



Computational study of some diselenide-based glutathione peroxidase mimics: Effect of E...N (E = Se/Te) intramolecular interaction and E-E bond strength

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There have been growing interests in studying small molecular weight organoselenium compounds as potential mimetics of glutathione peroxidase (GPx). In this regards, the intramolecular E...N (E = Se/Te) interactions and their effect on the E-E bond strengths in a series of diaryl dichalcogenides and their several derivatives have been investigated using density functional theory. The NBO, NBO deletion and AIM analyses suggest that the E...N interactions become stronger in polar solvent and correlate well with the E...N distances and E-E bond strengths. The calculated free energy changes of the different steps of the GPx-like catalytic cycle indicate that diselenides having stronger Se...N interactions have preference for the reverse GPx cycle, which is in agreement with the reported experimental observations.

Keywords: Secondary bonding, Natural Bond Orbital, Atoms-in-Molecule (AIM), organochalcogen, DFT.

Introduction

Glutathione peroxidase (GPx) is one of the first selenoprotein discovered in mammals that protects the cell against oxidative stress¹. Owing to the importance of GPx, several synthetic organoselenium compounds have been studied as potential mimetics of GPx². Ebselen (2-phenyl-1,2-benzisoselenazol-3(2H)-one) was the first successful synthetic GPx mimic reported in the literature³. The evidence that a diselenide should be a key intermediate in the catalytic mechanism of the ebselen motivated several research groups to take notice in this class of compounds as GPx mimics. Although, the role of the diselenide bonds in biology is not yet clear, recent report⁴ suggests that they could play a role in redox regulation. Because of the close proximity of the residues Trp-148 and Gln-70 to SeCys in GPx, molecules with nitrogen bonded to Se or close enough to form intramolecular interactions have been designed^{1,5}. The importance of such interactions in organochalcogens has been reviewed⁶. Investigations on the theoretical interpretation of such intramolecular interactions have also been carried out^{7,8}. An earlier mechanistic study of GPx like activities of several diaryl

diselenides by ⁷⁷Se NMR spectroscopy⁹ have shown that the diselenides having strong Se...N interactions were found to be inactive due to the preferential nucleophilic attack of thiol at selenium rather than the sulfur atom (Fig. 1a). In continuation to our work⁸ on study of the nature and strength of E...N interactions in various organochalcogen compounds, we have now reported the E...N interactions in a series of organo-dichalcogenides. Our aim is to study the nature and strength of E...N interactions in these compounds and their effects on E-E (E = Se, Te) bond strengths and the energetics of GPx-like catalytic cycle⁹.

Experimental

We have studied four diselenides (Se1-Se4) having tertiary nitrogen with different substituents and flexibilities of type R-Se-Se-R. Also, we have studied their derivatives (R-Se-X; X = H, OH, SPh) which are believed to appear in the GPx-like catalytic cycle of these diselenides. We have also studied the corresponding ditellurides (Te1-Te4) and their derivatives for comparison purpose. These compounds are listed in Fig. 1b.

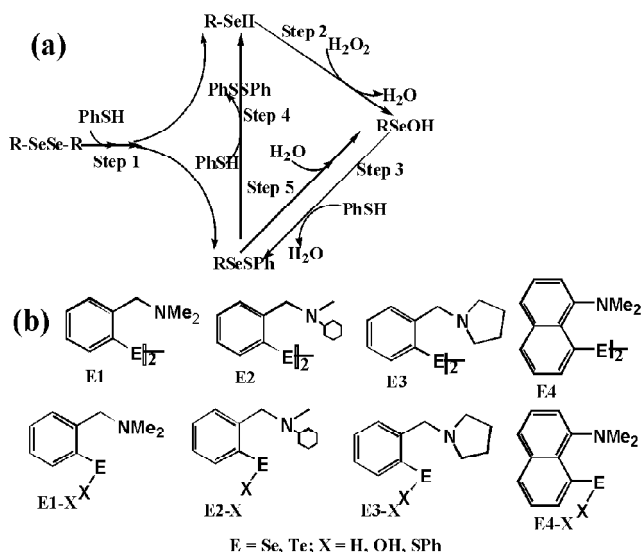


Fig. 1. (a) The GPx like catalytic cycle for diaryl diselenides⁹; (b) The dichalcogenides E1-E4 (E = Se, Te) and their derivatives investigated in this study.

