J|A|C|S COMMUNICATIONS

Published on Web 05/21/2010

Reduction of Copper(II) Complexes of Tripodal Ligands by Nitric Oxide and Trinitrosation of the Ligands

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Nitric oxide plays key roles in mammalian biology, such as in vascular regulation, neurotransmission, and immunocytotoxicity, and some of these activities are attributed to the formation of nitrosyl complexes of metalloproteins.[1,2] Hence, the interaction of nitric oxide with metal centers has long been of interest to chemists and biochemists.[3] The reduction of Cu(II) centers to Cu(I) in some proteins, such as cytochrome *c* oxidase and laccase, upon exposure to nitric oxide has also been known for a long time.[4] In cytochrome *c* oxidase, the NO reduction of Cu(II) to Cu(I) is believed to play a role in regulating the electron transport activity of this protein.[4a,b,5] Cu(II) is also known to facilitate the nitrosation of various thiolates, and this reduction has been found to correlate with formation of *S*-nitroso bovine serum albumin and *S*-nitroso glutathione.[6] These observations have been used to suggest a mechanism for the formation of RSNO compounds in blood.[7] Although, the autoreduction of ferriheme proteins such as methemoglobin and ferricytochrome *c* (Cyt^{III}) by nitric oxide has been studied extensively,[3,4] the Cu(II) reduction has not been studied to the same extent.[3]

In this context, here we report two examples where tripodal ligands coordinated to Cu(II) undergo nitrosation to the corresponding *N*-nitroso amines in the process of reduction of Cu(II) to Cu(I) by nitric oxide.

The two Cu(II) complexes **1** and **2** were synthesized using the tripodal tetraamine ligands $\mathbf{L_1}$ and $\mathbf{L_2}$ [$\mathbf{L_1}$ = tris(2-isopropylaminoethyl)amine; $\mathbf{L_2}$ = tris(2-ethylaminoethyl)amine], respectively, as their perchlorate salts [Figure 1; also see the Supporting Information (SI)]. The single-crystal X-ray structure of **1** revealed that Cu(II) is surrounded by five nitrogen donor atoms (four from $\mathbf{L_1}$ and one from coordinated acetonitrile solvent) in a distorted trigonal bipyramidal geometry (see the SI). The structural index parameter, τ, was found to be ~0.6. The three terminal nitrogen atoms of $\mathbf{L_1}$ occupy the equatorial positions, whereas the central nitrogen of $\mathbf{L_1}$ and the nitrogen from coordinated acetonitrile occupy the axial positions. Complexes **1** and **2** in acetonitrile solvent exhibit broad d−d bands at λ_{max} (ε/ M^{-1} cm^{-1}) = 826 nm (340) and 615 nm (110) (shoulder) for **1** and 620 nm (200) and 820 nm (150) (shoulder) for **2**, along with relatively strong intraligand absorptions in the UV region (see the SI).

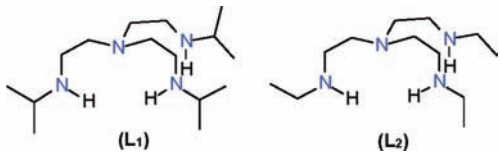


Figure 1

The complexes show magnetic moments corresponding to one unpaired electron (μ_{obs} = 1.56 and 1.64μ_B for **1** and **2**, respectively). The electron paramagnetic resonance (EPR) spectra of the complexes were recorded in acetonitrile solvent at 77 K. Both of the complexes exhibited characteristic four-line axial spectra (see the SI).[8]

Upon exposure to nitric oxide gas, deep-blue solutions of **1** and **2** in dry, degassed acetonitrile produced thermally unstable intermediates with shifts of λ_{max} to 640 and 605 nm, respectively (see the SI and Figure 2).

