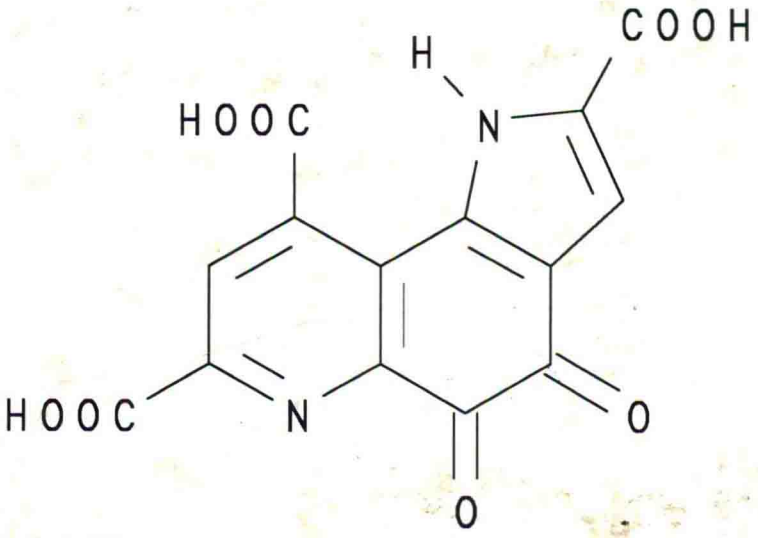
Principles and Applications of Quinoproteins



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Preface

The study of quinoproteins and their quinonoid cofactors is a relatively young and rapidly emerging field. The first major symposium on this topic was held in 1988, and aside from the proceedings of that symposium, this is the first book devoted entirely to basic and applied research on quinoproteins and quinonoid cofactors such as PQQ. It is rare that a relatively new field touches upon as wide a range of disciplines as does quinoprotein research. Recent meetings on this topic have drawn experts from such diverse fields as enzymology, microbiology, molecular biology, nutrition, pharmacology, analytical chemistry, physical biochemistry, medicine, and organic chemistry. Not surprisingly, the literature on quinoproteins can be found among a wide range of journals that relate to these disciplines. Because of this many people have heard of quinoproteins, but very few, including most workers in the field, are aware of the full body of knowledge that has accumulated. The intention of this book is to provide a single, comprehensive source of information on all aspects of basic and applied research that relate to quinoproteins and quinonoid cofactors. It will provide information to investigators on recent developments in their own and related areas, and also educate the general reader on the scope, direction, and potential value of research in this multi-disciplinary field.

Victor L. Davidson

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I

Introduction

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A Brief History of Quinoproteins

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I. THE DISCOVERY OF PYRROLOQUINOLINE QUINONE (PQQ)

The history of quinoproteins began in the 1960s. During that decade the investigations of two very different phenomena resulted in what is now recognized as the birth of quinoproteins. Research in the area of nonphosphorylative bacterial glucose metabolism revealed that a pyridine nucleotide-independent enzyme was responsible for the primary oxidation of the sugar substrate. Hauge [1] reported in 1964 the characterization of a bacterial glucose dehydrogenase with a dissociable cofactor that was neither a pyridine nucleotide nor a flavin. This cofactor had unprecedented properties, and it was suggested that it could be a substituted napthoquinone. At approximately the same time, several researchers began to study in detail the process of bacterial methanol metabolism. The realization that several bacterial species were capable of growth on either methane or methanol as a sole source of carbon had stimulated interest not only among microbial physiologists but also among commercial interests, which hoped to develop economically viable fermentation processes based on methylotrophic bacteria. A key enzyme in bacterial methanol metabolism is methanol dehydrogenase. Studies of this enzyme revealed that, like the above-mentioned glucose dehydrogenase, it also possessed a dissociable organic cofactor that was neither a pyridine nucleotide nor a flavin. Based upon its fluorescence properties, Anthony and Zatman proposed in 1967 [2] that this cofactor might be an unusual pteridine. For the next decade the

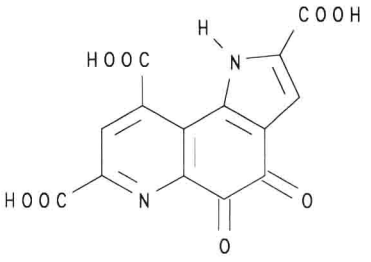

Figure 1 The structure of pyrroloquinoline quinone (PQQ).

