S-Nitrosothiol–Thiol Reactions of Biological Significance: Computational Modeling of *S*-Thiolation Pathway

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Nitric oxide (NO) is a signaling molecule of great biochemical and pharmacological interest. NO can also exist in a reduced state as nitroxyl (HNO) that also exhibits unique biological effects, different from NO. However, evidence of endogenous production of HNO in living cells is still inconclusive due to high reactivity of this molecule. One of the possible pathways of HNO formation can be through S-thiolation reaction of thiols with *S*-nitrosothiols (RSNOs) ubiquitous in biological environment. However, RSNOs usually tend to undergo a competing trans-*S*-nitrosation reaction rather than *S*-thiolation. Unfortunately, RSNOs are challenging to investigate not only experimentally but also computationally—due to the complex and unusual electronic structure of –SNO group, their calculated geometry and energetic properties are highly dependent on the method and the basis set used.

In this contribution, we present a computational model of S-thiolation reaction pathway calculated in the gas phase and polar solvents (diethyl ether and water) that mimic biological environment with and without explicit water molecules with density functional theory using standard global (PBE0) and range-separated (ωB97XD) hybrid functionals. Gas-phase calculations reveal that S-thiolation reaction has high energetic barrier ~48 kcal mol^{-1} with the significant open shell character of transition state due to the electron-coupled proton transfer nature of the first step of the reaction. However, water-assisted S-thiolation reactions in polar aqueous environment have much lower barriers, ~25 kcal mol^{-1} which makes formation of HNO plausible at physiological conditions especially when catalyzed by charged residues in proteins. Furthermore, we computationally identified the amino acid residues that can promote HNO formation and demonstrate a theoretical enzyme that can catalyze formation of HNO with energetic barrier of only ~7 kcal/mol.