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From Enzyme Models to Model Enzymes

In teaching, one always recommends books to complement the lectures or courses. This is particularly difficult when presenting a course on bioorganic chemistry for chemistry students, as there are only a few books that cover the area thoroughly. My favorite book was *Enzymatic Reaction Mechanisms* by Christopher Walsh. Unfortunately, this book published in 1979 was never updated and reissued. In my view the only book that comes close to "Walsh" is the one published more recently (in 2000) by Richard B. Silverman: *The Organic Chemistry of Enzyme Catalyzed Reactions*. That volume contains an enormous wealth of experimental data, and for that reason it is nowadays the leading reference source. However, it is probably too detailed and elaborate for students to swallow.

In contrast, the new book *From Enzyme Models to Model Enzymes*, by Anthony J. Kirby and Florian Hollfelder, can be highly recommended to students as a supplement to a corresponding lecture course. It is beautifully written, and it is relatively short because of the fact that it focuses on a small window of enzymatic reactions.

The introduction (about 60 pages) provides an adequate overview of the basic principles of enzymatic reactions, kinetics, and catalysis. The main part of the book deals with hydrolytic reactions that are catalyzed by various proteinogenic amino acids and corresponding metal complexes. Each chapter usually begins with a short introduction to the chemical problem of catalyzing a particular reaction to achieve a high k_{cat}/k_{uncat} ratio at a pH value of 7 at room temperature. After that, the relevant enzyme mechanisms and kinetics are discussed in detail, and that is complemented by a selection of intramolecular models and enzyme mimics, with a critical evaluation of their design and characteristic features.

The next part of the book is concerned with enzyme-catalyzed transfer of H^+, H^-, and $H^\bullet$. In this context the enolase super-family of enzymes is discussed, together with a few examples of dehydrogenases and corresponding model compounds. The significance of free-radical chemistry is briefly mentioned, with particular reference to ribonucleotide reductases.

Pericyclic reactions are of particular importance for synthesis, and a few examples of relevant enzymes, such as chorismate mutase and Diels-Alderases, are known in biological chemistry. As these reactions do not in principle require acid–base catalysis, the origin of the relatively modest enzymatic acceleration is of interest. This aspect is well discussed and is compared with the efficiency of synthetic enzyme mimics and reactions that are catalyzed by antibodies generated by means of transition-state analogues.

The following chapters of the book focus on the chemistry and procedures that could be useful to mimic nature's methods for the design and selection of active sites in order to obtain optimal catalysts. With regard to the design principles, concepts such as molecular imprinting and the use of dendrimers and catalytic antibodies are mentioned. It is found that the most efficient systems, by far, are those based on TSA-generated antibodies, which yield k_{cat}/k_{uncat} ratios of up to 10^6.

The principle of selection is the SELEX methodology, an iterative procedure that can, for example, optimize RNA to catalyze even non-natural reactions in a way that competes well with designed synthetic enzyme models. Protein evolution is a much more challenging task, mainly because of the "vastness of sequence space" and the "delicacy of protein structures". Nevertheless, the last part of the book describes the progress in this area by discussing a few examples.

The chapters on directed evolution are particularly helpful for advanced students, as they provide a very good introduction that serves as the basis for further reading. Recommendations for further reading are given at the end of each chapter, and altogether more than 480 references are cited.

Coenzymes, in particular metal complexes, are not covered in this book. For these subjects, books such as *Bioorganic Chemistry* by H. Dugas or *Principles of Bioinorganic Chemistry* by S. J. Lippard and J. M. Berg can be recommended.

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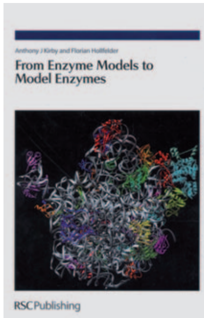

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