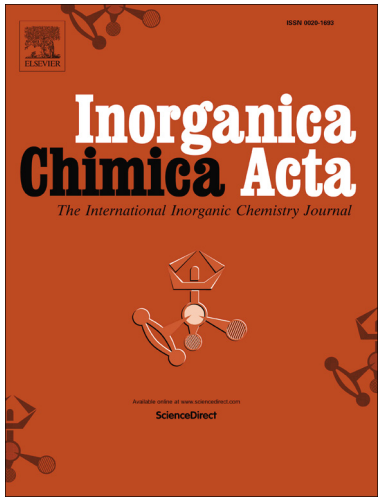

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Nitric oxide reactivity of copper(II) complexes of bidentate amine ligands

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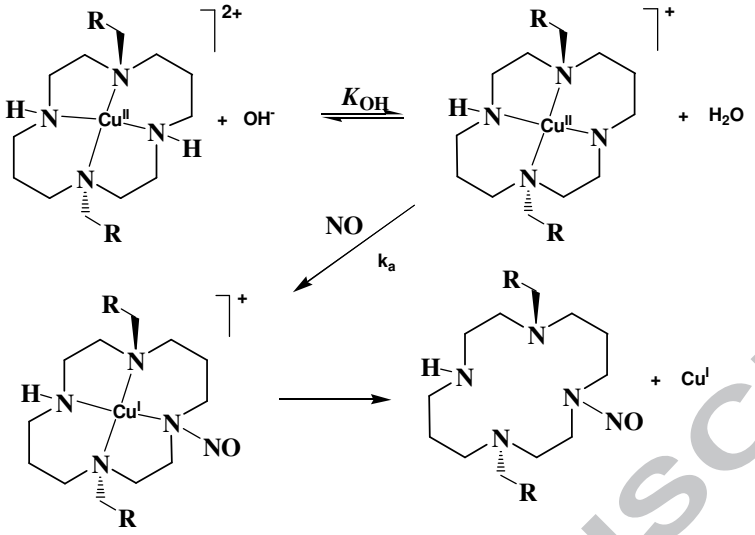
Abstract

Two copper(II) complexes, **1** and **2** with $\mathbf{L_1}$ and $\mathbf{L_2}$ [$\mathbf{L_1}$ = propane-1,3-diamine ; $\mathbf{L_2}$ = N-isopropylpropane-1,3-diamine], respectively, were synthesized and characterized structurally. In acetonitrile solution of the complexes, the Cu(II) centre was found to reduce in presence of nitric oxide gas. The formation of [Cu^{II}-NO] intermediate prior to the reduction of Cu(II) center was evidenced by UV-visible, solution FT-IR, X-band EPR studies. This reduction led to the ligand transformation through diazotization at primary amine site in complex **1**; whereas, N-nitrosation at the secondary amine site of the ligand was observed in **2**. The final organic products were isolated and characterized by spectroscopic studies.

Keywords: Copper(II) complexes, nitric oxide, Cu(II)-nitrosyl, N-nitrosation

Introduction

Interaction of nitric oxide (NO) with transition metal ions has been a subject of interest since the discovery of bioregulatory roles of NO in mammalian biology [1-16]. Much of these activities are attributed to the interactions of NO with metal ions leading to the formation of nitrosyl complexes of metallo-proteins [1-6]. In this context, iron-nitrosyls have been studied extensively [17-33]. The reduction of Cu(II) centres in cytochrome *c* oxidase and laccase by NO is known for a long time [34-41]. A number of Cu(II) complexes have been utilized recently to exemplify the reduction of Cu(II) by NO. For example, in $[Cu(dmp)_2(X)]^{2+}$ (dmp = 2,9-dimethyl-1,10-phenanthroline, X = solvent) and analogous complexes, Cu(II) undergoes reduction by NO. Detailed mechanistic study revealed that the reduction proceeds through a inner-sphere pathway [42-43]. The reduction was resulted in the nitrosation of the solvent resulting into methylnitrite or NO_2^- in case of methanol or water, respectively [42-43]. In contrast, in methanol solution, $[Cu^{II}(DAC)]^{2+}$ {DAC = 1,8-bis(9-anthracylmethyl) derivative of the macrocyclic tetraamine cyclam (1,4,8,11-tetraazacyclotetradecane)} in presence of NaOEt reacts with NO leading to the reduction of Cu(II) center with a simultaneous nitrosation of the ligand [44-45]. From detail quantitative and theoretical studies, a pathway analogous to the inner-sphere mechanism for electron transfer was suggested where NO is the reductant, Cu(II) is the oxidant and the coordinated amido anion behaves as the bridging ligand (Scheme 1).



