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Selenuranes as Cysteine Protease Inhibitors: Theorical Investigation on Model Systems

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Abstract : In the last four decades the biological activities of selenium compounds has received great attention, particularly for hypervalent derivates from selenium (IV) used as enzyme inhibitors. The unregulated activity of cysteine proteases are related to the development of several pathologies, such as neurological disorders, cardiovascular diseases, obesity, rheumatoid arthritis, cancer and parasitic infections. These enzymes are therefore a valuable target for designing new small molecule inhibitors such as selenuranes. Even tough there has been advances in the synthesis and design of new selenuranes based inhibitors, little is known about their mechanism of action. It is a given that inhibition occurs through the reaction between the thiol group of the enzyme and the chalcogen atom. However, several open questions remain about the nature of the mechanism (associative vs. dissociative) and about the nature of the reactive species in solution under physiological conditions. In this work we performed a theoretical investigation on model systems to study the possible routes of substitution reactions. Nucleophiles may be present in biological systems, our interest is centered in the thiol groups from the cysteine proteases and the hydroxyls from the aqueous environment. We therefore expect this study to clarify the possibility of a route reaction in two stages, the first consisting of the substitution of chloro atoms by hydroxyl groups and then replacing these hydroxyl groups per thiol groups in selenuranes. The structures of selenuranes and nucleophiles were optimized using density function theory along the B3LYP functional and a 6-311+G(d) basis set. Solvent was treated using the IEFPCM method as implemented in the Gaussian 09 code. Our results indicate that hydrolysis from water react preferably with selenuranes, and then, they are replaced by the thiol group. It show the energy values of -106,0730423 kcal/mol for dople substituition by hydroxyl group and 96,63078511 kcal/mol for thiol group. The solvatation and pH reduction promotes this route, increasing the energy value for reaction with hydroxil group to -50,75637672 kcal/mol and decreasing the energy value for thiol to 7,917767189 kcal/mol. Alternative ways were analyzed for monosubstitution (considering the competition between Cl, OH and SH groups) and they suggest the same route. Similar results were obtained for aliphatic and aromatic selenuranes studied.

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