INORGANIC BIOCHEMISTRY

VOLUME 1

edited by

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PREFACE

Until recently, the title "Inorganic Biochemistry" would have appeared paradoxical to most, and it may even now appear so to many, because biochemistry sounds "organic". The Wöhler synthesis of urea in 1828 may have demonstrated that organic chemistry need not be biochemistry, but for a century thereafter biochemical phenomena continued to be associated more with organic chemistry than with the other branches of chemistry. In recent years the compartmentalization between the classical chemical disciplines, and between the scientific disciplines generally, has broken down. In the process the usefulness of borderline fields between the classical chemical departments has become evident.

The community of interest between inorganic chemistry and biochemistry has, of course, been apparent to concerned individuals for a long time. Workers in the life sciences have encountered and solved problems of inorganic chemistry in their research. Inorganic chemists have sometimes realized the relevance of their work to biological processes and have occasionally allowed this relevance to guide the subsequent direction of their research. It was not until the late 1950s, however, that contacts between inorganic chemists and biochemists were encouraged through conferences on topics of mutual interest, and in the last few years such conferences have become commonplace.

The widespread interest that inorganic biochemistry has recently aroused makes the present work even more timely than it was when the publishers first suggested such a book. What had been intended as a book by one or two authors has evolved into a treatise involving 34 chapters by 45 authors. The vastness of the literature in this field makes it possible to come closer to achieving comprehensive coverage in this way.

Although some symposia in this field have led to publications, and a variety of reviews have previously appeared, the lack of a comprehensive work in this field makes it necessary to define and to limit the territory that such a work should comprise. Rather obviously, the inclusion of such elements as sulfur, nitrogen, or phosphorus in biochemical substances does not justify their discussion here, even though the chemistry of these substances as determined by these elements has "inorganic" implication, but such a course would identify inorganic biochemistry with all of biochemistry! The term "inorganic biochemistry" probably conveys the idea of the involvement of metal ions in biological processes to anyone to whom it conveys anything at all. We have therefore adopted an admittedly arbitrary but hopefully justified and profitable definition of inorganic biochemistry as the application of the principles of the coordination chemistry of metals

to biological problems. In order further to restrict the subject matter, pharmacological and nutritional uses of coordination compounds are not considered, except briefly in the introduction.

After defining the limits of the subject, it becomes necesary to organize it. Obviously numerous organizational schemes are possible. One that will occur to many is the treatment of the subject matter by metals; *i.e.* copper compounds would be considered together, as would iron compounds, zinc compounds, etc. Such a treatment would have unquestionable value. In this work, however, we have chosen to organize the subject on the basis of the structure of the ligands with the expectation that greater cohesiveness can be attained in this way. The subjects have been arranged to allow for a logical development based on structural similarities.

Many biological coordination compounds are macromolecules. It has been our aim to focus on the chemistry of the metal, but to understand this chemistry it is frequently essential to consider how the conformation of the macromolecule affects its metal component and therefore to pay considerable attention to the "organic" portions of the molecule. On the other hand, since coordination chemistry is basic to this book, some essentially "inorganic" chapters have been included. In this way the relationships between the biological coordination compounds and "model" inorganic complexes can be ascertained. In many chapters, biological substances and model compounds are considered together. The emphasis is on the biological substances.

Part I is designed to provide sufficient inorganic background for the biochemist to make it unnecessary for him to consult inorganic texts or literature to understand many (but of course not all) of the inorganic phenomena encountered in the later sections of this book or in his own research. Many clues to the elucidation of inorganic biochemical phenomena are provided. Chapter 1 is an introductory chapter on coordination chemistry and is not limited to the presently known "biological" metal ions, since structural and stereochemical features can be best understood by reference to the best examples, regardless of the metal ions used to furnish them. Moreover even platinum complexes can gain biological significance (see Introduction). In Chapter 2 the concepts relating structure and stability are developed, culminating in a comparison of the stabilities of biological complexes. Chapter 3 illustrates the usefulness of studies based on electronic configuration in the structural elucidation of some of the substances taken up later in the book.

Many biological coordination compounds are proteins and these are discussed in Parts II through VI. Part II begins with a systematic discussion, in Chapter 4, of the metal complexes of the protein monomers, the amino acids, and the simple oligopeptides. This chapter is followed by a review of some natural oligopeptides that have been specifically designed for iron (Chapter 5) and alkali metals (Chapter 6). Some of these substances are

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oligopeptides while others are not, but the coordination properties of the peptide and non-peptide compounds have many similarities. In Chapter 7, the interaction of metal ions with proteins is introduced to demonstrate the types of coordination sites to which metals can bind in the macromolecules.

In Part III are discussed some biological metalloproteins involved in the storage and transfer of iron (Chapters 8 and 9) and of copper (Chapter 10), as well as some oxygen-binding metalloproteins found in lower organisms (Chapters 11 and 12).

