

A Search for Hydride Shift Mechanism in Enzymatic Synthesis of TetrahydrobiopterinE. Bozkurt¹, R. Hovius¹, K. Johnsson^{1,2}, U. Röthlisberger^{1*}¹EPF Lausanne, ²Max Planck Institute for Medical Research Heidelberg

Sepiapterin reductase (SR) is a homodimeric enzyme responsible for the synthesis of tetrahydrobiopterin (BH₄), a multifunctional cofactor associated with neuropsychiatric diseases^{1,2,3}. Based on biochemical and crystallographic data^{4,5}, it has been hypothesized 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*-BH₄. 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 BH₄. 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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