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Without Enzyme Catalyst, Slowest Known Biological Reaction Takes 1 Trillion Years

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Summary: All biological reactions within human cells depend on enzymes. Their power as catalysts enables biological reactions to occur usually in milliseconds. But how slowly would these reactions proceed spontaneously, in the absence of enzymes - minutes, hours, days? And why even pose the question?

FULL STORY

CHAPEL HILL -- All biological reactions within human cells depend on enzymes. Their power as catalysts enables biological reactions to occur usually in milliseconds. But how slowly would these reactions proceed spontaneously, in the absence of enzymes - minutes, hours, days? And why even pose the question?

One scientist who studies these issues is Dr. Richard Wolfenden, Alumni distinguished professor of biochemistry and biophysics and chemistry at the University of North Carolina at Chapel Hill and a member of the National Academy of Sciences. In 1998, he reported a biological transformation deemed "absolutely essential" in creating the building blocks of DNA and RNA would take 78 million years in water.

"Now we've found one that's 10,000 times slower than that," Wolfenden said. "Its half-time - the time it takes for half the substance to be consumed - is 1 trillion years, 100 times longer than the lifetime of the universe. Enzymes can make this reaction happen in 10 milliseconds."

Wolfenden, along with co-authors Chetan Lad and Nicholas H. Williams of Sheffield University in England, published a report of their new findings April 29 in the online "early edition" of the Proceedings of the National Academy of Sciences. Print publication is slated for May 13.

The report highlights the catalytic power of phosphatase enzymes to tremendously enhance the transformation rate in water of a specific group of biochemicals: phosphate monoesters. Protein phosphatase enzymes acting on these monoesters help regulate the molecular cross-talk within human cells, the cell signaling pathways and biochemical switches involved in health and disease.

"We have esters floating around in our cells with all kinds of functions," Wolfenden said. "Every aspect of cell signaling follows the action of the type of phosphatase enzyme that breaks down phosphate monoesters. Other phosphatases highlighted in the study for their catalytic power help mobilize carbohydrates from animal starch and play a role in transmission of hormonal signals."

As to the uncatalyzed phosphate monoester reaction of 1 trillion years, "This number puts us way beyond the known universe in terms of slowness," he said. "(The enzyme reaction) is 21 orders of magnitude faster than the uncatalyzed case. And the largest we knew about previously was 18. We've approached scales than nobody can grasp."

Why would we want to know the rate of a biological reaction in the absence of an enzyme?

That information would allow biologists to appreciate what natural selection has accomplished over the millennia in the evolution of enzymes as prolific catalysts, Wolfenden said. It also would enable scientists to compare enzymes with artificial catalysts produced in the laboratory.

"Without catalysts, there would be no life at all, from microbes to humans," he said. "It makes you wonder how natural selection operated in such a way as to produce a protein that got off the ground as a primitive catalyst for such an extraordinarily slow reaction." Experimental methods used to observe very slow reactions can generate important information for drug design.

"Enzymes that do a prodigious job of catalysis are, hands-down, the most sensitive targets for drug development," Wolfenden said.

"The enzymes we studied in this report are fascinating because they exceed all other known enzymes in their power as catalysts. We've only begun to understand how to speed up reactions with chemical catalysts, and no one has even come within shouting distance of producing their catalytic power."

Wolfenden's research on enzyme mechanisms and water affinities of biological compounds has exerted major influences in these areas. His research also has influenced rational drug design; findings from his laboratory helped spur development of ACE inhibitor drugs, now widely used to treat hypertension and stroke.

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