

QM/MM Study of the Hydrolysis of Arginine Catalyzed by Arginase

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Arginase catalyses the hydrolysis of L-arginine to form L-ornithine and urea in the liver. According to the X-ray crystallographic structure (PDB code: 1RLA), rat liver arginase is homotrimer, each active site of which has two Mn(II) ions [1]. The chemical species of bridging oxo between two metals and catalytic reaction have been studied from both the experimental and theoretical sides [2-7]. In the present study, we used a combined quantum mechanics / molecular mechanics (QM/MM) approach to investigate the catalytic reaction. The spin-unrestricted density functional theory calculations with the empirical dispersion correction (D3) were applied to the QM region. Our QM/MM computations suggest that the structure-based mechanism proposed by Christianson and his co-workers [3,4] is likely to occur. The proton transfer step via Asp128 is found to be more favorable than the direct transfer process from the bridging oxo species to the leaving group.

- [1] Z. F. Kanyo et al. *Nature*, 383, 554 (1996).
- [2] S. V. Khangulov et al. *Biochemistry*, 34, 2015 (1995).
- [3] J. D. Cox et al. *Biochemistry*, 40, 2689 (2001).
- [4] E. Cama et al. *Biochemistry*, 42, 7748 (2003).
- [5] I. Ivanov, M. L. Klein, *J. Am. Chem. Soc.* 127, 4010 (2008).
- [6] M. Leopoldini et al. *Chem. Eur. J.* 15, 8026 (2009).
- [7] T. Saito et al. *Supramol. Chem.* 23, 22 (2011).