

Trivalent Copper Complexes with 1,4,8,11-Tetramethyl-1,4,8,11-tetraazacyclotetradecane in Aqueous Solutions. A Pulse Radiolysis and Electrochemical Study

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Abstract

The mechanisms and kinetics of the formation and decomposition of the complexes $\text{Cu}^{\text{III}}\text{L}_{\text{aq}}$ and $[\text{LCu}^{\text{III}}\text{N}_3]^{2+}$ are reported and discussed.

Introduction

In a relatively recent review “Copper – a modern bioelement” [1] it is proposed that contrary to earlier suggestions [2], later propagated in text books [3], the Cu(III) oxidation state is biologically irrelevant as the redox potentials of the $\text{Cu}^{3+/2+}$ couples are generally too high, they vary from 0.37–1.02 V vs. NHE for complexes with oligopeptides as ligands and even higher for other ligands [1–4]. Authentic Cu(III) compounds exist only with very strong ligands such as O^{2-} ; F^- or R_2N^- , the d^8 configuration favoring square planar or square pyramidal geometries. In this context the layered structures of high temperature superconductors which invariably contain $\text{Cu}^{\text{III}}/\text{Cu}^{\text{II}}$ mixed valent centers have to be mentioned [5]. However “nonauthentic” or very short lived highly reactive Cu(III) transient species are probably formed in biological systems [6a, b].

Recently it was shown that solutions of $[\text{LCu}^{\text{I}}(\text{CH}_3\text{CN})]—\text{O}_3\text{SCF}_3$ ($\text{L} = 1,4,7$ -triisopropyl-1,4,7-triazacyclononane) in CH_2Cl_2 at -80°C bind O_2 reversibly to form a $(\mu - \eta^2 : \eta^2\text{-peroxo})$ dicopper(II) species analogous to oxyhemocyanine [7a–d]. By performing the oxygenation reaction in THF or by starting with the Cu(I) complex of 1,4,7-tribenzyl-1,4,7-triaza-cyclononane in a variety of solvents new species which have been formally identified as bis(μ -oxo)dicopper(III) species [8, 9], akin to analogous cores containing iron (III and/or IV) [10] or manganese (III and/or IV) ions, are formed [11].

Derwan *et al.* [12] attached Gly_2His to the amine terminal of a DNA binding agent which, in the presence of copper(II) and oxidizing agents, caused site-specific DNA cleavage. The possibility that Cu(III) plays a role in site-specific substrate oxidation prompted this work.

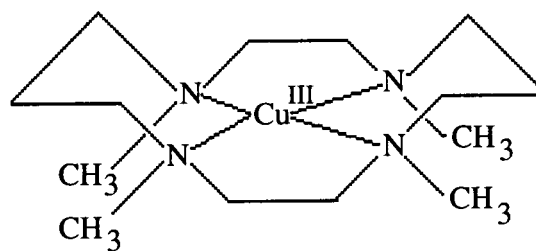


Figure 1. Cu(III) tetramethylcyclam-tmc-trans I.

Aqueous Cu(III) species in the presence or absence of peptide or peptide like ligands were previously studied by the pulse radiolytic technique [13] as well as by electrochemical techniques [4, 13, 14].

Recently it was shown that while tetraaza macrocyclic ligands with tertiary amines stabilize thermodynamically low valent transition metal complexes [15a], they also stabilize kinetically the high valent complexes by inhibiting their usual route of decomposition, i.e., oxidizing the macrocyclic ligand, forming an imine bond [15b].

Thermodynamical stabilization of Cu(I) by tetraaza macrocyclic ligands with tertiary amines might offer a route to the formation of $\text{Cu}^{\text{III}}—\text{O}^{2-}—\text{Cu}^{\text{III}}$ species *in vitro* analogous to those mentioned above but perhaps closer to *in vivo* conditions, i.e., in water and close to room temperature, goals which remained unachieved so far. Therefore it was decided to study the properties of $\text{Cu}^{\text{III}}\text{L}$ complexes ($\text{L} = \text{tmc}$), Figure 1, in aqueous solutions at ambient temperature.

