

Preface to Volume 3

The Ubiquitous Roles of Cytochrome P450 Proteins

Cytochrome P450 monooxygenases (P450s) own a dual functionality and are often referred to as 'mixed-function oxidases' because they possess both 'oxygenase' and 'oxidase' reactivities, meaning that they incorporate an oxygen atom from atmospheric dioxygen into a substrate molecule oxidizing it. The electron transfer functionalities of P450s also earned them the label of 'cytochrome'. The signature of all P450s is the heme Soret band at about 450 nm in the absorption spectrum of the Fe(II)-CO complex; this spectroscopic feature is diagnostic of a cysteinate residue bound *trans* to the carbon monoxide ligand.

This volume encompasses the breadth of research efforts focused on P450s from structure to function, including an appreciation of the diversity and complexity of the biotransformations they catalyze. The introductory Chapter 1, setting the scene, explores the many different levels at which these P450 enzymes (and their respective genes) have diverged in the process of evolution to yield the plethora of enzymes that are now termed 'P450 monooxygenases'. This broad and unprecedented reactivity of P450 enzymes which contain a heme iron center (most commonly iron(III)protoporphyrin IX) with a deprotonated cysteine side chain providing the fifth ligand to iron, has challenged the 'biomimetic community'. Indeed, much has been accomplished over the past five decades, e.g., regarding the understanding of the unusual activation of paramagnetic dioxygen by reductive oxygen cleavage, as is evident from Chapter 2 which provides an in-depth overview of structural and functional mimics of P450s.

The structures of P450 proteins and their molecular phylogeny are detailed in Chapter 3, together with the P450 nomenclature and classification. It is made clear in this account that the P450 protein fold is unique and highly conserved independent of the organism; astonishingly, the same fold is also used by some enzymes that catalyze non-P450 redox transformations. It is worthwhile to note that some P450s function at extremes of pH and heat, as was recently discovered with archaeans. The diversity of P450s is also reflected in aquatic species as

outlined in Chapter 4 where especially P450 activities in invertebrates are in the focus.

Chapter 5 examines the ability of electrochemical techniques to unravel fundamental aspects of the electron transfer process of P450 enzymes. This process is central to P450 catalysis and thus, in Chapter 6 extensive studies are summarized which have shown that interprotein electron transfer is facilitated by proper positioning, e.g., of the flavin mononucleotide- and heme-containing domains. Clearly, generation of a truly catalytic system that utilizes non-native redox cofactors in place of the reductase proteins is a 'holy grail' of P450 research.

The next four chapters center on mechanistic considerations. At first leakage reactions are considered which occur during the P450 catalytic cycle, followed by detailed evaluations of the structural basis for substrate recognition and catalysis, including the architecture of the active site. Roles of the secondary coordination sphere, i.e., at the proximal (thiolate) and the distal side (where activation of dioxygen and substrate binding occurs) are described next, as is the coordination to the heme iron of several small-molecule inhibitors, such as nitrogen monoxide (nitric oxide), carbon monoxide, cyanide, and imidazole.

P450-catalyzed hydroxylations and epoxidations, the biosynthesis of steroid hormones, and the catalyzed carbon-carbon bond cleavage are discussed in Chapters 11-13. The design and engineering of cytochrome P450 systems is detailed in Chapter 14 regarding the oxidation of non-natural substrates. Evidently, potential applications of altered P450s in the environmentally benign synthesis of chemical products and intermediates are expected in this research area.

In the terminating three chapters of *The Ubiquitous Roles of Cytochrome P450 Proteins* first the biotransformation of xenobiotics is comprehensively dealt with, i.e., the 'chemical defense' or response of an organism to foreign chemicals. Thereafter the metabolism of drugs by human P450 systems is described, an area of particular significance for drug development and finally also for daily life in the clinic, as is emphasized by a clinical pharmacist.

Astrid Sigel
Helmut Sigel
Roland K. O. Sigel