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Copper and Zinc Chelation as a Treatment of Alzheimer's Disease MIROSLAV HODAK, JERRY BERNHOLC, North Carolina State University — Alzheimer's disease (AD) is a neurodegenerative disorder affecting millions of people in the U.S. The cause of the disease remains unknown, but amyloid-β (Aβ), a short peptide, is considered causal its pathogenesis. At cellular level, AD is characterized by deposits mainly composed of Aβ that also contain elevated levels of transition metals ions. Targeting metals is a promising new strategy for AD treatment, which uses moderately strong metal chelators to sequester them from Aβ or the environment. PBT2 is a chelating compound that has been the most promising in clinical trials. In our work, we use computer simulations to investigate complexes of a close analog of PBT2 with Cu^{2+} and Zn^{2+} ions. The calculations employ KS/FD DFT method, which combines Kohn-Sham DFT with the frozen-density DFT to achieve efficient description of explicit solvent beyond the first solvation shell. Our work is based on recent experiments and examines both 1:1 and 2:1 chelator-metal stochiometries detected experimentally. The results show that copper attaches more strongly than zinc, find that 1:1 complexes involve water in the first coordination shell and determine which one of several possible 2:1 geometries is the most preferable.

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