PRESIDENTIAL ADDRESS

Metal Chelates

FRANK J. WELCHER, Indiana University, Indianapolis Downtown Campus

During the second half of the nineteenth century chemists recognized that many of the substances then known could not be fitted in to the ideas of valency which had previously been developed. For example, metals were found to form compounds, often with stable molecules, in which the metal exhibited a valency which was greater than the oxidation state (or valency) which was the basis for the theory then in vogue. A typical example of this was the reaction of copper sulfate in aqueous solution with ammonia to yield a dark blue solution, which upon crystallization yielded a substance which proved to be $Cu(NH_3)_4SO_4$, and not $CuSO_4$. Similarly, cobalt, platinum, zinc, and a number of other metals were found to yield similar complexes with ammonia. A number of theories were proposed to account for the existence of such compounds, but it was not until Werner (21) in 1893 proposed his now-famous coordination theory. Essentially, his theory contained the following postulates: (a) there are two types of valence, one of which is now called ionic valence, and the other coordinate valence; (b) for each central ion there is a fixed number of coordinate valences called the coordination number; (c) coordinate bonds may be formed by a metallic ion with either ions or molecules; and, (d) coordinate groups have a definite spatial arrangement about the central atom. The latter has proved to be a very significant part of the theory. In 1904 Ley (13) first studied the compound formed in the reaction of the copper (II) ion with glycine, or aminoacetic acid, $H_2N\text{-}CH_2\text{-}COOH$. As a result of these investigations, Ley found that the copper (II) ion combines with two molecules of glycine. Further, he learned from conductance measurements that the copper is no longer ionic, which indicated that bonding was not due to ordinary ionic bonding. It is now known that the copper atom is a part of a ring structure involving both glycine molecules. Through the amino and carboxyl groups, glycine occupies two positions in what is known as the coordinations sphere of the copper atom. A compound of this type is known as a **chelate** compound. The term chelate was proposed by Morgan (15) to designate those cyclic structures which arise from the union of metallic atoms with organic or inorganic molecules or ions. The name is derived from the Greek word *chela*, which means the claw of a lobster or crab. This term is used to indicate symbolically the manner in which the chelating group attaches to the central atom.

When a metal ion combines with an electron donor, the resulting compound is said to be a complex or coordination compound. If the substance which combines with the metal contains two or more donor groups, so that one or more rings are formed, the resulting compound is said to be a chelate, and the donor structure is called the chelating

agent. The electron pair bonds formed between the metal and the donor groups may be essentially ionic or essentially covalent, depending on the nature of the metal and the donor group involved. In general, in the following discussion, it is unnecessary to consider the nature of the bonds that are formed, but only to note the types and stabilities of the structures involved.

Some of the chemical and physical properties of metal chelates resemble those of simple complexes and differ only in a quantitative way. On the other hand, some properties are fundamentally different, and chelate compounds may properly be considered as a distinct class of compound with characteristic behavior. Among the more distinctive properties of this class of compounds are the following:

(a) They are generally insoluble in water.

(b) They are usually soluble in non-polar liquids.

(c) Many are extremely stable. For example, some of the metal chelates formed with acetylacetone may be volatilized without decomposition.

(d) Many chelates are highly colored and usually have a color different from that of the normal salts of the metals involved.

(e) Many chelating agents react in a specific or selective manner with only a few ions.

It is difficult to over-emphasize the importance of metal chelates in various branches of theoretical and applied chemistry and allied fields. One of the earliest of the recognized potential applications of chelating reagents was in qualitative and quantitative analysis. Reagents, such as dimethylglyoxime, which is essentially specific for the nickel ion, have contributed greatly to the elimination of interference in analytical procedures. Other reagents form such highly colored complexes that as little as 0.001 μg. of metals can be detected and determined with their use. The development of the theory of chelation provided a foundation for new developments in the field of colored lakes, such as, for example, the alizarin lakes and the chrome lakes of *o.o'*-dihydroxyazo compounds. Chelates have found useful application in physiological chemistry, and many important medicinal products have been developed. Blood pigment, chlorophyll, and cytochrome are interesting chelates which are indispensible for life processes. Certain metal chelate pigments, such as phthalocyanines, are now widely used. Recently a rather large class of new aminopolycarboxylic acids, which have the unusual property of forming water-soluble chelates, have been of remarkable application. Some of these such as ethylenediaminetetraacetic acid and condensed phosphates are now being manufactured in very large quantities and are used for numerous purposes wherever the removal of metallic ions is desirable, such as in water softening, as negative catalysts, and in the clarification of solutions.

