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Published in:
Inorganic Chemistry

Link to article, DOI:
10.1021/ic301356h

Publication date:
2012

Document Version
Publisher's PDF, also known as Version of record

Link back to DTU Orbit

Citation (APA):

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A Copper(II) Thiolate from Reductive Cleavage of an S-Nitrosothiol

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Supporting Information

ABSTRACT: S-Nitrosothiols RSNO represent circulating reservoirs of nitric oxide activity in the plasma and play intricate roles in protein function control in health and disease. While nitric oxide has been shown to reductively nitrosylate copper(II) centers to form copper(I) complexes and ENO species (E = R2N, RO), well-characterized examples of the reverse reaction are rare. Employing the copper(I) β-diketiminate [Me2NN]Cu, we illustrate a clear example in which an RS–NO bond is cleaved to release NOgas with formation of a discrete copper(II) thiolate. The addition of Ph3CSNO to [Me2NN]Cu generates the three-coordinate copper(II) thiolate [Me2NN]CuSCPh3, which is unstable toward free NO.

S-Nitrosothiols RSNO play an intricate role in the control of protein function in health and disease through the post-translational modification of cysteine SH residues.1 Low-molecular-weight S-nitrosothiols such as S-nitrosoglutathione (GSNO) represent circulating reservoirs of nitric oxide activity typically present at submicromolar concentrations in the plasma,2 which have protective effects against myocardial3 and lung/airway3 injuries among other functions.1 RSNO compounds are prone to homolytic loss of NO due to the relative weakness of the RS–NO bond (20–32 kcal/mol)3 and the strength of the RS–SR bond (65–66 kcal/mol).5 Trace amounts of copper ions serve as effective catalysts for RSNO decomposition to form NOgas and RSSR (Scheme 1).6

Scheme 1. Copper-Catalyzed Release of NO from RSNO Compounds

CuZnSOD is the most abundant source of copper in red blood cells and is effective at releasing NO from GSNO.7 It may be inhibited with neocuproine, a copper(+) chelator, suggesting copper(I) as an active oxidation state for NO loss.7 Moreover, medical polymers with embedded copper(2+) ions serve as long-lived NO-generating devices via the copper-catalyzed decomposition of endogenous S-nitrosothiols.8 Copper enzymes also generate RS–NO bonds from NO via reductive nitrosylation (Scheme 2).9 CuZnSOD has been shown to specifically S-nitrosylate β-Cys93 of hemoglobin.10

Scheme 2. Redox Interconversion of RSNO and NO

- reduce nitrosylation (metal reduced)
- reductive E-NO cleavage (metal oxidized)

Ceruloplasmin, the enzyme carrying ca. 95% of all copper in the plasma,11 generates GSNO from NO.12 In other environments, NO reduces copper(2+) in cytochrome c oxidase13 and laccase14 with concomitant N–O bond formation to give nitrite upon the formal attack of water on NO+. In a related fashion, Cu(dmp)2(H2O)2+ reacts with NO in MeOH to give Cu(dmp)2+ and MeONO.15 Intramolecular nitrosylation of a coordinated amine ligand bound to copper(2+) upon exposure of NOgas16 represents a chemical trigger in turn-on fluorescence-based approaches to sense NO.17

We recently reported the microscopic reverse of this process in the reductive cleavage of the N–NO bond in the nitrosamine Ph3NNO by an electron-rich β-diketiminato copper(I) complex to give the copper(II) amide [Me2NN]-CuNPh2.18 We describe herein cleavage of the RS–NO bond of a synthetic S-nitrosothiol by copper(I) to form a discrete copper(II) thiolate connected to the copper-promoted generation of NO from this important class of NO donors.

The addition of 2 equiv of Ph3CSNO to [Me2NN]Cu1 (1) in toluene (ca. 0.1 M) at 0 °C results in the rapid (ca. 10 s) formation of a new blue species, [Me2NN]CuSCPh2 (2), with λmax = 731 nm that is unstable under the reaction conditions. Over the course of ca. 30 min, the solution turns green because of the final major product [Me2NN]Cu(ON[Me2NN]) (3) with λmax = 647 nm.