Gaussian09¹⁰ was used as source program for geometry optimization, the natural bond orbital (NBO)¹¹ calculations, NBO deletion analysis and wavefunction calculation for Atoms-in-Molecules (AIM)¹² analysis. Following our earlier work⁸, geometries were optimized (without any constraint) using B3LYP functional¹³ with 6-31G(d) basis set for the selenium and LanL2DZ basis for the tellurium compounds. The minima on the potential energy surface were checked with frequency calculations. Effect of solvent was studied with Tomasi's polarizable continuum model (PCM)¹⁴. AIM2000¹⁵ software was used for analyzing the electron density. Since bond path cannot be traced to the nuclei of atoms described by effective core potential^{12(b)}, for calculation of wavefunction

for all tellurium compounds, we run single point calculations at B3LYP/DZVP (DFT orbital) level using the geometries optimized at B3LYP/LanL2DZ level. Homolytic bond dissociation enthalpy and free energy were calculated as the enthalpy/free energy change for the reaction $A-A \rightarrow 2A$ at the standard conditions. The spin contamination for the radicals (optimized with spin unrestricted formalism) was found to be negligible (mean value of the S^2 operator was close to the theoretical value of 0.75 for all radicals).

Results and discussion

To test the applicability of the method used, we have compared our (energy) optimized structures with X-ray crystallographic data of some available structures in Table 1. Our calculations reproduce reasonably the experimental structures of the said complexes. As a representative case, we have displayed the optimized structure of the diselenide Se1 in Fig. 2a. The phenyl ring (or naphthyl group) attached to E (= Se/Te) are near perpendicular to each other making the atoms N, E, E and N almost collinear to each other. The NEE angles are found between 175° to 177° for the diselenides while they are within 168° to 170° for the ditellurides. The distance between E and N atom ($r_{E...N}$) are found to be larger for Te complexes (between 2.74 Å to 3.1 Å) than the corresponding Se complexes ($r_{Se...N}$ varies from 2.62 Å to 2.81 Å). The structures of E1 and E4 are quite symmetric with equal E-C and E...N distances. However, for E2 and E3 they are not so symmetric with different E...N lengths (e.g. 2.811 Å and 2.694 Å for Se2, 2.681 and 2.72 for Se3, while 3.102 and 2.827 for Te2, 2.761 and 2.864 for Te3). The asymmetric structures of E2 and E3 may be because of crowding due to the ring substituent at the nitrogen center.

Table 1. Comparison of structural parameters of dichalcogenides to those determined by X-ray crystallographic analysis

Compounds	r_{E-E} (Å)	r_{E-C} (Å)	$r_{E...N}$ (Å)	θ_{C-E-E} (°)	Remark
Se2	2.362	1.94, 1.94	2.78, 2.96	100.6, 100.8	Ref. 16(a)
	2.388	1.954, 1.949	2.694, 2.811	100.6, 100.6	This work
	0.026	0.014, 0.009	0.086, 0.149	0, 0.2	Difference
Se4	2.383	1.943, 1.94	2.652, 2.628	100.6, 102.1	Ref. 9
	2.403	1.952, 1.952	2.620, 2.620	101.7, 101.7	This work
	0.02	0.009, 0.012	0.032, 0.008	1.1, 0.4	Difference
Te4	2.765	2.13, 2.126	2.743, 2.699	100.0, 99.5	Ref. 16(b)
	2.943	2.164, 2.164	2.741, 2.741	100.6, 100.6	This work
	0.178	0.034, 0.038	0.002, 0.042	0.6, 1.1	Difference

