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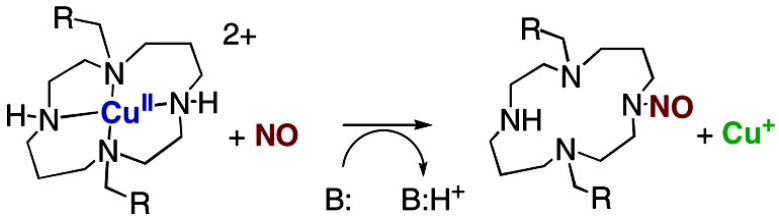

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Intramolecular Reductive Nitrosylation: Reaction of Nitric Oxide and a Copper(II) Complex of a Cyclam Derivative with Pendant Luminescent Chromophores

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Nitric oxide (nitrogen monoxide) serves important roles in mammalian biology involving interactions with metal proteins.[1] Among reactions of potential biological importance is "reductive nitrosylation", the nitric oxide reduction of an oxidizing metal center concomitant with nitrosation of a nucleophile,[2] e.g.

$$M^{n+} + NO + ROH \rightarrow M^{(n-1)+} + RONO + H^+ \quad (1)$$

Such reductive nitrosylation has been demonstrated for several ferriheme proteins,[3] for cupric centers in cytochrome *c* oxidase and laccase,[4] and for Cu(II)[5] and Fe(III)[6] model systems. This pathway has also received recent attention as a possible route to β-cys-93 S-nitrosylated hemoglobin,[7] the subject of a controversial proposal regarding NO transport in the cardiovascular system.[8] In this context, we have been exploring mechanistic routes to reductive nitrosylation[3a,5,6] and report an unprecedented intramolecular pathway in which a ligand nucleophile coordinated to copper(II) is thus nitrosylated to an *N*-nitroso secondary amine.

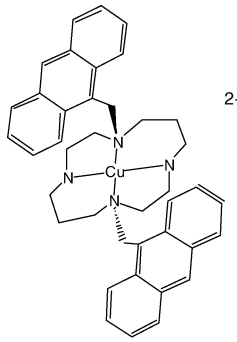
$$Cu^{II}\text{-}NR_2H + NO \rightarrow CuI + NR_2(NO) + H^+ \quad (2)$$

We have prepared[9] several salts of the Cu(II) complex Cu(DAC)$^{2+}$ (**I**), where DAC is the 1,8-bis(9-anthracylmethyl) derivative of the macrocyclic tetraamine cyclam (1,4,8,11-tetraazacyclotetradecane).[10] DAC has two pendant anthracenyl luminophores, and its coordination to the d^9 Cu^{2+} ion gives **I** a square-planar geometry. This configuration was documented by determining the X-ray crystal structure of [Cu(DAC)](ClO$_4$)$_2$, details of which will be described elsewhere.[11] Solutions of **I** in dimethylformamide/methanol (1/1) are orange, owing to a broad, weak d−d band at λ_{max} = 566 nm (ϵ = 266 M^{-1} s^{-1}). The optical spectrum also displays intense, structured $\pi-\pi^*$ absorption bands at 350−400 nm, characteristic of the anthracene groups. Free DAC is strongly luminescent from the pendant anthracenes in ambient solutions when excited at 350 nm. However, analogous solutions of [Cu(DAC)]$^{2+}$ (various salts) display little or no luminescence at room temperature or at 77 K (MeOH/EtOH, 1:4 frozen glass), and we attribute this to intramolecular quenching by the paramagnetic Cu(II) center. Analogous quenching of pendant ligand luminophores by metal centers has been copiously demonstrated.[10,12]

When deaerated methanol or acetonitrile solutions of [Cu(DAC)]Br$_2$ were exposed to NO, the colors progressively bleached, and structured emission characteristic of anthracene luminophores (380−480 nm) became apparent over a few minutes (Supporting Information Figure S-1). The temporal appearance of this luminescence paralleled bleaching of the d−d band and other changes in the absorption spectra. Before NO addition, the ^{1}H NMR spectra of analogous solutions displayed broad signals as expected for a paramagnetic Cu(II) complex. After reaction with NO, the product solutions displayed sharp resonances that were unchanged by vacuum removal of the NO remaining in the solution (see below). This would be consistent with reduction of Cu(II) to Cu(I). Electrochemical analysis of product solutions showed the presence of an oxidizable species with the same potential as solutions prepared by adding CuBr to the same solvent (0.4 V vs Ag/AgCl in 1/1 DMF/MeOH). Notably, analogous NO reduction of Cu(II) accompanied by solvent nitrosation (forming MeONO in methanol and NO_2^- in water) was reported for the complex Cu(dmp)$_2^{2+}$ (**II**) (dmp = 2,9-dimethyl-1,10-phenanthroline) as illustrated in eq 3.[5]

