Structure correlation analysis of the nucleophilic attack in the three Classes of L-asparaginases

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L-Asparaginases, which hydrolyze L-asparagine to L-aspartate and ammonia, are divided into three unrelated structural Classes, further subdivided into five types [1]. In each Class, the hydrolysis reaction is thought to proceed via a nucleophilic attack of an activated Thr or Ser residue on the carbonyl Csp^2 atom of the substrate amide group. In each Class, there is at least some ambiguity or controversy about the identity of the primary nucleophile. In Class 1 (e.g. EcAII), one Thr is part of a TKD triad and another is linked to a proton sink by a chain of water molecules. In Class 2 (EcAIII), the N-terminal Thr nucleophile is supposedly activated by the very N-terminal NH_2 group. In Class 3 (ReAV), the nucleophile is part of two S-K tandems. Structural chemistry has, however, excellent tools to figure out reaction mechanisms, based on the application of the structure correlation method (SCM) proposed by Bürgi [2]. Its principle allows one to predict a reaction trajectory if sufficiently many structural (crystallographic) examples of the reagents along the reaction path are known. In structural enzymology, SCM application is based on the availability of structural examples of the enzyme in complex with its substrate, product, or other mimic of the catalytic reaction. With respect to the nucleophilic attack on a carbonyl group, the stereochemistry is governed by the Bürgi-Dunitz angle [3], later supplemented with Flippin-Lodge angle [4] or the Φ_{attack} torsion angle of Herschlag [5]. In this work, we applied the SCM concept to the tree Classes of L-asparaginases in the PDB, identifying in each case the most probable nucleophilic residue.

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