Special methods for the purification and separation of metals have been developed which are based upon the high volatility and also the solubility of metal chelates in non-polar solvents. The use of chelating agents in connection with cation exchange resins and solvent extraction have also proved very important in the separation of radio-active metals.

These and many other applications, such as germicides, decontaminations, metal buffers, and many phases of agriculture have combined to make these substances among the more interesting developed in recent years.

Most of the more important applications of chelates depend upon the selective or specific action between the chelating agent or ligand and metal ion or ions, and also upon the control of the concentration of metal ions in a given medium. Both effects are related to the strength of the bonds formed between the ligand and the metal. Consequently, a fundamental understanding of the applications of chelate systems requires an understanding of those factors which effect chelate stability. This, of course, is a long and complex subject, and only the very briefest outline will be presented here. This is considered important in more detailed studies because most chelating agents are organic molecules, and the number of these which have been prepared or which are potentially possible is enormously large. Consequently, the selection of existing compounds, the design of new compounds, and an understanding of natural chelate functions are all facilitated by an understanding of the relationship between ligand structure, the nature of the metal, and the resulting stability of the chelate which they form.

Factors Affecting Chelate Stability

The stability of a metal chelate, that is, the strength of the bond between the metal and ligand atom, is determined by the following:

(a) The nature of the metal atom.

(b) The size of the ring structure formed. This depends upon the location of the acidic and/or coordinating groups in the ligand molecule. The most stable chelates contain saturated ligands that form 5-membered rings, and unsaturated ligands which form 6-membered rings.

(c) The number of rings. In general a metal chelate is more stable than an analogous non-chelate complex. This enhanced stability is referred to as the chelate effect. For example the nickel complex with ethylenediamine, which is a chelate, is more stable than the hexammine complex of nickel, which is not. Further, the more extensive the chelation, the more stable the system. Thus, for example, a molecule such as ammonia which can be attached at only one point is referred to as a unidentate ligand. A molecule such as glycine which has two groups that are capable of linking to a metal atom is referred to as a bidentate ligand, and is, of course, capable of chelate formation. Other molecules may contain three, four, five, six, or even more donor groups and are thereby capable of forming structures having more than one ring. In general, the more rings the chelating agent can form, the more stable is the resulting chelate. It must be emphasized, however, that ligands of entirely different chemical structure may result in chelates of widely different stability.

(d) Base strength of ligand. As a rule, the greater the base strength of the ligand the greater is its tendency to form a stable complex. Other factors, however, may out-weigh base strength. It is of interest at this

point to note that various substituent groups in organic molecules may have important effect on base strength, and in this way the controlled modification of the strength of chelate structures becomes possible.

(e) Resonance. The stability of a chelate ring is affected by the presence or absence of resonating structures. Consequently, ligands having the necessary resonating structures may form more stable chelates than those that do not.

(f) Steric factors. The actual size and spatial distribution of the various parts of the ligand molecule are often very significant in determining the stability of the chelate which it forms. In general, large and bulky ligands form less stable metal complexes than do analogous smaller ligands. Further, certain groups may be attached in such positions as to interfere with the coordination process, or interfere with the assumption of the necessary spatial configurations to make possible a stable chelate. It is in this connection, that some of the most interesting applications of the development of specific analytical reagents have derived.

Metal Chelates in Biological Systems

Although in one form or another the chemistry of metal chelates has touched upon almost every field of chemistry, a number of illustrative examples of their significance which are presented here have largely been drawn from the field of biochemistry.

