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Mechanistic insights into a copper–disulfide interaction in oxidation of imines by disulfides†

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The concept of using disulfides as an oxidant for Cu(I) is introduced as part of a Cu-catalyzed process leading to the formation of benzothiazole from an iminodisulfide under an inert atmosphere.

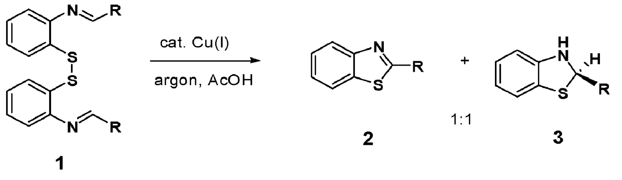
Copper-catalyzed oxidations have been at the center of chemists' interest for several decades. Coupled with molecular oxygen in an aerobic media[1] or with peroxides in anaerobic systems,[2] copper-catalyzed oxidations have become cornerstones of analytical, biological, and organic chemistry. While the oxidations have been generally accepted as a valuable tool, the nature of the reaction intermediates and the reaction mechanisms have, despite great efforts, often remained obscure, primarily due to the complexity of the multi-component processes involved. However, oxygen-based electron acceptors are not the only viable substrate for copper-catalyzed oxidations. Following examples of biological chemistry, copper–disulfide interactions have recently attracted growing attention.[3] This interest was found to be fully justified when a product of an oxidative addition of copper into a disulfide bond was isolated and characterized, endorsing thus the capability of disulfide as a copper oxidant.[4] Based on this concept, we wanted to explore the oxidative process without the complications associated with highly reactive oxygen-centered reagents (stoichiometric requirements, side reactions, *etc.*).[5] The forseeable advantages are the accurate analytical accessibility of all the reaction components, *i.e.* reduced and oxidized forms, in a closed system which should enable to accurately map the entire process.

Here we want to demonstrate our findings pertaining to the intramolecular oxidation of imines featuring a tethered disulfide function. The importance of ligands for the stabilization of high-valent copper species has been discussed and demonstrated in the literature.[6] In line with those findings, we based our model compounds on the 2,2′-anilinedisulfide platform, which accommodates the concept of "non-innocent" ligands.[7]

In our study, one equivalent of the imine disulfide **1a** (R = 2-chloro-4-nitrophenyl) was treated with a catalytic amount of copper(I) 3-methylsalicylate under inert atmosphere using acetic acid as a solvent. Under these conditions, the starting material was converted to a 1 : 1 mixture of 2-arylbenzothiazole **2a** and 2,3-dihydro-2-arylbenzothiazole **3a** (R = 2-chloro-4-nitrophenyl) (Scheme 1).

In the copper-catalyzed addition of disulfides to styrenes, a mechanism involving *in situ* generated cationic sulfur species attacking electron-rich substrates in an electrophilic fashion was proposed.[3a] The other plausible mechanism involving the oxidative addition of Cu(I) into the S–S bond of disulfide, as the first step of the catalytic cycle, is indirectly supported by similarities of other transition metals (Rh, Ru),[8] but would involve generally less favorable Cu(III) intermediates.[9] To gain some further insight into the mechanism, we set up the following experiment. With an intramolecular pathway unlikely due to bond constraints, we wanted to rule out an intermolecular addition–elimination mechanism, consistent with sulfur-centered cationic route,[3a] and trap the proposed electrophilic sulfur species by an established nucleophile. Thus, the mixture of the iminodisulfide **1a** (R = 2-chloro-4-nitrophenyl) and styrene was treated under the same conditions. The experiment led to a 1 : 1 mixture of **2a** and **3a**, while styrene remained intact, and no other products were observed. This observation strongly suggests that no free sulfur-electrophiles are formed as intermediates which could react with external nucleophiles. An option for an alternative route is a Cu(I) oxidative addition into the disulfidic S–S bond with subsequent hydrogen transfer leading to overall disproportionation of the disulfide **1** into **2** and **3**.

In order to lend further evidence to this mechanistic proposal, the unimolecular behavior of the isolated Cu(I) complex (**1**)Cu^+ in the gas phase was investigated by mass spectrometry. Specifically, a diluted mixture of the reactant **1b** (R = Ph) and the catalyst in methanol was probed *via* electrospray ionization (ESI).[10] Under mild conditions of ionization, the reactant complex (**1b**)Cu^+ is observed as a major cationic species,[11] whose assignment is confirmed by the characteristic isotope pattern (see inset in Fig. 1). Collision-induced dissociation (CID) of mass-selected (**1b**)Cu^+ is associated with loss of neutral **2b**, concomitant with an ionic species (*m*/*z* 276), which formally corresponds to the product complex (**3b**)Cu^+ (Fig. 1).