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Experimental section

Materials

The ligand 1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclotetradecane (tmc) was synthesized as described in the literature [16] and characterised by ^1H and ^{13}C NMR [16]. The Cu(III)-trans-I complex was prepared by mixing equimolar aqueous solutions of $\text{Cu}(\text{ClO}_4)_2$ and of the macrocyclic ligand. All other chemicals were of AR grade and were used without further purification. All solutions were prepared with heat distilled water, which was further purified by passing through a Millipore Milli-Q water purification system.

Irradiations

Pulse-radiolysis experiments were carried out using the Varian 7715 linear electron accelerator of the Hebrew University of Jerusalem. The pulse duration was 0.1–1.5 μs with a 200 mA current of 5 MeV electrons. The dose per pulse was 3–30 Gy. Irradiations were carried out in a 4 cm spectrosil optical cell, the analyzing light passing three times through the cell. A 150 W Xenon arc provided the analyzing light. The experimental setup was identical to that described earlier in detail [17].

For dosimetry an N_2O -saturated solution containing 1×10^{-3} M KSCN was used. The yield of $(\text{SCN})_2^-$ was measured by using $\epsilon_{475} = 7600 \text{ M}^{-1} \text{ cm}^{-1}$ and the dose per pulse was calculated assuming $G(\text{SCN})_2^- = 6.0$ [18] and an optical path of 12.3 cm. The dose per pulse was set so that the initial radical concentration was 2–20 μM . The values of the molar extinction coefficients calculated from the dosimetry measurements carry an error limit of 15% due to the scatter of the pulse intensity and uncertainties in G values.

Electrochemistry

Electrochemical studies were carried out using an EG&G Princeton Applied Research potentiostat/galvanostat, Model 263, operated by Research Electrochemistry Software EG&G PARC, using a three electrode assembly consisting of a glassy carbon electrode ($A = 0.07 \text{ cm}^2$), a platinum counter electrode and a Ag/AgCl electrode as a reference electrode separated from the organic solvent by a permeable Nafion membrane. Cyclic voltammetry was carried out under argon (though the presence of dioxygen was shown not to interfere) at room temperature using acetonitrile (HPLC grade) as the solvent and tetrabutylammonium perchlorate (0.1 M) as supporting electrolyte. Ferrocene was used as an internal standard and the ferricinium/ferrocene couple was observed at $\sim 0.4 \text{ V}$ at a scan rate of 80 mV/s.

Spectrophotometry

All spectrophotometric measurements were performed with a Hewlett Packard 8542 diode array spectrophotometer. When required, special cells for work with deaerated solutions were used.

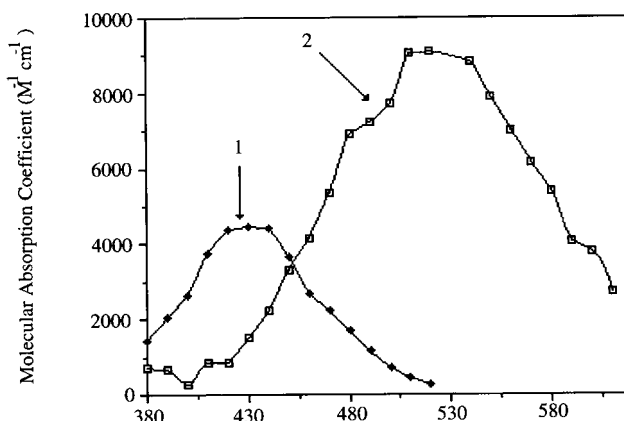


Figure 2. UV-vis spectra of the Cu(III)L complexes. (1) 0.00025 M Cu(II)L^{2+} ; N_2O saturated, pH 7.4; irradiated by 20 Gy; measured 80 μsec after the pulse. (2) 0.00025 M Cu(II)L^{2+} ; 0.1 M NaN_3 ; N_2O saturated, pH 7.4; irradiated by 20 Gy; measured 8 μsec after the pulse.