status of the identity of these unusual cofactors remained unchanged. In the late 1970s Duine and coworkers reinvestigated the question of the structure of the cofactor of methanol dehydrogenase. Studies that applied electron spin resonance, nuclear magnetic resonance, and mass spectroscopy to this problem led to the proposal in 1979 that the cofactor was not a pteridine but a quinone structure that contained two nitrogen atoms [3]. At approximately the same time, the precise structure of this cofactor was deduced by Salisbury et al. [4] from X-ray diffraction studies of a crystalline acetone adduct of the cofactor. The structure was that of 4,5-dihydro-4,5-dioxo-1-H-pyrrolo[2,3-f]quinoline-2,7,9-tricarboxylic acid (Fig. 1). For a brief time this cofactor was referred to by the trivial name methoxatin. It is now most commonly called pyrroloquinoline quinone, or PQQ.

II. THE CHARACTERIZATION OF PQQ-BEARING QUINOPROTEINS

Once the structure and certain properties of PQQ were known, it became possible to design analytical methods to detect PQQ in proteins and biological fluids. Early methods were based upon the comparison of certain physical and chemical properties, such as fluorescence [5] of the dissociable cofactors or derivatives of such molecules, with authentic PQQ and derivatives of it. Furthermore, it was demonstrated that PQQ could reconstitute the biological activity of an apoenzyme form of glucose dehydrogenase [6]. Reconstitution was possible with either the purified apoenzyme or with crude membrane preparations that contained the apoenzyme. This finding was the basis for development of a biological assay to identify and quantitate the presence of free PQQ in biological fluids and in extracts of proteins or cells. Given the knowledge of PQQ and the availability of analytical techniques to screen for its presence, a large number of bacterial methanol and glucose dehydrogenases were shown to possess noncovalently bound PQQ as a cofactor. Using the above-mentioned techniques, a bacterial pyridine nucleotide–independent aldehyde dehydrogenase [7] was also identified. Subsequently, sev-

eral similar PQQ-dependent bacterial enzymes were identified that catalyzed transformations of the following compounds: long-chain alcohols and polyethylene glycol [8,9], secondary and polyvinyl alcohols [10], polyhydroxy alcohols [11], hydroaromatics [12], lactate [13], and nitriles [14]. Thus, by the early 1980s it became clear that PQQ was a widely distributed and important cofactor in prokaryotic systems.

III. THE CHARACTERIZATION OF COVALENTLY BOUND QUINONE PROSTHETIC GROUPS

Whereas the characterization of PQQ from enzymes in which it is freely dissociable had become a reasonably straightforward process, the question of whether PQQ functioned as a covalently bound prosthetic group in other enzymes proved to be a far more difficult and controversial topic to address. An inherent problem in efforts to isolate covalently bound PQQ from enzymes lies in the *o*-quinone structure, which exhibits a high level of reactivity with amino acid side chains of proteins. As such it has never been possible to isolate native PQQ from a protein after it has been subjected to proteolysis and the subsequent treatments necessary to isolate those peptides that possess the covalently bound prosthetic group. The first suggestion of an enzyme with a novel covalently bound quinone was presented in 1980. Duine and coworkers proposed [15], based upon its redox behavior and electron spin resonance and electron-nuclear double resonance spectra, that bacterial methylamine dehydrogenase possessed such a prosthetic group. The absorption spectra of methylamine dehydrogenases were, however, significantly different from those exhibited by methanol and glucose dehydrogenases [16,17], leaving open to question the precise nature of this cofactor. In 1987, van der Meer et al. [18] reported that this cofactor was in fact PQQ based upon analysis of a phenylhydrazine derivative of the isolated cofactor. As discussed later, this conclusion proved to be incorrect.

Given the demonstrated presence of PQQ in bacterial enzymes, it was only natural that investigators would begin to search for this cofactor in eukaryotic enzymes. The foci of these studies were known enzymes for which the precise identity of an organic cofactor was uncertain and enzymes for which convincing reaction mechanisms were difficult to postulate given the presence of the redox center known to be present. The first class of eukaryotic enzymes proposed to contain such a previously unrecognized quinone prosthetic group was the copper-containing amine oxidases. These enzymes had long been thought to possess pyridoxal phosphate in addition to copper. In 1984 two independent studies implicated covalently bound PQQ as a redox cofactor of amine oxidases. Lobenstein-Verbeek et al. [19] based this claim on HPLC analysis of a dinitrophenylhydrazine derivative of the cofactor, and Ameyama et al. [20] based their proposal on fluorescence properties and the biological activity of acid hydrolysates