Part IV contains a consideration of the structure of metal enzymes and of the methods by which metal ions participate in enzymatic activity, particularly bond cleavage activity. In Chapter 13 are taken up the ways in which metal ions can induce chemical changes in ligands, without the benefit of the presence of proteins. Chapter 14 is an overview of metal enzymes not considered later in individual chapters. In Chapters 15 and 16 some metal enzymes are treated in depth partly because of the extent of information presently available on them, and other enzymes have been considered separately in Chapters 17 and 18 because of the relative ease of categorizing these groups of enzymes. Those enzymes that are primarily engaged in redox reactions or that involve porphyrins or other prosthetic groups are taken up later.

Enzymatic oxidation—reduction is the subject for Part V, which begins with a consideration, in Chapter 19, of oxidation—reduction in coordination compounds, with a theoretical treatment, and application to biological systems. Chapter 20 contains a classification of oxygenation reactions by metals in the presence or absence of enzyme. In Chapter 21 the different types of copper-containing oxidases are discussed. The ferredoxin-type proteins that engage in electron transfer are characterized in Chapter 22, followed by Chapter 23 on nitrogen fixation, in which the nitrogenase enzymes that require ferredoxins play an important role.

The metal ions in the proteins considered so far have been attached to the amino acid side chains of proteins. In Part VI we begin to take up proteins containing metal ions that are not attached directly to the protein, but to a "prosthetic group" or "coenzyme". The most versatile prosthetic group is the porphyrin, the discussion of the porphyrins in Chapter 24 is followed by Chapters 25—28 on the iron-porphyrin compounds, the hemoproteins, and then by Chapter 29 on the magnesium porphyrin derivative, chlorophyll. Because of their structural resemblance to porphyrins, the corrins and the B_{12} coenzymes and enzymes follow in Chapter 30.

Part VII is devoted to the metal complexes of other prosthetic groups. It is not certain that the metal complexes of vitamin B_6, in Chapter 31, play a biological role, but they are excellent models of B_6-catalyzed enzymatic processes. The metal complexes of flavins and, briefly, metal flavoproteins are discussed in Chapter 32.

Part VIII, on the interaction of metal ions with nucleic acids, begins in

Chapter 33 with the metal complexes of nucleosides and nucleotides; these bear some resemblance to metal flavin complexes. Finally, in Chapter 34, are taken up complexes of polynucleotides and nucleic acids and their biological implications.

While this order of presentation has many advantages, other sequences can be proposed with different advantages. Thus one could argue for the incorporation of the cytochromes under oxidation–reduction, rather than the porphyrins. It appears preferable, however, to discuss porphyrins generally before the cytochromes; in fact, much of Part VI is concerned with oxidation–reduction, and therefore logically follows Part V. The placement of Part VIII somewhere ahead of Part IV could be justified because the nucleotide complexes discussed in Chapter 33 are so important in Chapter 18. However, Chapter 34 would then have been out of place. Obviously there is no completely satisfactory sequence, and for this reason a certain number of points have to be repeated in various places. Overlap has been eliminated whenever consistent with clarity. To achieve this and other objectives, there has been considerable interaction between authors, as well as between authors and editor.

The cooperation of the authors, some of whom have made valuable suggestions about parts of the book not written by them, is deeply appreciated. I have received helpful advice from many others; I hesitate to name them for fear of omission. I am indebted to my colleagues Nathan A. Berger, James J. Butzow, Patricia Clark, Jane Heim, Josef Pitha, Carmen Richardson, Joseph Rifkind, Yong A. Shin and Edward Tarien for their understanding during the preparation of this book, as well as for help with some of the editing. I am grateful to the National Institutes of Health for making this endeavor possible. I am greatly indebted to my secretary, Jacqueline Blake, for her dedicated help in all facets of editing this book. Finally, I must acknowledge the patience of my wife and children during the course of this project, which took so much more time than they or I had hoped.

GUNTHER L. EICHHORN

INTRODUCTION

The name "bioinorganic chemistry" has appeared as the title of a number of recent symposia as well as a new scientific journal. The name of the present work was conceived before the appearance of its linkage isomer (see Chapter 1, p. 46). It would have been possible to follow the popular trend, but it was decided instead to retain the name that had been originally intended for this book. One of the reasons for this decision is that the existence of both titles illustrates the different emphasis that can be placed upon the components of these names by the biochemist and the inorganic chemist. The former has looked upon inorganic chemistry to explain the chemical behavior of biological metal complexes. The latter has looked upon biochemistry to find relevant applications for his findings. The end result of the two approaches is, of course, the same, just as the "linkage isomer" names have the same meaning. However, the scientist's point of origin is of some importance in determining what he must learn to gain his objective and therefore what he will discover on the way.