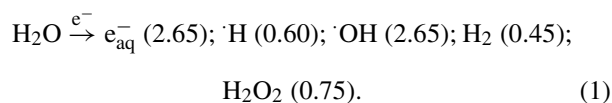
Formaldehyde yield

Formaldehyde was measured using the Hantzsch reaction [27] in which acetylacetone reacts with formaldehyde and ammonia producing stoichiometrically diacetyl-dihydro lutidine which absorbs light at $\lambda_{\text{max}} = 412 \text{ nm}$.

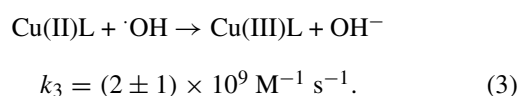
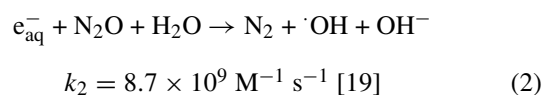
Results and discussion

Oxidation of the complex Cu(II)L by the hydroxyl radical

When N_2O saturated solutions containing $[\text{Cu(II)L}] = 0.05\text{--}0.5 \text{ mM}$, pH 7.4, are irradiated the formation and the decomposition of a transient species is observed. The rate of the formation of the transient obeys a pseudo-first-order rate law. From the linear dependence of the observed rate constant on $[\text{Cu(II)L}]$ a rate constant of $(2 \pm 1) \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$ was determined. The spectrum of the transient formed believed to be $\text{Cu(III)L}_{\text{aq}}$, for this assignment see below, is shown in Figure 2. The trivalent complex is obtained via:



Where the values in brackets give the relative yields of the primary products – number of molecules formed per 100 eV energy absorbed in the solution [19].



The decomposition of the transient complex thus formed consists of two consecutive reactions, Figure 3. The first process occurs on a millisecond time scale and obeys a first order rate law, with a rate which is independent of

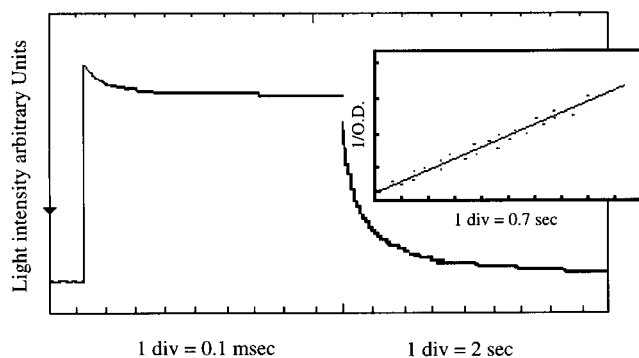


Figure 3. Decomposition kinetics of $\text{Cu(III)L}_{\text{aq}}$. Solution composition: 0.00025 M Cu(II)L^{2+} ; N_2O saturated, pH 7.4; irradiated by 13 Gy; measured at 450 nm.

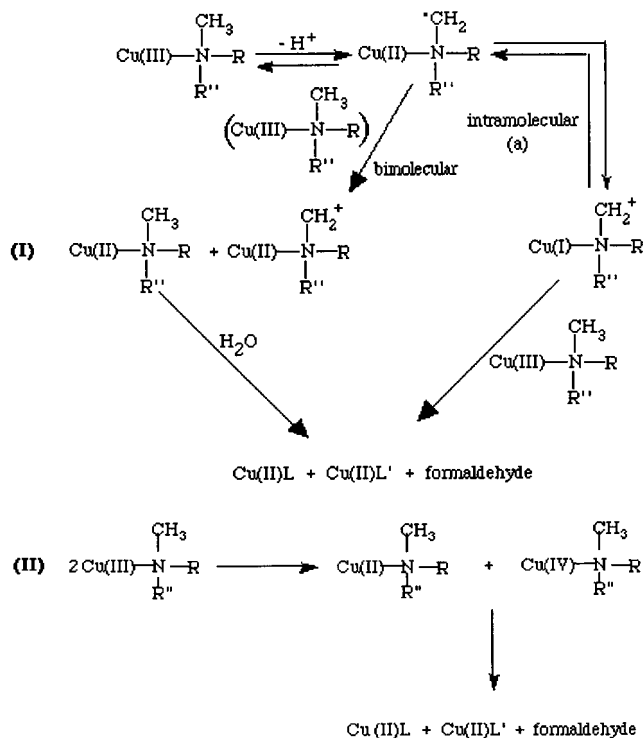
all [solute] present. This process changes insignificantly the transient spectrum and is attributed to an isomerization process. According to its nickel analogue a *trans I* \rightarrow *trans III* isomerization might be speculated [20], but another isomerization process might also occur [21]. The second process occurs on a time scale of several seconds and obeys a second order rate law with a rate constant of $2k = 64000 \text{ M}^{-1} \text{ s}^{-1}$. When different concentrations of dioxygen (0.02–0.18 mM) are added to the solutions prior to irradiation, the rate constant of the second decomposition process slightly increases (\sim a factor of 2), but the kinetics cannot be anymore described as a pure second order rate law, but rather a mixed one as a consequence of two reactions, either consecutive or parallel, which are not well separated in time. The very vague dependence on $[\text{O}_2]$ and the relatively long life-time of the transient species points out that $\cdot\text{OH}$ oxidizes the metal center rather than abstracting a hydrogen atom from the ligand. Furthermore the spectrum of the transient with $\lambda_{\text{max}} = 440 \text{ nm}$ is more likely Cu(III)L rather than an alkyl radical.

