

# The Simplest Enzyme Revisited

## *The Chicken and Egg Argument Solved*

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In the 6 December 2002 issue of *Science*, Mohammed Movassaghi and Eric N. Jacobsen presented a perspective entitled “The Simplest Enzyme.” Using proline as an example, they concluded that “synthetic small molecule catalysts can approach and sometimes even match the enantioselectivity and reactivity characteristic of enzymes.” The use of proline in aldol additions has been known for several decades, but the significance in biochemistry and biogenesis has not been given much attention. Fifty years ago enzymes were identified exclusively with proteins, polypeptides of 100 or more amino acids. Later, the discovery of ribozymes showed the catalytic potential of ribonucleic acids. We now deal with relatively small molecules as biocatalysts. Sandra Pizzarello and Arthur Weber (*Science* 2004, 303, 1151) have followed up these ideas in “Prebiotic Amino Acids as Asymmetric Catalysts.”

Small molecule catalysis is a finding of utmost importance for the origin of biochemistry. Think of the chart of intermediary metabolism. In graphic form the dots are substances and the lines are reactions. Next take a clear plastic overlay and connect dots to reactions that they catalyze. This is then a metagraph that organizes the array of substances, the concentration distribution, and the array of cycles in the network. The distributions and flows with the overlay will be vastly different from the uncatalyzed network. The distribution is an emergent feature of the catalytic property of small molecules.

Because both amino acids and nucleotides have molecules of catalytic potential, the chicken and egg argument between proteins and nucleic acid polymers disappears. The answer to “which came first, protein or nucleic acid” is: “metabolism.” They grew up together by catalyzing each other’s reactions. In this context sugars and amino sugars may also play a significant role. All of this opens up a study of the catalytic potential of functional groups in small molecules. This is related to the study of the functional groups of molecules that form the active sites in large polymers and their cofactors.

How does small molecule catalysis change our view of prebiotic evolution? Smith and Morowitz (*Proc Natl Acad Sci USA* 2004, 101, 13168–13173) have elaborated the arguments for the reductive citric acid cycle being the core of all anabolism in autotrophs, the starting points of all synthetic pathways. The introduction of nitrogen, largely through the amination of keto acids, begins the domain all small molecule catalysis. The introduction of polymerization, almost universally involving dehydration reactions driven by the hydrolysis of pyrophosphates, allows for more sophistication and fine tuning of catalysts. This fine

tuning is continued up to the macromolecular world of present day biology. Intermediate between the core intermediary metabolism utilizing relatively small molecules and contemporary biochemistry must have been an oligomeric world involving symbiosis between polypeptides and polynucleotides. Christian de Duve prefers multimer to oligomer, implying less specificity in what is bound together.

“Oligomeric” is used here because beyond the original chart increase in complexity and molecular size occurs today by polymerizations involving dehydration reactions driven by the breakdown of polyphosphates. With the introduction of coding, macromolecules (polymers larger than oligomers) took over aided by the horizontal exchange of genes. Thus, we have found to date few relics of the multimeric world, although such a search has

not been organized in a systematic fashion. One might look at tRNA cofactors and signaling peptides. Through all of the development of the polymer domain, core intermediary metabolism has robustly persevered, which allows us to reconstruct primitive metabolism through contemporary universal or almost universal metabolic pathways. One task ahead of us is to recover and understand the oligomeric and multimeric worlds.