Reversible RS–NO bond cleavage and formation at copper(I) thiolates†

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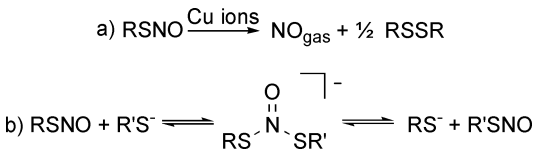
Two coordinate copper(I) thiolates IPrCu-SR undergo rapid, reversible transnitrosation with *S*-nitrosothiols RSNOs without catalyzing the loss of NO_{gas} from these biological carriers of NO.

S-Nitrosothiols RS–NO, first synthesized in 1909,[1] were not recognized until the 1990s as a biological source of nitric oxide.[2–4] They exhibit biological activities similar to NO itself including vasodilation and anti-platelet activity.[3,5] In contrast to NO which has a short lifetime (3–5 s) in the plasma owing to ready reaction with O_2 and O_2-carrying enzymes, cysteine- and peptide-based RSNOs circulate at near micromolar[6,7] levels (*e.g.* CysNO[8,9] $\approx$ 0.2–0.3 μM). Consistent with their modest RS–NO homolytic dissociation enthalpies of 20–32 kcal mol^{-1} determined by both theory and experiment,[10,11] these compounds are thermally and photochemically sensitive, releasing NO_{gas} and the disulfide RSSR (Scheme 1a).[12,13] *S*-Nitrosothiols may also serve as formal sources of NO^+ as in transnitrosation reactions between RSNOs and thiolate anions $R'S^-$ which proceed through nitroxyl disulfide intermediates $[RSNOSR']^-$ (Scheme 1b).[14,15]

Copper ions can be extremely efficient catalysts for the decomposition of *S*-nitrosothiols RSNOs to NO_{gas} and the corresponding disulfides RSSR (Scheme 1a).[12,16] In aqueous solution, Williams *et al.* have found that adventitious copper ions present in buffer solutions accelerate the rate of RSNO decomposition while the use of a Cu^{2+} chelator such as EDTA significantly halts this catalysis.[16,17] Copper containing enzymes also catalyze loss of NO from RSNOs and play a role in vasodilation,[18] anti-platelet aggregation[19] and regulation of intracellular RSNO levels.[20] For instance, CuZn-superoxide dismutase has been shown to catalyze the decomposition of RSNOs to NO.[21,22] This process is interrupted with neocuproine (2,9-dimethyl-1,10-phenanthroline), a potent chelator for copper(I). Copper catalysis also forms the basis of long-lived NO generation from medical devices containing polymer-bound Cu^{2+} ions which release NO upon contact with endogenous RSNOs in the plasma.[23,24]



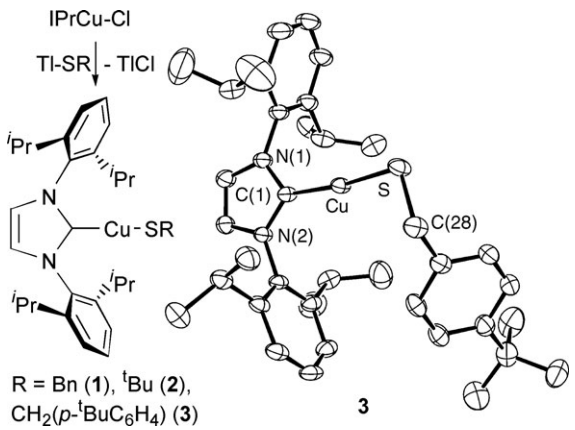
Scheme 1

To synthetically explore interactions between copper ions and RSNOs, we chose low-coordinate copper(I)-thiolates IPrCu-SR based on *N*-heterocyclic carbenes first reported by Gunnoe *et al.*[25] The unusually low coordination number of these metal-thiolates would appear to provide a clear opportunity for association of an RSNO with the copper center. In addition, copper(I)-thiolates would be expected to be considerably more thermally stable than the corresponding copper(II)-thiolates $[Cu^{II}]$-SR owing to their generally facile loss of disulfide RSSR with concomitant reduction to $[Cu^{I}]$ species.

Reaction of IPrCu-Cl[26] with TlSR in THF provides the two-coordinate IPrCu-SR (R = Bn[25] (**1**), ^{t}Bu (**2**), CH_2Ar^{tBu} (**3**)) complexes in good yields (70–78%) (Scheme 2). The X-ray structure of IPrCu-SCH_2Ar^{tBu} (**3**)‡ features a nearly linear C–Cu–S linkage (172.90(6)°) with a Cu–S distance of 2.130(1) Å, nearly identical to parameters reported in the X-ray determination of **1**.[25]

The addition of 1 equiv. BnSNO to IPrCu-SBn (**1**) or ^{t}BuSNO to IPrCu-S^{t}Bu (**2**) (each at *ca.* 55 mM) at room temperature in $CDCl_3$ results in no net change when monitored by ^{1}H NMR spectroscopy. Importantly, degradation of the *S*-nitrosothiols to the corresponding disulfides does not rapidly ensue. Addition of 1 equiv. BnSNO to IPrCu-S^{t}Bu (**2**), however, results in the immediate appearance of ^{t}BuSNO and IPrCu-SBn (**1**) with incomplete consumption of **2** and BnSNO. Thus a transnitrosation equilibrium is set up favoring **2** and BnSNO (K_{eq} = 0.25(5)) (Scheme 3).