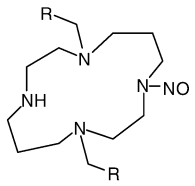
$$Cu(dmp)_2^{2+} + NO + CH_3OH \rightarrow Cu(dmp)_2^{+} + CH_3ONO + H^+ \quad (3)$$

However, in marked contrast to eq 3, NO reduction of the cupric ion of Cu(DAC)$^{2+}$ in aqueous methanol is accompanied by nitrosation and release of the modified DAC ligand itself. The positive ion ESI-mass spectrum of the product solution showed a large parent peak at 610 (*m*/*z*) corresponding to the combination, $M^+ = \{DAC + NO\}^+$ and a very small peak at 580. No peaks at the *m*/*z* ratios corresponding to copper complexes of DAC or its derivatives were evident. The solution resulting from the reaction with isotopically labeled $^{15}N^{18}O$ gave a parent peak at 613 (*m*/*z*), corresponding (in mass) to $\{DAC + {}^{15}N^{18}O\}^+$. Thus, the organic product is interpreted as being the nitrosylated DAC derivative **III**. This would have a mass of 609 au but would be protonated to give a 610 *m*/*z* cation in the ESI-MS experiment.



I

2+



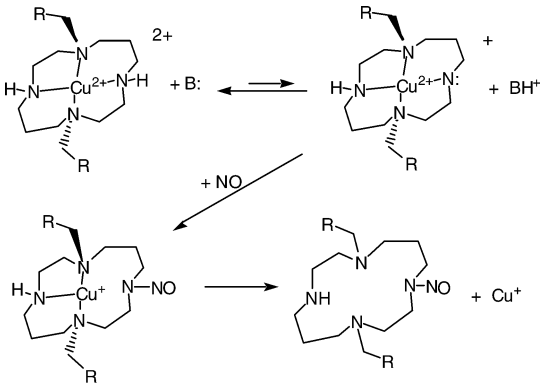
III (R = anthracenyl)

For comparison, the positive ion ESI-MS spectrum of free DAC gave a parent peak of 581 (*m*/*z*) corresponding to $M^+ = \{DAC + H^+\}$. The lower-intensity cation at 580 *m*/*z* in the product ESI-MS spectrum appears to result from NO loss from **III** followed by protonation to give a radical cation.

The ^{1}H NMR spectrum of **III** in perdeuterio acetonitrile confirms the amine nitrogen as the nitrosation site on DAC. The ^{1}H COSY

10.1021/ja049444b CCC: $27.50

Scheme 1



analysis indicates the presence of two independent DAC−NO species in a ∼1:1 ratio, and all protons could be assigned. The most plausible explanation is the presence of geometric isomers due to the *E*- and *Z*-isomers expected for the 1,3-dipolar form of an unsymmetrical *N*-nitroso amine.[13] An IR band at 1430 cm^{-1} consistent with the expected ν_{NO} of a nitrosoamine[14] was also observed for the modified ligand.

Release of **III** from the metal can be attributed to weakened Cu(I) binding to the amines in part due to the mismatch between the tetrahedral geometry favored by Cu(I) and the square-planar coordination favored by the cyclam ligand. We also surmise that nitrosation weakens the binding at the affected amine.

