REACTIONS OF CHELATED ORGANIC LIGANDS

Quintus Fernando

Department of Chemistry, University of Arizona, Tucson, Arizona

I. Introduction

A large number of organic reactions are influenced by the presence of metal ions. A study of such influences represents not only an interesting and useful means of extending methods of synthesis, but also provides a chemical approach to the understanding of the structure of metal chelates.

When a metal ion is coordinated to a ligand, the properties of the metal ion are affected to a remarkable extent. Since the time of Werner, coordination chemists have focused their attention on the changes in the properties of the metal ion, although some of the most obvious and dramatic changes occur in the properties of the coordinated ligand.

Numerous observations on the reactivity of coordinated molecules have appeared in the literature, but it is only recently that a systematic study of the reactions of coordinated ligands has been attempted. Several comprehensive reviews that have appeared recently reflect the interest that is being shown in this area of coordination chemistry (*72*, *92*, *104*, *110*).

A very wide field is encompassed by the reactions of coordinated ligands and it is impractical to describe all of these reactions. In order to provide a proper context for the material in this review, it is necessary to recognize the various types of coordinated ligand reactions and the areas in which these reactions are of importance. Reactions that fall into the following categories, although they are extremely important, will not be described since they have received considerable attention elsewhere: catalysis of enzymatic reactions by metal ions; polymerization reactions, especially stereospecific polymerizations in the presence of Ziegler-Natta catalysts; substitution reactions in metal cyclopentadienyls and all reactions involving complexes in which carbon atoms are the donor atoms.

When a system consisting of a metal ion, a ligand, and one or more metal-ligand complexes undergoes a reaction in which the ligand is transformed into one or more compounds, which may or may not be ligands, the reaction can be considered to be a coordinated ligand reaction. One of the inherent difficulties in systematizing a description of such reactions is that it is not possible to identify the reacting species, especially when labile complexes are involved.

There has been a great deal of recent interest in the reactions of metal chelate compounds. In most reactions of this type, the metal chelate ring remains intact throughout the course of the reaction, particularly when inert chelates of metals such as Cr(III), Co(III), or Rh(III) are used. In such systems, therefore, it is reasonable to assume that the kinetically active species is the metal chelate and this assumption has been verified in a few instances. Although in the course of the reactions of the labile chelates of metal ions such as Cu(II), Zn(II), or Mn(II) the chelate ring undoubtedly remains intact during some portion of the reaction, it is often difficult to determine the species that is kinetically important. Until detailed studies on the mechanisms of these reactions have been carried out, the role ascribed to the metal ion in such reactions is entirely speculative.

An aspect of coordination chemistry that has been of interest throughout the years is the nature of a metal chelate ring. The type of bonding present in these ring systems, the influence of these ring systems on the rest of the molecule, and especially the "aromaticity" of such rings have been controversial subjects. An important outcome of these controversies is that chemists have begun to regard metal chelates as organic compounds and to study their reactions from this viewpoint. Accordingly, the most appropriate method of describing these reactions would be in the terms used for describing organic reactions. This review will consist of a discussion of the reactions of chelated organic ligands in which the chelated ligand undergoes a chemical transformation.

A metal ion, when chelated, will cause the electrons in an organic ligand to be redistributed and, as a result, the reactivity at some point in the chelate ring itself, in an adjacent ring system, or in a pendant functional group in the chelate molecule will be altered to some extent. In addition to the location of the reaction center with respect to the metal ion, a number of factors control the extent to which the chelated ligand reactivity is affected, and it is pertinent to consider briefly some of these factors, although they will be dealt with more explicitly in the sections that follow.

The properties of a metal ion that determine the size and stability of the chelate ring that is formed with a ligand include its size, coordination number, and stereochemistry. All these properties become important in reactions where the metal ion serves to position the reactants by chelate ring formation in a manner suitable for reaction to occur. Such a reaction may take place, since the reactive sites are brought close together by chelate formation or the chelated ligand is forced into a configuration that is favorable for the reaction. In either event, the metal ion acts in such a manner as to increase the entropy of activation and the rate of the reaction.

One of the most important factors that has to be considered involves the magnitude of the positive charge on the metal ion and the charge displacement that occurs on chelation. Electron withdrawal by the metal ion can weaken a bond and result in its rupture or facilitate attack by a nucleophile. The effectiveness of the metal ion in such cases depends to a large extent on the charge as well as the size of the metal ion. Chelation with anionic ligands will reduce the net charge on the metal ion together with its effectiveness and so will back-bonding, if present.

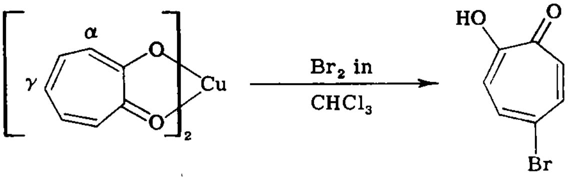
A related factor that affects the charge displacement is the donor atom electronegativity. The number and type of ligands that are chelated to the metal ion will undoubtedly be an important determining factor. The extent to which electronic effects can be transmitted through the ligand is dependent on the type of ligand. In a saturated ligand, only inductive and field effects will come into play, whereas in an unsaturated ligand, conjugative interactions may greatly increase the effect. Although a proton can also bring about electronic changes in an organic ligand in much the same way as a metal ion, the effect on the ligand reactivity is quite different, mainly because of the greater polarizing ability of the proton. Since at present there is no reliable method of evaluating quantitatively the effect of these factors on the electron density in a chelated molecule, it is not possible to predict the extent to which the reactivity of a chelated ligand is altered.

II. Electrophilic Substitution Reactions

Most of the information on the substitution reactions of chelated organic ligands has been obtained by Collman and co-workers, who have carried out extensive investigations on the β-diketone metal complexes, chiefly the metal acetylacetonates. Many of the usual organic chemical techniques can be used for the purification and characterization of these chelates. Moreover, with metal ions such as Cr(III), Co(III), and Rh(III), the acetylacetones form neutral, thermally stable, inert chelates ideally suited for studies of the type that are described below.

In electrophilic substitution reactions, the position of substitution is determined by the distribution of electron density in the molecule as well as the relative stabilities of the possible transition states. For example, in the case of ligands that are enols, this is generally the carbon atom adjacent to the enolic group, and in phenols the *para* and *ortho* carbon atoms. Obviously, the enolates and phenolates react more rapidly than the neutral species (hydrogen chelate), but the reactions take place in the same manner. The course of the reaction with metal chelates of such ligands might be expected to be similar to that of the neutral ligands, in view of the formal similarity of the proton and metal cation which are both Lewis acids. While it is true that the enolates or phenolates react much more rapidly than the corresponding metal chelates, a comparison of the neutral ligands and chelates is complicated by a number of factors. A metal ion is larger than the proton and its charge is distributed over a larger number of donor atoms than is the charge on the proton. This generally results in a reversal in the order of reactivity of the metal and hydrogen chelates from that which might be expected as a result of the more acidic nature of the metal ion. Moreover, the possibility of back-donation of electrons from some metal ions to the ligand would augment this effect.

In almost every case, the differences caused by metal chelation have been limited to changes in rates rather than in the pathway or the products of the reaction. The single exception that has been reported is the bromination of tropolone, in which γ-bromination (reaction I) occurs with the copper chelate and α-bromination with the neutral ligand (*60*).

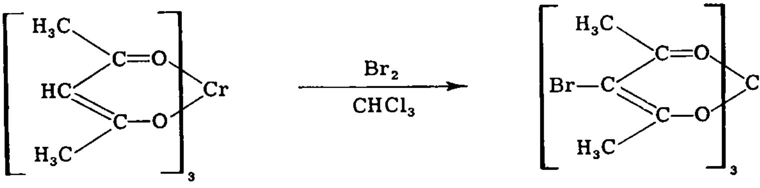


(I)

A. Halogenation

The halogenation of a metal chelate of a β-diketone was reported more than 40 years ago (*151*), when the Cu(II) chelates of benzoylacetone and acetylacetone were chlorinated in chloroform solution with chlorine to give 3-chlorobenzoylacetone and 3-chloroacetylacetone. Copper(II) chloride precipitated during the reaction, indicating that the chelate ring was ruptured in the course of the reaction.

The first example of a reaction in which a metal acetylacetonate ring was substituted without metal-ligand bond rupture was reported in 1925 (*171*). The treatment of tris(2,4-pentanediono)chromium(III) with bromine in chloroform gave the tribromo compound:



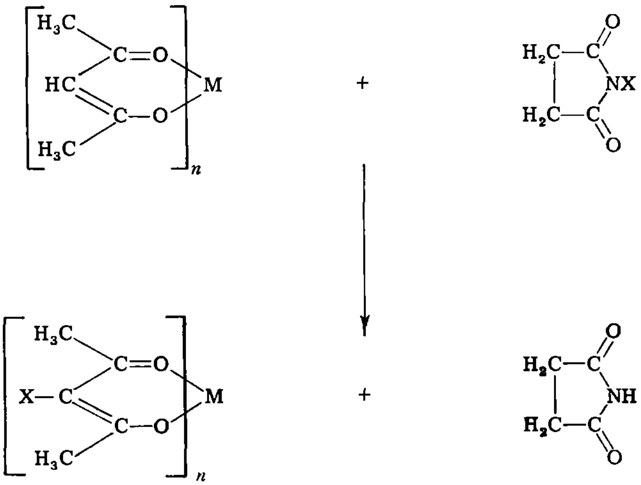
(II)

A hexabromo compound was also reported to have been obtained in which further bromination was presumed to have occurred in the methyl groups. This compound, however, was later shown to be a 1:1 chloroform solvate of the tribromo derivative (*112*).

The structure of tris(3-bromo-2,4-pentanediono)chromium(III) was not established conclusively and no evidence was available until quite recently (*57, 112*) to show that ring substitution occurred with the chelate ring intact. A comparison of the infrared spectra of the unsubstituted metal chelate and the corresponding 3-halo compound has proved to be useful in establishing that ring substitution has occurred. The absence of the in-plane bending mode of the ring hydrogen at 1190 cm^{-1} and the presence of a single band at about 1550 cm^{-1} in all chelates halogenated in the 3-position were sufficient evidence for substitution in the chelate ring (*50*).

The bromination of tris(2,4-pentanediono)chromium(III) has been shown to take place without ring cleavage by means of tracer studies with C^{14}-labeled acetylacetone (*112*). Approximately equivalent amounts of C^{14}-labeled acetylacetone and the chromium chelate were treated with sufficient *N*-bromosuccinimide to monobrominate both compounds. The exchange that occurred was found to be less than or equal to the exchange that occurred in the absence of the brominating agent. It was also shown by means of a competitive bromination of the acetylacetone and the chromium chelate that their rates of bromination were comparable. Therefore it is apparent that complete ring cleavage does not occur during the bromination of tris(2,4-pentanediono)chromium(III).

Several halogenating agents have been used to halogenate the chelates of Cr(III), Co(III), Rh(III), Al(III), Ga(III), Sc(III), Cu(II), Ni(II), Be(II), and VO(II) with acetylacetone and a number of related compounds (*57*, *112*). The halogenating agents that have given the best results are the *N*-halosuccinimides in hot chloroform solutions, since no active by-products are formed in the course of the reaction:



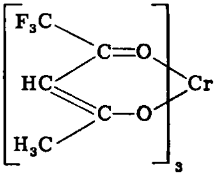
X = Br, Cl, or I
n = 2 or 3

(III)

Bromine and iodine monochloride in glacial acetic acid solutions in the presence of acetate ions were also found to be suitable halogenating agents for metal acetylacetonates (*57*). In all these cases a rapid reaction occurred in which three moles of halogen reacted with each mole of chelate and no further halogenation occurred in the presence of excess of halogenating agent. The use of a limited amount of halogenating agent gave mixtures containing mono-, di-, and trihalogenated chelates. Mono- and dibrominated chelates were also obtained by the action of cyanogen bromide on the metal acetylacetonate in the presence of boron trifluoride etherate or aluminum chloride (*48*, *113*).

By means of the above procedures, a variety of β-dicarbonyl metal chelates have been halogenated. For example, the chromium chelates of formylacetone (*52*), 1-phenyl-1,3-butanedione and dibenzoylmethane (*57*), ethylenediaminebis(2,4-pentanediono)copper(II) and the nickel(II) chelate of *N*-*n*-butylsalicylaldimine (*112*) have been brominated in chloroform solution with *N*-bromosuccinimide. The chromium chelates of a number of β-amino-α,β-unsaturated ketones have been prepared by a novel method and brominated with *N*-bromosuccinimide in chloroform solution (*53*).

The ease of bromination of the metal chelates of β-diketones varies greatly and in some instances bromination does not take place even under vigorous conditions. For example, the chromium chelates of trifluoro- and hexafluoroacetylacetone (structures IV and V) and bis(ethylenediamine)-2,4-pentanedionocobalt(III) cation (structure VI) cannot be brominated (*48*). This inertness undoubtedly reflects the effect of substituents on the β-diketones themselves.



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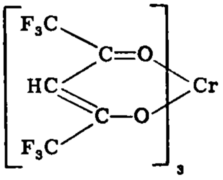

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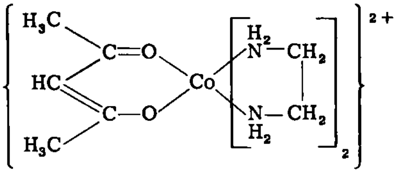
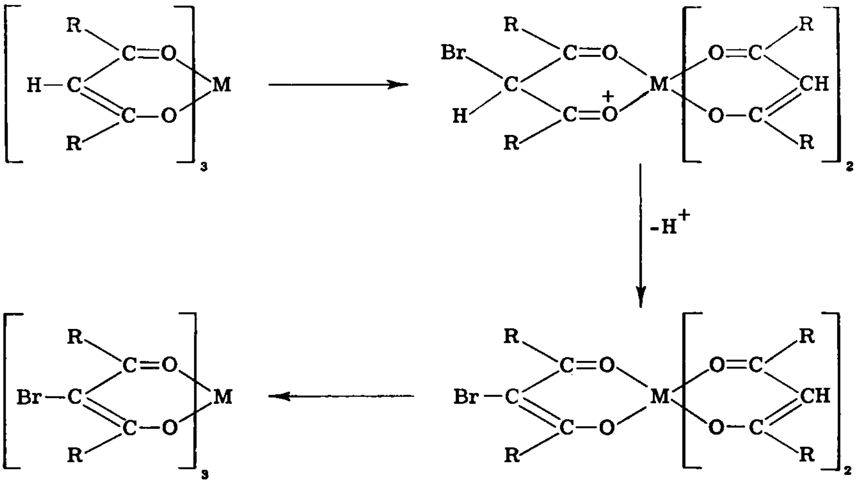


(VI)

Thiocyanogen is a pseudohalogen and behaves in a manner very similar to bromine. Cobalt(III) and aluminum(III) acetylacetonates undergo substitution in the 3-position and form the corresponding tris(3-thiocyanato-2,4-pentanedione) compounds, but the labile Cu(II) chelate of acetylacetone is cleaved in the presence of thiocyanogen. This ring cleavage is caused by the hydrogen ions formed in the course of the substitution reaction and can be prevented by the addition of sodium bicarbonate to the reaction mixture (*113*).

The chemical reactivity of the thiocyano groups in these chelate rings has not been investigated, but the halogen atoms in the 3-halo metal acetylacetonates have been found to be quite inert and their behavior is different from that of aryl halides, since treatment of the tris(3-bromo-2,4-pentanediono)chromium(III) chelate with magnesium or lithium in benzene or tetrahydrofuran resulted in no reaction. Attempted nucleophilic displacement of the bromine atoms in this chelate by azide, acetate, nitrate, and iodide ions in hot dimethylformamide also failed. In most of these reactions the starting material is recovered unchanged or, if the reaction conditions are too drastic, the chelate is destroyed; for example, the tris(3-bromo)chromium chelate is decomposed by sodium ethoxide in cold ethanol or zinc powder in boiling ethanol (*57*). The only reaction that has been successfully carried out with these halogenated compounds is the catalytic reduction of tris(3-chloro-2,4-pentanediono)chromium(III) to chromium acetylacetonate with hydrogen in the presence of a palladium hydroxide catalyst (*48*). The unreactive nature of the halogen atoms in the 3-position in 2,4-pentanediono metal chelates probably arises from the steric shielding by groups in positions 2 and 4 and from the resonance stabilization of the chelate ring system.

No complete study on the mechanism of halogenation of metal acetylacetonates has been carried out. Although the halogenating agents used in these reactions can form the 3-halo compounds via a radical or ionic mechanism, it seems reasonable to assume that these reactions are electrophilic substitution reactions. The probable mechanism is as follows (*49, 112*): the chelate ring undergoes S_N2 attack by the electrophile:



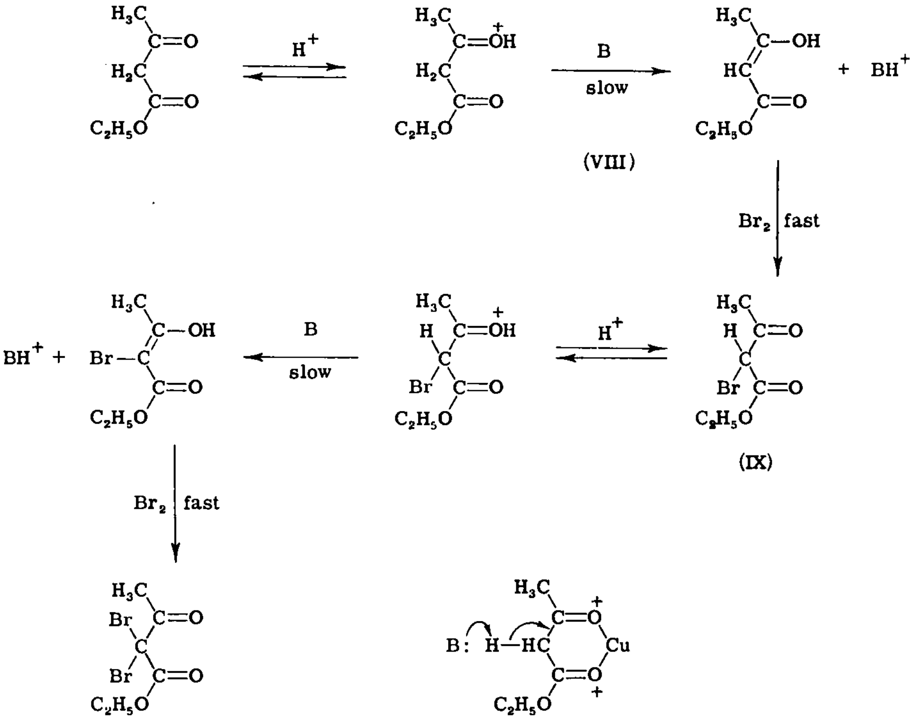
(VII)

Another possible mechanism involves the bromination of the free ligand which is in equilibrium with the metal acetylacetonate and the metal ion, the reaction proceeding until the metal acetylacetonate is completely converted into the 3-halo compound. The results of the experiments carried out with C^{14}-labeled acetylacetone have shown conclusively that for the inert metal chelates, at least, bromination does not occur via this mechanism (*112*).

Alternatively, one of the metal-oxygen bonds in the acetylacetonate can cleave before or after electrophilic attack on the chelate ring that is undergoing cleavage, forming a five-coordinate intermediate. With the subsequent loss of a proton, a chelate ring with a 3-halo substituent is obtained. The trisacetylacetonates of Cr(III), Co(III), and Rh(III) were partially resolved on a 16-foot column of D-lactose hydrate. The optical activity of each of these chelates was measured before and after being subjected to a number of electrophilic substitution reactions. It was found that the substitution reactions did not cause total racemization, and therefore it was concluded that this alternative mechanism is unlikely (*49*).

The only authenticated cases of reactions involving intact metal chelate rings are those of the metal acetylacetonates. In all the other systems that will be described in this review, it is presumed that the chelate ring retains its integrity throughout the course of the reaction or at least during some critical phase of the reaction.

The bromination of β-keto esters is quite similar to that of β-diketones. Ethyl acetoacetate was found to undergo electrophilic substitution at the



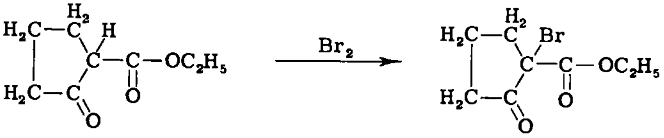
(VIII)

(IX)

(X)

β-carbon atom when reacted with bromine in aqueous solution (*163*, *164*). The rate-determining step (VIII in reaction scheme) is the removal of a proton by a base, B. Copper(II) ions increased the rate of bromination and are therefore more effective than the hydrogen ions which act as catalysts in this reaction. The increased rate can be explained if it is assumed that a Cu(II) chelate of the keto form of ethyl acetoacetate (structure X) is formed in which one hydrogen atom on the α-carbon can be very easily removed by a base. Barium(II), the only other metal ion that was studied, was found to have an insignificant effect on the rate of bromination of ethyl acetoacetate.

The effect of a number of metal ions on the rate of bromination of 2-carbethoxycyclopentanone (XI) was studied, since the presence of only one α-hydrogen atom in this β-keto ester should considerably simplify the kinetics (*164*).



