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# Thionitrite and Perthionitrite in NO Signaling at Zinc

Valiallah Hosseininasab, Jeffery A. Bertke, and Timothy H. Warren*

**Abstract:** NO and $H_2S$ serve as signaling molecules in biology with intertwined reactivity. HSNO and HSSNO with their conjugate bases $^-$SNO and $^-$SSNO form in the reaction of $H_2S$ with NO as well as *S*-nitrosothiols (RSNO) and nitrite ($NO_2^-$) that serve as NO reservoirs. While the elusive nature of HSNO and HSSNO renders their study challenging, their conjugate bases form isolable zinc complexes $^{Ph,Me}$TpZn(SNO) and $^{Ph,Me}$TpZn(SSNO) supported by tris(pyrazolyl)borate ligands. Reaction of Na(15-C-5)SSNO with $^{Ph,Me}$TpZn($ClO_4$) provides $^{Ph,Me}$TpZn(SSNO) that undergoes S-atom removal by $PEt_3$ to give $^{Ph,Me}$TpZn(SNO) and S=$PEt_3$. Unexpectedly stable at room temperature, these Zn-SNO and Zn-SSNO complexes release NO upon heating. $^{Ph,Me}$TpZn(SNO) and $^{Ph,Me}$TpZn(SSNO) quickly react with acidic thiols such as $C_6F_5SH$ to form $N_2O$ and NO, respectively. Increasing the thiol basicity in p-substituted aromatic thiols $^{4\text{-}X}$ArSH in the reaction with $^{Ph,Me}$TpZn(SNO) turns on competing *S*-nitrosation to form $^{Ph,Me}$TpZn-SH and RSNO, the latter a known precursor for NO.

Nitric oxide (NO) serves as a key signaling molecule in biology that is involved functions including vasodilation, neurotransmisssion and cytoprotection.[1] Intriguingly, $H_2S$ functions as a separate gasotransmitter that exhibits similar physiological effects as NO.[2] Endogenously produced $H_2S$ functions as a relaxant of smooth muscle cells and as a vasodilator.[3] Strong cellular communication involving NO and $H_2S$ suggests a mutually dependent mechanism of action between these two gasotransmitters.[4] The chemical basis for this crosstalk may be related to the reaction between $H_2S$ and NO and its counterparts *S*-nitrosothiols (RSNOs) and nitrite ($NO_2^-$) to form HSNO, the smallest *S*-nitrosothiol (Figure 1a).[5]

HSNO is an incredibly reactive species whose instabilty poses challenges in understanding its biochemistry and mechanisms of action.[6] Its reactivity may derive from the elongated S-N bond of 1.852 Å in trans-HSNO,[7] the longest among regular RSNOs with typical S-N distances of 1.70 - 1.80 Å (Figure 1b).[7] Contrary to typical RSNOs, HSNO easily diffuses through cell membranes and acts as a nitrosating agent for large proteins.[5c] HSNO may serve as a precursor for multiple downstream products connecting to NO signaling that includes HNO and $SSNO^-$.[6] Moreover, $SSNO^-$ also particpates in NO signaling and thiol trafficking pathways, formed in the reaction of RSNOs and $H_2S$ via unstable HSNO.[5a, 6]

Owing to their high acidity, HSNO and HSSNO likely exist as thionitrite ($SNO^-$) and perthionitrite ($SSNO^-$) under physiological conditions (calculated pKa's = 3.5 and 0.2, respectively for *syn*-isomers).[8] Charge balance by non-interacting cations enables isolation and X-ray characterization of [PPN][SNO] and [PPN][SSNO] (PPN = bis(triphenylphosphine)iminium). [PPN][SSNO] forms in the reaction of [PPN][$NO_2$] with elemental sulfur and undergoes desulfurization by triphenylphosphine to give [PPN][SNO].[9]