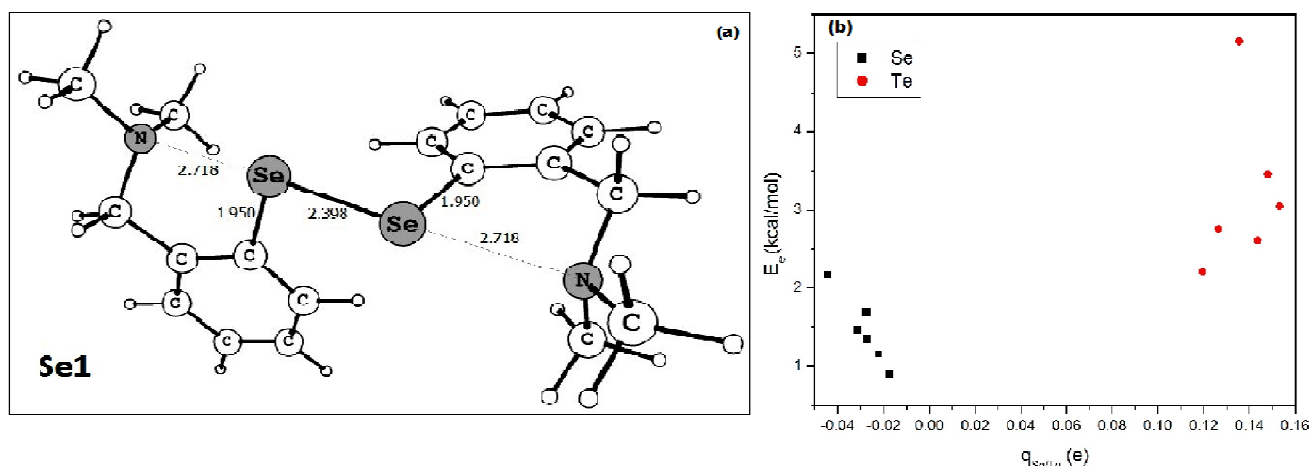


Fig. 2. (a) The B3LYP/6-31G(d) gas phase optimized structure of the diselenide Se1; (b) Plot of the magnitude of the ionic contribution E_{el} with the charge on the selenium/tellurium atom ($q_{Se/Te}$) for the dichalcogenides.

For all the studied compounds, we find a decrease in $r_{E-X/E}$ distances with increase of $r_{E...N}$ distances. There is very little variations in E-E ($E = \text{Se}, \text{Te}$) bond lengths in the studied dichalcogenides (2.388 Å to 2.403 Å for diselenides and 2.917 Å to 2.943 Å for the ditellurides). A somewhat similar near-linear NEX ($X = \text{H}, \text{OH}, \text{SPh}$) angles are observed among the studied derivatives. The $r_{E...N}$ distances become shorter (and the $r_{E-X/E}$ distances become longer) in polar solvent (methanol) than those corresponding gas phase values, indicating that $E...N$ interactions becoming stronger in polar solvent.

The $E...N$ interactions have both the electrostatic as well as covalent contributions⁸. We have estimated the electrostatic contribution (E_{el}) based on point charge model for E and N atoms. The charges on E (q_E) and N (q_N) atoms are obtained by the Natural Population Analysis (NPA). The magnitude of E_{el} is between the range 1–5 kcal/mol (Fig. 2b). For estimation of the covalent contribution to the $E...N$ interaction, we have focused on the orbital overlap between nitrogen lone pairs (n_N) and the antibonding orbital of E-E/X bond ($\sigma^*_{E-E/X}$) using the NBO method. Alternatively, we have deleted the n_N and $\sigma^*_{E-E/X}$ orbitals for NBO deletion study. The magnitude of $E_{E...N}$ is in the range 5–13 kcal/mol per $E...N$ interaction and decreases with increase of $E...N$ ($E = \text{Se}, \text{Te}$) distances ($r_{E...N}$) for the dichalcogenides E1-E4 (Fig. 3a). The values of $E_{E...N}$ become larger in polar solvent. A similar trend in $E_{E...N}$ has been obtained for the derivatives. However, the magnitude of $E_{E...N}$ for derivatives are higher side

