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Dehydroalanine formation from GPx inhibited by methylmercury: a DFT study

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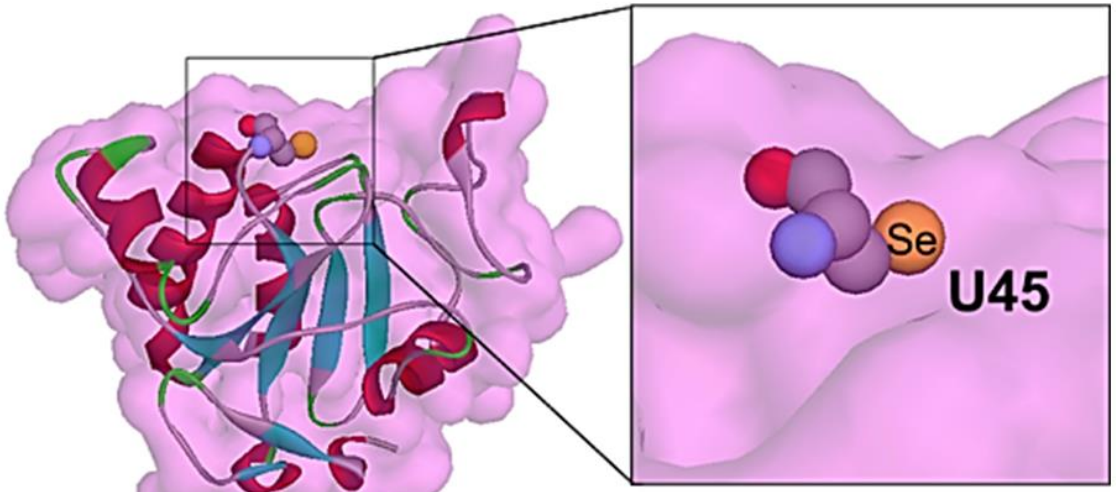
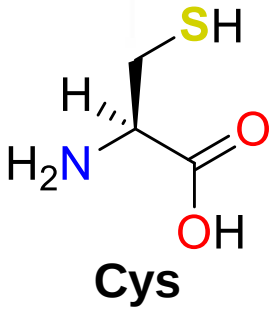
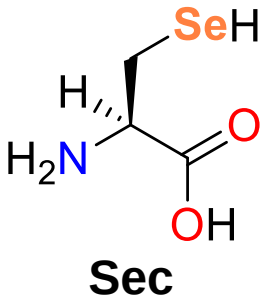
1. INTRODUCTION

Glutathione Peroxidase (GPx)





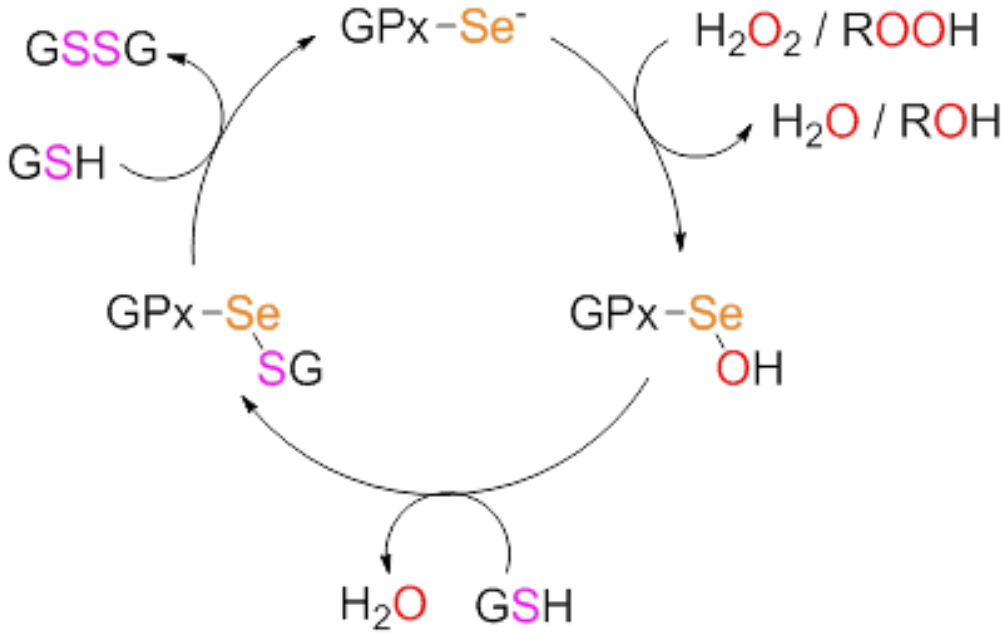
Cys



Sec

↓[ROS]

