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September 25, 2024

1 Results and Discussion

Our comprehensive study on the wild type and variants demonstrates the evolution of glutathione peroxidase protein 6 cys and selenium protein. Despite the differences in the cysteine and selenocysteine parameters in the system, they show a wide range of associated evolutionary pathways. We first optimized the reaction, one step in a stepwise mechanism going from selenol to selenolate of selenocysteine and from thiol to thiolate ion in the case of cysteine, while setting up the Empirical Valence Bond Simulation. The substrate hydrogen peroxide was placed at the distance from selenocysteine/cysteine and glutamine83 as mentioned in the QM/MM calculations by Morokuma.

1.1 Free Energy Changes

Here, we present the free energy changes for the wild type and mutant systems. The table below summarizes the mean free energy values (Mean dG* and Mean dG0) for the systems we analyzed.

System	Mean dG* (kcal/mol)	Mean dG0 (kcal/mol)
WT-Mouse Cys	16.45 ±- 0.56 kcal/mol	-59.70 ±- 1.54 kcal/mol
WT-Human Sec	13.69 ±- 0.95 kcal/mol	-64.82 ±- 1.69 kcal/mol
S47A,F48Y,T54Q,R99C	19.34 ±- 0.58 kcal/mol	-47.63 ±- 2.85 kcal/mol
F48Y,T52A,T54Q,R99C	19.83 ±- 0.72 kcal/mol	-39.63 ±- 2.80 kcal/mol
S47A,F48Y,T52A,R99C	18.03 ±- 0.62 kcal/mol	-52.45 ±- 2.62 kcal/mol
S47A,T52A,T54Q,R99C	14.40 ±- 0.80 kcal/mol	-61.56 ±- 2.70 kcal/mol
S47A,F48Y,T52A,T54Q	17.78 ±- 0.89 kcal/mol	-57.35 ±- 2.19 kcal/mol
Mouse Cys - S47A,F48Y,T52A,T54Q,R99C	16.27 ±- 0.50 kcal/mol	-62.54 ±- 1.60 kcal/mol
Mouse Sec - S47A,F48Y,T52A,T54Q,R99C	12.21 ±- 0.62 kcal/mol	-69.17 ±- 1.64 kcal/mol
Human Cys - A47S,Y48F,A52T,Q54T,C99R	12.31 ±- 0.51 kcal/mol	-52.07 ±- 3.12 kcal/mol
S47A	14.36 ±- 0.51 kcal/mol	-60.44 ±- 2.41 kcal/mol

Table 1: Free Energy Changes

All the systems listed have positive dG* values, indicating that the processes are non-spontaneous under the experimental conditions. All systems exhibit

negative dG0 values, suggesting that they are spontaneous under standard conditions. The variability in dG0 values among the mutant systems suggests that the specific mutations (e.g., S47A, F48Y) can significantly influence the free energy changes, potentially reflecting changes in stability or interactions within the system.