Analogous transnitrosation reactions are significantly faster in benzene-d_6. In the degenerate exchange between 1 equiv.



Scheme 2

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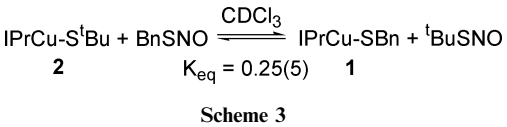


Scheme 3

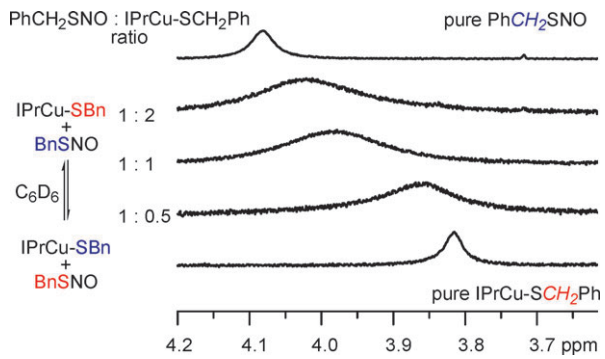


Fig. 1 ^{1}H NMR spectra (300 MHz, benzene-d_6, RT) illustrating fast, reversible transnitrosation between IPrCu-SCH$_2$Ph and PhCH$_2$SNO with increasing PhCH$_2$SNO : IPrCu-SCH$_2$Ph ratio (bottom to top).

each BnSNO and IPrCu-SBn (**1**) (40 mM in each component), only one broad resonance is observed for the combined SCH_2Ph resonances of the benzyl groups. Increasing the BnSNO : IPrCu-SBn (**1**) ratio results in a monotonic shift of the coalesced peak from δ 3.82 ppm (for **1**) to δ 4.08 ppm (for PhCH_2SNO) supporting fast exchange between these two species on the NMR timescale (Fig. 1). The rate of exchange is qualitatively related to the size of the *S*-substituent. Broadened, though still distinct, S^{t}Bu resonances are observed at δ 1.52 and 1.49 ppm in a 1 : 1 mixture of ^{t}BuSNO and IPrCu-S^{t}Bu (**2**) at RT (55 mM in each component). This indicates that transnitrosation is much slower owing to the considerably larger *S*-substituents.

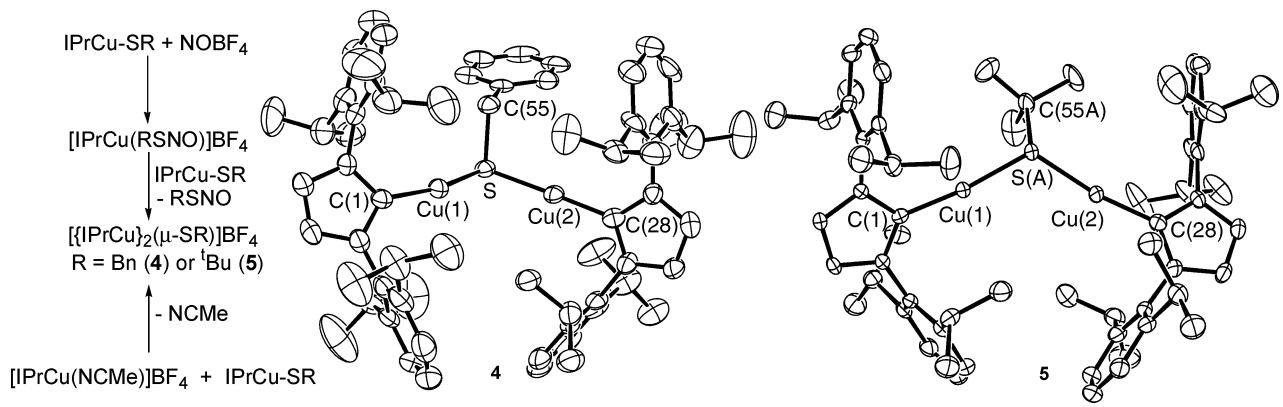
In an attempt to identify an intermediate in degenerate transnitrosation such as a nitroxyl disulfide [RSNOSR]$^-$, we carried out low temperature ^{15}N NMR studies in toluene-d_8 and chloroform-d_1 on both **1** and **3** in the presence of the respective ^{15}N-labeled *S*-nitrosothiols PhCH$_2$S^{15}NO and $^{t\text{Bu}}$ArCH$_2$S^{15}NO. We see no evidence for new ^{15}N-containing species other than *syn* and *anti* isomers of the respective *S*-nitrosothiols. In contrast, Estrin *et al.* observed a new upfield shifted ^{15}N-signal corresponding to a nitroxyl disulfide intermediate in a mixture of the cysteine ethyl ester anion with the corresponding RSNO species in methanol.[15] *S*-nitrosothiols exhibit *syn–anti* isomerization with a low barrier of S–N bond rotation of *ca.* 10 kcal mol^{-1}.[11,27]

