Investigation of substitution reactions on Selenuranes relevant to their biological activity on cysteine proteases.

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INTRODUCTION

Unregulated activity of cysteine proteases are related to the development of several pathologies, which makes them valuable targets for the design of inhibitors[1-3]. Although hypervalent selenium compounds have shown potent inhibition of cysteine proteases, the mechanism of reaction is not yet well understood, and the nature of selenium reactive species in solution under physiological conditions is not known[4]. It has been proposed that the inhibition occurs through the ligand exchange reaction between enzyme´s thiol group and the chalcogen atom[4]. Herein, efforts to clarify the reactivity profile of selenuranes in a multi-nucleophile medium were performed. In this approach, possible substitution reactions routes of a selenurane with H_2S, cysteine, glutathione and H_2O were studied. Effect of PH and the possibility of having water molecules explicitly participating in the reaction coordinate were also investigated.

METHODS

All optimized molecular geometries were obtained using Density Functional Theory along the B3LYP functional and 6-311+G(d) basis set using the Gaussian09 code. Reaction barrier estimates for the proposed mechanism were obtained by using relaxed geometry scans with the same basis set and functional as implemented in the Orca v3.03 code. Solvation effects were accounted for by using the SMD implicit solvent model.

RESULTS AND DISCUSSION

We found that the associative-dissociative mechanism is more favorable than the dissociative-associative mechanism for aliphatic and aromatic selenuranes. Results for the Cl^- by OH^- substitution reaction presented a barrierless path, whereas Cl^- by SH^- and OH^- by SH^- substitution have barriers. Our results suggest a two steps mechanism where the first step consists on the nucleophile attack while the second step consists on a subsequent rearrangement to seesaw geometry and departure of a leaving group. Nucleophile attack happens on the opposite side of the leaving group, except on the Cl^- by OH^- substitution reaction where the attack occurs on the same side. For OH^- by SH^- substitution reaction, a distinct oxidized intermediary is formed having Se bound to only tree substituents, $(CH_3)_2$ and Oxygen.

CONCLUSIONS

Starting from $R_2Se(Cl)_2$, chlorine is rapidly substituted by OH forming a Selenodiol compound. Depending on environment conditions (low pH, excess thiol) a Selenothiol derivative can be formed with barriers in the range of 13 – 16 kcal/mol. In all cases the associative mechanism had a lower energy barrier. Changes in mechanism due to explicit water or H_3O^+ participating in the reactive complex were minor for most systems. An exception happens for the Cl^- by OH^- substitution reaction where the explicit water has a stronger role in defining the orientation attack.

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