(XI)

A number of metal ions were found to be more effective than the hydrogen ion in increasing the rate of bromination of this compound. The effectiveness of the metal ions decreased in the following order: Cu(II), Ni(II), La(III), Zn(II), Pb(II), Mn(II), Cd(II), Mg(II), and Ca(II). This order parallels the sequence that is usually found for the stability constants of dipositive metal ions. The reason for the increase caused by these metal ions in the rate of bromination is presumably the same as that shown above for ethyl acetoacetate.

The ligand 8-hydroxyquinoline, which is a phenol, is readily halogenated in the 5- and 7-positions. Studies carried out on the halogenation of metal chelates of 8-hydroxyquinoline and its derivatives show that the effect of the metal ion is generally in accord with what is expected, i.e., the metal ion alters the reactivity of the ligand somewhat but not the orientation of substitution.

Dibromination of the Cu(II), Co(III), Cr(III), Fe(III), and Al(III) chelates of 8-hydroxyquinoline occurred when reacted with bromine in chloroform solution, and the products and yields were comparable to those obtained when the free ligand was brominated. The dichlorination of 8-hydroxyquinoline with chlorine in carbon tetrachloride solution gave a 40% yield, whereas the dichlorination of Cu(II) or Al(III) chelates gave 80–90% yield of 5,7-dichloro-8-hydroxyquinoline. On the basis of this increased yield it would appear that the intact metal chelate was halogenated rather than the free ligand (*140*).

No conclusion is possible from these results regarding the relative reactivity of the ligand and the metal chelates in view of the very rapid rate of halogenation of both species. A recent study of the iodination in the 7-position of 8-hydroxyquinoline-5-sulfonic acid and its metal chelates has been carried out by a technique specifically suited for the investigation of fast reactions (*29*). In aqueous buffered solutions at constant iodide concentration, the iodination reaction is first-order with respect to both the 5-sulfonic acid and iodine. The apparent second-order rate constant is inversely proportional to the iodide ion concentration and increases with increasing pH as well as with increasing concentrations of the buffer components. The mechanism for the iodination reaction is probably a general base-catalyzed removal of the proton from the addition product of the phenolate anion of 8-quinolinol-5-sulfonic acid and the cation I^+. The iodination reactions of the Mn(II), Zn(II), Fe(II), Co(II), Ni(II), and Cu(II) chelates of 8-hydroxyquinoline-5-sulfonic acid followed the same general rate expression that was found for the ligand. The presence of the metal ion significantly reduced the rate of iodination in all cases. It was shown by a study of the effect of metal:ligand variation that the observed rate could be attributed to the reaction of the metal chelate species rather than of the uncomplexed ligand anion. The rate of reaction of the metal chelates seems to be only 10 to 20 times slower than that of the ligand anion and does not depend to any significant extent on the nature of the metal ion. The mechanism of the iodination of the metal chelates is quite complex, probably involving consecutive reactions in which the effect of the metal ion on the over-all reaction rate tends to be counterbalanced (*28*). Despite the complexity of the reaction mechanism, the order of reactivity is the expected one, of ligand anion being faster than the metal chelate. From a related study of the bromination of 8-hydroxyquinoline (*118*) and its chelates (*169*), it was found that the neutral ligands react much more slowly than the metal chelates.

B. Nitration and Nitrosation

The metal acetylacetonates have been successfully nitrated with several nitrating agents that have been used to nitrate reactive aromatic systems. Nitrating agents commonly used to nitrate aromatic and aliphatic compounds will destroy the metal chelate.

Bis(3-nitro-2,4-pentanediono)copper(II) was obtained by the nitration of copper(II) bisacetylacetone with N_2O_4 in benzene or chloroform solutions. The acetylacetonates of Ni(II), Pt(II), and Pd(II) also gave bis(3-nitro) compounds, although a palladium(II) compound could not be separated from side reaction products. Tris(2,4-pentanediono)aluminum(III) gave a monomeric tris(3-nitro) compound under the same conditions. A dinitrated aluminum complex was obtained by the use of a smaller metal complex: N_2O_4 ratio (1:3) than that used in the nitration of the other acetylacetonates. An examination of the infrared spectra of the acetylacetonates and their deuteriated forms provided conclusive evidence for substitution in the 3-position (*66, 67*). Attempts to nitrate the more stable Fe(III) and Cr(III) acetylacetonates with N_2O_4 in benzene or in methylene chloride failed, probably because several intractable products were formed (*56, 67*). Chromium(III) acetylacetonate, however, was nitrated in methylene chloride with $N_2O_4 \cdot BF_3$ to give tris(3-nitro-2,4-pentanediono)chromium(III), but low yields were obtained (*54, 56*).

The most successful nitrating agent reported for chelated acetylacetones is a deep blue solution that is formed when copper(II) nitrate trihydrate is dissolved in acetic anhydride. This solution readily nitrated the Cr(III), Co(III), and Rh(III) chelates of acetylacetone to give the corresponding tris(3-nitro) compounds. The tris-3-nitromalonaldehyde chelate and tris(3-nitroformylacetone) chelate of chromium(III) were also prepared by this method (*52*). Anhydrous copper(II) nitrate was found to be insoluble in acetic anhydride and the resulting mixture was ineffective as a nitrating agent (*54*).

The ligand acetylacetone was also successfully nitrated by the mixture of copper(II) nitrate trihydrate and acetic anhydride or by a mixture of chromium(III) nitrate trihydrate and acetic anhydride. In the former case, bis(3-nitro-2,4-pentanediono)copper(II) precipitated and was thereby protected from cleavage of the chelate rings. In the latter case, a mixture of products was formed, presumably the mono-, di-, and trinitrated chromium chelates (*54*).

Metal acetylacetonates with bulky groups such as C_6H_5 in the 2- or 4-position could not be nitrated, since the 3-position is shielded from attack by electrophilic reagents, just as in halogenation reactions.

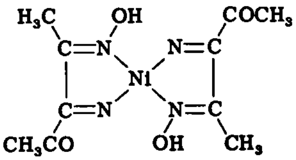
Substitution always occurs only in the 3-position in the metal acetylacetonates and no unusual reaction products in these nitration reactions have been observed. The 3-nitro chelates have been identified by their infrared and proton magnetic resonance spectra. In the 3-nitro chelates, as in the 3-halogenated chelates, the band corresponding to the bending mode of the hydrogen atom in the 3-position at 1200 cm^{-1} is absent. In the proton magnetic resonance spectra of the unsubstituted diamagnetic metal acetylacetonates, two signals are present, one at $7.8\,\tau$ assigned to the protons in the methyl groups and another at $4.4\,\tau$ assigned to the ring hydrogen. In all the nitro chelates, the low field signal at $4.4\,\tau$ is absent, thus showing conclusively that ring nitration occurred in the 3-position.

The reasons for the effectiveness of the unusual nitrating agent used in these nitration reactions are unknown, and the mechanisms of the reactions have not been investigated.

The reactivity of the 3-nitro groups in metal acetylacetonates is different from that of the nitro groups substituted in aromatic ring systems. The steric influence of the groups in 2- and 4-positions, as well as the unusual electron distribution in the metal chelate ring, are contributory factors to the unreactive nature of the 3-nitro groups. Many attempts to reduce these nitro groups by the use of conventional chemical reducing agents were unsuccessful, and in some instances gave anomalous results. For example, the mono- and dinitrochromium acetylacetone chelates, when treated with zinc dust in pyridine at 60°C, gave the unsubstituted acetylacetonates (*54*, *59*).

Although a report of the successful reduction of the nitro group in chromium acetylacetonate appeared a few years ago (*21*), experimental details of the first instance in which reduction was effected were reported only recently (*58*, *59*). Hydrogenation of the mononitrochromium chelate in ethanol over a palladium hydroxide catalyst gave the 3-amino chelate in about 70% yield (*58*, *59*).

The chelated metal ion does not seem to affect the pathway of the nitration reactions, but does have an effect on their course. The reaction of nickel(II) acetylacetonate with nitrous acid in water, ethanol, or ethanol-water solutions in the presence of ammonium acetate gave a red compound, $Ni(C_5H_7N_2O_2)_2$, which was diamagnetic, monomeric in chloroform solution, and a nonelectrolyte in nitrobenzene. A similar compound was obtained with Pd(II), and the presence of ammonia was found to be essential for the formation of these two compounds. The corresponding compounds of Cu(II) and Pt(II) could not be prepared under the same experimental conditions. The infrared spectra of the nickel and palladium complexes are compatible with the two structures (XII) and (XIII), and on this evidence alone it is difficult to assign a structure to the complexes formed. In any event, the metal acetylacetonate appears to have undergone a rather unusual type of reaction, which merits further investigation (*66*, *67*).



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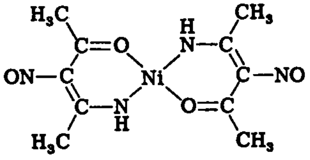
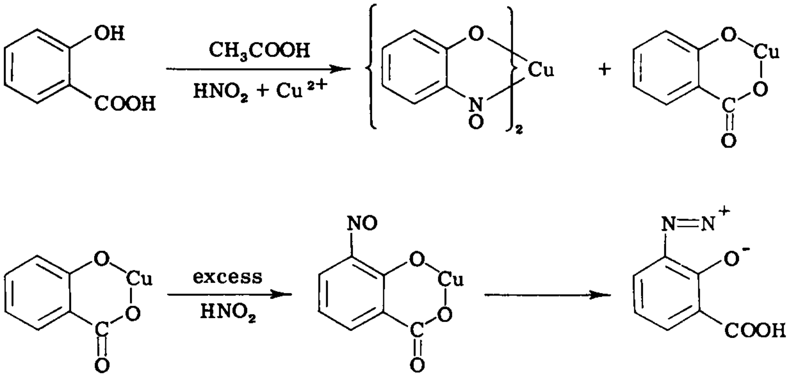


(XIII)

Another unusual reaction is that of acetylacetone with $K_2Pd(NO_2)_4$.

The compound $Pd(C_{10}H_{15}O_4)NO$ was formed and was assumed to be a 5-covalent compound with the nitroso group attached to the metal ion, since the infrared spectrum showed a characteristic NO stretching frequency at 1656 cm^{-1} (*66*).

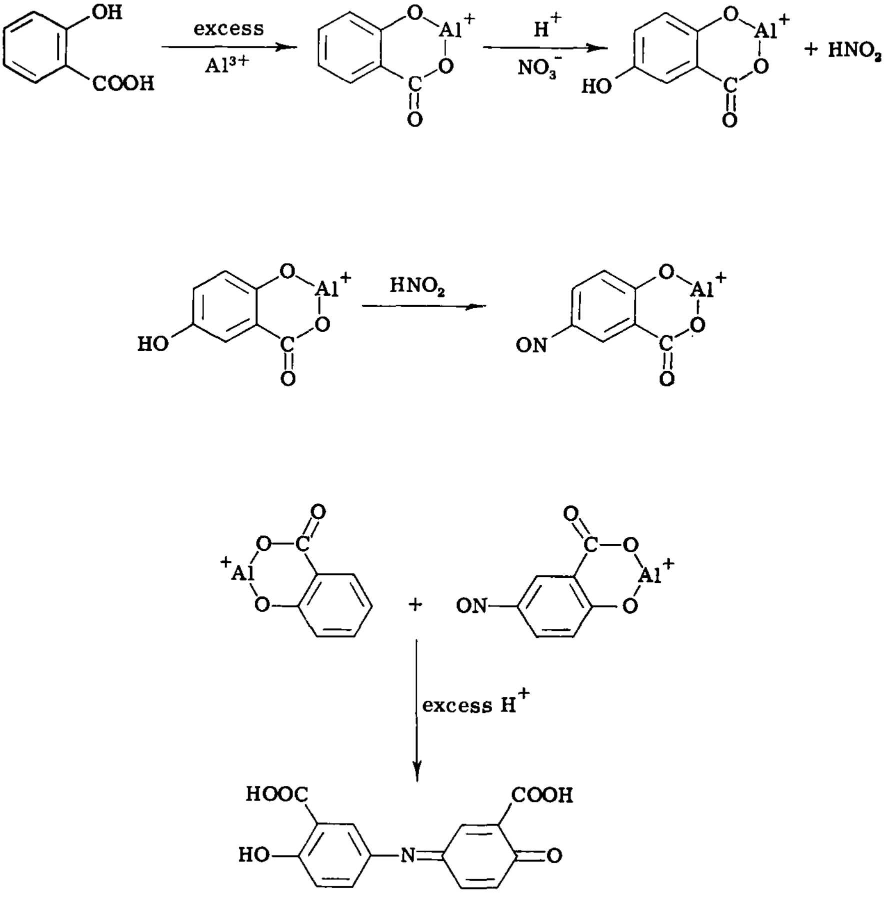
The treatment of platinum(II) acetylacetonate with nitrosyl chloride in benzene gave, instead of the expected nitrito or nitroso derivatives, a bis(3-chloro) complex. This chlorination is probably a result of the ease of dissociation of nitrosyl chloride to nitric oxide and chlorine (*67*). The reaction of nitrous acid with salicylic acid in an acetic acid medium results in the replacement of the carboxylic acid group in salicylic acid by a nitroso group. In the presence of excess of nitrous acid, however, the *o*-nitrosophenol undergoes a rapid reaction to form a diazo compound (*157*). The latter reaction can be prevented by the addition of copper(II) salts to the reaction mixture. The stable and insoluble copper chelate of *o*-nitrosophenol precipitates from solution and protects the nitroso group from further reaction with nitrous acid. The copper chelate can be cleaved with HCl and a 65% yield of *o*-nitrosophenol obtained from the reaction mixture (*158*). The copper chelate of salicyclic acid that is also formed undergoes further nitrosation, *ortho* to the hydroxy group, and a 2% yield of 5-nitrosalicylic acid is obtained. Since the conversion of a nitroso group to a diazo group occurs quite rapidly, a somewhat larger yield (about 10%) of 5-diazosalicyclic acid is also obtained. Thus it is evident (reaction scheme XIV) that the reactive positions in the copper(II) chelate of salicylic acid are the positions *ortho* to the hydroxy group, and there is no change in the orientation of substitution in the chelate. It is of interest to note in this case that 5-substituted compounds are obtained with the copper chelate of salicylic acid, whereas with salicylic acid itself or its sodium salt no such compounds have



(XIV)

been obtained. Furthermore, metal ions other than copper(II) have a considerably different effect on the course of the reaction (*126*).

A solution containing salicylic acid and an excess of aluminum nitrate develops an intense blue color when heated to about 100°C for 4–5 minutes. The aluminum chelates formed, when cleaved with HCl, give a 56% yield of phenolindophenol-3,3′-dicarboxylic acid and 5-hydroxysalicylic acid and 5-nitrosalicylic acid in 12% and 10% yields, respectively. Reaction scheme (XV) has been advanced to explain the products formed.



(XV)

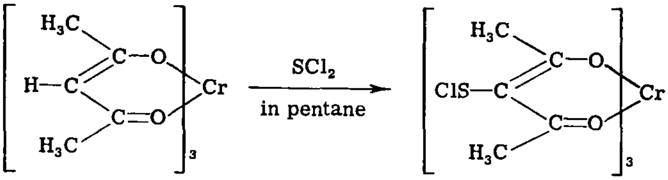
As a result of the partial oxidation of 5-nitrososalicylic acid, 5-nitrosalicylic acid is formed. The nitrates of chromium, zirconium, thorium, and gallium could be used in place of aluminum nitrate to give the same reactions, but beryllium and zinc nitrates were found to be somewhat less effective.

In the aluminum(III) chelate of salicylic acid, as well as in its copper(II) chelate, the positions susceptible to electrophilic attack are *ortho* and *para* to the hydroxy group. Since the course the reaction takes in the presence of the metal ions is quite different from that in their absence, it can be concluded that substitution occurs in the metal chelates rather than in the free ligands. This reaction is noteworthy in that it is one of the few reported instances in which a metal ion in a chelate ring has a marked influence on the course of a substitution reaction in an adjacent aromatic ring.

C. Reactions with Sulfur-Containing Electrophiles

Most metal chelates will not survive in the presence of conventional sulfonating agents, and it is therefore not surprising that sulfonation reactions of metal chelates have not been studied. There are, however, a few chelates, such as copper(II) phthalocyanine, which are stable in the presence of dilute mineral acids and might undergo sulfonation with their chelate rings intact. The sulfonation of less stable chelates might be accomplished by the use of mild sulfonating agents, such as a solution of sulfur trioxide in pyridine. The only sulfur-containing substituents that have been introduced into metal chelate ring systems are the thiocyanato group (Section II,A) and the sulfenyl chloride group, both of which have been introduced into metal acetylacetonate rings.

Sulfur dichloride reacts readily with the acetylacetonates of aluminum(III), beryllium (II), chromium(III), and cobalt(III) to form the corresponding sulfenyl chlorides (*113*):



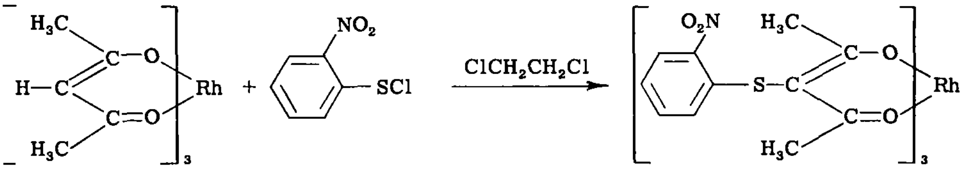
(XVI)

Further reaction of the sulfenyl chlorides to the sulfides does not take place. It can also be deduced that the substitution reaction occurred with the chelate ring unruptured, since no sulfides (usually obtained with sulfur dichloride and the enol form of 2,4-pentanedione) were obtained. The structures of the sulfenyl chlorides of the metal acetylacetonates were confirmed by their infrared spectra, and by conversion of the sulfenyl chloride to a thiocyano group by reaction with cyanide ions. The tris(3-thiocyano-

2,4-pentanediono)chromium(III) prepared by this method was found to be identical with the compound prepared by the action of thiocyanogen on chromium acetylacetonate (*113*).

The sulfenyl chloride groups in these metal acetylacetonates are quite reactive, which is in contrast to most of the other 3-substituents in metal acetylacetonates. The 3-sulfenyl chloride group reacted with amines, phenols, thiocyanates, olefins, and triethyl phosphite. In most of these cases the reaction products were not separated and characterized (*113*).

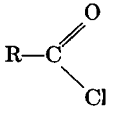
Arylsulfenyl chlorides react with metal acetylacetonates to form sulfides which are tris-3-substituted compounds. These sulfides are stable and resistant to oxidation with 30% hydrogen peroxide and are likely to be of little use as starting materials for synthetic purposes (*55*).



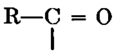
(XVII)

D. Acylation

Acylation reactions in this section are confined to substitution reactions in which an acylating agent, such as


$$R{-}C(=O)Cl$$

replaces a hydrogen atom by an


$$R{-}C{=}O$$

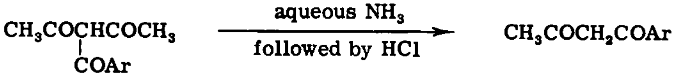
group and, as a result, this group is attached to a carbon, oxygen, or nitrogen atom in a metal chelate. It will be assumed (since no studies on the mechanisms of these reactions have been reported) that the acylating agent is the acylium ion R—CO$^+$, which is an electrophile, and that the atom at which acylation occurs is present in a nucleophilic substrate. Lewis acids such as $AlCl_3$, $SnCl_4$, $ZnCl_2$, or BF_3 promote acylation reactions by increasing the electrophilic nature of the acylating agent. Weak Lewis bases, such as carbon disulfide, and ethylene and methylene chlorides, serve an important purpose in many of these reactions by keeping the reactants in solution during the course of the reaction.

The acylation of the metal chelates of β-diketones has been studied quite extensively. In early work on the benzoylation of acetylacetone chelates, *C*-acylation as well as *O*-acylation was reported to occur (*47*, *156*), and a recent study on the benzoylation of dibenzoylmethane chelates confirmed this (*153*). In an investigation of the reaction of *m*- or *p*-nitrobenzoyl chloride with the copper(II) chelate of acetylacetone, it was found that on shaking the reactants together in $CHCl_3$ for 12–24 hours at room temperature a triketone was obtained together with a precipitate of cupric chloride. The triketone could be converted to a β-diketone by treatment with aqueous ammonia followed by acidification with HCl (*20*):

ArCOCl = *m* or *p*-nitrobenzoyl chloride

$$(CH_3COCHCOCH_3)Cu_{1/2} + ArCOCl \longrightarrow CH_3CO\underset{\displaystyle COAr}{\underset{|}{C}H}COCH_3$$

triketone

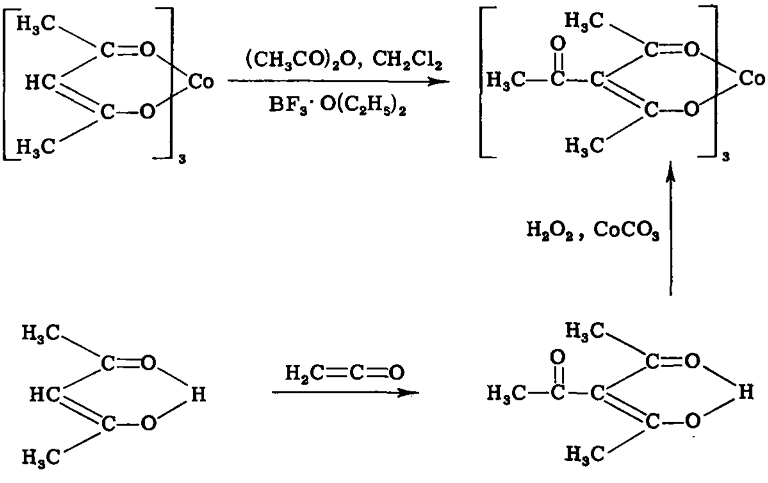


$$CH_3CO\underset{\displaystyle COAr}{\underset{|}{C}H}COCH_3 \xrightarrow[\text{followed by HCl}]{\text{aqueous } NH_3} CH_3COCH_2COAr$$

(XVIII)

It is probable that in all these cases the metal chelate rings were not intact during the course of the reaction and no special precautions were taken to ensure this. It cannot therefore, be construed that both *O*-acylated and *C*-acylated products are obtained from acylation of the metal chelate of a β-diketone itself. Collman and co-workers, in an extensive study of the acylation of the metal chelates of acetylacetone, have reported the formation of only the *C*-acylated products.

