

CHELATING AGENTS
AND
METAL CHELATES

EDITED BY F. P. DWYER AND D. P. MELLOR

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Preface

The aim of this book is primarily to provide a reference work for senior students and research workers in the chemistry of metal chelates. It is, however, hoped that it will also be of interest to biologists and medical scientists whose growing preoccupation with metal-binding is clearly evident in the published proceedings of recent conferences.*

The emphasis in the book has been placed mainly on the structure and properties of metal chelates. An attempt has been made to cover in some detail aspects of the subject that have not been so treated previously. Some overlapping with earlier works is inevitable but it is hoped that there is no more than is essential for an understanding of the new material.

The chemistry of metal chelates is at present undergoing a period of rapid development and is engaging the attention of research workers in many diverse disciplines, both experimental and theoretical. Progress in this area of chemistry has received an added impetus because of its many applications to biology. It has been known for some time that metal chelates play essential roles in the chemistry of living matter: chlorophylls in photosynthesis, vitamin B₁₂ in the formation of red cells and hemoproteins in respiration. While the structures and functions of these metal chelates are reasonably well known, there is a large number of metallo-proteins and other metal complexes of biological importance, whose structure and properties are much less completely understood. One of the most fruitful approaches to understanding the structures and properties of such complicated substances is almost certainly through a thorough knowledge of the structure and properties of simpler and possibly related substances.

The greater part of this book is devoted to relatively simple structures. It is only in the last few chapters that some of the biological aspects of metal chelation are considered.

February, 1964

D. P. MELLOR

*"Biological Aspects of Metal Binding" Federation Proc. 20, Nr. 3 (1960); "Metal Binding in Medicine." Lippincott, Philadelphia.

Francis P. J. Dwyer (1910–1962)

With the passing of Francis Dwyer, Australia lost one of her outstanding chemists. He and his colleagues and students maintained for many years a steady stream of contributions to the chemistry of metal complexes.

Dwyer was one of a group of chemists that came into being at the University of Sydney in the early thirties under the guidance of G. J. Burrows, to whom this book is dedicated. Every contributor to this book is either a one-time colleague or student of Burrows or a student of a student. Since those early days, interest in metal complexes has spread to other Australian universities including the National University at Canberra. It was here that Dwyer occupied the Chair of Biological Inorganic Chemistry and developed a lively center of research. His interest in the biological importance of metal complexes developed rather late in his career and only after he had gained considerable insight into the structure and properties of the complexes themselves. One of his most notable experimental skills was the ability to resolve metal complexes into their optical isomers. He was, of course, not so much interested in the phenomenon of optical activity itself as in the light it could throw on the structure of metal complexes. His last published paper described a novel method for the resolution of amino acids. It will be evident in the following pages that many of his most important contributions to our knowledge of metal complexes centered around the phenomenon of optical isomerism.

Dwyer conceived the idea and plan of this book and up to the time of his death in June 1962, he was an active co-editor. The last chapter embodies results, unpublished at the time of his death, of work carried out by Dwyer and his colleagues in the departments of physiology, biochemistry, and biology in the Universities of Sydney, Melbourne, and Adelaide.

D.P.M.

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CHAPTER 1

Historical Background and Fundamental Concepts

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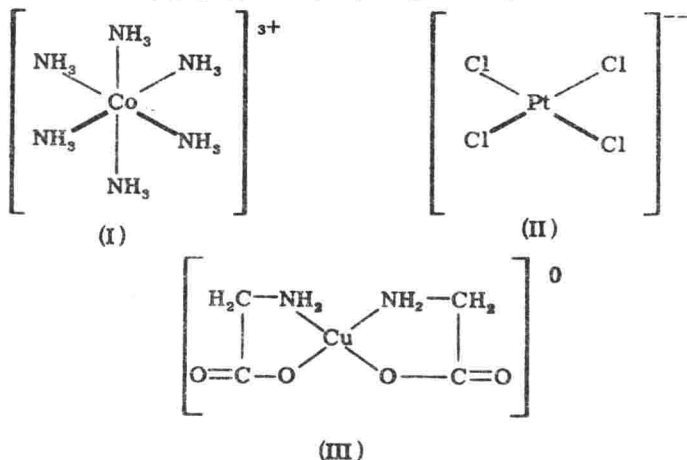
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I. Introduction