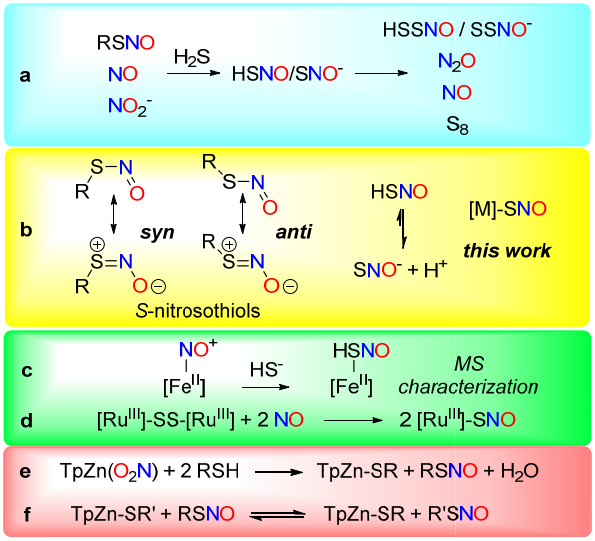


***Figure 1***. (a) Formation and reactivity of HSNO/$SNO^-$. (b) S*yn*- and *anti*-isomers for RNSOs and HSNO. (c, d) Transition metal complexes of HSNO/$SNO^-$ detected via mass spectrometry. (e) Reaction of $NO_2^-$ and thiols at TpZn sites to form RSNOs. (f) Transnitrosation reactions at TpZn-SR' complexes with RSNOs.

The coordination chemistry of HSNO/$SNO^-$ with biologically relevant metal centers is complex and not well understood.[10] Nitrite reduction at an iron(II) porphyrin results in the formation of an [$Fe^{III}$]-NO species that undergoes reaction with $HS^-$ proposed to give [$Fe^{II}$](HSNO) observed via high resolution cryospray ESI-TOF (Figure 1c).[11] Addition of $NO^+$ to a copper(I) hydrosulfide [$Cu^I$]-SH generates $N_2O$ and $S_8$, thought to proceed via an unstable {[$Cu^I$](HSNO)}$^+$ adduct.[12] Additionally, the disulfido complex[(edta)$Ru^{III}$-S-S-$Ru^{III}$(edta)]$^{4-}$ reacts with NO to give [(edta)$Ru^{III}$(SNO)]$^{2-}$ characterized by mass spectrometry (Figure 1d).[13]

$H_2S$ and NO species play important roles in zinc biochemistry. When exposed to $H_2S$, some zinc finger proteins undergo persulfidation (-SCys to -SSCys)[14] that releases structural $Zn^{2+}$ ions, but only under aerobic conditions and when the zinc sites are exposed and not enshrouded by RNA binding.[15] Carbonic anhydrase can convert carbonyl sulfide (COS) to $H_2S$,[16] inhibiting $CO_2$ hydration. Inspired by the generation of NO from $NO_2^-$ at carbonic anhydrase,[17] TpZn models of its $His_3Zn^{2+}$ active site reveal that thiols RSH react with zinc-bound nitrite to generate NO via thermally sensitive *S*-nitrosothiols RSNO (Figure 1e). Emulating the activation of $His_3Zn^{2+}$ via the cleavage of the Zn-SCys linkage,[18] TpZn-SR' complexes undergo reversible transnitrosation with *S*-nitrosothiols (RSNO) (Figure 1f).[19] Employing similar TpZn models, we examine the interaction of $SNO^-$ and $SSNO^-$ at Zn to explore their reactivity patterns that can inform the biochemistry of these species that result from NO / $H_2S$ crosstalk.

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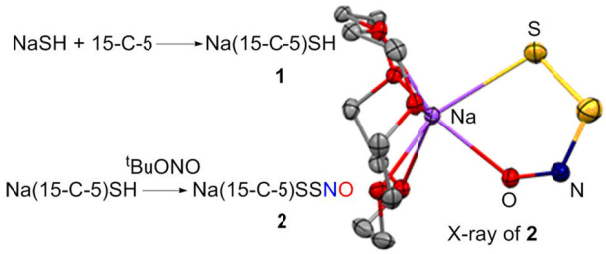