The acetylation of chromium acetylacetonate was accomplished by reacting it with acetic anhydride and boron trifluoride etherate in methylene chloride. A triacetylated chelate was obtained but could not be completely freed from the mono- and diacetylated chelates. The acetylation of cobalt(III) acetylacetonate under the same conditions gave a mixture of mono-, di-, and triacetylated products, together with some unreacted cobalt acetylacetonate. The reaction products were separated chromatographically on an alumina column with benzene as eluent. The structures of the acetylated chelates were assigned on the basis of their nuclear magnetic resonance and infrared spectra. The triacetylated chelate was synthesized by a different route by the reaction of triacetylmethane with cobalt(II) carbonate in the presence of hydrogen peroxide. This synthesis served to confirm the structure of the triacetylated chelate (*55*) (see reaction scheme XIX).



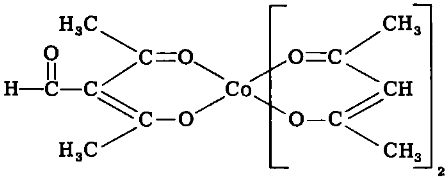
(XIX)

The acetylation of rhodium(III) acetylacetonate did not take place under the same mild conditions employed in the acetylation of the chromium(III) and cobalt(III) chelates. Under vigorous reaction conditions, a 19% yield of the monoacetylated rhodium chelate was obtained. Acetyl chloride and aluminum chloride in 1,2-dichloroethane as acetylating agent gave a mixture of the mono- and diacetylated rhodium(III) chelates, whereas the cobalt(III) and chromium(III) chelate rings were completely destroyed under these reaction conditions. A triacetylated rhodium chelate could not be prepared even under rigorous conditions (*55*).

Efforts to introduce larger acyl groups, such as propionyl and butyryl, into the 3-position of chromium and cobalt acetylacetonates failed, probably because steric hindrance by the 2- and 4-methyl groups allowed the chelate ring to be degraded rather than substituted. On the other hand, the increased stability of the rhodium(III) acetylacetonate permitted the synthesis of monobenzoyl, dibenzoyl, and monobutyryl acetylacetonates under Friedel-Crafts reaction conditions (*55*).

In these acylation reactions, it is evident that the rhodium(III) chelates are much less reactive than the chromium(III) and cobalt(III) chelates. This qualitative observation shows that the chelated rhodium(III) ion has considerably decreased the electron density of the carbon atom in 3-position.

The study of the reactivity of a substituent at the central carbon atom in a metal acetylacetonate ring is one method of obtaining information on the aromaticity of the chelate ring, although in many instances the interpretation of the results is complicated by the steric effects of the two flanking methyl groups. An essential requirement for this type of study is that the substituent introduced into the 3-position must be sufficiently reactive. The acetyl group does not fulfill the requirement, but an aldehyde group is a highly reactive group and can be readily introduced at the 3-position into the chelate ring systems of chromium(III), cobalt(III), and rhodium(III) acetylacetonates by reacting them with dimethylformamide in the presence of phosphorus oxychloride. These formylation reactions were found to take place much more slowly than the other electrophilic substitution reactions of acetylacetonates. The monoformyl chelates (structure XX) of Cr(III), Co(III), and Rh(III) were readily obtained and characterized by their infrared and NMR spectra. Under vigorous conditions, the dialdehyde cobalt(III) chelate was obtained, but could not be separated chromatographically from the monoaldehyde chelate. Trialdehyde chelates were probably obtained in small quantities, but could not be characterized (*54*). The availability of these monoaldehyde chelates such as



(XX)

afforded a convenient route for the synthesis of mixed ligand chelates, usually quite difficult to prepare. For example, the monoformylated cobalt(III) chelate could be readily brominated, chlorinated, or nitrated in the 3-position of the unsubstituted acetylacetonate rings (*54*).

Although the aldehyde group substituted in an aromatic nucleus is quite reactive, it was found to be surprisingly unreactive when substituted in a metal acetylacetonate ring. Positive Fehling and Tollens tests were given by these formylated compounds, but all attempts to oxidize these aldehyde groups on a preparative scale were unsuccessful (*54*).

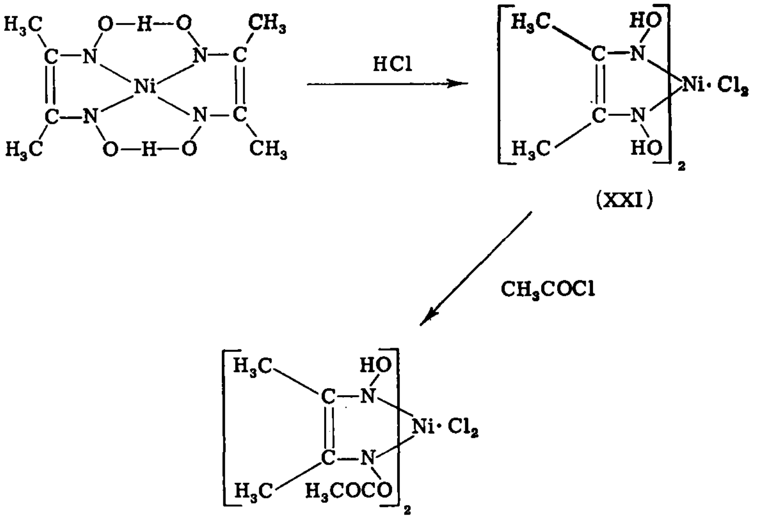
The benzoylation of a series of β-diketone metal chelates has been investigated for the purpose of assessing the steric and electronic factors involved in the production of *O*-acyl and *C*-acyl compounds (*153*). The benzoylation of the metal chelates of diisobutyrylmethane, di-*n*-butyrylmethane, and benzoylisobutyrylmethane was investigated by the following method. Benzoyl chloride (1 mole in the case of the sodium chelate and

2 moles for barium, copper, nickel, or zinc chelates) was added to a 2% solution of the metal chelate in cyclohexane and refluxed. It was found that in all cases mixtures of the *C*- and *O*-benzoylated products were formed and that the zinc chelates gave much smaller amounts of the *C*-benzoylated products than the rest of the metal chelates. It was also observed that the phenyl groups at the terminal positions in the β-diketones decrease, and large alkyl groups increase, the extent of *C*-benzoylation.

Since a precipitate of the metal chloride was obtained in every case, it is difficult to determine whether benzoylation of the compounds occurred when their chelate rings were partially or completely ruptured. Since benzoyl chloride did not react with either the copper or nickel chelate of diisobutyrylmethane in pyridine, it was assumed that the coordination positions, unoccupied by the donor atoms of the β-diketone, were occupied by pyridine, thereby preventing the coordination of the benzoylating agent and subsequent benzoylation of the chelate.

Although the observed effect of the metal ions on the extent of *O*-benzoylation or *C*-benzoylation is important for synthetic purposes, it is questionable whether any conclusions of significance to the reactions of chelated organic ligands can be obtained from these results. It would be of great interest to repeat these reactions with the inert chelates of Rh(III), Co(III), Al(III), and Cr(III).

In a metal chelate in which an oxygen atom is a donor atom, *O*-acylation at this atom occurs as a result of, or simultaneously with, the rupture of the metal-oxygen bond. It is therefore difficult to assess the effect of the metal ion on the reactivity of the donor oxygen atom, unless the mechanism of the reaction is unequivocally established. Another approach to determining the effect of a chelated metal ion on *O*-acylation reactions is the study of the reactivity of oxygen atoms not coordinated directly to a metal ion. For example, in the nickel dimethylglyoxime chelate the oxygen atoms are not bonded to the metal atom; several attempts to acylate these oxime oxygen atoms have resulted in conflicting reports. When the nickel dimethylglyoxime chelate, $Ni(DMG)_2$, was treated with HCl, a blue-gray compound, which is $Ni(HDMG)_2$ (XXI), was formed and this compound, when treated with acetyl chloride at room temperature for 15 hours or heated under reflux for 1 hour, gave a pale green paramagnetic compound reported to be the diacetyl derivative, $Ni(DMG{\cdot}COCH_3)_2Cl_2$ (XXII) (*182*, *183*). Subsequent work showed that when $Ni(DMG)_2$ was reacted with acetyl chloride at room temperature for 15 hours, a green-blue solid was formed and was identified by its infrared spectrum as $Ni(HDMG)_2{\cdot}Cl_2$. The diacetylated dimethylglyoxime was recovered from the solution. The same reactions occurred with $Pt(DMG)_2$ and $Pd(DMG)_2$ and in no case was there evidence for the presence of stable acylated complexes (*120*).



(XXI)

(XXII)

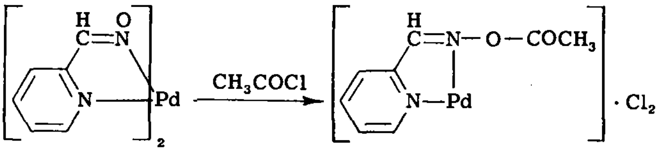
Attempts to prepare the acylated dimethylglyoxime complexes from nickel chloride and mono- or diacetylated dimethylglyoxime failed. The acetyl group is lost probably by a solvolytic reaction, which is promoted by the proximity of the metal ion. The only products isolated were $Ni(HDMG)_2Cl_2$, $Ni(HDMG)Cl_2$, and $Ni(DMG)_2$. From these results, it has been postulated that a stepwise reaction (XXIII) occurs, and the first step completely destroys the starting compound; the second step accomplishes the acetylation and removal of the remaining molecule of dimethylglyoxime (*120*):

$$Ni(DMG)_2 + 2\,CH_3COCl \longrightarrow Ni(HDMG)\cdot Cl_2 + DMG(COCH_3)_2$$

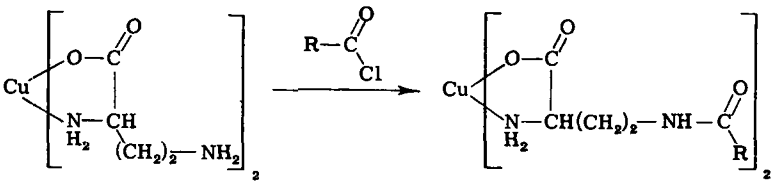
$$Ni(HDMG)\,Cl_2 + 2\,CH_3COCl \longrightarrow NiCl_2 + DMG(COCH_3)_2 + 2\,HCl$$

(XXIII)

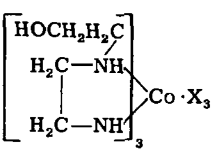
On the other hand, the palladium and platinum complexes of pyridine-2-aldoxime, when treated with acetyl chloride in hot chloroform, gave stable chelates containing the acylated ligand. A monoacetylated palladium chelate was isolated in which 1 mole of pyridine-2-aldoxime was replaced by two chloride ions (see reaction XXIV). This compound was identified by its infrared spectrum, which had a strong carbonyl absorption band near 1790 cm^{-1}. The platinum complex of pyridine-2-aldoxime gave a



(XXIV)



(XXV)



X = Cl^- or Br^-

(XXVI)

similar monoacetylated compound but could not be easily purified. The nickel chelate of pyridine-2-aldoxime, however, undergoes a decomposition on treatment with acetyl chloride (*120*).

An amino group attached to a metal chelate ring is reactive, whereas an amino group coordinated to a metal ion is unreactive. This is shown in the following reaction, carried out with the idea of protecting one of two amino groups in the same molecule (reaction XXV) (*124*, *125*).

A hydroxy group attached to a metal chelate ring would also be expected to undergo ready acylation. An investigation of the cobalt(III) complex of *N*-hydroxyethylethylenediamine (structure XXVI) gave the unexpected result that the tris complex was extremely stable and that the hydroxy groups in the complex were quite unreactive (*111*).

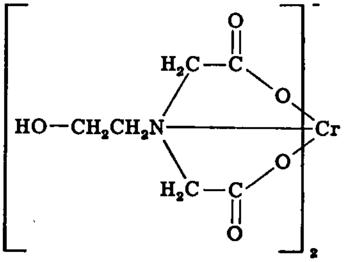
The solid cobalt(III) complex was refluxed with benzoyl chloride, acetyl chloride, acetic anhydride, phosphorus tribromide, or thionyl chloride. In none of these cases was there any evidence that a reaction had occurred. Prolonged refluxing with concentrated HCl gave no reaction and attempts to oxidize the hydroxy groups with 70% nitric acid were unsuccessful.

The tris(*N*-hydroxethylethylenediamine)cobalt(III) chloride that was used in these reactions was reported to be an orange crystalline solid (*111*). In a subsequent investigation (*69*), attempts to prepare this compound by the air oxidation of a mixture of cobalt(II) and the amine failed. The compound was, however, prepared by the displacement of ammonia from $[Co(NH_3)_6]Cl_3$ by *N*-hydroxyethylethylenediamine and a dark red compound was obtained. Attempts to react the hydroxy groups in this red complex with a variety of reagents (nitric acid, thionyl chloride, benzoyl chloride, and acetyl chloride) were as unsuccessful as the previously reported attempts to react the hydroxy groups in the orange cobalt complex.

The chemically unreactive nature of the hydroxy groups in this complex is certainly not a result of the coordination of this group to the metal ion. If the coordination number of cobalt(III) increased to 9 in this complex, or if the coordination number was 6, leaving the amine groups free, the resulting complex would not have the properties of an extremely stable chelate.

The three hydroxy groups in this complex can be hydrogen bonded to each of the hydrogen atoms of the coordinated nitrogen atom, but it is unlikely that these hydrogen bonds would be sufficiently strong to prevent any reaction of the hydroxy groups. It is possible that the chemical unreactivity of these hydroxy groups is a result of the large positive field of the cobalt, preventing the approach of a positively charged center of a reactant toward the hydroxy groups (*69*).

If the acetylation of uncoordinated hydroxy groups were prevented by the presence of a positive charge in the chelate molecule, it would be expected that an ionic chelate would undergo rapid reaction. Therefore the acetylation of the hydroxy groups in the anion, bis(2-hydroxyethyliminodiacetato)chromium(III) (structureXXVII) (*119*), was investigated.



(XXVII)

This anionic complex did not undergo acetylation under usual conditions. The reaction was successfully accomplished by refluxing the tetramethylammonium salt of the anionic complex with ketene in acetonitrile, and a diester was produced. This acetylation reaction, however, occurs very slowly; the reason for this is unknown.

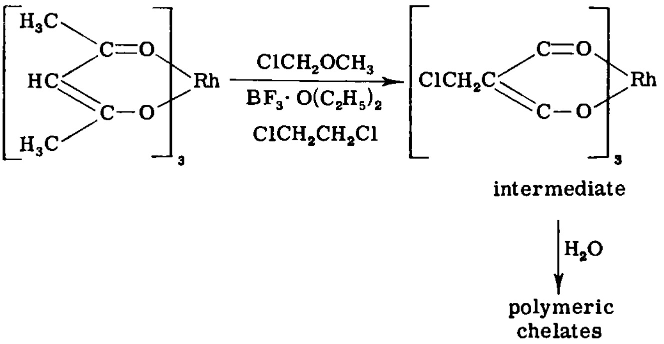
Another acetylation reaction in which a pendant group is readily acetylated has been reported recently (*107*). *N*,*N*′-bis(2-hydroxyethyl)-dithiooxamidenickel(II), which is a brown monomeric or polymeric complex (structure XXVIII), is readily acetylated with acetic anhydride in the presence of a catalytic amount of concentrated H_2SO_4 and gives a blue acetylated product. Analysis of the product showed that only half the hydroxy groups present in the compound were acetylated. Whether this represents the acetylation of each *N*,*N*′-bis(2-hydroxyethyl)dithiooxamide group in the complex, or whether random acetylation occurs, is not known.

$$[Ni(HOCH_2CH_2NCS{\cdot}CSNCH_2CH_2OH)]_n \qquad n \geq 1$$

(XXVIII)

E. Chloromethylation

The chloromethyl group is another highly reactive group when substituted in an aromatic nucleus. When introduced into the rhodium acetylacetonate ring system, the chloromethyl group is so reactive that instead of the tris(chloromethyl) chelate, polymeric products were formed (*48*):

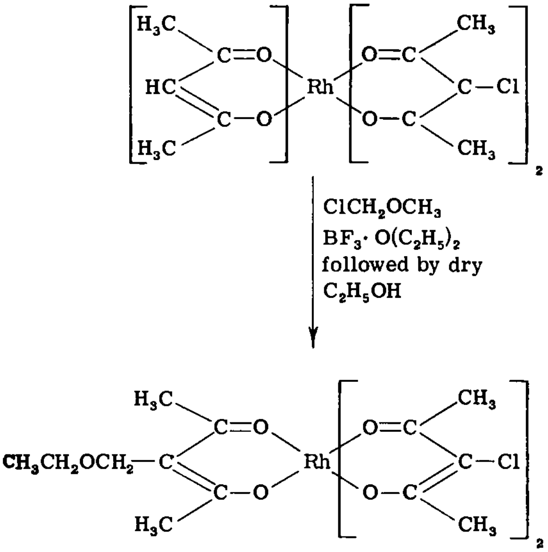


(XXIX)

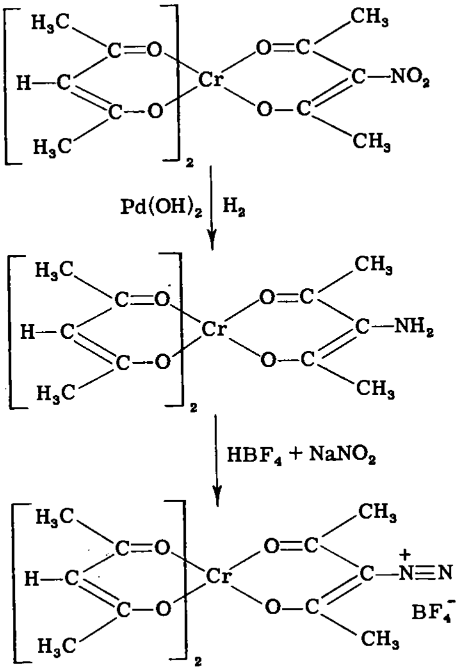
Even when one chloromethyl group was introduced into a mixed ligand rhodium chelate, the reactivity of the chloromethyl group was too great for the intermediate to be isolated (*48*).

F. Diazotization and Diazo Coupling

The successful reduction of the mononitrochromium chelate of acetylacetone to the corresponding monoamino compound provided a direct route to the preparation of the diazonium salt. An aqueous solution of the


$ClCH_2OCH_3$
$BF_3 \cdot O(C_2H_5)_2$
followed by dry
C_2H_5OH

(XXX)

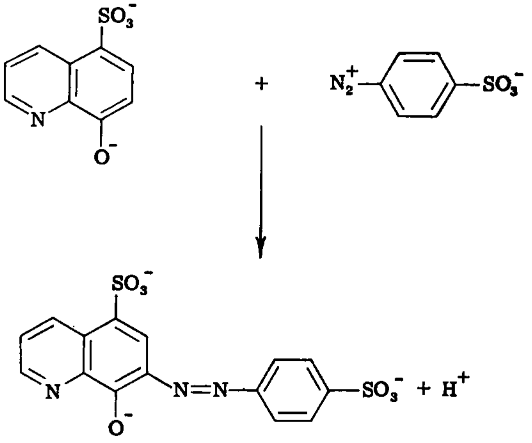

$Pd(OH)_2$
H_2
$HBF_4 + NaNO_2$

(XXXI)

monoamino compound and fluoroboric acid was treated with an aqueous sodium nitrite solution at 0°C. A purple solid was formed and was proved to be the chelate diazonium fluoroborate (*59*) (reaction scheme XXXI).

Attempts to carry out a Sandmeyer reaction and a Schiemann reaction on the diazonium salt failed. This is the first reported case in which a diazonium salt of a metal chelate was prepared and isolated; it is of interest since the formation of a stable diazonium salt of a ring compound is one of the classic tests of the aromaticity of the compound.

A great deal of evidence has accumulated to show that a metal ion in a chelate ring can alter the electron density in a molecule. One method of obtaining quantitative data on such changes in electron density is to compare the rates of electrophilic attack at a point in the unchelated and chelated molecules as, for example, in the iodination of 8-hydroxyquinoline chelates (Section II,A). Another such kinetic study has been carried out on the diazo coupling of 8-hydroxyquinoline-5-sulfonic acid and its zinc(II) chelate with diazotized sulfanilic acid (*141*).