Scheme 1

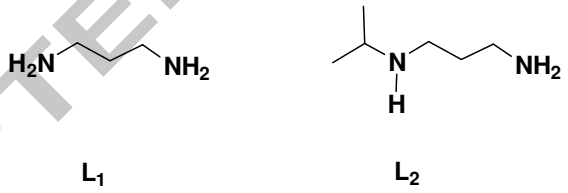
On the other hand, for the reduction of Cu(II) by NO, another mechanism involving the initial NO coordination to the Cu(II) center to form [Cu^{II}-NO ↔ Cu^{I}-NO^{+}] was suggested by Wayland [46-47]. Subsequent amine deprotonation and migration of NO^{+} to the coordinated amide would result into the nitrosoamine.

Recently, with $[Cu^{II}(tren)(CH_3CN)]^{2+}$, $[Cu^{II}(taea)(CH_3CN)]^{2+}$, $[Cu^{II}(tiaea)(CH_3CN)]^{2+}$, $[Cu(pymea)_2]^{2+}$ and $[Cu(baea)(CH_3CN)]^{2+}$ [tren = *tris*-(2-aminoethyl)amine; taea = *tris*-(2-ethylaminoethyl)amine; tiaea = *tris*-(2-isopropylaminoethyl)amine; pymea = pyridine-2-methylamine and baea = *bis*-(2-aminoethyl)amine], the reduction of Cu(II) center by NO was found to proceed through the formation of a thermally unstable [Cu^{II}-NO] intermediate [48-50]. However, in the reaction of Cu(II) complexes of ppmea and mimpea [ppmea, 2-(pyridin-2-yl)-N-((pyridin-2-yl)methyl)ethaneamine; mimpea, N-((methyl-1H-imidazol-2-yl)methyl)-2-(pyridine-2-yl)ethanamine], with NO, the formation of an [Cu^{II}–NO] complex has not been observed prior to the reduction [51]. This is attributed to the much lower values of the equilibrium constants, K_{NO} (equation 2) as reported earlier in case of $[Cu(dmp)_2(X)]^{2+}$ [43].

$$[(L)_2Cu^{II}]^{2+} + NO \underset{}{\overset{K_{NO}}{\rightleftharpoons}} [(L)_2Cu^{II}(NO)]^{2+} \quad \text{--------- (eq.1)}$$

In addition, in case of $[Cu(mtad)]^{2+}$ [mtad = 5,5,7,12,12,14-hexamethyl-1,4,8,11-tetraazacyclotetradecane], the reduction takes place in methanol in presence of sodium methoxide through a deprotonation pathway as reported earlier in case of $[Cu(DAC)]^{2+}$ [52]. However, $[Cu(tmd)_2]^{2+}$, tmd = 5,5,7-trimethyl-[1,4]-diazepane], facile reduction was observed in dry acetonitrile through a [Cu^{II}-NO] intermediate. Hence, the ligand frameworks definitely have a significant role in controlling the mechanistic pathway for the reduction of copper(II) by NO.

In this context, two copper(II) complexes with ligands $\mathbf{L_1}$ and $\mathbf{L_2}$ [$\mathbf{L_1}$ = propane-1,3-diamine ; $\mathbf{L_2}$ = N-isopropylpropane-1,3-diamine] (Figure 1) have been prepared and their interactions with NO have been studied.



$\mathbf{L_1}$ $\mathbf{L_2}$

Figure 1: Ligands used for the present study.

Experimental

Materials and methods

All reagents and solvents of reagent grade were purchased from commercial sources and used as received except specified. Ligand $\mathbf{L_1}$ was procured from Sigma Aldrich and used as received. $\mathbf{L_2}$ was synthesized from the reaction of $\mathbf{L_1}$ with acetone followed by the reduction

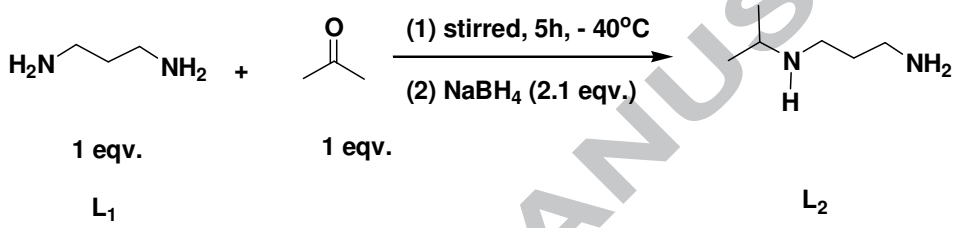
with $NaBH_4$. Acetonitrile was distilled from calcium hydride. Deoxygenation of the solvent and solutions was effected by repeated vacuum/purge cycles or bubbling with nitrogen for 30 minutes. NO gas was purified by passing it through a KOH and P_2O_5 column. UV-visible spectra were recorded on a Perkin Elmer Lambda 25 UV-visible spectrophotometer. FT-IR spectra were taken on a Perkin Elmer spectrophotometer with samples either prepared as KBr pellets or in solution in sodium chloride cell. Solution electrical conductivity was measured using a Systronic 305 conductivity bridge. ^{1}H-NMR spectra were recorded in a 400 MHz Varian FT spectrometer. Chemical shifts (ppm) were referenced either with an internal standard (Me_4Si) or to the residual solvent peaks. The X-band Electron Paramagnetic Resonance (EPR) spectra were recorded on a JES-FA200 ESR spectrometer, at room temperature and 77 K with microwave power, 0.998 mW; microwave frequency, 9.14 GHz and modulation amplitude, 2. Elemental analyses were obtained from a Perkin Elmer Series II Analyzer. The magnetic moment of complexes was measured on a Cambridge Magnetic Balance.