GPx catalytic cycle



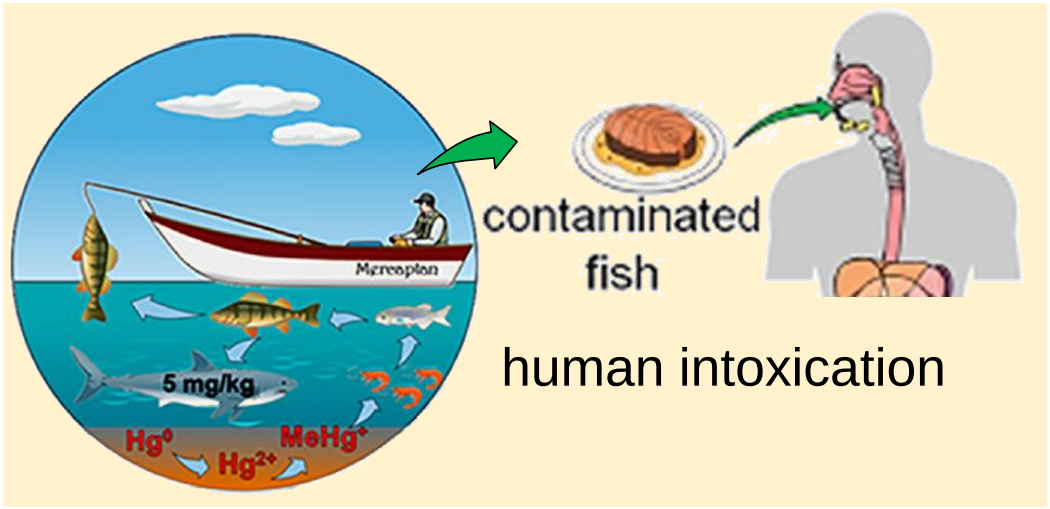
GPx → important role in biological systems reducing the toxic hydrogen peroxide (H_2O_2) to water, using cysteine (Cys) or selenocysteine (Sec) amino acids.

BARBOSA *et al, Metallomics*, **2017**, *9*, 1703-173; WAGNER *et al., Biometals*. **2010,** 23, 1171-1177; CARVALHO *et al., J. Biol. Chem.* **2008**, 2, 11913-11923

