OXIDATION OF THIOETERS BY ORGANIC COMPLEXES OF COPPER

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The presence of cupric ions is essential for proper metabolism of many organisms. The best recognized and appreciated function of cupric ions is their participation in the active centers of numerous enzymes [1]. On the other hand, the faults in copper homeostasis in humans are frequently related to disorders with neurological symptoms [2,3]. For example, copper is bind by β-amyloid peptide (βA), the most abundant constituent of senile plaques observed in Alzheimer's disease (AD) brains [2,3]. The βA-bound copper can be involved in the cycle of Fenton like reactions, in which free radicals and other reactive oxygen species (ROS) presented in pathology of AD may be formed [4].

In this work, we continue investigation of the mechanisms that may explain the ability of βA to reduce copper in reaction:

$$MetS + \beta A(Cu^{II}) \leftrightarrow \beta A(Cu^{I}) + MetS^{\bullet +} \quad (1)$$

Such process seems thermodynamically unfavorable [5], since in normal conditions the difference between the reduction potentials of $\beta A(Cu^{I}/Cu^{II})$ (0.5-0.55 V *vs*. Ag/AgCl) [6] and $MetS^{\bullet +}/Met$ (1.26-1.5 V *vs*. Ag/AgCl) [7-10], is about *ca*. 0.7-1.0 V, thus equilibrium (1) should be shifted to the far left-hand side [5].

However, reaction (1) may occur if coupled with the other exergonic reaction. One of possible scenario is the removing of $MetS^{\bullet +}$ from the equilibrium by the formation of α-(alkylthio)alkyl radicals ($\alpha S^{\bullet}$) in exergonic, general base catalyzed reaction:

$$MetS^{\bullet +} + B \rightarrow Met(\alpha S)^{\bullet} + BH^{+} \quad (2)$$

Therefore, in this work we studied, on the model systems, reactions that may spontaneously lead to the formation α-(alkylthio)alkyl radicals, potentially influencing equilibrium (1) and accelerating oxidation of the methionine (Met) residue in peptides.

We examined a molecular system, in which the complex of Cu^{II} with imidazole mimics cupric site of βA. The fifth fold excess of imidazole (Im) over Cu^{2+} guarantee that at least 95% of copper is in the form of $Cu(Im)_4^{2+}$-type complex of known properties: $\lambda_{max} \approx 590$ nm ($\varepsilon = 53 \pm 2$ $M^{-1}cm^{-1}$) [11] and $E^0(Cu^{II}/Cu^{I}) \leq 0.2$ V and $E^0(Cu^{I}/Cu^{0}) \leq 0.6$ V *vs*. SCE [12]. The methionine residue was mimicked by organic α-substituted thioethers: 2,2'-thiodiacetic acid (TDEA, $HO_2C\text{-}CH_2\text{-}S\text{-}CH_2\text{-}CO_2H$), and 2-(methylthio)acetic acid amide (MTAA, $CH_3\text{-}S\text{-}CH_2\text{-}CO_2\text{-}NH_2$). In both cases the reduction of $Cu(Im)_4^{2+}$-complexes should be accompanied by a simultaneous formation of the resonance stabilized α-(alkylthio)alkyl radicals. For TDEA, entropy driven decarboxylation is the main source of α-(alkylthio)alkyl radicals, whereas for MTAA the facilitated deprotonation, due to the captodative effect stabilizing α-(alkylthio)alkyl radicals, will dominate [13]. Contrary to fast decarboxylation of TDEA, deprotonation in MTAA should be susceptible to the presence of proton acceptors [14].

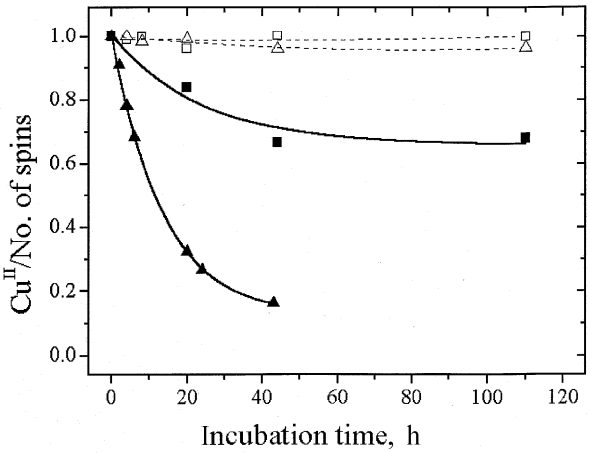


Fig.1. The ESR signal changes *vs*. incubation time in argon-saturated (solid symbols) and oxygen-saturated (open symbols) solutions containing: 1.5×10^{-3} M $CuCl_2$, 7.5×10^{-3} M Im and 0.75×10^{-3} M (square) or 3.0×10^{-3} M (triangle) of MTAA.

The reduction of $Cu(Im)_4^{2+}$ by thioethers was investigated in oxygen- or argon-saturated aqueous solution containing 1.5×10^{-3} M $CuCl_2$, 7.5×10^{-3} M Im, and $(0.75; 1.5 \text{ or } 3.0)\times10^{-3}$ M of thioethers at neutral pH, incubated at 50°C. The progress of reaction was monitored using three independent methods: high performance ion chromatography exclusion (HPICE) [15] was applied for quantitative determination of products and substrates. Decay of Cu^{II} was monitored by electron spin resonance (ESR) spectroscopy (in the redox pair Cu^{II}/Cu^{I} only Cu^{II} cations are paramagnetic). The formation of Cu^{I} was followed using UV-VIS absorption spectroscopy of 2,2'-bicinchoninic acid (BCA) complex with Cu^{+} cations ($Cu(BCA)_2^{3-}$: $\lambda_{max} \approx 562$ nm, $\varepsilon \approx 7700$ $M^{-1}cm^{-1}$) [16].