Single crystals were grown by slow diffusion followed by slow evaporation technique. The intensity data were collected using a Bruker SMART APEX-II CCD diffractometer, equipped with a fine focus 1.75 kW sealed tube MoK_α radiation (λ = 0.71073 Å) at 273(3) K, with increasing ω (width of 0.3° per frame) at a scan speed of 3 s/frame. The SMART software was used for data acquisition. Data integration and reduction were undertaken with SAINT and XPREP software [53]. Multi-scan empirical absorption corrections were applied to the data using the program SADABS [54]. Structures were solved by direct methods using SHELXS-97 and refined with full-matrix least squares on F^2 using SHELXL-97 [55]. All non-hydrogen atoms were refined anisotropically. Structural illustrations have been drawn with ORTEP-3 for Windows [56-57].

Synthesis

Ligand L_1: Propane-1, 3-diamine (L_1) was purchased from commercial source.

Ligand L_2: Propane-1, 3-diamine (740 mg) was allowed to react with acetone at - 40 °C for 5 h and then temperature was elevated to room temperature to result in the formation of corresponding imine. It was then reduced by using 2.1 equivalent of $NaBH_4$ in methanol (scheme 2).



Scheme 2

L_2: Yield: 986 mg (~85%). Elemental analyses: calcd. (%): C, 62.01; H, 13.88; N, 24.11; found (%): C, 62.11; H, 13.88; N, 24.19. FT-IR (in KBr): 3420, 2829, 1648, 1568, 1474, 1325, 1037 cm^{-1}. ^{1}H-NMR: (400 MHz, $CDCl_3$): δ_{ppm}: 3.19 (1H, N-H), 2.59-2.52(3H, m), 2.45 (2H, t), 1.81(2H, s), 1.44 (2H, m), 0.85 (6H, d). ^{13}C-NMR: (100 MHz, $CDCl_3$) $\delta_{ppm:}$ 48.6, 45.0, 40.2, 33.7 and 22.6. Mass ($M+H^+$)/z: calcd: 117.1313; found: 117.1445.

Synthesis of complexes:

Both the complexes were prepared by using similar protocol. The details are given for complex **1**.

Complex 1:

To a stirring solution of copper(II) perchlorate hexahydrate, $Cu(ClO_4)_2 \cdot 6H_2O$ (0.741 g, 2 mmol) in 15 ml methanol, solution of ligand L_1 (0.296 g, 4 mmol) in 10 ml methanol was

added dropwise. The reaction mixture was allowed to stirr for 2 h at room temperature. The blue solid pracipate of complex **1** was filtered and dried in vaccuo. Yield: 0.660 g (~80%). UV-vis. (acetonitrile): λ_{max}, 570 nm. FT-IR (KBr pellet): 3211, 1587, 1141, 1112, 1087, 496 cm^{-1}. EPR data: $g_{\parallel}$, 2.334, $g_{\perp}$, 2.013 and $A_{\parallel}$, 203×10^{-4} cm^{-1}. The complex **1** behaves as 1:2 electrolyte in methanol solution [Λ_M (S cm^{-1}), 270]. The observed magnetic moment is found to be 1.64 BM. τ, 0.17.

Complex 2:

Yield: 0.690 g (~70%). UV-vis. (acetonitrile): λ_{max}, 579 nm. FT-IR (KBr pellet): 3307, 3263, 1590, 1092, 1045, 1014, 623 cm^{-1}. EPR data: $g_{\parallel}$, 2.302, $g_{\perp}$, 2.010 and $A_{\parallel}$, 198×10^{-4} cm^{-1} The complex **2** behaves as 1:2 electrolyte in methanol solution [Λ_M (S cm^{-1}), 265]. The observed magnetic moment is found to be 1.60 BM. τ, 0.23.

Isolation of modified ligands:

Both the modified ligands are isolated following same experimental procedures. The details are given for $\mathbf{L_1'}$.