The decomposition mechanism, based on the observation that the major product in the absence of dioxygen is formaldehyde, $G(\text{CH}_2\text{O}) = 3.0 \pm 0.1$, is proposed to be analogous to that suggested by Tolman et al. [22], Scheme 1, route I, in which for every two molecules of complex, one molecule of formaldehyde is formed. However, route II in Scheme 1 cannot be ruled out.

Oxidation of the Cu(II)L by azide radical

As the hydroxyl radical might at least partially react also via hydrogen abstraction from the macrocyclic ligand it was decided to use also $\text{N}_3\cdot$ as an oxidizing agent, the latter being a weaker but still powerful oxidizing agent, +1.3 V vs. N.H.E. [23]. This radical is known to prefer reactions via the outer sphere mechanism [24].

Prior to irradiation it was observed that adding azide to Cu(II)L solutions turns the latter from blue to green. This observation suggests that a complex of the type $[\text{LCu(II)}(\text{N}_3)]^+$ is formed. The binding constant K was evaluated by measuring the O.D. at 364 nm. (λ_{max}) as a function of azide concentration. As explained elsewhere [25] by plotting $1/[\text{N}_3^-]$ versus $1/\text{O.D.}_{364 \text{ nm}}$, Figure 4, the intercept obtained yields $K_{[\text{LCu(II)}(\text{N}_3)]^+} = (51 \pm 5) \text{ M}^{-1}$.



Scheme 1. Mechanisms proposed for the decomposition of $\text{Cu(III)L}_{\text{aq}}$.

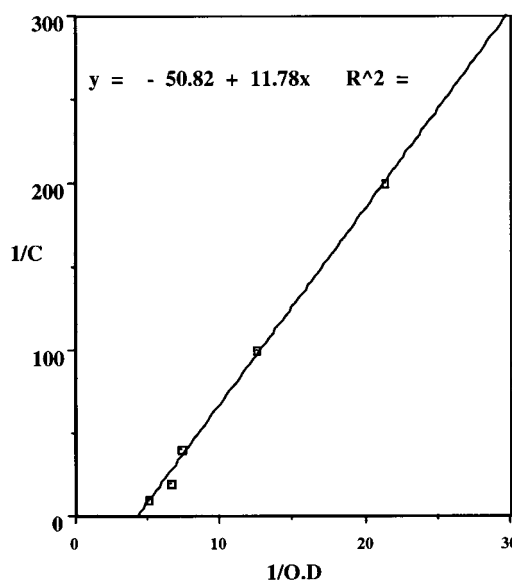


Figure 4. The dependence of $1/[\text{N}_3^-]$ on $1/\text{O.D.}_{364 \text{ nm}}$. $[\text{Cu(II)L}] = 0.0005 \text{ M}$; $[\text{N}_3^-] = 0.005 - 0.1 \text{ M}$; pH 7.4.