***Figure 2***. Synthesis and X-ray structure of Na(15-C-5)SSNO (**2**).

A synthetically versatile source of the $SSNO^-$ anion results from crown ether complexation of its sodium salt. Addition of 1 equiv. $^t$BuONO to Na(15-C-5)SH (**1**) (obtained from addition of 15-C-5 to NaSH in MeOH) in fluorobenzene leads to rapid development of a dark red color. Crystallization from fluorobenzene yields Na(15-C-5)SSNO (**2**) as red crystals in 42% yield (Figure 2). X-ray diffraction analysis shows $\kappa^2$-S,O binding of the $SSNO^-$ anion to sodium with Na-S and Na-O distances of 2.889(4) and 2.378(7) Å (Figures 2 and S25). The S-S, S-N, and N-O bond distances of 1.982(3), 1.655(5), and 1.269(6) Å are in agreement with the reported values for the free $SSNO^-$ anion in [PPN][SSNO] (S-S 1.9750(9), S-N 1.696(3), N-O 1.246(3) Å)[9] as well as the potassium salt K(18-C-6)[SSNO] (S-S 1.9526(9), S-N 1.669(2), N-O 1.247(2) Å) isolated upon NO addition to a nickel-sulfide [$Ni^{II}$]-S-K(18-C-6).[20]

Addition of Na(15-C-5)SSNO (**2**) to a solution of $^{Ph,Me}$TpZn($ClO_4$)[21] in dichloromethane leads to a rapid color change from dark red to light orange. Crystallization from THF affords $^{Ph,Me}$TpZn(SSNO) (**3**) in 51% yield (Figure 3). The X-ray structure of **3** reveals $\kappa^2$-S,O binding of the $SSNO^-$ anion to the zinc center with Zn-S and Zn-O distances of 2.3132(9) and 2.302(3) Å. Such symmetric $\kappa^2$-S,O binding of the perthionitrite anion at zinc as compared to the sodium salt **2** likely reflects the much greater thiophilicity of zinc. On the other hand, the S-S, S-N and N-O bond lengths for **3** of 1.9826(15), 1.666(4) and 1.232(4) Å, respectively, are quite similar to those in free $SSNO^-$.[9]

Comparison of IR spectra of $^{Ph,Me}$TpZn(SSNO) (**3**) and its $^{15}$N-isotopologue $^{Ph,Me}$TpZn(SS$^{15}$NO) (**3-$^{15}$N**) allowed assignment of S-N and N-O stretches at 686 and 1330 $cm^{-1}$ for **3**. Coordination to Zn results in a strengthening of both the S-N and N-O bonds relative to Na(15-C-5)SSNO (**2**) which appear at 677 and 1313 $cm^{-1}$, respectively. The UV-vis spectrum of **3** in dichloromethane shows a band centered at $\lambda_{max}$ = 402 nm (1800 $M^{-1}cm^{-1}$), shifted towards lower wavelengths relative to **2** ($\lambda_{max}$ = 427 nm (5330 $M^{-1}cm^{-1}$)). The $^{15}$N NMR spectrum of **3** in MeCN exhibits a resonance at 641.3 ppm compared to 706.7 ppm for Na(15-C-5)SSNO (**2**).

Addition of an equimolar amount of triethylphosphine to $^{Ph,Me}$TpZn(SSNO) (**3**) in dichloromethane leads to a color change from light orange to reddish-green that affords light pink $^{Ph,Me}$TpZn(SNO) (**4**) in 52% crystallized yield (Figure 3). X-ray analysis reveals both syn and anti conformers that exhibit positional disorder. The anti conformer is the major species (75%) with $\kappa^1$-S binding (Zn-S 2.250(3)Å, Zn-S-N = 94.7(4)°) while the syn conformer (25%) exhibits $\kappa^2$-S,O binding of the thionitrite group (Zn-S 2.254(8), Zn-O, 2.302(3) Å, Zn-S-N = 112.2(8)°). Notably, the Zn-S bond in each conformer of **4** is shorter than that of the corresponding perthionitrite **3**. The S-N and N-O bond lengths in the anti (1.748(10), 1.206(10) Å) and syn (1.741(12), 1.211(12) Å) conformers of **4** are both shorter (S-N) and longer (N-O) than in organic derivatives such as the *S*-nitrosothiol $Ph_3CSNO$ (S-N, 1.792(5) Å, N-O, 1.177 Å).[22] The IR spectrum of **4** shows a S-N stretch at 717 $cm^{-1}$, higher than 650 $cm^{-1}$ reported for $Ph_3CSNO$. Moreover, the NO stretch for **4** at 1436 $cm^{-1}$ appears at lower energy than in $Ph_3CSNO$ (1514 $cm^{-1}$). The UV-vis absorption spectrum of **4** in $CH_2Cl_2$ shows a sharp band centered at 340 nm (4440 $M^{-1}cm^{-1}$) as well as a low intensity broad band feature at 578 nm (8 $M^{-1}cm^{-1}$). Such a low energy feature typically occurs in *S*-nitrosothiols such as $Ph_3CSNO$ (600 nm (39 $M^{-1}cm^{-1}$) in $CH_2Cl_2$).[22]