L_1':

To 30 ml of degassed acetonitrile solution of complex **1** (410 mg), freshly prepared NO was bubbled. The blue color of the solution turned green and finally becomes colorless. After removal of excess NO the reaction mixture was opened to air and stirred for 2 h. The volume was reduced to 5 ml and saturated solution of Na_2S was added to ensure complete precipitation of copper ions. The precipitate was filtered off and 50 ml of water was added. The organic part was extracted using Chloroform (25 ml × 3 portions). The collected organic

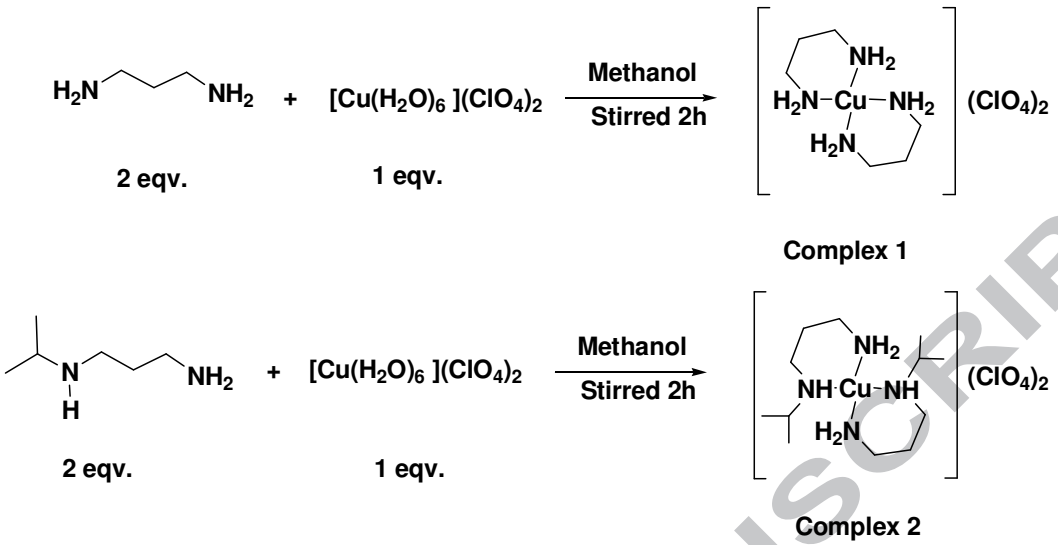
solution was dried over vacuum and subjected to column chromatography using silica gel to get the pure $\mathbf{L_1'}$. Yield: 70 mg (~55%). Elemental analyses: calcd. (%) C, 54.92; H, 13.06; N, 32.02; found (%): C, 54.98; H, 13.07; N, 32.13. FT-IR (in KBr): 3427, 2943, 1641, 1493, 1492, 694 cm^{-1}. ^{1}H-NMR: (400 MHz, $CDCl_3$): δ_{ppm}: 4.26 (4H, b s), 2.54-2.51 (4H, t), 2.45-2.42 (4H, t), 1.45-1.38 (4H, m), 0.914 (1H, b s). ^{13}C-NMR: (100 MHz, $CDCl_3$) $\delta_{ppm:}$ 47.6, 40.1 and 33.4. Mass $(M+H^+)/z$: calcd: 132.1422, found: 132.0756.

Isolation of modified ligand $\mathbf{L_2'}$:

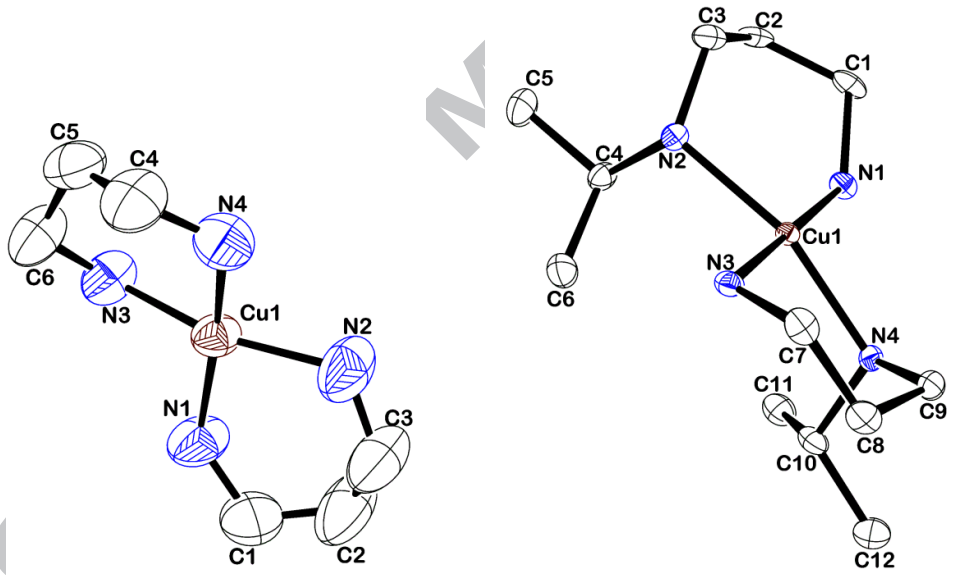
Yield: 95 mg (~80%). Elemental analyses: calcd. (%) C, 49.63; H, 10.41; N, 28.94; found (%): C, 49.68; H, 10.42; N, 29.03. FT-IR (in KBr): 3418, 2930, 1564, 1386, 910, 734 cm^{-1}. ^{1}H-NMR: (400 MHz, $CDCl_3$): δ_{ppm}: 4.63-4.58 (1H, m), 3.56-3.53 (2H, t), 2.67-2.64 (2H, t), 2.12 (2H, b s), 1.66-1.59 (2H, m), 1.44-1.42 (6H, d). ^{13}C-NMR: (100 MHz, $CDCl_3$) $\delta_{ppm:}$ 55.5, 40.3, 39.6, 30.3 and 21.7. Mass $(M+H^+)/z$: calcd: 146.1215, found: 146.1279.

