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BOOK REVIEWS

Cytochrome P450: Structure, Mechanism, and Biochemistry, 3rd ed. Edited by Paul R. Ortiz de Montellano (University of California, San Francisco). Kluwer Academic/Plenum Publishers: New York. 2005. xx + 690 pp. $149.00. ISBN 0-306-48324-6.

The three editions of *Cytochrome P450: Structure, Mechanism, and Biochemistry* have appeared at approximately ten-year intervals and present a snapshot of the field of cytochrome P450 at each decade, with some retrospective on the previous edition's unanswered questions. This edition continues the tradition established in the first two volumes and covers exactly what the title suggests. Eleven of the authors from the second edition contributed to the third, providing considerable continuity in their stories. The third edition focuses exclusively on P450, and two earlier chapters comparing P450s to peroxidases, chloroperoxidase, and nitric oxide synthase have been dropped. This has permitted the welcome addition of two excellent chapters on P450s in plants and the diversity of P450s in microbes, including bacteria and fungi.

This book is really two books in one. In 1959, C. P. Snow delivered his famous Rede Lecture on the "two cultures", meaning the humanities and the sciences, in which he discussed how practitioners of the two disciplines know little about each other and how communication between the two camps is difficult as a consequence (Snow, C. P. *The Two Cultures and the Scientific Revolution*; Cambridge University Press: New York, 1959). In much the same way, I think that the practitioners in the P450 field can be divided into chemists and molecular biologists, all of whom appear to suffer from the same difficulty. I find myself in the molecular biology camp. This made reading the chapters on models and mechanisms, computational approaches, substrate oxidation, and inhibition very challenging, but in the end quite rewarding. I gained a much greater appreciation for the elegant and difficult biochemistry that cytochrome P450 must experience without itself being destroyed with each turn of the catalytic cycle. I also learned how the subtleties of the active site architecture influence the "push effect" of the thiolate ligand and control uncoupling by providing thermodynamic barriers to undesired side reactions. These chapters especially emphasized the exquisite dependence of function on structure, down to the presence of water molecules at precise locations, the importance of hydrogen bond networks to fine-tune the electrical properties of the thiolate, and the effect of single side chains on substrate orientation and product formation. The richness of detail in these chapters was remarkable.

Every book has a particular emphasis, and scientific books are no different. One idea that is referred to multiple times in the book by several authors is the two-state reactivity model of Shaik. Chapter two by Shaik and De Visser describes this model in some detail. The basic idea is that the reactive iron−oxygen complex at the heart of the P450 mechanism can exist in two electronic configurations, with electrons occupying different orbitals of nearly the same energy. The outcome of the reaction depends on which state (high-spin or low-spin) is involved in completing the reaction. This model, based on computational studies of the mechanism, appears to explain many experimental results that were difficult to reconcile previously. This two-state model is certainly one of the scientific highlights presented in the third edition.

One take-home message from the chemistry and quantum chemistry chapters is that structure matters, and it matters both in terms of the physical 3D space as well as the electronic landscape. One comes away with a strong sense of the perfection of each active site and how key changes at the level of a few tenths of an angstrom would ruin a P450 enzyme. This realization has implications for P450 modelers who compute models based on the crystal structures of cytochrome P450 from bacteria, as in CYP102, or from mammals, as in CYP2C5. Usually these models are for other families of P450 proteins, and the sequence similarity is low, often less than 25%. Information in the chemically based chapters of the third edition would suggest that models of this type could never achieve the necessary accuracy needed to predict substrate binding or mechanism and may be pointless exercises.

The molecular biology side of the third edition also has some gems. The chapter by Guengerich on human P450s fills one-quarter of the book, and it is the most comprehensive detailing of these 57 enzymes that exists anywhere. It would be worth buying the book just to have this chapter with its 1500+ references. The chapter by Williams et al. on induction of P450 enzymes was the clearest exposition on this topic I have read. In another chapter, Poulos and Johnson, who have solved bacterial and mammalian P450 structures, provide a basic introduction to the structure of these enzymes, with emphasis on the bacterial structures.

In reading this book, I began at the back because I was very interested in the plant, bacterial, and fungal P450s, and I wanted to see what these chapters contained. Plant P450s are a huge topic in themselves, with over 300 different P450 genes in a single plant like rice or poplar. Nielsen and Møller provide a useful introduction covering brassinosteroid, flavonoid, alkaloid, and glucosinolate biosynthesis and additional topics. This chapter will be very helpful to those who need a summary of this broad area. The chapter on biodiversity in microbial CYPs spans many areas, including fusions to electron transport proteins, evolution of CYP51, mycobacterial, archaebacterial, and streptomycete CYPomes, and the basis of antifungal drug resistance.

In another chapter, Capdevila et al. cover P450s involved in arachidonic acid metabolism and the potential importance of P450s in hypertension and cardiovascular disease. The Cyp4a14 mouse knockout enhances this story by providing a novel mouse model. Waxman and Chang cover the sex-specific P450s CYP2C11 and CYP2C12 in the rat and the regulation of P450s by steroid hormones, growth hormones, thyroid hormones, and various drugs, chemicals, and diseases such as diabetes. Of course, none of these enzymes will run without a source of

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electrons. Chapter 4 on electron-transfer partners covers this quite thoroughly, including the enigmatic cytochrome b_5 that can enhance P450 activity, in some cases even in the apoenzyme form. The chapter on activation of molecular oxygen, though ostensibly aimed at the chemist, is very accessible to the molecular biologist. The authors, Makris, Denisov, Schlichting, and Sligar, should be commended for bridging the two cultures in their presentation. Current views are given on the P450 catalytic cycle, and this is related to the role of particular side chains, such as T252 and D251 in CYP101.

The whole book is of uniformly high quality. Even the appendix, which lists inducers, substrates, inhibitors, and noninvasive markers, including structures, will be very useful. There is much that can be learned even by experts in the field. I was surprised to find out that CYP17 and CYP19 (aromatase) have very similar three-step oxidations in their mechanisms that break a carbon−carbon bond, even though the substrates and products of these enzymes are very different. Such observations may provide clues to the origin of the aromatase enzyme, which does not resemble any other P450 in its sequence. This book may serve as a reference or as an introduction to specific areas. P450 researchers will want a copy within easy reach, while the nonspecialist will be grateful to have the book in the campus library.

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