To our knowledge, this is the first well-defined example of intramolecular nitrosation coupled to reduction of the metal center, although there is an earlier case where a nitrosylated ligand is a probable intermediate.[15] It should be noted that nitrosation of the coordinated ligand with concomitant reduction of the metal as seen here is effectively the reverse of a key step by which compounds such as *S*-nitrosothiols (RSNO) are proposed to react with certain metal complexes, such as metalloporphyrins.[14,16]

It is valuable to evaluate the conditions that define the system as a basis for predicting reactivities of different metal centers with NO. Reduction of **I** did not proceed in acidified solutions as evidenced by the absence of changes in UV−vis absorption or emission properties, but the rates were markedly accelerated upon addition of base. In a buffered methanol/water (4/1) solution, the rates increased logrithmically with pH with a slope near unity, and also increased in a nearly linear fashion with increasing [NO].

Scheme 1 offers a speculative mechanism for this intramolecular nitrosylation. The key step is the attack of NO on a deprotonated amine site with concerted electron transfer to the coordinated copper ion. If the first equilibrium constant were small and the redox-assisted formation of the N−N bond rate-limiting, this would predict rates first order in NO and in base. An alternative would be prior coordination of NO to the copper followed by NO^+ migration to the secondary amine assisted by base deprotonation of that site. While the latter would also be consistent with the preliminary kinetics behavior, we favor the former sequence, since initial complexation of NO to the Cu(II) should decrease the acidity of the coordinated amine. Also, no IR bands consistent with $Cu^{II}(NO)$ formation or other spectral changes were observed initially upon mixing neutral CD_3CN solutions of $[Cu(DAC)](PF_6)_2$ with NO, under which conditions further reaction was very slow.

Once reduced, the cuprous ion is apparently released from the macrocyclic ligand, owing to its preference for tetrahedral coordination and the inability of cyclam to satisfy that preference. In contrast, **II** readily undergoes reduction to a stable $Cu(dmp)_2^+$ complex owing to the preference of dmp for (nearly) tetrahedral coordination. These differences are reflected in the respective reduction potentials of **I** (−0.03 V) and **II** (+0.39 V) in acetonitrile vs Ag/AgCl. Nonetheless, while **I** is less reactive with NO than is **II** under similar conditions, the qualitative reactivity of **I** is greater than expected, given the respective reduction potentials. We attribute the unexpected reactivity of **I** to the unusual pathway leading to irreversible destruction of the square-planar coordination.

In summary, NO reduction of the square-planar Cu(II) complex $Cu(DAC)^{2+}$ is shown to be facilitated by an unprecedented intramolecular nitrosylation of the nitrogen of an amine coordination site. This observation emphasizes that, when redox active complexes are involved, *intramolecular*, as well as intermolecular, reductive nitrosylation is viable, especially if an electron-rich ligand such as the amine conjugate base depicted in Scheme 1 is present. Such pathways involving NO attack at the coordinated ligand promoted by electron transfer to the metal should be among those considered in evaluating the reactivity of NO with biologically relevant metal centers.

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Supporting Information Available: Figures showing the optical absorption and emission changes upon NO reduction of **I**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) For example, $[Cu(DAC)]Br_2{\cdot}2H_2O$: A methanol solution of $CuBr_2$ (13 mg, 5.8×10^{-5} mol/2 mL) was added to a DMF suspension of DAC (20 mg, 3.5×10^{-5} mol/8 mL). After sonication, the green solution was concentrated to ca. 2 mL. The deposited orange crystals were collected by filtration and washed with MeOH. Yield: 24 mg, 79%. UV−vis (DMF/MeOH, 1/1) (λ_{max} in nm (ϵ M^{-1} cm^{-1})): 338 (8.69×10^3), 356 (1.32×10^4), 374 (1.82×10^4), 394 (1.60×10^4), 566 (2.66×10^2). Anal. Calcd for $C_{42}H_{52}Br_2CuN_4O_2$: C, 58.10; H, 6.04; N, 6.45. Found: C, 58.00; H, 5.76; N, 6.84. The ClO_4^- and PF_6^- salts were prepared by anion-exchange methods.

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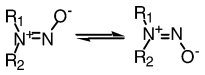

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(15) (a) Armor, J. N.; Pell, S. D. *J. Am. Chem. Soc.* **1973**, *95*, 7625−7633. (b) These authors reported that NO reduction of $Ru(NH_3)_6^{3+}$ in alkaline solution gives $Ru(NH_3)_5(N_2)^{2+}$ and proposed that this occurs via NO reaction with the coordinated amide of the Ru(III) intermediate $Ru(NH_3)_5(NH_2)^{2+}$.

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