Results and discussion

Complexes **1** and **2** were synthesized by the reaction of copper(II)perchlorate hexahydrate with the respective ligands in 1:2 ratio (experimental section and scheme 2). Both the complexes were isolated as solid. They displayed satisfactory elemental analyses (experimental section). Further characterization of the complexes has been done using various spectroscopic methods (experimental section and supporting information). The formation of the complexes is authenticated by their X-ray single crystal structure determination. Perspective ORTEP views are shown in figure 2. Crystallographic data, important bond angles and distances are listed in tables 1, 2 and 3, respectively.



Scheme 3



(a) **(b)**

Figure 2: ORTEP diagram of complexes (a) **1** and (b) **2** (50% thermal ellipsoid plot, hydrogen atoms, perchlorate molecules and solvent molecules are omitted for clarity). For complex **1**: Bond distances/Å: Cu(1)-N(1), 1.995(6); Cu(1)-N(2), 2.020(5); Cu(1)-N(3), 2.020(6); Cu(1)-N(4), 2.005(7); Bond angles/°: N(3)-Cu(1)-N(4), 92.5(3); N(3)-Cu(1)-N(1), 88.4(3); N(1)-Cu(1)-N(2), 92.7(2); N(2)-Cu(1)-N(4), 90.4(2). For complex **2**: Bond

193 distances/Å: Cu(1)-N(1), 2.036(3); Cu(1)-N(2), 2.050(2); Cu(1)-N(3), 2.047(2); Cu(1)-N(4),
194 2.052(2); Bond angles/°: N(3)-Cu(1)-N(4), 89.6(1); N(4)-Cu(1)-N(1), 90.4(1); N(1)-Cu(1)-
195 N(2), 89.3(1); N(2)-Cu(1)-N(3), 91.2(1).

196

197 In both the complexes, Cu(II) center is surrounded by four N-atoms, two from each of the
198 ligand unit in an overall distorted square planar geometry. The Cu-$O_{perchlorate}$ distances are
199 2.642 Å and 2.398 Å, respectively for complexes **1** and **2**; which are little more than the
200 bonding distances [48-50, 58-59]. Average Cu-N distances in complexes **1** and **2** are 2.020 Å
201 and 2.050 Å, respectively. These are within the range in other reported complexes [48-50, 58-
202 59].
203 In acetonitrile solution, complexes **1** and **2** displayed absorption at 570 nm and 579 nm in the
204 visible region which are attributed to the *d-d* transitions. The small shift in λ_{max} in case of
205 complex **2** compared to **1** is attributed to the increasing covalent character of σ-bond on
206 moving from H to isopropyl group at N-substitution [60]. Both the complexes exhibited axial
207 EPR spectra at 77 K corresponding to the square planar copper(II) complexes having
208 $dx2-y2$ ground state (experimental section and supporting information) [61-64].

209

210 **Nitric oxide reactivity**

211 To a dry and degassed acetonitrile solution of complex **1**, addition of NO gas resulted in a
212 green intermediate. In UV-visible study, a shift of λ_{max} of the *d-d* transition from 570 nm to
213 615 nm was observed immediately after purging NO in acetonitrile solution of complex **1**
214 (Figure 3). This new band is assigned as the *d-d* band of corresponding [Cu^{II}-NO]
215 intermediate complex. In acetonitrile solution, [Cu^{II}-NO] intermediate of
216 $[Cu(tiaea)(CH_3CN)]^{2+}$ and $[Cu(teaea)(CH_3CN)]^{2+}$ [tiaea = *tris*(2-isopropylaminoethyl)amine