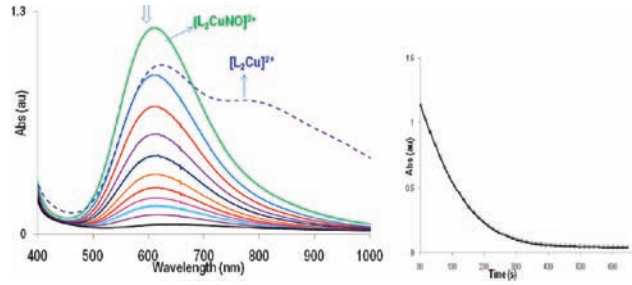
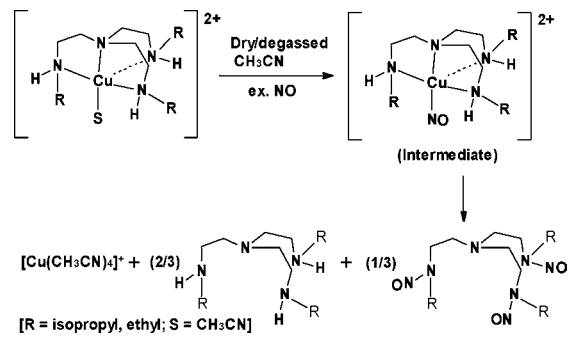


Figure 2. (a) UV−vis spectroscopic monitoring of the formation of a [Cu^{II}−NO] intermediate and its gradual decomposition to Cu^{I} species in the case of complex **2**. (b) Time scan plot at 605 nm in the case of complex **2** at 298 K.

EPR studies of the frozen solutions (77 K) of the intermediates revealed that these are EPR-silent.[9] Hence, it is logical to believe that in both the cases, [Cu^{II}−NO] intermediates were formed (Scheme 1). These intermediates gradually decomposed to afford colorless solutions following first-order kinetics, and the spectral changes were monitored by UV−vis spectrophotometry (Figure 2). The rate constants at 298 K for the decomposition of the intermediates were found to be 5.64 × 10^{-2} and 6.45 × 10^{-3} s^{-1} for complexes **1** and **2**, respectively. Though both of the complexes in acetonitrile solvent showed characteristic axial EPR spectra, the colorless solutions were observed to be EPR-silent (see the SI). All of these results are consistent with the reduction of Cu(II) to Cu(I). In the present case, both complexes presumably form an unstable Cu(II)−nitrosyl intermediate prior to the reduction of Cu(II) to Cu(I).

Scheme 1



10.1021/ja102279c

It would be worth mentioning here that Cao and co-workers[9] reported the reduction of a series of copper(II) dithiocarbamates with nitric oxide in aqueous solution to form air-stable copper nitrosyl and dinitrosyl species. Detailed kinetics studies of Cu(II)/NO reactions are scarce.[3,10] In this regard, Tran et al.[4c] studied NO reduction of the copper(II) complex $Cu(dmp)_2(H_2O)^{2+}$ (dmp = 2,9-dimethyl-1,10-phenanthroline) in aqueous solution and various mixed solvents.

It is interesting to note that the nitric oxide reductions of Cu(II) ion in complexes **1** and **2** in acetonitrile were accompanied by concomitant nitrosation of the ligands and release of the modified nitrosoamine ligands $\mathbf{L_1}'$ and $\mathbf{L_2}'$, respectively (~30% yield in each case) (Scheme 1). $\mathbf{L_1}'$ was found to precipitate from the reaction medium as its perchlorate salt. The formation of $\mathbf{L_1}'$ perchlorate was confirmed by single-crystal X-ray structure determination (Figure 3). The ^{1}H NMR spectra of $\mathbf{L_1}'$ perchlorate and $\mathbf{L_2}'$ indicate that the terminal amine nitrogens are the nitrosation sites on both the cases. The 1446 and 1449 cm^{-1} bands in the FT-IR spectra of $\mathbf{L_1}'$ perchlorate and $\mathbf{L_2}'$, respectively, are consistent with the expected ν_{NO} of nitrosoamine.[11] It is important to note that the free ligands do not react with NO under the reaction conditions.