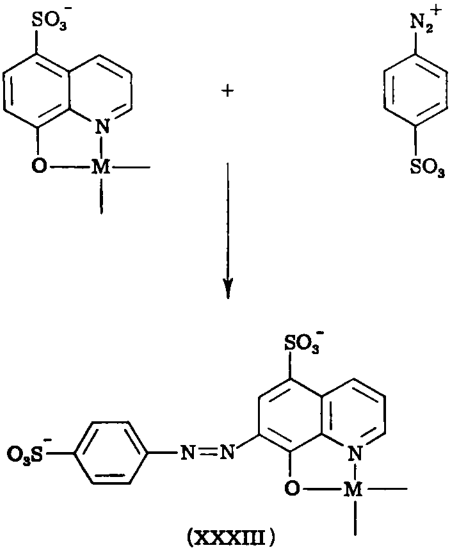
(XXXII)

Since the 5-position is blocked by a sulfonic acid group, the position of electrophilic attack is the 7-position in both the free ligand and the zinc chelate. The kinetic data were obtained at pH 5.00 in an acetate–acetic acid buffer at temperatures between 5° and 15°C. The diazo coupling reaction is a second-order reaction, but a pseudo first-order rate was obtained, since a large excess of *p*-diazobenzenesulfonate was used.

Kinetic measurements on the zinc(II) chelate were carried out on solutions containing a 100:1 ratio of zinc(II):8-hydroxyquinoline-5-sulfonic acid, thereby ensuring that only the 1:1 zinc(II) chelate was present.

The derived second-order constants for the reaction of the phenolate anion of the ligand and the 1:1 zinc(II) chelate at 15°C were found to be 4.1×10^2 liter $mole^{-1}sec^{-1}$ and 2.6×10^{-2} liter $mole^{-1}sec^{-1}$, respectively. Therefore, the ligand anion reacts approximately 10^4 times faster than the metal chelate. The effect of the metal ion was not merely to reduce the concentration of the free ligand anion, since a linear decrease in the reaction rate did not occur with an increase in the concentration of zinc(II). Therefore it is clear that the zinc ion in the chelate ring is capable of deactivating the aromatic system. Protonation, however, deactivates the aromatic ring to a very much greater extent, since the undissociated phenol will undergo the diazo coupling reaction approximately 10^{10} times slower than the phenolate anion.

The above study was extended to determine the effect of the metal ion on the diazo coupling reaction (*30*). The rate of coupling of all the 1:1 metal complexes studied was at least 100 times slower than the rate of coupling of the free ligand.

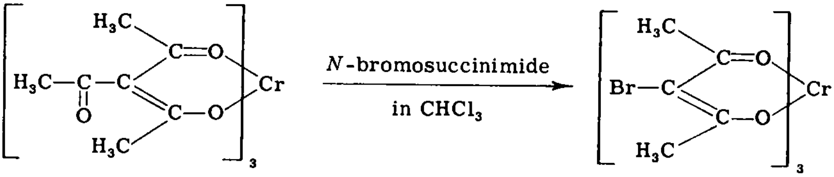


(XXXIII)

The results of these kinetic studies confirm the observation that, in electrophilic substitution reactions, the rate of reaction of the chelated ligand is slower than that of the free ligand.

III. Electrophilic Displacement Reactions

The 3-substituted metal chelates of acetylacetone undergo some unusual electrophilic displacement reactions. The acetyl groups in the acetylated chelates of chromium(III), cobalt(III), and rhodium(III) are displaced by *N*-bromosuccinimide in chloroform solutions to yield the brominated chelates:



(XXXIV)

The acetyl groups are also displaced by nitrating agents (a mixture of copper(II) nitrate and acetic anhydride), chlorinating agents (*N*-chlorosuccinimide), and thiocyanogenating agents (thiocyanogen). Electrophilic displacement reactions in metal acetylacetonates occur much more readily than electrophilic displacement reactions in aromatic systems. The central metal ion and the electrophile, however, have a combined effect on the specificity of the leaving group (*48*).

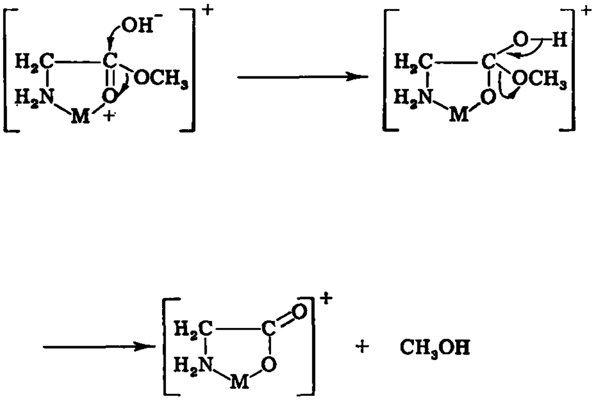
IV. Nucleophilic Reactions

A. HYDROLYSIS

1. Esters and Thiol Esters

A number of amino acids esters that can form chelates with metal ions have been found to be readily hydrolyzed, whereas the hydrolysis of esters having only one oxygen donor atom per molecule was found to be comparatively unaffected by metal ions. In the examples of ester hydrolysis described below, it is postulated that a metal chelate ring system is formed and undergoes hydrolysis via a nucleophilic process.

The hydrolysis of α-amino acid esters in the pH region 7–8 is negligible, but in the presence of metal ions such as Co(II), Cu(II), Mn(II), Ca(II), and Mg(II), rapid hydrolysis occurs and the rate of hydrolysis increases with increasing metal:ester ratio until a maximum value is reached when the metal:ester ratio is 1:1 (*122*). It can therefore be concluded that the rate-determining step is the hydrolysis of the 1:1 species. The reaction was found to be independent of buffer concentration but quite sensitive to pH changes. An increase in the hydroxide ion concentration by a factor of ten caused a fourfold increase in the rate constant of hydrolysis. It is unlikely that this increase in the rate constant is caused by the increased concentration of hydroxide ions which participate in a second-order reaction with the metal chelate. A more plausible explanation is that the increase in hydroxide ion concentration results in the neutralization of the protonated amino acid ester and the formation of a larger amount of the metal chelate (*24*). It was also found that the more stable the metal chelate, the greater the rate of ester hydrolysis. Thus, the copper(II) chelate hydrolyzed twice as fast as the cobalt(II) chelate, which hydrolyzed five times faster than the manganese(II) chelate. The calcium and magnesium chelates, which are not as stable, hydrolyzed very slowly. The rate of hydrolysis of the methyl and benzyl esters was approximately twice that of the ethyl ester of glycine (*122*). In all these reactions, the metal ion is chelated by the amino group and by the carbonyl oxygen and not by the ether oxygen (*128*). The manner in which the metal chelate is attacked by the hydroxide ion is shown (reaction scheme XXXV).

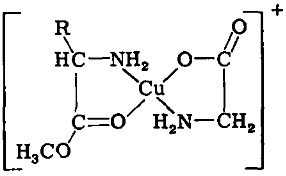


(XXXV)

The rates of alkaline hydrolysis of glycine methyl ester and cysteine methyl ester were determined in the presence of copper(II) and nickel(II). The complex formation constant of the 1:1 complex of glycine methyl ester and copper(II) ($\log k_1 = 2.45$) is greater than the corresponding formation constant with nickel(II) ($\log k_1 = 3.83$). The bimolecular rate constant for the hydrolysis of the copper(II) complex was found to be nearly 1.5 times that for the nickel(II) complex. The methyl ester of cysteine formed a very stable complex with nickel(II) ($\log k_1 = 8.95$), but its rate of hydrolysis was only about twice that of the nickel(II) complex of the methyl ester of glycine. The net positive charge on the nickel(II) complex of glycine methyl ester and the zero charge on the cysteine methyl ester complex were claimed to be responsible for the anomalously slow rate of hydrolysis of the latter complex (*209*).

Several features of the above studies were reinvestigated in a detailed kinetic study of the copper(II) complexes of glycine methyl ester and phenylalanine ethyl ester in glycine buffer at pH 7.3 (*26*). Glycine was selected as a buffer in this study in order that a small increase in the glycine concentration caused by the hydrolysis reaction would not increase the concentration of copper(II) complexes to a significant extent. It was found that the rate constant for the hydrolysis of the copper(II) complex of DL-phenylalanine ethyl ester was 10^6 times greater than the rate constant obtained for the alkaline hydrolysis of the free ester (*25*).

This factor of 10^6 is much too large to be explained only on the basis of an electrostatic effect that arises from the reaction of a negatively charged hydroxide ion with a positively charged copper(II) complex (*25*). It is therefore necessary to postulate that the copper(II) ion which is coordinated to the nitrogen atom of the amino group also interacts directly with the ester group (structure XXXVI).

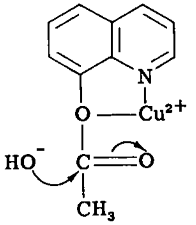


(XXXVI)

A molecule of glycine occupies two more coordination positions in the copper(II) ion, since these kinetic studies were carried out in the presence of a glycine buffer. Oxygen-exchange experiments carried out with this system are consistent with the kinetic evidence and indicate that the carbonyl oxygen, rather than the ether oxygen, is coordinated to the metal ion (*26*).

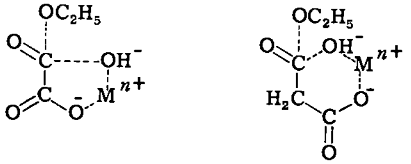
Specific buffer effects encountered in these studies were eliminated by automatically compensating for pH changes in the system by means of a pH-stat (*159*). The kinetics of hydrolysis of the methyl esters of benzoylglycine and acetyl-L-valine were studied in the presence of calcium(II) ions at pH values of 7.9 and 8.4 by means of this technique, without the use of conventional buffers (*145*). The kinetic results were found to be consistent with the formation of a 1:1 metal-ester complex which is attacked by hydroxide ions. In this work a rather surprising result was found, namely, that the more stable calcium(II)–acetyl-L-valine ester complex reacted with hydroxide ions at a hundredfold slower rate than the less stable calcium(II)–benzoylglycine methyl ester complex. It is not certain whether the intermediate is a chelate which is formed between the carbonyl group and the secondary amide group or a complex in which the calcium(II) is coordinated to the carbonyl oxygen of the ester.

A kinetic investigation of the hydrolysis of 8-acetoxyquinoline in solutions of pH between 1 and 9, and in the presence and absence of copper(II) ions, yielded some interesting results (*205*). In the absence of copper(II), it was found that the rate of hydrolysis was first-order with respect to 8-acetoxyquinoline, but the rate equation that fitted the kinetic data was quite complex since the ester and the ester cation reacted with both the hydrogen and the hydroxide ion. In the presence of copper(II), the hydrolysis of the ester occurred more rapidly and the rate equation was found to be first-order with respect to 8-acetoxyquinoline copper(II) and hydroxide ion. Therefore, the reaction intermediate (structure XXXVII) is presumably a 1:1 chelate of copper(II) which is attacked by hydroxide ion, just as in the case of the amino acid ester.



(XXXVII)

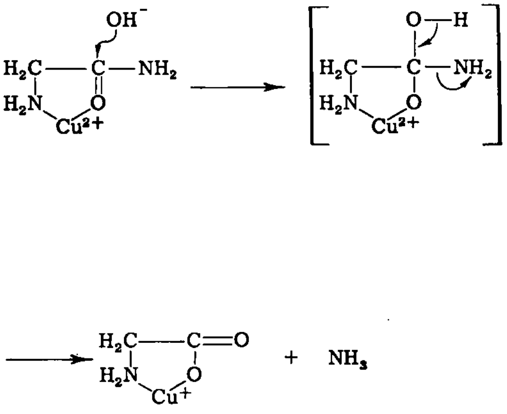
The rates of alkaline hydrolysis of the half-esters, potassium ethyl oxalate, malonate, adipate, and sebacate were studied in the presence of potassium, sodium, lithium, thallium(I), calcium(II), barium(II), and hexamminecobalt(III) ions (*106*). On the basis of the results obtained, chelate formation between the metal ions and the transition state of the substrate was postulated. In these chelate structures (structures XXXVIII), formally similar to those postulated in the hydrolysis of α-amino esters (*26*), the metal ion facilitates the attack by the hydroxide ion by positioning it in a suitable manner. The rate of hydrolysis of the oxalate half-ester is greater than that of the malonate, which in turn is greater than that of the adipate. This is in the expected order of the stability of the metal chelates. The order for the rate of hydrolysis of the ethyl oxalate and ethyl malonate is $Ca^{2+} \sim Ba^{2+} > [Co(NH_3)_6]^{3+} > Tl^+$. The hexamminecobalt(III) ion seems to be less effective than expected, since it is too large to satisfy the steric requirements of the chelate structures. The alkali metals were found to have marked negative specific salt effects on the rates of reaction of the adipate and sebacate, but only a small negative salt effect on the hydrolysis of potassium ethyl malonate.



(XXXVIII)

The alkaline hydrolysis of acetylcitric acid and benzoylcitric acid in the presence of calcium(II) ions probably occurs via a similar mechanism involving chelate formation (*187*).

Heavy metal ions such as Hg(II), Pb(II), or Ag(I) hydrolyze thiol esters quite easily with the formation of a metal mercaptide as a reaction product (*139*, *174*, *192*). Although in many cases metal chelates can be postulated as intermediates in these hydrolysis reactions, there is some evidence to show that the bond formed by the coordination of the sulfur atom with a heavy metal ion is sufficiently strong to initiate the cleavage of the thiol esters. For example, simple thiol esters having no other donor atoms and therefore incapable of forming metal chelates will readily undergo hydrolysis in the presence of Hg(II) (*24*).

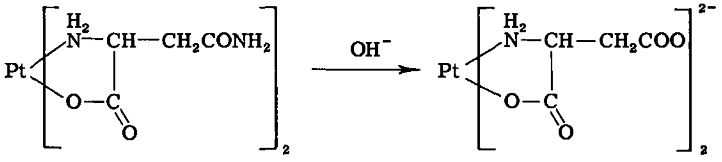


(XXXIX)

2. Amides

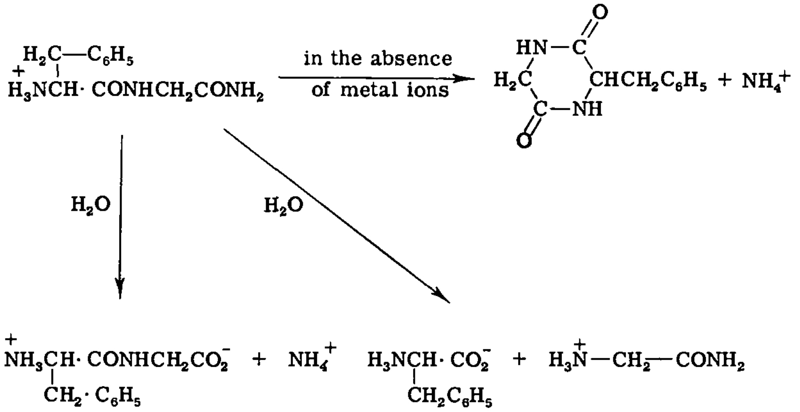
The hydrolysis of glycine amide hydrochloride in sodium carbonate–sodium bicarbonate buffers is promoted by copper(II) and to a lesser extent by cobalt(II) and nickel(II) (*148*). The presence of 0.02 *M* copper(II) between pH 7.9 and 9.3 increases the rate of hydrolysis by a factor of about 30. This effect of metal ions on the rate of hydrolysis of glycine amide is surprisingly small when compared with the effect on the rate of hydrolysis of esters. Despite this, it can be postulated that the mechanism of the hydrolysis is similar to that put forward for the hydrolysis of esters.

The free amide groups in bis(asparagine)platinum(II) are easily hydrolyzed by hot dilute alkali (reaction XL). The rate of hydrolysis of the neutral chelate is approximately twice that of the free asparagine anion (*203*). It is possible in this case that the effect of the metal ion is small when compared with the charge effect.



(XL)

Phenylalanylglycine amide was found to undergo ring closure to form 3-benzyl-2,5-diketopiperazine in the absence of metal ions (reaction XLI). In the presence of copper(II) at pH 5, the protonated form of the amide underwent hydrolysis reactions at both the peptide and amide bonds.



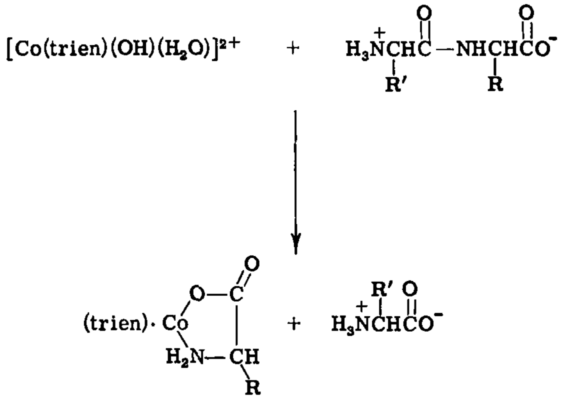
(XLI)

These hydrolytic reactions were competitive with the ring-closure reaction (*148*). Although the structure of the intermediates is not known in this hydrolytic cleavage reaction, it is possible that the reaction proceeds via a copper(II) chelate intermediate.

3. Peptides

Many metal ions are known to form complexes with peptides, but the structures of these complexes are mostly unknown and many proposed chelate structures are purely speculative. The hydrolysis of dipeptides and tripeptides in the presence of a number of metal ions, especially in the lanthanide series, was investigated in alkaline solution in an ammonia–ammonium chloride buffer (*13, 17, 18, 19*). For example, in the presence of an equivalent concentration of metal ion, the rate of hydrolysis of glycylleucine was found to be greater with cerium(IV) than with cerium(III), and lanthanum(III) had a very much smaller effect on the rate than cerium(III). Under the conditions of these experiments, the metal ion existed in the form of a hydroxide gel. Although chelate formation between the metal ion and the peptide was postulated to explain the results of the kinetic studies, the reaction system is too complex for any such simple interpretation of the kinetic data.

A novel method has been worked out recently for the hydrolysis of the *N*-terminal amino acid residues of simple peptides, e.g., glycyl-DL-phenylalanine, DL-phenylalanylglycine, L-leucylglycine, and di-, tri-, and tetraglycine. The cationic chelate, *cis*-hydroxyaquotriethylenetetraminecobalt (III), was found to react readily with peptides in aqueous solution at pH 7.5 and 65°C. The rate of the hydrolysis is pH and temperature dependent and the course of the reaction can be followed spectrophotometrically. The *N*-terminal amino acid group that is hydrolyzed from the peptide chain forms a mixed ligand chelate with the cobalt(III) chelate. Thus, although the details of the mechanism have not been established, chelation must be the driving force for the reaction (*51*).



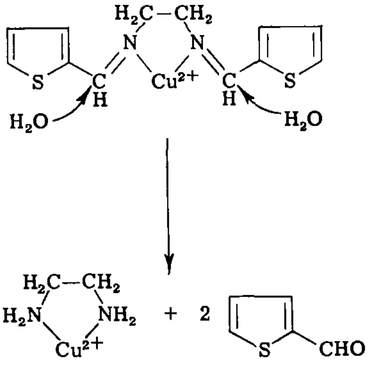
(XLII)

An area of considerable importance in which a great deal of work has been carried out concerns the role of metal ions in the reactions of metal-activated peptidases. Many of the published results have been controversial and, although metal chelate formation does occur, the extent and importance of chelate formation in these systems are not known. The reader is referred to several extensive reviews on the subject (*184*, *185*, *201*, *210*).

4. Schiff Bases

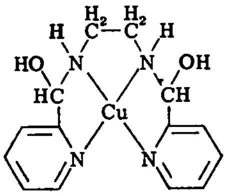
Schiff bases are hydrolyzed in aqueous solution in the absence or presence of dilute acids (*41*, *46*). A molecule of water attacks the reactive site, namely, the azomethine carbon atom. The formation of a metal chelate with a Schiff base can result in an electronic shift away from the azomethine carbon, which makes the chelate more susceptible to hydrolysis, or the chelate ring formation can stabilize the molecule sufficiently to counteract the electronic shift caused by the metal atom.

The condensation of 2-thiophenaldehyde with ethylenediamine gives a Schiff base which is rapidly hydrolyzed in the presence of copper(II) ions, whereas in the absence of copper(II) ions, the rate of hydrolysis is very slow (*74*). Although the Schiff base is a quadridentate chelating agent, the sulfur atoms are sterically hindered from participating in chelate formation. The Schiff base, therefore, acts as a bidentate ligand to form a 1:1 complex that is attacked by water molecules at the two imine carbon atoms, which are made electron-deficient by the electron-withdrawing action of the copper(II). This hydrolysis reaction releases two molecules of 2-thiophenaldehyde and leaves the original chelate ring intact in the molecule of the ethylenediaminecopper(II) chelate that is also formed. The nickel(II) complex of this Schiff base also undergoes a hydrolytic cleavage reaction, and a kinetic study of the reaction has shown the nickel(II) complex to be less readily hydrolyzed than the copper(II) complex (*77*).



