BOOK REVIEWS

Enzyme Frontiers

Cytochrome P450. Structure, Mechanism, and Biochemistry. PAUL R. ORTIZ DE MONTELLANO, Ed. Second edition. Plenum, New York, 1995. xii, 652 pp., illus. $125.

Cytochrome P450 is a heme enzyme that has something for everybody. Its ability to activate molecular oxygen for incorporation into unactivated hydrocarbons has intrigued organic chemists; its unusual heme iron coordination structure and sequence of intermediates have challenged inorganic chemists; its unique spectral properties and electronic structure have engaged physical and theoretical chemists; its ability to metabolize xenobiotics and potential for use in bioremediation have excited environmental chemists; its importance in drug metabolism has garnered the attention of medicinal chemists and pharmacologists; its inducibility and ever-growing gene superfamily have fascinated molecular biologists; and its involvement in natural-product biosynthesis, membrane detoxification, and chemical carcinogenesis have stimulated biochemists around the world. In keeping with this interest, cytochrome P450 has since its discovery in the 1950s been the subject of several books, numerous review articles, and countless conferences. The 1986 edition of *Cytochrome P-450: Structure, Mechanism, and Biochemistry* is probably the most frequently cited single source of information about the subject. Hoping that lightning will strike twice, Ortiz de Montellano has now produced a second edition with 15 new chapters. In my estimation, he has again succeeded in bringing the P450 field into sharp focus.

The new edition is divided into four sections. The opening section contains a chapter each on two types of model systems often used to study P450. Groves and Han provide a thorough discussion of functional metalloporphyrin model systems, and Marnett and Kennedy review how studies of peroxidases can provide insight into the mechanism of P450. These authors do excellent jobs blending the results on the model systems with related research on P450 enzymes. Groves and Han, for example, describe how synthetic models can be used to directly study the crucial O–O bond cleavage step in an iron peroxo species and the mechanism of olefin epoxidation and then cover the relevant work on how P450 carries out hydroxylation and epoxidation reactions. Marnett and Kennedy compare the two classes of heme enzymes at all levels of structure as well as their mechanisms of handling peroxides, an especially important matter as there are now several types of P450 enzymes that react directly with peroxides without requiring electron transfer.

Part 2 is devoted to how structurally defined bacterial P450s function. Mueller, Loida, and Sligar summarize 25 years of effort, largely from the Sligar lab, to unravel the inner workings of $P450_{cam}$. Through the use of native enzyme and numerous carefully chosen mutants, significant progress has come from studies designed to probe substrate binding, electron transfer, and the mechanism of oxygen transfer utilizing camphor as well as camphor analogues. The first edition of this book was published shortly after the crystal structure of $P450_{cam}$ was reported by Poulos and Kraut. Three additional structures have now appeared, two from the labs of Deisenhofer and Peterson and one more by Poulos. In the next two chapters, the four structures are compared and the authors describe how knowledge of them has improved our understanding of oxygen activation by P450. In particular, Poulos, Cupp-Vickery, and Li relate the structures to those of peroxidases and provide insight into the role of distal catalytic groups in P450 and the factors that stabilize the critical anionic cysteinate proximal ligand. Peterson and Graham-Lorence make a good effort to extrapolate from bacterial structures to those of membrane-bound eukaryotic P450s.

In part 3, devoted to membrane-bound P450s, von Wachenfeldt and Johnson lead off with a review of eukaryotic P450 structures predicted through indirect approaches such as homology modeling and site-directed mutagenesis as well as protease and antibody probes of topology. Strobel, Hodgson, and Shen next focus on the evidence for functional domains in cytochrome P450 reductase. Two further chapters, by Ortiz de Montellano with Correia as co-author of one, cover oxygen activation by P450 and the inhibition of P450 enzymes. The first of these considers in detail all the major types of oxygen activation reactions catalyzed by the various P450 enzymes and compares the dioxygen-dependent P450 cycle with that involving other oxygen donors. Mechanistic evidence derived from studies of the stereochemistry of hydroxylation, kinetic isotope effects, and radical clock experiments is presented that supports the view that hydrocarbon hydroxylation by P450 follows a nonconcerted path involving a carbon radical intermediate. The chapter on inhibition deals with reversible as well as catalysis-dependent irreversible inhibitors and is augmented by an appendix by Correia tabulating substrate and inhibitor specificities and functional markers.

The final six chapters in the book cover a range of topics broadly categorized under the heading of regulatory mechanisms and physiological roles. Whitlock and Denison review the mechanisms of induction of P450s that metabolize xenobiotics, with emphasis on the Ah receptor, induction by phenobarbital, peroxisome proliferator-inducible P450s, and steroid- and ethanol-inducible P450s. Waxman and Chang next discuss hormonal regulation of liver P450s, and the regulation of steroidogenic P450s is discussed by Kagawa and Waterman. Capdevila *et al.* describe the role of P450s in the metabolism of arachidonic acid and oxygenated eicosanoids, presenting examples of both NADPH-dependent and NADPH-independent ("peroxide isomerase") reactions as well as several oxygenation reactions catalyzed by arachidonic acid monooxygenase. Guengerich reviews the properties of over 20 human P450s, some, such as $P450_{19}$ (aromatase), in considerable detail. The significance of human P450 enzymes in the metabolism of drugs and xenobiotics is also discussed. Mansuy and Renaud delineate the role of P450 in several "nonclassical" reactions: dehydrogenation including allene oxide synthesis and aldoxime dehydration, deformylation, peroxide isomerization, and nitric oxide reduction to N_2O. This leads into a discourse on the mechanisms of two novel thiolate-ligated heme proteins that are not generally called P450 hemoproteins, nitric oxide synthase and chloroperoxidase. Finally, factors that might explain the great diversity of reactions catalyzed by thiolate-ligated heme proteins are considered. The sheer number of P450 enzymes is further emphasized in an appendix in which Nelson, the guru of P450 sequences, provides a summary of sequence data for over 360 P450s.

