Design - Insights from valence bond

Avital Sharir-Ivry, Rajapandian Vartharaj, Avital Shurki

The Institute for Drug Research, School of Pharmacy,

The Hebrew University of Jerusalem, Jerusalem 91120, Israel

Understanding enzyme catalysis and developing ability to control it, is an important challenge in biochemistry. The significant progress of ab-initio valence bond (VB) methodology within the 21st century together with its implementation within the hybrid ab-initio VB and molecular mechanics approach (VB/MM), enables, in turn, progress within the field of enzyme catalysis.[1,2] The VB/MM method uses the unique ability of the valence bond approach to provide chemical insight for the studied reactions, which is not available in other MO based methodologies. Our work uses this ability and offers a conceptually simple scheme to further our understanding of reactivity within enzymes. Using this scheme, we can identify the specific role that each residue within the enzyme plays in catalysis. The scheme is based on breakdown of the total catalytic effect into contributions of individual protein residues, which are further decomposed into chemically interpretable components, using valence bond. The scheme will be demonstrated. It will be shown to shed light on the origin of catalysis in wild-type Haloalkane dehalogenase and its mutants. Overall, the VB/MM is shown to be a powerful tool to study the mechanism of enzymatic catalysis as it provides information from ab-initio VB which is not readily available in other methods today.

[1] A. Sharir-Ivry, T. Shnerb, M. Štrajbl, A. Shurki, *J. Phys. Chem. B 114*, 2212-2218 (2010).

[2] Sharir-Ivry, V. Rajapandian, A. Shurki, *Chem. Eur. J. 21*, 7159-7169 (2015).