A. DEFINITIONS

A complex has been defined as "a species formed by the association of two or more simpler species each capable of independent existence" (Rossotti and Rossotti, 1961). When one of the simpler species is a metal ion, the resulting entity is known as a metal complex. A characteristic feature of such a complex is that the metal atom occupies a central position in it, as exemplified by cobalt in hexamminecobalt(III) ion, platinum

in tetrachloroplatinate(II) ion, and copper in bis(glycinato)copper(II). These are shown in (I), (II), and (III) respectively.



The metal-centered structure may carry a positive, negative, or zero charge. Complex ions are, of course, always associated with ions of opposite charge and the term metal complex is customarily applied to the compound itself.

Almost every kind of metal atom can serve as a central atom although some kinds do so more readily than others. Atoms of the transition series, for example, function in this way par excellence but atoms of the alkali metals are rarely found in this role.

When the central metal atom of a complex is bound to its immediate neighbors by covalent bonds formed as the result of the metal atom accepting an electron pair from each nonmetal atom, it is customary to call the latter the donor and the former the acceptor atom; alternatively, the nonmetal atom is called the coordinating atom and the bond between it and the metal atom a coordinate bond. However, metal atoms themselves sometimes contribute electrons to the bond as they do in π bonding. A more generally used convention which is preferable because it avoids any implication about the nature of the bond is to call any negative ion or polar molecule, bound to a metal atom, a ligand (L) and the bond between them a metal-ligand bond (M—L).

Since its introduction about 20 years ago, the term ligand has been used in two different senses. It is sometimes applied to the particular atom in a molecule by means of which the molecule is attached to a central metal atom, for example, the nitrogen atom in ammonia, or it may be applied to the molecule as a whole. This dual usage is well established and causes little or no confusion since the context generally indicates the sense in which

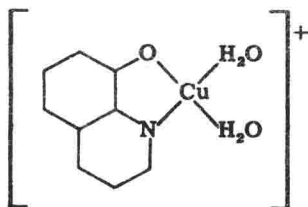
it is being employed. Where there is any risk of ambiguity, it may be avoided by using the term ligand atom to denote the atom attached to a metal.

Some ligands are attached to the metal atom by more than one donor atom in such a manner as to form a heterocyclic ring. An example of such a ring is the one formed in (III) by the glycinate ion. This type of ring has been given a special name—chelate ring—and the molecule or ion from which it is formed is known as a chelating agent. The process of forming a chelate ring is known as chelation. The first chelating molecules discovered were those with two donor atoms and it was the caliperlike mode of attachment of the molecules to the metal atom that led Morgan and Drew (1920) to suggest the name *chelate*, which is derived from the Greek word *χηλή* meaning a lobster's claw.

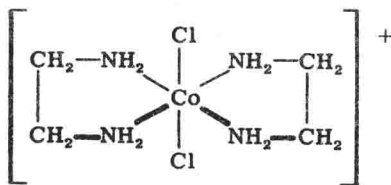
Any metal complex in which one or more chelate rings are present is defined as a metal chelate¹ and it is with these and the molecules and ions that form such rings that this book is concerned.

It should be pointed out that not every author uses the term metal complex in the all-embracing sense indicated above. Some prefer to confine it to structures like (I) and (II), in which no chelate rings are present. On the other hand, use of the term metal complex as a synonym for metal chelate is fairly widespread. The essential point of the terminology used here is that a metal chelate is regarded as a special kind of metal complex. A minor disadvantage of this terminology is that there is no distinctive name for the class of complex exemplified by (I) and (II), though no confusion is likely to arise from calling them metal complexes.

In accordance with the definition given above, complexes like diaquo-8-hydroxyquinolinatocopper(II) ion (IV) and *trans*-dichlorobis(ethylenediamine)cobalt(III) ion (V) which contain ligands that are chelates as well as some that are not will be called metal chelates.



