Potential of Mean Force and Umbrella Sampling Simulation for the Transport of 5-Oxazolidinone in Heterotetrameric Sarcosine Oxidase

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Abstract

The structure of heterotetrameric sarcosine oxidase (HSO) contains a highly complex system composed of a large cavity and tunnels, which are essential for the reaction and migration of the reactants, products, and intermediates. Previous molecular dynamics (MD) simulation of HSO has identified the regions containing the water channels from the density distribution of water. The simulation is consistent with the selective transport hypothesis of the migration of the iminium intermediate, 5-oxazolidinone (5-OXA), of the enzyme reaction whereby tunnel T3 is the exit pathway of 5-OXA. In the present study, the potential of mean force (PMF) for the transport of 5-OXA through tunnels T1, T2, and T3 was calculated using umbrella sampling (US) MD simulations and the weighted histogram analysis method. The maximum errors of the calculated PMF were estimated by repeating the US simulations using different sets of initial positions. The PMF profiles for the three tunnels support the notion that tunnel T3 is the exit pathway of 5-OXA and that 5-OXA tends to stay at the middle of the tunnel. The PMF profile for the transport of glycine through tunnel T3 was also calculated to investigate where 5-OXA is converted into glycine, and how glycine is released to the outside of HSO was explained.

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Table 1. The five PMF profiles.

Profile	Molecule	Tunnel	Channel	Direction[α]
1	5-OXA	T1	CH1	Forward
2	5-OXA	T2	CH2	Forward
3a	5-OXA	T3	CH3	Forward
3b	5-OXA	T3	CH3	Inverse
G	glycine	T3	CH3	Forward

[α]"Forward" denotes the direction of SMDS from tunnel entrance to exit and "Inverse" denotes that from exit to entrance.