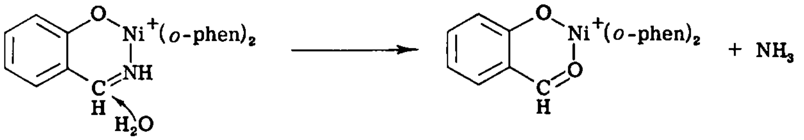
(XLIII)

The Schiff base, bis(2-pyridinal)ethylenediamine, forms a purple complex with iron(II), but this complex too undergoes repeated hydrolytic cleavage in water. With copper(II) a green complex is formed, which is slowly converted into a blue complex that is probably an intermediate hydrolysis product (*33*).



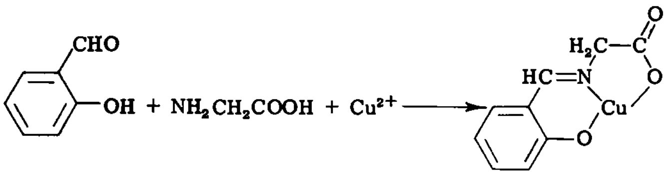
(XLIV)

The salicylaldiminebis(1,10-phenanthroline)nickel(II) chelate is hydrolyzed rapidly in aqueous solution to the corresponding salicylaldehyde chelate and ammonia. In this case the imine group in the chelate ring is replaced by an oxygen atom (*103*).



(XLV)

The chelation of copper(II) with the Schiff base obtained from salicylaldehyde and glycine stabilizes the aldimine bond to such an extent that the metal chelate remains undissociated at pH 3, whereas the Schiff base itself is dissociated at this hydrogen ion concentration (*76*, *155*). In this case, the formation of the bicyclic chelate ring system completely counteracts the electron-withdrawing effect of the metal ion.

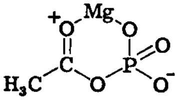


(XLVI)

Thus a metal ion can either labilize or stabilize a Schiff base via chelate formation. The latter property of a metal ion has been found to be advantageous in the synthesis of certain Schiff base chelates, to be discussed in a later section.

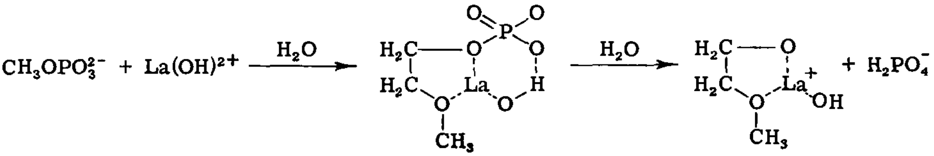
5. *Phosphate Derivatives*

Nucleophilic reactions of ligands coordinated to a metal ion are influenced by the metal ion in two ways. The positively charged metal ion can neutralize the negatively charged ligand sufficiently to enable a nucleophilic reagent, such as the hydroxide ion, to attack the ligand. Also, the metal ion can cause an electron shift, which may facilitate a bond cleavage. These two effects are evident in the hydrolysis of acetyl phosphate in the presence of Mg(II) in neutral or acid solution, for which an intermediate chelate has been proposed. The formation of a chelate intermediate obtains support from the experimental observations that the rate of hydrolysis is first-order with respect to Mg(II) as well as to acetyl phosphate, and that the effect of Mg(II) is greater at pH 7.7 than at pH 0.63, where Mg(II) is unable to compete with protons for the ligand (*117*).



(XLVII)

In the alkaline region (pH 7–10) the rate of hydrolysis of α-glyceryl phosphate is increased by a factor of 10^3 by chelation of an ion such as La(III) between two oxygen atoms in the α- and β-substituents. This was shown to occur with certain rare earth hydroxides, e.g., lanthanum hydroxide present in the form of a gel (*14*, *16*). Although it is probable that the α-glyceryl phosphate is adsorbed on the gel, it is the La(III) in solution and not the La(III) ion in the gel that is chelated, since an increase in the rate of hydrolysis is observed upon dilution of the gel with water. Two maximum rate effects were found, one at pH 8.6 and the other at pH 10.4. It is possible that the two species $La(OH)^{2+}$ and $La(OH)_2^+$ are involved at these two pH values (*15*). That intermediate chelate formation occurs is further confirmed by the observation that the rate of hydrolysis is greatly increased by the presence of a substituent containing a nitrogen or oxygen donor atom in the β-position of the ester. Thus, the rate of alkaline hydrolysis of ethyl phosphate is not affected by the presence of lanthanum hydroxide gel, but the rates of alkaline hydrolysis of β-aminoethyl, β-hydroxyethyl, and β-methoxyethyl phosphates are considerably increased. The last compound is hydrolyzed as follows (*35*):



(XLVIII)

The alkaline hydrolysis of 1-methyl-2-propyl phosphate by lanthanum hydroxide gel proceeds in a similar manner with cleavage of the P—O bond and complete retention of configuration (*12*).

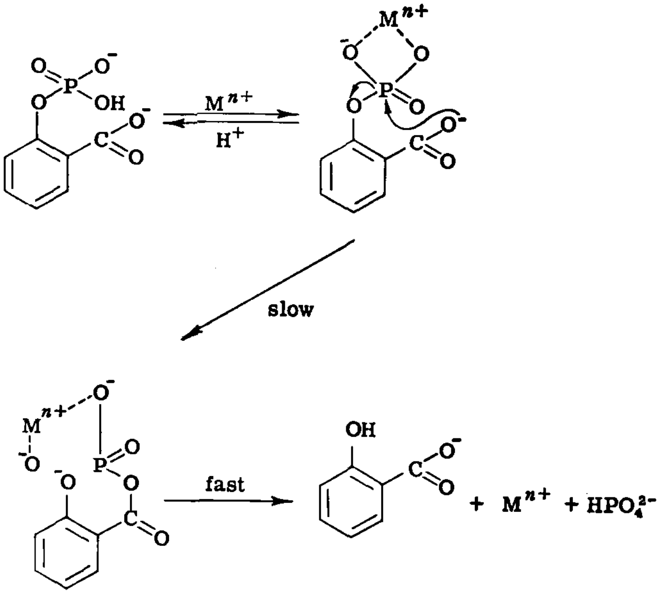
In the hydrolysis of all these monophosphate esters, cleavage of the P—O bond occurs exclusively and in this respect resembles enzymatic reactions involving alkaline phosphatases. Although dipositive metal ions influence the hydrolysis of certain diesters of phosphoric acid, there is insufficient evidence for the postulation of chelated intermediates (*186*).

The effect of metal ions or metal chelates on the rate of hydrolysis of salicyl phosphate is difficult to evaluate quantitatively, for several reasons. Salicyl phosphate itself undergoes intramolecular acid-base-catalyzed hydrolysis in a series of reactions, each of which is pH dependent and has its own rate constant. Moreover, salicyl phosphate reacts with metal ions or chelated metal ions to give a variety of metal chelates, some of which are mixed ligand chelates. The hydrolysis reaction, however, does not take place via all of these chelates. From a careful study of the solution equilibria involved and the effect of various solution parameters on the rate of hydrolysis of salicyl phosphate, the following conclusions have been reported (*105*).

Chelated metal ions having uncoordinated positions increase the rate of hydrolysis of salicyl phosphate, although in general a free metal ion has a greater effect than a chelated metal ion. The following metal ions are arranged in the order of increasing effect on the hydrolysis: Cu(II), UO_2(VI), VO(IV), ZrO(IV), and Fe(III), whereas Ni(II), Co(II), Zn(II), and Cd(II) have no effect.

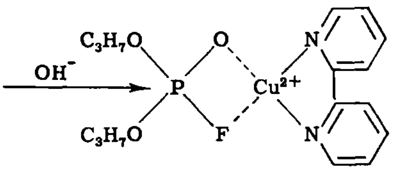
A general mechanism that has been proposed for the effect of a metal ion or metal chelate on the hydrolysis reaction involves the combination of salicyl phosphate with the metal ion or metal chelate in such a manner that an intramolecular nucleophilic attack of the phosphate group by the carboxylic acid group can take place (*142*).

The copper(II) ion as well as a number of copper(II) chelates with incompletely filled coordination shells, e.g., the 1:1 chelates of 2,2′-dipyridyl, 1,10-phenanthroline, ethylenediamine, or histidine, were found to increase the rate of hydrolysis of diisopropylphosphorofluoridate, a cholin-



(XLIX)

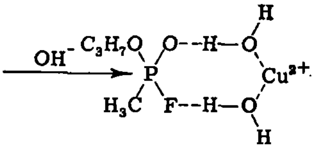
esterase inhibitor (*204*). The advantage of using partially chelated copper(II) is that this species remains in solution at a pH where the hydroxide would normally precipitate. Kinetic measurements of the hydrolysis of diisopropylphosphorofluoridate in the presence of copper(II) ions and 2,2′-dipyridyl indicate that an intermediate copper(II) chelate is formed, which facilitates the nucleophilic attack by the hydroxide ion on the phosphorus atom and the resulting cleavage of the P—F bond (*85*).



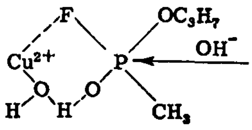
(L)

An extensive kinetic study of the hydrolysis of another cholinesterase inhibitor, isopropylmethylphosphonofluoridate (Sarin), in the presence of a variety of metal chelates, confirmed the formation of intermediates chelated to the oxygen and fluorine atoms in the hydrolytic reaction (*64*).

The copper(II) chelates of diamines that are bidentate ligands, e.g., *N*,*N*,*N*′,*N*′-tetramethylethylenediamine, had the greatest effect on the



(LI)



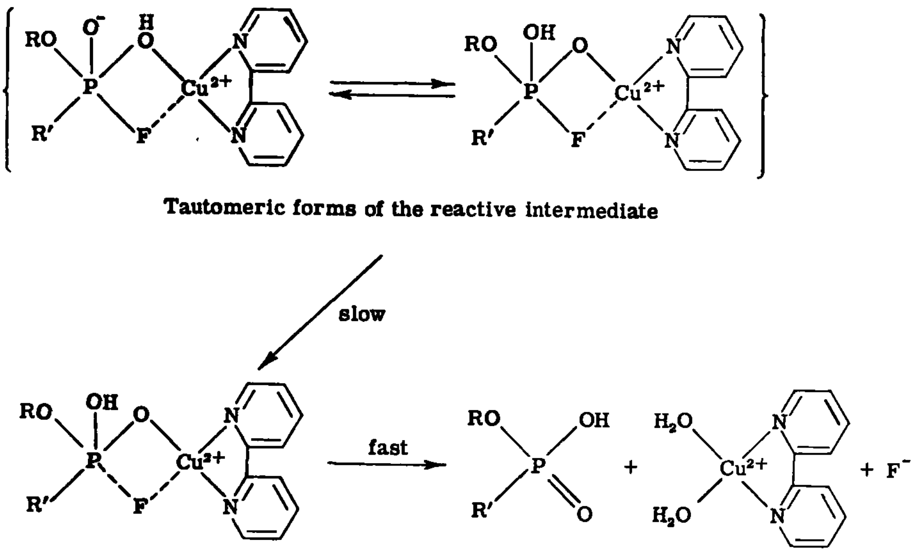
(LII)

rate of hydrolysis. Chelating agents such as amino acids, peptides, and phenolic ligands that reduce the positive charge on the metal ion were somewhat less effective, while ligands such as EDTA (ethylenediaminetetraacetic acid), which form anionic chelates, had very little effect. Several chelates of other metal ions, such as UO_2(VI), ZrO(IV), Th(IV), and MoO(VI), were also found to promote the hydrolysis reaction. In all these cases where a chelated metal ion is coordinated between the oxygen and fluorine atoms, it is necessary for the metal ion either to be incompletely coordinated or to have oxy groups (or hydrated oxy groups) attached to it. The hydrated hydroxy complexes of Ce(II), Mn(II), and Cu(II) were also found to accelerate the hydrolysis reactions of Sarin, and it is quite likely that in these cases too, a chelated intermediate is responsible for this effect (*78*).

It has been shown in detailed studies of the effect of a series of copper(II) diamine chelates, over a range of pH and concentration, that a maximum of two coordination sites on the copper(II) ion should be occupied by the ligand and that the greater the positive charge on the chelate the greater its effect on the rate of hydrolysis of Sarin or diisopropylphosphorofluoridate. An analysis of the variation of the rate of hydrolysis with the composition of the solutions showed that the effect on the rate was not a simple function of the total chelate species in solution. The presence of hydroxy and dihydroxy mononuclear forms of the copper(II) chelate together with binuclear μ-dihydroxy species was deduced. All these species participated in a number of interdependent reactions, all of which led to a single reactive intermediate that underwent the rate-determining cleavage of the phosphorus-fluorine bond (*63*, *97–99*).

A related reaction in which a similar chelate intermediate can be postulated is the hydrolytic replacement of the cyano group in dimethylaminoethoxycyanophosphate in the presence of hydrated cations and the chloro complexes of several transition metal ions. The order of decreasing activity is Cu(II) > Pd(II) > Au(III) > Ag(I) > Ni(II) > Co(II) > Zn(II) (*6*).

The effect of metal ions on the rates of hydrolysis of polyphosphates is of great biochemical interest. Calcium and magnesium ions probably form six-membered chelate rings with a long-chain polyphosphate, although it



($R' = CH_3$, $R = C_3H_7$)
Sarin

($R' = OC_3H_7$, $R = C_3H_7$)
Diisopropylphosphorofluoridate

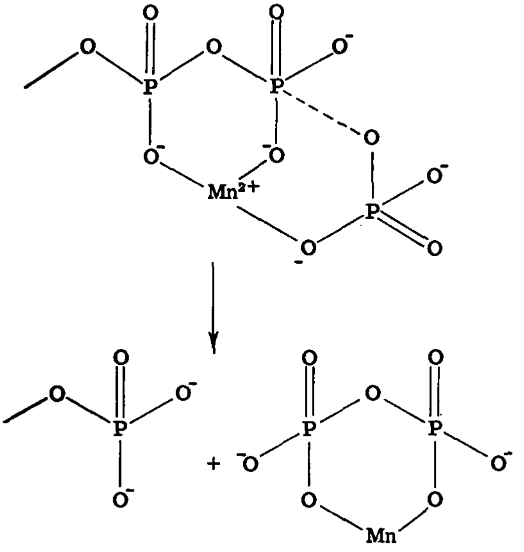
(LIII)

is possible that the latter can act as a tridentate rather than a bidentate ligand (*39*). The resulting positive charge on the chelated molecule increases its susceptibility to nucleophilic attack. For example, magnesium(II) increases the rate of hydrolysis of polymetaphosphate in alkaline solution at elevated temperatures (*93*, *200*), and the rate of the nonenzymatic hydrolysis of adenosine triphosphate (ATP) is markedly increased by calcium(II), manganese(II), copper(II), and cadmium(II) (*133*, *194*).

B. Miscellaneous Nucleophilic Reactions

1. *Transphosphorylation*

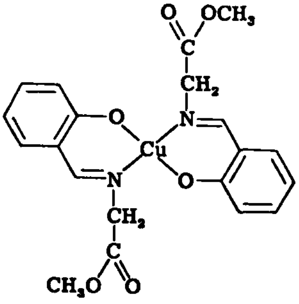
Certain dipositive metal ions not only accelerate the hydrolysis of ATP, as mentioned above, but also assist in the transfer of a phosphoryl group from one molecule to another. Such a nonenzymatic transphosphorylation takes place between ATP and an orthophosphate ion or its monoester in the presence of calcium(II), cadmium(II), and manganese(II). This type of nonenzymatic process can serve as a model for the biologically important enzymatic transphosphorylations that involve ATP, although the mechanisms of the two types of reaction may be entirely different, especially since the enzymatic reactions are known to be very much faster. In the mechanism proposed for the nonenzymatic process, the metal ion is bound to the ATP by two or more donor oxygen atoms, and also bound to the nucleophile, in this case the orthophosphate ion. Thus, the metal ion serves to suitably orient the ATP molecule and the nucleophile and also to make a phosphorus atom in the ATP molecule more susceptible to nucleophilic attack, by formation of a chelate ring (*135–138*).



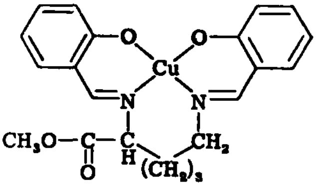
(LIV)

2. Transesterification

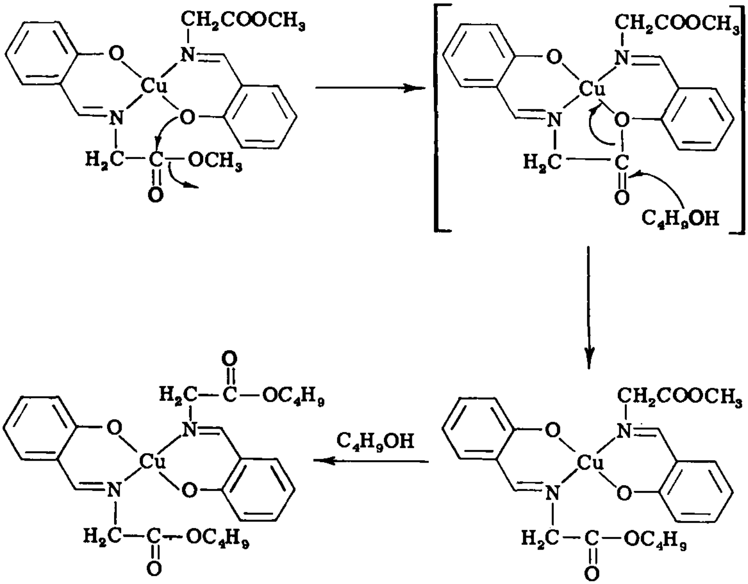
A number of chelates, structurally similar to bis[*N*-(carboxymethyl methyl ester)salicylaldimine]copper(II), undergo repeated ester exchange. When this compound, which has a *trans* square-planar structure (LV), is refluxed in *n*-butyl alcohol for about 10 minutes, transesterification of the amino acid methyl ester occurs to give the butyl ester. When the compound is refluxed with *n*-butylamine, the corresponding butylamide is obtained (*168*, *202*). Transesterification does not occur, however, with (1-carbomethoxy)pentamethylenebis(salicylaldimine-1,5)copper(II), since the configuration of this compound is fixed in the *cis* form by the pentamethylene ring (LVI) (*202*). An important function of the metal ion is therefore to position the reactive centers in such a manner that the reaction is facilitated. The mechanism proposed for transesterification involves an attack by the oxygen of the salicylaldehyde portion of the molecule on the ester carbonyl linkage to form an intermediate lactone-type structure, which undergoes a ring opening by the nucleophilic attack of *n*-butyl alcohol or *n*-butylamine to give the product (LVII) (*202*).



(LV)



(LVI)

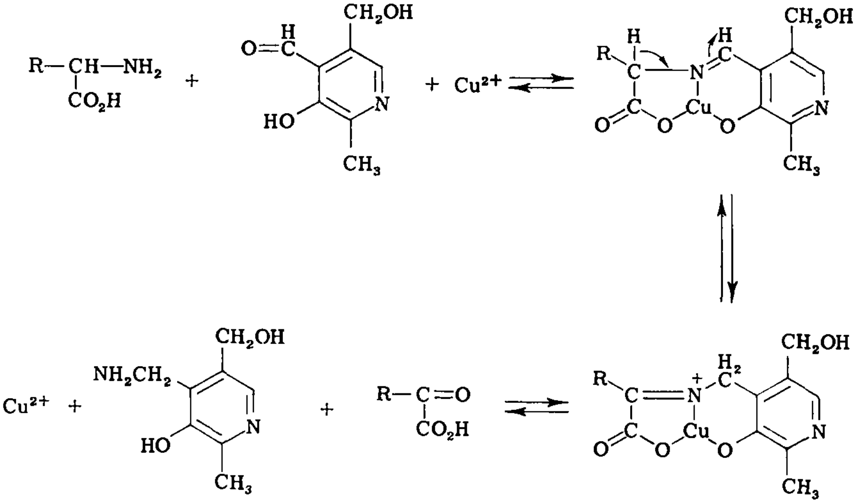


(LVII)

The failure of several (β-ketoimine)copper(II) complexes to undergo exchange with butylamine is in sharp contrast to the reaction mentioned above (*143*). It is possible, therefore, that this proposed mechanism is not of general validity.

3. *Transamination*

A number of reactions involving pyridoxal, an amino acid, and a metal ion have been attributed to the formation of a Schiff base chelate in which a hydrogen atom on the α-carbon of the amino acid is labilized, and the Schiff base can now undergo a variety of reactions resulting in a transamination, racemization, aldol condensation, α,β-elimination, or decarboxylation reactions (*188*).



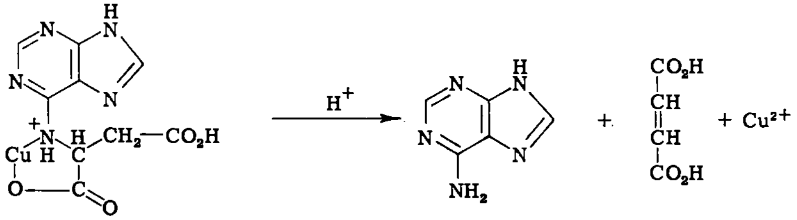
(LVIII)

In the transamination reaction (shown in reaction scheme LVIII), a pyridoxal–amino acid Schiff base chelate is first formed, and a shift of the hydrogen atom in the α-carbon takes place to give a tautomeric Schiff base, which finally undergoes hydrolytic cleavage. The result is a transamination reaction in which the amino acid is converted to a keto acid and the pyridoxal to pyridoxamine. In this type of reaction, the metal ion serves to maintain the planarity of the Schiff base chelate and exerts an electron-withdrawing action in the same direction as the heterocyclic ring (*149*).