(IV)



(V)

¹ When Morgan first introduced the word *chelate*, he used it as an adjective. Nowadays, it plays a more versatile role appearing as an adjective, verb, or noun. In this book, it will be used in all three ways, though the adjectival form will, as often as not, be the word *chelating* as used in the title of the book.

There is a good case for having a special name for metal chelates like (III) which are nonelectrolytes, since these compounds usually have characteristics that set them apart from metal chelate ions like (IV) and (V). Electrically neutral metal chelates were originally called "inner complex metallic salts," a name generally attributed to Ley (1904) who first used it in the title of a paper dealing with bis(glycinato)copper(II). Strangely enough, in this paper, he gave no explanation of the significance of the term "inner." It is presumed, however, that it originates from Werner's custom of referring to inner and outer spheres of coordination when describing a compound like $[\text{Co}(\text{NH}_3)_6]\text{Cl}_3$. Ammonia molecules belong to the inner sphere, ionized chlorine atoms to the outer sphere. An inner complex is therefore one that has no outer sphere; in other words, it is an electrically neutral metal complex or a nonelectrolyte. If this presumption is correct, it would be inconsistent to extend the name inner complex to include metal chelate ions like (IV) and (V) as advocated by some authors (Liebhafsky, 1946; West, 1960). On the grounds that there may be some confusion with the term inner orbital complex, some authors prefer to use the term neutral rather than inner complex. An objection may be raised to the use of the term neutral in this manner. Since neither term has any advantage over the other, they will be used interchangeably.

B. NOMENCLATURE

The Commission on the Nomenclature of Inorganic Compounds set up by the International Union of Pure and Applied Chemistry (1957) has drawn up rules for the naming of metal complexes. Only a brief summary of the principal relevant rules will be given here.

When writing the formula of a metal complex the symbol for the central metal atom is placed first, and is followed by formulas of anionic and neutral ligands in that order. The formula of the whole complex entity (molecule or ion) is enclosed in square brackets.

However, in naming a metal complex, the opposite order is used. Ligands are cited first—anionic and neutral in that order—and then the metal, followed by a Roman numeral indicating its oxidation state. Thus (III) is written $[\text{Cu}(\text{NH}_2\text{CH}_2\text{COO})_2]$ and named bis(glycinato)copper(II).

Some ligands are so constituted that there are alternative ways in which they may be attached to a metal atom. The dithiooxalato ion, for example, may be attached through either S and O or S or O. It is, in fact, attached through S and this is indicated by adding to the name the symbols *S, S'*.

When the central metal atom forms part of an anion, as in $\text{K}_2[\text{Ni}(\text{C}_2\text{S}_2\text{O}_2)_2]$, potassium bis(dithiooxalato-*S, S'*)nickelate(II), the ending *-ate* is used with the name of the metal. For a more detailed discussion

of nomenclature, the reader should consult the Report of the Commission on the Nomenclature of Inorganic Compounds (1957).

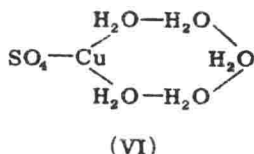
II. Historical Background

A. EARLIEST ATTEMPTS TO DISCOVER THE STRUCTURE OF METAL COMPLEXES

In order to understand how the phenomenon of chelation was discovered, it is necessary to glance briefly at the history of the early attempts to elucidate the structure of metal complexes. Since these attempts were made soon after the birth of structural organic chemistry, it is not surprising that the first formulations of the structure of metal complexes (metal amines in particular) should have been in terms of chains and rings that had proved such common features in the structure of organic molecules. Thus Blomstrand, in 1869, proposed a structure for hexamminecobalt(II) chloride in which ammonia molecules were linked together in chains reminiscent of hydrocarbon chains:



Copper(II) sulfate pentahydrate, on the other hand, was formulated as possessing a ring structure (VI).