The new edition of *Cytochrome P450*, like the first, emphasizes the chemical and physical side of the subject, although chapters on other aspects provide balance. A number of key issues are discussed more than once, but the different viewpoints underscore their importance. Many of the chapters do overemphasize their authors' work. However, the topics considered in the book are timely. The chapters are all

thoroughly referenced; with full titles included and citations as recent as the summer of 1995, the references actually occupy a quarter of the text. In summary, this new edition lives up to the high standards of the first and should quickly become a standard reference for experts while providing a logical starting point for newcomers to the field.

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Oceanic Vents

Seafloor Hydrothermal Systems. Physical, Chemical, Biological, and Geological Interactions. SUSAN E. HUMPHRIS, ROBERT A. ZIERENBERG, LAUREN S. MULLINEAUX, and RICHARD E. THOMSON, Eds. American Geophysical Union, Washington, DC, 1995. xiv, 466 pp., illus. $65; to AGU members, $45.50; to AGU student members, $42.25. Geophysical Monograph 91.

Hydrothermal activity in the deep sea was first observed directly on the Galápagos Spreading Center in 1977 after the accumulation of much indirect evidence that it had to exist. This initial discovery has been gradually followed up with the identification of vent fields at numerous other locations on oceanic and back-arc spreading ridges and on submarine hot-spot volcanoes. Emplacement of a magmatic heat source into permeable, water-saturated oceanic crust induces convection; the operating fluid is seawater. The scale of this phenomenon is such that a volume of seawater equivalent to the entire ocean is cycled through these high-temperature convection cells in about eight million years. This much had been guessed at prior to the actual discovery. What had not been anticipated was that reduced gases in the venting fluids, principally H_2S, derived from the seawater-basalt reactions could support a unique fauna of chemosynthetic macro-organisms, that the fluid compositions produced by the hydrothermal process could be extremely diverse despite the quite constant composition of the initial reactants, and that these compositions could be stable on decadal time-scales. In addition, the vent fluids were found to feed the accumulation of ore bodies, massive Fe-Cu-Zn sulfides, identical to those exploited in ophiolite bodies and ancient greenstone belts on land. Thus the discovery has led to a revolution in marine biology and geochemistry and in economic geology and has spawned an entirely new branch of the oceanographic sciences. The work reviewed here contains a series of surveys of the current state of play by some of the leading participants in this revolution.

The collection leads off with an excellent discussion of the tectonic and volcanic controls on hydrothermal activity at open ocean ridge axes, replete with maps and diagrams of the best-explored sites. The second paper, on the hydrothermal plumes that ascend for hundreds of meters over the vent fields, seems out of sequence since, though interesting, these are secondary phenomena and their understanding depends on knowledge of the primary fluid compositions at the vent orifices. This is followed by a very brief discussion of the vent organisms accompanied by some remarkably good color plates of the biota. Discussion then turns to the sub-seafloor processes that control the vent fluid compositions. Despite heroic efforts, it has not yet proved feasible to drill directly into the reaction zone. Processes there have to be reconstructed from fossil systems preserved in the geologic record either at off-axis locations on the ridge flanks or in ophiolites, fragments of seafloor often of uncertain provenance that have been obducted on land during tectonic collisions. The synthesis of this information suggests a continuum of processes extending from magmatic temperatures to those of the ambient oceanic water column. This discussion is then continued with a survey of the known actively forming ore deposits and the factors influencing their relatively broad range in size, morphology, and composition. This chapter is largely based on systematic observations of mineralogy and is followed by an excellent review of the thermodynamic modeling of deposit growth and evolution. Then the question is addressed of the interaction of the biota with all this. Certainly organisms are intimately associated with the growing deposits, living on and in them. Whether they actively influence growth and morphology is unresolved, but healthy speculation abounds.

About halfway through the book we finally get explicit information on vent fluid compositions, specifically the range in stable isotope values. In principle these give insights into the origins of the various components and the reaction mechanisms that introduce them to the fluids and, eventually, to the precipitates. This discussion is continued with a systematic presentation of the chemical features of the known active vents; this is a very useful data compilation and synthesis and leads naturally into a presentation of the bacterial processes that sustain the macro-organisms. These are then discussed from the point of view of their physiological ecology.

The succeeding section is composed of a series of papers on the hydrothermal plumes, their distribution, dynamics, propagation, and eventual dispersal. The mysterious problem of sustaining the vent populations, dependent as they are on transient habitats, is then addressed. How do larvae "find" and colonize new vent fields? What controls the basin-scale faunal boundaries as evidenced by the differences between the biota of the East Pacific Rise and the ridges of the Northeast Pacific and the North Atlantic? We appear to be a long way from satisfactory answers.

"The Rose Garden vent on the Galápagos Rise in 1979. Vestimentiferan tube worms and mussels dominate. Bresliid shrimp and archaeogastropod limpets walk on them." [From R. R. Hessler and V. A. Kaharl's chapter in *Seafloor Hydrothermal Systems*]

The final two papers attempt estimates of the global hydrothermal flux. The first utilizes conductive heat flow data and runs into the thorny problem of axial versus off-axis heat transport. The second uses the chemical flux approach. As usual the values obtained are irreconcilable: heat budgets give relatively low hydrothermal fluxes, and the integral chemical effects require high ones.

One is left with a good appreciation of the present understanding of hydrothermal activity in the deep sea. We still have three persistent problems: larval dispersal and colonization and faunal distributions, the mechanisms controlling the temporal compositional stability of the fluid compositions, and the true magnitude of the chemical fluxes. Much remains to be done.

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