When N_2O saturated solutions containing $[\text{Cu(II)L}] = 0.05\text{--}0.5 \text{ mM}$, pH 7.4, $[\text{NaN}_3] = 0.1 \text{ M}$ are irradiated the formation and decomposition of a short-lived transient is observed, Figure 5.

The spectrum of the new transient shows a strong absorption band at 520 nm., Figure 2. The transient is formed in a reaction which obeys a first order rate law, the rate depending linearly on $[\text{Cu(II)L}]$, Figure 6, and on $[\text{N}_3^-]$, Figure 7.

The intercept in Figure 6 is partially due to:

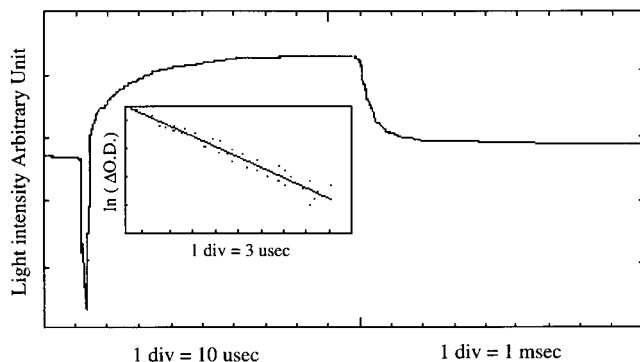


Figure 5. Kinetics of the reaction of $\text{LCu(II)(N}_3\text{)}^+$ with N_3^- . Solution composition: $0.00025 \text{ M Cu(II)L}^{2+}$; 0.1 M NaN_3 ; N_2O saturated, pH 7.4; irradiated by 20 Gy; measured at 500 nm.

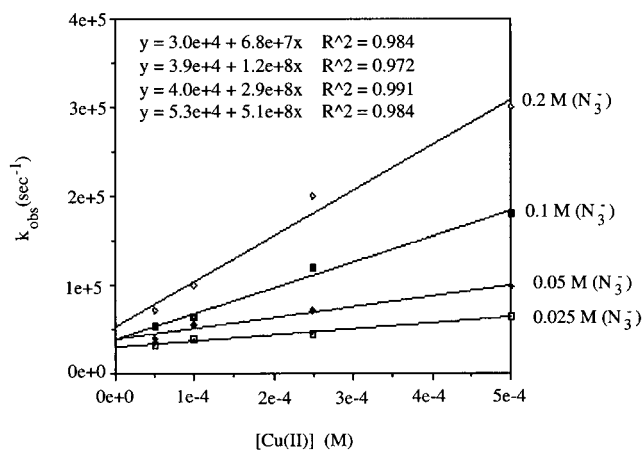


Figure 6. Dependence of the observed rate constant of the formation of $\text{LCu(III)(N}_3\text{)}^{2+}$ on $[\text{Cu(II)L}]$. Solution composition: Cu(II)L^{2+} ; $0.025\text{--}0.2 \text{ M NaN}_3$; N_2O saturated, pH 7.4; irradiated by 20 Gy; measured at 500 nm.

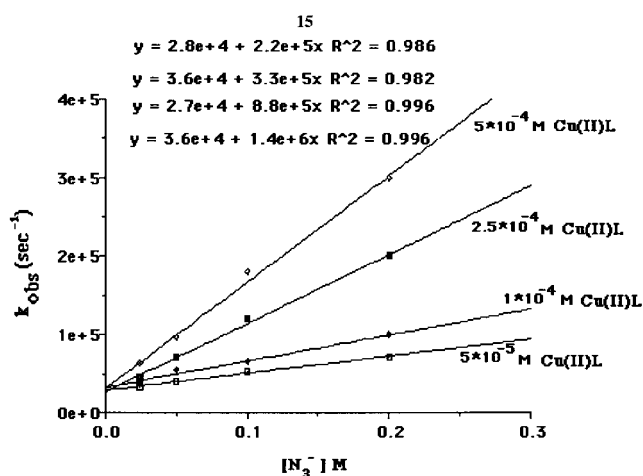


Figure 7. Dependence of the observed rate constant of the formation of $\text{LCu(III)(N}_3\text{)}^{2+}$ on $[\text{NaN}_3]$. Solution composition: $(0.5\text{--}5) \times 10^{-4} \text{ M Cu(II)L}^{2+}$; $(0.025\text{--}0.2) \text{ M NaN}_3$; N_2O saturated, pH 7.4; irradiated by 20 Gy; measured at 500 nm.

