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Formate-NAD interaction during formate oxidation in the active site of Candida boidinii formate dehydrogenase

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NAD-dependent formate dehydrogenase (FDH) uses NAD+ as cofactor to catalyze the oxidation of formate to CO_2 (Figure 1). The interaction between the formate anion and NAD+ is a case of an anion-π interaction. It has expectedly a strong electrostatic component, however, the low-lying empty π orbitals of NAD+ make this oxidant also a potential acceptor for donor-acceptor covalent bonding. In the present work, we used two energy decomposition schemes, EDA1 and NEDA2 to monitor the physical nature of the substrate-cofactor interaction during the reaction (H-COO- + NAD+ → CO_2 + NADH). The coordinates of the substrate-cofactor pair were taken from a QM/MM simulation of the reaction inside the Candida boidinii FDH by Guo et al.;3 these coordinates enabled us to study the interaction in the reactants state, transition state, and products state in the conformation and orientation the reacting partners have in the active site of the enzyme.

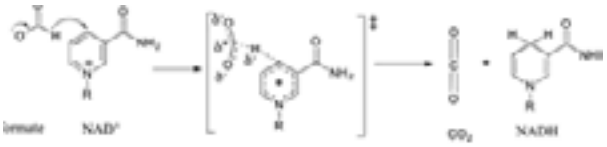

Figure 1: Mechanism of formate oxidation in the active site of FDH (reprinted with permission from Ref. 5)

Recent Publications

1. Te Velde G, Bickelhaupt FM, Fonseca Guerra C, van Gisbergen JA, Snijders JG, Ziegler T (2001) Chemistry with ADF. J. Comput. Chem. 22:931-967.
2. Glendening ED (2005) Natural energy decomposition analysis: Extension to density functional methods and analysis of cooperative effects in water clusters. J. Phys. Chem. A 109:11936- 11940.
3. Guo Q, Gakhar L, Wickersham K, Francis K, Vardi-Kilshtain A, Major DT, Cheatum CM, Kohen A (2016) Structural and kinetic studies of formate dehydrogenase from Candida boidinii. Biochemistry 55: 2760-2771.
4. Castillo R, Oliva M, Martí S, Moliner V (2008) A theoretical study of the catalytic mechanism of formate dehydrogenase. J. Phys. Chem. B 112: 10012-10022.
5. Ranasinghe C, Guo Q, Sapienza PJ, Lee AL, Quinn DM, Cheatum CM, Kohen A (2017) Protein mass effects on formate dehydrogenase. J. Am. Chem. Soc. 139:17405-17413.

Biography

Jiri Kozelka is Directeur de Recherche Emeritus in the laboratory « Dynamique des Systèmes et Interactions des Macromolécules Biologiques » (Université Paris Diderot, France) and Professor of biophysics at Masaryk university in Brno, Czech Republic. His domains of research include platinum antitumor drugs, DNA and protein structure, and weak interactions in chemistry and biology. In the present work, his team took profit from the availability of QM/MM models for the formate oxidation inside formate dehydrogenase to analyze the energy components of the interaction between the substrate (formate) and the cofactor (NAD+), in the orientation that the reaction partners have in the active site.