A major difference between inorganic chemists and biochemists is that the former are accustomed to dealing with relatively small molecules that can sometimes be considered "models" of the more complex systems with which the latter are concerned. A fundamental question which inorganic biochemists face constantly is whether it is useful to study the model when the "natural" substance is at hand.

To answer this question it is required to make a realistic appraisal of the ways in which biological mechanisms are elucidated. The living cell is so complex that its workings can be understood only by isolating component parts, always with the inherent risk that the parts in isolation do not function as they do in the cell. The isolated components are therefore "models" of the components in the cell. For example, cytochrome *c in vitro* is really a model of cytochrome *c* in the cell. But it is most likely that isolated cytochrome *c* shares many characteristics with cellular cytochrome *c*, and eventually, after all the other molecules to which cytochrome *c* is bound in the cell have also been isolated and studied, it should be possible to understand the behavior of cytochrome *c* in the cell.

In the same way, an inorganic substance, such as a simple porphyrin complex that can engage in electron transfer, perhaps with approximately the same oxidation potential as isolated cytochrome *c*, can serve as a model for cytochrome *c* at a time when the mechanism of electron transfer in cytochrome *c* is not yet understood. Studies with the simple porphyrin complex can aid in understanding isolated cytochrome *c*, and studies with isolated cytochrome *c* can in turn aid in the understanding of cellular

cytochrome *c*. From such a perspective, it seems that models at every level can be useful. It is necessary, of course, in the investigation of models always to remember the axiomatic limitation of the model — a model of a system is not the system itself. Inorganic chemists, as well as biochemists, can make a positive contribution when they remember this fact, and a negative one when they forget it.

Although the emphasis in this work is on the biological systems, many models are also considered, sometimes in separate chapters and sometimes alongside the more natural substances that they are designed to emulate. Correlations are frequently made, hopefully with the above limitation in mind. If inorganic biochemistry has any reason for existence, such correlations should lead to fruitful results.

What, then, is the importance of these results? What are the ultimate objectives of inorganic biochemistry?

These questions can be answered by considering this borderline field a part of biological science. There are two objectives in the study of biological science. The first, as in all discovery, is to study it because it is "there", to see what makes things tick. The second is to gain an understanding of normal and abnormal cellular processes, culminating in sufficient knowledge to lead to the conquest of disease. Inorganic biochemistry shares these objectives with the other biological sciences. The curiosity of the scientist and his desire for "relevance" at this point in history frequently causes him to be motivated by both of these objectives.

No attempt is made in this work to catalog the medical applications of inorganic biochemistry, partly because these are considered beyond the scope of this book. The pharmacological and nutritional aspects of coordination chemistry have been previously reviewed[1,2]. This introduction nevertheless provides an appropriate place to illustrate some of the useful consequences of the study of inorganic biochemistry.

The most obvious and widespread medical use of complexing agents is in the removal of undesired metal ions from the body. Such ligands as ethylenediamine tetraacetic acid, penicillamine, etc., have been employed in the treatment of diseases involving an overload of iron or copper (see Chapter 10) as well as in combatting the toxic effects of ingested metal ions[3–5].

Recently, it was discovered that the administration of penicillamine can lead to a pronounced decrease in taste acuity[6–8]. Such a decrease does not occur, however, in the treatment of Wilson's disease, in which an accumulation of copper(II) ions occurs in the body (Chapter 10). It was hypothesized that the decrease in taste acuity is due to the complexing of copper ions, and that the copper ions therefore are somehow involved in producing the sensation of taste. The failure to decrease taste acuity in Wilson's disease was attributed to the presence of such a high level of Cu^{2+} that the administered penicillamine cannot overcome the effect of the Cu^{2+}

If this hypothesis is correct, the administration of Cu(II) should restore taste acuity lost through the action of complexing agents. Experiments have shown that copper ions indeed restore taste; furthermore, Zn(II) and Ni(II) have effects similar to Cu(II) in restoring taste that is lost through treatment with penicillamine or through diseased states. Thus metal ions seem to be implicated in producing the sensation of taste[4].

It has recently been discovered that certain complexes of platinum exhibit potent anti-tumor activity[9]. Active complexes are *cis*-$[Pt^{II}(NH_3)_2Cl_2]$, $[Pt^{II}en\ Cl_2]$, *cis*-$[Pt^{IV}(NH_3)_2Cl_4]$ and $[Pt^{IV}en\ Cl_4]$*. On the other hand, $[Pt^{II}(NH_3)_4]Cl_2$ and *trans*-$[Pt^{IV}(NH_3)_2Cl_4]$ are inactive. Tumor-inhibiting activity has been correlated with the inhibition of DNA replication[10] (see Chapter 34). Needless to say, these biological phenomena are intriguing to inorganic chemists.

It is to be expected that such discoveries as the use of metal ions in the recovery of taste and the use of metal complexes in tumor regression should help to stimulate activity in inorganic biochemistry.

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*en = ethylenediamine

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