

**A Search for Hydride Shift Mechanism in Enzymatic Synthesis of Tetrahydrobiopterin**E. Bozkurt<sup>1</sup>, R. Hovius<sup>1</sup>, K. Johnsson<sup>1,2</sup>, U. Röthlisberger<sup>1\*</sup><sup>1</sup>EPF Lausanne, <sup>2</sup>Max Planck Institute for Medical Research Heidelberg

Sepiapterin reductase (SR) is a homodimeric enzyme responsible for the synthesis of tetrahydrobiopterin (BH<sub>4</sub>), a multifunctional cofactor associated with neuropsychiatric diseases<sup>1,2,3</sup>. Based on biochemical and crystallographic data<sup>4,5</sup>, 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*-BH<sub>4</sub>. 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<sub>4</sub>. 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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