The $^1$H NMR spectrum of $^{Ph,Me}$TpZn(SNO) (**4**) in MeCN-$d_3$ confirms the presence of two isomers in an 85 / 15 ratio in solution at room temperature. Two sets of resonances appear for the pyrazole C-H (6.37 and 6.33 ppm) and pyrazole-Me (2.61

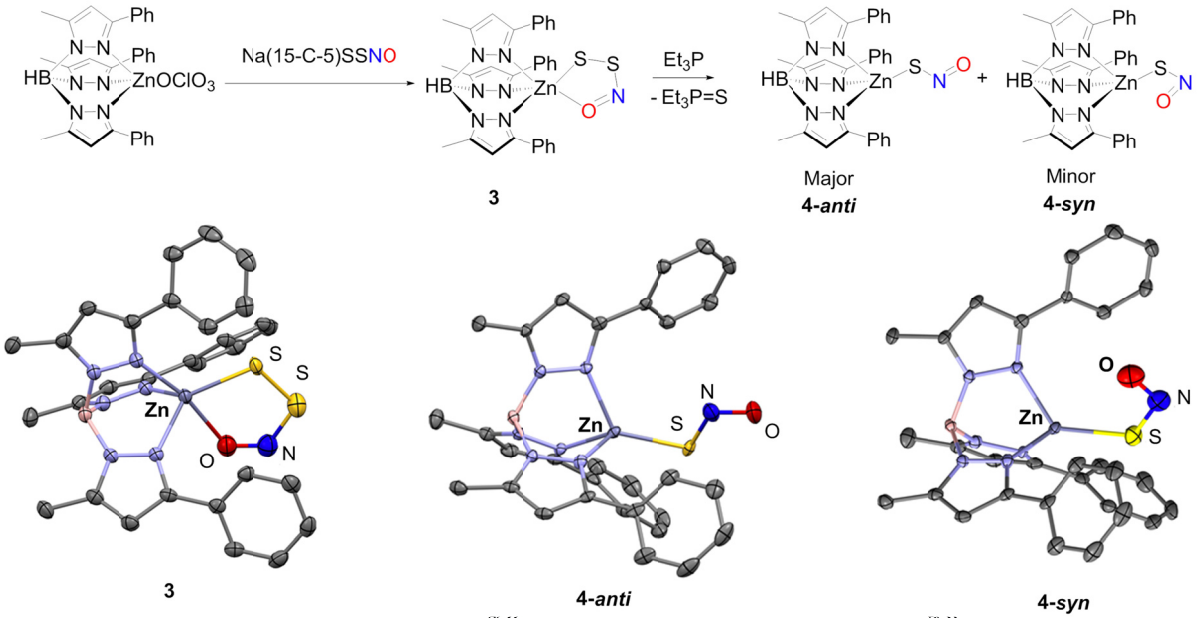


***Figure 3***. Synthesis and X-ray structures of $^{Ph,Me}$TpZn(SSNO) (**3**) and *syn* and *anti* isomers of $^{Ph,Me}$TpZn(SNO) (**4**).

