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Simultaneous Platinum and Copper Ion Attachment to a Human Copper Chaperone Protein MIROSLAV HODAK, North Carolina State University, JOHN CVITKOVIC, Worcester Polytechnic Institute, COREY YU, OLEG DMITRIEV, University of Saskatchewan, GEORGE KAMINSKI, Worcester Polytechnic Institute, JERRY BERNHOLC, North Carolina State University — Cisplatin is a potent anti-cancer drug based on a platinum ion. However, its effectiveness is decreased by cellular resistance, which involves cisplatin attaching to copper transport proteins. One of such proteins is Atox1, where cisplatin attaches to the copper binding site. Surprisingly, it was shown that both cisplatin and copper can attach to Atox1 at the same time. To study this double metal ion attachment, we use the KS/FD DFT method, which combines Kohn-Sham DFT with frozen-density DFT to achieve efficient quantum-mechanical description of explicit solvent. Calculations have so far investigated copper ion attachment to CXXC motifs present in Atox1. The addition of the platinum ion and the competition between the two metals is currently being studied. These calculations start from a molecular mechanics (MM) structural model, in which glutathione groups provide additional ligands to the Pt ion. Our goals are to identify possible Cu-Pt structures and to determine whether copper/platinum attachment is competitive, independent, or cooperative. Results will be compared to the ^{1}H, N^{1}5-HSQC NMR experiments, in which binding of copper and cisplatin to Atox1 produces distinct secondary chemical shift signatures, allowing for kinetic studies of simultaneous metal binding.

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