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Noël R. M. de Kler and Jana Roithová
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 Noël R. M. de Kler and Jana Roithová *

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The mechanism of oxidation of arylamines by copper enzymes is not clarified yet. Here, we explored a reaction between a possible high-valent copper(II)-oxyl intermediate and arylamine. We have employed a TPA ligand (TPA = tris(2-pyridylmethyl)amine) with the NH₂ group in position 2 of one of the pyridine rings (TPA^{NH₂}). This model system allows generation of [(TPA^{NH₂})Cu(O)]⁺ in the gas phase, which immediately undergoes a reaction between the arylamino group and the copper oxyl moiety. The reaction leads to elimination of H₂O and formation of a copper–nitrene complex. The structure of the resulting copper–nitrene complex was confirmed by infrared spectroscopy in the gas phase. We show that the copper–nitrene complex reacts by hydrogen atom transfer with 1,4-cyclohexadiene and by an order of magnitude faster by a double hydrogen atom transfer with ethanethiol and methanol. DFT calculations explain the formation of the copper nitrene as well as its reactivity in agreement with the experimental findings.

Aniline containing chemicals are a class of industrially produced chemicals that are toxic and harmful for the environment and need to be processed in an effective and economic approach. Oxidation of aniline substrates with enzymes is one of the green strategies to process aniline-based waste streams.^{1,2} For example, multi-copper laccases are known for the oxidization of phenol- and aniline-type pollutants.³ The large biodiversity of this enzyme family can be linked to different selectivities in the oxidations of various aniline and phenol derivatives.⁴

Laccases contain a mononuclear copper active site (T1) where the substrate oxidation takes place and a trinuclear copper cluster (T2/T3) that mediates four-electron reduction of oxygen to form water.^{5–7} Both active sites are interconnected and thereby capable of oxidising various substrates. The electron transfer pathway has been well studied, but the overall

oxidation mechanisms of aniline-type molecules is not clarified yet.^{8–11} One of the possible scenarios is that the reaction with oxygen leads to the formation of reactive [copper(II)-oxyl]⁺ (CuO⁺) intermediates that subsequently oxidize aniline-type molecules. CuO⁺ has been thought to be an important reactive species in enzymes such as particulate methane mono-oxygenases and polysaccharide mono-oxygenases.^{12–14} However, copper(II)-oxyl complexes were not directly detected in solution because of their high reactivity; so far the only structural and reactivity assessment comes from gas phase studies.^{15–19} The copper(II)-oxyl functionality is extremely reactive and oxidizes a broad spectrum of substrates even in the gas phase.¹⁸ Here we will show how the nascent copper(II)-oxyl with the TPA ligand (TPA = tris(2-pyridylmethyl)amine) reacts with aniline-type molecules and investigate the mechanism of this oxidation.

The gaseous copper(II)-oxyl complexes can be best generated by electrospray ionization from their copper(II)chlorate precursors.¹⁸ Electrospray ionization of methanol solution of [(TPA)Cu(ClO₃)₂] yields initially the [(TPA)Cu(ClO₃)]⁺ ion (**1a**, *m/z* 436) that can lose a ClO₂ radical in collision-induced dissociation (CID) to generate the desired [(TPA)Cu(O)]⁺ complex (**2a**, Fig. 1a). The extreme reactivity of the copper(II)-oxyl species leads to oxidation of any C–H bond in proximity, which usually results in oxidation of the ligand.^{15,16,20} Accordingly, we have spectroscopically proved that the nascent [(TPA)Cu(O)]⁺ complex immediately activates a C–H bond of one of the pyridine ligands leading to an isobaric copper(I) complex with hydroxylated TPA ligand [(TPA^{OH})Cu]⁺ (see Fig. S13, S14 and the related discussion in the ESI†).

In order to be able to study the arylamine oxidation, we had to link the amine functionality directly to the ligand. Hence, we functionalized the TPA ligand with one (TPA^{NH₂}, **b**) and two (TPA^{(NH₂)₂}, **c**) amino group(s) according to a slightly modified literature procedure.^{21–24} The precursor complexes [Cu(TPA^{NH₂})(ClO₃)]⁺ (**1b**, *m/z* 451) and [Cu(TPA^{(NH₂)₂})(ClO₃)]⁺ (**1c**, *m/z* 466) were generated by electrospray ionization of a methanol solution of the corresponding ligand and Cu(ClO₃)₂ (Fig. S1, ESI†). Dissociation of complexes **1b** and **1c** (Fig. 1b and c)

Institute for Molecules and Materials, Radboud University, Heyendaalseweg 135, 6525 AJ Nijmegen, The Netherlands. E-mail: jana.roithova@ru.nl

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Fig. 2 Potential energy surface for the fragmentation and rearrangements of $[\text{Cu}(\text{TPA}^{\text{NH}_2})(\text{ClO}_3)]^+$ (**1b**). The structures were calculated at the B3LYP/6-31+G* level and the relative energies refer to 0 K and are in kcal mol^{-1} . Some structures are displayed with a truncated ligand, but all calculations were performed with the full ligand.