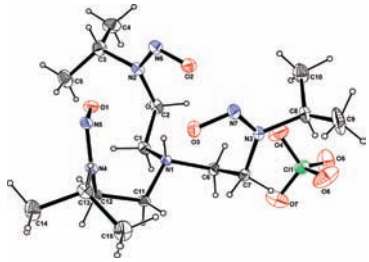


Figure 3. ORTEP diagram of $\mathbf{L_1}'$ perchlorate.

Ford and co-workers[12] reported their observations on the complex $[Cu^{II}(DAC)]^{2+}$ {DAC = the 1,8-bis(9-anthracylmethyl) derivative of the macrocyclic tetraamine cyclam (1,4,8,11-tetraazacyclotetradecane)} in methanol solution. However, the marked difference between their results and the present work is that here nitrosation took place at all the three terminal nitrogens, whereas with the DAC ligand it occurred at one nitrogen only.

In case of $[Cu^{II}(DAC)]^{2+}$, after reduction and nitrosation, the release of the modified ligand was attributed to the fact that Cu(I) favors a tetrahedral geometry, whereas the DAC ligand favors a square-planar one. At the same time, the nitrosation also weakens the binding ability of the amine nitrogen.[12] However, in the present case, both Cu(I) and the ligands favor tetrahedral coordination, so the release of $\mathbf{L_1}'$ perchlorate and $\mathbf{L_2}'$ can be attributed to the weakening of amine binding to the Cu(I) as a result of nitrosation; this weakening is further enhanced by the protonation of the central nitrogen, which results in the formation of the $\mathbf{L_1}'$ perchlorate salt in case of complex **1**.

To the best of our knowledge, this report demonstrates the first example in which the nitrosation takes place at all three equatorial nitrogens of the tripodal ligands with prior reduction of the metal center. There is only one well-defined example of nitrosation with a cyclam ligand and another with a nitrosated ligand as a probable intermediate.[12,13] It is important to note that this nitrosation of the coordinated ligand with concomitant reduction of the metal center is effectively the reverse of the key step in which *S*-nitrosothiols (RSNO) are proposed to react with metalloprophyrins.[11,14]

One mechanism could involve attack of nitric oxide on the deprotonated amine site followed by electron transfer to the copper center, as reported in case of $[Cu^{II}(DAC)]^{2+}$.[12] Alternatively, the key step could be initial NO coordination to the copper ion followed by NO^+ migration to the secondary amine.[12] The observation of the transient intermediates in the UV−vis and EPR spectra prior to reduction supports the second possibility. However, the reason for trinitrosation in the present case is not very clear. In comparison with the other reported results, one could think of the trinitrosation as a result of the combined effect of the geometry of the complexes, the presence of electron-donor groups at the terminal amine positions, and the difference in mechanistic pathways. However, the presence of some other disproportionation processes facilitated by the metal center cannot be ruled out.

In conclusion, the nitric oxide reduction of the Cu^{II} centers in complexes **1** and **2** to Cu(I) have been found to result in concomitant nitrosation at the nitrogen of amine coordination sites. Nitrosation at all three secondary amine sites was observed in the case of the present electron-rich amines $\mathbf{L_1}$ and $\mathbf{L_2}$.

Acknowledgment. The authors thank the Department of Science and Technology, India; BRNS-YSA for financial support; and DST-FIST for the X-ray diffraction facility.

Supporting Information Available: Synthetic processes; UV−vis, FT-IR, ^{1}H NMR, and ^{13}C NMR spectra of complexes **1**, **2**, $\mathbf{L_1}'$ perchlorate, and $\mathbf{L_2}'$; spectroscopic monitoring of the formation of $[Cu^{II}-NO]$ intermediates and the reduction of Cu^{II} to Cu^{I}; and crystallographic data and CIF files for complex **1** and $\mathbf{L_1}'$ perchlorate. This material is available free of charge via the Internet at http://pubs.acs.org.

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JA102279C