Electrostatic stress in catalysis: structure and mechanism of the enzyme orotidine monophosphate decarboxylase

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Orotidine 5'-monophosphate decarboxylase (ODCase) catalyzes the conversion of orotidine 5'-monophosphate (OMP) to uridine 5'-momophosphate (UMP), which is the last step in biosynthesis of pyrimidine nucleotides. As part of a Structural Genomics Initiative, the crystal structures of the ligand-free and the 6-azauridine 5'-monophosphate-complexed forms have been determined at 1.8 and 1.5 Å respectively. ODCase is a functional dimer. Each monomer assumes a TIM-barrel fold with one side of the barrel closed off and the other side binding the inhibitor where residues from both monomers are involved. A unique array of alternating charges (Lys-Asp-Lys-Asp) combined with a hydrophobic pocket in the active site prompted us to apply quantum mechanical and molecular dynamics calculations to analyze the relative contributions of ground state destabilization and transition state stabilization to catalysis. The remarkable catalytic power of ODCase is almost exclusively achieved via destabilization of the reactive part of the substrate, which is compensated for by strong binding of the phosphate and ribose groups. The computational results are consistent with a catalytic mechanism that is characterized by Jenck's Circe effect.

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