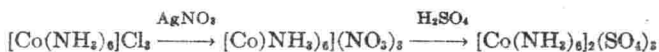


One of the most notable exponents of the chain theory was Jorgensen (1887). Though he was able to modify and extend it to account for some of the chemical behavior and isomerism of metal amines, the theory eventually broke under the weight of facts that he himself accumulated in the course of his extensive investigations. In his attempts to vindicate the chain theory Jorgensen provided most of the experimental evidence for the revolutionary structural theory introduced by Werner (1893).

About this time, many chemists regarded metal amines as molecular compounds. For example, they wrote the formula for hexamminecobalt(III) chloride as: $\text{CoCl}_3 \cdot 6\text{NH}_3$. Their view was that in this compound cobalt has a valency of three as also has nitrogen. The question that greatly puzzled them was: by what mechanism did molecules in which the valencies of the atoms were, so it seemed, fully satisfied combine together to form such a highly stable compound as hexamminecobalt(III) chloride?

Werner was aware that certain structural entities—"complexes," he

called them—persisted² through a series of chemical transformations; that the entity $[\text{Co}(\text{NH}_3)_6]^{3+}$, for example, remained intact throughout the following changes:



Having recognized the existence of this entity, his next step was to abandon the view that the valency of an atom and the number of bonds it can form are one and the same thing: that trivalent cobalt, for example, could only form three bonds. He introduced the idea of a metal-centered, octahedral structure. "If," he wrote, "we think of the metal atom as the center of the whole system, then we can most simply place the molecules bound to it at the corners of an octahedron" (Werner, 1893). This involved a complete break with contemporary ideas of valency and led him to the realization that it was necessary, as a modern chemist has put it, to "dissociate the concept of valency into several new concepts" (Pauling, 1948). This Werner did by distinguishing between what he called principal valency and auxiliary or "neben" valency. For cobalt in the hexamminecobalt(III) complex, these are three and six; for platinum in the tetrachloroplatinate(II) ion, they are two and four respectively. These concepts are, of course, still used though they go under other names—oxidation number and covalence—and are interpreted in terms of the electronic structure of atoms.

B. SUBSTITUTION IN METAL COMPLEXES

Several years before Werner published his revolutionary ideas on the structure of metal complexes, Arrhenius (1887) had announced the theory of electrolytic dissociation. Werner was quick to see how measurements of electrolytic conductance could be used to support his views.

He was able to show, for example, that the result of the progressive substitution of ammonia molecules in the tetrammineplatinum(II) ion by chlorine ion is to reduce the charge on the complex ion by one for each substitution (Werner and Miolati, 1894).

By comparing the molecular conductivities of the above metal complexes with the molecular conductivities of simple salts like BaCl_2 and KCl , Werner reached the conclusion that the complexes yielded 3, 2, and 0 ions, respectively, when dissolved in water (Fig. 1). He introduced the convention of square brackets to indicate the entity which functioned as a complex. Fundamental to all Werner's structural thinking was the concept of coordination number which he defined as the number of atoms bound

² Persistence of structure was first recognized by von Liebig and Wohler (1832) in the course of their studies of the benzoyl radical. Werner recognized that the principle was also valid for inorganic compounds.

