CYCLE DE CONFÉRENCES DE CHIMIE

Avec le concours de : Université Clermont Auvergne
INP Clermont Auvergne

Jeudi 5 décembre à 15 h

Amphi Rémi (site des Cézeaux)

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The role of identical charges in enzyme catalysis: Friends or foes?

The origins of enzyme catalysis have been attributed to both transition-state stabilization as well as ground-state destabilization of the substrate. For the latterparadigm, the enzyme orotidine-5'-monophosphate decarboxylase (OMPDC)serves as a reference system as it contains a negatively charged residue at the active site that is thought to facilitate catalysis by exerting electrostatic stress on the equally charged substrate carboxylate leaving group. Snapshots of how the substrate binds to the active site and interacts with the negative charge had remained elusive. In this talk, I will discuss ultrahigh-resolution crystallographic snapshots of human OMPDC in complex with the genuine substrate, substrate analogues, transition-state analogues and product that defy the proposed ground-state destabilization by revealing that the substrate carboxylate is protonated and forms a favorable low-barrier hydrogen bond with a negatively charged residue. The catalytic prowess of OMPDC mostly results from transition-state stabilization by electrostatic interactions of the enzyme with charges spread over the substrate but also in part from ground-state destabilization through physical distortions of the substrate. Our findings bear relevance for the design of (de)carboxylase catalysts.

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