to those of dichalcogenides and roughly follow the trends $\text{H} < \text{SPh} < \text{OH}$ among the derivatives. The values for E_{del} also decrease with increase of $r_{E...N}$ for all the compounds. The NBO deletion analysis show significant decrease of charges in the $\sigma^*_{E-E/X}$ orbitals and an equivalent increase of charge in the n_N orbital(s), confirming that the nature of orbital interaction is electron delocalization from n_N to $\sigma^*_{E-E/X}$ orbitals (i.e. $n_N \rightarrow \sigma^*_{E-E/X}$). The values for E_{del} varies in the order $E4 > E3 > E1 > E2$, a trend of decreasing the rigidity among the dichalcogenides. Thus, more rigid the dichalcogenide, greater is the E_{del} .

We have also applied Bader's theory of Atoms-in-Molecules (AIM)¹² to investigate the $E...N$ interactions. According to this theory, the magnitude and the nature of electron density at the critical points give valuable information about the strength and nature of interaction. For all our studied compounds, the presence of critical points (bond critical points (BCP) between E and N atoms, the ring critical point (RCP) for the five membered ring formed with the phenyl ring due to $E...N$ interaction) were observed. We have analyzed the electron density ($\rho_{E...N}$), the Laplacian ($\nabla^2_{E...N}$) and the total energy density ($H_{E...N}$) at the BCP due to $E...N$ and E-E interactions for the dichalcogenides and their derivatives. The values of $\rho_{E...N}$ for the studied compounds correlate well with the corresponding $E...N$ distances (Fig. 3b) and range from 0.017 to 0.035 $e/\text{Å}^3$ which are in between typical covalent bond (e.g. $\rho_{C-C} \approx 0.24 e/\text{Å}^3$) and that of hydrogen bond ($\rho_{H-Bond} \approx 0.002-0.04 e/\text{Å}^3$). The negative sign of (all) the

