How enzymes work: UB chemists publish a major discovery

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In a publication selected as a "2007 Hot Article" by the journal *Biochemistry*, University at Buffalo chemists report the discovery of a central mechanism responsible for the action of the powerful biological catalysts known as enzymes.

The UB research provides critical insight into why catalysis is so complex and may help pave the way for improving the design of synthetic catalysts.

“The more that is known about catalysis, the better chances we have of designing active catalysts,” said John P. Richard, Ph.D., professor of chemistry in the UB College of Arts and Sciences and co-author of the paper with Tina L. Amyes, Ph.D., UB adjunct associate professor of chemistry.

“Attempts to replicate evolution and design catalysts of non-biological reactions with enzyme-like activity have failed, because scientists have yet to unravel the secrets of enzyme catalysis,” Richard said.

But, he said, these secrets, once revealed, have the potential to transform the chemical industry in processes ranging from soft-drink manufacturing to the production of ethanol and countless other industrial processes. “Enzymes are the products of billions of years of cellular evolution,” he said.

While attempts to design catalysts have been somewhat successful, the

catalysis that results is far less efficient than that produced by reactions with enzymes.

Richard explained that protein catalysts are distinguished by their enormous molecular weights, ranging from 10,000 to greater than 1,000,000 Daltons, whereas a synthetic molecule with a weight of 1,000 would be considered large.

The recent results by Richard and Amyes provide critical insight into why effective catalysis requires such large molecules.

Catalysis starts with molecular recognition of the substrate by the catalyst, Richard explained.

The so-called “catalytic” recognition is limited in man-made catalysts to several atoms that participate in the chemical reaction.

Amyes and Richard have provided compelling evidence that interactions between enzymes and non-reacting portions of the substrate are critical for large catalytic rate accelerations.

“These findings demonstrate a simple principle of catalysis that is important for many enzymes that catalyze reactions of substrates containing phosphate groups and which can be generalized to all enzymes,” said Richard.

He explained that the chemistry between a catalyst and substrate occurs where groups of amino acid residues interact with the substrate.

But enzymes also have domains that interact with the non-reacting parts of the substrate, he continued.

“A flexible loop on the enzyme wraps around the substrate, burying it in

an environment that's favorable for catalysis," he said. "In order to bury the substrate, certain interactions are necessary that allow the loop to wrap around the substrate and that's what the phosphate groups on the substrate are doing."

The UB research demonstrates just how important this process is to catalysis.

"We've shown that these interactions are critical to the process of making reactions faster," said Richard. The critical experiment by the UB researchers was to clip the covalent bond that links the phosphate groups to the substrate.

"We have found that the interactions between phosphate groups and several enzymes are used to promote the chemistry even in the absence of a covalent linkage," said Richard. "These results have surprised many enzymologists."

To conduct the research, Richard and Amyes developed a specialized and technically difficult assay for enzyme activity that uses nuclear magnetic resonance spectroscopy to detect chemical reactions that would normally be invisible.

Link: www.buffalo.edu/news/pdf/June0 … hardBiochemistry.pdf

Source: University at Buffalo