Tracking active-site solvents in human carbonic anhydrase II

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Human carbonic anhydrase II (hCA II) is a zinc metalloenzyme that catalyzes the reversible hydration/dehydration of carbon dioxide and water to bicarbonate and a proton. In this study, ultrahigh-resolution crystallographic structures of hCA II cryocooled under various CO_2 internal pressures are presented. The structures reveal new intermediate solvent states of hCA II that provide crystallographic snapshots during the restoration of the proton-transfer water network in the active site. Based on these structures, a water network-restructuring mechanism is proposed. This mechanism explains how waters in the active sites are replenished, which are directly responsible for the reconnection of the proton-transfer water network. This study provides the first 'physical' glimpse of how a water reservoir flows into the hCA II active site during its catalytic activity.