Synthesis and Model Studies on Biologically Relevant Reactions of Reactive Supersulfides Utilizing Molecular Cavities

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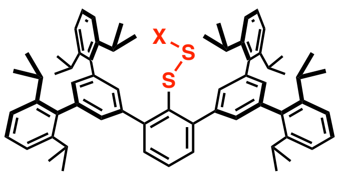
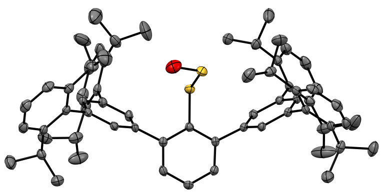
Reactive supersulfides, such as perthiosulfenic acid (R-SSOH) and *S*-nitrosodithioperoxol (R-SSNO), generated via oxidative modification of dithioperoxol (R-SSH) have been proposed as important intermediates in redox regulation and signal transduction. However, synthetic examples of stable compounds of reactive supersulfides have not been reported due to their susceptibility to decomposition via bimolecular reactions. Previously, we developed cavity-shaped substituents, the Bpq and Bpsc groups, which can effectively suppress undesired bimolecular reactions while maintaining sufficient space around the central functionality. In this study, we successfully synthesized and isolated several kinds of reactive supersulfides by utilizing these protective groups. Furthermore, we conducted model studies on biologically relevant reactions.

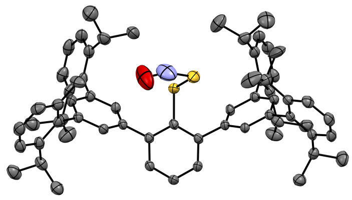
R-SSOH has been attracting much attention as a novel class of intermediates in redox regulation.[1] However, the synthesis of R-SSOH is challenging due to its inherent instability. Inspired by the synthetic approach for R-SOH, we successfully synthesized Bpq-SSOH by the thermal decomposition of a thiosulfinate precursor. R-SSNO has been postulated to be involved in nitric oxide release in biological systems.[2] However, as with R-SSOH, there has been no example of even observation of the species due to its instability. After careful optimization of reaction conditions, nitrosation of Bpq-SSH using ethyl nitrite at −30 °C provided Bpq-SSNO, presenting the first synthesis of the stable R-SSNO. Model studies using R-SSNO (R = Bpq or $BpqCH_2$) provided chemical evidence supporting the NO-release mechanism postulated in biological investigation. We also discovered a spontaneous desulfurization of R-SSNO yielding R-SNO, a reaction pathway that had not been anticipated in either chemistry or biology.



Bpq-SSX (X = OH, NO)



Bpq-SSOH



Bpq-SSNO

1) D. E. Heppner, M. Hristova, T. Ida, A. Mijuskovic, C. M. Dustin, V. Bogdándi, J. M. Fukuto, T. P. Dick, P. Nagy, J. Li, T. Akaike, A. Vliet, *Redox Biol.* **2018**, *14*, 379. 2) J. Zarenkiewicz, C. Perez-T., V. Kojasoy, C. McGinity, V. S. Khodade, J. Lin, D. J. Tantillo, J. P. Toscano, A. J. Hobbs, M. J. Fukuto, *Free Radical Biol. Med.* **2022**, *188*, 459.