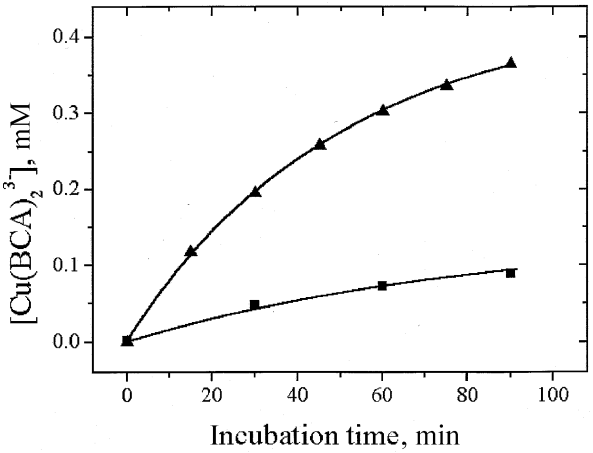


Fig.2. The concentration of $Cu(BCA)_2^{3-}$ complexes *vs*. incubation time for argon-saturated solutions containing: 3.0×10^{-3} M of thioether (MTAA – squares, TDEA – triangles), 1.5×10^{-3} M $CuCl_2$ and 7.5×10^{-3} M Im.

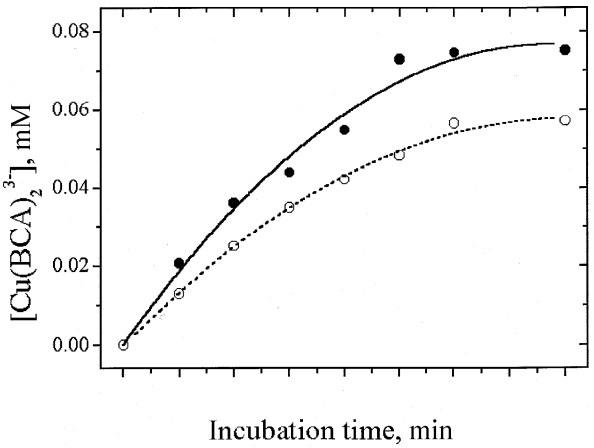
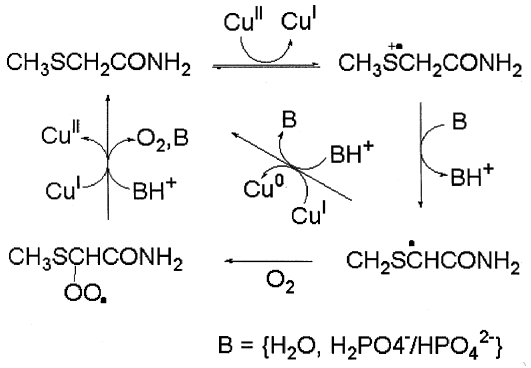


Fig.3. The influence of phosphate ions ($H_2PO_4^-/HPO_4^{2-}$) on the kinetics of Cu^{II} reduction by MTAA in argon-saturated solutions containing: 0.75×10^{-3} M thioether, 1.5×10^{-3} M $CuCl_2$, 7.5×10^{-3} M Im and (solid symbols) 0.15×10^{-3} M phosphate buffer, (open symbols) phosphate free solution.

For the all samples containing TDEA, and for argon-saturated samples containing MTAA we observed the decay of ESR signal. Whereas for oxygen-saturated samples of MTAA the intensity of ESR signal remained on the same level for more than 300 h of incubation (see example in Fig.1). Also, the HPICE measured changes of MTAA concentration during incubation in oxygen-saturated solutions were insignificant. Similarly, the formation of $Cu(BCA)_2^{3-}$ complexes was observed in the presence of both thioethers in argon-saturated samples (Fig.2). Generally, the significant differences in kinetics between thioethers were observed. For the same concentrations of TDEA and MTAA, both the ESR and the UV-VIS experiments show faster changes for TDEA, which reduces Cu^{II} with more than two times higher efficiency than MTAA. On the other hand, we obtained the evidence that the process of Cu^{II}-complexes reduction, induced by deprotonating thioether such as MTAA, could be accelerated in general acid-base catalysis by phosphate ions (Fig.3). The mechanism shown in Scheme is a preliminarily attempt to rationalize current observation for MTAA. It requires, however, additional consideration especially on the mechanistic details of the conversion of peroxyl radicals regenerating the mother compounds.



Scheme.

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ORGANOSILVER RADICALS IN ZEOLITES

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During radiolysis of solutions containing silver salts, Ag^+ cations are reduced to Ag^0 atoms which initiate silver agglomeration process. The solvent radicals formed radiolytically compete with Ag^0 to react with Ag^+ cations. Just after irradiation at 77 K in frozen solution of methanol containing silver perchlorate the electron paramagnetic resonance (EPR) measurements reveal a doublet with silver hyperfine splitting in the range 60-70 mT representing Ag^0 atoms [1]. During thermal annealing, a doublet with much smaller splitting $A_{iso}(Ag)=13.6$ mT appears together with a less intense triplet with $A(Ag)=30.0$ mT. Based on the electron spin echo envelope modulation (ESEEM) result, the doublet