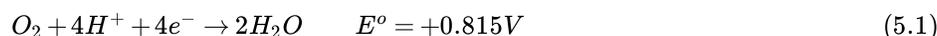


5: Dioxygen Reactions

I. Introduction¹

The major pathway of dioxygen use in aerobic organisms is four-electron reduction to give two molecules of water per dioxygen molecule:²



This reaction represents the major source of energy in aerobic organisms when coupled with the oxidation of electron-rich organic foodstuffs, such as glucose. Biological oxidation of this type is called respiration, and has been estimated to account for 90 percent or more of the dioxygen consumed in the biosphere. It is carried out by means of a series of enzyme-catalyzed reactions that are coupled to ATP synthesis, and the ATP produced is the major source of energy for the organism. The actual site of the reduction of dioxygen in many organisms is the enzyme cytochrome c oxidase.²

Another use of dioxygen in aerobic organisms is to function as a source of oxygen atoms in the biosynthesis of various molecules in metabolic pathways, or in conversions of lipid-soluble molecules to water-soluble forms for purposes of excretion. These reactions are also enzyme-catalyzed, and the enzymes involved are either monooxygenase or dioxygenase enzymes, depending on whether one or both of the oxygen atoms from dioxygen are incorporated in the final organic product. Many of these enzymes are metalloenzymes.²⁻⁴

The advantages of life in air are considerable for an aerobic organism as compared to an anaerobic organism, mainly because the powerful oxidizing power of dioxygen can be controlled and efficiently converted to a form that can be stored and subsequently used.⁵ But aerobic metabolism has its disadvantages as well. The interior of a living cell is a reducing environment, and many of the components of the cell are fully capable thermodynamically of reacting directly with dioxygen, thus bypassing the enzymes that control and direct the beneficial reactions of dioxygen.⁶ Luckily, for reasons that are discussed below, these reactions generally are slow, and therefore represent minor pathways of biological dioxygen consumption. Otherwise, the cell would just burn up, and aerobic life as we know it would be impossible. Nevertheless, there are small but significant amounts of products formed from nonenzymatic and enzymatic reactions of dioxygen that produce partially reduced forms of dioxygen, i.e., superoxide, O_2^- , and hydrogen peroxide, H_2O_2 , in aerobic cells. These forms of reduced dioxygen or species derived from them could carry out deleterious reactions, and enzymes have been identified that appear to protect against such hazards. These enzymes are, for superoxide, the superoxide dismutase enzymes, and, for peroxide, catalase and the peroxidase enzymes. All of these enzymes are metalloenzymes.²⁻⁴

Much of the fascination of the subject of biological reactions of dioxygen stems from the fact that the mechanisms of the biological, enzyme-catalyzed reactions are clearly quite different from those of the uncatalyzed reactions of dioxygen or even those of dioxygen reactions catalyzed by a wide variety of nonbiological metal-containing catalysts.⁷ Investigators believe, optimistically, that once they truly understand the biological reactions, they will be able to design synthetic catalysts that mimic the biological catalysts, at least in reproducing the reaction types, even if these new catalysts do not match the enzymes in rate and specificity. To introduce this topic, therefore, we first consider the factors that determine the characteristics of nonbiological reactions of dioxygen.

II. Chemistry of Dioxygen

- A. Thermodynamics
- B. Kinetics
- C. Free-Radical Autoxidation
- D. How Do Enzymes Overcome These Kinetic Barriers?

III. Dioxygen Toxicity

- A. Background
- B.

Biological Targets

C. Defense and Repair Systems

1. Nonenzymatic Oxidant Scavengers
2. Detoxification Enzymes
3. Systems for Sequestration of Redox-active Metal Ions
4. Systems for the Repair or Replacement of Damaged Materials

D. Molecular Mechanisms of Dioxygen Toxicity

E. Summary of Dioxygen Toxicity

IV. Cytochrome c Oxidase

A. Background

B. Spectroscopic Characterization

1. Models
2. Spectroscopy of the Enzyme

C. Mechanism of Dioxygen Reduction

1. Models
2. Mechanistic Studies of the Enzyme

V. Oxygenases

A. Background

B. Dioxygenases

1. Intradiol Catechol Dioxygenases

C. Monooxygenases

1. Cytochrome P-450
2. Other Metal-containing Monooxygenase Enzymes

VI. Catalase and Peroxidase

A. Description of the Enzymes

B. Mechanism

C. Comparisons of Catalase, Peroxidase, and Cytochrome P-450

VII. Copper-zinc Superoxide Dismutase

A. Background

B. Enzymatic Activity

C. Structure

D. Enzymatic Activity and Mechanism

E. Anions as Inhibitors

F. Metal-Ion Substitutions

1. SOD activity
2. Spectroscopy

VIII. References

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125. The author gratefully acknowledges research support from the National Science Foundation and the National Institutes of Health while this chapter was being written, editorial assistance from Dr. Bertram Selverstone, and patience and support from Dr. Andrew J. Clark.
126. It has been suggested recently that the Cu_A site in cytochrome c oxidase may contain two copper ions. See P. M. Kroneck *et al.*, *FEBS Lett.* **268** (1990), 274-276.
127. An excellent review relevant to this chapter has recently appeared. K. D. Karlin, *Science* **261** (1993), 701-708.

Contributors and Attributions

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