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A Feast for Chemists

R. B. Woodward was once asked, of a particularly arcane piece of bioorganic chemistry, "But is it really *chemistry*?". He answered, with that splendid broadmindedness that refused to recognize intellectual constraints, "If it's *interesting*, then it's chemistry". This special issue on Mechanistic Enzymology is in happy testimony to that spirit, for herein are collected more than a dozen chapters in which several exciting areas of enzymology are dissected and described. One can barely begin, of course, to cover the chemical and mechanistic aspects of enzyme-catalyzed reactions in only 14 articles. Yet we do not need to experience every taste of every dish at every meal: Even at a feast, the menu must be selected and balanced.

The main course, at this sitting, brings biosynthesis to the enzyme level. For decades, the goal of most biosynthetic work was simply to define the transformations and to produce a sort of "secondary metabolic pathways chart" where all chemical change was (magically) mediated by arrows. But now, as illustrated by the contributions of Battersby, Baldwin, Cane, and Walsh, we start to see, with enzymes that have been cloned and overproduced, answers to the question of *how* one metabolite is transformed into another. We need not now be content merely to arrive (by straight arrows); we can ask how we got there (via curly arrows). In each of these four chapters, the problems of oligomer assembly and product manipulation are evident, as porphyrins are elaborated from four porphobilinogen units, penams are forged from Arnstein's tripeptide, farnesyl pyrophosphate is wrapped up into cyclic sesquiterpenes, and enterobactin is assembled from dihydroxybenzoate.

A second set of selections for those with a more physical–organic appetite is provided by the mechanistic contributions of Frey, Johnson, Kluger, and Sinnott. Here several enzymic processes are subjected to detailed mechanistic scrutiny of the kind that defines the structure of relatively fleeting reaction intermediates, by trapping and structure elucidation, by detection of their spectroscopic signatures, and by correlations of structure and reaction rate. Both the firepower of direct bombardment and more indirect data-gathering exercises are used to expose the intermediacy of covalent adducts, of carbocations, of carbanions, and of radical species. Enzymologists sometimes ponder on the possibility that mechanistic definition of an enzymic reaction may be achieved to a resolution higher than is possible for uncatalyzed reactions in free solution, since the substrate's surroundings (the constellation of groups at the active site) are characterized so much more precisely. Whether or not this is true, there is certainly room for more intellectual traffic between the chemist and the enzymologist.

The third group of contributions carry us to reactions involving the movement of small items like protons (Schwab), electrons (Malmström), and one-carbon units (Matthews) and to processes involving macromolecular substrates such as DNA and RNA (Benkovic and Schimmel). Here, there are new lessons and new challenges, and we can enjoy the use of unfamiliar methods and unusual approaches in the unraveling of the apparent complexity of the catalytic assemblies that nature has produced to handle both very small and very large substrates. Finally, while the modification of enzymes by site-directed mutagenesis is touched on in several chapters, the contribution by Armstrong asks a question of especial interest to the chemist who seeks new reagents. What can we expect from the manipulation of whole chunks of proteins, in the search for enzymes of altered substrate specificity and changed catalytic activity?

In the face of all these delectable items, must we not recognize that the mechanistic problems of biochemistry are really very interesting and that Woodward was, once again, correct?

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