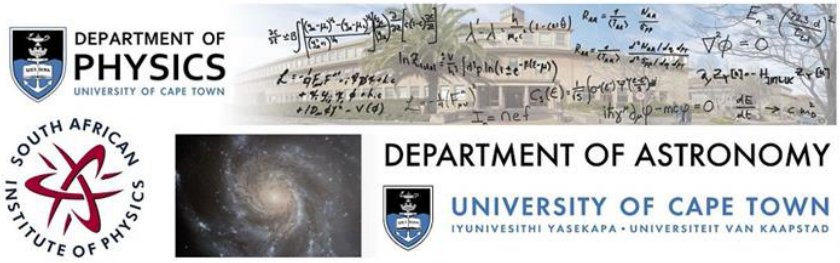

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An Experimental Physicist's view of Enzyme Reaction Mechanisms

Monday, 4 July 2016 15:20 (40 minutes)

Abstract content
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Enzymes assist in the making and breaking of chemical bonds. They do this with astonishing specificity and economy. Sometimes Nature utilizes very similar active sites to catalyze different chemical reactions or to selectively catalyze a reaction with some substrates but not other, similar substrates. Biochemistry textbooks are replete with naïve explanations that seek to generalize to a point that would have students believe that the field is well understood, but close inspection reveals that this is not the case. We have studied amidases and nitrilases that belong to the same superfamily and in the crystalline forms have clusters of four amino acids that are directly superimposable. Yet nitrilases convert nitriles to the corresponding carboxylic acid and ammonia and amidases convert amides to the same products. However nitrilases differ from amidases in forming spiral oligomeric forms, which, evidence suggests, are essential for activity. In the case of the amidases, we have mutated the putative catalytic residues and determined the structures of the complexes that result when the mutated, inactive enzyme reacts with substrate. In most cases the observed reaction products were not predicted by the prevailing mechanistic hypotheses and this has prompted the proposal of a new mechanism supported by quantum mechanical computations of the transition states. Understanding of the amidase mechanism presents a conundrum for the prevailing nitrilase mechanism. This can be resolved only by postulating an entirely novel reaction sequence that must be experimentally verified.

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