No reaction between these copper(I) thiolates occurs in the presence of 1–10 equiv. anaerobic NO$_{gas}$ in CDCl$_3$. Addition of nitrosonium (NO$^+$) as NOBF$_4$, however, to colorless solutions of IPrCu-SBn (**1**) and IPrCu-S^{t}Bu (**2**) in CDCl$_3$ results in immediate formation of red and green solutions. These are the respective colors of the *S*-nitrosothiols BnSNO and ^{t}BuSNO. ^{1}H NMR spectroscopy verifies the formation of each *S*-nitrosothiol along with one new copper-containing species in each case (Scheme 4).

The new copper complexes are the dinuclear thiolates [{IPrCu}$_2$(μ-SR)]BF$_4$ (R = Bn (**4**) or ^{t}Bu (**5**)) which may be crystallized from each reaction mixture. Despite the bridging interaction, the Cu–S distances in **4**‡ (2.146(2) and 2.157(2) Å) and **5**‡ (2.185(5) and 2.164(4) Å) are not markedly different than found in the thiolates **1** (2.127(1) Å) and **3** (2.130(1) Å). The copper centers are separated by 3.575(1) and 3.732(1) Å with Cu–S–Cu angles of 112.34(7)° and 118.19(18)°. ^{1}H NMR spectra reveal upfield shifted thiolate resonances at δ 2.93 ppm (SCH_2Ph) and δ 0.58 ppm (S^{t}Bu), likely due to the ring current of the NHC ligands.

Based on these findings, reaction of NO$^+$ with **1** and **2** may generate an equivalent of *S*-nitrosothiol RSNO within the coordination sphere of copper (not spectroscopically observed) which could be formally displaced by another equivalent of IPrCu-SR to form dinuclear **4** and **5**. Consistent with this suggestion, reaction of {IPrCu(NCMe)}BF$_4$[28] with IPrCu-SR results in displacement of NCMe and isolation of **4** and **5** in 86 and 89% yield (Scheme 4).

Despite the important biological role of copper ions in the interconversion of NO$_{gas}$ and RSNOs,[18–22,29,30] these two-coordinate Cu(I) thiolates IPrCu-SR allow clean transnitrosation equilibria to be observed with RSNOs without catalyzing the loss of NO$_{gas}$. Moreover, we find that rate of transnitrosation is enhanced in non-polar solvents. The use of nitrosonium cation leads to the loss of RSNO from IPrCu-SR and generation of novel two-coordinate dicopper cations [{IPrCu}$_2$(μ-SR)]$^+$. Current studies target the interactions of RSNOs with other copper model complexes to illuminate the role of the copper coordination environment and oxidation state in the release of NO$_{gas}$ from RSNOs.



Scheme 4

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Notes and references

‡ Crystal data: **2**: $C_{38}H_{51}CuN_2S_1$, M = 631.39, monoclinic, $C2/c$, a = 29.689(3), b = 15.6315(13), c = 17.0794(14) Å, β = 94.8040(10)°, V = 7898.4(11) Å^3, Z = 8, T = 100(2) K, λ(Mo-Kα): 0.71073 Å, μ = 0.630 mm^{-1}, F(000) = 2704 (SQUEEZE refinement excluded 1/3 molecule pentane per **2**), 32 710 reflections collected, 8618 independent reflections, R_{int} = 0.0299, GoF = 1.078, R = 0.0405 [$I > 2\sigma(I)$], wR_2 = 0.1078 (all data).

4: $C_{61}H_{79}BCu_2F_4N_4S_1$, M = 1114.23, monoclinic, $C2/c$, a = 32.857(3), b = 12.3716(12), c = 31.680(3) Å, β = 95.4190(10)°, V = 12 820(2) Å^3, Z = 8, T = 100(2) K, λ(Mo-Kα): 0.71073 Å, μ = 0.745 mm^{-1}, F(000) = 4704 (SQUEEZE refinement excluded 1 molecule pentane per **4**), 46 584 reflections collected, 11 276 independent reflections, R_{int} = 0.1259, GoF = 0.898, R = 0.0684 [$I > 2\sigma(I)$], wR_2 = 0.1697 (all data).

5: $C_{58}H_{81}BCu_2F_4N_4S{\cdot}2OC_4H_8$, M = 1224.43, triclinic, $P\bar{1}$, a = 12.348(3), b = 17.138(4), c = 17.187(4) Å, α = 75.961(3)°, β = 75.033(3)°, γ = 72.937(3)°, V = 3303.9(14) Å^3, Z = 2, T = 100(2) K, λ(Mo-Kα): 0.71073 Å, μ = 0.731 mm^{-1}, F(000) = 1304, 32 174 reflections collected, 11 602 independent reflections, R_{int} = 0.0460, GoF = 1.059, R = 0.0503 [$I > 2\sigma(I)$], wR_2 = 0.1377 (all data).

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