The main aspects of the proposed mechanism have been confirmed by showing that the same Schiff base chelate is formed in solution when either copper(II) or nickel(II) ions are treated with either pyridoxal and alanine or pyridoxamine and pyruvic acid (*75*), and also by a study of the properties of the strongly fluorescent pyridoxal-alanine-aluminum Schiff base chelate (*80*).

The mechanism of this reaction is of importance in biological systems, since there is a similarity between reactions involving pyridoxal and pyridoxal phosphate in the presence of amino acids and metal ions. This type of mechanism, involving an intermediate Schiff base, will be further considered in a later section.

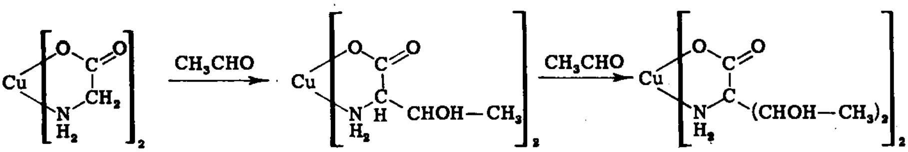
The above example demonstrates the manner in which a study of model nonenzymatic reactions can elucidate enzymatic reactions. Another example of such a model reaction that has been studied is the decomposition of 6-succinoaminopurine and its derivatives in the presence of metal ions (*8*). The results of this study indicated that a side-chain carboxyl group is essential for the reaction, and that in the α-position it was much more effective than in the β-position. Therefore a metal chelate intermediate for the reaction was postulated in which cleavage of the C—N bond could occur quite readily to give adenine, a product which was identified, and fumaric acid. The latter compound was not identified but is obtained in analogous enzymatic reactions involving adenylsuccinic acid. The most effective metal ions were copper(II) and manganese(II), although protons in the absence of metal ions were also able to carry out this reaction at a slow but measurable rate.



(LIX)

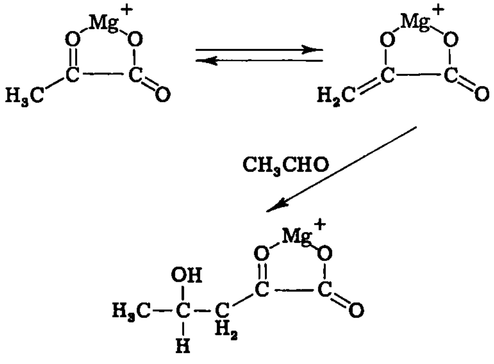
4. Aldol Condensation

The reaction of the chelate of copper(II) and glycine at elevated temperatures in basic solution (100°C and pH 11) with formaldehyde gives the copper complex of serine and with acetaldehyde gives the copper complexes of threonine and allothreonine in 64% yield (*1*, *175*).



(LX)

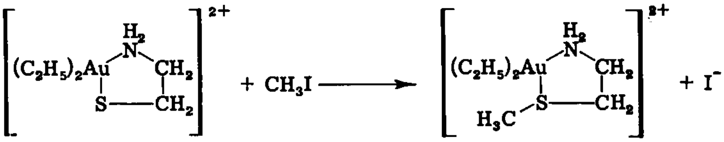
These reactions occur since the amino group is protected by chelation and the reactive site in the chelate molecule is, therefore, the methylene group. The proximity of the carboxyl group facilitates the formation of an enolate anion, and it is possible that all these aldol condensations proceed via an intermediate enolate ion, e.g., the aldol condensation of the magnesium-pyruvate chelate with acetaldehyde (reaction scheme LXI) (*24*). The positive charge on the metal chelate is an important factor in promoting the formation of the enolate ion. It has been reported that the bis(ethylenediamine)cobalt(III) chelate, which forms a dipositively charged 1:1 chelate with glycine, undergoes aldol condensation with acetaldehyde very readily at room temperature to give an 80% yield of the mixed amino acids (*152*), whereas tris(glycinato)cobalt(III) gave a 34% yield (*6*).



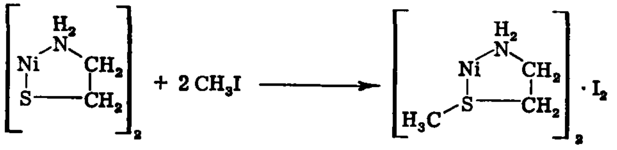
(LXI)

5. *S-Alkylation*

The reaction of (β-mercaptoethylamine)diethylgold(III) with alkyl halides such as CH_3I and C_2H_5Br gave *S*-alkylated products without rupture of the chelate ring (*79*). In an extension of this early study, the alkylation of bis(β-mercaptoethylamine)nickel(II) with alkyl halides in dimethylformamide solution also gave the *S*-alkylated compounds; their structures were confirmed by their infrared spectra (*34*). With benzyl halides, the rate of benzylation was found to be dependent on the particular benzyl halide and increased in the order $C_6H_5CH_2Cl$, $C_6H_5CH_2Br$, $C_6H_5CH_2I$.

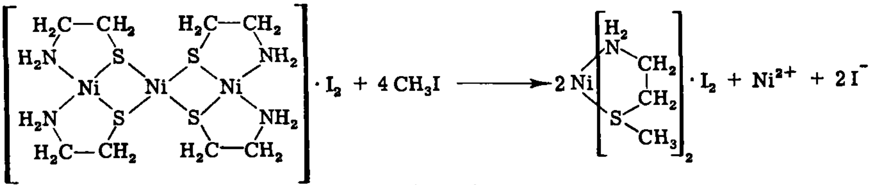


(LXII)



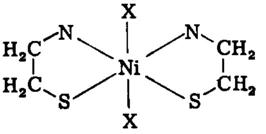
(LXIII)

The reaction of a trinuclear complex of nickel(II) (reaction scheme LXIV) with methyl iodide in dimethylformamide solution gave a product identical with that obtained by the methylation of bis(β-mercaptoethylamine)nickel(II), and if the latter methylation reaction is interrupted, the trinuclear complex is formed and can be isolated from solution.



(LXIV)

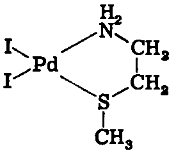
From magnetic susceptibility and conductance measurements, it can be shown that all these halogen-containing compounds obtained by alkylation reactions are nonelectrolytes in nonpolar organic solvents and have the structure (LXV).



X = Cl, Br, or I

(LXV)

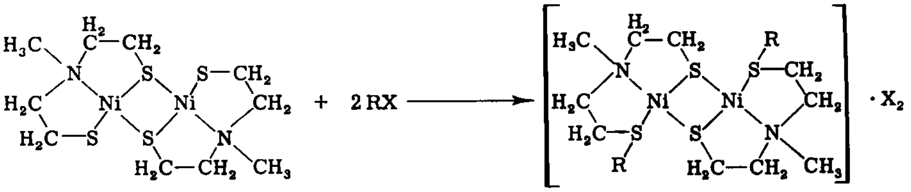
The alkylated product obtained by the reaction of methyl iodide and bis(β-mercaptoethylamine)palladium(II) was shown to have the structure (LXVI). In this compound, one mole of the coordinated ligand is replaced



(LXVI)

by two atoms of the halogen, since the coordinating ability of the ligand is weakened by *S*-alkylation.

The nickel(II) and palladium(II) complexes of methyl-2,2′-dimercaptodimethylamine show a similar tendency to be alkylated by methyl iodide or benzyl bromide.

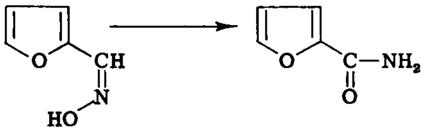


(LXVII)

The product obtained in this reaction indicates that terminal mercaptide groups are much better nucleophiles than bridged groups (*34*).

V. Rearrangement Reactions

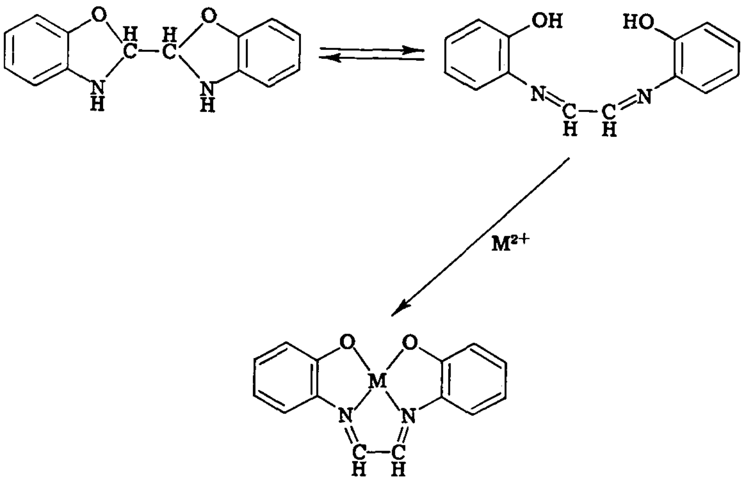
Several aldoximes have been found to rearrange to give amides in the presence of Raney nickel at 100°C (*81*). For example, the furfuraldoxime (reaction LXVIII) gives furamide in good yield together with a small amount of a nickel chelate (*162*). Although the structure and composition of the nickel chelates of the oxime are uncertain, it is probable that the mechanism of the rearrangement reaction is similar to the Beckmann conversion of ketoximes to alkyl acid amides (*31*, *32*).



(LXVIII)

Another example of a metal ion-induced rearrangement has been described recently in which 2,2′-bisbenzoxazoline was found to rearrange under the influence of metal ions to give the Schiff base chelate (*23*). Experimental evidence was given in this case to show that an equilibrium existed between the oxazoline and the Schiff base. The reaction, therefore, proceeds as shown in the scheme (LXIX).

This type of rearrangement should be possible in cases involving an equilibrium in which a molecule that is not a ligand itself can be reversibly transformed to one that can act as a ligand. Thus, 2,2′-bisbenzothiazoline and its 2,2′-dimethyl derivative were found to rearrange under the influ-



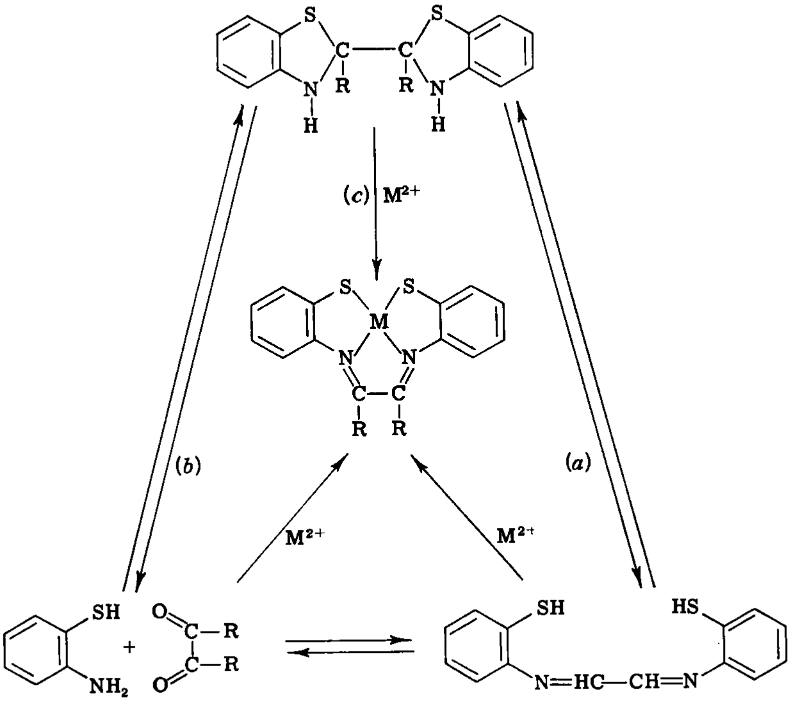
(LXIX)

ence of several metal ions to give the corresponding Schiff base chelates (*22, 108, 109*).

There are three possible routes for the formation of a Schiff base chelate (LXX): (*a*) There can be an equilibrium between the heterocycle and the Schiff base. In this event, a metal chelate could be formed with the Schiff base. (*b*) There can be an equilibrium between the heterocycle and the two starting materials. The latter can react with the metal ion in a stepwise manner to give the Schiff base chelate. (*c*) Alternatively, the metal ion can react directly with the heterocycle inducing a rearrangement reaction which results in the Schiff base chelate. From a kinetic study of the reactions of 2,2′-bisbenzothiazoline and its 2,2′-dimethyl derivative with Cd(II) and Zn(II), it was determined that the pathway (*b*) was inconsistent with the experimental results in all cases. The most probable course of the reaction involves a metal ion-induced rearrangement reaction, although it is possible in some instances that pathway (c) might simultaneously contribute to the formation of these Schiff base chelates (*109*).

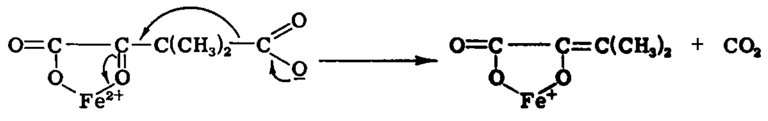
VI. Decarboxylation and Carboxylation

A variety of metal ions have been found to increase markedly the rate of decarboxylation of several β-keto acids, but to have no effect on the decarboxylation of ketomonocarboxylic acids such as acetoacetic acid. Moreover, only those β-keto acids having a second carboxylic acid group adjacent to the β-keto group are affected by the presence of metal ions, e.g., oxaloacetic or oxalosuccinic acids (*90, 116, 166, 170, 190, 191, 208*).



(LXX)

One of the best studied decarboxylations of this type is that of α,α′-dimethyloxaloacetic acid in the presence of heavy metal ions such as copper(II) and iron(III) (*190, 191, 208*). Much experimental evidence has accumulated to support the formation of a 1:1 chelate as an intermediate in these decarboxylation reactions. An illustration of such evidence is as follows: The dimethyloxaloacetate ion forms a bright yellow chelate with iron(III) and has the structure (LXXI), since the dimethyloxaloacetate ion cannot enolize.



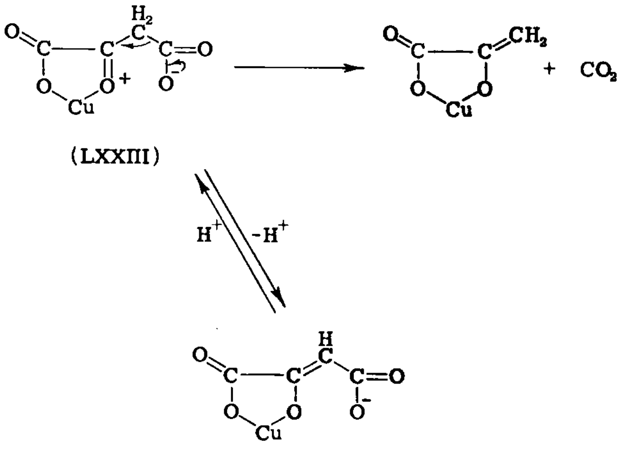
(LXXI) (LXXII)

The decarboxylation of this chelate approximates to a first-order reaction at a pH of 2.3, and as the reaction proceeds the color deepens, becoming progressively green, blue, and deep blue. This blue color must be the iron(III) complex of the enol form of α-oxo-β-methylbutyric acid (structure (LXXII) since, if the decarboxylation is allowed to proceed in the absence of iron(III) until the concentration of the enol form is at a maximum (measured spectrophotometrically) and iron(III) added at this point, the solution turns blue.

When the decarboxylation reaction is complete, the blue color fades and leaves the yellow 1:1 chelate of iron(III) with α-oxo-β-methyl-butyrate ion. The pH-rate profile shows that it is the metal ion complex of the dianion that is decarboxylated and not a complex of the singly charged anion or the undissociated acid. Also, the ester of dimethyloxaloacetic acid is decarboxylated in the absence of metal ions, indicating that the metal ion is chelated to the carboxyl group that is γ to the group that is lost.

Therefore the role of the metal ion in the decarboxylation reaction can be summarized: a chelate is formed with the dianion of the keto acid and the metal ion, thereby providing a center of positive charge at the carboxyl group, and this assists in the stabilization of a pair of electrons left behind by the cleavage of a carbon-carbon bond when CO_2 is evolved. The greater the positive charge on the metal ion and the stronger the bond formed between the metal ion and the carboxyl oxygen, the more readily will decarboxylation occur. This has been confirmed experimentally, since the following metal ions were found to have a decreasing effect on the rate of decarboxylation of α,α′-dimethyloxaloacetic acid: Fe(III), Cu(II), Al(III), Ni(II), Fe(II), Mn(II).

Another thoroughly investigated reaction is the decarboxylation of oxaloacetic acid in the presence of metal ions (*89, 116, 121, 189*). In this case the reaction proceeds via a metal chelate of the keto form of the dian-



(LXXIII)

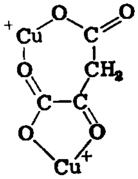
(LXXIV)

ion of the acid (structure LXXIII). The metal complex of the enol form of the acid (structure LXXIV) is stable and does not decarboxylate (*90*).

The following sequence of dipositive metal ions shows a decreasing effect on the rate of decarboxylation of oxaloacetic acid: Cu(II), Zn(II), Co(II), Ni(II), Mn(II), Cu(II) (*91*). The rate constants for these decarboxylations approximately parallel the formation constants of the corresponding metal oxalates. A similar result was found in the decarboxylation of acetonedicarboxylic acid in the presence of certain transition metal ions; the decarboxylation rates paralleled the formation constants of the metal malonates (*170*). These parallelisms indicate that the effectiveness of a metal ion in these decarboxylation reactions depends on its ability to chelate with the oxalate ion and the malonate ion, which resemble the transition states of the oxaloacetic and acetonedicarboxylic acids, respectively.

It is significant that in all these decarboxylation reactions, although the β-keto acid is present in large excess, only a 1:1 complex is formed with the added metal ion. Therefore, other coordinating agents such as citrate or acetate, and chelating agents such as 8-hydroxyquinoline-5-sulfonic acid or *o*-phenanthroline, can occupy the vacant positions in the coordination sphere of the metal ion (*173*). The effect of these auxiliary complexing agents on the rates of decarboxylation of β-keto acids is of importance in understanding certain decarboxylation reactions promoted by enzymes (*86*, *181*). One such effect is that if the positive charge on a 1:1 metal complex is reduced by the coordination of an anionic ligand, the rate of decarboxylation is diminished. If neutral ligands capable of π-bonding are coordinated, the effective charge on the metal ion is increased and the rate of decarboxylation is also increased.

In the presence of large metal ion concentrations, the decarboxylation of oxaloacetic acid is inhibited, probably because the labile carboxyl group is bound in a second six-membered metal chelate ring (structure LXXV) (*91*, *189*).



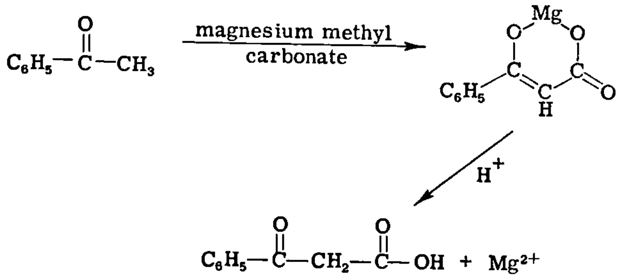
(LXXV)

The same reason, i.e., the formation of a metal chelate ring with the labile carboxyl group, can be advanced for the unexpectedly small effect of copper(II) on the decarboxylation of acetosuccinic acid (*167*), or for the inhibition of the decarboxylation of nitroacetic acid by metal ions (*165*). In the latter case, the undissociated acid, the dianion, and the metal chelates do not decarboxylate, whereas the monoanion decomposes in aqueous solution to CO_2 and the anion of the aci-nitromethane:

$$O_2NCH_2COO^- \rightarrow CO_2 + {}^-O_2NCH_2$$

It is of interest to synthetic chemists and biochemists that the reverse of the reaction shown above, namely, a carboxylation, can be carried out by the treatment of nitromethane with magnesium methyl carbonate, ($CH_3OMgOCO_2CH_3$ and CO_2), in dimethylformamide. A magnesium chelate of the nitroacetate dianion is formed which, when hydrolyzed under acid conditions, gives nitroacetic acid. The success of this carboxylation of a nitroparaffin depends on the formation of the magnesium chelate, which was identified spectrophotometrically (*37, 84, 194*).

Magnesium methyl carbonate can be used to carboxylate ketones containing enolizable methyl or methylene groups (*193*). For example, acetophenone can be converted to benzoylacetic acid via an intermediate magnesium chelate, which has an intense absorption in the ultraviolet.