and teaea = *tris*(2-ethylaminoethyl)amine], displayed *d-d* transition at 640 nm and 605 nm, respectively [48-50]. In cases of $[Cu(amepy)_2]^{2+}$ and $[Cu(aeta)_2]^{2+}$ [amepy = 2-aminomethyl pyridine; aeta = *bis*-(2-aminoethyl)amine], the *d-d* band appeared at 660 nm and 595 nm, respectively [48-50]. The intensity of this absorption band diminished with time suggesting the reduction of Cu(II) center to Cu(I) following pseudo-first order kinetics (Figure 3, inset). The rate constant was calculated to be 1.028×10^{-2} s^{-1} at 298 K. The λ_{max} of the *d-d* transition of complex **2** was shifted from 579 nm to 608 nm in presence of NO in acetonitrile solvent suggesting the formation of $[Cu^{II}$-NO] intermediate (Figure 4). The rate constant for the reduction of Cu(II) to Cu(I) in this case was 1.099×10^{-3} s^{-1} at 298 K (Figure 4, inset).

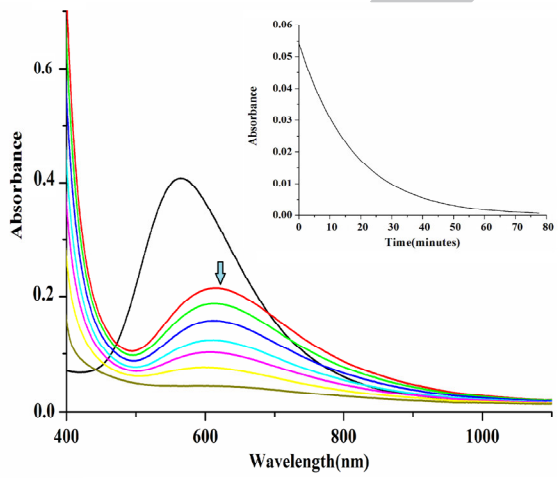
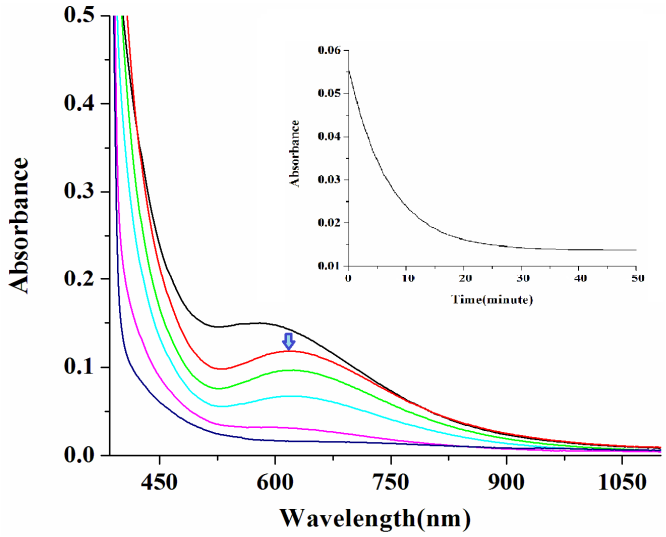


Figure 3: UV-visible spectra of complex **1** before (black trace) and after purging NO in acetonitrile.



229

230 **Figure 4**: UV-visible spectra of complex **2** before (black trace) and after purging NO in

231 acetonitrile.

232

233 The faster rate of decomposition of the intermediate in case of complex **2** compared to **1** is

234 attributed to the presence of electron donating isopropyl group in $\mathbf{L_2}$. In case of

235 $[Cu(tiaea)(CH_3CN)]^{2+}$ and $[Cu(teaea)(CH_3CN)]^{2+}$, the order of rate constants was

236 $[Cu(tiaea)(CH_3CN)]^{2+}$ > $[Cu(teaea)(CH_3CN)]^{2+}$ at 298 K indicating the effect of bulk of N-

237 alkyl group on the ligand framework [48-50].

238 The *d-d* transition for corresponding $[Cu^{II}\text{-NO}]$ intermediate in case of $[Cu(amepy)_2]^{2+}$,

239 $[Cu(aeta)_2]^{2+}$, $[Cu(tiaea)\text{-}(CH_3CN)]^{2+}$ and $[Cu(teaea)(CH_3CN)]^{2+}$ appeared at 660, 595, 640

240 and 605 nm [48-50]. The difference in absorption band in the visible region of $[Cu^{II}\text{-NO}]$ for