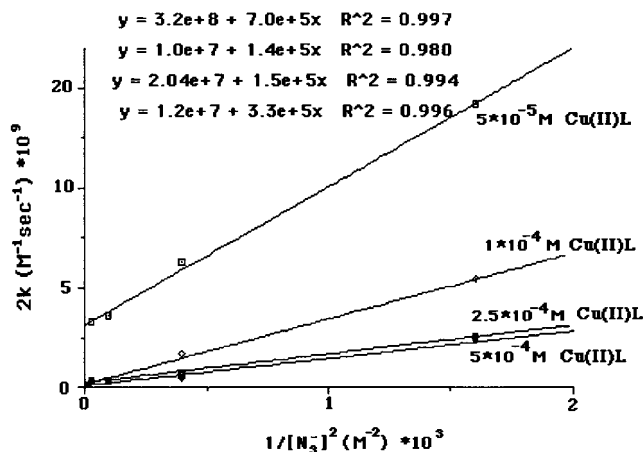
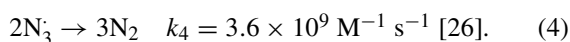
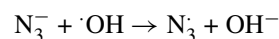


Figure 8. Dependence of the observed rate constant of decomposition of $\text{LCu(III)(N}_3\text{)}^{2+}$ on $1/[\text{NaN}_3]^2$. Solution composition: $(0.5\text{--}5) \times 10^{-4} \text{ M Cu(II)L}^{2+}$; $(0.025\text{--}0.2) \text{ M NaN}_3$; N_2O saturated, pH 7.4; irradiated by 20 Gy; measured at 500 nm.



However the relatively high value of the intercept and the dependence on $[\text{N}_3^-]$ indicate that the oxidation reaction (6) is better described by an equilibrium process.

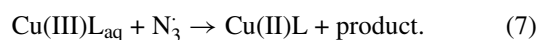


$$k_5 = 1.2 \times 10^{10} \text{ M}^{-1} \text{ s}^{-1} \quad [19]. \quad (5)$$

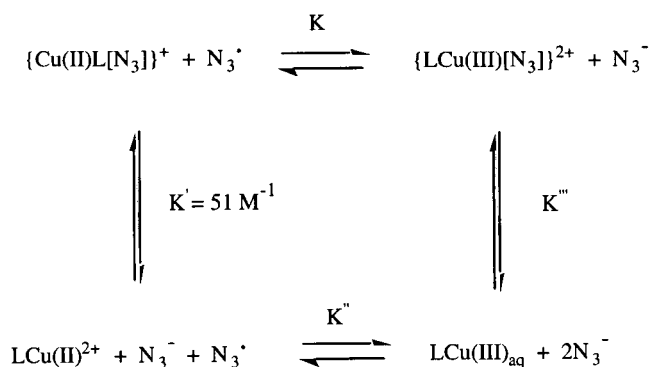


Even though it was proposed that in the case of oxidation of $\text{Fe(II)}_{\text{aq}}$ by N_3^- a transient of the type $[\text{Fe}^{\text{II}}(\text{N}_3)]^{2+}$ is formed [24] and an analogous transient might be suggested here, this seems unreasonable as one expects a very fast intramolecular electron transfer. Therefore we propose the trivalent complexes as the species observed in both systems (in the iron system probably $[\text{Fe}^{\text{III}}(\text{N}_3)_2(\text{H}_2\text{O})_4]^+$).

