Electrochemical Analysis of Neurometallome on Dopamine Oxidation Utilizing the Gaussian Computational Framework

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Contemporary studies have shown that alpha-synuclein oligomers may have a pivotal role in the pathogenesis of Parkinson's Disease (PD) by inducing cellular toxicity leading to dopaminergic neuronal cell death. Simultaneously, it is found that the formation of these oligomers is promoted by the intermediates of dopamine oxidation (DOX), which can be catalyzed via transition metals in the neurometallome. Here, the study seeks to establish an understanding of which metals are the most capable of inducing such toxicity in PD, and the DOX mechanisms of these metals in the metal-dopamine complex (MDC) pathway. Gaussian software was employed to compute Gibbs free energies of resulting optimized geometries (M06/def2-SVP) via single-point energy calculations (wB97X-D/def-TZVPP). The energies of each MDC were used to derive redox potentials and the electron-transfer barrier energies to oxygen for comparison. The potentials were also compared against DOX-driving biological processes (Drivers) as a proxy to evaluate the frequency of occurrence. MDCs with Mn exhibited the strongest DOX tendencies (-0.19 V, 19.545 kcal/mol, favored by all Drivers) out of the metals investigated. The additional ligation of dopamine to trivalent transition metals also exhibited varying degrees of a shift in behavior favoring DOX, with Mn and Co being most significantly affected, suggesting a crucial orbital interplay for prospective investigation. The study proposes a strategic basis for therapeutic treatment of PD, leveraging the suggested DOX mechanism of Mn, while presenting the coexistence of both MDC and redox cycling pathways for other metals relevant in the neurometallome.

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