(LXXVI)

VII. Free Radical Reactions

All the preceding reactions of chelated ligands can be shown or have been presumed to occur via an ionic mechanism. A preliminary report on the free radical reactions of a series of chelated acetylacetonates has been published recently. A solution of the metal chelate in bromobenzene was heated with *tert*-butyl peroxide. The *tert*-butoxy radicals that were formed either abstracted a hydrogen atom by cleavage of a carbon-hydrogen bond in the acetylacetonate molecule to form *tert*-butyl alcohol, or decomposed to form acetone and a methyl radical. Thus, the ratio alcohol:acetone that is obtained experimentally is a measure of the strength of the carbon-hydrogen bond that is cleaved. The *tert*-butoxy radical abstracted a hydrogen atom from the 3-position in unchelated acetylacetone. With the metal chelates of acetylacetone, an interesting result was obtained. A hydrogen atom was abstracted from the methyl group in the 1-position. The resulting intermediate chelate radical added to another unreacted chelate molecule in the 3-position to form a metal chelate which, when hydrolyzed, yielded a dimer, 3-acetyloctane-2,5,7-trione. The structure of this dimer was confirmed by an independent synthesis. Thus, it appears that chelation of acetylacetone to a metal ion changed the site of radical attack. Moreover, the nature of the metal ion had a profound effect on the rate of radical attack. The rate ratios (alcohol:acetone) from the substituted toluenes were used to determine the Hammett ρ value for the reaction, and this was used to calculate σ values for the chelate rings (*96*). A detailed interpretation of these important results must, however, await more experimental work in this area.

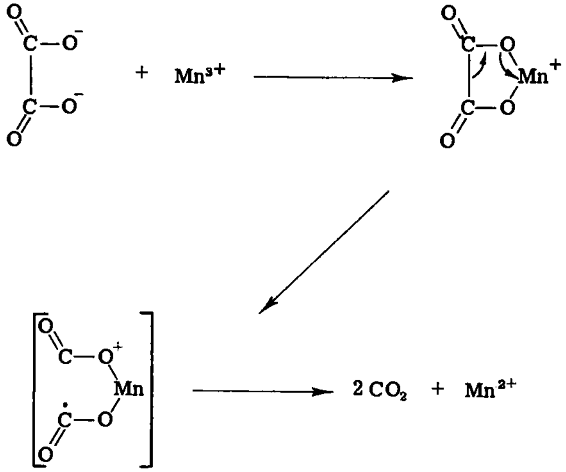
VIII. Oxidation-Reduction Reactions

A. REACTIONS IN AQUEOUS MEDIA

The ability of a metal ion to exist in several oxidation states is primarily responsible for its use as an electron carrier in oxidation-reduction reactions. When a metal ion is bound in a chelate ring, the resulting metal chelate can participate in oxidation-reduction reactions in which the chelating agent undergoes no chemical change. Reactions involving systems of this type, e.g., the oxygen-carrying cobalt(II) chelate of histidine, hemoglobin, peroxidase, and cytochrome, although extremely important, are outside the scope of this review and will not be discussed. Only those chelates in which the chelating agent undergoes a chemical transformation as a result of an oxidation-reduction reaction will be described in this section.

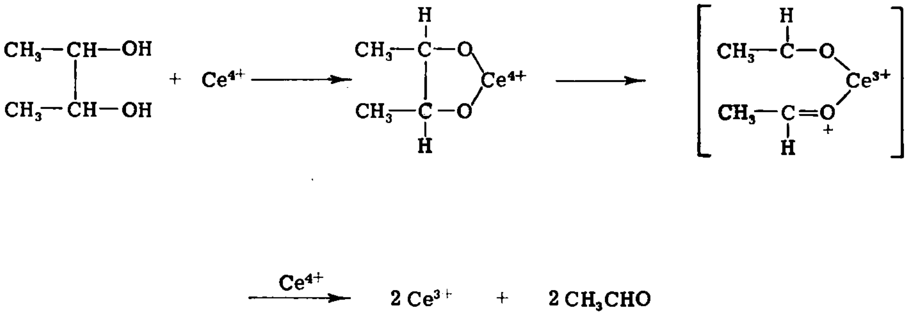
The spontaneous oxidation of organic chelating agents does not take place readily, and reactions with specific oxidizing agents are usually extremely slow. In the presence of a metal ion, these reactions can be greatly accelerated, since a kinetically easier path for the oxidation is provided by the formation of a suitable intermediate metal chelate. The electron transfer reaction is facilitated by the metal ion, since it can exist in a lower or higher oxidation state and can also fix the organic ligand in an orientation appropriate for the reaction. Of the vast number of oxidation-reduction reactions involving metal chelates in the literature, only a few illustrative examples will be given below.

One of the most familiar examples of an oxidation reaction in which a metal chelate intermediate has been postulated, is the conversion of the oxalate ion to carbon dioxide by permanganate ion. An induction period is observed, in which a sufficient amount of Mn(III) is formed for the reaction (LXXVII), where the metal ion is reduced to a lower oxidation state by the abstraction of an electron from the oxalate, thereby cleaving the carbon-carbon bond in the oxalate (*195*, *196*).



(LXXVII)

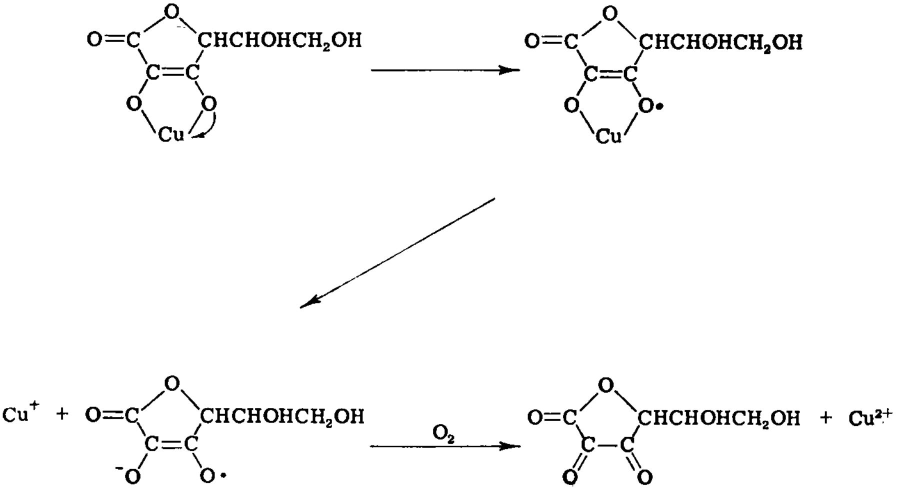
Similarly, the specific oxidation of glycols and related compounds has been found to proceed through the formation of intermediate chelates. For example, in the oxidation of 2,3-butanediol in nitric acid solution by cerium(IV) ions, the metal ion probably forms an intermediate chelate with the glycol, extracts an electron from the ligand, and is reduced to its lower oxidation state. A carbon-carbon bond in the glycol is broken in this process with the resultant formation of acetaldehyde (*71*).



(LXXVIII)

Cerium(IV) was also used as an oxidizing agent in a study of the oxidation of the inert chelates formed with chromium(III) and oxalate ion. From kinetic measurements in aqueous sulfuric acid media, it was concluded that the oxidation of tris(oxalato)chromium(III) ion, *cis*-bis(oxalato)-chromate(III) ion, and the monooxalatochromium(III) ion follow initial second-order kinetics, and 1 mole of oxalate is oxidized to carbon dioxide for every 2 moles of cerium(IV) reduced to cerium(III). A detailed study of the oxidation of the bisoxalato chelate indicated that cerium(III) inhibits the reaction (*197*).

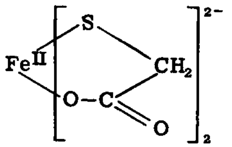
An example of a reaction in which the reduced form of the metal ion is converted back to its higher oxidation state by molecular oxygen, is the autoxidation of ascorbic acid by copper(II) (*206*, *207*). The probable course of the reaction is as follows: The ascorbate ion forms an intermediate copper(II) chelate which undergoes an internal oxidation-reduction reaction, thereby forming a copper(I) semiquinone chelate. Dissociation of the relatively unstable copper(I) chelate occurs and the copper(I) ion is oxidized by molecular oxygen and the semiquinone is oxidized by molecular oxygen or copper(II) (*160*).



(LXXIX)

The effect of adding chelating agents, such as EDTA and 8-quinolinols, in varying concentrations to this system indicates that at least two coordination sites in the copper(II) must be available for the internal rate-determining electron transfer reaction to take place (*36*). The addition of EDTA inhibits the reaction completely, presumably because the ascorbate ion is prevented from occupying two adjacent coordination sites in the metal ion. An interesting result was found when 1,10-phenanthroline was added in a large excess of the copper(II) present; although the activity of the copper(II) was reduced by about 50%, the reaction could not be completely inhibited as with EDTA. One of the copper(II) chelates of 1,10-phenanthroline must, therefore, participate in an electron transfer reaction involving the ascorbate ion. Since electron transfer can take place through chelated molecules of ligands such as 1,10-phenanthroline or 2,2′-dipyridyl, metal chelates of this type would seem to hold promise as mild and selective oxidizing agents (*7*, *65*, *172*).

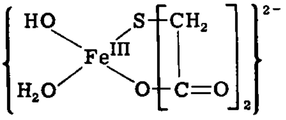
The oxidation of a variety of mercapto compounds, e.g., cysteine and thioglycolic acid, by molecular oxygen is accelerated in the presence of metal ions of the first transition series by the formation of intermediate metal chelates (*38*, *150*, *177–179*). The nature of this type of reaction is best understood by considering the reaction of iron(II) with the thioglycolate ion, which forms an almost colorless anionic chelate (structure LXXX) in the complete absence of oxygen. If air or oxygen is admitted to an acid solution of this chelate, a labile blue dimeric iron(III) complex is formed (LXXXI) (*127*). In alkaline solutions in the presence of air or oxygen, a red color is formed very rapidly but fades gradually. The red color can be regenerated by shaking with air as long as unreacted thioglycolate is present. The red-colored complex was found to have the structure (LXXXII). The slow fading of the red color was attributed to the reduction of iron(III) to iron(II) in the complexed form and the oxidation of the thioglycolate to the disulfide $^{-}O_2CCH_2SSCH_2CO_2^{-}$. This cycle of reactions, therefore, shows the manner in which iron can catalyze the oxidation of the thioglycolate ion (*129*, *130*). The oxidation rate calculated on the basis of this scheme could, however, account for only 1–3% of the



(LXXX)

$[Fe_2(SCH_2COO)_3(OH)_2]^{2-}$

(LXXXI)



(LXXXII)

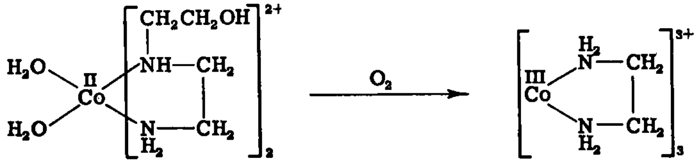
experimentally observed oxidation rate. Hence, a modification of the scheme involving a free radical mechanism was proposed (*127*) and has been recently confirmed (*131*). The experimental results can be explained by the mechanism (LXXXIII) in the presence of relatively high concentrations of iron(II) and thioglycolate ion.

$$\begin{aligned}
&\mathrm{Fe(II)} + \mathrm{O_2} \longrightarrow \mathrm{Fe(III)} + \mathrm{HO_2\cdot} \\
&\mathrm{HO_2} + \mathrm{RSH^-} \longrightarrow \mathrm{H_2O_2} + \mathrm{RS\cdot} \\
&\mathrm{Fe(II)} + \mathrm{H_2O_2} \longrightarrow \mathrm{Fe(III)} + \mathrm{HO\cdot} \\
&\mathrm{HO\cdot} + \mathrm{RSH^-} \longrightarrow \mathrm{H_2O} + \mathrm{RS\cdot} \\
&2\,\mathrm{RS\cdot} \longrightarrow \mathrm{RSSR}
\end{aligned}$$

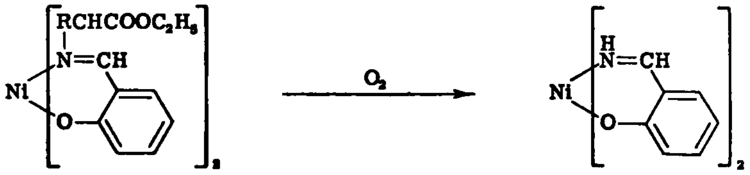
(LXXXIII)

In intermediate concentration ranges, the free radicals, as well as oxygen, react with the iron(III) chelate, $[\mathrm{Fe(OH)(RS)_2}]^{-2}$, to form iron(II) and the disulfide (*131*).

At some stage in all the preceding reactions, the metal ion undergoes a change in its oxidation state. This occurs, in most cases, by the abstraction of an electron from the chelated ligand, resulting in the subsequent oxidation of the ligand. An oxidation reaction of a chelated ligand involving a completely different reaction mechanism has been studied recently (*69, 70*). When air was passed through a heated solution containing cobalt(II) chloride, *N*-hydroxyethylethylenediamine, and an activated carbon catalyst, the cobalt(II) was oxidized to cobalt(III) with the simultaneous formation of large amounts of ethylenediamine. The oxidation products of the hydroxyethyl group that were identified included ammonia, formic



(LXXXIV)



(LXXXV)

acid, and formaldehyde. An oxygen-cobalt(II) complex has been postulated as an intermediate in this oxidative cleavage reaction.

A similar side-chain cleavage reaction has been observed, under oxidative conditions, with the copper(II) and nickel(II) chelates of the Schiff base of salicyl aldehyde and an alanine ester (*168*).

B. Reactions in Nonaqueous Media

A detailed study has been carried out on the destructive autoxidation of a series of metal acetylacetonates in diphenyl ether at 100°C in the presence of oxygen (*3*, *147*). The volatile products obtained upon the autoxidation of iron(III) acetylacetonate were carbon dioxide and water, as well as diacetyl and acetic acid, together with small amounts of acetylacetone and mesityl oxide. The rate of oxidation of the iron(III) chelate was found to depend on the structure of the ligand. Substituents, such as phenyl or benzyl, in the 3-position or bulky substituents, e.g., *tert*-butyl, in the 2- and 4-positions, greatly retarded the autoxidation of the chelate. On the other hand, the rate of autoxidation of the iron(III) chelate of dibenzoylmethane was seven times faster than that of the iron(III) acetylacetonate. Variation of the metal in a series of acetylacetonates was also found to affect the rates of autoxidation. One group of chelates of the metal ions Al(III), Zr(IV), Be(II), Cr(III), and In(III) were inert, whereas the following decreasing order of reaction was observed with the rest of the chelates: V(III) > Ce(IV) > Ni(II) > Mn(III) > Fe(III) > Co(II) > Co(III) > Th(IV). From these results, it can be deduced that only those acetylacetonates with metal ions capable of existing in several oxidation states readily undergo autoxidation.

Kinetic studies were carried out in order to determine the mechanism of the autoxidation reactions. The results indicate that the reactions do not proceed via the usual type of radical-chain mechanism involving hydroperoxides, and that not all metal acetylacetonates follow the same mechanism. A relatively simple mechanism has been proposed for the destructive autoxidation of iron(III) acetylacetone that postulates an intramolecular oxidation-reduction of the chelate with the formation of stable radicals, which are intercepted by highly reactive radicals produced by the decomposition of initiators. A triketone, 2,3,4-pentanetrione, is postulated as the intermediate from which most of the reaction products are derived (*4*, *5*).

The free ligands, acetylacetone, dibenzoylmethane, and 3-phenylacetone, do not undergo autoxidation under the same reaction conditions used for the autoxidation of their metal complexes. This is not surprising, since acetylacetone is much more stable than its metal chelates when subjected to pyrolysis (*42*).

C. Pyrolysis of Metal Chelates

Despite the recent interest in the preparation and properties of thermally stable metal chelates, only a few attempts have been made to study in a systematic manner the chemical reactions that take place when metal chelates are thermally decomposed. The thermal stabilities of the acetylacetonates of a number of metal ions were compared by measuring the increase in pressure caused by the formation of volatile decomposition products in a closed system containing the metal acetylacetonate and nitrogen gas. A comparison of the data obtained at 191°C indicated that the rate and extent of decomposition were dependent on the nature of the metal ion. The acetylacetonates of Zr(IV), Co(III), Fe(III), and Mn(III) had the lowest thermal stability whereas the Li(I), Mg(II), Be(II), Cu(II), Ni(II), Ga(III), and Cr(III) chelates were among the most stable (*44*). In contrast, acetylacetone itself does not decompose under the same conditions (*42*).

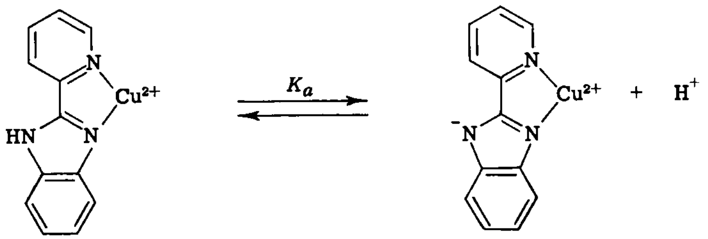
One possible route suggested for the decomposition of the metal acetylacetonate involves the formation of acetylacetone, which subsequently breaks down to form acetic acid, acetone, carbon dioxide, carbon monoxide, and methane (*42*).

Several metal chelates of 8-quinolinol were found to have high thermal stability, but a direct comparison with the free ligand stability is not possible since 8-quinolinol volatilizes at low temperatures (*43*). When the metal chelates of 8-quinolinol were heated in the absence of air or in an inert atmosphere of argon, the main gaseous product identified was hydrogen; smaller amounts of methane, carbon monoxide, carbon dioxide, and nitrogen were also found. From a titrimetric determination of the unchelated metal ion present, it was deduced that the metal chelate rings were at least partially retained intact in the pyrolyzed residues. The order of decreasing thermal stability of a series of dipositive metal chelates of 8-quinolinol was: Ca $>$ Mg $>$ Sr $\sim$ Cd $\sim$ Mn $>$ Ba $>$ Co $>$ Ni $>$ Zn $>$ Pb $>$ Cu (*40, 45*).

The chelates of copper(II), nickel(II), cobalt(II), cadmium(II), and lead(II) gave the free metal, whereas manganese(II) and zinc(II) formed the oxides when pyrolyzed. From these observations it would appear that the relative thermal stabilities of the metal chelates of 8-quinolinol are determined by the relative ease with which the metal cations are reduced to the metal (*45*). Until more experimental data become available, speculations on the mechanisms of these reactions will be of little value.

IX. Deprotonation Reactions

A thermodynamic study of the role of the metal ion in reactions of chelated ligands provides results that can be interpreted more easily than those of kinetic studies. The measurement of the change in the acid dissociation constant (K_a) of an appropriate substituent suitably located in the ligand molecule is a useful method of evaluating the influence of metal ion chelation on the properties of a ligand. In a potentiometric examination of the solution equilibria of 50% aqueous dioxane systems containing a series of transition metal ions and the ligand, 2-(2-pyridyl)benzimidazole, it was shown that metal chelate formation decreased the electron availability at the imino nitrogen and facilitated a deprotonation reaction, i.e., the dissociation of the imino hydrogen.



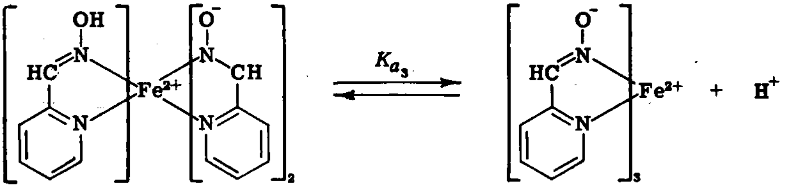
(LXXXVI)

The magnitude of K_a was dependent on the nature of the metal ion, and the more stable the metal chelate, the more easily dissociation occurred (*102*). It is of interest to note, therefore, that an electronic shift which occurs as a consequence of metal-nitrogen bond formation can be relayed through an aromatic nucleus.

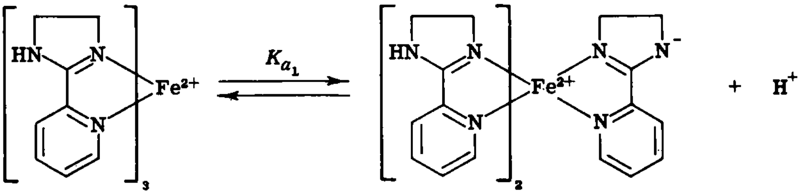
In studies of this type, proton release from a ligand substituent quite often occurs in approximately the same pH region in which proton release occurs, as a result of metal ion hydrolysis. Unless the latter effect is negligible, the interpretation of experimental data becomes ambiguous. For example, although proton release did occur in systems containing metal chelates of 2-(2-pyridyl)imidazoline, the pH region in which it occurred overlapped the pH region in which metal ions were hydrolyzed (*102*).

The deprotonation of the iron(II) and iron(III) chelates of pyridine-2-aldoxime was studied spectrophotometrically (*100*). On the basis of a series of color changes that were observed, the deprotonation of the 1:3 chelate of iron(II) was assumed to take place in three successive steps, the last of which is shown in reaction (LXXXVII). The thermodynamic acid dissociation constant, K_{a_3}, for the last step was $10^{-7.13}$; $\Delta H° \approx 1$ kcal mole^{-1} and $\Delta S° \approx -30$ cal mole^{-1}deg^{-1}. For the second dissociation step, K_{a_2} was $10^{-3.36}$; $\Delta H° \approx -1 \pm 1$ kcal mole^{-1} and $\Delta S° \approx -18$ cal mole^{-1}deg^{-1}. K_1 could not be determined since the chelate decomposed rapidly in acid solutions. The acid dissociation constant of the oxime group in unchelated pyridine-2-aldoxime is $10^{-10.22}$. Chelation with iron(II), therefore, gives rise to a very large acid-strengthening effect in the oxime group and is largely an enthalpy effect, since there is no significant difference in the entropy values. Only the third acid dissociation constant, K'_{a_3}, of the 1:3 chelate with iron(III) could be measured and was found to be $10^{-3.5}$, the difference in charge type being primarily responsible for the difference between K_{a_3} and K'_{a_3}.