Metal buffers. It was mentioned earlier that a carefully regulated control of the concentration of metal ions in solution, that is, as metal buffers, is provided by chelate compounds. Metal buffers are analogous in their action to pH buffers in that they provide a fairly constant concentration of the metal ion. An example of the use of chelating agents as metal buffers is provided by the behavior of algae with chelated copper. Algae are very susceptible to an exact concentration of copper in solution. In the complete absence of copper, these organisms suffer deficiency symptoms. It is well known that the presence of large amounts of copper in water is a normal method for the destruction of algae. It appears that algae can thrive on a very low concentration of copper, provided that it is constantly renewable. This can be provided by the equilibrium concentration of copper in a chelate solution. Studies have shown that the optimum concentration of copper for algae is so low that if provided by a normal salt, such as copper sulfate, either the concentration is just suitable, and hence rapidly exhausted, since there is no reservoir; or, if there is sufficient copper that it will not be rapidly exhausted, then it is too high for healthy growth. Only in the form of a chelate can it be both fully available, and yet never present in too high a concentration. In this connection it should be clear, that copper chelates are quite ineffective in controlling aquatic weeds. Metal chelates have also been used in the nutrition of microorganisms to maintain trace amounts of metals at low nontoxic concentrations and to provide a reservoir for the metal in nutrient media.

Trace Elements. Thirty-eight elements have been detected in biological systems, and approximately fifteen of these are known to be

required by both plants and animals. In plants trace amounts of zinc, manganese, molybdenum, copper, cobalt, and perhaps vanadium are required. Since iron is frequently unavailable to plants, even when present in soils in moderately large amounts, and since iron deficiency leads to serious effects in plants, iron is usually included with essential trace elements. Others may be aluminum, barium, and boron, and in animals also cobalt, fluorine, and iodine. The over-all essential elements for both plants and animals include the following: iron, manganese, zinc, copper, cobalt, boron, molybdenum, vanadium, iron, and iodine.

Biological functions of trace metals. Trace metals appear to be essential for the formation and functioning of many enzymes (20). Studies indicate that the site of reactivity of enzyme and substrate is the metal itself. Many naturally occurring chelates in biological systems have functions vital to the organism. These include the catalysis of redox reactions; oxygen-carrying powers; hydrolysis and synthesis of proteins; decarboxylation and carbon dioxide-carrying power; and in addition many others that are less familiar.

Among the more familiar chelates in biological systems are the prosthetic groups of hemoglobin and of chlorophyll. These are porphin derivatives, and include such well-known catalysts as cytochromes, catalases and peroxidases. These also appear in Vitamin B_{12}, which contains a cobalt (III) porphyrin chelate, and seems to function as part of an enzyme system (2).

Hemoglobin is an iron(II) porphin derivative with an enzyme-like function of oxygen storage and transport. This is probably due to the bonding of oxygen to the iron atom in the chelate. The oxygen-binding function of hemoglobin can be completely blocked by any group which forms a stronger bond with iron than does oxygen, which is the substate in this case. For example, the oxygen-binding function is completely destroyed by both carbon monoxide and the cyanide ion, which form very strong bonds with iron.

It was mentioned earlier that the bonding in coordination compounds usually occurs in definite spatial patterns. In this connection it is interesting to note that in biological syntheses metal ions appear to exercise directive effects which lead to what might be called programming in the joining together of certain organic structures. The phosphatase enzymes afford an example of interest in this connection. Almost every phosphatase that has been studied in detail has been found to require either magnesium or manganese for maximum activity. The following possible explanation has been offered: All enzymes which involve phosphate transfer of one sort or another participates in the action of one of a group of coenzymes, all of which contain a pyrophosphate or a diphosphate group. Such groups form chelates with metal ions. Thus, it is logical to assume that enzymes and coenzymes are probably brought together by simultaneous combination with the metal ion. This apears to apply to such coenzymes as ATP (adenosine triphosphate; ADP (adenosine diphosphate); DPN (diphosphoropyridine nucleotide); TPN (triphosphoropyridine nucleotide); and CoA (coenzyme A (1).

A further interesting example of the directive effect of a metal ion in biological syntheses is the role of iron in the formation of chlorophyll (18). One of the essential functions of iron in plants, and perhaps its most essential function, is the catalytic role in the synthesis of chlorophyll. The chemistry of this reaction is complex, but iron (III) ion appears to act as an organizer for the combination of the pyrrole groups to bring them into proper position to form uroporphyrin. Thus the coordinate bonds of iron serve to hold the porphobilinogen groups in the correct position for condensation to a cyclic porphyrin rather than in a random linear fashion. It is of further interest that chlorophyll is not an iron chelate, but in some manner magnesium displaces iron once the porphin structure has been formed. The iron forms a stronger bond with the ligand, but possibly the iron atom passes on in the formation of a new stable porphin ring and is replaced by magnesium.