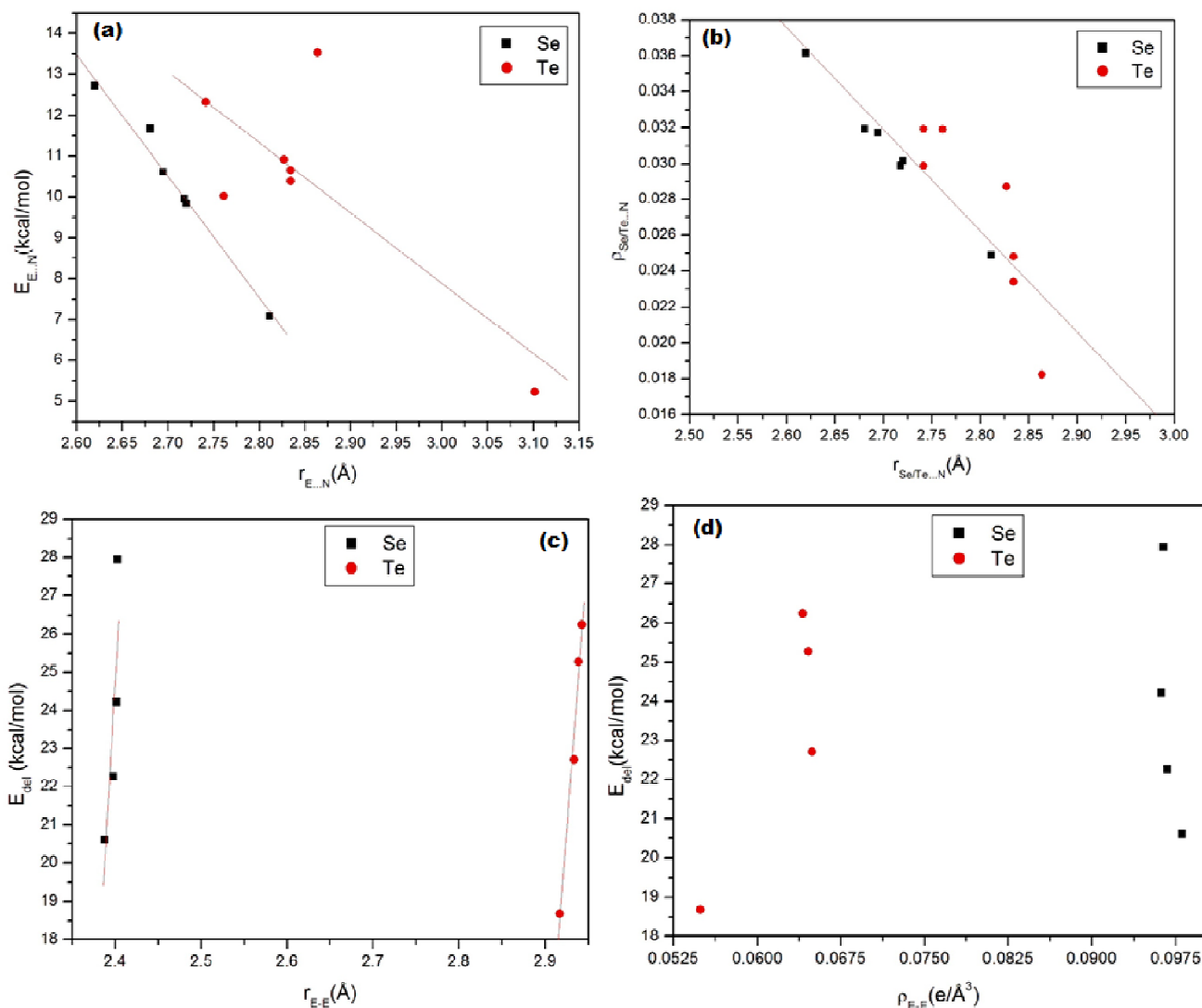


Fig. 3. Top panel: variations of (a) NBO second order perturbation energies ($E_{E...N}$), and (b) electron density at the BCP ($\rho_{Se/Te...N}$) with $E...N$ distances ($r_{Se/Te...N}$) of the dichalcogenides. Bottom panel: variations of NBO deletion energies (E_{del}) with (c) E-E distances, and (d) with the electron density (ρ_{E-E}) at the E-E BCP, for the dichalcogenides (E = Se, Te). $\rho_{Se/Te...N}$ are in unit of $e/\text{Å}^3$.

total energy density at BCP suggest a dominant covalent nature of the $Se...N$ interaction.

An estimation of the E-E bond strength is quite important since the reactivity of dichalcogenides implies the breaking of this bond. For this purpose, we have calculated the homolytic bond dissociation enthalpy (ΔH) for the diselenides in gas phase as well as in methanol. These values along with the homolytic bond dissociation free energies in methanol medium are displayed in Fig. 4(a). The ΔH values obtained for the diselenides are in the range 45–57 kcal/mol which are almost double the values for the ditellurides (23–

26 kcal/mol). As we go from gas phase to polar solvent, these values decrease indicating that the E-E bond strength decreases in polar solvent. A similar trend is observed for the bond dissociation free energy (ΔG) values. A good correlation between E_{del} and the E-E bond length (and similarly with ρ_{E-E} , the electron density at E-E BCP, which is a measure of E-E bond strength) was also found (Fig. 3c and 3d).

