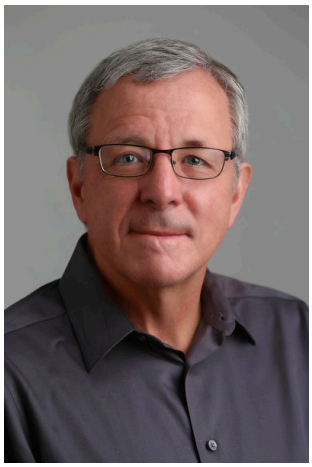
ERSBQ, Federal University of Juiz de Fora, November 10, 2018

Protein Conformational Stability and Stiffness: The Yin and Yang of Enzyme Catalysis

John P. Richard

Department of Chemistry, University at Buffalo, Buffalo, NY 14260, USA
jrichard@buffalo.edu



Abstract: The utilization of substrate binding energy to drive the thermodynamically unfavorable conversion of protein catalysts from a flexible, entropically rich, unliganded form to the stiff and catalytically active Michaelis complex, which shows a high affinity for the enzymatic transition state, is a common motif in enzyme catalysis (*1*). The coexistence of distinctive flexible and stiff enzyme forms provides a mechanism for the utilization of substrate binding energy to drive large enzyme conformational changes, that avoids the tight and irreversible binding of substrate. It is shown that the existence of flexible and stiff enzyme conformations favors efficient catalysis at physiological reaction conditions, and that these conformations comprise two halves which together complete the whole catalyst in enabling the extraordinary operational proficiency of enzymes. Recent experimental results will be discussed which show that dianion binding energy is utilized to drive the thermodynamically unfavorable enzyme conformational changes that activate enzymes for catalysis of proton (*2*), hydride (*3*) and phosphoryl transfer, and decarboxylation reactions (*4*). The use of this model in uncovering and rationalizing novel design elements that enable efficient enzyme catalysis, in providing unifying interpretations for disparate experimental, and in defining the role of protein dynamics in enzyme catalysis is discussed. The results of recent computational studies to model enzyme activation by ligand driven conformational changes are presented (*5, 6*).

---

1. Amyes, T. L., Malabanan, M. M., Zhai, X., Reyes, A. C., and Richard, J. P. (2017) *Prot. Eng. Des. & Sel. 30*, 157-165.
2. Zhai, X., Amyes, T. L., and Richard, J. P. (2015) *J. Am. Chem. Soc. 137*, 15185-15197.
3. He, R., Reyes, A. C., Amyes, T. L., and Richard, J. P. (2018) *Biochemistry 57*, 3227-3236.
4. Reyes, A. C., Amyes, T. L., and Richard, J. (2017) *J. Am. Chem. Soc. 139*, 16048-16051.
5. Kulkarni, Y. S., Liao, Q., Byléhn, F., Amyes, T. L., Richard, J. P., and Kamerlin, S. C. L. (2018) *J. Am. Chem. Soc. 140*, 3854-3857.
6. Kulkarni, Y. S., Liao, Q., Petrović, D., Krüger, D. M., Strodel, B., Amyes, T. L., Richard, J. P., and Kamerlin, S. C. L. (2017) *J. Am. Chem. Soc. 139*, 10514-10525.