Inhibition mechanism of Monoamine Oxidase B

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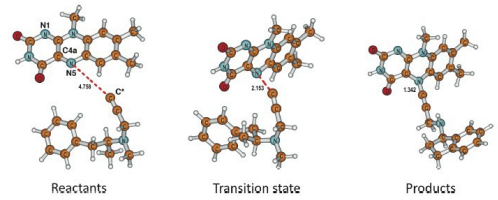
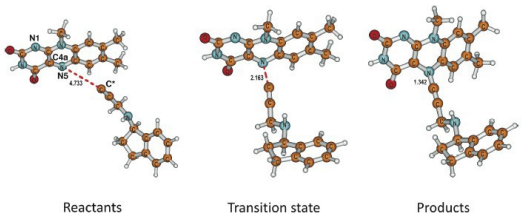
Monoamine oxidase (MAO) is an enzyme from the familly of flavoenzymes attached with its C-terminal end [1] to the outer mitochondrial membrane of brain, liver, intestinal, placental cells, and platelets. It is responsible for metabolism of important neurotransmiters serotonin, dopamine and norepinephrine, and it exists in two isozymic forms MAO-A and MAO-B. This two isozymic forms differ in selectivity to substrates and consequently to the inhibitors. MAO-A mainly metabolizes norepinephrine and serotonin. Inhibitors of MAO-A are used to elevate the norepinephrine and serotonin concentrations and thus improving the symptoms of depression. In contrast MAO-B is involved in metabolism of dopamine [2], a neurotransmitter involved in control of voluntary movement. Insufficient dopamine stimulation of the basal ganglia has been established to be a characteristic for Parkinson's disease [3, 4], therefore MAO-B inhibiton is one of the strategies for treatment of Parkinson's disease [3, 4] as a covalent bond between the inhibitor and MAO-B is formed upon inhibiton, i.e. in clinical use are for now irreversible inhibitors of MAO-B.



Structures of reactants, transition state and products for selegiline reacting with flavin.

Geometries were optimized at the HF/6–31G(d) level of theory.



Structures of reactants, transition state and products for rasagiline reacting with flavin.

Geometries were optimized at the HF/6–31G(d,p) level.

Despite huge efforts, there is no consensus about the mechanism of catalytic step. There have been three distinct mechanism proposed, by which MAO oxidazes substrates: 1) hydride mechanism, 2) radical mechanism [5] and 3) polar nucleophyllic mechanism [6-11]. They have in common the fact that the rate-limiting step is abstraction of the α-C proton proximal to amino group at the substrate, and being picked up by the N5 atom of flavin. As up to now no mechanistic or computational studies were performed for clinically used irreversible acetylenic inhibitors selegiline and rasagiline, we did the first computational study for the reaction between flavin moiety of flavin adenine dinucleotide (FAD) co-factor and acetylenic inhibitors selegiline and rasagiline. As the nature of covalent bond, despite many studies [12], is thus far unknown, we assumed a mechanism where an adduct between acetylenic inhibitor and FAD is formed, and we got a covalently formed inhibitor-flavin adduct. We believe that polar nucleophylic mechanism adopted in our study is more probable than the radical one, as the Hammet correlation coeficient indicates the negative charge buildup upon formation of the transition state [12].The results of this quantum-chemical study are promising and together with additional experimental and theoretical work they will lead toward better understanding of the nature of MAO inhibition and design of novel inhibitors.

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