CHEMICAL REVIEWS

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Introduction: Radical Enzymology

The paucity of known radical reactions stands in striking contrast to the plethora of biosynthetic reactions that generate complex metabolomes in organisms. Thus, while the human metabolome is estimated to be an order of magnitude simpler than its proteome, i.e., comprising ~3000−4000 metabolites, catalysis of only a handful of reactions leading to these diverse products is presently recognized as being accomplished by bona fide radical enzymes. Nature appears to have reserved the deployment of radical chemistry for some of its greatest chemical challenges and has resorted to both cofactor-derived and protein-based radicals to effect these reactions. Coenzyme B_{12}, or adenosylcobalamin, is an organometallic cofactor that functions as a free radical reservoir and is exploited by enzymes to catalyze carbon skeleton rearrangement reactions (reviewed by Banerjee) or isomerization/elimination reactions (described in an article by Toraya). A chemically simpler version, *S*-adenosylmethionine, originally dubbed "a poor man's adenosylcobalamin" by Perry Frey, supports a richer spectrum of radical reactions including isomerization, reductive rearrangement, glycyl radical generation (described in an article by Frey), and insertion of sulfur into unreactive C−H bonds (reviewed by Fontecave).

Ribonucleotide reductases represent perhaps the best-characterized group of the protein radical enzymes, and Nature exhibits a surprising variety of strategies for generating the working radicals in these enzymes that are of fundamental importance to biology. Stubbe and Nocera discuss mechanistic considerations for long-range proton-coupled electron transfer for generating a thiyl radical in the active site from a distant tyrosyl radical in the class I ribonucleotide reductases. The thread of this discussion, i.e., the role of long-range (proton-coupled?) electron transfer in the photorepair of UV-induced pyrimidine dimers in DNA by photolyase, is continued in an article by Sancar, and the similarity to the cryptochrome blue light photoreceptors that appear to be important for entraining the circadian clock to light−dark cycles is discussed.

Marnett reviews the role of protein radicals in the pharmacologically important cyclooxygenase targets, COX-1 and COX-2. The chemistry of autocatalytic radical reactions for modification of hemes in heme oxygenase, mammalian peroxidases, and cytochrome P450s is reviewed by Ortiz de Montellano. The spectroscopic and kinetic characterization of a hybrid substrate−cofactor radical, i.e., the hydroxyethyl−thiamine pyrophosphate radical in pyruvate:ferredoxin oxidoreductase, is discussed in an article by Ragsdale. Whittaker reviews galactose oxidase, a prototype for radical-copper oxidases. A new addition to the family of cofactor-based radical catalysis is exemplified by the participation of a tetrahydrobiopterin radical in the reaction catalyzed by nitric oxide synthase, which is reviewed along with molybdopterin radicals in tungsten and molybdenum enzymes by Stuehr. The use of substrate probes designed to distinguish between radical and nonradical pathways is discussed in an article by Lippard and co-workers in the context of methane monooxygenase, and insights into the reaction mechanism from computational chemistry are reviewed. The final article in this issue, by Siegbahn, reviews quantum chemical studies on a variety of radical enzymes. The past decade has witnessed an explosion in our understanding of how enzymes modulate radical reactivities, control radical trajectories, and suppress unwanted side reactions in active sites that are often lined with polar residues. These advances have stimulated development of computational models for assessing the energetic feasibility of alternative pathways and have fostered a synergistic interplay between simulation and experiment that is destined to continue well into the next decade.

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