Carriers of trace metals in soils. A number of anions commonly occurring in the aqueous systems of plants and animals, as well as in soils, form stable, soluble chelates with trace metals. Among the more common of these are citrate, tartrate, malate, and the anions of the amino acids. Roots of plants secrete and release small amounts of organic acids which solubilize and transport trace metals. The exact nature of these is not known, but almost certainly they are chelating agents, and are probably hydroxy acids or amino acids. If all the metal content in soil were present in the dissolved state, as, for example, a chelate, it would rapidly be leached into the subsoil and lost. Some metal is present absorbed on the surface of cation-exchange components of soils, such as humic acids, clays, and similar macromolecular structures, and may readily be removed to a solution phase by natural or synthetic chelating agents. Most metals in soil, however, are locked in the mineral portion in the form of insoluble inorganic salts such as silicates, phosphates, aluminates, carbonates, and sulfates. These are released by decomposition of rock structure and the metal slowly is converted into soluble form such as bicarbonates and chelates.

Carriers of trace metals in physiological systems. The physiological pH is sufficiently high to convert heavy metals completely to insoluble hydrolysis products. Therefore, no appreciable concentration of trace metal ions can be present in animal systems. A number of hydroxy acids are present, however, which form chelates, and can be considered as carriers for trace metals. The anions of such hydroxy acids are citrate, lactate, and malate (9). Heavy metals, including lead and mercury, which have no essential biological function can combine quickly with serum proteins to form complexes of considerable stability. Most metals, except sodium, potassium, calcium, and magnesium, are believed to be transported in blood serum as protein complexes, although these are actually colloidal.

Use of Synthetic Chelates in Biological Systems

The addition of unnatural chelating agents may produce profound effects on biological systems. Such substances may inhibit, partially or

completely, a metal-enzyme function if powerful enough to compete for the metal. If the enzyme is essential to the functioning of the organism, death may result, or the organism otherwise weakened. This principle is used in bactericidal and fungicidal action.

Antibacterial substances. Various studies have revealed interesting correlations between chelation and antibacterial properties. For example, of all the monohydroxyquinolines, only 8-hydroxyquinoline shows any bacterial activity, and this the only one capable of forming metal chelates. Further, the substitution of some inert groups, that is some group presumably not affecting chelation, in some cases adversely affects activity, and in some cases results in no effect at all. Thus, in 2-methyl-8-hydroxyquinoline the activity is greatly reduced. 5-Methyl-8-hydroxyquinoline, on the other hand, has the same order of activity as 8-hydroxyquinoline. The 2-position is known to inhibit chelation, either because of steric effects or because of its effect on the basicity of the ligand, and accordingly it may be presumed that the relationship between 2-position substitution of the methyl group and antibacterial activity are dependent on chelate formation (14).

Iron chelates in plant nutrition. Iron deficiency has been observed in soils of almost all parts of the United States. Frequently soil contains iron, but in many cases it is unavailable to plants. This may be the result of pH or other soil characteristics which render iron compounds too insoluble for absorption by plants. Under these conditions the use of synthetic chelating agents as carriers for iron has been indicated. Satisfactory reagents for this purpose should have sufficient iron chelate stability to prevent the formation of insoluble salts, but on the other hand they should not be so stable as to prevent the metal from being released to the plant. In recent years a number of experiments have been carried out on the use of various chelating agents to alleviate iron chlorosis. The work of Stewart, Leonard, and coworkers (19, 16, 12, 1) has yielded spectacular results in the treatment of iron chlorosis of citrus trees growing in the acid aerated soils of Florida through the use of iron chelates of some of the aminopolycarboxcyclic acids and other materials. These soils are sandy in nature, and of low organic content, and considerable amounts of oxygen are present. Although iron is usually present in quantities sufficient for most plants, the concentration of natural carriers is very low in view of the small amount of organic material present. Under these conditions the iron is completely hydrolyzed either to the hydroxide or to a basic salt. Ethylenediaminetetraacetic acid forms an iron(III) chelate which is quite stable in mildly acidic solutions. The influence of this chelate in restoration to health of chlorotic trees has been very pronounced. In certain instances recovery has resulted after such extensive damage that little more than the trunk of the tree remained.