In a continuation of the above study the first acid dissociation constant, K_{a_1}, in the deprotonation of the 1:3 chelate of 2-(2-pyridyl)imidazoline with iron(III) was found to be $10^{-6.09}$ (ΔH° = 6.9 kcal mole^{-1}).



(LXXXVII)



(LXXXVIII)

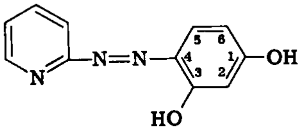
If the value of K_{a_1} is compared with the dissociation constant of the imidazolinium group ($\geqslant NH \rightleftharpoons \geqslant N—$) in the unchelated molecule ($K_2 = 10^{-8.92}$, ΔH° = 13.7 kcal mole^{-1}), then the effect of chelating iron(II) is to decrease the pK of the imidazolinium group by 2.8 and the enthalpy by 6.8 kcal mole^{-1}. Despite the difference in charge type between the ligand deprotonation and the chelate deprotonation reactions, the effect of chelation on the acid dissociation constant is quite large (*101*).

One method of experimentally confirming that a chelated ligand is being deprotonated is to use a closely related ligand that forms metal chelates of comparable stability, but has no substituent capable of dissociating. For example, when 2,2′-(dipyridyl) was used in place of 2-(2-pyridyl)benzimidazole, no proton release corresponding to the deprotonation of the imino group in the latter compound was observed (*102*).

In the potentiometric titration of solutions containing zinc(II) or nickel(II) and the ligand, pyridine-2-aldoxime, a single buffer region was observed in which proton release occurred as a result of metal chelation (*27*). In similar titrations in which pyridine-2,5-dialdoxime was the ligand, a second buffer region was observed and was attributed to the proton release from the unchelated oxime groups (*10*). The chelated metal ion again showed an acid-strengthening effect that paralleled the chelate stability.

A phenolic group is a useful ligand substituent in this type of investigation, since its pK_a is usually higher than the pH range in which most metal chelate formation occurs. Several systems have been studied in which changes in the acidity of a phenolic group are caused by metal chelation.

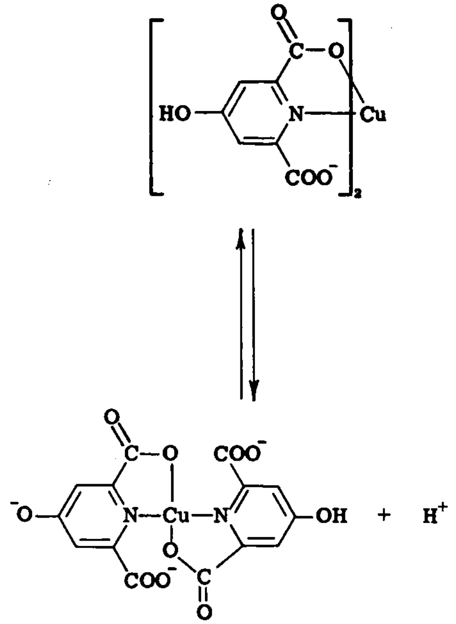
Most of the metal chelates of 4-(2-pyridylazo)resorcinol (structure LXXXIX) are stable and form at low pH (*62*). The pH ranges of chelate formation and of the dissociation of the 1-hydroxy group in the chelated ligand should, therefore, not overlap appreciably. Potentiometric titration curves of the 4-(2-pyridylazo)resorcinol chelates show two distinct buffer regions. The first region corresponds to the release of protons owing to chelation and the second to proton release from the hydroxy groups in the metal chelate (*61*). Protons are released, when metal chelate formation occurs, from the 3-hydroxy group despite its very weakly acidic nature (pK = 12.4). Since chelate formation takes place at pH values well below 7, the more acidic 1-hydroxy group (pK' = 7.0) is left intact. Titrations of the metal ions in the presence of 1-(2-pyridylazo)-2-naphthol (in which the hydroxy group *para* to the azo group is absent) did not show a second buffer region and metal ion hydrolysis could, therefore, be ruled out. The acid strengths of the 1-hydroxy groups in the 4-(2-pyridylazo)resorcinol chelates increase in the order, Mn(II) < Zn(II) ~ Ni(II) < Co. This parallels the known chelate stability order for Mn, Zn, and Ni. An apparent anomaly in this system is that the pK values of the 1-hydroxy groups in the Mn(II), Zn(II), and Ni(II) chelates are somewhat greater than the pK of the hydrogen-bonded chelate (pK' = 7.0) instead of being much less than 7.0. In the molecule of 4-(2-pyridylazo)resorcinol, the azo group is hydrogen bonded to the 3-hydroxy group, forming a planar system in which it can



(LXXXIX)

exert a very large electron-withdrawing action on the 1-hydroxy group, whereas in the metal chelates the azo group and the resorcinol ring are not in the same plane and its effect on the 1-hydroxy group is much less. Hence it is the position of the hydrogen chelate of 4-(2-pyridylazo)resorcinol that is anomalous in the chelate acidity series.

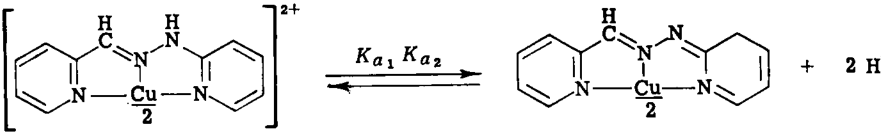
The presence of a phenolic group in 2,6-dicarboxy-4-hydroxypyridine promotes the formation of the pyridone tautomer (reaction XC) in the unchelated ligand. The acid dissociation constant of the phenolic group is $10^{-11.4}$. Metal chelation has a remarkable effect on this apparent dissociation constant (which includes the tautomeric equilibrium constant), since it is increased by a factor of 10^4 to 10^6. The usual acid-strengthening effect of metal ions is augmented in this case by a further electron shift away from the phenolic oxygen, probably caused by the transformation of the pyridone structure in the ligand to the pyridine tautomer in the metal chelate. The pK_a of the phenolic groups in the metal chelate increased in the order: Cu(II) < Co(II) < Zn(II) < Ni(II) < Mn(II) (*2, 9*).



(XC)

As with 2,6-dicarboxy-4-hydroxypyridine chelates, a sizable enhancement of the acidity of the 4-hydroxy group is seen in the metal chelates of both 4-hydroxy- and 4,8-dihydroxyquinaldinic acids (*11*). In a comparison of the effect of metal chelation on the pK_a of the hydroxy groups in these three compounds, variations in charge type must be taken into account. For example, with 4-hydroxyquinaldinic acid the pK_a of the hydroxy group in the free ligand involves the dissociation of a singly charged anion, whereas that of the chelate corresponds to the dissociation of a neutral species when the dissociation of only one of the hydroxy groups is considered. If an appropriate correction (about 1.0 log unit) is made for this, values of ΔpK for the three ligands with each of the metal ions can be compared (ΔpK is the difference between the pK values of the hydroxy groups in the free ligand and in the chelate). Copper(II) is found to exert a significantly greater effect than Co(II), Ni(II), Zn(II), and Mn(II). There is a great similarity in the effect of metal chelation on the acid dissociation constants of the hydroxy group in 2,6-dicarboxy-4-hydroxypyridine and of that in 4-hydroxyquinaldinic acid, both of which have the same chelate ring in the same position relative to the 4-hydroxy group. In the case of the 4,8-dihydroxyquinaldinic acid, the effect is smaller with all the metal ions. The greater portion of the acid-strengthening effect on the 4-hydroxy group could undoubtedly be attributed to the metal ion. The change in the location of the dissociating hydroxy group relative to the chelate ring, as well as differences in the tautomeric equilibrium constants of the ligands, has a smaller but unknown effect on the deprotonation reaction.

Pyridine-2-aldehyde-2-pyridylhydrazone is a tridentate ligand that forms cationic complexes with dipositive transition metal ions. The protons attached to the nitrogen atoms are readily lost from the chelate rings and an uncharged metal chelate, soluble in organic solvents, is formed, accompanied by a marked color change (*87*, *88*, *132*).



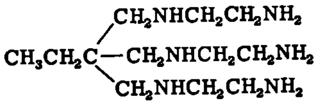
(XCI)

The acid dissociation constant of the free ligand, when the proton attached to the nitrogen dissociates, is approximately $10^{-14.5}$, and the effect of metal chelation is to increase this dissociation constant by a factor of 10^5 to 10^8. The values of K_{a_1} and K_{a_2}, the stepwise dissociation constants, were determined spectrophotometrically and potentiometrically, and the acid-strengthening effect on the NH group was found to depend markedly on the chelated metal ion (*95*). The order of increasing acidity is Mn(II) < Cd(II) < Zn(II) < Ni(II) < Fe(II). The values of pK_{a_1} and pK_{a_2} for any one metal were found to be within 1.3. It therefore appears that these chelates behave like diprotic acids in which the difference between the two pK values is attributable to combined electrostatic and statistical effects.

Related to the above mentioned deprotonation reactions are reactions that involve the addition or removal of a proton from a donor atom that is not coordinated to a metal ion. This situation arises with multidentate chelating agents in which all the donor atoms are unable to coordinate with a central metal ion for steric reasons. For example, the sexadentate ligand "penten" has six nitrogen donor atoms (structure XCII), all of which may not be coordinated to copper(II) or zinc(II). This can be ascertained by the determination of equilibrium constants for the formation of the protonated metal chelates (*180*). If a nitrogen atom is not coordinated or very weakly bound to the metal ion, it can be readily protonated, and the larger the equilibrium constant for the formation of the protonated metal chelate the less strongly coordinated is the nitrogen atom. The formation constant for the monoprotonated chelate of copper(II) and penten is $10^{8.2}$, whereas that for the diprotonated complex is only $10^{3.6}$. It may be concluded from this that probably only one nitrogen atom in penten is not coordinated or very weakly bound to copper(II).

(XCII)

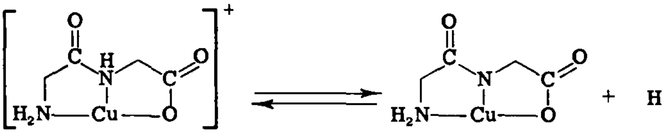
The protonated chelates of another amine (XCIII) that is a sexadentate chelating agent have been studied (*94*).



(XCIII)

Copper(II) forms a strongly monoprotonated chelate and a diprotonated chelate with this amine (*94*) whose formation constants are $10^{9.0}$ and $10^{4.9}$, respectively. Although manganese(II), cobalt(II), nickel(II), zinc(II), and cadmium(II) also form protonated chelates, their formation constants are smaller than those of the corresponding penten complexes and are present only in solutions of high acidity. It is therefore probable that four nitrogen atoms in this amine are strongly coordinated to copper(II), whereas the fifth is weakly bound and the sixth is not coordinated.

Deprotonation reactions have been known to take place upon metal chelate formation with a number of complex molecules, such as enzymes and proteins, and are undoubtedly of importance in biological systems (*73*). One such system that has been studied by a number of workers is the deprotonation of a number of glycine-containing dipeptides in the presence of copper(II) and nickel(II). Chelate formation occurs between the free α-amino group and the carboxylate ion and the peptide nitrogen, from which a proton is lost (*68*, *114*, *115*, *144*, *154*).



(XCIV)

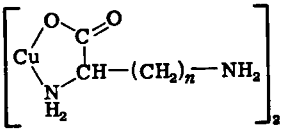
X. Synthetic Applications of Chelated Ligand Reactions

A metal ion is an extremely versatile reagent for use in synthetic organic reactions since it is a positively charged polybasic Lewis acid and electrophilic in nature. The effectiveness of a metal ion in these reactions can be traced to its coordination of one or more donor atoms in the course of the reaction. Organic chemists have utilized the coordinating properties of a metal ion in many synthetic procedures, but the selection of a metal ion for a given reaction has been largely empirical. On the basis of a systematic study of the reactions of chelated ligands, it should be possible to develop a number of useful synthetic procedures.

By reducing the rate of reaction, metal chelation can be used in the synthesis of reaction intermediates. By involving a sensitive functional group in chelation, protection of this group during various synthetic procedures can be achieved. By altering the pathway of a reaction with chelation, products not otherwise obtainable can be formed.

The following example illustrates the manner in which changes that occur in the rate of a ligand reaction upon metal chelate formation can be used for synthetic purposes. Two halogen atoms are introduced into a molecule of 8-hydroxyquinoline rapidly and almost simultaneously to give the 5,7-dihalo derivative (*118*). Studies on the rate of bromination of the Cr(III) or Cu(II) chelates of 8-hydroxyquinoline showed that monobromination in the 5-position occurred extremely rapidly, whereas the subsequent introduction of another bromine atom in the 7-position was quite slow. Advantage was taken of this difference in reaction rates to prepare the 5-bromo-, 5-chloro-, and 5-iodo-substituted compounds of 8-hydroxyquinoline and its 2-methyl and 4-methyl derivatives in good yields (*169*).

Tropolone usually undergoes electrophilic attack in the γ-position, but is brominated in the α-position. The bromination of the Cu(II) chelate of tropolone, however, takes place in the γ-position and is therefore a route for the preparation of γ-bromotropolone (*60*). Similar changes in the orientation of substitution reactions that can be brought about by metal chelation will be of value for synthetic procedures.

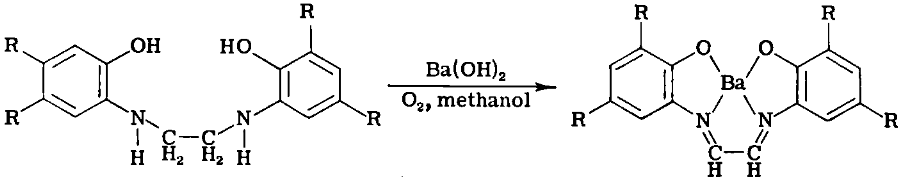


$n = 2, 3,$ or 4

(XCV)

A reactive group in a ligand can be protected by metal chelate formation. For example, in the compound (XCV) one of the amino groups is protected and the terminal amino group is free to react (*124*, *125*). The reactive nitroso group in *o*-nitrosophenol can be protected by the formation of a stable and water-insoluble copper(II) chelate (*159*). It is possible that other reactive groups, such as the mercapto group in 8-mercaptoquinoline, could be protected by metal chelation in the course of a synthetic procedure.

The direct method of synthesizing a Schiff base by the condensation of an *o*-hydroxy, *o*-amino, or *o*-mercaptoamine with a dicarboxyl compound often results in the formation of a heterocyclic compound by ring closure. This difficulty can be overcome by reacting the metal complex of one of the starting materials with the other to give the Schiff base chelate (*168*, *176*). Another route to these chelates is to start with the reduced form of the ligand, e.g., *N*,*N*′-bis(2-hydroxy-3,5-di-*tert*-butylphenyl)ethylenediamine (XCVI), which is itself a chelating agent, and to oxidize it in the presence of a metal ion to the Schiff base chelate (XCVII) (*134*).



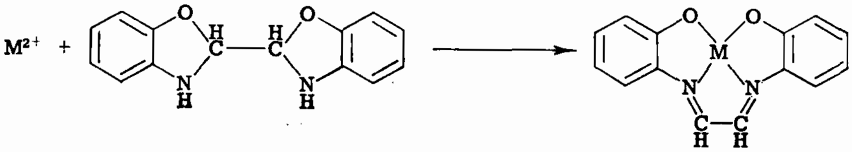
(XCVI) (XCVII)

R = *tert*-butyl

Another approach to the synthesis of these Schiff base type of chelates is to use a metal ion-induced rearrangement reaction. The compound

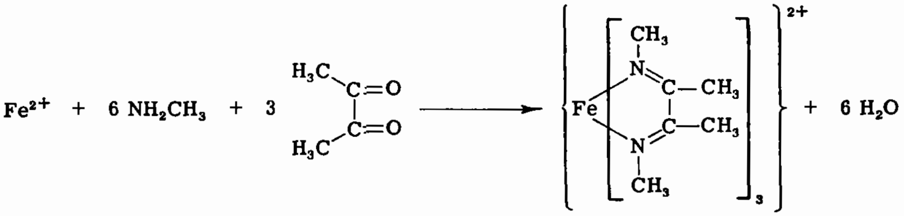
2,2′-bisbenzoxazoline rearranges in the presence of certain metal ions to give the Schiff base chelate in quantitative yields (*23*).

The related compounds, 2,2′-bisbenzothiazoline and its 2,2′-dimethyl homolog, were also found to rearrange under the influence of Zn(II), Cd(II), and Hg(II) to give the corresponding Schiff base chelates (*22, 108, 109*) (Section V).

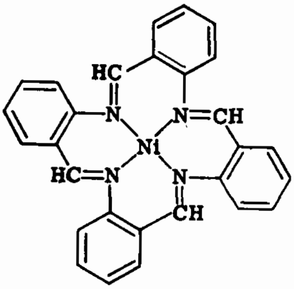


(XCVIII)

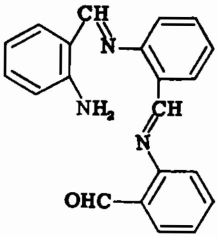
The stability of the metal chelate ring formed with Ni(II), Co(II), or Fe(II) and the donor group —N═C—C—N═ (*123*) is responsible for the formation of Schiff base chelates of α-diketones and methylamine (reaction XCIX) instead of the polymeric condensation products obtained in the absence of metal ions (*82, 83*). A related example is the formation of a cyclic tetramer of *o*-aminobenzaldehyde (structure *C*) in the presence of metal ions such as Zn(II), Ni(II), or Co(II) rather than the trimer (structure CI) that is formed, in the absence of metal ions, by the self-condensation of *o*-aminobenzaldehyde (*146*).



(XCIX)

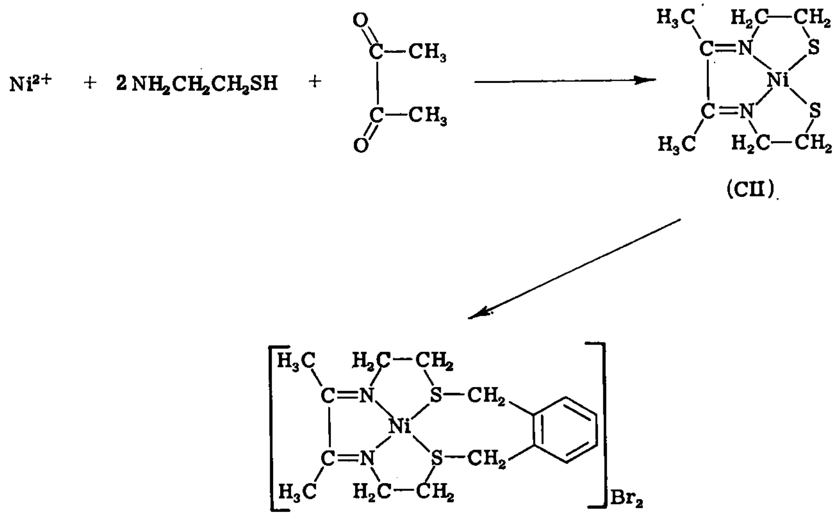


(C)



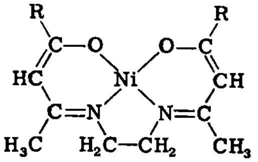
(CI)

The metal ion not only stabilizes the chelate rings and prevents the formation of undesirable products but also acts as a "template." Several reactions have been described in which Schiff base chelates are formed via a metal template or a metal chelate template mechanism. In the presence of nickel(II), β-mercaptoethylamine and α-diketones give a Schiff base chelate, whereas in the absence of metal ions, thiazolidines are obtained (*198*, *199*). The planar metal chelate (structure CII) has the coordinated sulfur atoms positioned in such a manner that they can undergo an addition reaction with α,α′-dibromo-*o*-xylene to give a ring system that completely encloses the metal ion (structure CIII) (*34*). Another reaction in which a metal chelate template mechanism has been postulated is the amine-catalyzed condensation of a β-diketone or related compound with tetrakis(ethylenediamine)-μ-dichloronickel(II) chloride to form compounds such as (CIV) or (CV) (*161*).



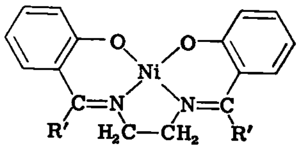
(CII)

(CIII)



R = CH_3 or C_6H_5

(CIV)



R′ = H or CH_3

(CV)

The introduction of substituents into the 3-position in acetylacetone is difficult and in some cases impossible unless the ligand is chelated. For example, the free ligand 3-nitroacetylacetone is unknown, but its chelates, bis(3-nitro-2,4-pentanediono)copper(II) or tris(3-nitro-2,4-pentanediono)-chromium(III), can be obtained by nitration of the metal chelate with a mixture of copper(II) nitrate and acetic anhydride (*54*). It is possible in this case that the pathway, as well as the rate of the ligand nitration, is altered as a result of chelate formation.

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