Contribution ID: **23** Type: **Contributed talk**

L-DOPA Autoxidation is Controlled by Water Proteolysis

Tuesday 16 September 2025 12:30 (20 minutes)

L-DOPA (tyrosine with an additional OH group) is dopamine (a monoaminergic neurotransmitter) precursor and is used in pharmacological treatment of Parkinson disease. Both dopamine and L-DOPA are unstable and beside MAO B enzyme catalysed dopamine decomposition [1] they can enter autoxidation reactions giving rise to hydrogen peroxide [2][3]. Moreover, L-DOPA is randomly built to proteins instead of aromatic amino acids where it is also autoxidized. The rate limiting step of the intramolecular Michael addition is water proteolysis. A similar rate-limiting step has been observed in carbonic anhydrase II [4] and staphylococcal nuclease [5]. Using the Empirical Valence Bond (EVB) method, we computed the free energy profiles for the reaction of L-DOPA incorporated into MAO A, replacing Tyr407 by considering full enzyme and water dimensionality. Critical step for EVB is evaluation of the experimental free energy profile for water proteolysis in bulk water and early experimental work of Eigen and De Maeyer [6] was critically revisited. The calculated barrier of 33.93 kcal mol-1 is 6.38 kcal mol-1 higher than the experimental barrier of 27.55 kcal mol-1 for L-DOPA in aqueous solution [3][7].

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Keywords

This abstract is submitted for....

HBond 2025 conference

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