Trace elements other than iron in plant nutrition. In addition to iron, trace amounts of zinc, copper, manganese, boron, and molybdenum are essential to plant growth, and must be present in trace quantities in soils if the health of the plant is to be maintained. With the exception

of boron and molybdenum, which are present in soils as anions, these metals form stable complexes with chelating agents such as the aminopolycarboxcyclic acids. It is therefore possible to control the levels of zinc, copper, and manganese in the soils and in nutrient solutions by supplying the proper amount of metal chelate and chelating agents in a specified pH range. The use of the zinc chelate of EDTA in maintaining healthy growth of plants has been reported, and it has also been found that under conditions of excess arsenic in the soil the addition of zinc and iron(III) chelates have improved plant growth. In many areas, such as the fruit-growing sections of Florida and California, it is customary to apply a yearly leaf spray containing a zinc salt (2). Experimental work is being carried out in the use of various zinc chelates in foliage sprays. Excellent growth response has been observed with roses in the soil application of manganese EDTA, and the application of chelated manganese has been shown to produce an increase both in the yield and the sugar contents of grapes.

Metal chelates in animal nutrition. Metal chelates have also been used in a variety of ways in animal nutrition. Perhaps the most satisfactory way to introduce trace metals into the body is to employ food which contains ample amounts of these metals. Therefore, when plant products are deficient in a metal, such as iron, the resulting deficiency causes adverse effects in the animals which consume these products. Therefore indirectly, the use of metal chelates in plant nutrition may also well insure that animals fed on the products which are harvested from these plants will obtain sufficient amount of the metals required. There is, however, the possibility of the direct introduction of the metal chelate compounds into feeds and drinking water. Little experimental work has been done on direct animal nutrition with metal chelate compounds, but there is some evidence to indicate that the addition of metal chelates to feed increases the efficiency of oral ingestion of the metal compared to that which is obtained by the use of inorganic metal salts.

The anemic condition resulting from lack of iron is one of the most common trace metal deficiencies encountered in general medical practice. Houlihan and coworkers (10) have developed an effective iron chelate for oral administration of iron which has superior properties to other materials commonly employed. It has been reported that the copper(II)-EDTA chelate is four times as effective as inorganic copper salts in copper nutrition of dogs when the copper chelate is added directly to the feed.

One of the more important applications of metal chelates in animal nutrition is in the use of various chelating agents in food preservation. Traces of metals in various foods may be introduced by the processing machinery used, or by containers used in the storage of food. For example nickel is frequently introduced in the production of fats from the catalysts used in the hydrogenation of vegetable oil. Traces of such metals as copper, nickel and iron have catalytic activity toward chemical oxidation reactions which frequently result in the destruction of important food constituents. For example, traces of copper may cause the destruction of Vitamin C; traces of copper, nickel and iron promote

oxidative destruction, i.e., oxidative rancidity of vegetable oils, fats, and soap. It is now a common practice to add chelating agents to food products when such metal contamination may cause serious trouble. For example, certain soft drinks, which contain appreciable quantities of ascorbic acid, frequently contain small amounts of EDTA to chelate catalytic traces of metals which may be derived from metal containers in which the materials may have been stored. Metal chelates are also used in jams and jellies primarily for the purpose of clarification, since many of the turbidity-producing solids are merely due to calcium, magnesium, or other polyvalent metal compounds which are dissolved by EDTA. As mentioned above, one of the most common uses of chelating agent in food products is the addition of traces to soaps, fats, and oils to counteract this effect of catalytic amounts of metal residues.

In many of the applications of chelating agents in food processing, the chelating agent is not retained in appreciable amounts in the final product. For example, EDTA has been found very effective in the removal of poisonous spray residues from fruits, particularly when lead compounds are used. The removal is simply accomplished by the addition of chelating agents to the washing medium. Both the EDTA and the metal chelates are soluble in water, and consequently are removed by rinsing.

Treatment of heavy metal poisoning. Chelating agents, such as EDTA, are frequently used to suppress the ionic form of metals which are effective poisons. In many cases, too, such reagents aid in the excretion of chelated metals through retention of solubility. For example, aluminon, the ammonium salt of aurintricarboxylic acid, has been used as an antidote for acute beryllium poisoning. It is of interest to note that fresh fruits were once used as a treatment for nickel "itch." The citric acid present in the fresh fruits served as the chelating agent to complex the nickel. 2,3-Dimercaptopropanol (BAL) has also been used to form chelates with toxic metals. It is said to be superior to EDTA for mercury poisoning. EDTA, however, is widely used, notably for lead. It is administered in the form of the disodium calcium EDTA.

