

# ABSTRACT

## STABILITY OF THE S-N BOND IN S-NITROSOTHIOLS: COMPUTATIONAL AND EXPERIMENTAL APPROACH

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S-Nitrosothiols (RSNOs) are chemical compounds capable to transport nitric oxide (NO) and show promise in the treatment of cardiovascular diseases. RSNOs occur naturally *in-vivo*, and others have been synthesized *in-vitro* as potential drug candidates for NO transport and release. However, RSNOs are inherently unstable due to their weak S–N bond ( $D_0(\text{S-N})=25\text{--}30$  kcal/mol), so developing a deeper understanding of the factors influencing the RSNOs stability is crucial.

In Chapter 2, we investigated the substituent effect on the -SNO group properties. Substituting R– in RSNOs with more electro-donating character can stabilize the -SNO group according to the Natural Resonance Theory (NRT). But modeling the RSNOs is a complex task requiring usage of CCSD(T)/CBS<sub>(Q-5)</sub> or CCSD(T)-F12a/CBS<sub>(T-Q)</sub> methods with the inclusion of different corrections (core-valence( $\Delta\text{CV}$ ), scalar relativistic( $\Delta\text{SR}$ ), spin-spin coupling( $\Delta\text{SO}$ ), and high order corrections( $\Delta\text{HO}$ )) to predict properties of RSNOs accurately, specifically  $r(\text{S-N})$  and  $D_0(\text{S-N})$ . Here, H-SNO, H<sub>3</sub>C-SNO, H<sub>3</sub>Si-SNO were studied using high-level coupled cluster methods, CCSD(T)/CBS<sub>(Q-5)</sub> and CCSD(T)-F12a,b,c/CBS<sub>(T-Q)</sub>, with various basis sets, *cc-pVnZ-F12* and *aug-cc-pV(n+d)Z* (where n=D, T, Q and 5 (for *aug-cc-pV(5+d)Z*) with the addition of various corrections to correlation effects ( $\Delta\text{CV}$ ,  $\Delta\text{SR}$ ,  $\Delta\text{SO}$ ,  $\Delta\text{HO}$ ). It was found that  $r(\text{S-N})$  is longer in the *cis*-H<sub>3</sub>Si-SNO and *cis*-H-SNO than in the *cis*-H<sub>3</sub>C-SNO. Additionally,  $D_0(\text{S-N})$  is higher in the *cis*-H<sub>3</sub>C-SNO than in the *cis*-H-SNO and *cis*-H<sub>3</sub>Si-SNO.

In Chapter 3, experimentally, Ph<sub>3</sub> SiSNO and *i*-Pr<sub>3</sub> SiSNO were synthesized and characterized at temperatures below  $-35$  °C. These silicon-containing RSNOs are stable at  $-45$  °C but begin to decompose above  $-41$  °C. Variable-temperature NMR studies determined the rotational energy barrier for *cis*-*trans* isomerization of Ph<sub>3</sub> SiS<sup>15</sup>N to be approximately 8.60 kcal/mol, which is 3–4 kcal/mol lower than for carbon-substituted RSNOs. UV-Vis spectroscopy and TD-DFT calculations supported the formation of these compounds. The EPR spectroscopy at 77 K was used to study the relatively stable Ph<sub>3</sub> SiS<sup>•</sup> and *i*-Pr<sub>3</sub> SiS<sup>•</sup> radicals.

In Chapter 4, DFT and NBO analyses provided insights into the electronic origins of the observed instability of silicon-substituted RSNOs. Hyperconjugative interactions, specifically  $n(\text{S}) \rightarrow \sigma^*(\text{Si-H})$ , play a crucial role in modulating the properties of the -SNO group. Deletion of these interactions led to a decrease in the S–N bond length ( $\sim 0.05$  Å) and an increase in bond dissociation energy, indicating that the silicon atom enhances interactions  $n(\text{S}) \rightarrow \sigma^*(\text{Si-H})$  that weakens the S–N bond strength. A correlation was established between the electronegativity of the substituent and the S–N bond strength; increase in electronegativity decreases the bond strength due to increased hyperconjugative  $n(\text{S}) \rightarrow \sigma^*(\text{R-X})$  interactions.

In Chapter 5, we are expanding investigation on the crucial influence of non-covalent interaction with  $\sigma$ -hole of Sulfur on stability of S-Nitrosothiols using the high-level ab initio and DFT methods. It was found that  $\pi$  systems can interact with -SNO group via  $\sigma$ -hole of sulfur. Such interaction promotes the partial double bond character in the S–N bond, or promotion of D resonance structure, and simultaneously reduces the ionic character of RS<sup>•</sup>/NO<sup>+</sup> (which destabilizes the -SNO group). Additionally, our calculation predicts that in the protein environment interaction of  $\pi$  systems with  $\sigma$ -hole of -SNO group tends to profoundly effect on the -SNO group properties (electronic structure and reactivity).