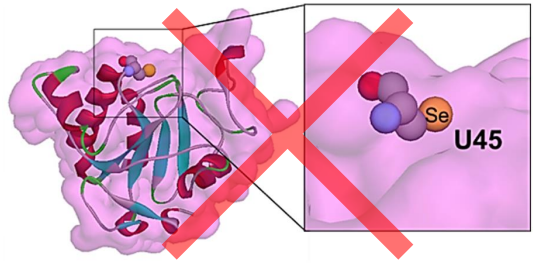
ROS: reactive oxygen species

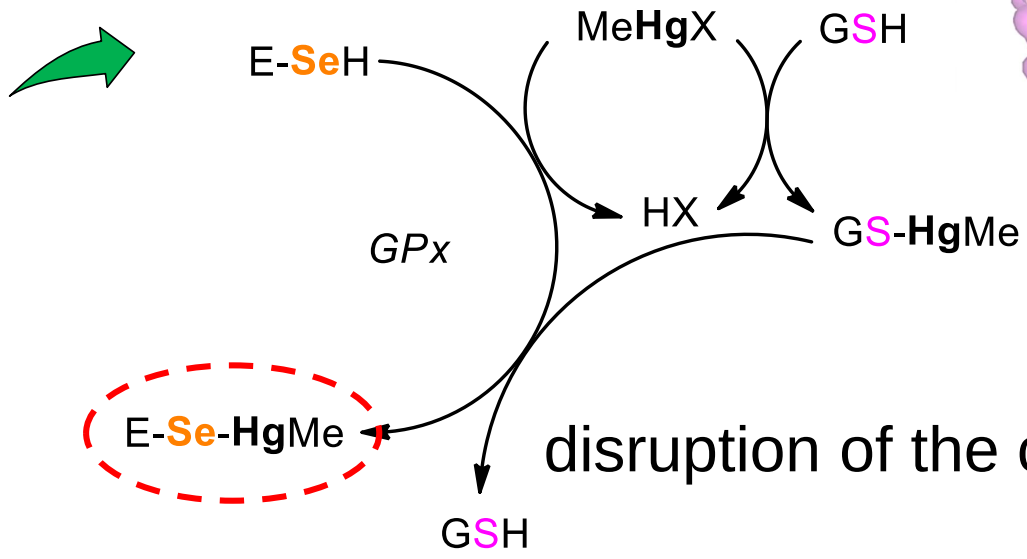
1. INTRODUCTION

MeHg⁺ → potent neurotoxin



♦ **GPx** inhibition

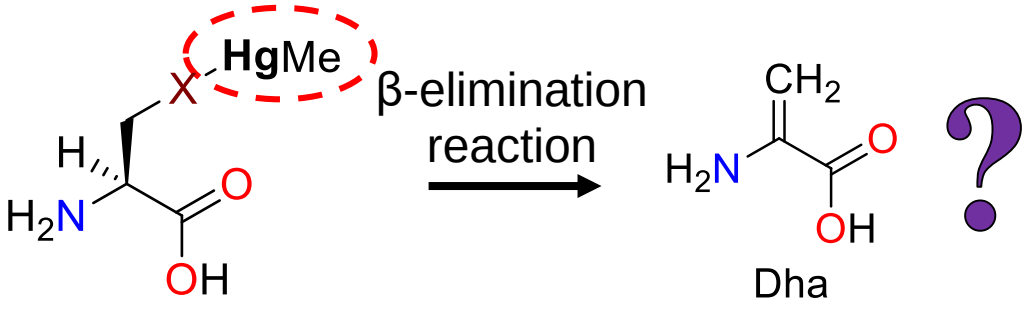




disruption of the catalytic cycle

~~GPx~~ → ↑[ROS] → toxic → cell death

♦ Mechanism:

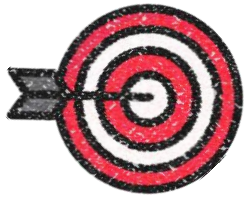


dehydroalanine (**Dha**) formation

NOGARA *et al., BBA - General Subjects*, **2019**, 1863, 129284; NOGARA *et al*, *Chem. Res. Toxicol*. **2019**, 32, 8, 1459–1461; WAGNER *et al., Biometals*. **2010,** 23, 1171-1177.

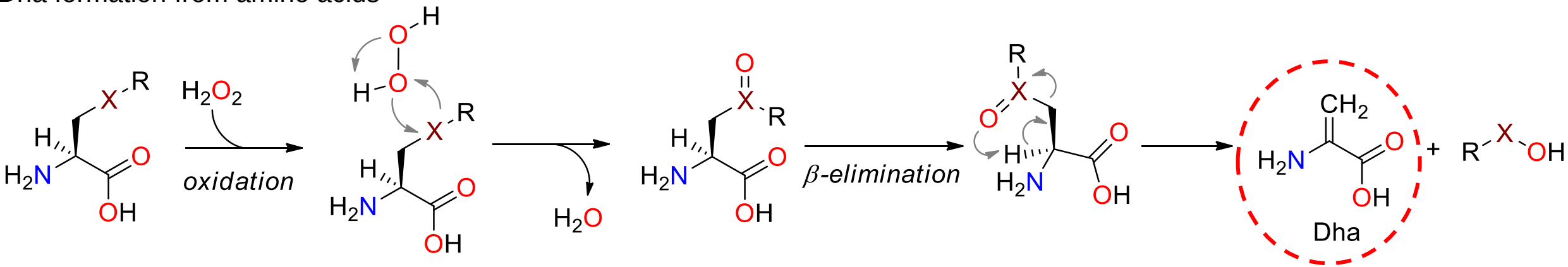
GSH: glutathione

2. GOAL



To investigate the **Dha** formation as the product involved in the possible mechanism of GPx inhibition by MeHg, by DFT studies.

Dha formation from amino acids



X = S, Se, Te R = **Hg**Me, Me

3. METHODS

Cys and **Sec** bonded to MeHg and Me groups were modeled at the ZORA- BLYP-D3(BJ)/TZ2P level of theory.

Tellurocysteine (**Tec**) was studied for completeness and comparison.