Surplus iron is absorbed by the body, but this may be partially removed by treatment with calcium EDTA. Due to the relatively stronger bond formed with iron, the calcium is replaced by iron and the iron excreted as the chelate. An analogous condition occurs with copper. A copper storage disease, known as Wilson's disease, results from excessive storage of copper in the tissue. This has been treated with EDTA and BAL.

Chelates have also been used in medical diagnosis by x-ray studies. It is necessary for this purpose to introduce certain heavy metals into the body which will impede the passage of x-rays. Unfortunately most of these metals are toxic, and cannot be taken in soluble inorganic forms. Chelates with strong chelating agents, such as those with EDTA, are relatively non-toxic, and can be used for this purpose. Thus lead-EDTA chelate can be used for x-ray contrast purposes (17).

Disodium calcium EDTA has been used for radioactive decontamination, and to accelerate excretion of radioactive products. The use of

EDTA in the treatment of plutonium poisoning has been described by Foreman and coworkers (6, 4, 5, 7) and by Hamilton and Scott (8). Plutonium destroys bone marrow and causes osteitis and osteosarcoma. Studies have indicated that elimination of plutonium is rapid and effective when EDTA is administered immediately after exposure. Yttrium is also readily eliminated as the EDTA complex (3).

Literature Cited

1. CALVIN, M. 1954. In: Symposium on the Mechanism of Enzyme Action, W. D. MCELROY and B. GLASS, eds. Johns Hopkins Press, Baltimore.
2. CHABEREK, S. and A. E. MARTELL. 1959. Organic Sequestering Agents. John Wiley, New York.
3. FOREMAN, H. 1950. AECD—2901, UCRL—683.
4. FOREMAN, H. 1953. J. Amer. Pharm. Assoc., Sci. Ed. **42**:629.
5. FOREMAN, H. 1955. Ind. Med. and Surg. **24**:287.
6. FOREMAN, H., P. A. FUQUA, and W. D. WOODWARD. 1954. Arch. Ind. Hyg. Occupational Med. **10**:226.
7. FOREMAN, H., T. T. TRUJILLO, O. JOHNSON, and C. FINNEGAN. 1955. Proc. Soc. Exptl. Biol. Med. **89**:339.
8. HAMILTON, J. G. and K. G. SCOTT. 1953. Proc. Soc. Exptl. Biol. Med. **83**:301.
9. HASTINGS, A. B., F. C. MCLEAN, L. EICHELBERGER, J. L. HALL, and E. DACOSTA. 1934. J. Biol. Chem. **107**:351.
10. HOULIHAN, J., J. PRINCIOTTO, and M. RUBIN. 1953. American Chemical Society, 124th meeting. Chicago.
11. LEONARD, C. D. and I. STEWART. 1952. Proc. Florida State Hort. Soc. **64**:20.
12. LEONARD, C. D. and I. STEWART. 1954. Proc. Florida State Hort. Soc. **66**:49.
13. LEY, H. 1904. Zeit. Elektrochem. **10**:954.
14. MARTELL, A. E. and M. CALVIN. 1952. Chemistry of Metal Chelate Compounds. Prentice-Hall, New York.
15. MORGAN, G. T. and H. D. K. DREW. 1920. J. Chem. Soc. **117**:1456.
16. REITZ, H. J., C. D. LEONARD, J. W. SITES, W. F. SPENCER, and I. W. WANDER. 1954. Bulletin 536. Florida Univ. Agr. Expt. Sta. (Gainesville).
17. SAPEIKA, N. 1954. S. Afr. Med. J. **28**:759, 953.
18. SHEMIN, D. 1959. In: Organic Sequestering Agents, S. Chaberek and A. E. Martell, eds. John Wiley, New York.
19. STEWART, I. and C. D. LEONARD. 1952. California Citrograph **37**:427,444. (See also: Citrus Magazine, June, 1952, and Science **116**:564.)
20. WARBURG, O. 1949. Heavy Metal Prosthetic Groups. Oxford Univ. Press, London.
21. WERNER, A. 1920. Neuere Anschauungen auf dem Gebiete der anorganischen Chemie. 4th ed. Friedrich Vieneg & Sohn, Brunswick.