

Computational Calculations of pK_a Values of Metal Ligands in Proteins

Maryam Haji Dehabadi,^a Sonia Jafari,^a Ulf Ryde,^b Mehdi Irani^{*,a}

^a*Department of Chemistry, Faculty of Science, University of Kurdistan, Sanandaj, Iran*

^b*Department of Theoretical Chemistry, Lund University, Lund, Sweden*

*E-mail: m.irani@uok.ac.ir

Metalloenzymes are enzymes that use a metal cation as a cofactor in their active site. They catalyze various reactions, such as hydrolysis, oxidation, and reduction. Some examples of metalloenzymes are hydrogenases, which facilitate the uptake of molecular hydrogen; superoxide dismutase, which inhibits the oxidative damage to cells; nitrogenase, which enables the fixation of atmospheric nitrogen; proteases, which break down peptide bonds; and phosphodiesterases, which cleave phosphate ester bonds [1-4]. Many metalloenzymes are involved in acid-base reactions and have experimentally determined pK_a values. In this study, we calculate the pK_a values of 18 acid-base reactions in nine different metalloenzymes with varying metal ligands, metal centers (Zn, Mn, or Fe), protein cofactors, enzyme variants (wild type or mutated), or redox states of the metal centers. We compare our calculated values with the experimental ones. The metalloenzymes we study are alcohol dehydrogenase, superoxide dismutase, Rieske protein, thioredoxin-like ferredoxins, carbonic anhydrase, heme nitric oxide/oxygen binding protein, cytochrome P450, and myoglobin. We use quantum mechanics/molecular mechanics (QM/MM) calculations and the QM-cluster method in a continuum solvent to perform the calculations. We explore different variations of the approach, such as the QM method, the basis set, the size of the QM system, and the inclusion of the environment either implicitly as a continuum dielectric or explicitly as point charges. We also use the QM/MM thermodynamic cycle perturbation (QTCP) method to examine the effect of environmental dynamics on the calculations. Additionally, we use the Big-QM method, which employs a large QM system to do single-point QM/MM calculations on the structure that has been optimized using the original QM/MM technique. This study aims to determine which of the methods we test are the most accurate and whether they can be used for predictive analyses. We have obtained a set of data for pK_a using various methods, but we have not yet reached a conclusion on which method is the best.

Keywords: Metalloenzyme, pK_a, QM/MM, BigQM, QTCP

References

- [1] C. E. Valdez, Q. A. Smith, M. R. Nechay, A. N. Alexandrova, *Acc. Chem. Res.* **2014**, 47, 3110–3117.
- [2] D. K. Karlin, *Science*, **1993**, 261, 701–708.
- [3] A. F. Miller, *FEBS Lett.* **2012**, 586, 585–595.
- [4] B. M. Hoffman, D. Lukoyanov, Z.-Y. Yang, D. R. Dean, L. C. Seefeldt, *Chem. Rev.* **2014**, 114, 4041–4062.