

Theoretical Modelling of Selenuranes Substitution Reactions

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Unregulated activity of cysteine proteases is related to the development of several pathologies, which makes them valuable targets for the design of inhibitors. Although hypervalent selenium compounds have shown potent inhibition of cysteine proteases, details of the reaction mechanism are not yet well understood. Moreover, the nature of selenium reactive species in solution under physiological conditions is not known. It has been proposed that the inhibition occurs through the ligand exchange reaction between the enzyme's thiol group and the chalcogen atom. Herein, efforts to clarify the reactivity profile of selenuranes in a multi-nucleophile medium were performed. Possible substitution reactions mechanism for chlorinated selenurane ((R)₂Se(Cl)₂) with H₂S, cysteine, glutathione and H₂O were investigated. Optimized molecular geometries were obtained using DFT along the B3LYP functional and a 6-311+G(d) basis set using the Gaussian09 and Orca v3.03 codes. Solvation effects were included by using the SMD implicit solvation model. Results for (Ph)₂Se(Cl)₂ in basic pH indicate a favorable two-step mechanism consisting on an initial thermodynamically favorable substitution of Cl⁻ by OH⁻ followed by a further replacement of OH⁻ by a thiol group. In these pH conditions a double Cl⁻ substitution reaction by OH⁻ has a $\Delta G_{\text{rxn}} = -68$ kcal/mol while a double substitution by SH⁻ as the nucleophile has a $\Delta G_{\text{rxn}} = +28$ kcal/mol. Therefore, at high pH the (Ph)₂Se(OH)₂ species is favored by a large 96 kcal/mol difference when compared to the (Ph)₂Se(SH)₂ species. However, the substitution reactions are strongly pH dependent and in acid pH (using protonated nucleophiles) the equilibrium favors the (Ph)₂Se(SH)₂ species by 25 kcal/mol. Several other substitution routes were investigated that enabled us to paint a picture of the equilibrium species in solution as a function of pH. Preliminary results for reaction profiles support a view that Cl⁻ gets quickly replaced by OH⁻, followed by a single or double substitution reaction by SH⁻ with an appreciable barrier.