Insights on Enzyme Catalysis

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Catalysis and enzyme design are among the most fascinating and challenging aspects of chemical and biological research. Recent years have witnessed great progress in this area with computational techniques playing a central role as manifested by several recent de-novo designs of enzymes. Unfortunately, the improvement in catalytic rates of the resulting designs leave lot to be desired, emphasizing the complexity and variability of enzymes. We believe that part of the reason is insufficient consideration of factors that control enzyme reactivity.

Here we propose a better understanding of various factors that govern enzyme reactivity. We will use the valence bond (VB) based QM/MM approach.[1-3] VB is a quantum method that provides unique chemical insights and explanations to reaction mechanisms. The distinctive abilities of VB stem from the description of the wave-function as a mixture of well-defined electronic configurations which are easily interpreted as chemical structures. Our work will emphasize the contribution and advantage of the VB based methods compared with the other QM/MM methods in providing insights into chemical reactivity and enzyme catalysis. We will show the potential of these insights to improve enzyme design. We will focus on the S_N2 reaction which is the first step in the conversion of haloalkanes into alcohols within Haloalkane Dehalogenase (DhlA), and try to better understand the effect of the protein on the catalytic behavior.

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