Histidine Protonation State Regulates the Structural Stability of R state Hemoglobin

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The biological functions of proteins are derived from their unique structures and are regulated by effectors and substrate molecules. O_2-carrying Hemoglobin (Hb) is the most well-studied example, its function being regulated by O_2 and heterotropic allosteric effectors (H^+, Cl^-[1], *etc.*). The pH dependence of its O_2 affinity is known as the Bohr effect and the contribution of βHis143 and βHis146 was indicated to be especially significant, but the mechanism has not yet been elucidated in detail. Therefore, we investigated the effect of the protonation states of βHis143 and βHis146 on the structural stability of the high O_2 affinity states of Hb using molecular dynamics (MD) simulations, and observed the conformational transitions among the R, R2, RR2, and R3 states. These protonation states promote the conformational transitions from the R state to the RR2 and R2 states, while they have no effect on the transitions from the R2 state. This suggests that these protonated states affect the stability of the R state[2]. The result that the protonated His promotes the R→R2 conformational transition is consistent with the experimentally confirmed fact that the R2 state crystallizes under low pH conditions.

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[2] H. Yotsuya, M. Tanaka, Y. Kitamura, M. Nagaoka, *ibid., in preparation*.