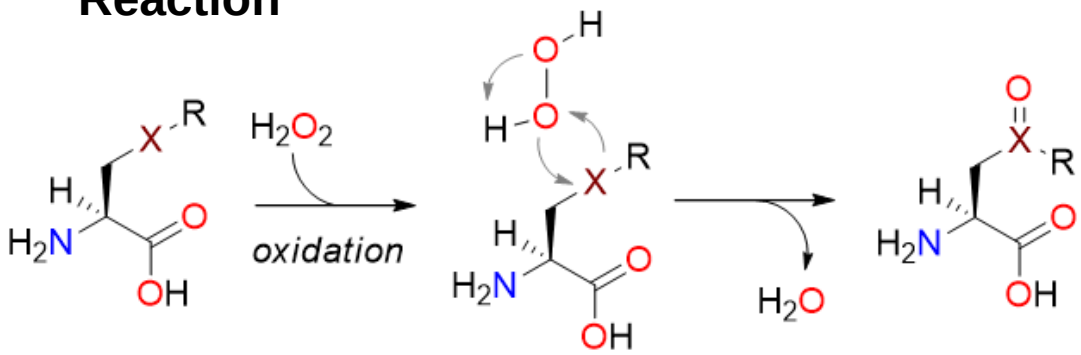
MADABENI et al, *J Comput Chem*. **2020**, 41, 2045–2054.

4. RESULTS

Oxidation reaction energies (ΔE in kcal/mol)

ΔE			oxidation		
Molecule	**X**	**R**	**r**	**TS**	**p**
CysHgMe	S	**Hg**Me	0.00	12.8	-33.8
SecHgMe	Se	**Hg**Me	0.00	9.8	-24.3
TecHgMe	Te	**Hg**Me	0.00	3.9	-28.7
CysMe	S	Me	0.00	11.8	-47.7
SecMe	Se	Me	0.00	8.0	-37.8
TecMe	Te	Me	0.00	1.2	-43.6

Reaction



- ΔE < 0 → favorable
- $\Delta E^{\ddagger}$ favorable: Te > Se > S

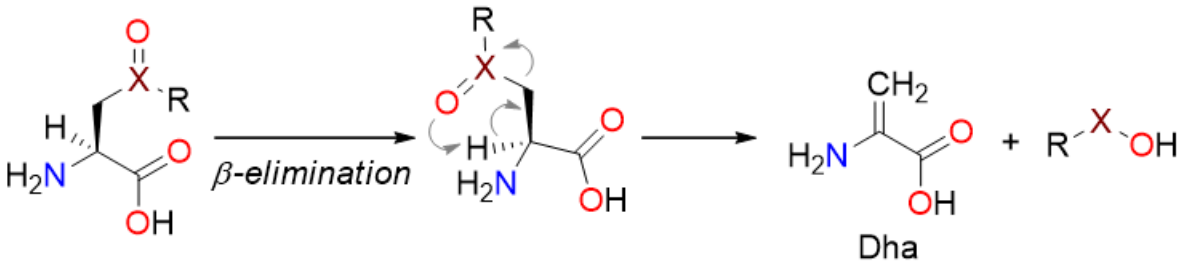
Energies relative to the most stable free reactants. ZORA-BLYP(BJ)/TZ2P. r, TS, and p mean reactants, transition state, and products, respectively.

4. RESULTS

β-elimination reaction energies (ΔE in kcal/mol)

ΔE			β-elimination		
Molecule	**X**	**R**	**r**	**TS**	**p**
CysHgMe	S	**Hg**Me	0.00	13.0	8.1
SecHgMe	Se	**Hg**Me	0.00	4.1	-5.3
TecHgMe	Te	**Hg**Me	0.00	1.8	-8.8
CysMe	S	Me	0.00	20.0	14.5
SecMe	Se	Me	0.00	11.8	1.7
TecMe	Te	Me	0.00	10.8	-0.1

Reaction



- ΔE‡ and ΔE

Te > Se >> S

favorable

- ΔE‡ '**Hg**Me' < 'Me'

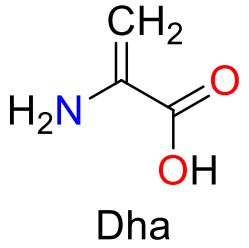
Energies relative to the most stable free reactants. ZORA-BLYP(BJ)/TZ2P. r, TS, and p mean reactants, transition state, and products, respectively.

5. CONCLUSION

→ **Dha** formation from Me- and MeHg- chalcogenides amino acids can occur following the favorable trend: **Tec** > **Sec** >> **Cys**

→ kinetically, the *β*-elimination reactions of R= **Hg**Me compounds are more favorable than the R= Me molecules

→ This information helps us to better understand the **MeHg** toxicity



Dha

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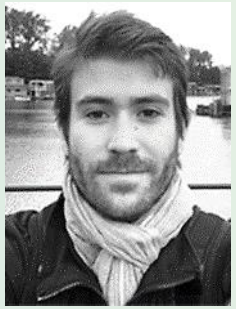
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FAPERGS

CAPES - PrInt

CAPES

ISCRA
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