and 2.58 ppm) groups that exhibit only modest broadening upon heating to 80 °C (Figure S12). This allows us to assign a barrier of more than 18 kcal/mol for the interconversion of the syn and anti-isomers of $^{Ph,Me}$TpZn(SNO) (**4**) in solution. This is markedly higher than the barrier for S-N bond rotation of 10.7 kcal/mol determined for the *S*-nitrosothiol $Ph_3CSNO$,[22] consistent with the stronger S-N bond in **4** revealed by IR spectroscopy. The $^{15}N$ NMR spectrum of **4** in MeCN-$d_3$ at RT reveals a single resonance centered at 836.6 ppm for the major isomer, similar in chemical shift for the anti conformer of $Ph_3CS^{15}NO$ (δ 843.8 (anti) and 754.8 (syn) ppm).[22]

Zinc perthionitrite and thionitrite complexes **3** and **4** are

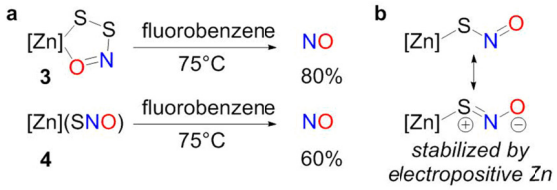


***Figure 4***. (a) Heating **3** and **4** to 75 °C slowly releases NO. (b) Enhanced S-N bond character in Zn-SNO species **4.**

quite thermally stable at room temperature. UV-vis studies in fluorobenzene reveal that they degrade slowly upon heating to 75 °C with half-lives of ca. 5 and 7 h, respectively, dramatically longer than the *S*-nitrosothiol $Ph_3CSNO$ ($t_{1/2}$ ≈ 10 min) under similar conditions. Analysis of the headspace gas in the thermolysis of 3 and 4 each reveal NO in 80 and 60% yield, respectively (Figure 4a). Unfortunately, these transformations did not follow well defined kinetics nor were we able to track the fate of the zinc complexes following NO release. The high thermal stability of the Zn-SNO complex **4** as compared to organic *S*-nitrosothiols RSNO may result from greater stabilization of the resonance form with increased S-N π-bond character due to the increased electropositive nature of Zn (Figure 4b). Both IR (higher ν(SN)) and NMR (higher barrier for S-N rotation) spectroscopy indicate strengthening of the thionitrite S-N bond upon coordination to an electropositive element such as zinc.

Owing to their biological significance, we examined the reactivity of $^{Ph,Me}$TpZn(SSNO) (**3**) and $^{Ph,Me}$TpZn(SNO) (**4**) with thiols. We examined aromatic thiols ArS-H for the ability to predictably modulate their acidity. Reaction of $^{Ph,Me}$TpZn(SSNO) (**3**) with the highly acidic thiol $C_6F_5SH$ at room temperature leads to a rapid color change from orange to light yellow. $^1H$ NMR analysis of the reaction confirms the formation of $^{Ph,Me}$TpZn-$SC_6F_5$ (**5**) in near quantitative yield (Figure 5a).

In the reaction between $^{Ph,Me}$TpZn(SSNO) (**3**) and the acidic thiol $C_6F_5SH$, we envision an acid-base exchange mechanism that releases HSSNO that subsequently converts to NO and $S_8$, known products in the decomposition of HSSNO.[5a, 23] Moreover, NO forms in 82% yield and we observe $S_8$ as well. Further supporting HSSNO formation via acid-base exchange from M-SSNO species, addition of 1 equiv. $CF_3COOH$ to sodium salt Na(15-C-5)SSNO (**2**) leads to NO formation in 78% yield also with observation of $S_8$ (Supporting Information Section S11). These reaction products are consistent with the decay of unstable HSSNO.[6a, 9b, 24]

Reaction of $^{Ph,Me}$TpZn(SNO) (**4**) with $C_6F_5SH$ appears to proceed by a similar acid-base mechanism with release of HSNO since $^{Ph,Me}$TpZn-$SC_6F_5$ (**5**) forms in near quantitative yield. Headspace gas analysis reveals that the reaction generates $N_2O$ estimated in 39% yield, assuming a reaction stoichiometry of [Zn](HSNO) : 1/2 $N_2O$ (Figure 5b). $S_8$ also forms as by-product. These observations are consistent with the formation of HSNO that leads to the transient generation of HNO which decays into $N_2O$.[5a, 6a, 9b, 24] Thus, protonation of the $SSNO^-$ and $SNO^-$ anions in zinc complexes **3** and **4** by the acidic thiol $C_6F_5SH$ leads to different signaling outputs, generating NO and HNO, respectively.

