Copper(II) Reduction by Methylthioether Sulfur: Relevance to ROS Generation in Alzheimer’s Disease β-Amyloid Peptides

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While the direct reduction of copper(II) by thioether sulfur should be precluded by their respective redox potentials, recent studies support this pathway if a powerful electron donating group is interacting strongly with the thioether sulfur. This mechanism brings with it significant implications regarding the much debated proposal by which copper(I) and Reactive Oxygen Species (ROS) may be formed by Met sulfur oxidation in the β-amyloid peptides of Alzheimer patients. We have synthesized a series of pyridine diamide ligands based on 2-methyl-2-(2-pyridinyl)-1,3-propanediamine (MPPD). Reaction of MPPD with (methylthio)acetic acid was achieved using standard peptide coupling procedures to yield the desired di(methylthio)-diamide product (L Py(NS)²). L Py(NS)² reacts instantly with copper(II) in acetonitrile or methanol under strictly dry and anaerobic conditions to yield a dark green copper(II) product that surprisingly undergoes spontaneous redox decomposition at room temperature, becoming pale yellow over the course of several hours. Copper(I) was quantitatively isolated from this decomposition mixture. To indirectly probe the role of the thioether as a possible copper(II) reductant in this system, an identical ligand was prepared without the thioether groups (L PyN²) by reaction of MPPD with acetic acid anhydride. L PyN² reacts instantly with copper(II), but does not promote redox decomposition under identical reaction conditions. The syntheses, properties, and copper reactivities of L Py(NS)², L PyN², and related ligands will be presented in conjunction with other synthetic evidence for direct copper(II) reduction by thioether sulfur.