The selective occurrence of double hydrogen atom transfer suggests that the aminyl radical formed from the nitrene in the first step can readily abstract a hydrogen atom from the carbon atom of the thiolate. The analogous dehydrogenation proceeds with methanol also (Fig. 4), which we investigated further in more detail.

The reaction of **7b** with methanol leads selectively to dehydrogenation of methanol without formation of an adduct (Fig. 4). The labelling experiments showed that the kinetic isotope effect (KIE) for the hydrogen atom abstraction from the oxygen atom is ~ 2.5 , whereas KIE for the HAT from the methyl group is about 1 (compare the red, blue and green spectra in Fig. 4, detailed evaluation of KIEs using different approaches is in the ESI† Fig. S5–S7). Exploratory DFT calculations confirm that the initial O–H bond activation is the rate

determining step followed by HAT from the methyl group leading *via* a smaller energy barrier (Fig. 5 and Fig. S8, ESI†), while the first HAT proceeds in the triplet state, the second HAT from the methyl group is associated with a spin flip to the singlet state of the products.

The distribution of the spin density in **7b** shows that one of the unpaired electrons stays localized at the nitrene nitrogen atom. The electronic structure can be probably best represented as a mixture of two configurations: copper(i)/nitrene diradical and copper(II)/aminyl radical (note that an analogous structure has been found for copper(II)-oxyl complexes).¹⁹ Hence, the first HAT with methanol leads to a complex between copper(II) methanolate and the aminyl radical. The final step leads to a copper(i) complex with an amine ligand.

In conclusion, we have shown that a copper(II)-oxyl complex reacts readily with arylamines by hydrogen atom transfer



Fig. 3 Helium tagging infrared photodissociation spectrum of $[\text{Cu}(\text{TPA-N})]^+$ (m/z 366) (top panel). Theoretical IR spectra of **37b**, **35b** and **16b** were calculated for the optimized structures at the B3LYP/6-31+G* level and scaled by 0.97. $\delta(\text{C-H})$, $\nu(\text{C=C})$ and $\nu(\text{C=N})$ correspond to the absorption bands in the pyridine rings whereas $\delta(\text{C-H})'$, $\nu(\text{C=C})'$ and $\nu(\text{C=N})'$ correspond to the absorption bands in the nitrene-pyridine ring.



Fig. 4 Gas phase reactivity of **7b** with 1,4-cyclohexadiene (purple), ethanethiol (black), methanol (red), $\text{CH}_3\text{OH}/\text{CD}_3\text{OH}$ (1:1) (blue), and $\text{CH}_3\text{OH}/\text{CH}_3\text{OD}$ (1:1) (green). The experiments were performed at zero collision energy with a pressure of the reactant gas of 0.2 mTorr, except for 1,4-cyclohexadiene for which it was raised to 0.3 mTorr (see also Fig. S11, ESI†). The relative concentrations of the isotopically labelled methanols were determined by an association reaction with the $[\text{Au}(\text{PMe}_3)]^+$ cation (see the ESI† for details).





Fig. 5 Potential energy surface for the reaction of $37b^+$ with methanol calculated at the B3LYP level with the 6-311+G(2d,p) basis set for copper and 6-31+G* basis set for all other atoms. The relative energies refer to 0 K and are in kcal mol⁻¹. The spin densities were obtained from Mulliken analysis at the B3LYP/6-311G(2d,p) level. The structures are displayed with a truncated ligand, but all the calculations were performed with the full ligand.

reactions. In the gas phase, this reaction leads to the formation of copper nitrene complexes. We have characterized the formed copper nitrene complex **7b** by its IR spectra and tested its reactivity. **7b** reacts with 1,4-cyclohexadiene by hydrogen atom transfer with a KIE of ~ 2.5 . In addition, **7b** reacts readily with methanol or ethanethiol by two subsequent hydrogen atom transfers. With methanol, the hydrogen atom transfer from the oxygen atom is the rate determining step with the kinetic isotope effect of ~ 2.5 .

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Conflicts of interest

There are no conflicts to declare.

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