

Multiple catalytic promiscuity

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‘Promiscuous’ enzymes possess additional activities on top of their native ones. We demonstrate this principle with observations of strong promiscuous activities with rate accelerations between 10^9 and 10^{15} in a class of hydrolytic enzymes that share an unusual formylglycine active site nucleophile. Promiscuity in these enzymes is not limited to a single activity, but allows the same active site to catalyse up to six activities efficiently in addition to its native activity. Promiscuous activities could be remnants from the evolutionary ancestor that has been gene duplicated and adapted to fulfill a new function. Alternatively the observation of promiscuity could indicate that an enzyme is ‘pregnant’ with another activity, i.e. has the potential to be mutated or evolved into a new catalyst. Thus the observation of promiscuity could define functional relationships in enzyme superfamilies, to serve a basis for drawing up phylogenetic relationships for catalysis. We underpin this analysis with structural and kinetic data on members of this class of promiscuous hydrolases