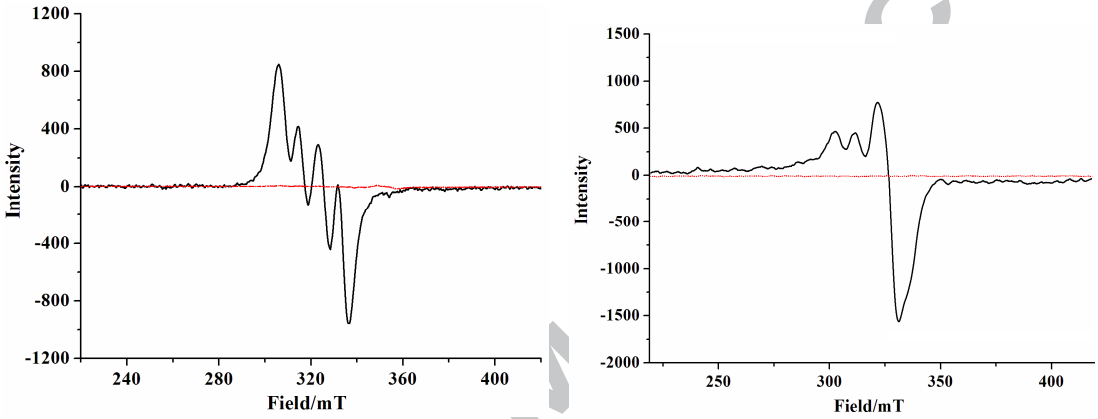
241 complexes **1** and **2** compared to $[Cu(amepy)_2]^{2+}$ is, presumably, because of the greater chelate

242 ring size.

243 Although complexes **1** and **2** exhibit characteristic EPR signals in acetonitrile solvent; the

244 respective intermediates formed in their reaction with NO were EPR silent at 298 K owing to

the anti-ferromagnetic coupling of the paramagnetic Cu(II) center with NO (Figure 5 and supporting information). Further, complete reduction of Cu(II) center by NO also results in to EPR silent Cu(I) solution; however, the presence of the *d-d* band of the intermediate complexes indicates the existence of [Cu^{II}-NO] rather than Cu(I). It should be noted that structurally characterized $[Cu(CH_3NO_2)_5(NO)][PF_6]_2$ complex was reported as EPR silent [65].



(a) **(b)**

Figure 5: X-Band EPR spectra of complexes **1** (a) and **2** (b) before (black trace) and after purging NO (red trace) at room temperature in acetonitrile.

Further support of the formation of the [Cu^{II}-NO] intermediate came from the solution FT-IR studies. Complexes **1** and **2** in acetonitrile solution displayed the formation of new stretching bands at ~1638 and 1635 cm^{-1}, respectively, after their reaction with NO (Figure 6, supporting information). These are attributed to the stretching frequencies of NO coordinated to Cu(II) centers. The intensity of these bands diminished with time indicating unstable nature of the intermediates. For $[Cu(tren)(CH_3CN)]^{2+}$ [tren = N,N-*bis*(2-aminoethyl)ethane-1,2-diamine], ν_{NO} stretching appeared at 1650 cm^{-1} in acetonitrile [49-51]. On the other hand,

the ν_{NO} frequency appears at 1642 and 1635 cm^{-1} in cases of $[Cu(amepy)_2]^{2+}$ and $[Cu(aeta)_2]^{2+}$, respectively, in acetonitrile [48-50].

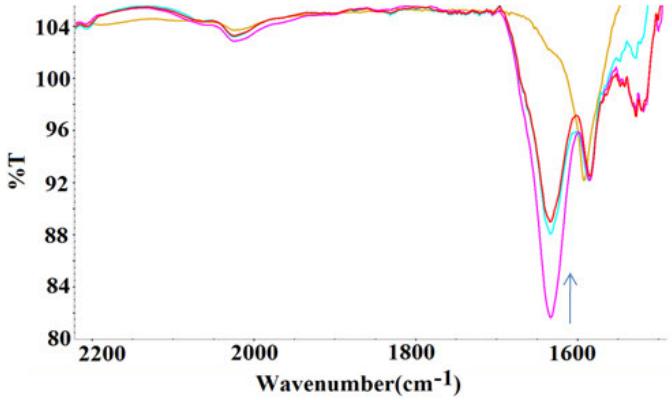
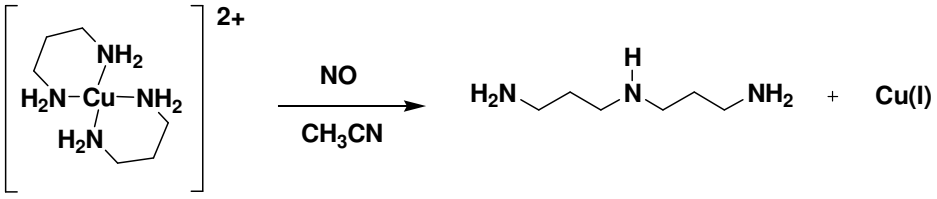


Figure 6: FT-IR spectra of complex **1** after purging NO (pink trace) and gradual decay of the peak at 1638 cm^{-1} in acetonitrile at room temperature.