The fact that the spectrum of the intermediate formed in this system, Figure 2, is totally different from that of Cu(III)L^{3+} proves that N_3^- is ligated to the trivalent complex as well as to the divalent one. The mixture of the trivalent copper species formed (one should remember that the trivalent complex might isomerize and then ligate a second azide) decomposes in a process which obeys a second order rate law with a rate proportional to $1/[\text{N}_3^-]^2$, Figure 8. This result indicates that the decomposition process involves first a ligand loss (an azide) followed by:

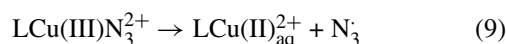


These results seem to be in contradiction with the fact that reaction (6) is an equilibrium process. Furthermore the experimental results show that the rate constant k_6 depends linearly on $[\text{N}_3^-]$. The following might solve this apparent contradiction: Cu(III)LN_3^{2+} once formed isomerizes in



Scheme 2. Mechanism proposed for the oxidation of [Cu(II)L(N₃)⁺] by azide radicals.

a fast reaction to yield a more stable species for which the reactions:



are significantly slower than reaction (10).



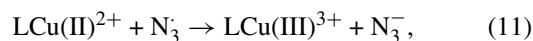
Hence the decomposition process occurs via reaction (10) followed by reaction (4) and/or (7). The whole process might be described by the multiequilibria system shown in Scheme 2.

The redox potential of $\text{LCu}^{3+/2+}$ measured by cyclic voltammetry

In order to confirm our experimental finding that reaction (6) is shifted to the right only when the oxidized metal center ligates azide one should evaluate the redox potential of the couple $\text{LCu}^{3+/2+}$ and if possible of $\text{LCuN}_3^{2+/+}$. Unfortunately, as already described, the life time of LCu(III)N_3^{2+} is extremely short for electrochemical measurements.

As the redox potential of the couple $\text{LCu}^{3+/2+}$ is too anodic to be measured in aqueous solutions it was decided to measure it in an organic media, acetonitrile, for which the anodic electrochemical interval is larger. The CV measurements, Figure 9, were performed with tributyl ammonium perchlorate as the supporting electrolyte, and a redox potential of $E_{1/2} = 2.05 \pm 0.05 \text{ V vs. Ag/AgCl}$ was measured. The observation that the electrochemical wave is not reversible, is attributed to the ligand oxidation within the measurement time scale.

Even though it is reasonable to believe that water is a better ligand to high valent copper than acetonitrile, shifting the redox potential mentioned above cathodically, one can still assume that the reaction:



is endothermic. The fact that the presence of azide anions transforms this reaction to an exothermic one, indicates that the binding constant of azide to Cu(III) is several orders

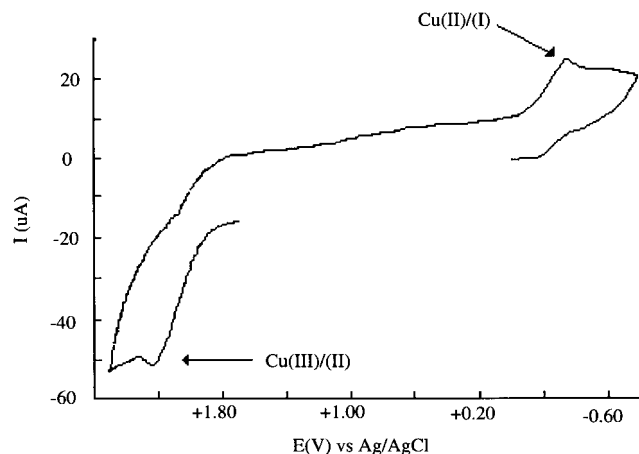


Figure 9. Cyclic voltammetry of Cu(II)L in acetonitrile. Solution composition: 0.0005 M Cu(II)L; 0.1 M TBAP; $v = 80 \text{ mV/sec}$. Working electrode: glassy carbon.

of magnitude higher than the binding constant of azide to Cu(II), this result being at least qualitatively in accord with the pulse-radiolytic measurements.

Concluding remarks

1. Cu(III)L species may be produced in aqueous solutions by oxidizing Cu(II)L either by the hydroxyl radical or by the azide radical.
2. The presence of dioxygen slightly enhances ligand oxidation by the trivalent metal center.
3. The azide anion ligates both to Cu(III)L and to Cu(II)L.
4. The azide anion which is a weak reducing agent reduces Cu(III)L.
5. Electrochemical measurements indicate that Cu(III)L is a strong one electron oxidizing agent.

Acknowledgements

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