Reactions involving $^{Ph,Me}$TpZn(SSNO) (**3**) and $^{Ph,Me}$TpZn(SNO) (**4**) with thiols are quite sensitive to the thiol acidity. While the less acidic thiol $^{4\text{-}Me}$ArSH does not react with dithionitrite **3** in dichloromethane at RT, addition of $^{4\text{-}Me}$ArSH to $^{Ph,Me}$TpZnSNO (**4**) results in a slow reaction. $^1H$ NMR analysis after 5 h reveals formation of both $^{Ph,Me}$TpZn-$SAr^{4\text{-}Me}$ (75%) and $^{Ph,Me}$TpZn-SH[25] (21%) indicating two distinct pathways (Figures 5b and 6a). Suggesting HSNO formation, $N_2O$ gas forms (29% based on **4**) in addition to the disulfide $^{4\text{-}Me}$ArS-$SAr^{4\text{-}Me}$ (21% based on **4**) that likely arises from decomposition of the corresponding *S*-nitrosothiol $^{4\text{-}Me}$ArSNO[26] that forms along with $^{Ph,Me}$TpZn-SH. Following the reaction of $^{Ph,Me}$TpZn(SNO) (**4**) with $^{4\text{-}F}$ArSH by UV-vis spectroscopy confirms the initial formation of

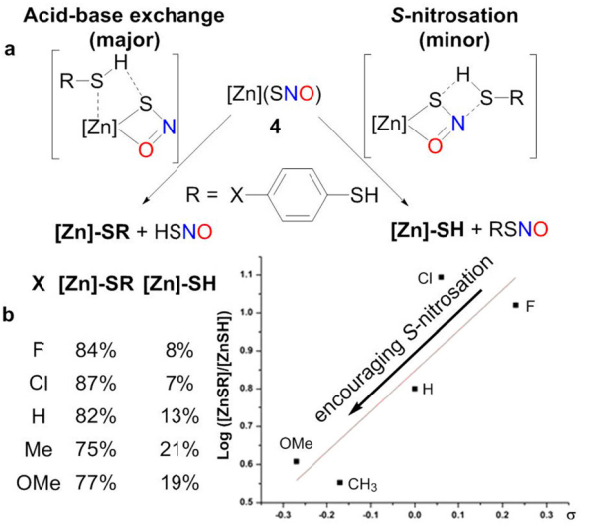


***Figure 6***. (a) Mechanistic pathways considered for the reaction of $^{Ph,Me}$TpZnSNO (**4**) and ArSH. (b) Hammett plot comparing [Zn]-SR and [Zn]-SH products upon reaction of [Zn](SNO) (**4**) with *p*-substituted thiols $^{4\text{-}X}$ArSH.

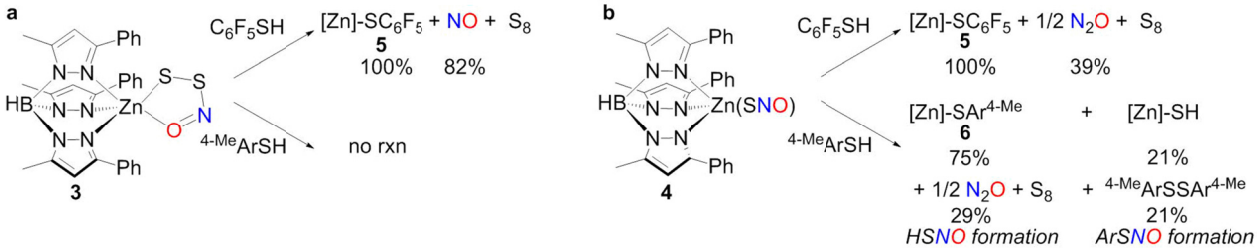


***Figure 5***. Reactivity of (a) $^{Ph,Me}$TpZn(SSNO) (**3**) and (b) $^{Ph,Me}$TpZn(SNO) (**4**) with $C_6F_5SH$ and $^{4\text{-}Me}$ArSH.

