be due to similar shift in HOMO character if metal coordination is involved in prevention of ROS production. Given the smaller field splitting in tetrahedral coordination, the same trends in HOMO character are expected if Fe(II) species are

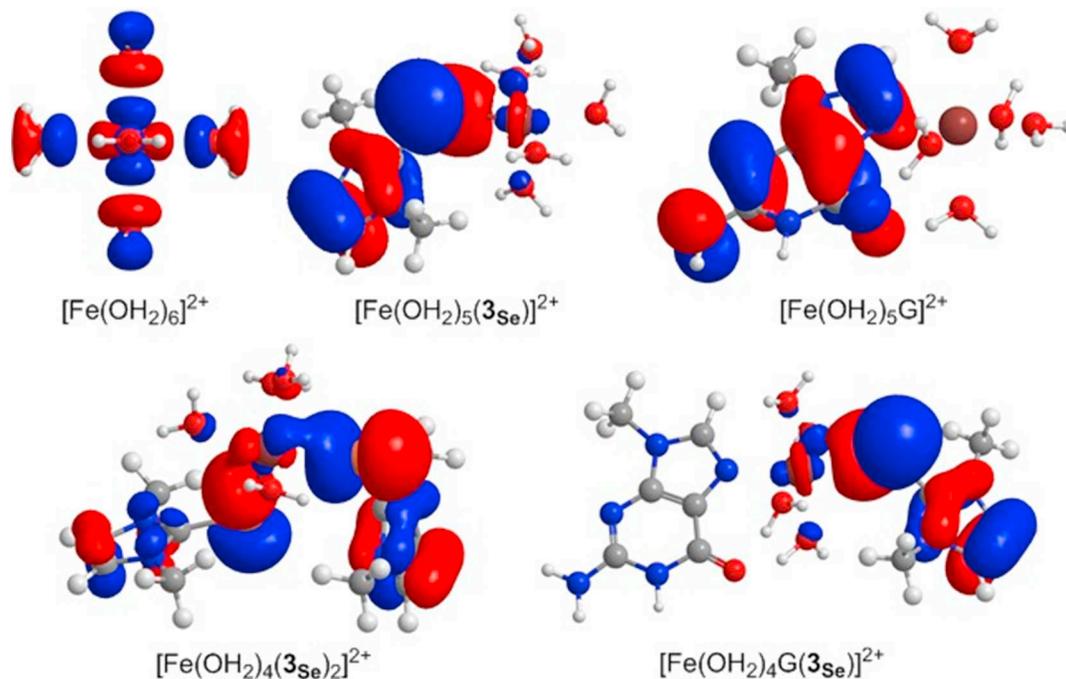


Fig. 3. HOMOs of the representative Fe(II) complexes.  $3\text{Se}$  was chosen as an example for all Fe(II)-L complexes, since The HOMOs of the thione complexes have the same character as the selones.

four-coordinate rather than the six- as modeled.

#### 4. Conclusions

DFT calculations were performed for a series of thione/selone derivatives as free ligands and coordinated to aquated Fe(II) ions. The zwitterion character of the selone/thione ligands increased with substitution of electron donating methyl groups, as shown in longer C–E bonds in the free ligand and more energetically favorable complexes with Fe(II). Selone derivatives have more zwitterionic character and coordinate more strongly to Fe(II), consistent with their greater effectiveness against Fe(II)-mediated DNA damage experimentally. Examination of the HOMO of the Fe(II) complexes indicates that Fe(II) binding to guanine makes the DNA more prone to oxidative cleavage. However, the localization of the HOMO character of the Fe(II)-guanine complex changes upon thione/selone coordination from nucleobase- to thione/selone-centered. This shift in character is consistent with preferential oxidation at the thione/selone and protecting the metal and nucleobase. However, unlike other biochalcogen-based antioxidants, this protection is non-catalytic and DNA damage would be expected to resume once thiones/selones are exhausted unless the process could be coupled with a reductant. This modification explains the antioxidant activity of S/Se compounds in preventing Fe(II)-mediated redox DNA damage. Although our modeling has focused on six-coordinate complexes of Fe(II), the same trends are expected if the metal prefers tetrahedral coordination.

#### Abbreviations

DFT	Density functional theory
HOMO	Highest occupied molecular orbital
NBO	Natural Bond Orbital
NPA	Natural Population Analysis
ROS	Reactive oxygen species
WBI	Wiberg Bond Index

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#### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jinorgbio.2018.12.015>.

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