Scheme 1 Cu(I)-catalyzed transformation of imine disulfide.

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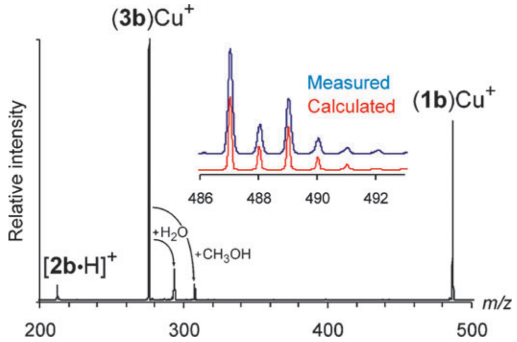
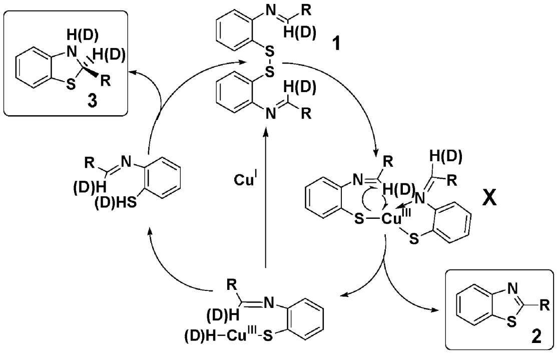


Fig. 1 CID spectrum of mass-selected (**1b**)Cu$^+$ (m/z 487 for the ^{63}Cu isotope) showing the highly preferential loss of neutral **2a** to formally afford (**3b**)Cu$^+$ (m/z 276). The protonated benzothiazole [**2b**·H]$^+$ (m/z 212) arises from consecutive loss of neutral CuH from (**3b**)Cu$^+$. The signals at m/z 294 and 308 are due to subsequent addition of water and methanol, respectively, present as residuals from the spray solvent in the background of the mass spectrometer. The inset shows the measured and calculated isotope pattern of the (**1b**)Cu$^+$ precursor ion.

The apparent threshold of this fragmentation of about 2 eV[12] is qualitatively consistent with a reaction in the condensed phase occurring at ambient conditions.[13] Thus, the gas-phase experiments demonstrate a purely intramolecular reaction of a mononuclear copper species as a viable scenario for the overall reaction. To further support these conclusions, also the Cu(I) complex of the derivative **1a** (R = 2-chloro-5-nitrophenyl) and a specifically deuterated isotopolog, [D$_2$]-**1a**, were investigated by means of ESI MS. Again, loss of the neutral thiazole is observed as the by far predominating fragmentation of mass-selected (**1a**)Cu$^+$, and for ([D$_2$]-**1a**)Cu$^+$ the deuterium label is completely left in the ionic product, as expected.

Further insight into the reaction mechanism was obtained by kinetic investigations. A primary isotope effect (k_H/k_D = 2.3) was observed when H(D)-iminodisulfides were treated with Cu(I) under the reaction conditions, indicating that C–H(D) abstraction constitutes the rate-determining step.

Accordingly, we propose an oxidative addition of Cu(I) into the S–S bond of disulfide as the first step of the catalytic cycle (Scheme 2).[14,15] The resulting intermediate **X**, formally corresponding to a Cu(III) compound, subsequently undergoes a hydrogen transfer, either *via* a CuH(D) species or, more likely, directly to the product **2** concomitant either the product complex (**3**)Cu$^+$ or that of the corresponding Cu$^+$ thiol moiety, where the latter easily forms the dihydrobenzothiazole **3** under the reaction conditions; note that the added acid may serve to return Cu(I) back to the catalytic cycle. An alternative to the proposed mechanism may be the reaction pathway involving a multi-centered transition state,[16] *i.e.* simultaneous cleavage of the S–S bond resulting in formation of a new C–S bond, and accompanied by hydrogen migration. This scenario would thus circumvent the oxidative addition of copper to the disulfide. Indirect evidence for the involvement of an intermediate Cu–H bond is also provided by the loss of neutral CuH from (**3b**)Cu$^+$ (Fig. 1).



Scheme 2 Tentative mechanism of the Cu(I)-catalyzed imine oxidation.

In conclusion, we present a concise mechanism of the interaction between Cu(I) and a disulfide moiety involved in a useful chemical transformation and thus introduce the concept of using disulfides as an oxidant for Cu(I). The key intermediate of the suggested mechanism does not contradict the involvement of Cu(III) species. Supported by the chemical experiments and corroborated by the gas-phase data, the present results thus provide vital insight into the origin of this increasingly important interaction.

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