It has been observed that diaryl diselenides having strong $Se...N$ interactions show reduced GPx-like activities^{9,17}. To understand the effect of $Se...N$ interactions on the GPx like catalytic cycle of the studied diselenides, we have calculated

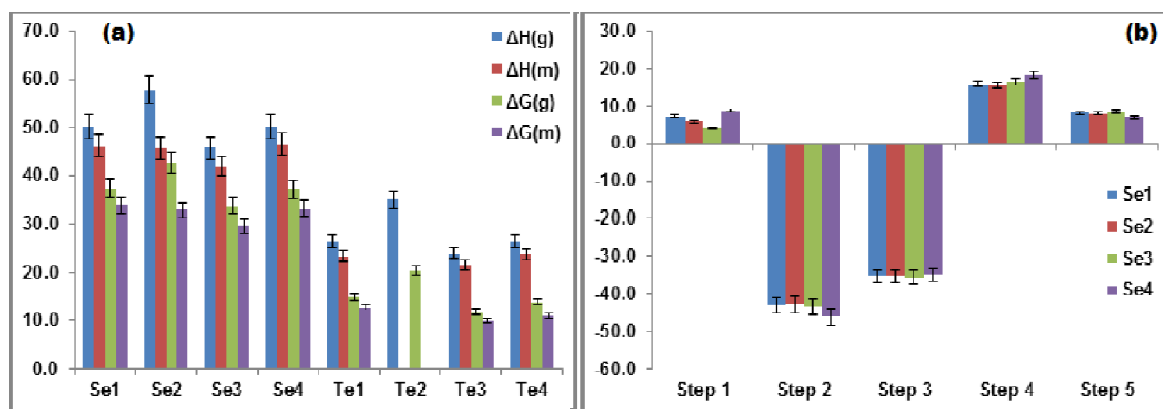


Fig. 4. Comparison of (a) the homolytic bond dissociation enthalpy (ΔH) and Gibbs free energy (ΔG) of the dichalcogenides in gas phase (g) and in solvent methanol (m); (b) the Gibbs free energy change for the various steps (see Fig. 1a) in the GPx like catalytic cycle of diselenides in methanol medium (All values are in kcal/mol).

the Gibbs free energy change (ΔG_i) for various steps in the catalytic cycle (see Fig. 1a) and are presented in Fig. 4(b). Except for Step 2 and Step 3, all other steps of the catalytic cycle were found to be non-spontaneous ($\Delta G > 0$). However, the overall free energy change for the cycle was found to be negative. The free energy change of Step 1 (ΔG_1) for diselenide having strongest Se \cdots N interaction (Se4) is higher than the other diselenides. Also, the ΔG_5 is more favourable for diselenide Se4 than the other diselenides (Se1-Se3). This is in accordance with the experimental observation⁹ that the active selenol (RSe-H) cannot be regenerated easily for diselenides with strong Se \cdots N interactions due to the preference for the thiol exchange reactions (Step 5) rather than disulfide formation (Step 4).

Conclusions

We have applied the density functional methods to study the nature and strength of intramolecular E \cdots N (E = Se/Te) interactions in a series of diaryl dichalcogenides. Similar to our earlier studies on organochalcogens, the E \cdots N interaction involves primarily the electron delocalization between $n_N \rightarrow \sigma^*_{E-E/X}$ orbitals. The electron densities at the E \cdots N bond critical points exhibit good correlation with the E \cdots N distances. The E-E homolytic bond dissociation enthalpy of the diselenides are about 20–25 kcal/mol higher than the corresponding ditellurides. From the calculated free energy changes, it appears that the diselenide Se4 (with strongest Se \cdots N interactions, more rigid structure) has preference over the reverse GPx cycle than the other diselenides, which is in

accordance with the reported experimental observations. A detailed mechanistic study leading to each intermediate is under investigation and will be communicated separately.

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