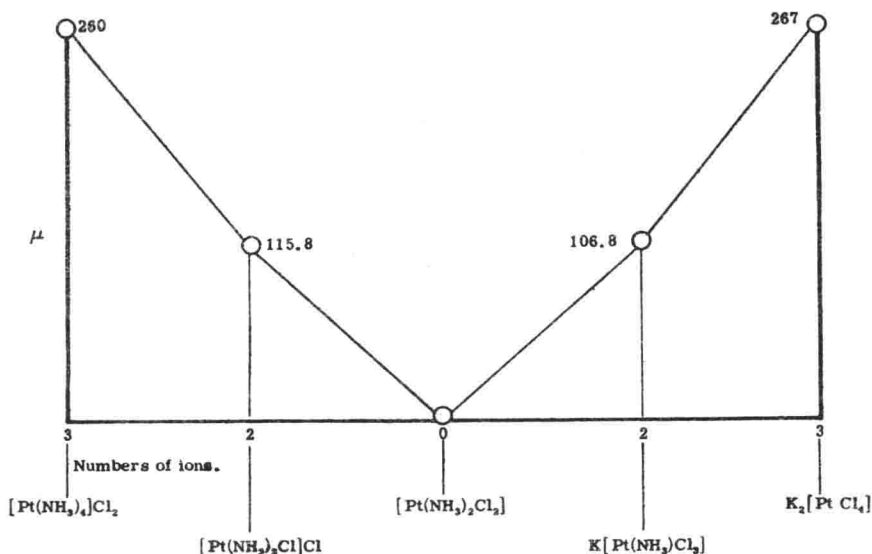


FIG. 1. Molecular conductivities (μ) of aqueous solutions ($10^{-3} M$) of platinum(II) amines.

directly to the central metal atom. Throughout the transformations shown above, the number of atoms directly bound to platinum remains constant. It is, in fact, characteristic of platinum in the bivalent state to have a coordination number of four. A far more common coordination number is six which is often found to be independent of the principal valence of the metal. To illustrate this point, Werner cited as examples:

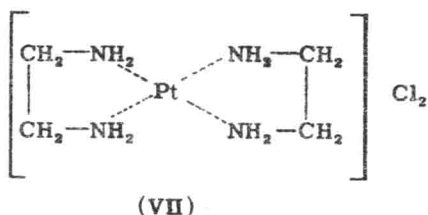


where the principal valences of the metal are 4, 3, and 2, respectively.

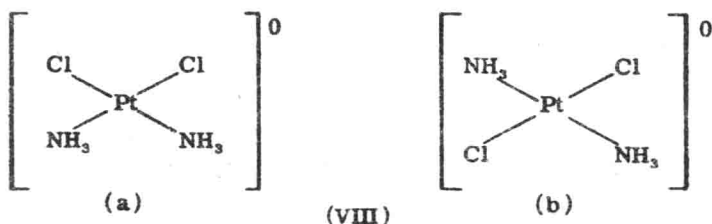
C. DISCOVERY OF CHELATION

Two distinct steps were involved in this discovery. The first was the recognition of the fact that each metal has a characteristic coordination number which it exhibits in most, if not all, its compounds. For bivalent platinum, this number, as already stated, is four. Werner's insight into molecular structure led him unerringly to the concept of ring formation which he exemplified by discussing the structure of the compound $[\text{Pt}(\text{C}_2\text{H}_4(\text{NH}_2)_2)_2]\text{Cl}_2$. It was clear to him that in this compound two molecules of ethylenediamine had replaced the four molecules of ammonia in $[\text{Pt}(\text{NH}_3)_4]\text{Cl}_2$. He concluded that each molecule of ethylenediamine occupied two of the four coordination positions and that, in so doing, it

formed a five-membered heterocyclic ring. It has been stated that "the idea of the ring structure in ethylenediamine complexes runs subconsciously through the early papers of Werner without being definitely expressed" (Diehl, 1937). In his classical paper of 1893, Werner was quite explicit about the structure of this ethylenediamine compound of platinum representing it as shown in (VII).



At this point he made no mention of the stereochemistry of the platinum, but later in the same paper he put forward the view that the four bonds of platinum(II) are coplanar, that is, the metal is square-coordinated. He based this conclusion on the observation that dichlorodiammineplatinum(II) exists in two forms which he believed to be *cis* and *trans* geometrical isomers (VIIIa and b).



In the same paper, he also discussed the structure of the compound $[\text{Co}(\text{en})_2\text{X}_2]\text{X}$ (en = ethylenediamine) which Jorgensen (1890) had prepared in two isomeric forms. Werner regarded the isomerism as evidence for the octahedral disposition of the six bonds about the cobalt atom and thus clearly indicated that he thought of ethylenediamine as a chelating agent.

D. SOME OF THE FIRST CHELATING MOLECULES TO BE STUDIED

The number and variety of molecules recognized as having the ability to chelate grew so rapidly after the discovery of the phenomenon that, in this brief introduction, it is possible to mention only a few of the most important ones.

Oxalic acid was probably the next molecule after ethylenediamine to be recognized as a chelating agent. Werner and Vilmos (1899) described the