A Search for Hydride Shift Mechanism in Enzymatic Synthesis of Tetrahydrobiopterin

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Sepiapterin reductase (SR) is a homodimeric enzyme responsible for the synthesis of tetrahydrobiopterin (BH_4), a multifunctional cofactor associated with neuropsychiatric diseases[1,2,3]. Based on biochemical and crystallographic data[4,5], it has been hypnotized that SR reduces the C1’ carbonyl and then catalyses an isomerization reaction shifting the C2’ carbonyl group to the C1’ position. The final catalytic step includes NADPH-dependent reduction of the carbonyl group and generates *L-erythro*-BH_4. However, underlying mechanistic details of every step are not completely understood. In this computational study, we seek an answer for the following outstanding question: Is there a potential hydride shift mechanism in the isomerization step? Molecular dynamics and QM/MM molecular dynamics are in progress to provide precise information for enzymatic formation of BH_4. The underlying chemistry of this intriguing reaction may facilitate drug design for diseases such as Alzheimer’s and Parkinson’s disease.

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