For $[Cu(CH_3NO_2)_5(NO)][PF_6]_2$, it appear at 1933 cm^{-1} in nujol mull. This higher ν_{NO} frequency in case of $[Cu(CH_3NO_2)_5(NO)][PF_6]_2$ can be attribute to the combined effect of nature of ancillary ligands attached to the metal center and bent geometry [Cu1-N1-O1) 121.0(3)°] of the nitrosyl ligand at an equatorial site [65].

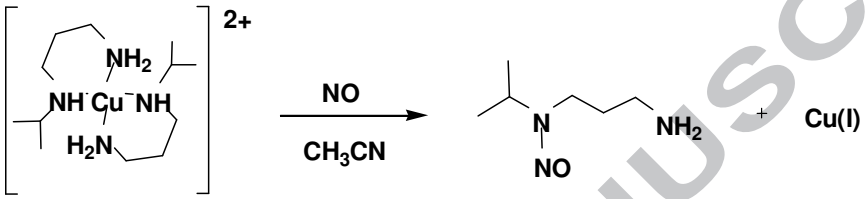
The reduction of Cu(II) center by NO in complex **1** was associated with concomitant diazotization of the primary amine center of the ligand which resulted into the formation of $\mathbf{L_1}'$ (scheme 3). The diazotization of primary amines by during the reduction of Cu(II) by nitric oxide was observed earlier also [48-50].

However, N-nitrosation at the ligand framework was observed in case of complex **2** under similar reaction condition (scheme 4). This is attributed to the better nucleophile character of secondary amine compared to the primary one.



(1)

Scheme 4



(2)

Scheme 5

The organic products were isolated and characterized by the regular spectroscopic studies.

Conclusion

In conclusion, the reactivity of NO with two Cu(II) complexes in acetonitrile has been studied. The formation of unstable [Cu^{II}-NO] intermediate prior to the reduction of Cu(II) was observed upon addition of NO in acetonitrile solution of the complexes. The stability of the [Cu^{II}-NO] intermediate formed depends on the chelate ring size and substitution present in the ligand frameworks. The reduction was resulted into modification of the ligand through diazotization or N-nitrosation of the ligand frame works.

Acknowledgement

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386

Highlights

- Cu(II) complexes of propane-1,3-diamine and N-isopropylpropane-1,3-diamine are prepared.
- Reduction of the Cu(II) centre of the complexes are observed by nitric oxide in acetonitrile solution.
- Spectroscopic studies revealed the formation of [Cu^{II}-NO] intermediate prior to the reduction of Cu(II).
- This reduction led to the ligand modification in case of both the complexes.

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399 **Graphical abstract**

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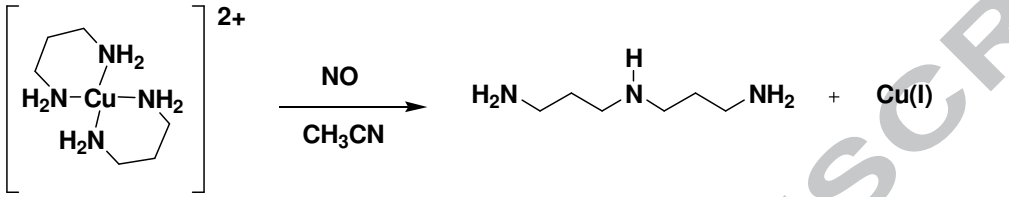
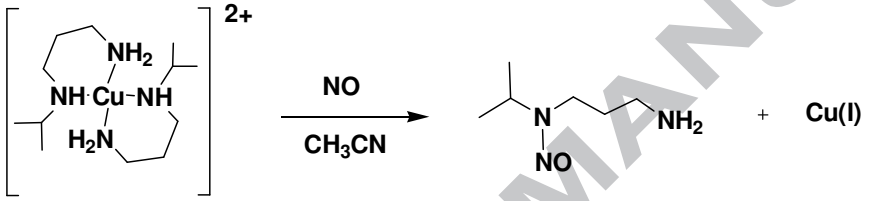


401 (1)



402 (2)

403 Addition of nitric oxide in acetonitrile solution of copper(II) complexes of ligands $\mathbf{L_1}$ and $\mathbf{L_2}$
404 [$\mathbf{L_1}$ = propane-1,3-diamine ; $\mathbf{L_2}$ = N-isopropylpropane-1,3-diamine], resulted in the
405 formation of [Cu^{II}-NO] intermediate prior to the reduction of Cu(II). This reduction led to
406 the ligand transformation through diazotization at primary amine site in complex **1**; whereas,
407 N-nitrosation at the secondary amine site of the ligand was observed in **2**.

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