Crystallization of the reaction mixture involving 1 and Ph3CSNO allows for identification of the final green species 3. The highly soluble 3 [λmax = 647 nm (1700 M–1cm–1)] is isolated in 70% yield as green crystals from ether/hexamethyldisiloxane (Scheme 3). X-ray characterization of 3 (Figure 1) reveals a distorted square-planar copper(II) species with one “normal” and one nitrosated anionic β-diketiminate ligand in which the backbone methine hydrogen atom has undergone formal substitution by NO+.18 The π-delocalized nitrosated ligand coordinates through two different types of
Scheme 3. Reactivity of Ph3CSNO with 1

Because we anticipated the formation of 2 in the reaction of 1 with Ph3CSNO, we sought a convenient route for its independent synthesis. The addition of 1 equiv of ‘BuOOBu to 1 in toluene allows for the isolation of [Me2NN]CuOtBu (4) on a preparative scale in 86% yield (Scheme 3) as red crystals obtained from ether at −35 °C. The X-ray structure of 4 (Figure 1) reveals a planar, three-coordinate copper center due to the steric bulk of the tert-butoxy ligand. Related to Tolman’s β-diketiminate copper(II) phenoxides20 and our [Cl2NN]CuOtBu,21 4 possesses particularly short Cu−O [1.788(2) Å] and Cu−Nβ,δk distances [1.879(2) and 1.890(2) Å] with a Cu−O−C22 angle of 123.82(12)°. The reaction of 4 with HSCPh3 in toluene provides a smooth, quantitative conversion to 2 [λmax = 731 nm (5800 M−1cm−1)] in toluene. Crystals of thermally sensitive 2 may be obtained from ether at −35 °C. The X-ray structure of 2 (Figure 1) features a trigonally coordinated copper center with Cu−S [2.137(1) Å] and Cu−Nβ,δk distances [1.896(2) and 1.907(2) Å] along with a Cu−S−C angle of 116.80(7)° closely related to metrical parameters in Tolman’s [Cu2(d)SCPh3] complex employing an o-isopropyl-N-aryl variant of the β-diketiminato ligand.22a

Conceptually related, the tertiary thiolate 2 and alkoxide 4 possess subtle but important differences in their electronic structure. Each exhibits a nearly axial frozen-glass electron paramagnetic resonance (EPR) spectrum [2, Ω1 = 2.165(3), Ω2 = 2.039(8), Ω3 = 2.031(8); 4, Ω1 = 2.233(5), Ω2 = 2.06(1), Ω3 = 2.04(1)] and quasi-reversible cyclic voltammetry of 2 in tetrahydrofuran reveals that thiolate 2 is considerably easier to reduce (E1/2 = −0.18 V vs NHE) than alkoxide 4 (E1/2 = −0.52 V; Figures S10 and S11 in the SI). The rapid conversion of 2 to other species under its synthesis conditions from Ph3CSNO that leads to NO formation suggests that 2 is unstable toward NO (Scheme 3). We find that the addition of 2 equiv of Ph3CSNO to 1 at 0 °C in toluene is followed by the immediate flushing of the solution with N2 to remove all NO gas formed in the reaction, 2 may be observed in 73% spectroscopic yield (Scheme 4). Importantly, the addition of 2 equiv of NO to pure 2 leads to 3 (79% yield) and Ph3CSSCPh3 (83% yield) (Scheme 4). We have not detected any intermediates by UV−vis spectroscopy at −80 °C in toluene during the addition of Ph3CSNO to 1.

In conclusion, an electron-rich copper(I) complex reacts with RSNO species to give a well-defined [Cu2]SR complex with the
loss of NO\textsubscript{gas}. This reaction represents the microscopic reverse of reductive nitrosylation commonly observed at copper(II) species upon the addition of NO\textsubscript{gas} and sheds light on mechanistic possibilities in the copper-catalyzed interconversion of NO and RSNO species (Scheme 2). We note that NO reacts reversibly with oxidized type I copper sites in ceruloplasmin\textsuperscript{25} and ascorbate oxidase,\textsuperscript{26} returning to their mechanistic possibilities in the copper-catalyzed reductive cleavage and reductive nitrosylation at a β of clean CuSR reductive nitrosylation with NO gas. We are species upon the addition of NO gas and sheds light on

\section*{References}


(19) Closely related ligand nitrosylations have been previously observed at a copper(II) β-diketiminate complex (ref 18) as well as at Fe(II)-acac\textsuperscript{26} (a) and Co(acac)\textsuperscript{26} (b): (a) White, D. A. J. Am. Chem. Soc. A 1971, 233–243. (b) Herberhold, M.; Kratzer, H. Z. Naturforsch., Teil B 1977, 32B, 1263–1267.