$^{4\text{-F}}$ArSNO (Figure S24).

We envisioned two competitive pathways for the reaction of $^{Ph,Me}$TpZn(SNO) (**4**) with aromatic thiols ArSH (Figure 6a). Acid-base exchange between $^{Ph,Me}$TpZnSNO (**4**) and ArSH leads to the formation of HNSO along with corresponding zinc thiolate $^{Ph,Me}$TpZn-SAr. HSNO released further decomposes to observed $N_2O$. Alternatively, $^{Ph,Me}$TpZn(SNO) (**4**) may undergo *S*-nitrosation with ArSH to form $^{Ph,Me}$TpZn-SH and the corresponding *S*-nitrosothiol ArSNO. Increasing thiol nucleophilicity in a series of thiols $^{4\text{-X}}$ArSH (X = F, Cl, H, Me, OMe) increasingly turns on thiol *S*-nitrosation, better competing with acid-base exchange as measured by ratios of $^{Ph,Me}$TpZn-SH (from *S*-nitrosation) and $^{Ph,Me}$TpZn-SAr$^{4\text{-X}}$ (from acid-base exchange) (Figure 6b).

Tris(pyrazolyl)borate zinc complexes $^{Ph,Me}$TpZn(SSNO) (**3**) and $^{Ph,Me}$TpZn(SNO) (**4**) enable the isolation, characterization and reactivity study of the perthionitrite and thionitrite anions at zinc. Unlike HSSNO and HSNO, these zinc complexes possess high stability, decomposing with NO release only after heating to 75 °C. In particular, [Zn](SNO) species **4** is much more stable than related *S*-nitrosothiols such as $Ph_3CSNO$, attributed to a stronger S-N interaction in **4** supported by IR and NMR spectroscopy. Importantly, $^{Ph,Me}$TpZn(SSNO) and $^{Ph,Me}$TpZn(SNO) each react with acidic thiols, releasing HSSNO and HSNO that ultimately form NO and $N_2O$, respectively. Nonetheless, increasing thiol nucleophilicity RSH turns on competing *S*-nitrosation in reactions with [Zn](SNO) complex **4** to release *S*-nitrosothiols RSNO. As *S*-nitrosothiols serve as mobile carriers for NO, this work illustrates subtle effects at play that control the signaling output of perthionitrite and thionitrite at zinc.

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## Conflict of interest

The authors declare no conflict of interest.

**Keywords:** Nitric oxide • *S*-nitrosothiol • Thionitrite • Zinc • Bioinorganic

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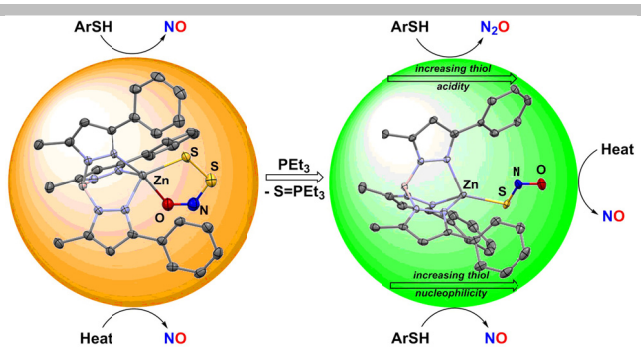
Layout 1:

# COMMUNICATION

NO and $H_2S$ serve as signaling molecules in biology with intertwined reactivity through formation of HSNO and HSSNO. Zinc complexes of their conjugate bases $^{Ph,Me}$TpZn(SNO) and $^{Ph,Me}$TpZn(SSNO) result in stabilization of these anions at a biologically relevant metal site yet reveal disparate signaling output upon reaction with thiols.

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**Thionitrite and Perthionitrite in NO Signaling at Zinc**